Major Psychiatric Disorders Are both Neurological and Neuropsychological Disorders:

The Neuropsychology of Schizophrenia

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Bio: Charles J. Vella, PhD

- Retired Neuropsychologist
- 2 years Psychiatric Halfway House experience (post hospital SMI)
- 34 years, Kaiser San Francisco, 1975-2009
  - Chief Psychologist/Manager
  - Founder & Director, Neuropsychology Service; still attend weekly NP seminar
- Neuropsychology Lecturer, 2009-Present

- Download this talk at:
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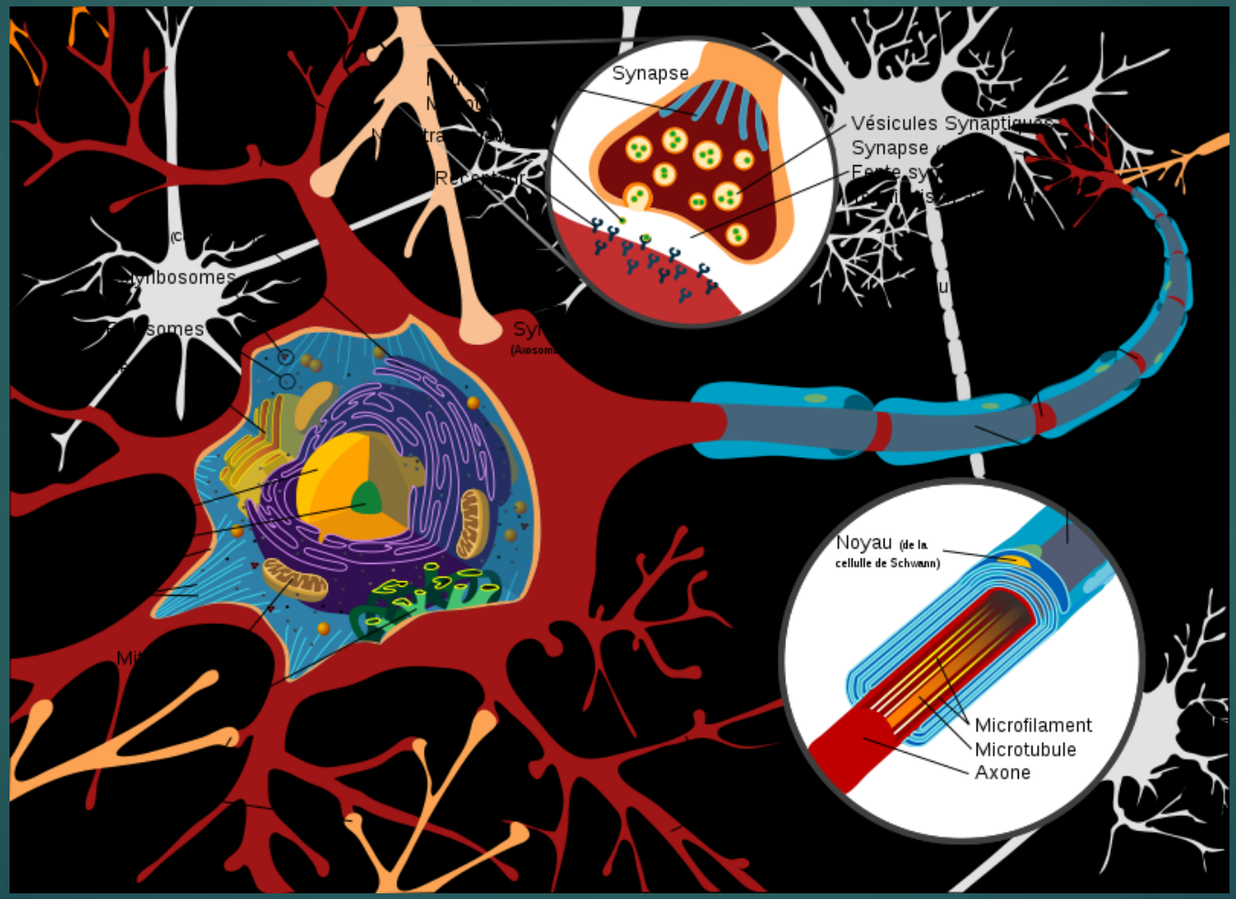
Focus of today’s presentation

- I am a retired neuropsychologist who spent first 10 years of my work as a clinical psychologist who did psychotherapy and 25 years as a clinical neuropsychologist who did clinical assessment.
- Today’s talk will focus mostly on the brain status of persons with chronic schizophrenia
- Please forgive me if I use the term schizophrenic (talk shorthand); as with all psychiatric conditions, individuals have a neurological condition; they are not just that condition
- We will review the neurology, neurodevelopment, and neuropsychology of schizophrenia
- Schizophrenia is a brain disease with not only psychiatric symptoms but also significant neuropsychological deficits

Neurons: We have 170 billion brain cells with 10,000 synapses each (10 trillion connections)

Neuron

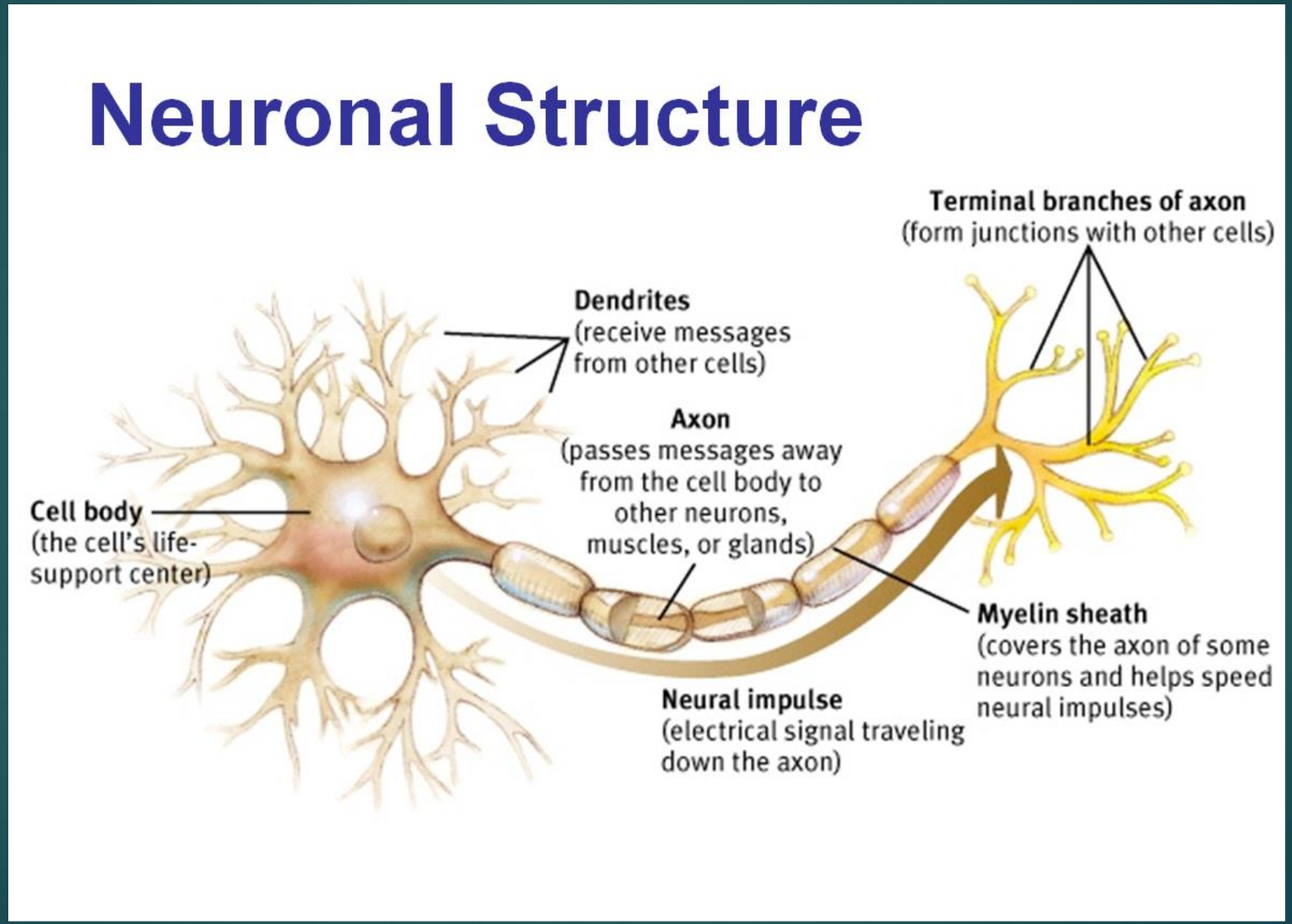


Axon

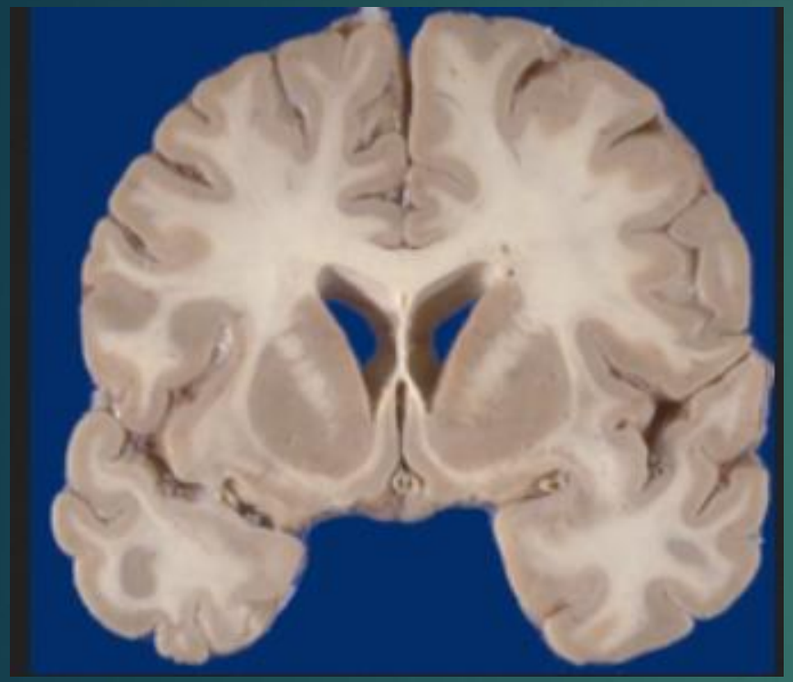
Dendrites

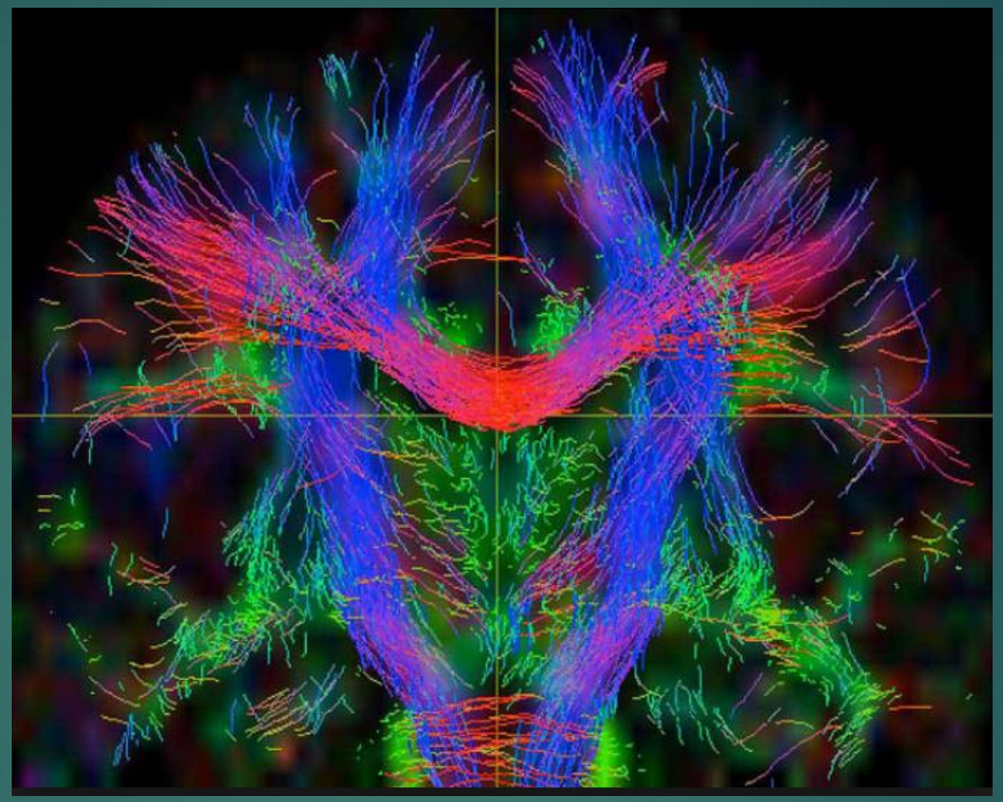
Suzana Herculano-Houzel et al., 2009

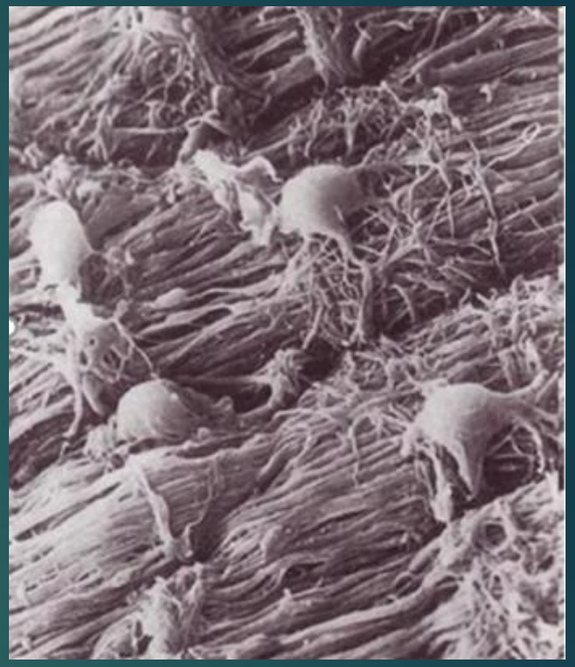
Neuron


Neuronal Structure
Terminal branches of axon
(form junctions with other cells)
Dendrites
(receive messages
from other cells)
Axon
(passes messages away
from the cell body to
other neurons,
muscles, or glands)
Cell body
(the cell's life-
support center)
Myelin sheath
(covers the axon of some
neurons and helps speed
neural impulses)
Neural impulse
(electrical signal traveling
down the axon)

White Matter: Insulation on your Neuronal axons



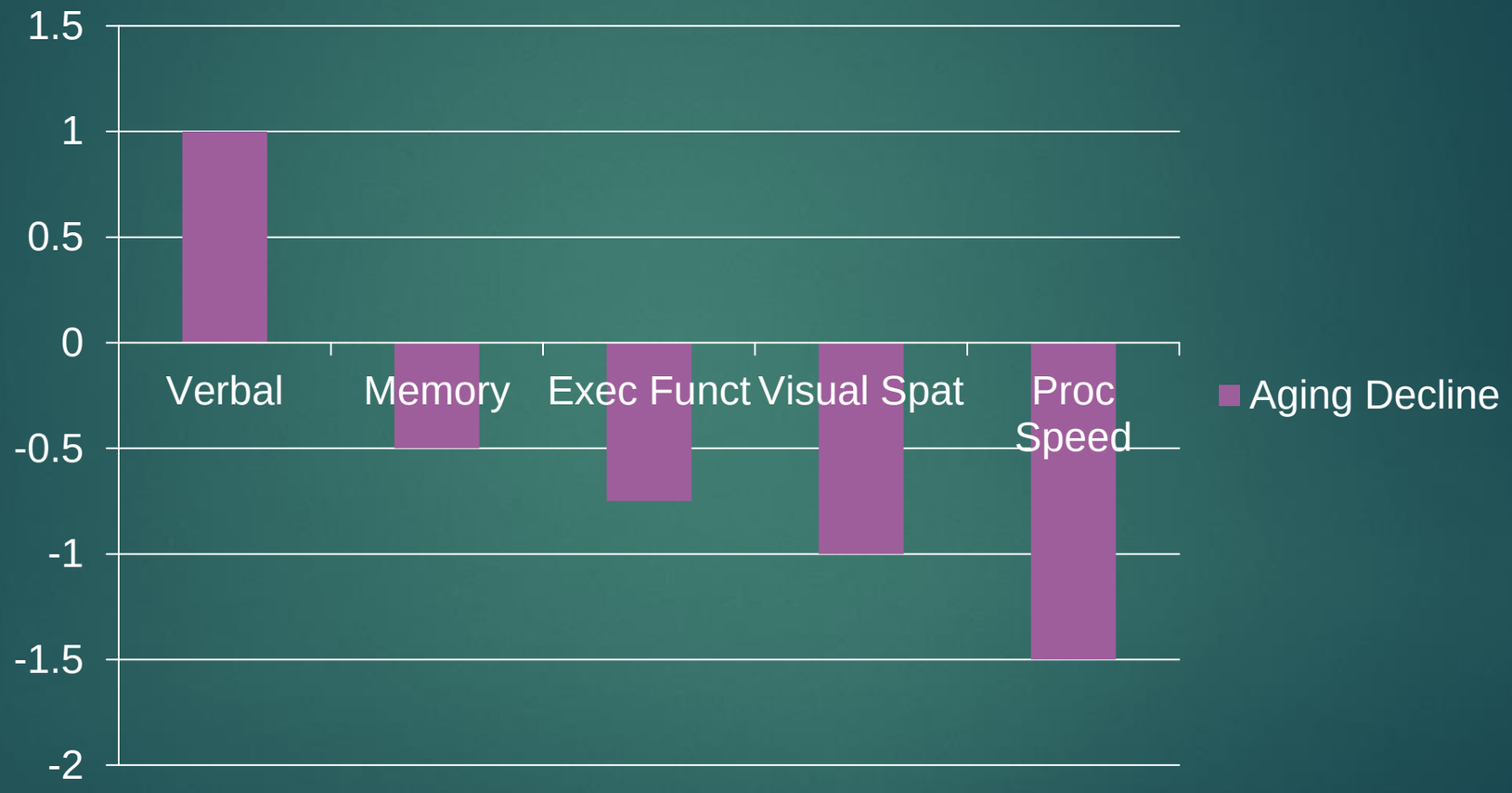




Brain DTI of WM Electron Microscope of WM

The Internet of your brain:
How fast you process information

Normal Aging Cognitive Decline
in the absence of brain pathology



Based on Schaie and Salthouse

Neuropsychology

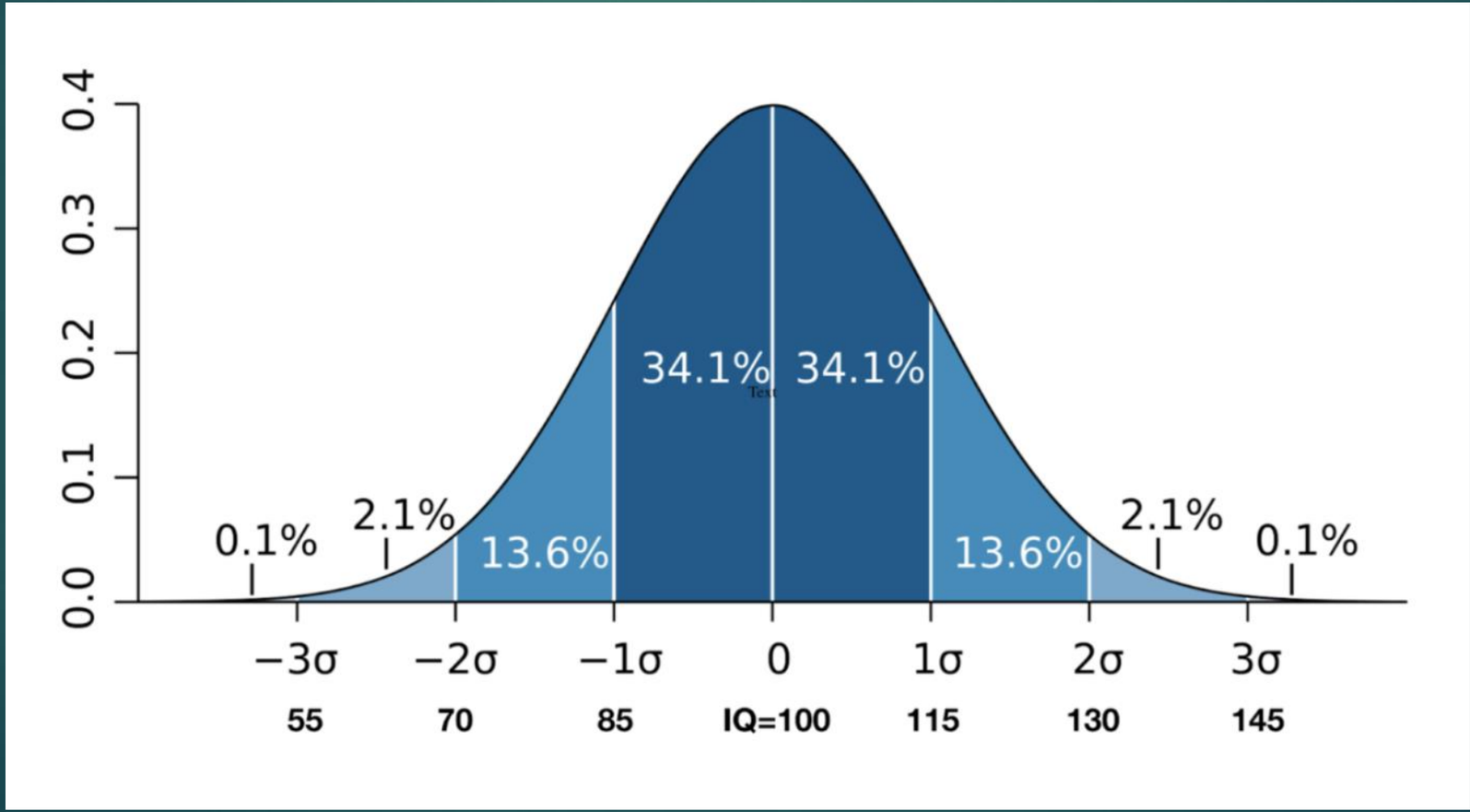
- Neuropsychology is the science of measuring the capabilities of a person's brain.

- A neuropsychological evaluation is an in-depth assessment of a person's cognitive skills and real-world abilities linked to their brain functioning.

- By comparing an individual's NP performance to normative standards, objective conclusions can be drawn about the examinee's real-world strengths and weaknesses

NP Assessment

- NP depends on normative comparisons. This involves taking the performance of an individual at the time they are tested and comparing that performance to reference groups of the same age, sex, race, and educational attainment.



Assessment areas

- The NP evaluation, using a wide variety of cognitive tests, measures such areas as:
  - working, declarative, and prospective memory,
  - attention
  - I.Q.
  - information and motoric processing speed,
  - executive functioning (EF) (reasoning, judgment, planning, and problem-solving)
  - visual-spatial skills,
  - language functions,
  - social-emotional functioning.
  - adaptive functioning
- Test Validity of the assessment – tests person’s effort during testing

Neuropsychological assessment

- A neuropsychological evaluation is different from tests included in a neurological evaluation (e.g., EEG) or neuroimaging (e.g., CT or MRI scan).
- Neuroimaging tells us what brain looks like and if there are visible neurological diseases (stroke, cancer, brain atrophy). NP testing tells us how separate normal & abnormal brain areas are actually functioning cognitively
- NP testing is not school testing like achievement testing (math level, klg of history, specific language proficiency, etc.)
- Poor NP results can be the best evidence for treatment recommendations, Social Security Disability Applications and School Accommodations.

NP assessment

- Uses of NP:
  - diagnostic assessment of clinical conditions
  - differential diagnosis,
  - assessment of treatment response, and
  - prediction of functional potential and functional recovery

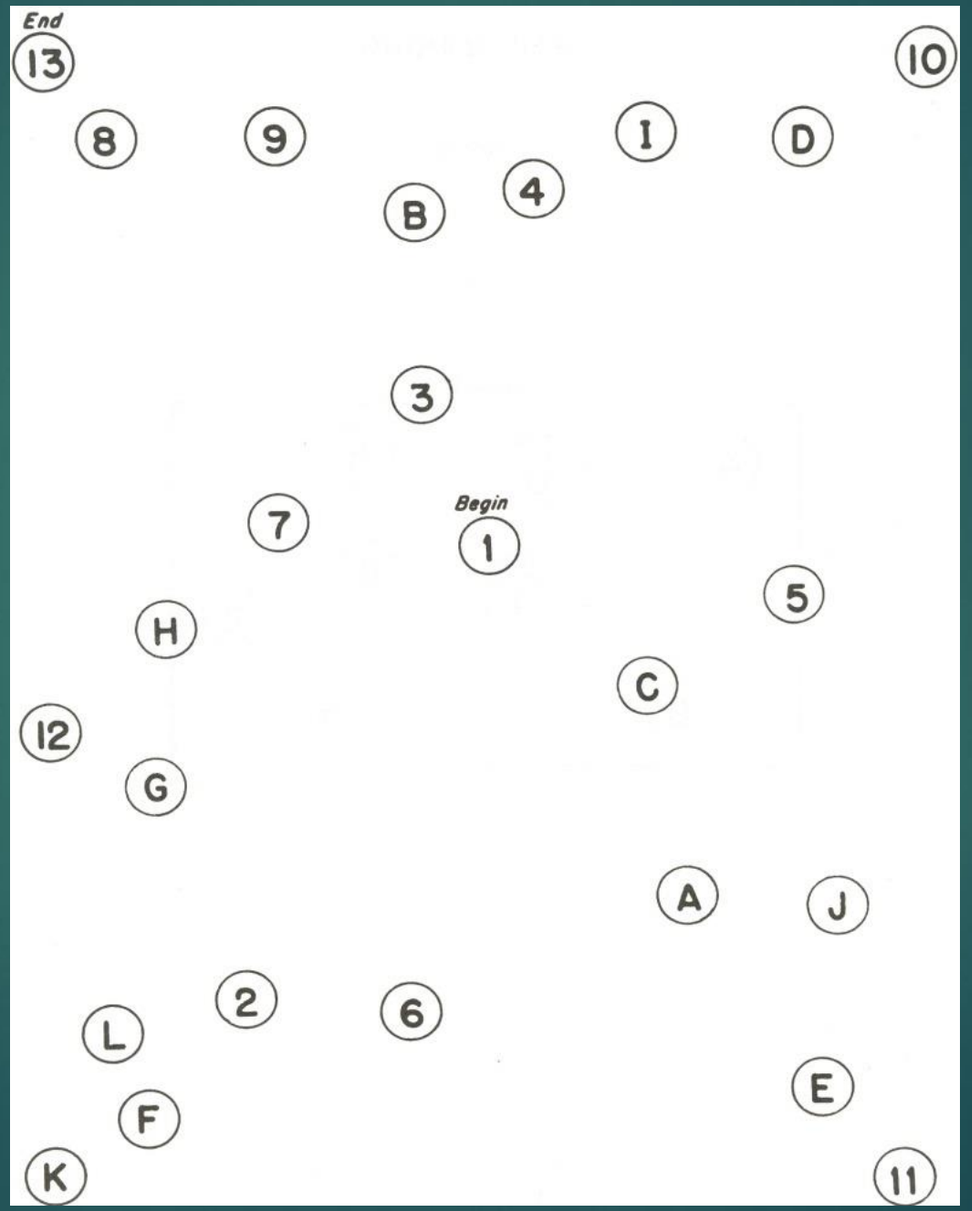
- Individuals with no lesions detectable on neuroimaging can have substantial cognitive and functional limitations.

NP assessment: diagnostic assessment of clinical conditions

- NP testing can identify whether a patient has various neurologically based disorders:
  - Very low intellectual ability (ID)
  - Types of Neurological Dementias (Major Neurocognitive Disorder)
  - Traumatic brain injury
  - ADHD
  - Memory disorder; amnesia
  - Executive function disorder
  - Cognitive effects of neurotoxins, chemotherapy, Covid 19
  - Cognitive disorders in psychiatric disorders: Bipolar, Schizophrenia, MDD

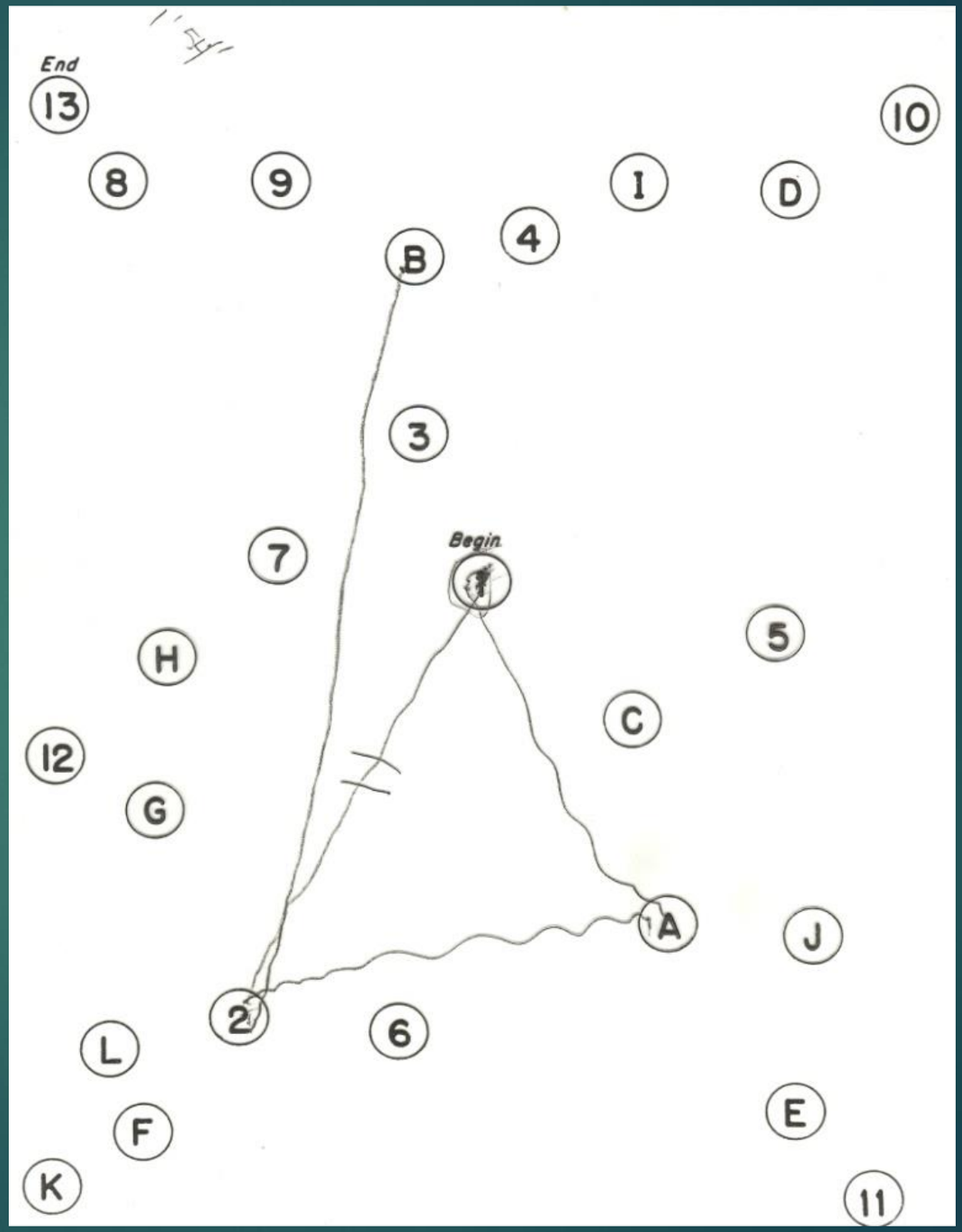
Trailmaking Test-B: Processing speed, visual spatial ability, EF

With pencil touching the paper, as quickly as you can, connect number, letter in correct sequence: 1-A-2-B, etc.

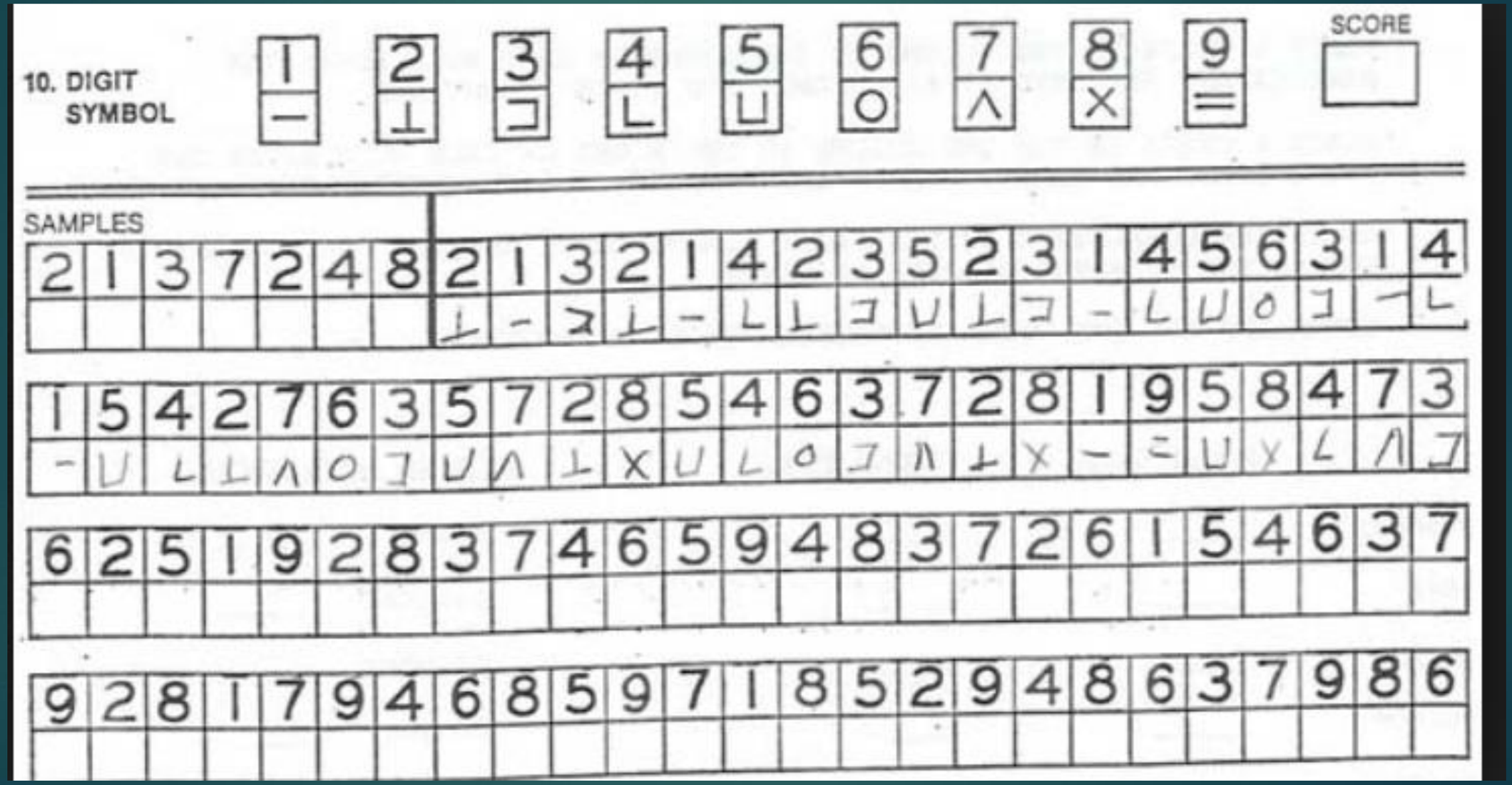


TMT-B: Alzheimer's

AD pts rarely
make it past "3-C"

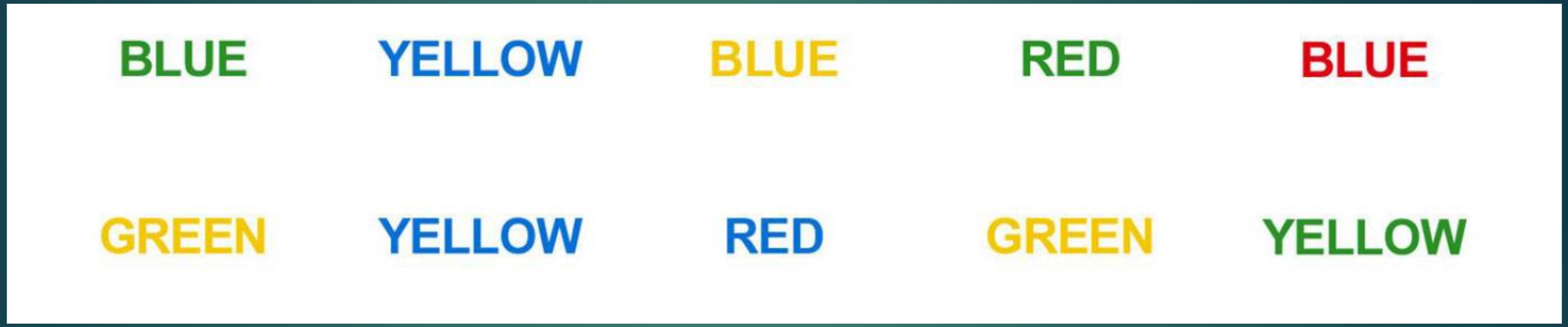


How we test processing speed

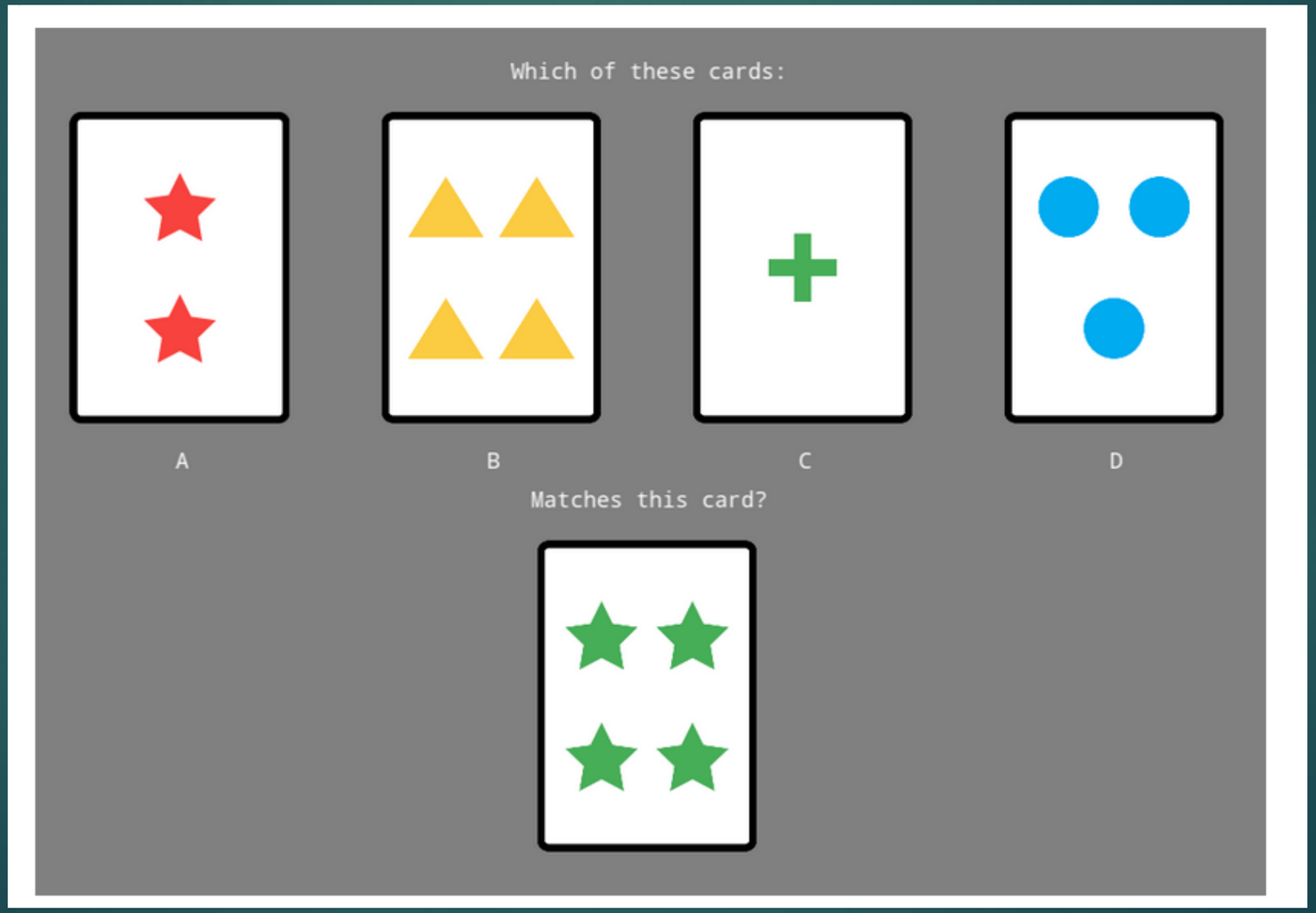


Stroop: test of cognitive inhibition ability

Read the color of ink not the word



Gold standard of EF: WCST: not told what principle to match by; after series of correct, principle changes



Prospective Memory is the best predictor of ability to function independently in the real world

- Prospective memory: remembering to remember, carrying out an intention, imaging a future event = an executive function

- Prospective Memory is a predictor of:
  - everyday functioning capacity,
  - medication adherence,
  - unemployment,
  - declines in instrumental activities of daily living
  - crashing an airplane (Airline industry has done most research)

Memory for Intentions Test (MIST):
2 of 8 questions

1. In 15 minutes, tell me it is time to take a break.

2. When I later show you a red pen, immediately sign your name on your paper

IADLs: Instrumental Activities of Daily Living

- 1. Basic communication skills: use a telephone
- 2. Transportation
- 3. Meal preparation
- 4. Shopping
- 5. Housework /laundry
- 6. Managing medications
- 7. Managing personal finances

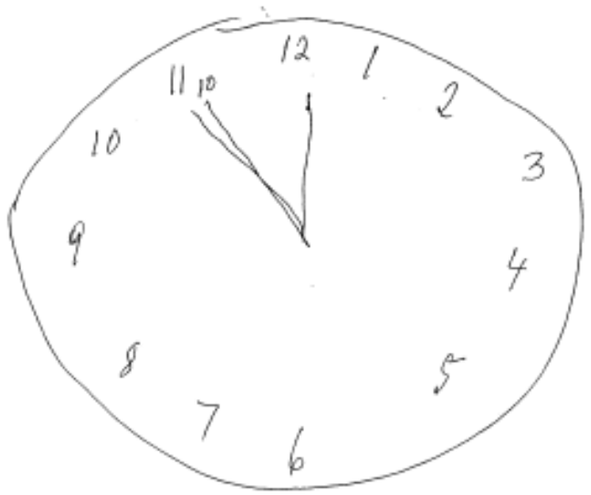
Spontaneous Clock Drawing requires executive functioning

- Complex executive task:
  - Initiation
  - Abstract conceptualization
  - Numerical ability
  - Verbal memory
  - Sequencing

Ferrucci, et al., 1996

Executive Function: Clock Drawing

Executive Function
Draw A Clock: “10 after 11”



79 year old right handed male
Mild Vascular Dementia

79 year old right handed male
Mild Vascular Dementia

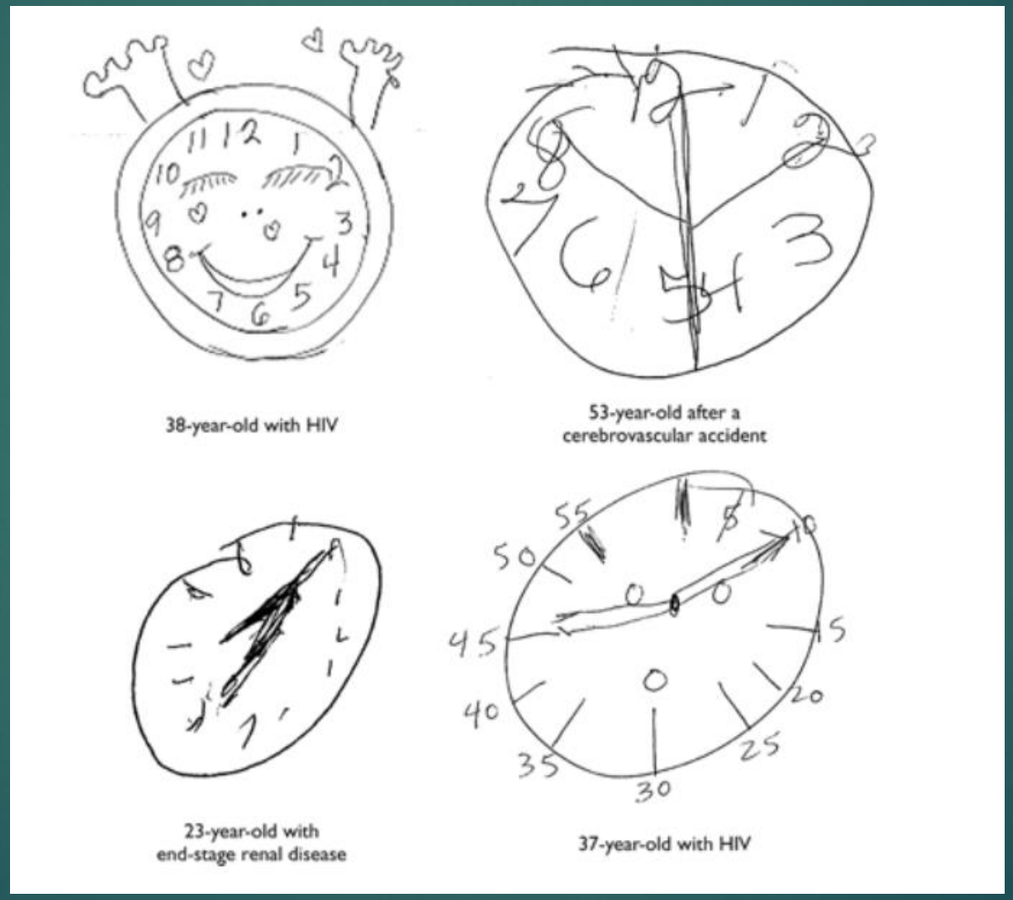
Clock Drawing in Medically Ill Patients

HIV

Stroke

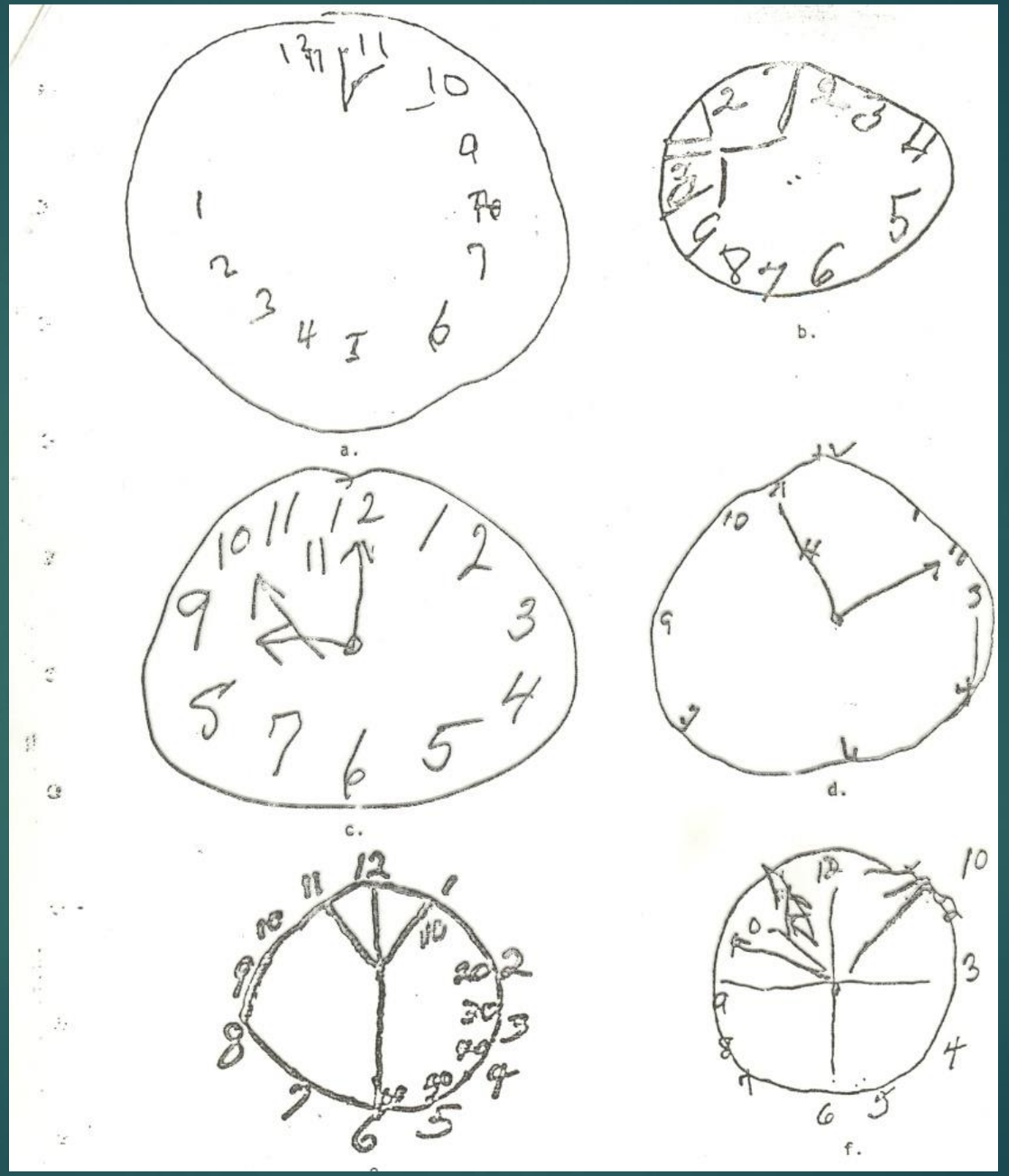
Renal Disease

HIV



Donald Royall

Clocks



DSM-5: Major Neurocognitive Disorder (Old term = dementia)

1. Evidence of significant cognitive decline from prior level of performance in 1 or more cognitive domains
    1. Concern of person, informant, or clinician of a significant cognitive decline
    2. Significant cognitive impairment on NP testing
2. Deficits interfere in independence in everyday activities

Specify severity (Mild (IADLS), Moderate (ADLS), Severe (full dependence)

NCD can be and often is present in schizophrenia

Objectives

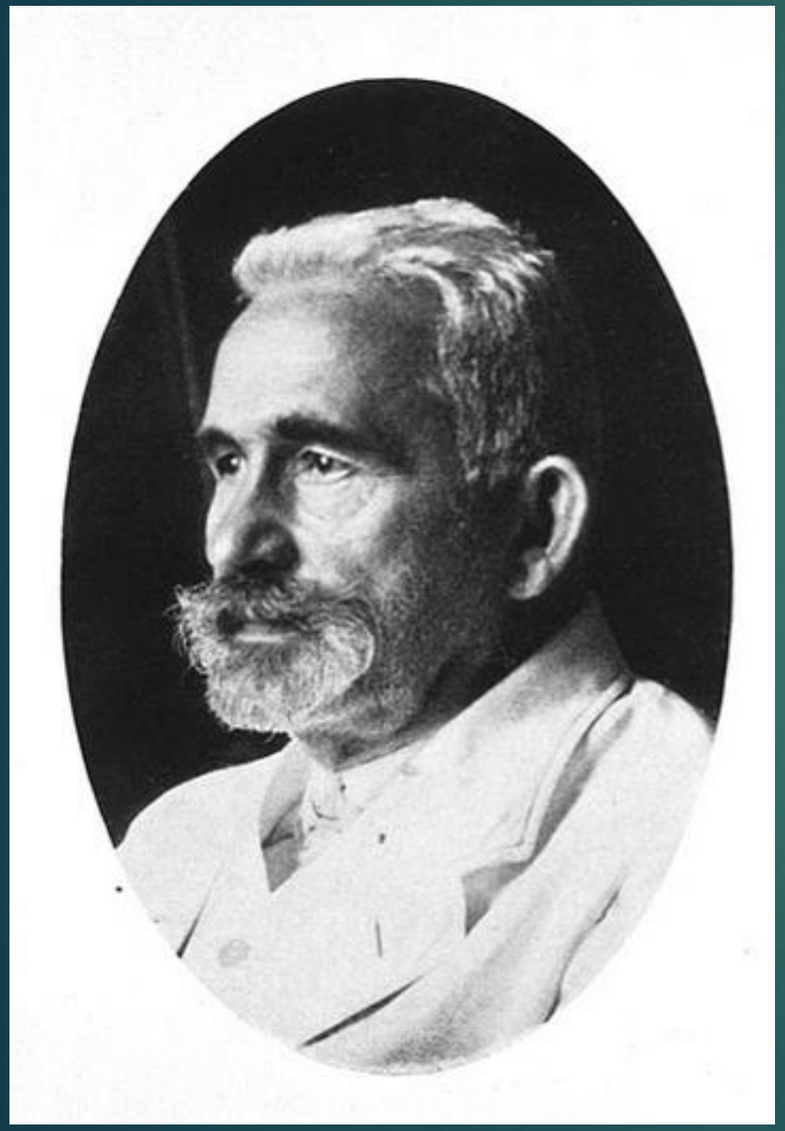
- 1. Review the neurodevelopmental basis of schizophrenia, bipolar disorder, and depression
- 2. Review the functional implications of cognitive dysfunction in these disorders.
- 3. Participants will be able to describe how co-morbid conditions such as medical disorders (e.g., metabolic syndrome), TBI, substance abuse, NCDs and medications impact cognition in persons with schizophrenia and complicate neuropsychological assessment.

Going Crazy quilt by Lin Schiffner

Schizophrenia is a Neurological Disorder

1809 - Phillipe Pinel & John Haslam: first “premature dementia” description of psychosis

1896 – Emil Kraeplin: Schizophrenia is a brain disease

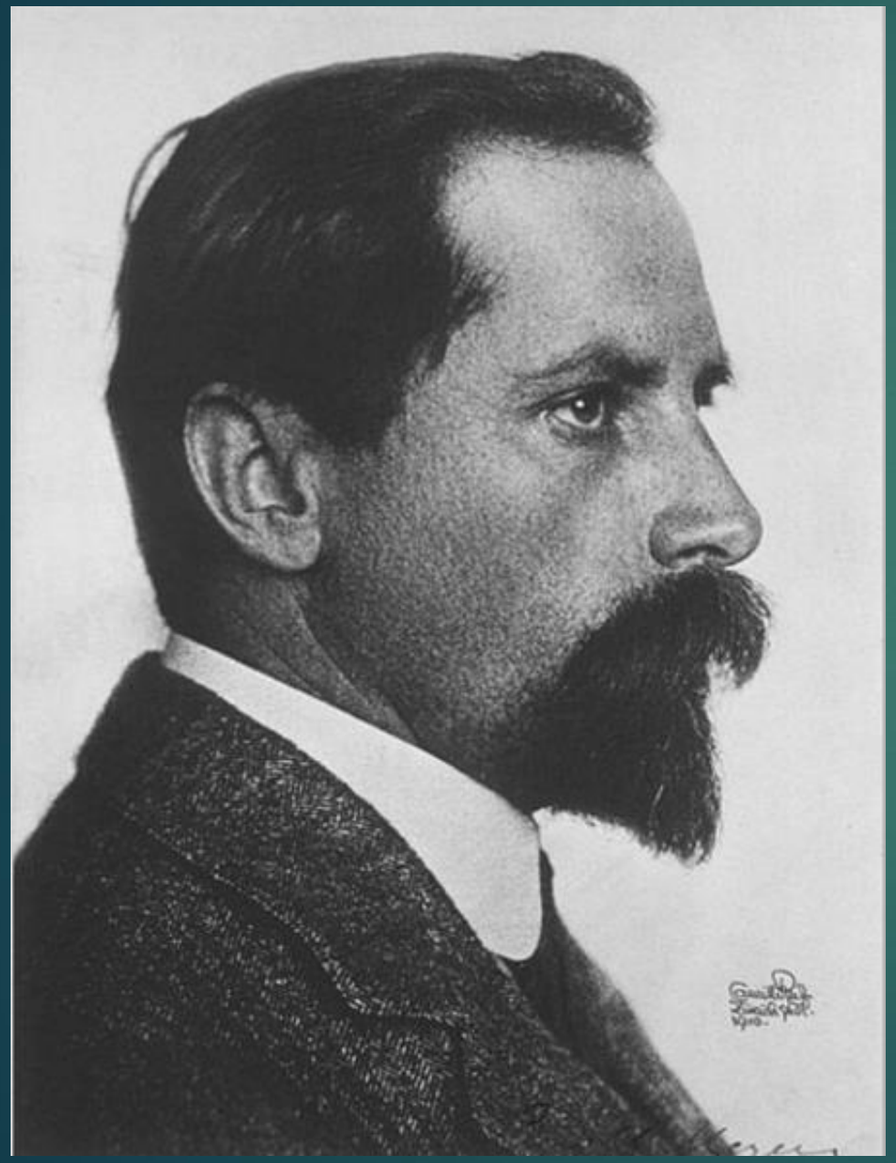


Emil Kraeplin redefines dementia praecox as a distinct neurological disease, with a course and prognosis.

Syndromes of “dementia praecox” (dementia of the young)

For the next 100 years, psychiatry lost its way In understanding causation of this disorder

1906 Adolf Meyer: Nature or Nurture

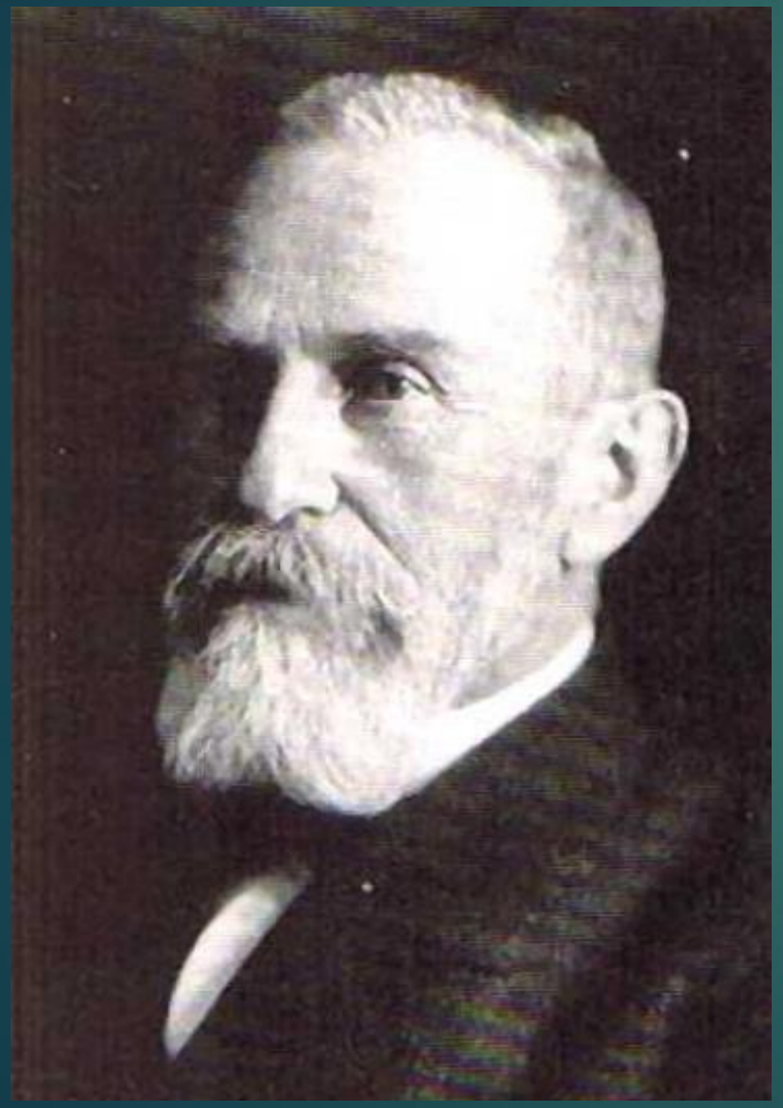


Swiss psychiatrist Adolph Meyer rejects Kraepelin's concept of dementia praecox as a biological disease.

He argues that mental illness is triggered by psychosocial phenomena.

Meyer's ideas influence *DSM-I* and *–II*, descriptions of schizophrenia.

1908 Eugene Bleuler

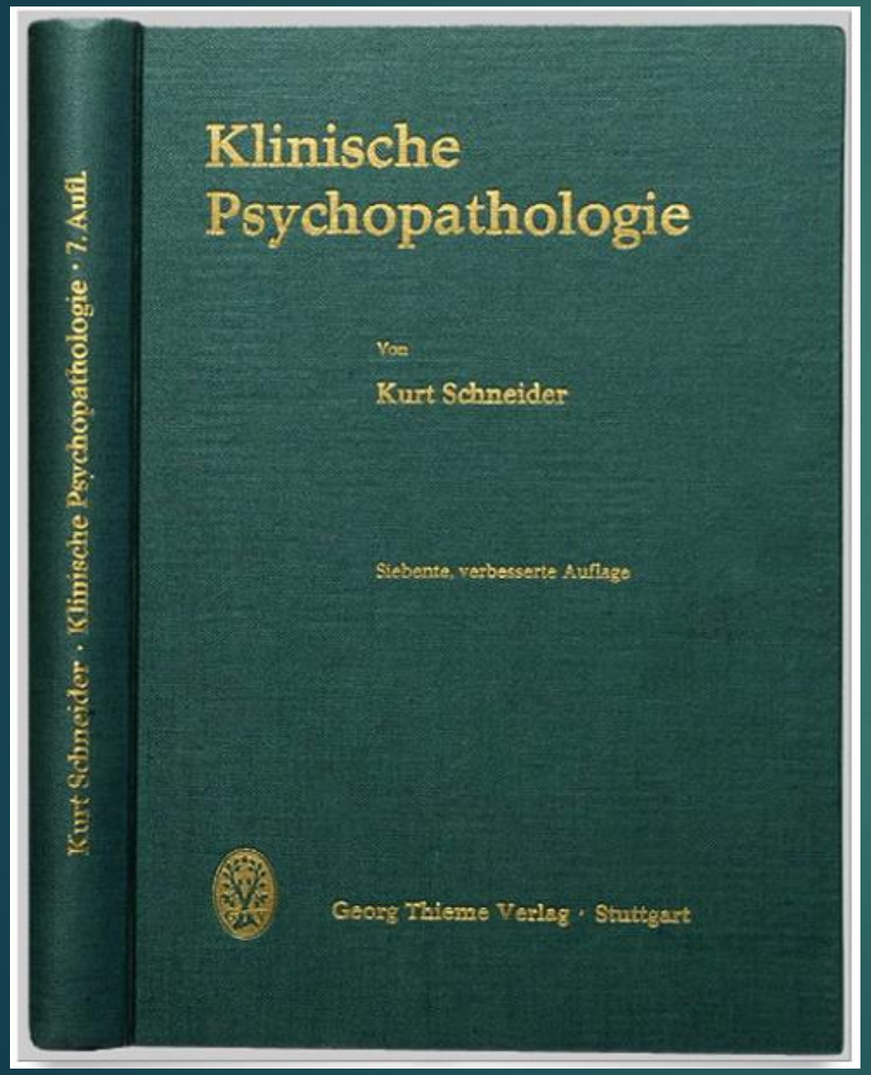


Swiss psychiatrist Bleuler did not believe that dementia praecox always involved deterioration or only struck adolescents.

He coined the term Schizophrenia, “splitting from reality”.

4 As: Association, Affect, Ambivalence, Autism

1959 Clinical psychopathology



German psychiatrist Kurt Schneider, in an effort to differentiate between various psychotic conditions, distinguishes the core symptoms that characterize schizophrenia. His criteria greatly Influence *DSM*'s list of symptoms

California: Deinstitutionalization of hospitalized psychosis patients

- In 1966, Ronald Reagan is elected governor of California.
- California has been aggressive in moving MH patients out of state hospitals (50% have been removed by 1966).
- In 1967, California passed the landmark Lanterman-Petris-Short (LPS) Act, which virtually abolished involuntary hospitalization except in extreme cases. Close to 1,000 individuals are on 5150 holds in California hospitals on an average day, data shows.
- Thus, by the early 1970s California had moved most mentally ill patients out of its state hospitals.

Deinstitutionalization

- California thus became a canary in the coal mine of deinstitutionalization.
- Deinstitutionalization was a catastrophic social experiment, one of the worst we've ever had.
- It ended up creating the mentally ill homeless population and prisons as psych wards crisis that still plague us today.

Thomas Crow 1980: Positive vs Negative sxs

Two major syndromes:

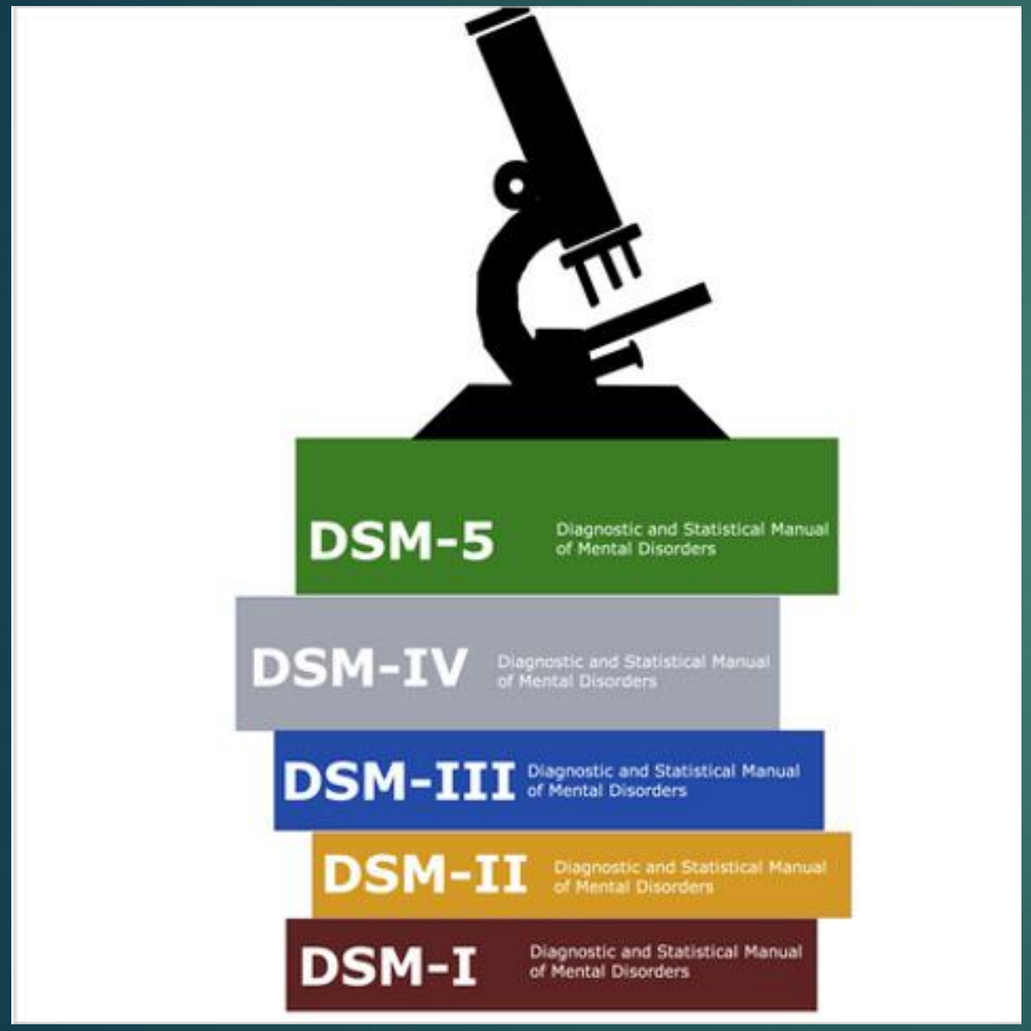
1. Dominance of positive sxs, better response to treatment.

2. Dominance of negative sxs, structural brain abnormalities, impaired cognitive functioning, poor response to treatment.

DSM-III: 5 subtypes

- In 1980, *DSM-III* includes 5 subtypes of schizophrenia building on Kraepelin's definition:
- disorganized (hebephrenic),
- catatonia,
- paranoid,
- residual,
- undifferentiated

2013 Publication of the *DSM-5*

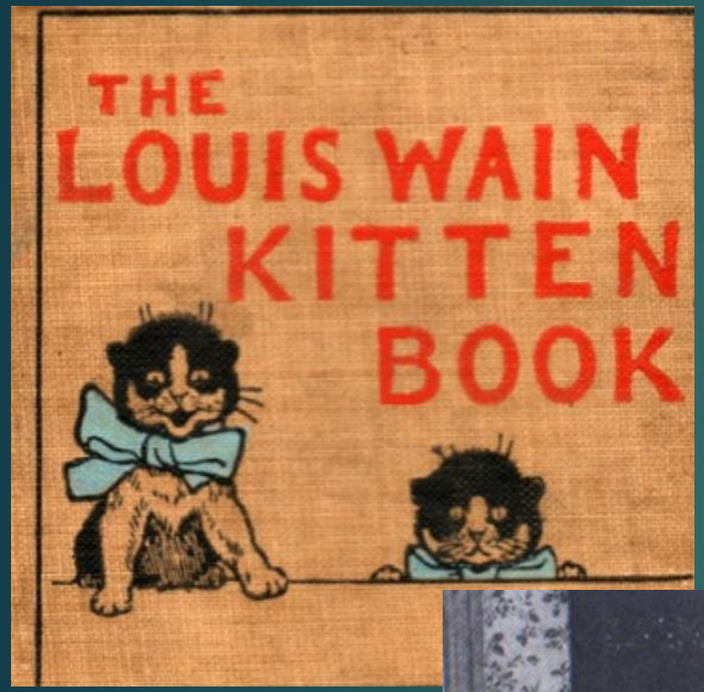


The *DSM-5* removes all subtypes of schizophrenia.

Symptoms now include delusions, hallucinations, and disorganized speech.

They may also experience motor difficulties (catatonia) and negative sxs (social withdrawal or lack of emotional responsiveness)

The Neuropsychology of Schizophrenia



Schizophrenia

- Schizophrenia is a chronic and disabling neurological and psychiatric disorder marked by significant disruptions in perception, cognition, mood, & behavior.

- 3 major sets of clinical symptoms:
  - Positive symptoms = delusion, hallucinations
  - Negative symptoms = anhedonia (lack of pleasure), flat affect
  - Disorganized symptoms = disorganized speech & behavior

- There is significant diversity in clinical presentation.

DSM-5 (Diagnostic & Statistical Manual): Schizophrenia

- Criteria:
  - 2 or more of 5 specified sxs
    - with 1 “positive” sx required: delusions, hallucinations or disorganized speech

- Caution:
  - No Cognitive sxs listed in DSM-5.
  - Despite DSM-5, Cognitive deficits are now recognized as core features & are more associated with real-world outcomes than are the other 3 symptom groups.

DSM-5: Key 5 Psychotic Features

- Delusions +: Fulbright scholar patient
  - Fixed beliefs not amenable to change due to conflicting evidence
- Hallucinations +
  - Perception-like experiences that occur without an external stimulus
- Disorganized Thinking (Speech) +
    - Inferred from speech
- Grossly Disorganized or Abnormal Motor Behavior (including Catatonia)
  - Childlike silliness to agitation, or marked decrease in reactivity
- Negative Symptoms
  - Diminished emotional expression, avolition, alogia, anhedonia

DSM-5: Clinician-related dimensions of Psychosis symptom severity (Back of book)

- Rate 0 (not present) to 4 (severe)
- Item VI - Impaired cognition:
  - 0 Not present
  - 1 Equivocal (cognitive function not clearly outside range expected for age or SES; 0.5 SD of mean
  - 2 Present but mild (some reduction in cognitive function); 0.5 – 1 SD from mean
  - 3 Present & moderate (clear reduction in cognitive function); 1-2 SD from mean
  - 4 Present & severe (severe reduction in cognitive function); > 2 SD from mean

Symptom Subtypes

- Symptom Types:
  - Positive: hallucinations, delusions
    - anterior cingulate-basal ganglia-thalamocortical and language paths
    - Have a better response to treatment.
  - Negative: anhedonia, avolition, asociality, alogia, and blunted affect
    - dorsolateral prefrontal-basal ganglia-thalamocortical
    - structural brain abnormalities, impaired cognitive functioning, poor response to treatment.

Hallucinations

- Hallucinations: perceptions without corresponding sources in the external world.
- Main positive symptoms of schizophrenia: 60%-70%
- 25% have chronic drug resistant variety
- Positive sxs improve with age

Types of Hallucinations & Delusions

- Positive:
  - Delusions: 85-90%
  - Hallucinations: 35-50%
  - Thought Disorder: 19-24%
  - Catatonic behavior: 0-15%
- Negative:
  - Affective flattening: 86-88%
  - Inappropriate affect: 37-50%

Auditory Hallucinations: 3 step Model

- 1- Internally generated speech mis-representations lateralized to the left superior temporal gyrus and sulcus. In the case of auditory hallucinations, there is compelling evidence that hallucinations arise through the misattribution of internal events (for example, inner speech) as external auditory stimuli.

- 2 - Enhanced parietal attention to the “voices”; not cognitively suppressed

- 3 - Failure of prefrontal & anterior cingulate mediated executive inhibition

- Due to reduction of grey matter density and volume and reduced activation in temporal areas. Reduced arcuate fasciculus integrity in the case of auditory hallucinations

Summary of Negative Symptoms

- Lack of emotion
- Low energy
- Lack of interest in life
- Affective flattening
- Alogia
- Inappropriate social skills
- Inability to make friends
- Social isolation

Racial disparities in psychotic disorder diagnosis

- Vast majority of diagnoses of psychotic disorders are made via clinical interview by a psychiatric clinician (MD, PhD, LCSW, MFT).

- African Americans/ Latinx diagnosed as psychotic at a rate of on average three to four higher than Euro-American/White consumers.
- African Americans are almost five times more likely to be diagnosed with Schizophrenia compared with Euro-Americans admitted to state psychiatric hospitals.

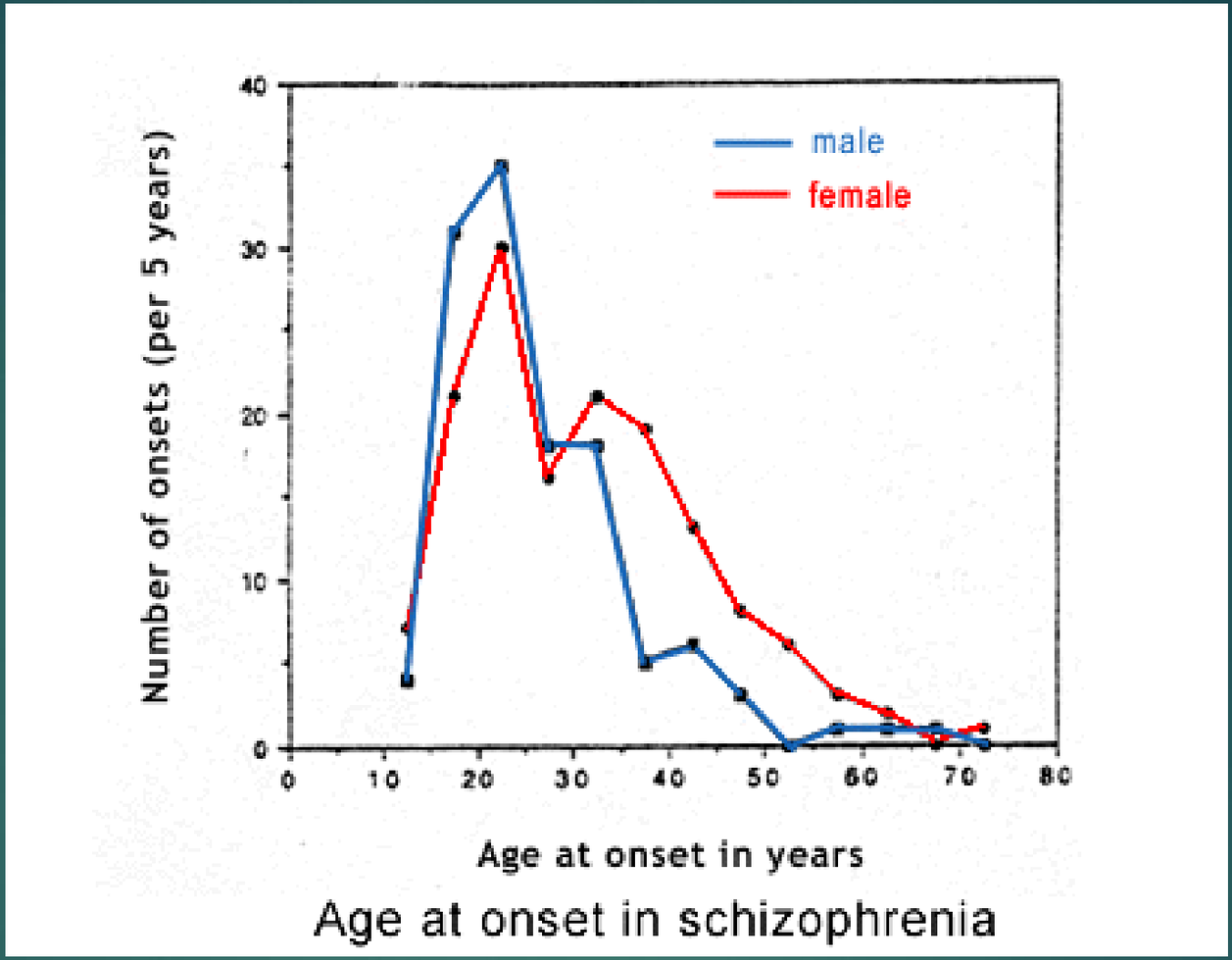
- Clinicians' own race appears not to alter this diagnostic trend

- Due to racial bias, underdiagnosis of psychotic MDD and Bipolar, cultural misinterpretations of sxs, minority avoidance of MH services until sxs are severe

Schizophrenia & left handedness

- About 10% of the normal population is left-handed
- 40% of those with schizophrenia & schizoaffective disorder are left-handed.
- 10% of depressives

Age of Onset

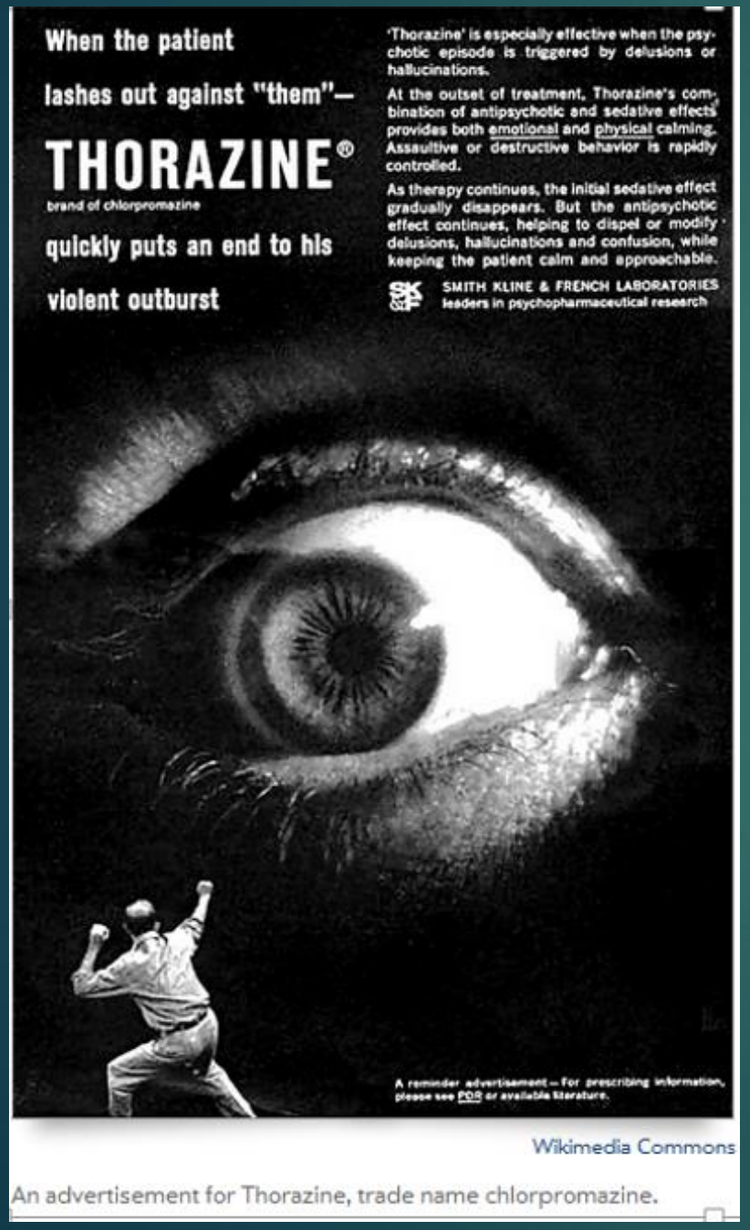


Begins in early adulthood; between the ages of 15 and 25. The average age of onset is 18 in men and 25 in women.

Epidemiology

- 24 million individuals with dx worldwide; 2.6 million in USA
- Incidence = 0.5 to 2% of population
- Onset of sxs: ages 15 to 25
- Incidence is low, but prevalence is high, due to chronicity
- 69% do not receive treatment; of those who do receive it, there is a 9-year gap exists between start of symptoms and treatment.

1954: Thorazine, First Antipsychotic



Wikimedia Commons

An advertisement for Thorazine, trade name chlorpromazine.

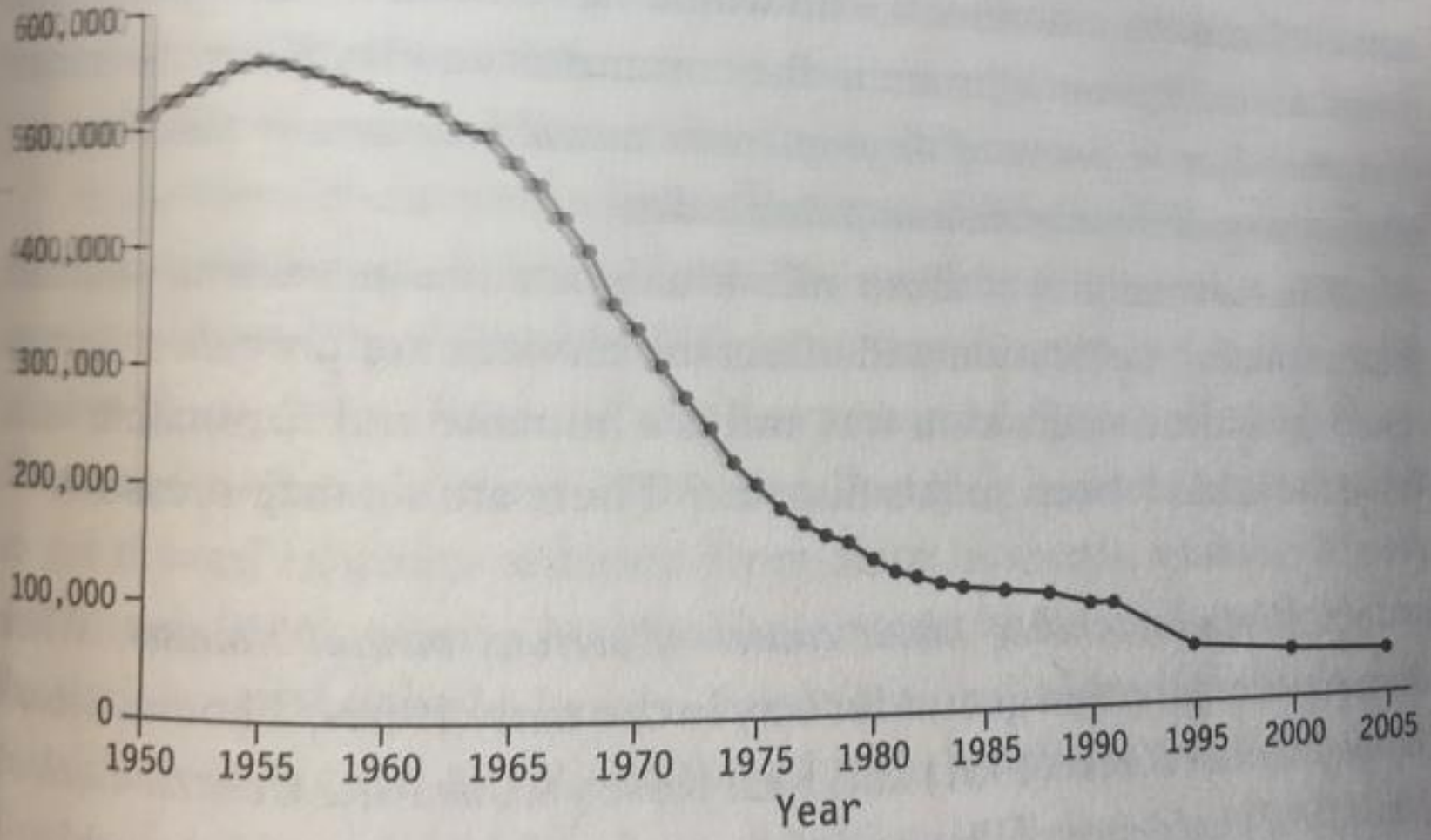
U.S. Food and Drug Administration (FDA) approves chlorpromazine, the first drug developed specifically as an antipsychotic.

Blocks dopamine receptors. 1st patient: French agitated manic bipolar

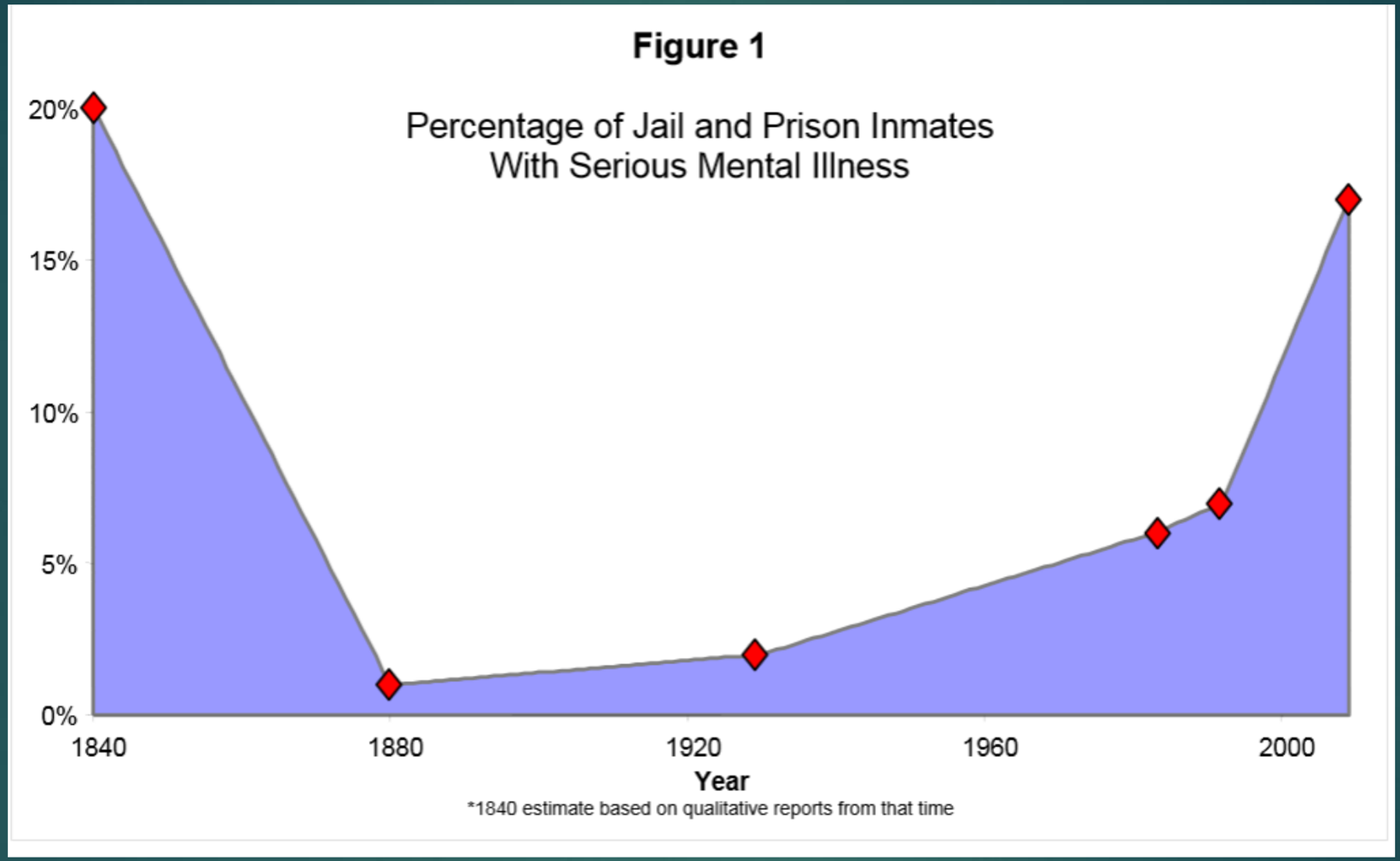
Within a few years state hospitals will begin deinstitutionalizing patients.

In CA, happened by 1967, without replacement by community services.

The Magnitude of Deinstitutionalization: Number of Patients in Public Mental Hospitals, 1950–2005



Back to the 1840s: Jail, not Psych Hospitals, for severe MH patients



2014: 20 % of inmates in jails and 15 % in state prisons have a serious mental illness.
356 K inmates with serious mental illness in jails and state prisons.
There are 35 K within state psych hospitals.

Statistics: Homelessness

- 20% of individuals with schizophrenia are homeless.
- Represent 30% of the homeless population .
- Number of schizophrenia homeless = number in all psych. hospitals
- Prisons are now largest psychiatric “hospitals”
- Direct consequence of deinstitutionalization & legal opinions about involuntary holds and right to refuse treatment, which often assume brain normality

Prisons and Mentally Ill

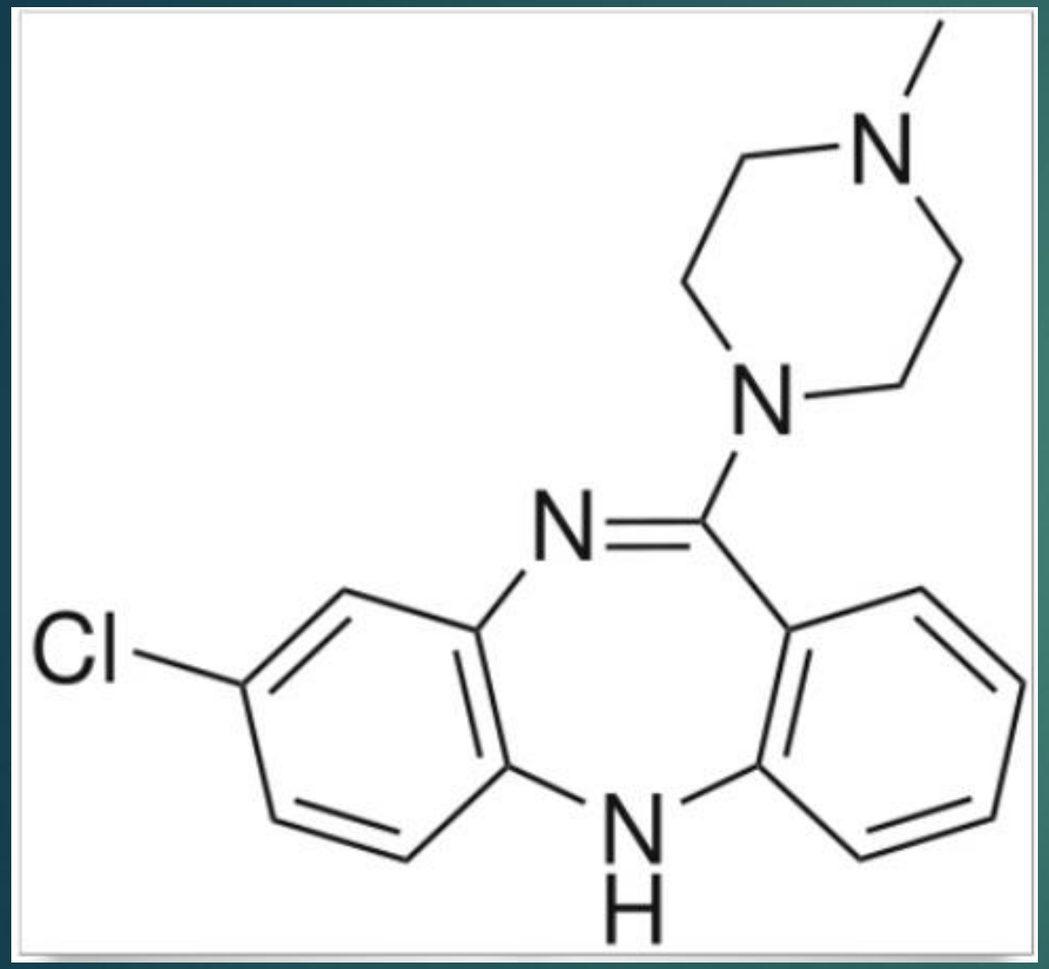
- From the 1960s to the present the U.S. incarceration rate more than tripled, and around 2.2 million people are currently incarcerated nationwide.

- During that same period of time, the population of institutionalized mental patients shrank by 90 percent to under 60,000.

- Large urban jail systems in Chicago, Los Angeles and New York City are now the largest psychiatric care providers in the nation. In Chicago's Cook County jail system, the proportion of its 6,000 prisoners with mental illness has increased to 33 percent.

- In 2018, the Bureau of Justice Statistics (BJS) reported that 14 percent of prisoners in state and federal facilities met the criteria for having serious mental health conditions. In local jails the number was 26 percent.

1989 Second Generation Antipsychotics



Clozapine, the first in a new line of "atypical antipsychotics," is approved for treatment of schizophrenia by the FDA.

Claim of fewer side effects compared to first generation antipsychotics.

Both generations present similar metabolic side effects.

DSM-5: Schizoaffective Disorder

- Criteria (more longitudinal):
  - Uninterrupted period of illness involving a major mood episode concurrent with sxs of schizophrenia
  - Presence of delusions & hallucinations without prominent mood symptoms for at least 2 weeks

- The primary change to schizoaffective disorder is that a major mood episode be present for the majority of the disorder's total duration after criterion A has been met; (not just current episode)

Schizophrenias

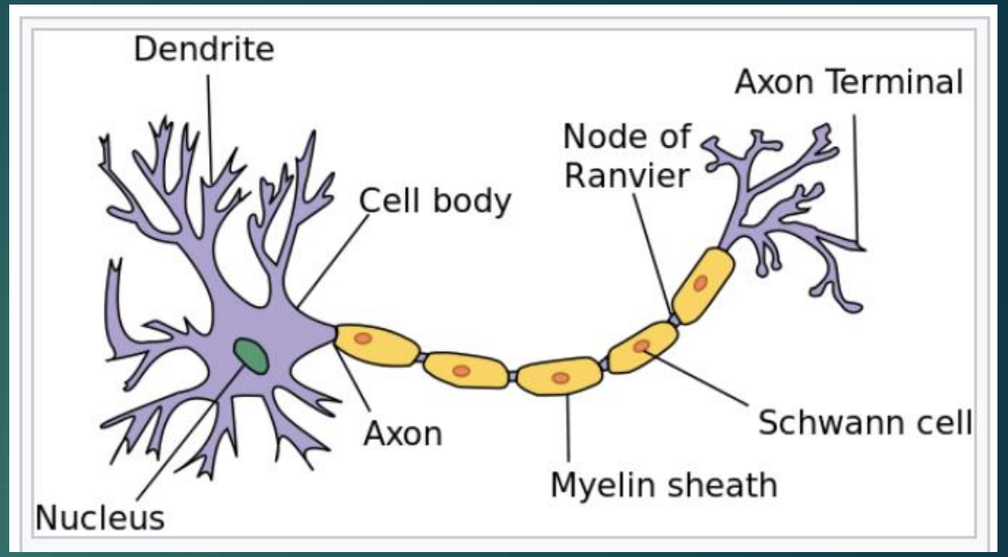
- Most severe psychiatric disorder
- Stable lifelong neurodevelopmental and psychiatric disorder
- Neuronal dysfunction leads to positive sxs and neurocognitive deficits; latter lead to real life functional impairment and disability
- Plenty of, but not consistent, neuropathology: the schizophrenias

Schizophrenia is a neurological disorder

- Schizophrenia:
  - Multifactorial causes
  - neurodevelopmental disorder
  - with genetic vulnerability
  - Triggered by an abnormal excessive synaptic pruning process

- Schizophrenia is associated with changes in the structure and functioning of a number of key brain systems, including prefrontal and medial temporal lobe

Schizophrenia is a neurological disorder



- Deterioration of dendrites and spines in the dorsolateral prefrontal cortex
- Schizophrenia is fundamentally a disorder of disrupted neural connectivity between brain areas
- Reduced “neurophil” (axon plus dendrite volume) due to reduced synaptic density

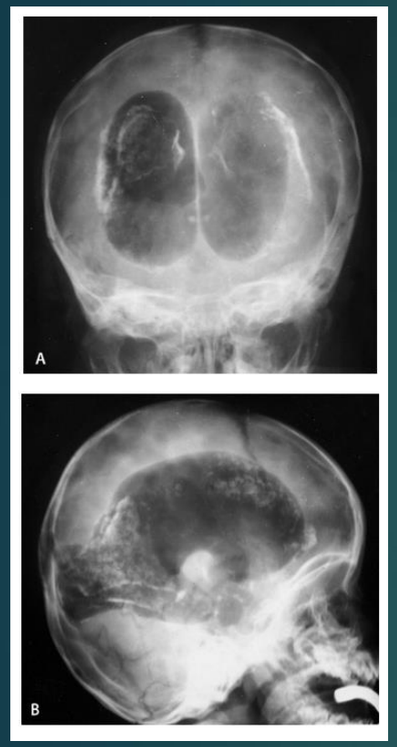
Neuropathology

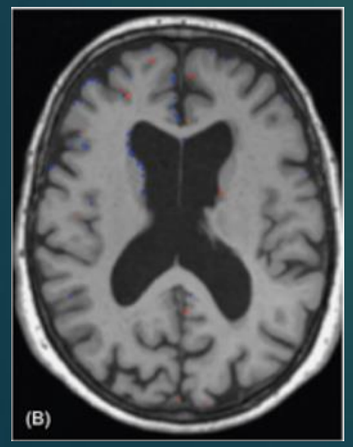
- Schizophrenia is marked by widespread changes in the cortex, with
  - cortical thinning/atrophy
  - reductions in white matter integrity,
  - ventricular enlargement,
  - and abnormalities of deep subcortical structure.

- Multiple neurodevelopmental factors are suspected, including flaws in cell migration, establishment and/or pruning of synapse

- Due to a combination of genetic and early developmental risk factors; increasing vulnerability to stressors

1976 First Neuroimaging: Schizophrenics have neuro abnormalities





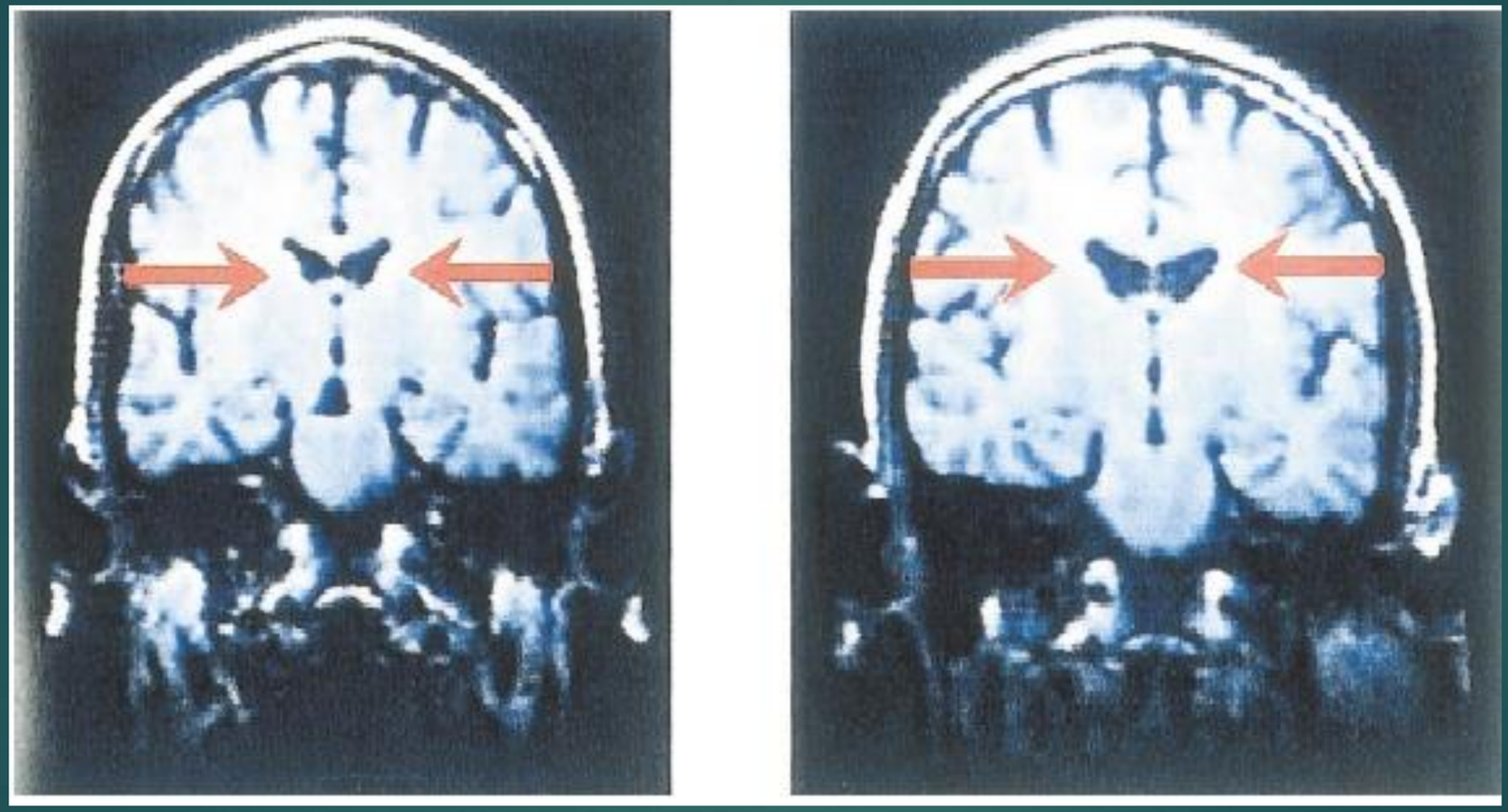
Larry Seidman, at Harvard, reviewed pre-1920 German studies of pneumoencephalgraphs of schizophrenics (prior to antipsychotic medications), noting consistent enlarged ventricles, implying cortical atrophy.

- 1st CT study suggested differences in size of schizophrenic patient's cerebral ventricles.
- Recent studies: 26% larger ventricles
- Among the first of many studies to identify brain abnormalities associated with schizophrenia.

Neuropathology Structural abnormalities

- Enlarged ventricles = brain atrophy
  - Relationship between poor functional outcome & enlarged ventricles stays consistent throughout the life span
- Hippocampal (memory central) volume loss correlates with enlarged ventricles
- There is a central deficit in dorsolateral prefrontal cortex (DLPFC) function (EF central).

Ventricular enlargement in monozygotic twin with schizophrenia



Neuropathology Structural alterations

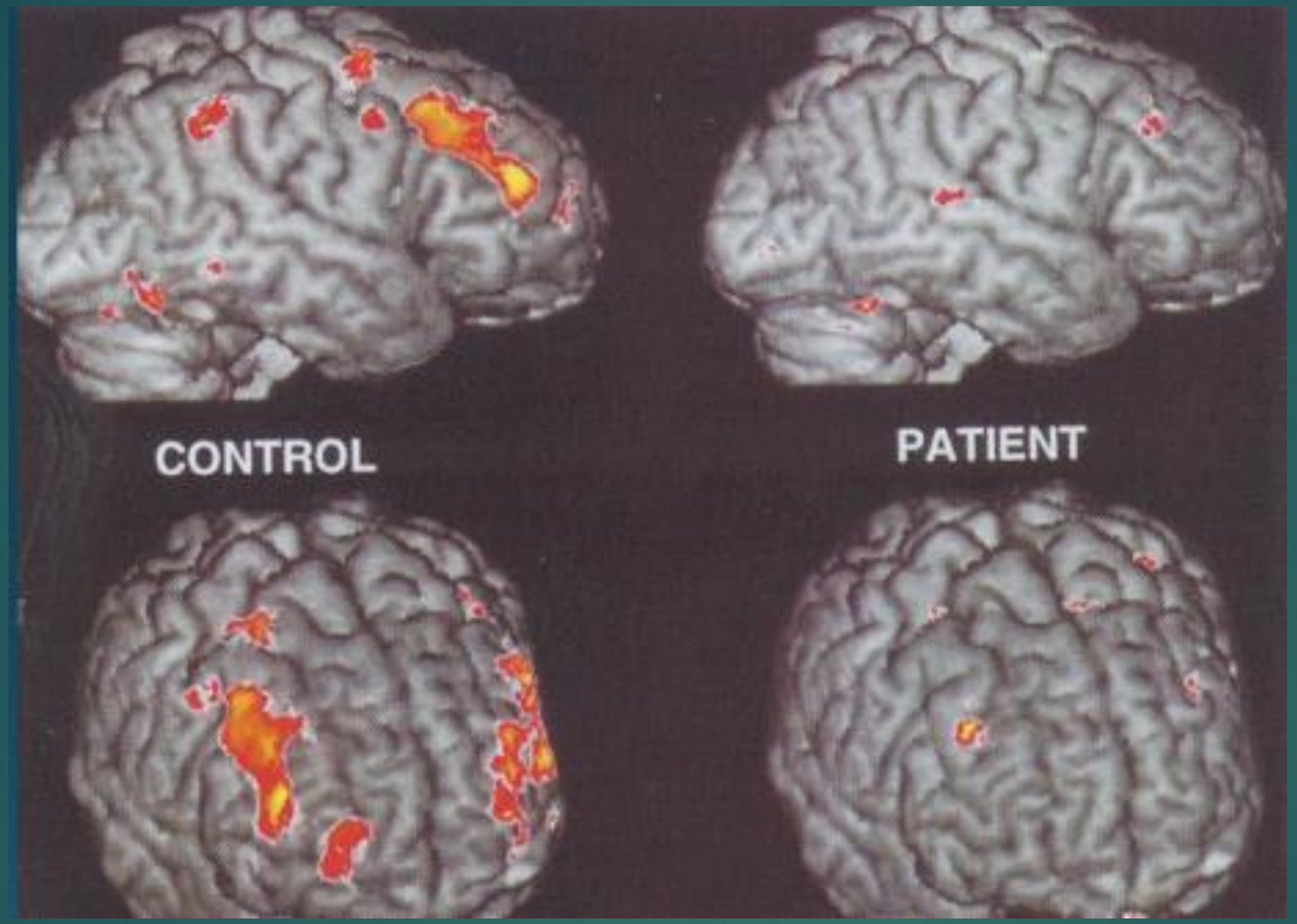
- Changes in numerous brain areas, including frontal lobes, medial temporal lobes, lateral temporal lobes, parietal lobe, basal ganglia, corpus callosum, thalamus and even the cerebellum
- White matter deficits: axon covering = reduced processing speed
- Evidence of disorganized neurons and failures of neurodevelopmental migration

Gray Matter Loss

- In first-episode psychosis, there is a progressive loss of cortical and subcortical gray matter (cortical thinning) in schizophrenia associated with acute psychotic episodes.

- In childhood-onset schizophrenia, the cortical volume loss was estimated at 1%-3% per year during the first 5 years.

fMRI: Reduced working memory in schizophrenia



Reduction in blood flow in dorsolateral Prefrontal cortex in schizophrenia

Anatomical Brain Images Alone Can Accurately Diagnose Chronic Neuropsychiatric Illnesses

- Patterns of morphological variation across brain surfaces, extracted from MRI scans alone, can successfully diagnose the presence of chronic neuropsychiatric disorders

- Differentiation from MRI datasets of persons with ADHD, Schizophrenia, Tourette Syndrome, Bipolar Disorder, or persons at high or low familial risk for Major Depressive Disorder

- Sensitivity 81-100%, specificity 71-100%; mostly >94%

- CJV: Use of differences in known groups with 10+ years of clear clinical diagnosis, and using the technique in predictive or differential diagnostic classification. This study is a proof of concept, not a proof of clinical utility.

Ravi Bansal, et al., Plos one, 2012

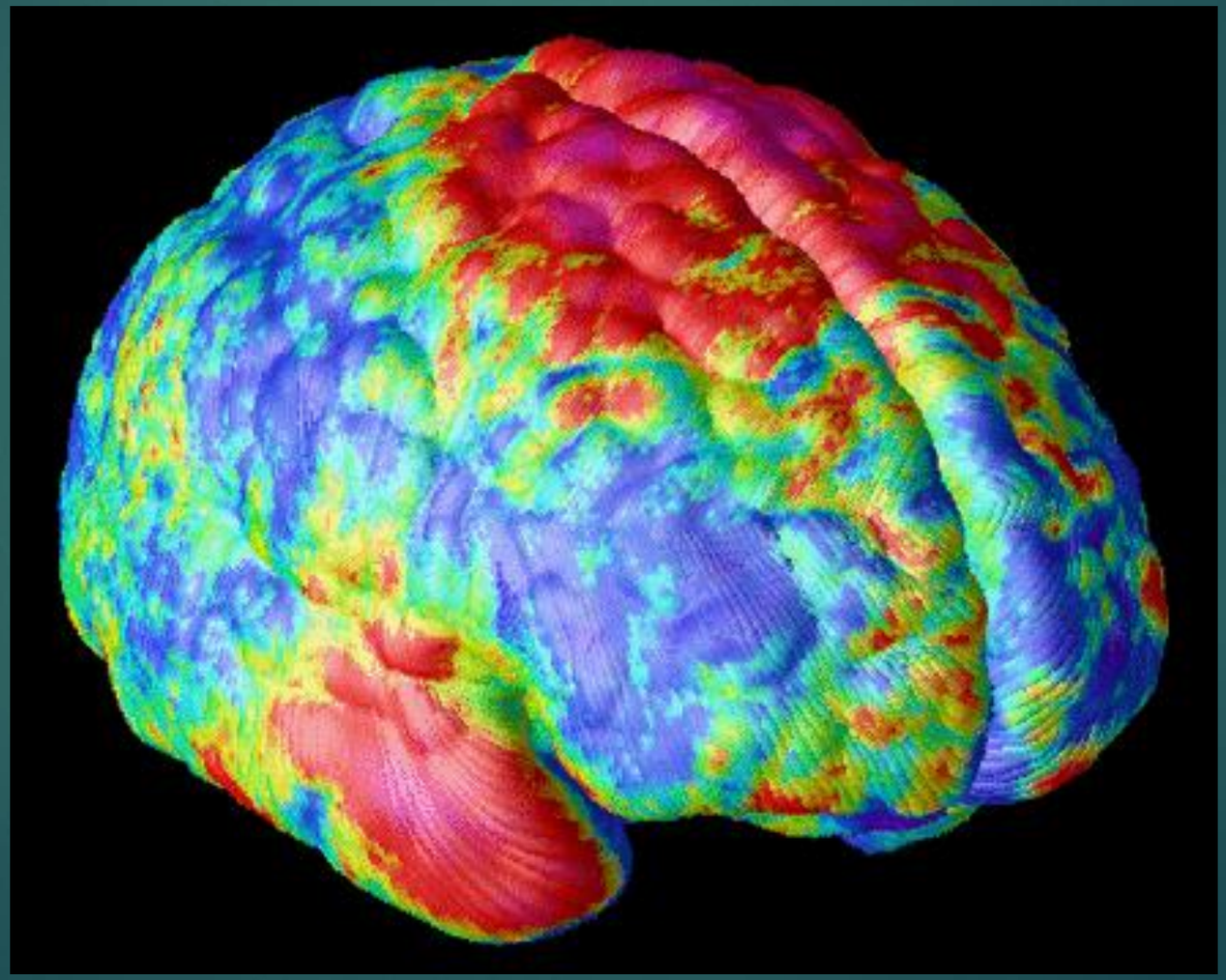
2021 study: Cortical thinning in at-risk youths

- MRI scans from 3,169 volunteer participants at an average age of 21 who were recruited at 31 different institutions.
- About 50% —1,792 of the participants—had been determined to be at “clinical high risk for developing psychosis.”
- Of those high-risk participants, 253 went on to develop psychosis within two years.
- Those at high risk for psychosis already had widespread cortical thickness reduction. Even in those 12 to 16.
- Due to aberrant postnatal brain development, including pruning and myelination.

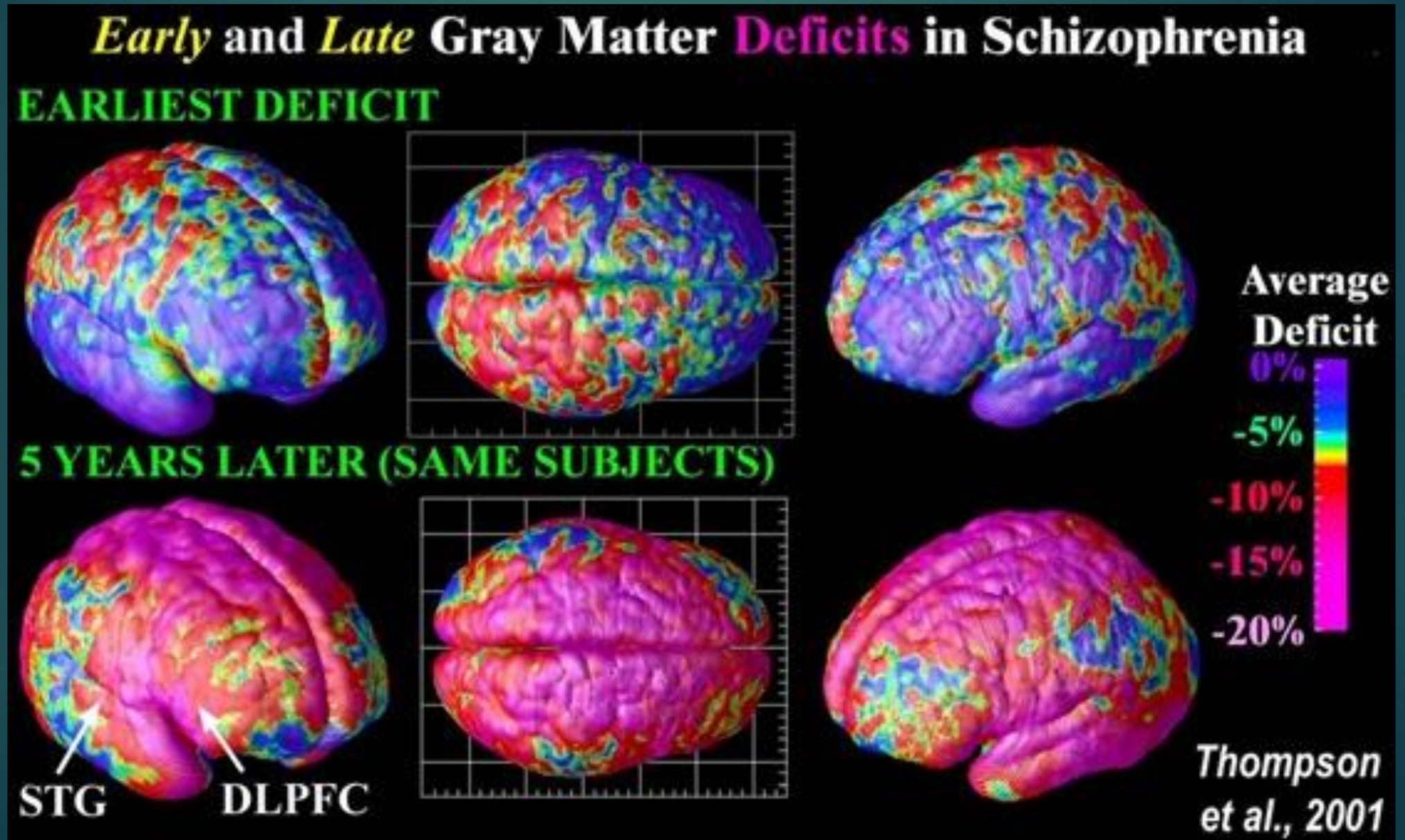
2021 study: Cortical thinning in at-risk youths

- In high-risk youth who later developed psychosis, a thinner cortex was most pronounced in several temporal and frontal regions.
- Lower CT measures in the fusiform, superior temporal, and paracentral regions were associated with psychosis conversion
- In younger participants between 12 and 16 years old who developed psychosis the thinning was already present

Gray matter loss (red) in teenagers with early-onset schizophrenia:
Most loss in the temporal and frontal brain regions



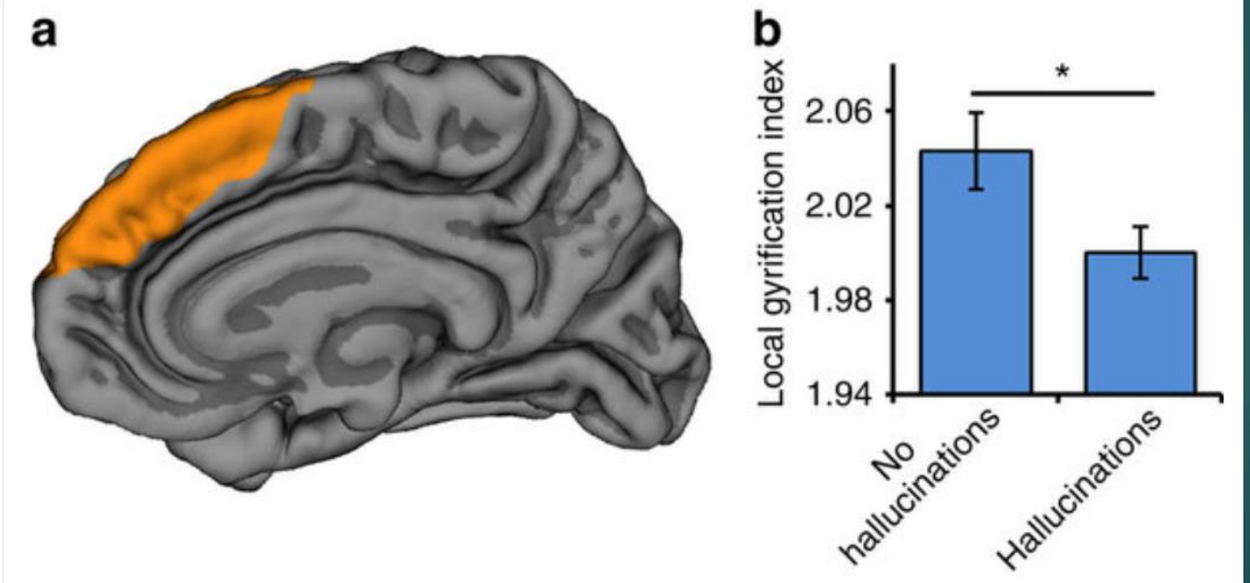
Accelerated gray matter loss in very early-onset schizophrenia (14 yo**):** 12 Schizophrenia pts over 5 years: Severe loss of gray matter. STG denotes the superior temporal gyrus, and DLPFC denotes the dorsolateral prefrontal cortex.



Paracingulate Sulcus (PCS) = source of hallucinations

- Bilateral absence of the PCS is associated with reductions in reality monitoring performance in healthy individuals with no neurological damage. 1 cm reduction in sulcal length increasing the likelihood of hallucinations by 20%, The PCS is one of the last sulci to develop *in utero*.

Figure 3: Whole-brain cortical gyrification differences as a function of hallucination status.



(**a**) mPFC regions surrounding the PCS exhibiting significantly reduced gyrification in 79 patients who experienced hallucinations compared with 34 patients without hallucinations, rendered on a canonical pial cortical surface, viewed from the midline. (**b**) Local gyrification index in regions surrounding the PCS significantly differentiates patients with schizophrenia as a function of hallucination status, $t(111)=2.165$, $P=0.033$, $d=0.448$. Error bars represent standard error of the mean.

CT and MRI findings

- Postmortem studies: not loss of neuronal bodies but reduced dendritic complexity and synaptic density
- Nestor et al, 2004: Impairment in two anatomically and functionally connected networks have been implicated:
  - Frontal-temporal network
  - Dorsolateral prefrontal – anterior cingulate network

Abnormal Functional connectomics of affective and psychotic pathology

- Severe mental illness is a disorder of brain networks. Presence of altered default network functioning marks psychotic illness
- Psychiatric diagnoses are not separated by clear neurobiological boundaries
- Connectome functioning that are commonly disrupted across distinct forms of pathology, scaling with clinical severity.
- Impaired frontoparietal network function marks patient populations characterized by manic episodes and symptoms of psychosis, including delusions, hallucinations, and formal thought disorder;
- Disruptions in frontoparietal network connectivity increase with diagnostic severity.

Justin T. Baker,, et al., 2019

Network Abnormality: negative network connections

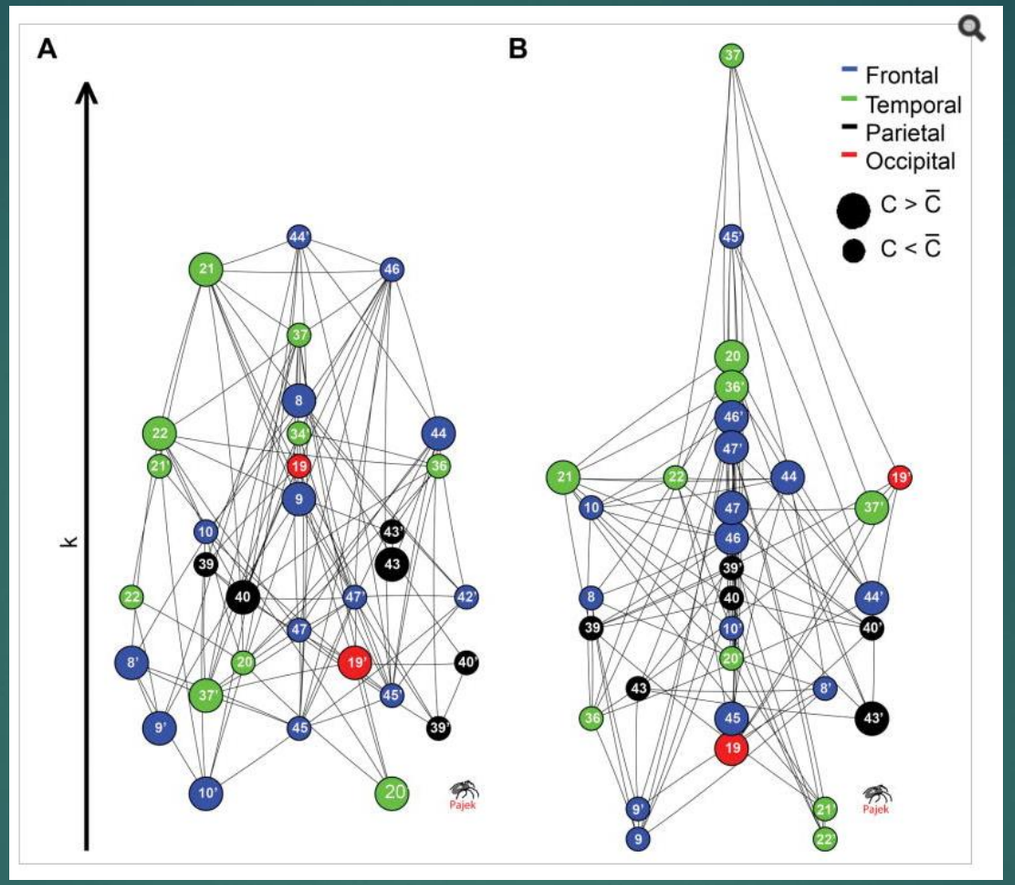
- Normal brain = frontally-dominated hierarchical network of multimodal centers

- Abnormal connectivity in schizophrenia: network organization/connectivity of brain areas is abnormal
  - reduced hierarchy,
  - loss of normal frontal hub and the emergence of non-frontal hubs,
  - increased connection distance.

- In people with schizophrenia,
  - strength of functional connectivity is significantly decreased,
  - diversity of functional connections was increased.

Dysconnectivity syndrome: Frontal lobe Disconnects

Normal network



Network in Schizophrenia: Impaired frontoparietal network function

Less efficiently wired; hubs of the network tend to be abnormally clustered.

The predominantly prefrontal hubs of the normal network are replaced by inferior temporal, insular and cingulate hubs in people with schizophrenia

Default Mode Network does not suppress in Schizophrenia

- In the Normal Default Mode Network: task-related deactivation across fMRI studies
  - Normal suppression of DMN when you are focused on task;
  - but not in Schizophrenia, where it is hyperactive
- Correlates with Episodic memory dysfunction
- Antipsychotic medications helps to improve thalamic network functioning; psychotherapy helps to normalize DM network

Reduced Neuroplasticity in Schizophrenia, MDD, Bipolar Disorder

- Schizophrenia, Stress Disorders, Depression, & Bipolar Disorder are associated with:
  - reduced neurogenesis (new memory stem cells in hippocampus)
  - reduced nerve growth factor (NGF) and BDNF
  - hippocampal atrophy.

- Risk of NCD correlates with increase in the number of episodes in depressive and bipolar affective disorders.

- All 4 syndromes increase risk for Alzheimer's Disease.

- Risk of Major NCD/dementia increases with the number of episodes in depressive and bipolar affective disorders.

Research measures of severity of positive & negative symptoms

- Measures of negative sxs:
  - Scale for the Assessment of Negative Symptoms (SANS)
  - Brief Negative Symptom Scale (BNSS)
  - Clinical Assessment Interview for Negative Symptoms (CAINS)
- Structure Clinical Interview for DSM-IV (SCID)
- WHO Composite International Diagnostic Interview (CIDI)
- Brief Psychiatric Rating Scale (BPRS)
- Positive & Negative Symptom Scale for the Assessment of Positive Symptoms (PANSS)

Therapy and medication and network function

- Antipsychotic-naive patients with first episode psychosis showed:
  - widespread functional dysconnectivity at baseline,
  - followed by an early normalization of default mode network and cortical limbic dysfunction in patients receiving placebo and psychosocial intervention.
  - Antipsychotic exposure was associated with functional connectivity changes concentrated on thalamocortical networks.

Psych medications and positive symptoms

- Improvement of positive symptoms (i.e. hallucinations or delusions) via psych. medications
  - is not associated with
  - major benefits in real world functioning between episodes i.e. occupational attainment, independent living, or social relations

Cognitive Symptoms predict functional outcome

- Lewis & Lieberman, 2000: “Long term prognosis for individuals with schizophrenia appears to be best predicted, not by the severity of positive symptoms, but the degree of cognitive impairment.”

- Elvevag & Goldberg , 2010: “Cognitive impairment in Schizophrenia is the core of the disorder."

- While Psychiatry, with its medication orientation, has waged the positive symptoms war, they have not dealt with the impact of cognitive deficits on life functions.

Cognitive Deficits Predicts Functional Outcome

- Variety of real world functional outcomes in schizophrenia are better correlated with:
  - neurocognitive and social cognitive deficits
  - than with psychotic symptoms most often used to diagnose schizophrenia.

- Cognitive impairment is the strongest predictor of functional outcome in the real world.

- Always need to do some NP/cognitive testing at beginning of Tx

Social Cognitive Deficits in Schizophrenia

Deficits in social cognitive skills:

- Facial affect recognition - identification of primary facial emotions
- Social cue perception - body language or voice intonation
- Theory of Mind (ToM) - ability to understand that other people may have different mental states than oneself
- Attributional style - make appropriate attributions of the causes of events
- These have a significant impact on functional outcome in schizophrenia and explains variance in functional outcome beyond that accounted for by neurocognition

Neurocognitive Deficits Predict Adaptive Functioning

- Deficits in cognition predict between 20 to 60% of the variance in adaptive and community functioning
- Verbal memory is related to social community outcome; Attentional vigilance predicts social effectiveness.
- Neuropsych deficits play a role in acquisition of social skills
- Executive function are related to work/productivity, independence in ADLs, social competence and global measures of functioning

Harvey et al., 1998; Velligan et al., 1997, 2000)

Vocational Outcome

- Fully independent living = < 10% of patients
- Full time work = 10%; Part time work: 30%
- 50% receive disability within 6 months of diagnosis
- Vocational Rehab:
  - Helpful in only 27% of individuals with schizophrenia,
  - and of the remaining, only 30-50% of those who were ‘successes’ are working two years later.
  - Vocational rehabilitation as “prosthesis for the frontal lobe”

Mueser KT, et al. 2001; Ho BC, et al. 1997; Harvey PD. Schizophrenia in Late Life: 2004

Vocational Outcome 2

- Only 16 to 30% of patients with schizophrenia are employed
  - effective med tx has little functional impact
  - no correlation with positive psych sxs
  - cognitive variables most predictive
    - processing speed
    - working memory
    - executive function

Common Neurobiological Substrate for Major Mental Illness: EF network

- Major 2015 metaanalysis of 193 studies:
- 6 diverse Axis I diagnostic groups (schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety)

- Results: Gray matter loss converged across these diagnoses in 3 regions:
  - Dorsal anterior cingulate, right & left insula
  - Primary sites of Von Economo neurons (social salience network; core of FTD degeneration)

- Lower gray matter in this network was associated with poor executive functioning and social interaction

Madeleine Goodkind, et al, 2015

Tip #1: Executive Function Groups

- There is a need for all psych. clinics to have a regular Executive Function group for Psychiatric patients.
- Many serious psychiatric disorders have common executive difficulties.
- Need for teaching behavioral memory techniques, external prosthesis/reminder systems, problem solving strategies
- Need to do routine MOCAs on psych pts.
- www.mocatest.org

A Neurodevelopmental Disorder

- Schizophrenia is a neurodevelopmental disorder:
  - abnormal embryogenesis,
  - excessive synaptic pruning &
  - disruptions of white matter integrity

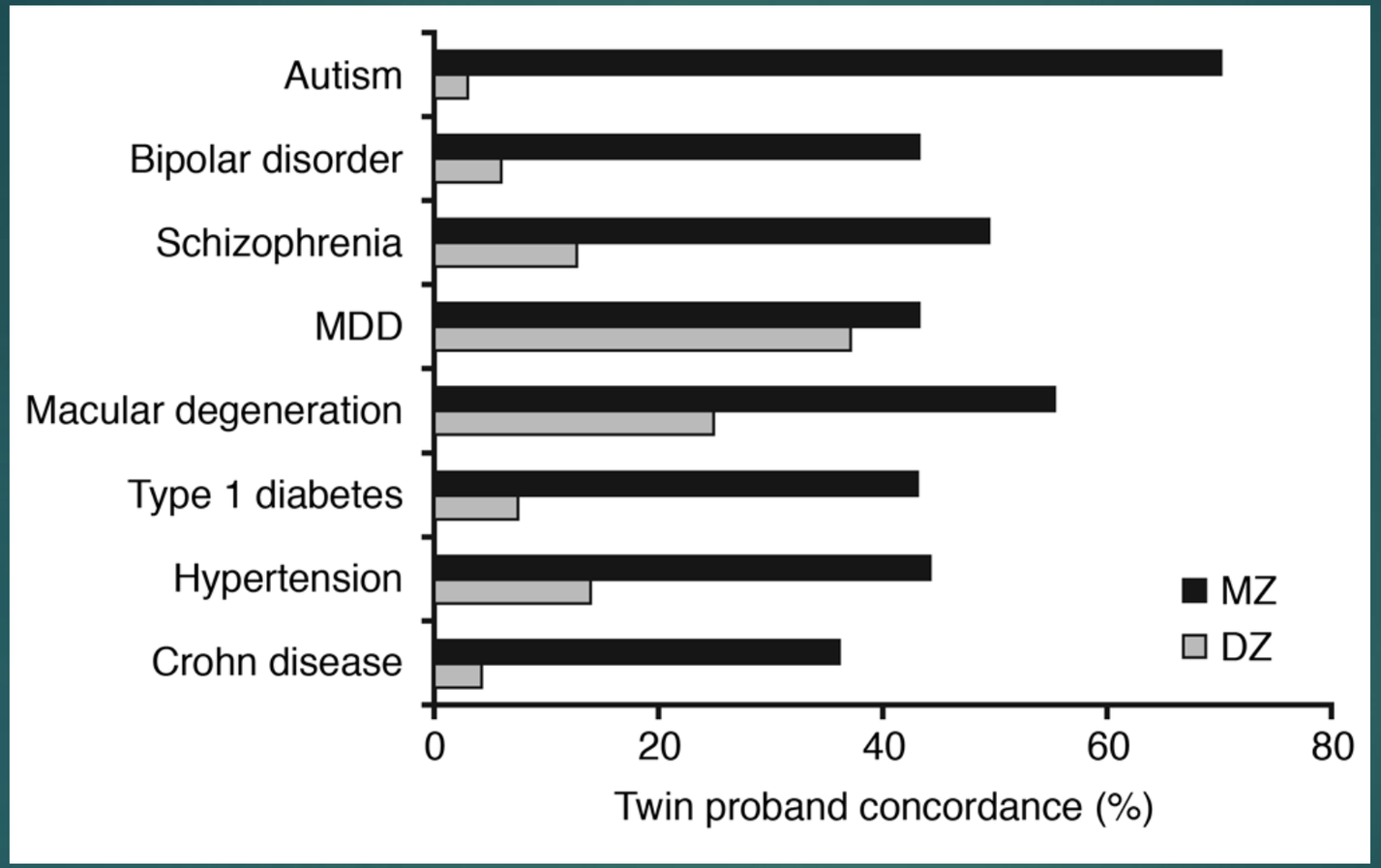
- Diathesis (genetic vulnerability)-Stress (environmental) model:
  - Early: Genes affect neurodevelopment and brain maturation (cell migration, pruning, and brain circuits),
  - Impact may be early (e.g. embryonic) and/or later (e.g. excessive pruning in adolescence)
  - Deficient early circuitry is susceptible to later environmental stress.

2021 Parent study: nonrandom mating

- The Danish High-Risk and Resilience Study: 872 parents
- 50% of the parents who have children with a partner who suffers from schizophrenia or bipolar disorder themselves meet the criteria for a mental disorder; vs.18 % for parents in the control group
- Dx of Partners: 6% had depression, 6% had schizophrenia
- These partners had lower processing speed scores and a lower functional level compared to the control group
- Familial risk is the highest known risk factor for later development of schiz and bipolar disorders.

Aja Neergaard Greve, et al., 2021

Genetics plays a major role in major psychiatric disorders



Complex genetics at play in psychiatric disorders

(Tom Insel, Director NIMH, JCI, 2010)

Genetics

Genetic effects appear to be the dominant overall cause of schizophrenia = 80 to 85% of liability to develop disease. First degree relatives show similar, yet lessened, forms of the illness.

Genetic Contribution

- Prevalence 1% of population
- Identical twins 48% concordance
- Siblings 9%
- 1st degree relative 10%
- Only 1/3rd of schizophrenia pts have family hx

Rather than being a pure genetic disease, schizophrenia involves a *genetic predisposition* to the causative agent.

Genetic component of psych. disorders

- *All major psychiatric disorders have a familial and heritable component.*
- Twin studies have documented significant heritability across the spectrum of psychopathology, with estimates ranging from:
- 20% to 45% for anxiety disorders, obsessive-compulsive disorder, posttraumatic stress disorder, and major depressive disorder; from
- 50% to 60% for alcohol dependence and anorexia nervosa;
- 75% upward for autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), schizophrenia, and bipolar disorder.

- A specific biological pathway for last group—voltage-gated calcium-channel signaling

Susceptibility Genes

- Schizophrenia is significantly polygenic; hundreds or perhaps thousands of genes are involved, each with small effect.
  - Up to a dozen genes: DISC1, Dysbindin, Neuregulin and G72 genes,
  - COMT: prefrontal functioning, affecting dopamine
  - NRG1
  - GRM-3: affects glutamate synapses
  - DISC1: hippocampal function
  - C4a: an immunity gene that affects synaptic pruning

- All effect synaptic plasticity & development & stability of cortical mircocircuitry

- This genetic risk profile largely shared with all major psychiatric disorders (ADHD, MDD, Bipolar, Autism)

Genetics loads the gun and Environment pulls the trigger

Risk factors for developing schizophrenia:

- *** Mother, father, or sibling diagnosed with schizophrenia
- During pregnancy, preeclampsia (i.e., hypertension), bleeding, and diabetes
- Low birth weight
- The complications of labor & delivery: asphyxia, uterine atony (i.e., loss of tone in the uterine musculature), prematurity, and emergency caesarean section
- ** Advance biological father’s age (> 55)
- ** Season of birth: winter birth

Risk factors

- Maternal infections (rubella increases risk 500x)
- Person born with antibodies to *Toxoplasma gondii*
- ** Birth in an urban area, lead exposure
- Maternal malnutrition in pregnancy (Dutch Hunger of 1941)
- Prenatal maternal stress
- Low prenatal Choline & Vitamin D
- Role of epigenetics: environmental factors change how genes turn on or off.

- People with rheumatoid arthritis almost never develop schizophrenia and vice versa

Risk factors

- Obstetric complications
- Premorbid IQ and Pervasive Development Disorders: Intellectual disability and ASDs
- Substance Abuse: SA and frequent cannabis use in adolescence
- Age: late adolescence and young adulthood; earlier onset, worse prognosis; reducing gap between onset and Tx initiation improves outcome
- SES: occurs at higher rates in families with parents who are unmarried or divorces; low income and increased poverty increase risk

Epigenetics and environment

- Role of epigenetics: environmental factors turn off gene expression (i.e. ACEs increase schizophrenia)

- One in every 200 genes is methylated differently in people with major psychosis; many genes are regulated differently in people with schizophrenia and bipolar disorder.

- Earlier the age of onset, the worse the eventual outcome.
- Environmental factors, including early brain damage, childhood trauma, living in an urban environment, coming from an immigrant family, and especially cannabis use, were significantly associated with earlier onset.
- The average age of onset was nearly 10 years earlier for patients who had four or more environmental risk factors than for those who had none

Bad news: Male Gender results in worse Schizophrenia

- Male schizophrenics =
  - more negative sxs
  - longer duration of illness
  - worse premorbid adjustment
  - lower education
  - more cognitive Impairment
  - worse outcome
  - most don’t marry

Female Gender

- Females =
  - Incidence slightly lower
  - Bimodal age of onset; Age of onset later, with a 2nd mid-life (> age 40) peak
  - Greater affective sxs
  - More psychotic sxs; more propensity for sxs to worsen in later life;
  - Less negative sxs
  - Better social, cognitive, & premorbid functioning
  - If briefer episodes (better outcome)

Course

- Negative sxs predict prognosis and are most persistent
- Cognitive deficits are permanent
- Late-onset cases (after 40) are mainly married females

Outcome: Functional Deficits

- Schizophrenia is still a diagnosis with a relatively poor outcome
- Negative sxs predict prognosis and are most persistent
- Cognitive deficits are permanent
- Functional impairment is due to cognitive disorder.

What are the cognitive deficits in schizophrenia?

Larry J. Seidman, 1957-, Harvard Medical School

Social Neuroscience: Brain, Mind, and Society - 2015

Neuropsychology of schizophrenia and attention deficit/hyperactivity disorder (ADHD)

1983: extensive review of the world literature (1920-1982) evaluating brain dysfunction in schizophrenia (1st frontal lobe deficit hypothesis & presence of cognitive deficits):

Core is dysfunctional attentional network involving the frontal lobe, limbic system, and sub-cortical areas

1991: executive dysfunctions in ADHD, and an emphasis on response inhibition, working memory and vigilance deficits

Neurocognitive Deficits Determine Functional Outcome

- Heinrichs (2005) has cogently argued for the primacy of cognition in characterizing schizophrenia, stating:
  - Neurocognitive deficits are a core, stable trait of schizophrenic illness that accounts for much of the functional impairment observed

(Green, 1996; Green, Kern, Braff, & Mintz, 2000; Green & Nuechterlein, 1999)

Do all Pts. with Schizophrenia have Cognitive Deficits?

- Neurocognitive impairment is evident in virtually all patients
- Meta-analysis: moderate to severe deficits across almost all NP functions, esp. in memory, attention, and executive functioning
- Severity of impairments from 1.0 to 1.5 SD below normal.
- Attention deficits are central to psychiatric disorders such as schizophrenia or bipolar disorder, and precede the onset of the illnesses

Cognitive Variability

- No prototypic NP profile in schizophrenia
- Debate: Schizophrenia has a generalized problem solving deficit: more difficult a task, worse they perform vs more specific deficits
- Large variability in cognitive profiles
- Lower Halstead-Reitan Battery Performance

Cognitive variability in schizophrenia spectrum disorders

- Cognitive impairment:
  - in schizophrenia is the result of atypical neurodevelopment,
  - In bipolar disorder is increasingly conceptualized as a neuroprogressive disorder; result of number of manic episodes

- Review of 30 years of studies concluded:
  - A subgroup: relatively intact cognitive functioning.
  - An intermediate subgroup: moderate/mixed levels of impairment.
  - A globally impaired subgroup: severe cognitive dysfunction.

Impaired cognition is a core, disabling feature of schizophrenia

Neurocognitive deficits are the core, stable trait of schizophrenic illness that accounts for most of the functional impairment.

Cognitive Deficits are pervasive: Present before onset of clinical symptoms

- Seen in unaffected first-degree relatives
- Stable across both clinical state and life span until late adulthood
- Low correlations with psychotic symptoms
- Current antipsychotic meds effect clinical positive, but not cognitive, sxs

Lower IQ in Schizophrenia

- Great variability in IQ: heterogeneity of intellectual ability
- Twin studies:
  - Cognitive decline prior to onset of psychotic sxs;
  - global premorbid cognitive deficits begin in early childhood
- Just below-average IQ scores prior to and during illness-onset

IQ 2

- Impairments in nonverbal IQ that are typically 50% greater than observed in verbal IQ

- Fluid IQ (Attention, working memory, problem solving, processing speed) are reliably more impaired prior to onset than crystalized IQ (knowledge),(incl. achievement tests)

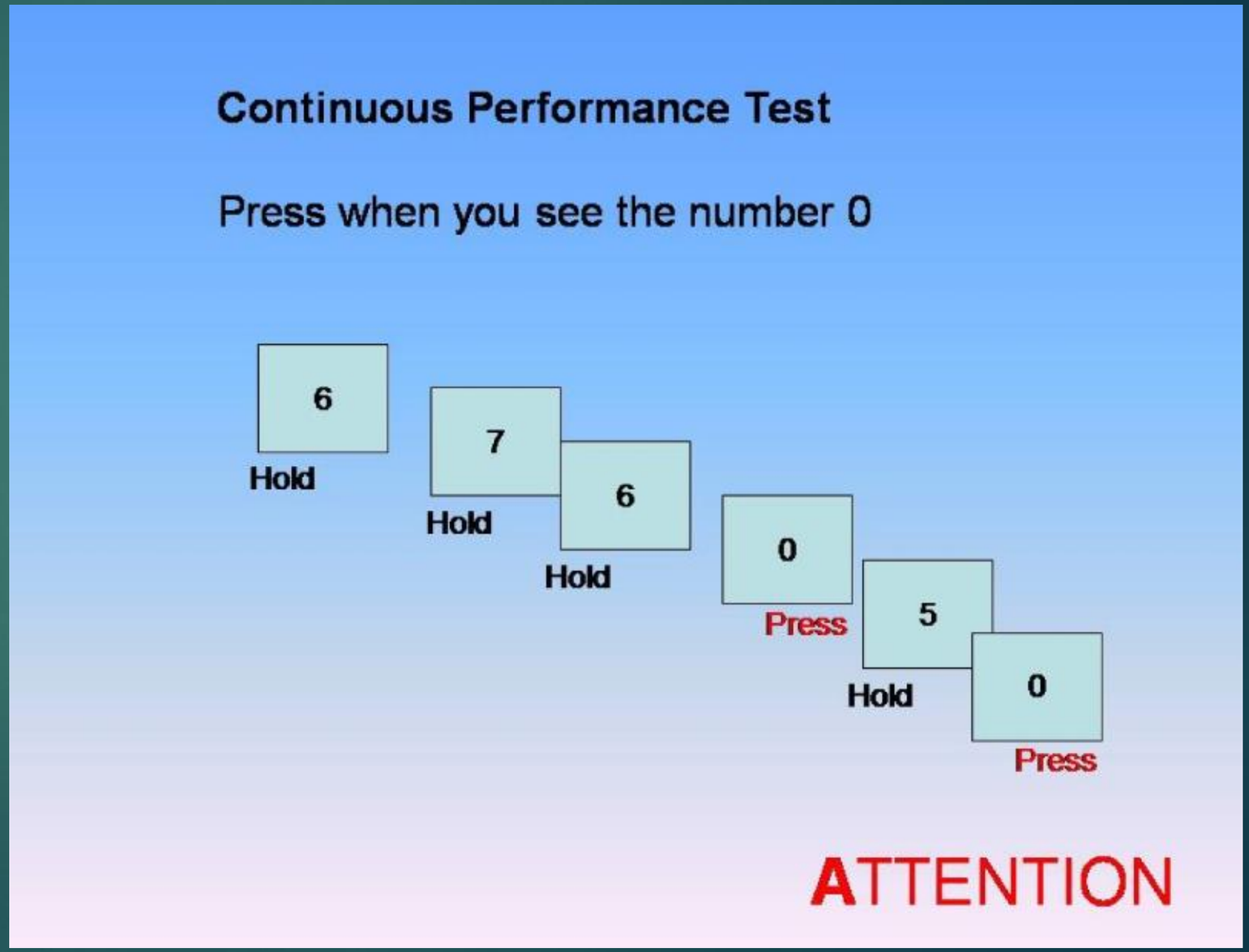
Attention in schizophrenia

- Attention deficits are a fundamental feature of schizophrenia.
- During attention tasks:
  - slowed reaction time,
  - poor vigilance (selective attention to relevant; ignore distractors)
  - impaired selective attention.
- Highly correlated with deficits in working memory and executive functioning

Deficits in sustained attention and distractibility

Sustained Attention:

Deficits in moderate to large range on CPT tasks



N- Back Test

Press when you see the number (n) 2 digits ago

6

Hold

7

Hold

3

Hold

7

Press

5

Hold

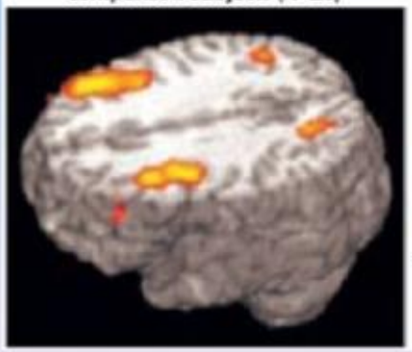
3

Hold

5

Press

Comparison Subjects (N=28)



→ Normally activates

WORKING MEMORY

Abnormal WM in Schizophrenia: a core deficit

Language

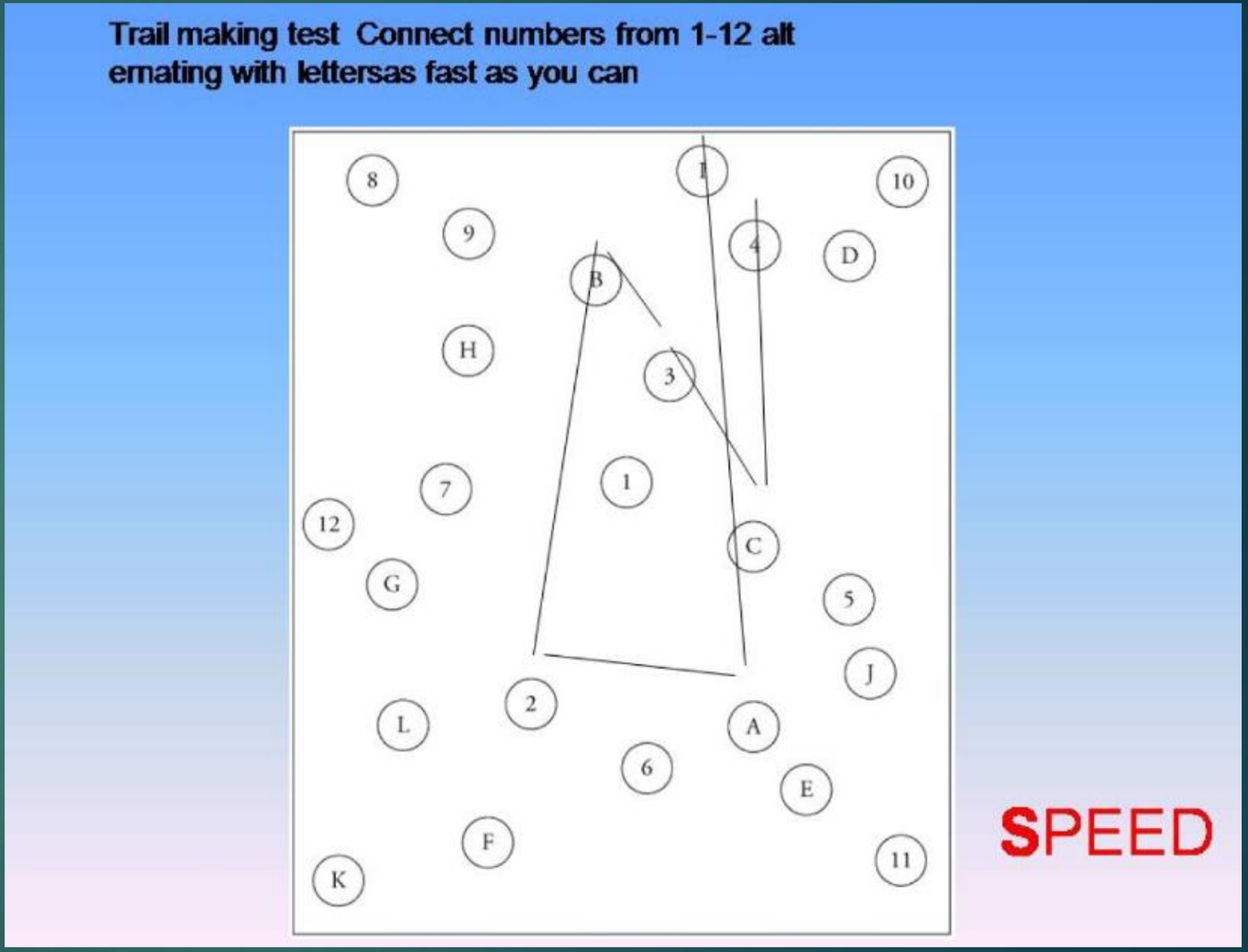
- Basic tests of language (reading, spelling, vocabulary) are relatively preserved, with only mild impairments seen.
- Higher level language processing (comprehension of complex syntax or ease of semantic access) show moderate levels of impairment.
- Measures of initiation, generation, & speed of processing (word-list generation tasks: letters beginning with letter F, A, S) show marked impairments
- Verbal fluency and verbal comprehension are significantly effected

Visuospatial Abilities

- Basic visuospatial skills are typically better preserved.
- Timed tasks relying on good attention and psychomotor skills show the significant deficits

Processing speed is one of the most severely impaired ability in schizophrenia.

But is also linked to antipsychotic medication dosage; so may be worsened by medication treatment



Sensorimotor Functions

- Deficits in gross and complex motor functions are often present, and precede onset of clinical symptoms
- Heightened occurrence of subtle involuntary movements (as early as infancy), suggesting subcortical abnormalities
- Robust olfactory deficits that are related to negative symptoms;
- Among ultra high risk adolescents, impairment in odor identification is one of best predictors of future onset of schizophrenia

Home Movies: Premorbid behavioral abnormalities

- Elaine Walker and colleagues (1993, 1994) study of home movies
- Home movie identification: Pre-schizophrenia (0-5 yo) children can be reliably identified
- These children show less joy and more negative facial expressions
- Unusual movements and coordination problems
- More likely to have delayed milestones (Jones et al, 1994)
- Danish school lunch time studies: more motoric difficulties, less social interaction

Home Movies

Increased frequency of minor physical anomalies in schizophrenia

- enlarged ventricles
- head circumference
- hair whorls
- very fine hair
- covered epicanthus
- low seated ears
- furrowed tongue
- curved 5th finger
- single palmar crease
- webbed toes
- 3rd toe longer than 2nd

MATRICS: Key Cognitive Domains that need assessment in Schizophrenia

1) Speed of Processing
2) Attention / Vigilance
3) Working Memory
4) Verbal Memory
5) Visual Memory
6) Executive Functioning (Reasoning and Problem Solving)
7) Social Cognition

From NIMH-MATRICS Consensus Process

Schizophrenia and Memory

- Working memory: RAM, hold current info while processing
- Working Memory deficit (dopamine effect): core deficit; large range of impairment
- Declarative memory (both episodic & semantic) deficits: among the most severe NP impairments in schizophrenia
  - deficits in encoding, consolidation, organization & retrieval
  - no use of semantic categorization (poor deep encoding)
  - use phonemic rather than semantic cues
  - acquisition failure

Memory

- Recognition memory superior to recall – cuing helps
- Memory deficits predict more rapid conversion to psychosis in at-risk youths
- Do not appear to benefit from repeated testing – no positive memory practice effect
- Disproportionate deficit in time-based prospective memory (need external reminders) (best NP predictor of ability to live independently)
- Normal Procedural memory (important for Cog Rehab)

Schizophrenia and Memory 2

- Cognitive Memory Types in schizophrenia:
  - 35% ~Normal Memory (on CVLT – 16 new words, 5 trials)
  - 50% Subcortical Type: poor free recall, normal recognition, frontal pathology
  - 15% Cortical (Major NCD) Type: poor encoding with impaired free recall and recognition; need forever supervision; temporal lobe pathology

Executive Function

- Significant similarity between clinical features of schizophrenia and frontal system dysfunction: reduced spontaneity, avolition, mental rigidity, lack of social judgment, poor planning, poor problem solving

- Functional neuroimaging indicates frontal atrophy

- Executive dysfunction in schizophrenia is severe.

Anosognosia: Neurological Lack of Awareness

- Anosognosia = neurologically based unawareness of deficits. Not psychological denial.
- Severity of poor insight strongly correlated with degree of frontal lobe dysfunction and executive dysfunction (WCST, verbal fluency, Trails)
- Present in 50% of Schizophrenia and Bipolar pts
- Basis of not seeking treatment and refusal of medication
- Strong cause of homelessness & need for greater supervision

Anosognosia

- The number one reason that people with severe mental illness (SMI) do not accept help or treatment is due to a “lack of insight” into being ill, otherwise known as anosognosia—a neurological symptom that leaves a person unable to understand that s/he is ill, consequently becoming non-compliant, treatment resistant, and isolated.
- Anosognosia causes refusal of, or inconsistent, treatment, worsening of symptoms over time, deterioration in long-term prognosis and other devastating outcomes: i.e., repeated cycle of involuntary hospitalizations followed by noncompliance then relapse, criminalization, poorer psycho-social functioning, increased aggression, homelessness, and suicide .
- Non-adherence rates in schizophrenia and bipolar disorder continue to hover around 50% while partial adherence rates are even higher (75%).

Favorite repetitive response in hospitalized elderly:

- “I am fine. There is nothing wrong with me.”
- “I can take care of myself”
- “I can live by myself”

= Anosognosia

Blind to deficits: No correlation between NP deficits and Self-Report

- Patient mood ratings for mania and depression are not significantly correlated with objective neuropsychological assessment.
- The findings suggest that most bipolar (and schiz) patients:
  - Have NP deficits
  - Unable to report them accurately
- Such discrepancies could relate to impaired insight/ansognosia, efforts to conceal deficits, or to subthreshold affective symptoms.
- As a clinician, the chance of knowing whether a patient had objective cognitive dysfunction based on only their report was about 50-50, making assessment based on interview likely worthless.

Executive Functioning

Executive Functioning: not 1 process

- Executive functioning ability is based on frontal and parietal lobe functioning.

- Executive functioning consists of numerous self-regulatory processes
  - novel problem solving,
  - modification of behavior in response to new information
  - regulating inappropriate behavior
  - planning and generating of strategies for complex actions.

Executive Functioning

- EF is distinct from more automatic cognitive processes that have been overlearned by repetition.
- EFs allow us to respond flexibly to the environment
- Impairments in EF thus have very serious consequences

The frontal lobe problem:
Executive dysfunction and anosognosia

- Nothing insures that a person who knows how to do something is capable of doing it on their own when it's actually needed.

- Anosognosia: Person whose frontal lobes are impaired cannot tell you what the problem is or that they even have a problem because normal frontal lobes are what give you the ability to be aware of the problems you are having.

- It is not psychological resistance or denial. It is a neurological disorder.

- Examples: Addiction, BD, TBI, Stroke, NCD, FTD, most severe psychiatric diagnoses

Executive Dysfunction

- Neurogenic denial of deficit (anosognosia): Do not know they have a problem (“I can drive; I can live alone”)

- Poor Self Monitoring leads to inability to understand the consequences of one’s actions.

- Executive dysfunction associated with:
  - Functional (real world ability) decline
  - Increased need for care

- Executive deficits correlate with decline in IADLS (inability to use phone, letter, finances, meal prep)

Classic Neuropsych Testing vs. Real World

- Patients with frontal lobe deficits tended to do normally on classic structured NP tests of memory, spatial ability, language, etc.

- What they can do in your testing room (quiet, unemotional, you = frontal prosthesis) is often very different from their real world performance ability.

- Listen to collaterals: People in their lives or family see the real EF disabilities.

Real world EF complaints of families

- poor or unreliable judgment/decision making,
- carelessness,
- apathy,
- poor adaptability to new situations,
- blunted affect,
- being stimulus bound,
- poor delayed responses,
- poor abstraction,
- poor flexibility,
- perseveration

Executive Dysfunction dissociation

- Executive Dysfunction dissociates the **Capacity** (knowing how) to perform a complex task and **Actual Execution** (the when and how of doing it appropriately).

- Difference between what they say they can do in clinic or hospital and what they can actually do at home

- How to do it versus when and whether to do it appropriately

EF dysfunction Predicts:

- Making inappropriate choices
- Functional autonomy decline
- Behavioral Impulsivity & apathy increase
- ADLs and IADLs decrease
- Money management problems
- Medication management inability

Executive Dysfunction

- Executive ↓ can be independent of Memory ↓

- New changes in behavior:

  psychosis, personality changes, dysinhibition, hypomania, apathy

Executive Functioning Measures

- WCST
- Category Test
- TMT B
- Clock Drawing
- Stroop
- Category (Animal) Naming
- Behavioral Dyscontrol Scale (BDS)
- Action Fluency
- EF items on MoCA

Frontal prosthesis: Acting as someone else's frontal lobe

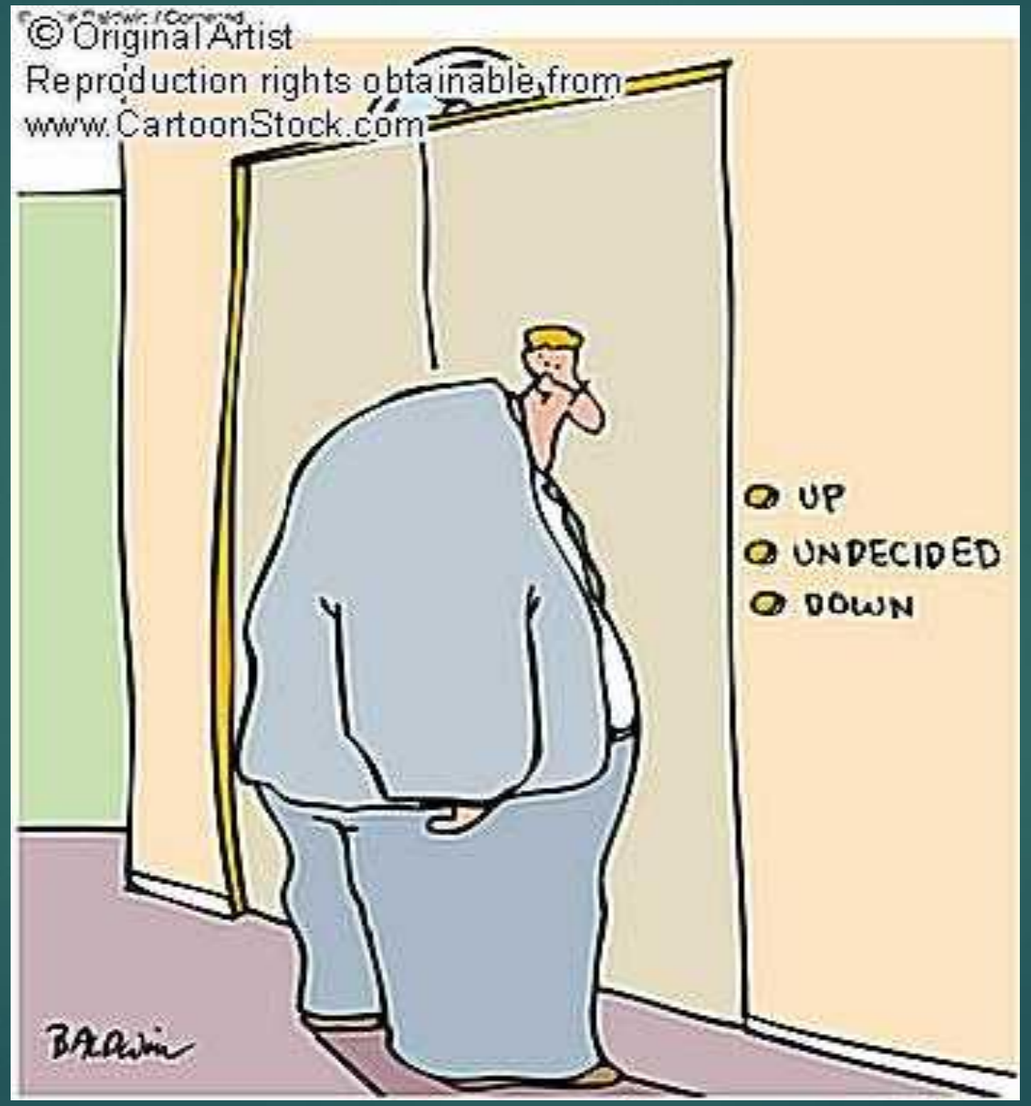
- Being Frontal: When another person directs an activity, sets the pace, starts and stops the activity, makes all major decisions, i.e.
  - Neuropsychologist during testing
  - Parent supervising kid's homework
  - Home visit nurse setting up pill box

- All represent forms of external frontal prosthesis: assuming other person has normal executive functioning while we act as their external executive monitor

- We need to be aware of when we are doing the executive work for someone else

- Difference between claiming an ability and actual real-world ability

Decision Making



What is “Decision Making Capacity”?

California Health Care Decisions Law:

“…a person’s ability to understand the nature and consequences of a decision and to make and communicate a decision, and includes in the case of proposed health care, the ability to understand its significant benefits, risks and alternatives.”

California Health Care Decisions Law
AB 1278, 2002 revisions

Capacity to make medical decisions

- "Capacity to make medical decisions" means that, in the opinion of an individual's attending physician, consulting physician, psychiatrist, or psychologist, pursuant to Section 4609 of the Probate Code, the individual has the ability to understand the nature and consequences of a health care decision, the ability to understand its significant benefits, risks, and alternatives, and the ability to make and communicate an informed decision to health care providers."

- Immunities: like 5150 evaluation

Decision Making Capacity vs Legal Competency

- **Capacity**: clinical status determined by a health care professional. Now the preferred term.
  - It is a clinical term regarding the integrity of mental functions.
  - Probate Code 810: Person is assumed to have capacity
  - Present in more or less ability (not yes/no) & can vary over time
  - Tangible evidence is key - this can be clinical observations, a mental status exam, and/or formal test results.

Legal Competence

- **Competence:** a legal term, in part, based upon capacity, and is determined by someone in a court of law.
- It is the ability to make decisions by yourself.
  - The revocation of this ability can deprive an individual of rights and autonomy (self determination). Legally, competence is either present or absent
  - A competent adult patient has the right to refuse treatment. Even if it means that they may die.

Capacity ≠ Competency

- Clinical judgment
- Can be assessed by physician or psychologist
- Usually question-specific, time-specific, short-term
- Surrogate decision-makers, if necessary

- Legal concept
- Can only be adjudicated by a court
- Usually more global, long-term
- Judge designates a decision-maker

Capacity is the Presumption

- A person is assumed to have capacity unless proven otherwise. In all states, the law starts with the presumption of capacity.

- Generally, a **competent adult patient has** the right to **refuse treatment**. Even if it means that he/she may die.

- The burden of proof is on the party bringing the petition to establish sufficient diminished capacity to justify the appointment of a guardian or conservator.

Capacity

- Need evidence of a deficit; a diagnosis of a disorder is insufficient to prove lack of capacity
- Need description of deficit and how it connects to incapacity to make decisions
- Deficit must impair one or more of 4 basic abilities: understanding, appreciation, ability to reason, ability to communicate

Decision Making Capacity: 4 criteria

- 1. Ability to understand information relevant to decision: “Tell me in your own words what your understanding is of… i.e. CT scan shows cancer of stomach

- 2. Appreciation: Ability to understand how information applies to their situation (vs. overvalued ideas, delusions): Test: “Do the risks your doctor told you apply to you?” i.e. patient denies stomach cancer and states “my stomach is just full” = delusional

- 3. Ability to reason: Ability to weigh information in a rationally defensible way. “How did you come to decide to accept/reject this treatment?” i.e. “Angel Gabriel tells me to reject it”

Applebaum & Grosso, 1998

Decision Making Capacity 2

- 4. Ability to communicate decision. Test: Can they tell you their decision & repeat it after several minutes or hours later

- People are allowed to make decisions that are contrary to their physician's best advice, as long as all 4 of these criteria are met.

- Informed Consent requires Decision Making Capacity; without DMC, there is no capacity for informed consent

Applebaum & Grosso, 1998

Groups at high risk for lacking decision making capacity

- Diagnoses or treatment that compromises cognition (delirium, sedation, etc.)
  - Alzheimer's patients; universal with severe dementia (Major NCD).
  - Schizophrenia
  - Manic bipolar disorder.
  - Patients in ICU and Extended Care Facilities.
  - Low IQ

- Decision making impairment correlates with increasing age and fewer years of education

- Incapacity correlates with measures of NP impairment.

(Walaszek, 2009).

Risk Assessment

- Capacity evaluations are, at heart, a risk assessment.

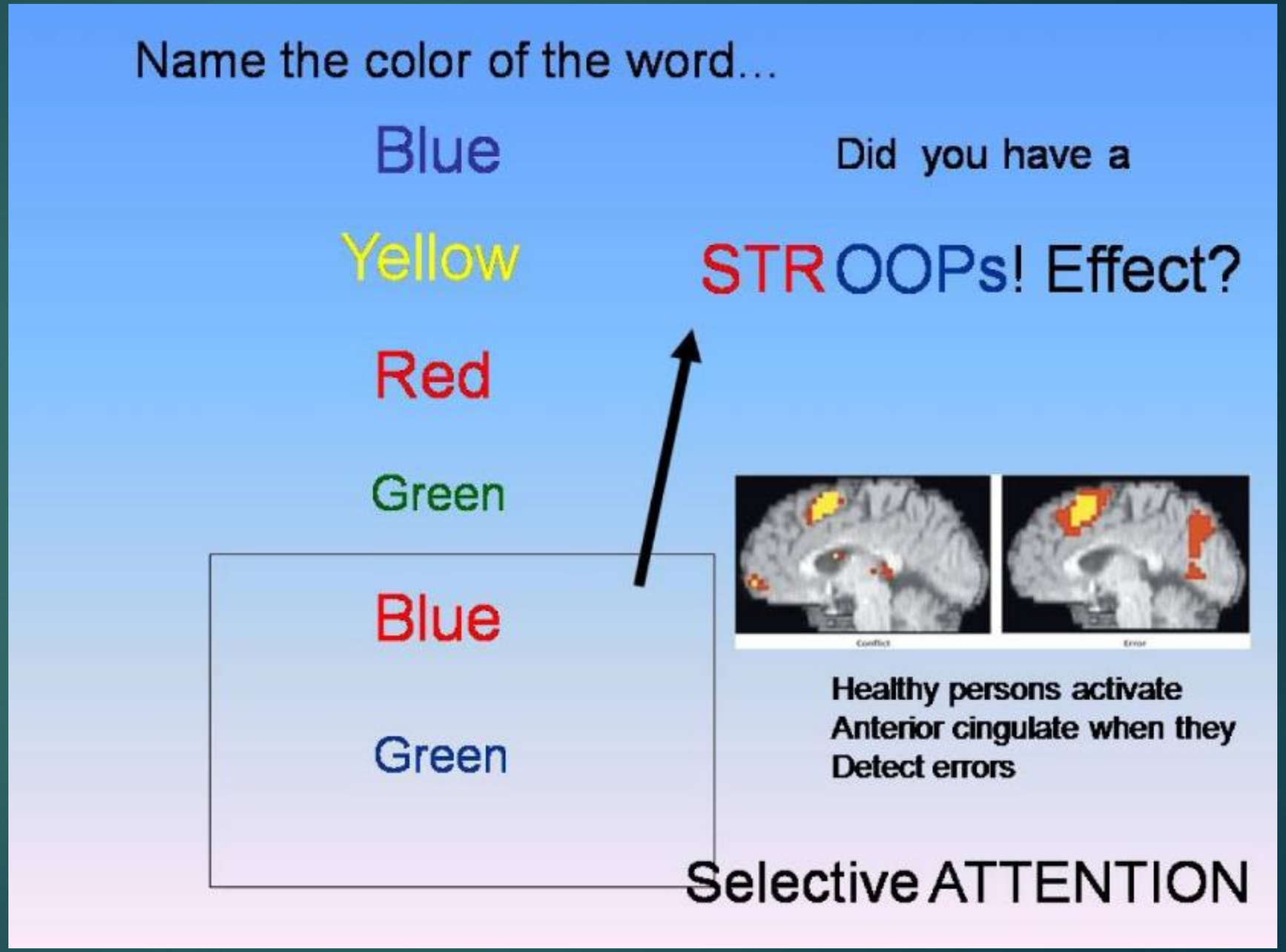
- Is the person a danger to themselves

Similar to 5150 decision regarding “grave disability” = “a person, **as a result of a mental disorder**, is unable to provide for his or her basic personal needs for food, clothing, or shelter.”

Self Neglect: Incapacity to live independently

- Is an individual a significant danger to her or himself due to
  - limited functional abilities, or
  - cognitive or psychiatric disturbances
  - And cannot accept or appropriately use assistance that would allow him or her to live independently.
  - Implies executive dysfunction

Abnormal inhibition performance on STROOP; abnormal ACC conflict resolution

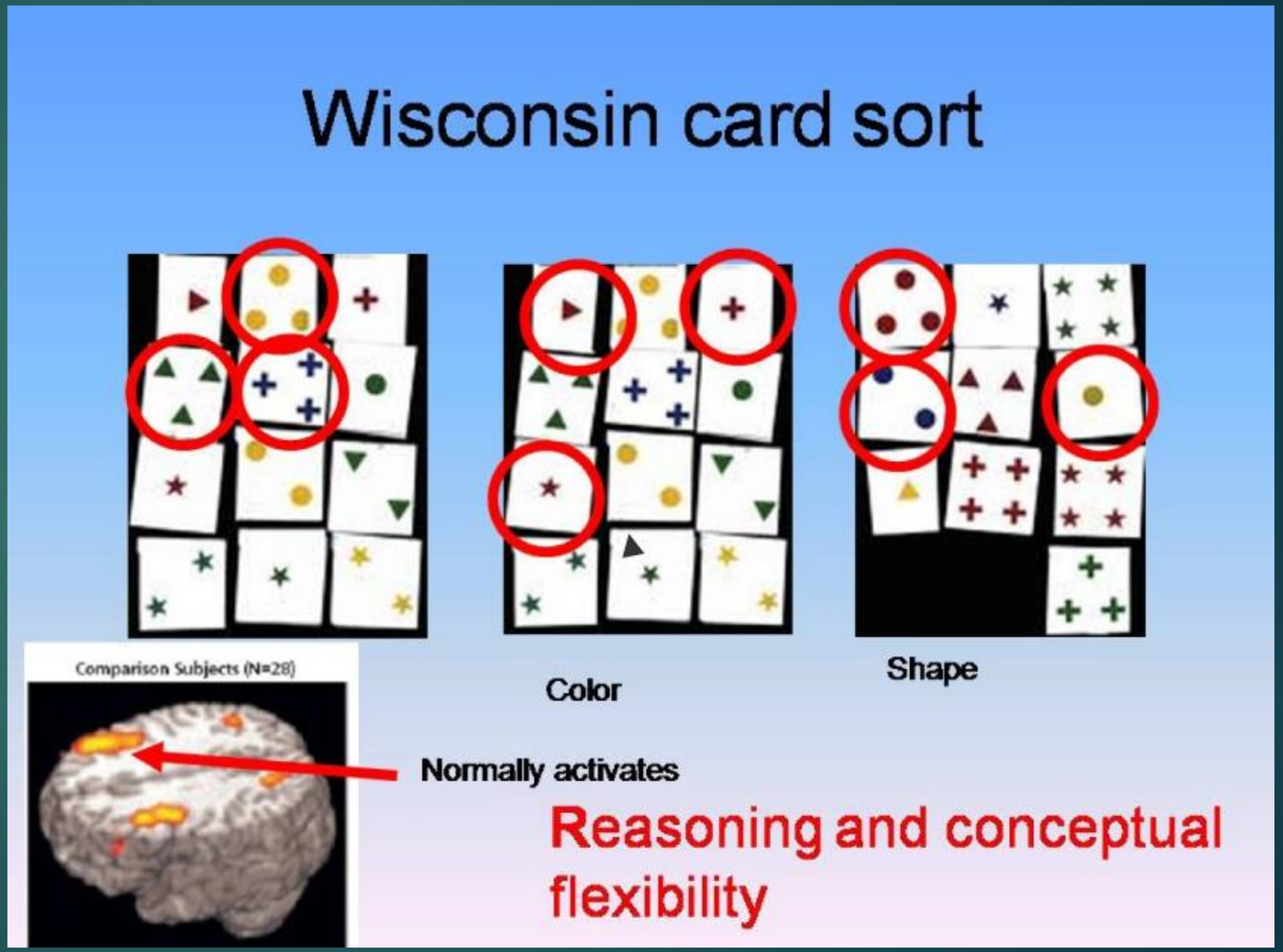


Abnormal EF Performance on WCST

Match cards by shape, color, number; but rule then changes

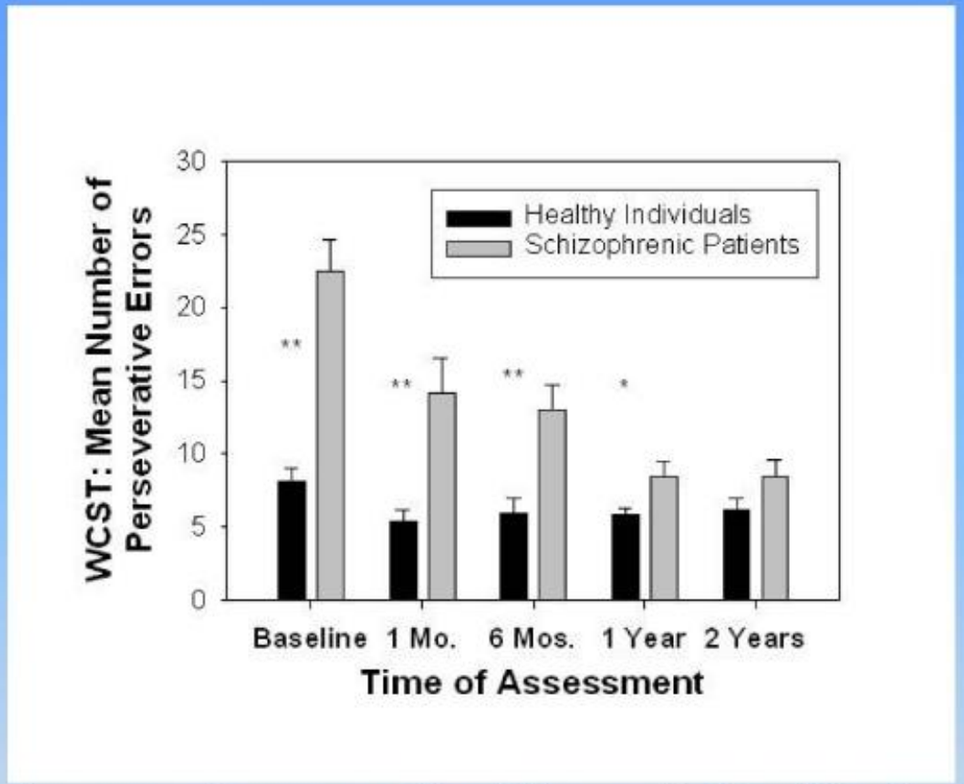
When I was intern, question was why Reitan Category test was usually Impaired in schiz?

Debate: Bad test or picking up neurological disorder.



WCST:
increased Perseverative Errors % at 1st episode & ongoing =

Impaired EF pre and post onset



Increased errors on the Wisconsin Card Sorting test in first episode neuroleptic naïve schizophrenia

Hill, Sweeney Keshavan Am J Psychiatry 2003

Cognitive deficits **persist during illness**

Executive Functioning

- **Executive Functioning:**
  - Poor planning, organization, problem-solving, cognitive flexibility, self-monitoring
  - Impaired insight and social judgment
  - Lack of initiative/ motivation
- **Impaired EF - NP measures:**
  - WCST perseverative errors (large effect size range)
  - Category test errors
  - Verbal Fluency (COWAT): decreased
  - TMT-B: slower
  - Stroop
- **As your WCST goes, so does your Rorschach and PAI thought disorder scales: poor inhibition of odd thoughts**

Emotional / Social Cognition

- Impaired social cognition
  - facial recognition
  - emotion processing,
  - social perception,
  - attribution bias,
  - Mentalization / Theory of Mind

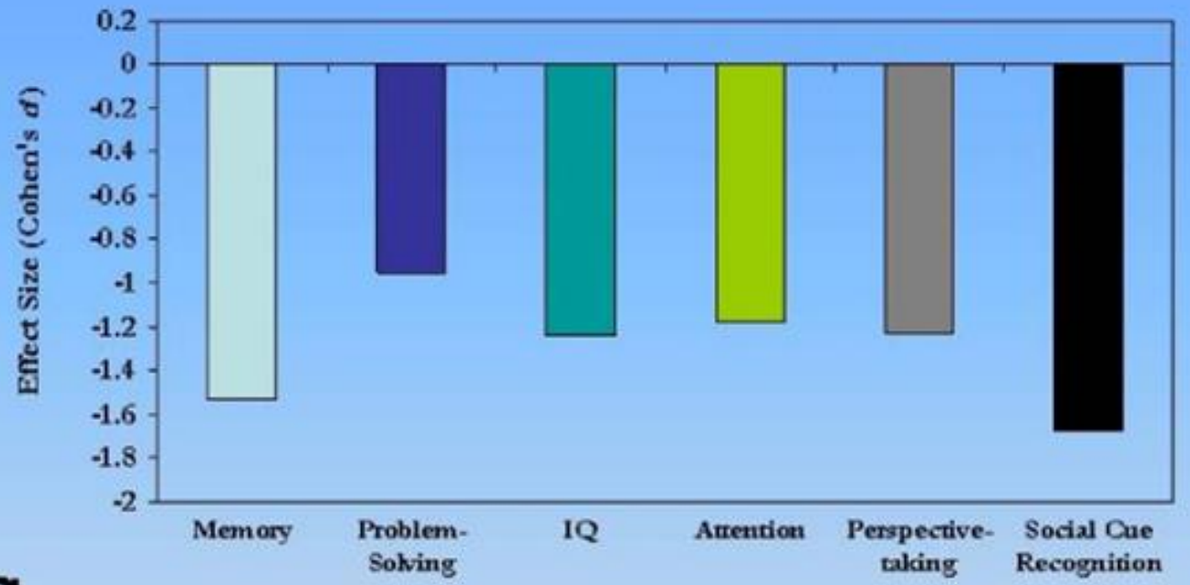
- A key determinant of functional disability in people with schizophrenia

- Social cognition may mediate the relationship between neurocognition and functional outcome

- Abnormal mirror neuron activity may exist among patients with schizophrenia during the active (psychotic) phase of the illness and correlates with severity of psychosis.

Summary: Cognitive deficits in Schizophrenia

- Speed
- Memory
- Attention
- Reasoning
- Tact/Social cognition



1 to 1.5 SDs below normal

Cognitive heterogeneity in schizophrenia

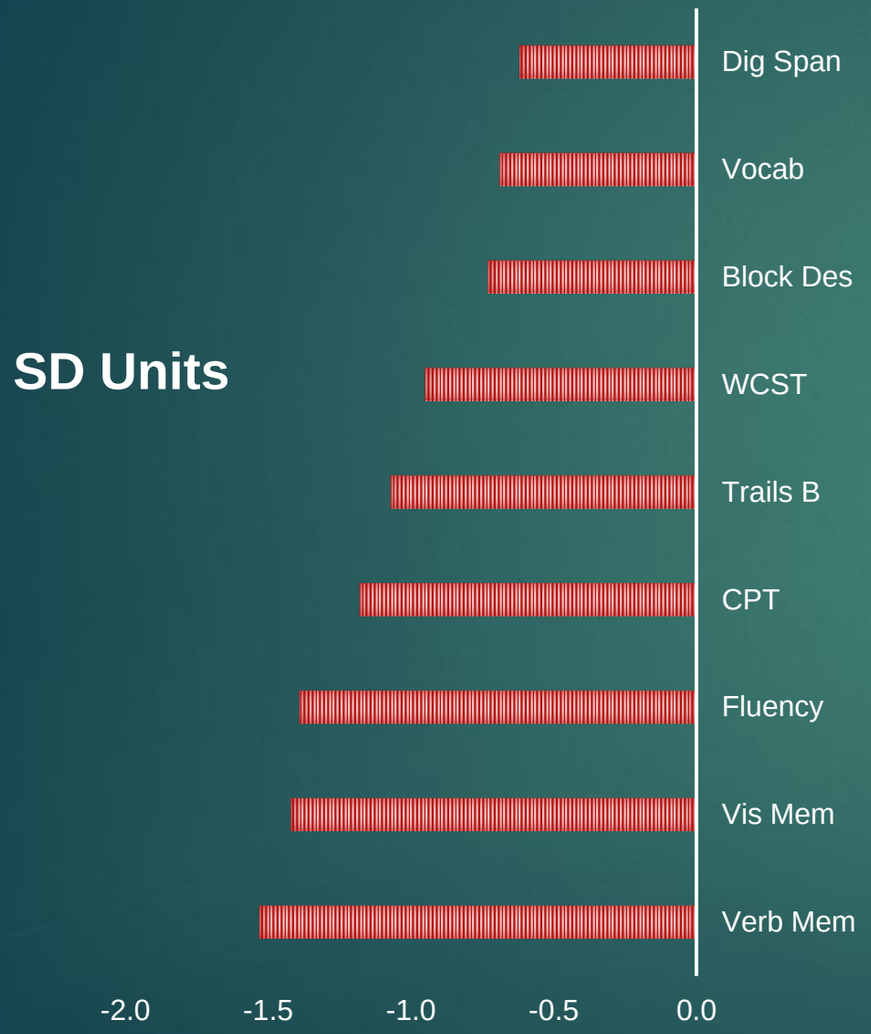
- Goldstein, et al., 2013: Cognitive variability in schizophrenia

- Neurocognitive functions in schizophrenia may be:
  - Essentially normal
  - Globally and severely impaired
  - Reflect a global profile that is associated with a specific brain system (spared verbal, impaired motor)

- Older idea of generalized deficit implied increasing difficulty across all domains as items got more difficult

Cognitive Impairment Magnitude in Schizophrenia

Meta-Analysis; 204 studies, 7420 patients and 5865 controls



Characteristic profile in schizophrenia:

maximal impairment: memory, attention, and executive function

Relative preservation of old learning and visual perceptual skills.

Memory

	Mild	Moderate	Severe
Memory: Long-Term Factual	X		
Memory: Episodic Verbal Learning			X
Memory: Nonverbal (Spatial)		X	
Memory: Delayed Recall		X	
Memory: Delayed Recognition	X		
Memory: Procedural Memory		X	

Definition of ranges in Standard Deviations:
Mild: Impairment: < -0.5 SD
Moderate Impairment: - 0.5 – - 1.5 SD
Severe Impairment: > - 1.5 SD

From Harvey and Keefe, 2009

	Mild	Moderate	Severe
Verbal Skills: Naming	X		
Verbal Skills: Fluency		X	
Perceptual Skills	X		
Processing Speed			X
Manual Dexterity		X	

Definition of ranges in Standard Deviations:
Mild: Impairment: < -0.5 SD
Moderate Impairment: - 0.5 – - 1.5 SD
Severe Impairment: > - 1.5 SD

Primary Deficits

	Mild	Moderate	Severe
Working Memory: Verbal			X
Working Memory: Spatial			X
Attention: Sustained			X
Attention: Selective		X	
Executive Functions			X

Definition of ranges in Standard Deviations:
Mild: Impairment: < -0.5 SD
Moderate Impairment: - 0.5 – - 1.5 SD
Severe Impairment: > - 1.5 SD

Relative Impairment by Domain (Summary Definition of ranges in Standard Deviations: Mild Impairment: < -0.5 SD; Moderate Impairment: - 0.5 – - 1.5 SD; Severe Impairment: > - 1.5 SD	Mild	Moderate	Severe
Memory: Episodic Verbal Learning			X
Processing Speed			X
Working Memory			X
Attention: Sustained			X
Executive Functions			X
Memory: Procedural Memory		X	
Memory: Spontaneous Recall		X	
Manual Dexterity		X	
Language: Fluency		X	
Memory: Recogntion	X		
Perceptual	X		

Summary: NP measures I

I: Frontal lobe dysfunction

a. Impaired attention

- I Filtering
- II Selective attention
- III Sustained and focused attention

b. Abstraction Difficulties

c. Problem solving deficits (WCST)

d. Poor planning on Clock Drawing, (secondary to problems with verbally mediated planning)

e. Distinguishing relevant from irrelevant information impaired

Summary: NP measures II

2. Memory deficits
   a. Impaired CVLT-II, WMS-III, BVRT
   b. CVLT research: impaired learning and recall; delayed recognition superior to recall
3. Possible deficits on language tests
   a. If speech disturbance noted (e.g., Disorganized Type), BNT may be impaired
   b. On the COWAT, Phonemic fluency better than Semantic Fluency
4. Slower reaction time to both auditory and visual signal on the RT

Summary: NP measures III

- Expect 1-2 SDs below normal with moderate to severe impairment in specific cognitive areas
- Factor in comorbidities: Substance abuse, TBI, medication effects
- **** Must address functional implications of results (academic, vocational), including everyday consequences & need for compensatory strategies for memory deficits
- More severe the cognitive deficits, the more the need for conservatorship and supervision!

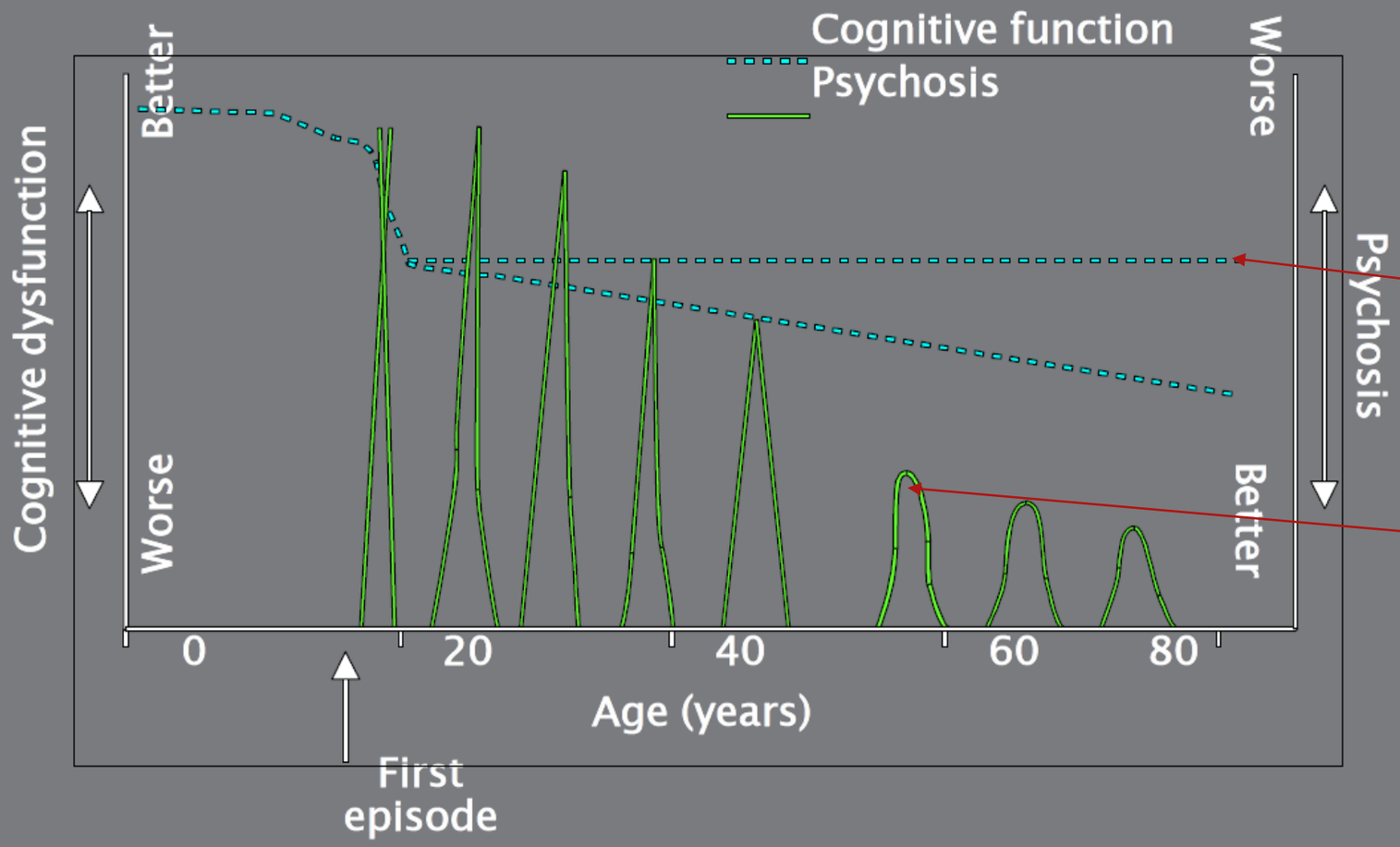
Psychiatric Course of Schizophrenia

10 years later:
25% completely recovered
25% much improved, relatively independent
25% improved but requiring extensive support network
15% hospitalized, unimproved
10% dead, mostly suicide

35 years later:

25% completely recovered
35% much improved, relatively independent
15% improved but requiring extensive support network
10% hospitalized, unimproved
15% dead, mostly suicide

Cognitive dysfunction is a lasting feature of schizophrenia



Cognitive deficits are permanent

Psychosis declines

Evaluation and Intervention

Evaluation:

- Cooperation may be difficult
- Shorter batteries are better
- Use SVTs: very high rates of failure (but not for 2ndary gain)
- Reduced test engagement
- Attempt to monitor engagement, esp. lapses in attention

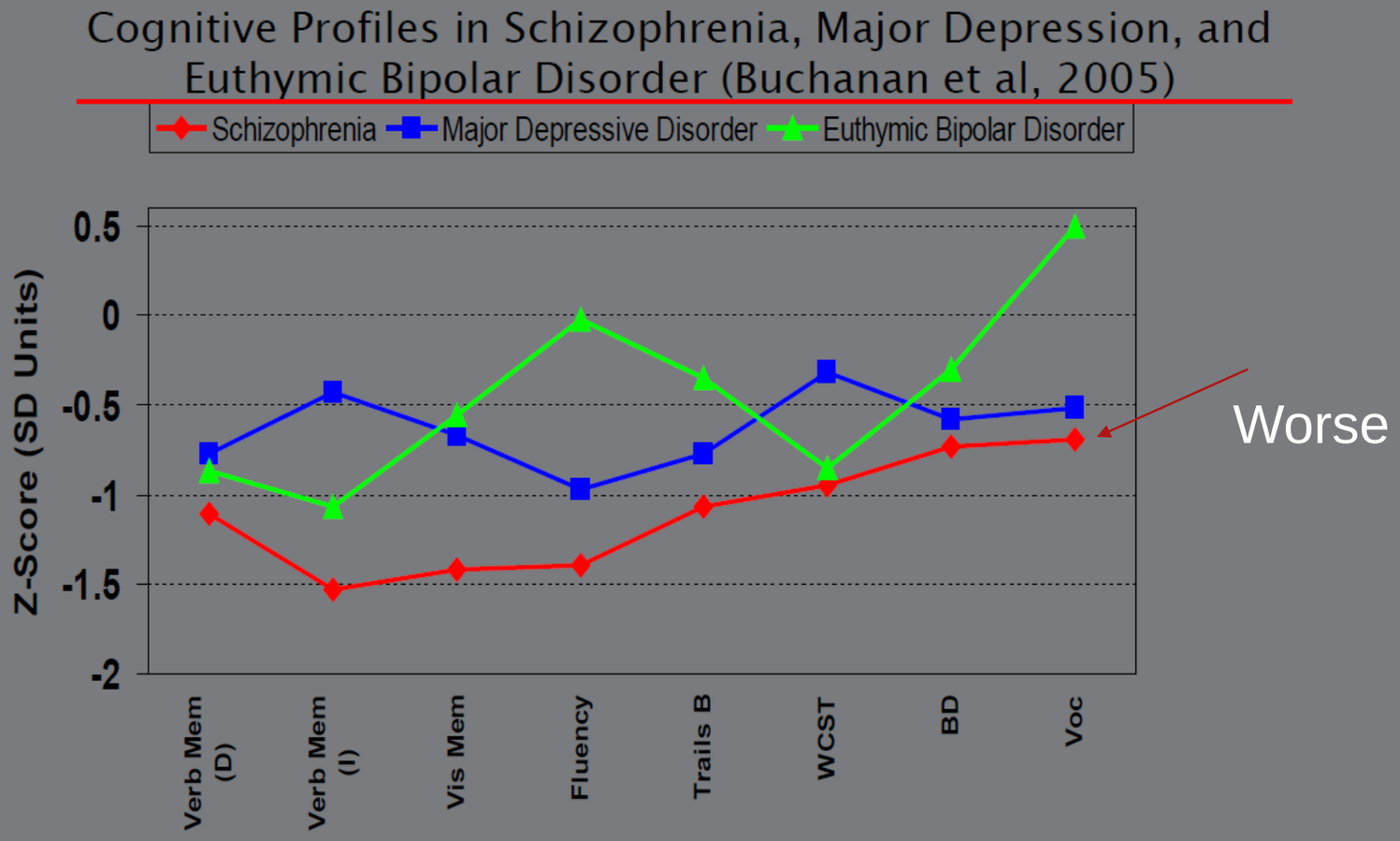
Intervention:

- Antipsychotic Meds: Mixed evidence
- Minimal improvement (approx. 0.25 SD)

Harvey and Keefe, 2009

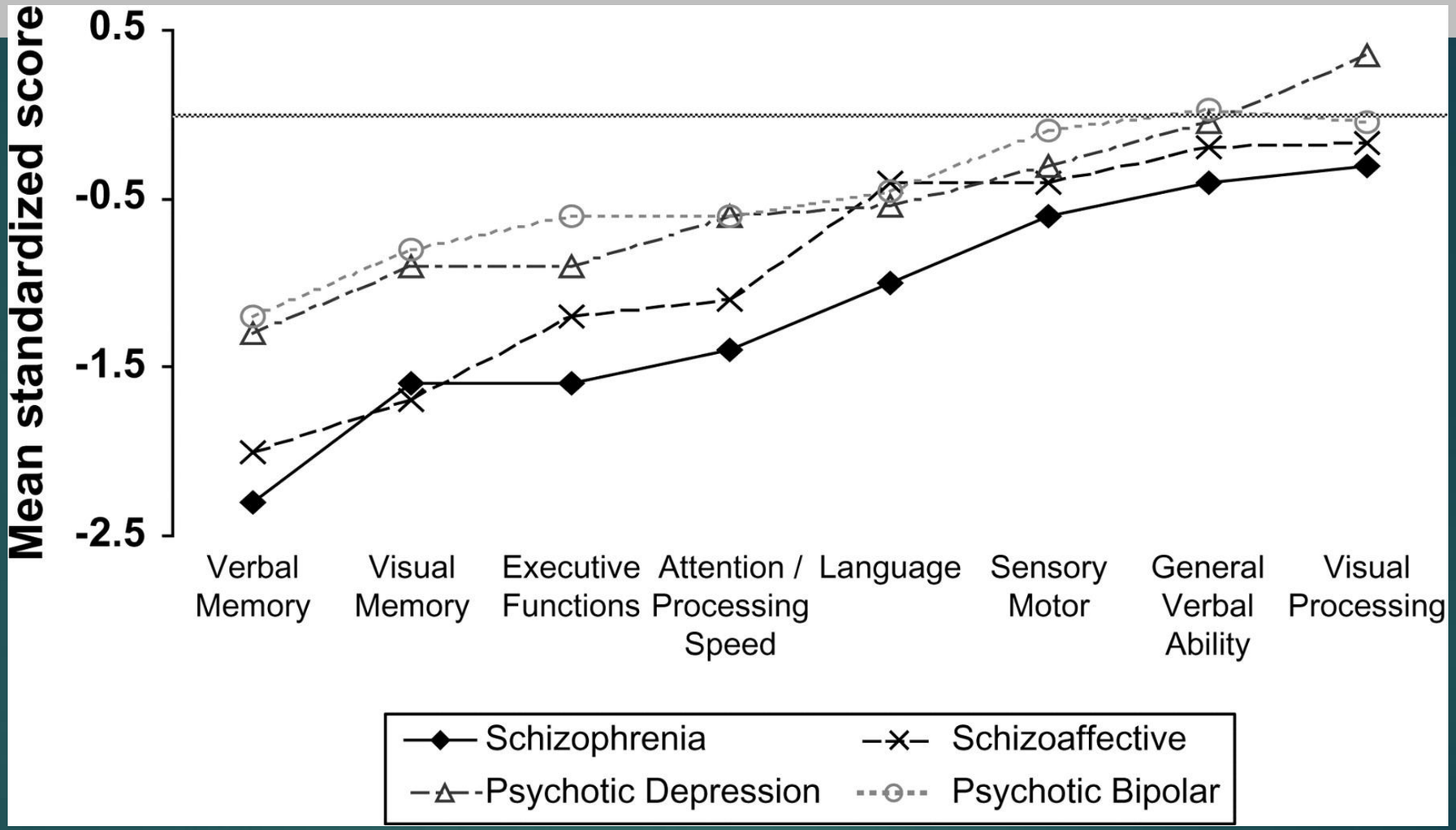
Cognition in Schizophrenia, MDD, & Euthymic Bipolar

Similar deficits in Schiz & euthymic Bipolar: Verbal memory & EF (WCST)



Note: Data from Heinrich and Zakzanis (2), Zakzanis, Leach, and Kaplan (12), and van Gorp et al (14). Healthy group mean = 0. Verb Mem (D) = Delayed Verbal Memory; Verb Mem (I) = Immediate Verbal Memory; Vis Mem = Visual Memory; Trails B = Trail Making Test, B; WCST = Wisconsin Card Sorting Test; BD = Block Design; Voc = Vocabulary.

4 psychotic groups vary minimally; Schizophrenia most severe



4 psychotic groups vary only minimally in their NP performance profiles. This may further suggest similar pathophysiology, possibly involving frontal lobe circuits, underlying the NP deficits in different psychotic disorders.

Reichenberg A et al. Schizophr Bull 2008;35:1022-1029

Comorbid Developmental Disabilities

- Intellectual Disability: 3-5%; a risk factor for Schizophrenia
- Learning disability: 3 x higher; increases poorer functioning outcome
- ADHD:
  - inattention predates 1st psychotic episode in Schizophrenia
  - those with both syndromes, more cognitively impaired;
  - schiz = less LH activation; ADHD = less RH activation

Driving

- Most patients with Schiz who are stable and in Tx are relatively safe drivers.
- Person’s accident hx and record of violations is likely better predictor of driving risk than a dx of schiz.
- Severity of cognitive deficits present should raise concern

Conclusions: Cognition in in Schizophrenia

- Functional outcome in schizophrenia:
  - poor
  - level of disability is generally high

- Cognitive impairments are key determinants of poor functional outcome in schizophrenia.

- The cognitive impairments of schizophrenia:
  - Are core features of the illness
  - Can be reliably measured
  - Are not well-treated by any current medications
- Not caused by medications (although meds can make cognition worse)

Cognitive difficulties in schizophrenia

- 3 specific neurocognitive domains are significantly associated with functional outcomes:
  - executive functioning,
  - verbal memory,
  - sustained attention/vigilance.
- Community activity (e.g., working, going to school) was predicted by measures of executive functioning and delayed verbal memory.

- Psychosocial skill acquisition was most frequently linked with verbal memory.

Decision Making Capacity

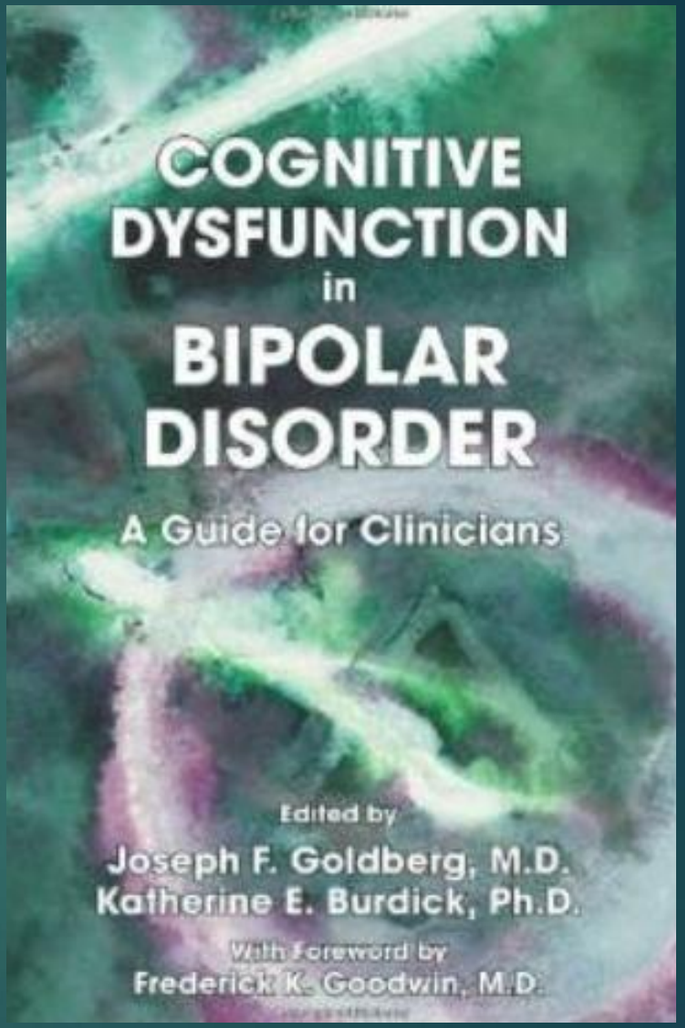
- Applebaum research:
- Symptomatic inpatient schizophrenia pts have the worst decision making capacity
- Differences in capacity appeared more related to cognitive functions than to severity of psychopathology
- Majority of pts have adequate capacity for most decision-making roles, but there is enormous variation;
- Unfortunately, unlike it's decisions related to adolescence, Supreme Court has upheld right to refuse treatment & high standards for involuntary Tx

Summary: Course of Cognitive Deficits in Schizophrenia

- Cognitive deficits in schizophrenia are:
  - Pervasive
  - Persistent
  - Present early
  - Progresses early
  - Predicts functional disability

Bipolar Disorder: The Book

- **Cognitive Dysfunction in Bipolar Disorder: A Guide for Clinicians by** Joseph F. Goldberg & Katherine E. Burdick, 2008



Bipolar Disorder

- Depression represents the predominant abnormal mood state for treated outpatient bipolars. 3x more depression than mania

- Highly genetic: 69% in identical twins; minor EF deficits in first degree relatives

- There are neurotoxic effects of repeated manic episodes on the developing juvenile brain

- Diffuse cognitive dysfunction during the acute phases of bipolar illness;
  - bipolar depression = psychomotor slowing and impairment of memory;
  - hypomania = severe frontal-executive deficits
  - euthymia = a milder disturbance of attention, memory and executive function.

Neurocognitive Deficits in Bipolar Disorder

2nd 3rd

- Bipolar disorder produces cognitive deficits, even during periods of symptom remission:
  - Marked deficits in executive-function and verbal learning
  - Worse the more intense the disease process
  - Are persistent, despite psychiatric symptom reduction
- Significantly affect psychosocial functioning

Core Feature: Sustained Attention Deficit

- Attention: attentional abnormalities were seen in symptomatic BD patients and persisted in remission in measures of sustained attention and inhibitory control.

- **Conclusions:** Sustained attention deficit may represent a neuropsychological vulnerability marker for bipolar disorder.

L. Clark, *The British Journal of Psychiatry* (2002)

Major Deficit in Bipolar disorder: Executive Functioning

- Executive dysfunction is the main long-term neuropsychological deficit of bipolar disorder.
- All aspects of executive function (planning, abstract concept formation, set shifting) were impaired in symptomatic BD patients.
- May be normal in fully recovered patients with uncomplicated BD.
- Frontal and subcortical hypometabolism in bipolar illness

NP deficits predict Social & Vocational Functioning

- Verbal memory impairments and/or executive dysfunction are associated with:
  - reduced social and vocational functioning in patients with bipolar disorder,
  - even in the absence of manic or depressive symptoms

Martinez-Aran et al., 2004; Dickerson et at., 2004

Social Cognitive Deficits in BD

- BD 1 pts have significant impairments in:
  - Identification of primary facial emotions
  - Social perception
  - Mirror neuron firings

Bipolar Course: Mania is bad for your brain

- No cognitive deficits prior to illness onset of BPD
- Evidence of minor EF deficits in first degree relatives
- Positive correlation between number of manic episodes and verbal memory, memory retention, and executive dysfunctions.
- Toxic to Brain: Deleterious effects of repeated manic episodes and psychotropic medication on cognitive performance

G. Goodwin, et al., Europ Neuropharm, 2007

Meta-Analysis of BD I: Enlarged ventricles & WM Hyperintensities

- N = 98 MRI studies

- Increase size in bilateral ventricles & increased WM hyperintensities (2 most replicated BD1 finding) – mostly in frontal & parietal in deep white
- Increased amygdala volume is prototypical of BD I
- Abnormalities in cerebellum

Kempton, et al., 2008

Antidepressants: Increase Hippocampal Volume

Neurogenesis in mood disorders

- Psychotropic medications used in treating those disorders are neuroprotective and induce neurogenesis
- All antidepressant drugs and ECT increase neurogenesis & BDNF.
- Mood stabilizers such as lithium and valproate increase neurogenesis.

H. Nasrallah, 2008; Reif, et. al., 2006

Tip #2 - NP recommendations: Schiz & BP pts are not Cognitively Normal

- Use NP assessment not for diagnosis of schizophrenia, but for cognitive profile needed for treatment, rehabilitation, evaluation of need for supervision/conservatorship (if major NCD), disability status

- Once symptomatically stable, all Schiz and BP pts should receive a MoCA

- If MoCA (especially Executive Functioning (EF) items) are impaired (<25), then refer for fuller NP assessment.

Tip #2 - NP recommendations: Schiz & BP pts are not Cognitively Normal

- If Schiz & BP pts. have significantly impaired EF (or major NCD), then need more supervision recommendations. Meds alone will not help them.

- Psychiatry departments should have Cognitive Rehabilitation groups

- Most significant psychiatric conditions (Schz, BP, MDD, BPD, ADHD) have impaired EF; meds don’t effect EF

Functional domains and their most consistent predictors.

- Functional domain — Predictors
- Social functioning
  - Social cognition
  - Social competence (modest predictor)
  - IA of social cognition
  - Negative symptoms
  - Long-term clinical stability
- Vocational functioning
  - Neurocognition
  - Impaired IA of neurocognition disability
  - Physical capacity
  - Functional capacity
  - Social competence
  - Long-term clinical stability

- Residential functioning
  - Neurocognition
  - Impaired IA of neurocognition
  - Functional capacity
  - Physical capacity
  - Long-term clinical stability

Note: IA = introspective accuracy.

Risk factors for Poor Functional Outcome in Schizophrenia

- Neuropsychological impairments
- Early age of onset
- Insidious onset with poor premorbid social function (vs acute with ok social)
- Family history of schizophrenia
- Having predominantly negative and disorganization sxs
- Greater number of relapses
- Poor social support (“expressed emotionality” in family setting is strong predictor of relapse)
- Assault or trauma history
- Poor compliance with prescribed medications

Psychosis & Suicide Risk

- 3 in every 100 “normal” people have psychotic episode in their lifetime
- 1 in 100 will have schizophrenia
- High Suicide Risk:
  - 1 of every 10 young males with schizophrenia commits suicide
  - 20% attempt suicide

Medical Co-morbidities are Common

- 2-3 times more likely to die prematurely due to suicide rate (12x higher), high risk behaviors, accidents & substance abuse.
- 20% reduction in lifespan due to greater cardiovascular morbidity, due to smoking, obesity, diabetes, HTN, hyperlipidemia, glucose dysregulation and insulin dysfunction
- Increased risk of metabolic syndromes raises risk of MIs & CVAs
- Long term use of antipsychotic medication increases weight gain & metabolic syndrome & CV risk; also effects of poor diet, and sedentary lifestyle

Medical Co-morbidities are Common 2

- Number of medical comorbidities in schizophrenia has been linked to degree of cognitive dysfunction.
- No relationships between positive symptom severity and medical comorbidities.
- Schiz with HTN have more memory deficits; schiz with DM2, more NP deficits; both medical conditions have own cognitive deficits; synergistic cognitive effects
- Nearly 75% of people prescribed medications for the disorder stop taking them within a year and a half, studies find.

Cardiovascular Disease

- Die 10-20 years earlier than normals
- Cardiovascular disease (CVD) is the leading cause of premature death among schizophrenia
- CVD due to: smoking, obesity, diabetes, hypertension, hyperlipidemia
- 2x greater death rate from heart and blood vessel disorders
- Schizophrenia and CVD: shared genetic risk factors: triglyceride and lipoprotein levels, waist-hip ratio, systolic blood pressure and body mass index.

Anders M. Dale, et al., American Journal of Human Genetics, 2013

Schizophrenia and Smoking:
Nicotine as poor man's Stimulant

- 50-85% of people who have schizophrenia are heavy cigarette smokers (and ~65% of people with bipolar disorder)
- 44% of all cigarettes used in the US are smoked by the mentally ill.
- Schizophrenia pts. do better on NP tests when smoking;
- Poor man's stimulant?
- Or nicotinic receptor aide?

Substance Abuse: 50%

- Approximately 50% of people with schizophrenia develop a substance use disorder
- 25-35% have active substance use problems at any point during their illness.
- Alcohol abuse and dependence are independently associated with impaired cognitive functioning.

- **When in the course of schizophrenia do cognitive deficits occur?**
- **Do they persist/progress?**

Presentation & Disease Course

- First-Episode Psychosis: full psychotic sxs; severe NP deficits already apparent (Mem, Attn, EF), paralleled with social, academic, & occupational problems

- Acute phase: active experience of psychotic sxs (thought disorder, hallucinations, delusions); several weeks or months if untreated; need inpatient tx; psychotic sxs fluctuate from acute exacerbation to stability or remission

- Residual: psychotic sxs largely remitted; individual is stable; continued experience of negative sxs, poor social functioning

- Cognitive deficits persist throughout all phases.

Cognitive Change in Schizophrenia and Other Psychoses in the Decade Following the First Episode, Jolanta Zanelli, et al., 2019

- 2019 study: Following first episode, the schizophrenia group exhibited declines in IQ and in measures of verbal knowledge and of memory, but not declines in processing speed or executive functions.

- Processing speed and executive function impairments were already present at the first episode and remained stable thereafter.

- Decline in memory is present in all psychotic disorders.

- Patients with schizophrenia and other psychoses experience cognitive decline after illness onset, but the magnitude of decline varies across cognitive functions

Zanelli: continued cognitive decline

- This study demonstrates that while a substantial proportion of the cognitive impairment seen in adult patients with schizophrenia is already present at the first episode, these patients continue to experience cognitive decline after illness onset.

- While large deficits in processing speed & EF are already apparent at the first episode, deficits in verbal knowledge and memory continue to increase.

- Schizophrenia patients showed continued IQ decline between baseline and follow-up assessments. This finding contrasts with earlier studies reporting stabilization of cognitive deficits after the onset of psychosis.

- Consistent with neuroimaging studies of greater age-associated brain volume loss.

Zanelli

- Schizophrenics experience cognitive decline from the premorbid to the post-onset period:
  - moderate cognitive deficits in children and adolescents who later develop schizophrenia, with an
  - average premorbid deficit = 8 IQ points.
  - 14-point IQ deficit in first-episode schizophrenia patients
  - 15- to 21-point IQ deficits in chronic schizophrenia patients.

- Longitudinal studies of cognitive change in schizophrenia from before to after illness onset have shown evidence for cognitive decline.

Zanelli

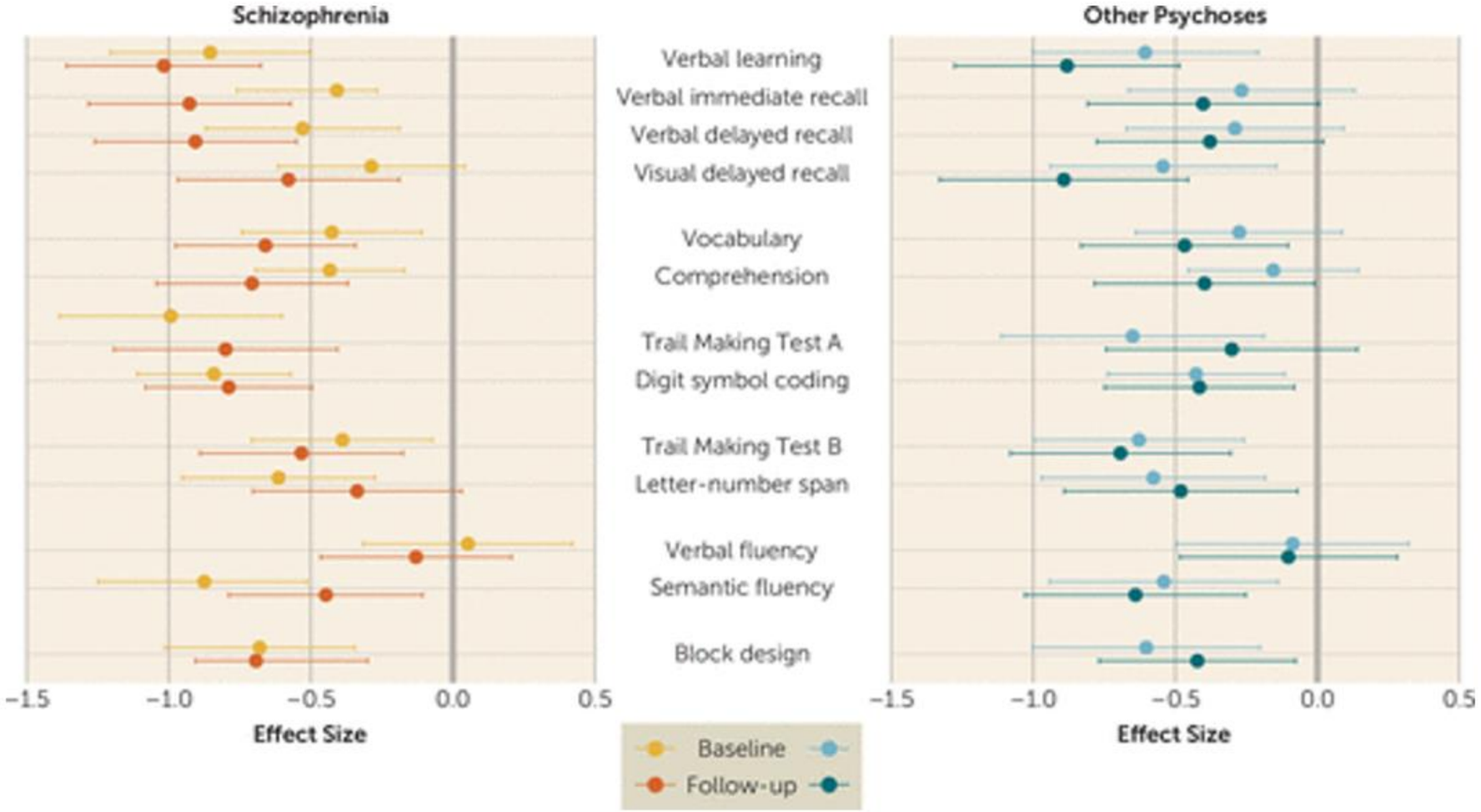
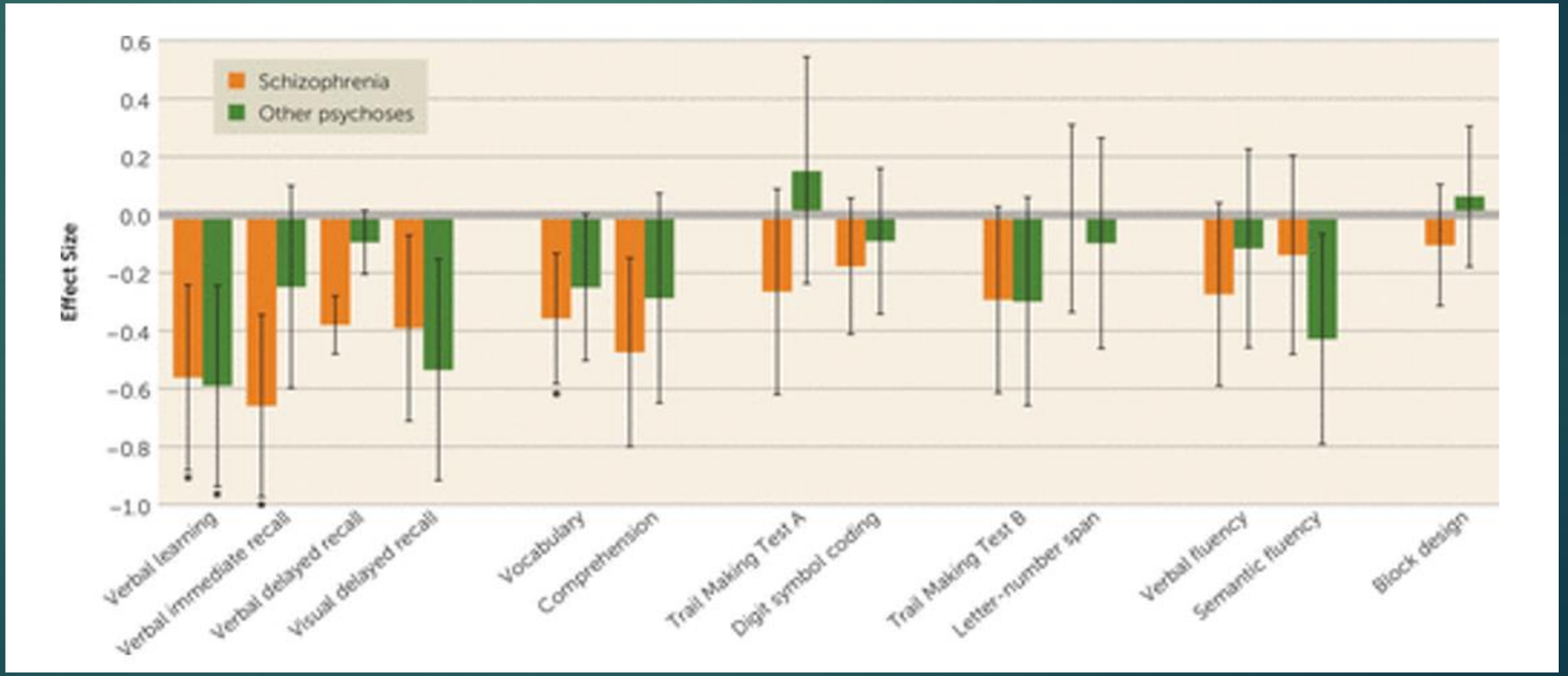


FIGURE 2. Neuropsychological performance among patients with schizophrenia and other psychoses at baseline and follow-up[a]

Zanelli: Change in neuropsychological performance among patients with schizophrenia and other psychoses[a]

- Patients with schizophrenia and patients with other psychoses showed deficits in IQ and individual neuropsychological tests at baseline. Schizophrenia patients exhibited widespread, persistent cognitive impairment, performing significantly worse than comparison subjects at both at baseline and follow-up on 11 of the 14 measures. Patients with other psychoses also showed widespread impairments, but these were generally of smaller magnitude than among schizophrenia patients
- IQ decline in the schizophrenia group was significantly larger than among comparison subjects, who showed no evidence of IQ decline



Zanelli

- Schizophrenia group showed a larger cognitive decline across tests in the memory and verbal knowledge domains. In the memory domain, there were declines on verbal learning, immediate recall, and delayed recall
- Other psychoses group showed static deficits in tests of processing speed, executive functions and working memory, and visuospatial ability
- Duration of antipsychotic medication did not reduce IQ decline in schizophrenia
- Schizophrenia patients with severe symptoms at baseline showed statistically significantly greater memory decline than patients with mild or moderate symptoms.
- However, there was no association between change in symptom severity and change in cognitive functioning

Zanelli: Decline after onset

- Conclusions: evidence for cognitive decline after illness onset in patients with schizophrenia.

- Schizophrenia patients showed IQ decline between baseline and follow-up assessments. This finding contrasts with earlier studies reporting stabilization of cognitive deficits after the onset of psychosis.

- Consistent with neuroimaging studies of greater age-associated brain volume loss.

- Reduction in cortical volume has been associated with IQ decline in schizophrenia patients.

Zanelli: Not generalized decline

- The schizophrenia group exhibited
  - declines in verbal knowledge and memory.
  - No decline in processing speed, executive functions, and visuospatial ability

- Decreasing crystallized abilities and memory scores between baseline and follow-up suggest that increasing deficits in these domains may reflect actual loss of ability rather than abnormal cognitive development.

- Measures of fluid abilities already showed a large deficit at the first episode, which remained static thereafter.

Zanelli

- Our findings suggest that most of the decline in fluid IQ abilities occurs before the first episode, while crystallized abilities may continue to decline after onset. Importantly, the decline in IQ after onset is likely to be due to the decline seen in crystallized abilities.

- Longitudinal evidence also suggests a minimal association between change in positive & negative symptoms and change in cognition.

Zannelli

- Hence, cognitive functions that develop and peak relatively early in life, such as processing speed and visuospatial abilities, may show aberrant development, resulting in slowed growth before the onset of schizophrenia, but relative stabilization throughout the illness course.

- On the other hand, cognitive functions that continue to evolve through adult life, such as language, may show further deterioration throughout the course of schizophrenia.

- Finally, functions sensitive to age-related cognitive decline, such as memory, may begin to decline in middle adulthood, before normative aging becomes apparent.

Schizophrenia: Cognitive Changes over Time

- NP deficits present before first psychotic episode
  - Verbal memory and olfactory functions
  - Working memory/attention- noticeable as early as childhood/ early teens.

- From first psychotic episode, to later life, no significant further cognitive decline
  - HOWEVER, Neuroimaging studies do reveal cortical changes over time.
  - Neuroimaging show large early decline → more impaired, more refractory sxs
  - In a subset, at later age, more marked decline than normal aging.

Dementia, Alzheimer’s disease and Schizophrenia

- 2021 study: Using data from a national sample of Medicare recipients, the prevalence of diagnosed dementia by age 66 was at 28% for schizophrenics versus 1% in individuals without a history of serious mental illness

- By age 80, prevalence in these groups increased to 70%

- Prevalence of Alzheimer's disease was 8% by age 66 in the schizophrenia group and 37% by age 80.

- Vascular dementia accounted for 5% of diagnoses in the schizophrenia group by age 66 and 16% by age 80.

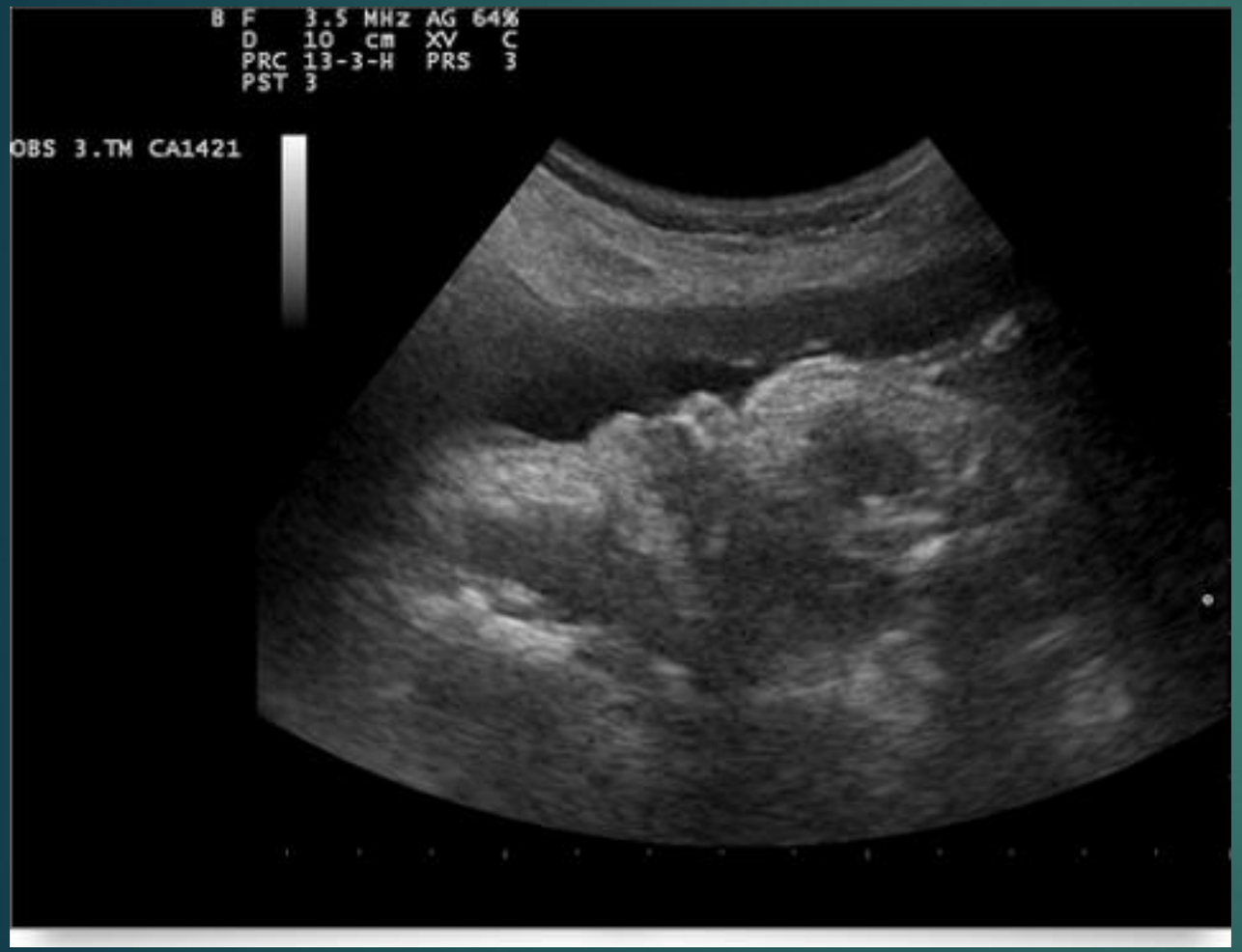
T. Scott Stroup, et al., 2021

Brain still under construction

“It’s sort of unfair to expect (teens) to have adult levels of organizational skills or decision making before their brains are finished being built.

-- Jay Giedd, MD, NIH, 2002

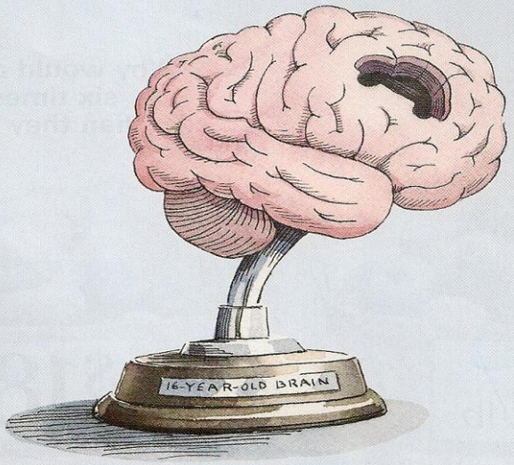
1987 Neurodevelopmental Hypothesis



Neuroscientists Daniel Weinberger, Robin Murray And Shon Lewis hypothesize that schizophrenia could be traced back to anomalies during brain development.

Why do most 16-year-olds drive like they're missing a part of their brain?

BECAUSE THEY ARE.



Even bright, mature teenagers sometimes do things that are "stupid."

But when that happens, it's not really their fault. It's because their brain hasn't finished developing. The underdeveloped area is called the dorsal lateral prefrontal cortex. It plays a critical role in decision making, problem solving and understanding future consequences of today's actions. Problem is, it won't be fully mature until they're into their 20s.

It's one reason 16-year-old drivers have crash rates three times higher than 17-year-olds and five times higher than 18-year-olds. Is there a way for teens to get their driving experience more safely — giving their brains time to mature as completely as their bodies? **Allstate thinks so.**

STRENGTHEN GRADUATED DRIVER LICENSING (GDL) LAWS.
GDL laws put limitations on teen driving so kids can gain experience safely. Since North Carolina implemented one of the most comprehensive GDL laws in the country, it has seen a 25% decline in crashes involving 16-year-olds.

HAVE THE DRIVING TALK.
75% of teens surveyed said their parents would be the best influence in getting them to drive more safely. The Allstate Parent-Teen Driving Contract can help start the conversation. **Contact an Allstate Agent to get a free copy or visit Allstate.com/teen for the interactive contract.**

Let's help our teenagers not miss out on tomorrow just because they have something missing today.

It's time to make the world a safer place to drive. That's Allstate's Stand.

Allstate. You're in good hands.
Auto
Home
Life
Retirement

Normal sculpting the adolescent brain

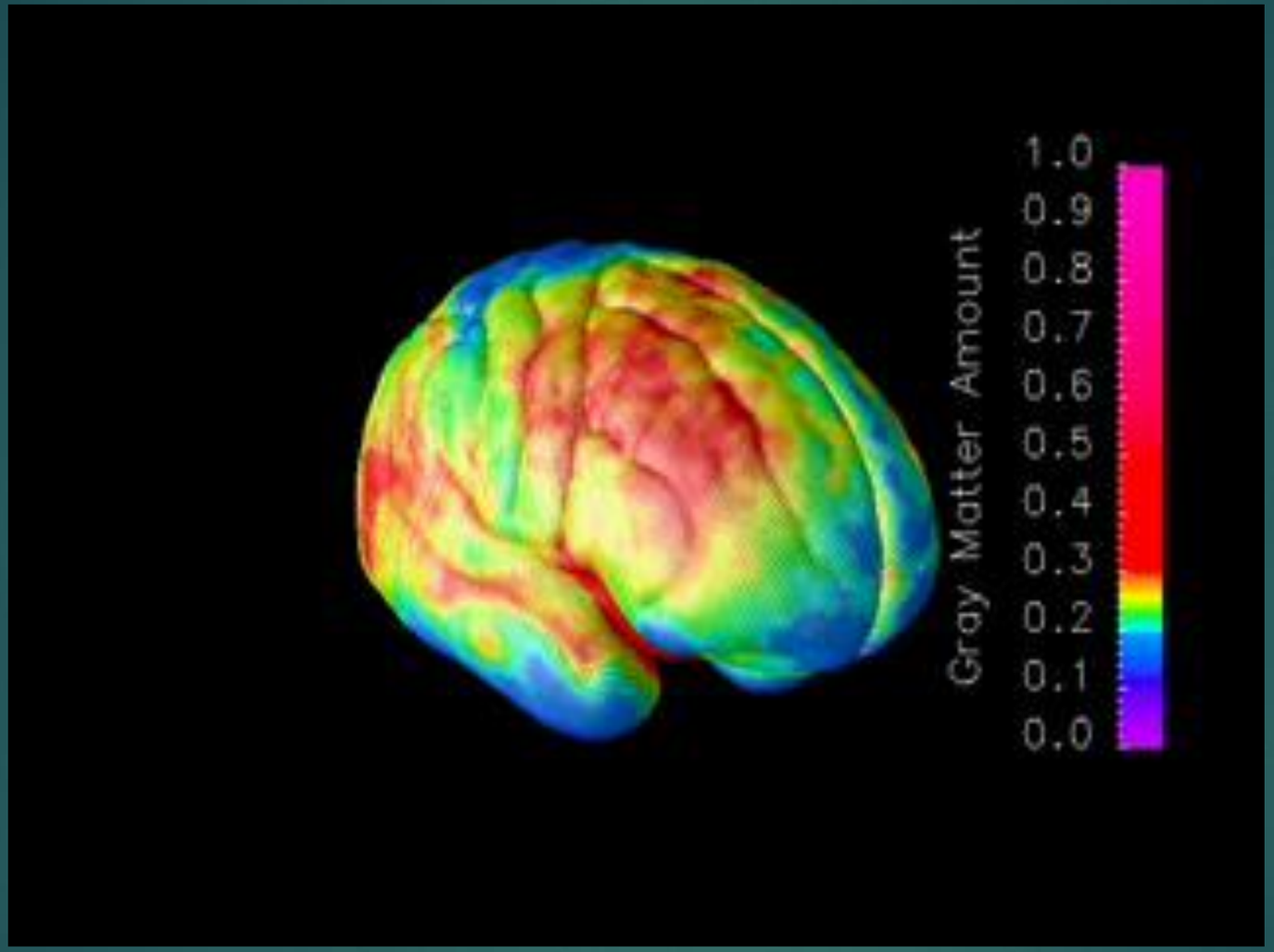
- Cortical gray matter volume: cortical volume size peaks around ages 12-14.
- There is normal cortical gray matter reduction related to synaptic pruning, beginning in dorsal parietal cortices, then the sensorimotor areas, then frontal cortex, then posterior brain.
- There are volume declines in medial parietal, temporal, frontal and cerebellar areas.
- White matter characterized by volume increases, esp. in frontal & corpus callosum (resulting in greater connectivity and speed of processing).

Normal sculpting the adolescent brain

- Adolescence is a critical neurodevelopmental period and therefore vulnerable to any neurotoxins.

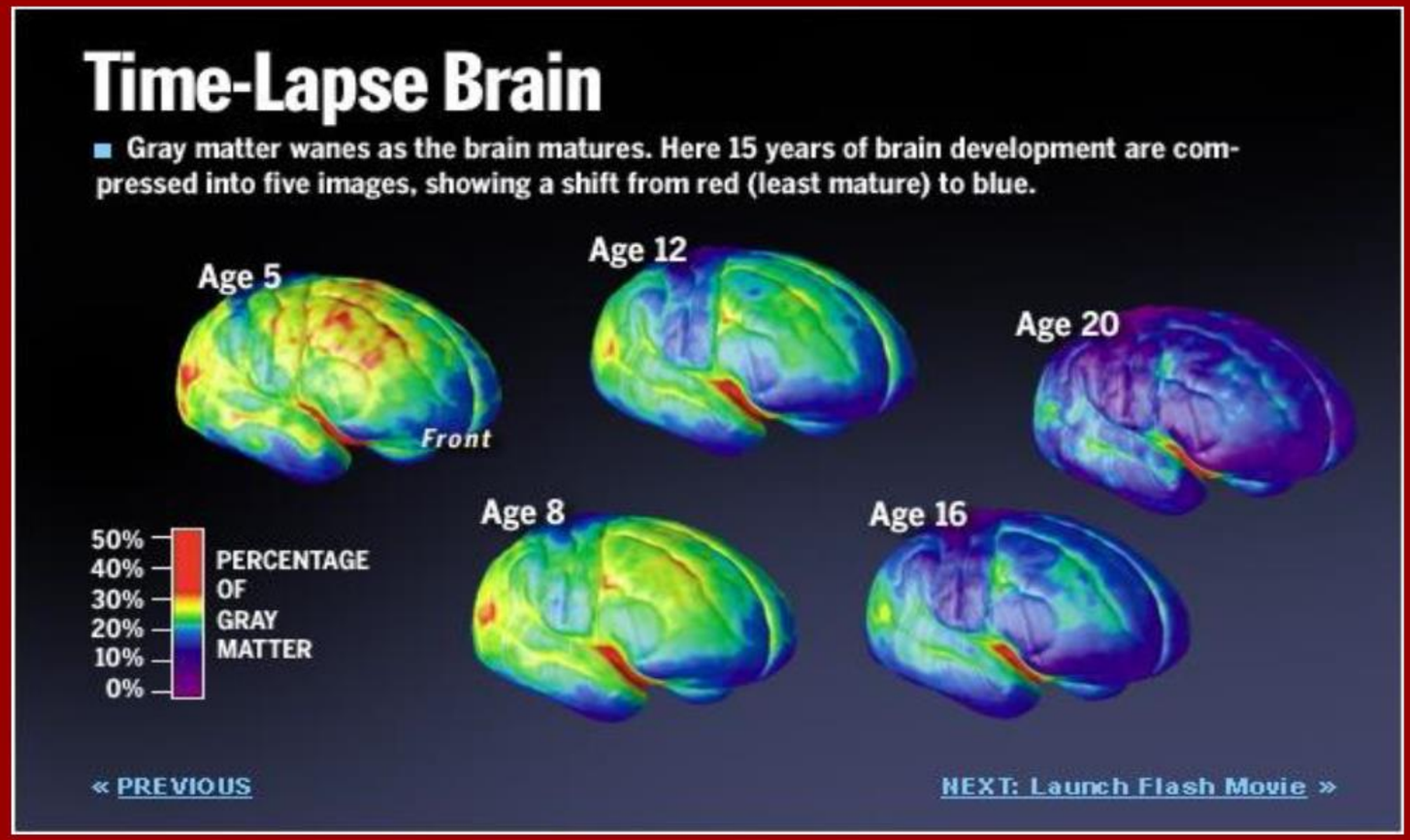
- During the period of adolescent neurodevelopment (12-18), the brain is thought to be particularly sensitive to damage from drug exposure, esp. the frontal cortex.

Normal Teen Brain: cortical pruning, age 5 to 21



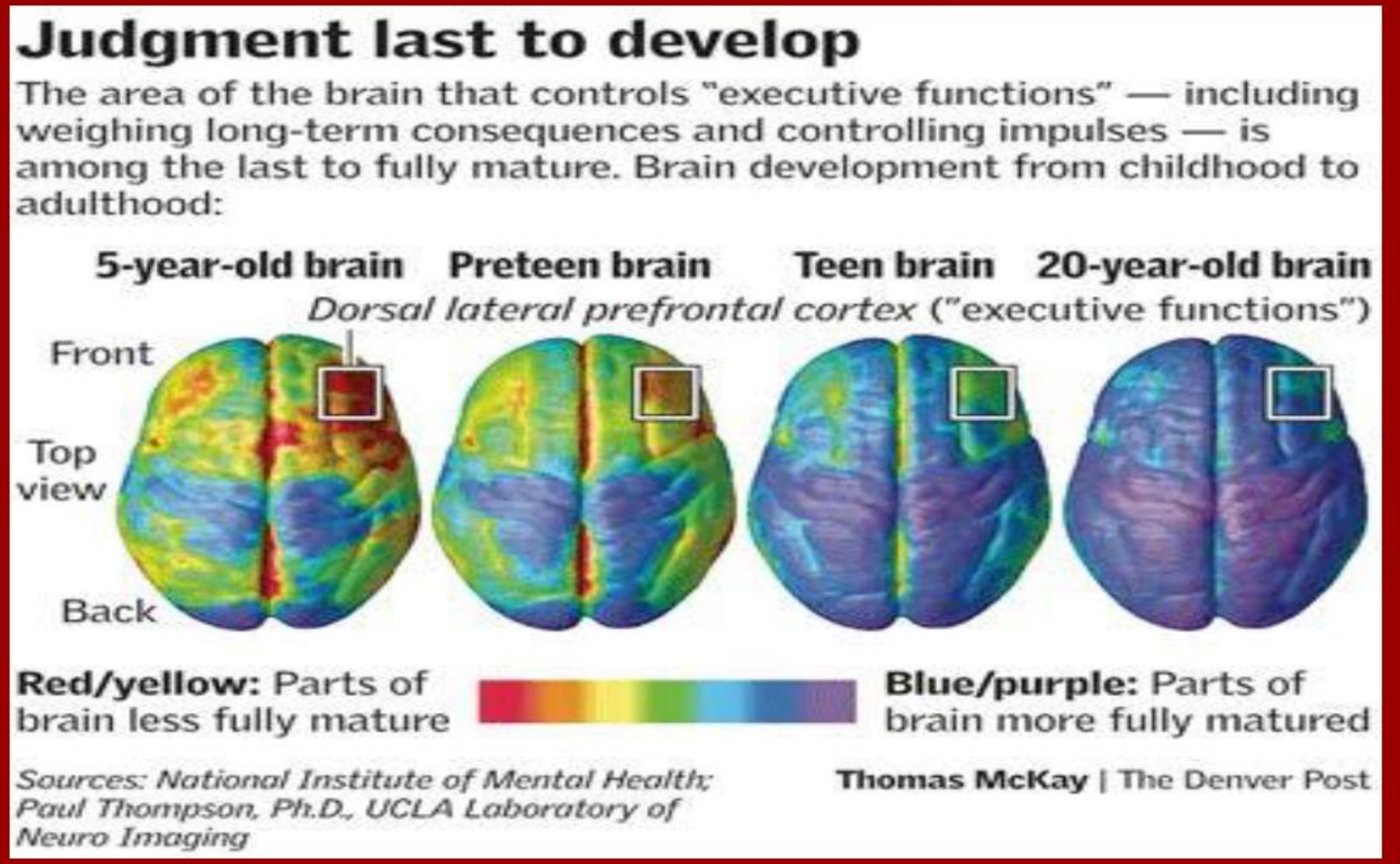
Lose 50% of all your synaptic connections;
Motor areas first, frontal last to develop

Brain loss of gray matter and increase in white matter from age 5 to age 20

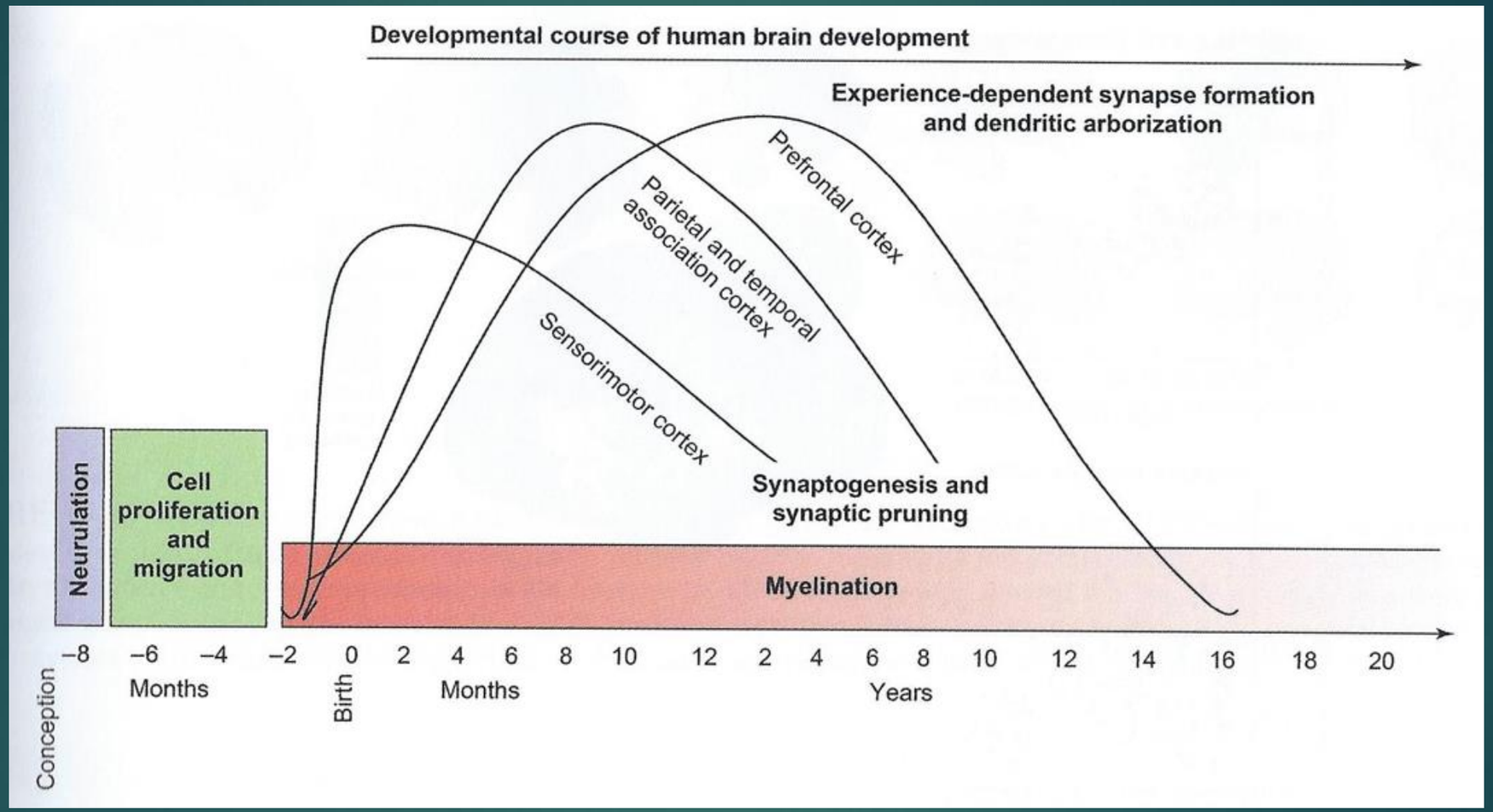


Prefrontal based Executive Functioning (judgment and planning)

Why we all make such "great" decisions before age 25



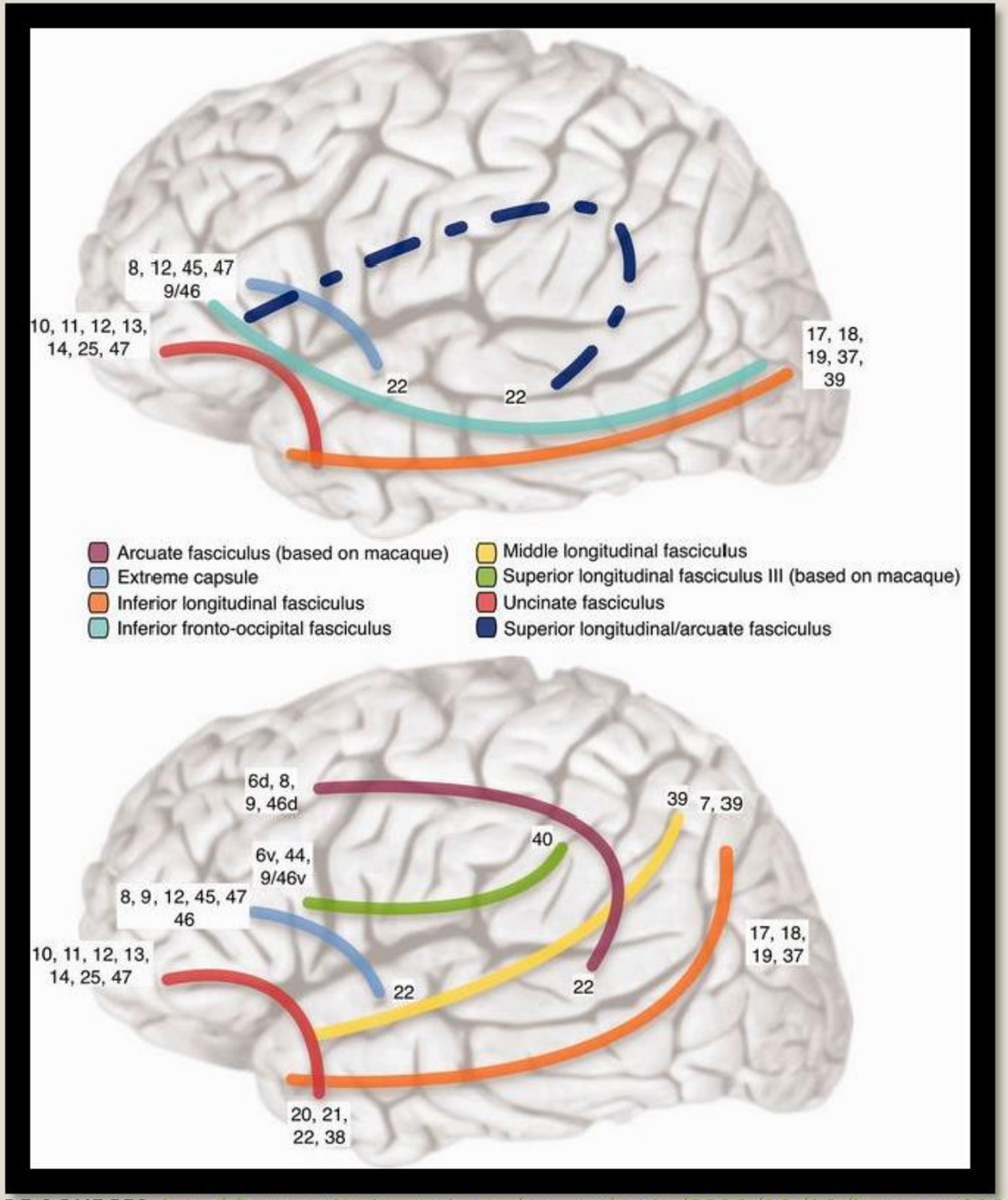
The Great Pruning: A leaner brain is a better brain

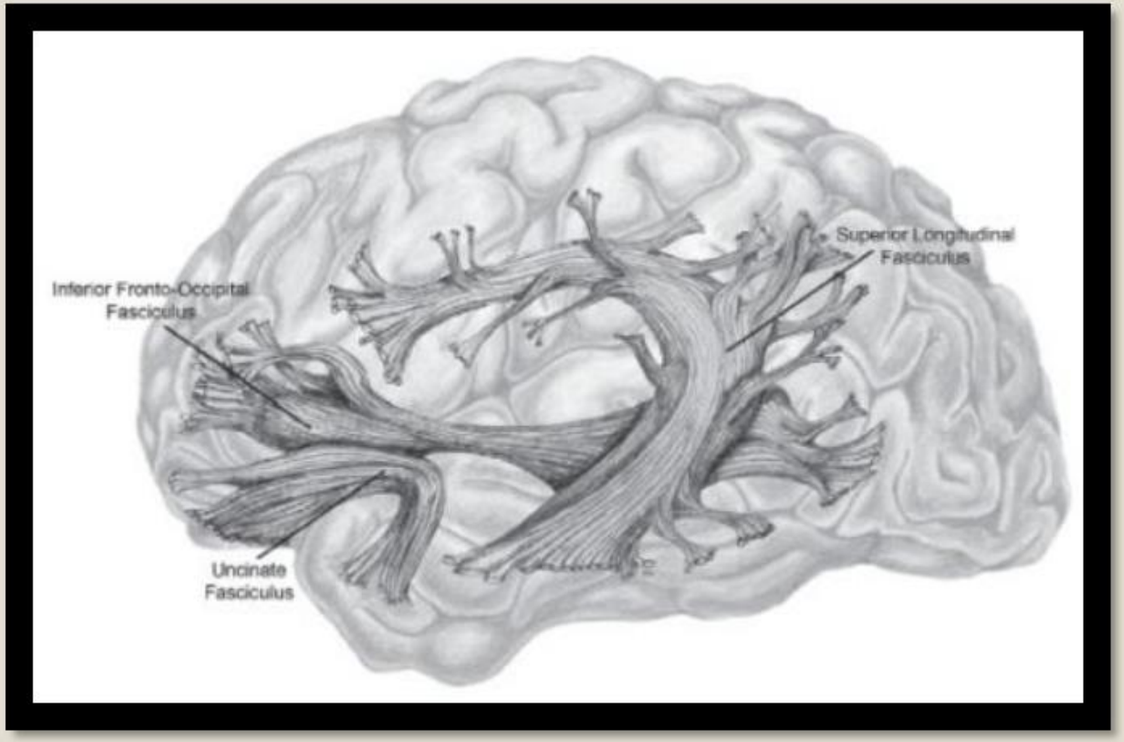


Intellectually disabled have significantly more synaptic connections than gifted do; as do autistic; but schizophrenia, ADHD = fewer synapses

Adolescence Brain

- More vulnerable to neurotoxic events because brain is in last major developmental period
- Arrested Development: Substance use can impair normal brain development
- Period of maturation of frontal and limbic regions
- Increase in myelinization (15x faster processing), particularly in frontal region: increase in impulse control
- Dopamine distribution changes (risk taking↑↑, reward seeking); adolescents are hypersensitive to reward, which leads to risker behavior



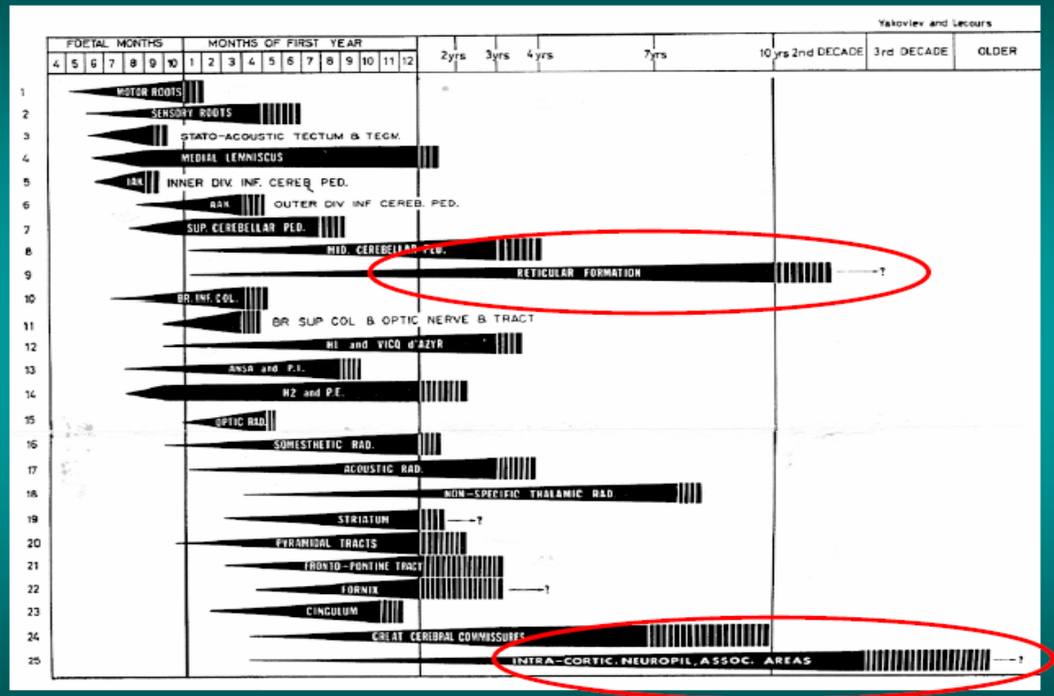


White matter, (tracts and fibers), is tissue found in the brain that contains nerve fibers, and is **responsible for transmitting information from one brain region to another.**

IMAGE SOURCES: http://brain.oxfordjournals.org/content/early/2012/10/28/brain.aws222 and http://openi.nlm.nih.gov/imgs/512/188/3190544/3190544_MSM-06-110-g002.png

Myelin Sheets on Axons Mature Slowly in Frontal Lobes; may increase into 30s.

Regional Maturation: Myelogenetic Cycles



Taken from Yakovlev & Lecours, The Myelogenetic Cycles

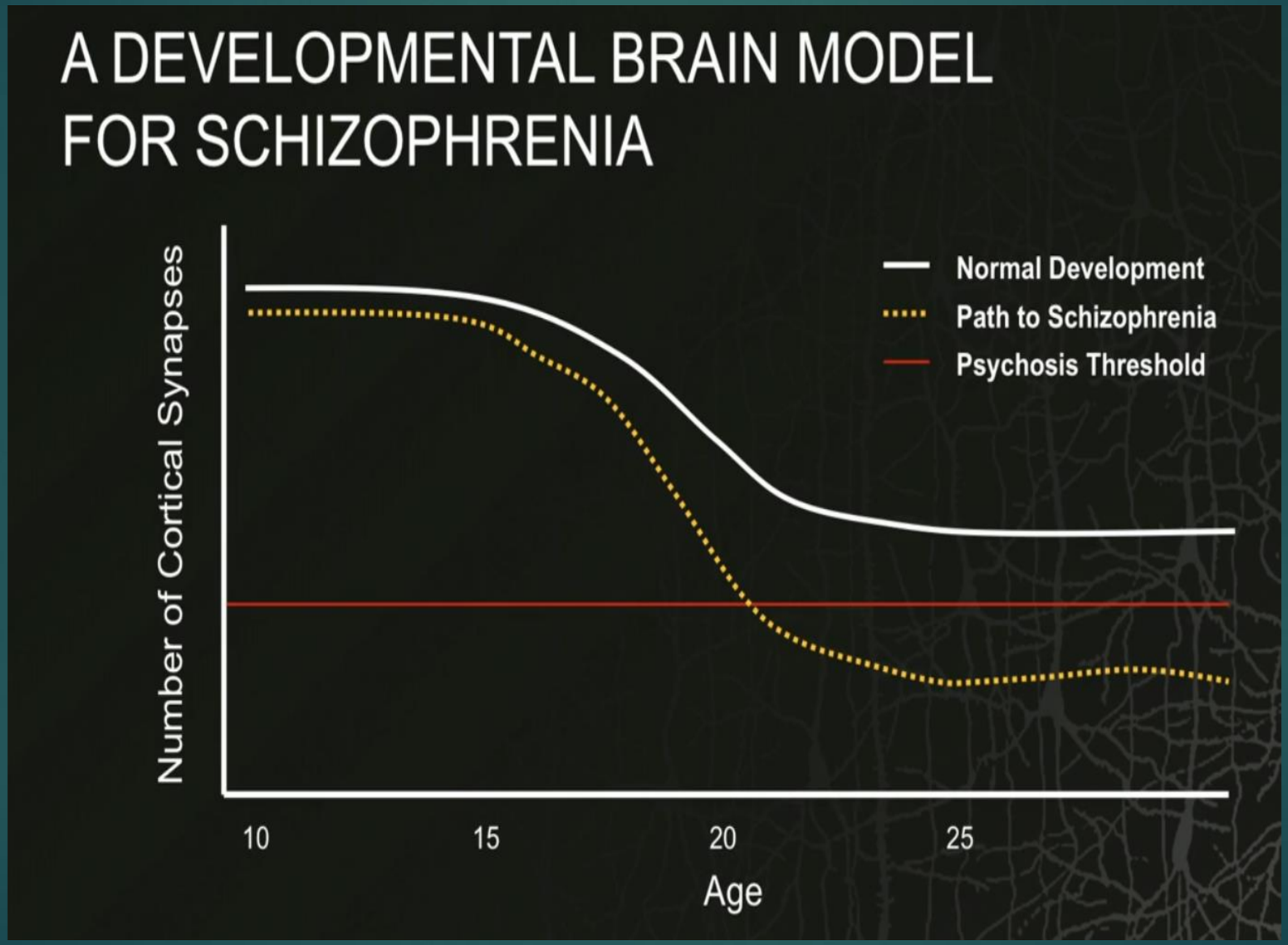
Amount of white matter (axon interconnections) distinguishes us from primates, not size of prefrontal lobes. Creates “greater bandwidth” and processing speed. Einstein had more white matter, not neurons.

Yakovlev & Lecours 1967

Dendritic, not Neuronal, Loss

- Brain atrophy: brain volume decrement was due to shrinkage of the neuropil surrounding the neurons:
  - reduction in dendrite length by a half
  - decrease in the number and size of dendritic extensions
  - decrease in synaptic connections

Developmentally reduced synaptic density/connectivity

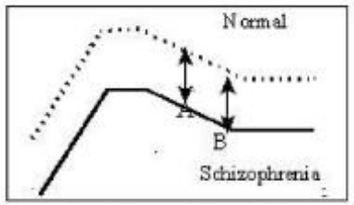


Abnormal immune cell reduction of synapses

Excessive synaptic pruning hypothesis

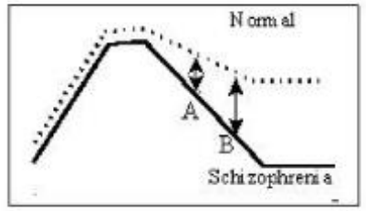
Abnormal synaptic plasticity in schizophrenia?

The early developmental hypothesis of schizophrenia

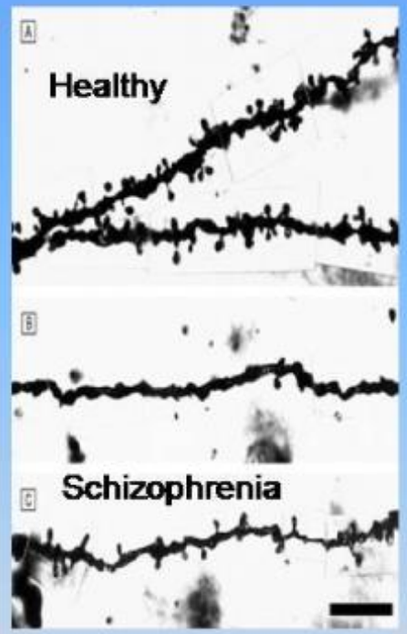


A =Baseline; B= Followup studies

Figure 2: The hypothesis of exaggerated synaptic pruning in schizophrenia



A =Baseline; B= Followup studies



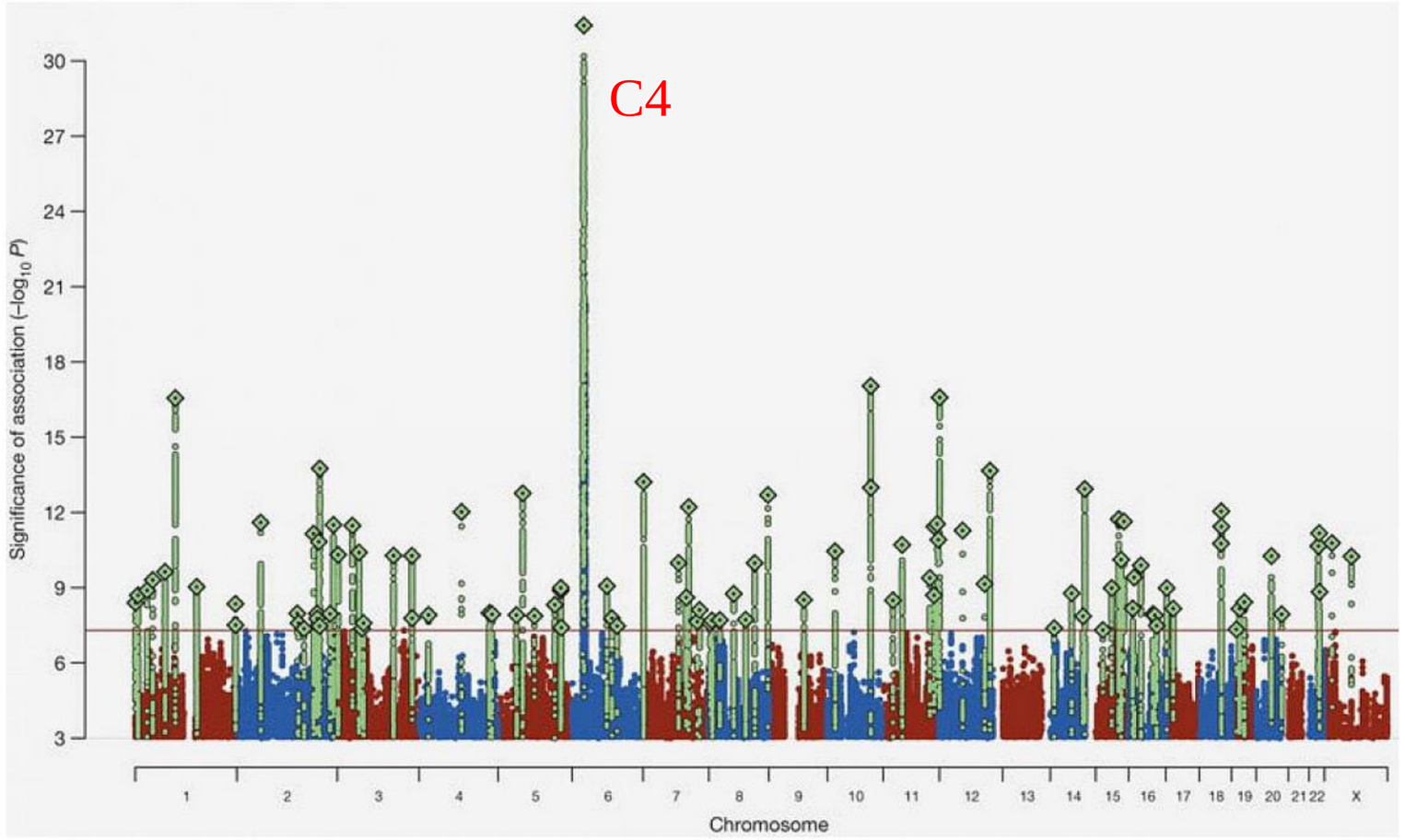
Glantz, L. A. et al. Arch Gen Psychiatry 2000;57:65-73.

ARCHIVES OF GENERAL PSYCHIATRY

Χαμηλογλυπτο ρεσταυρεκτιονσο μαφ απηλιθ.

Overactive C4 immune gene: The genetic cause of schizophrenia?

GWAS = Genome wide association studies

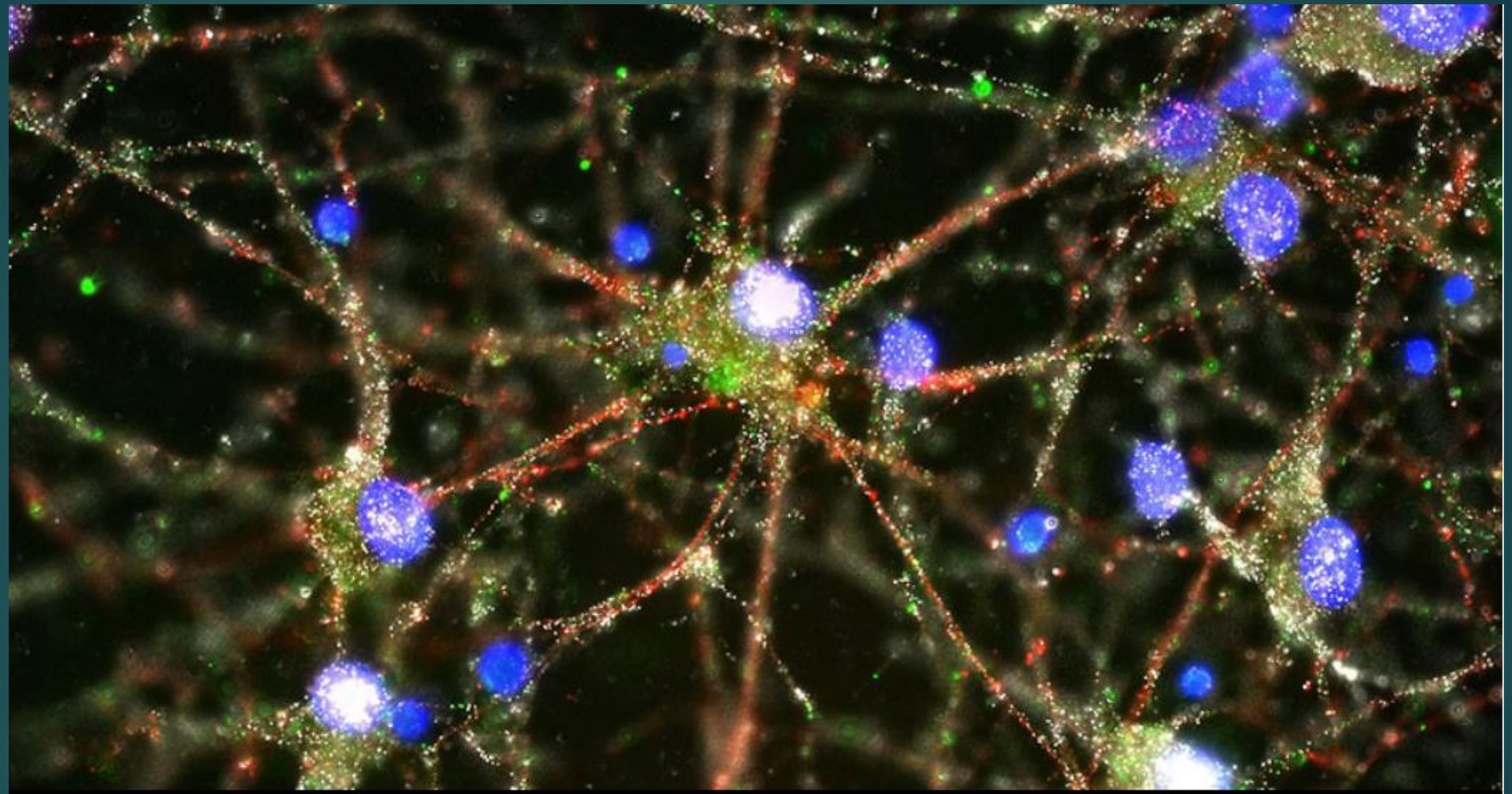


The site in Chromosome 6 harboring the gene C4 towers far above other risk-associated areas on schizophrenia's genomic "skyline," marking its strongest known genetic influence. The new study is the first to explain how specific gene versions work biologically to confer schizophrenia risk.

Aswin Sekar, et al., 2016

Information from GWAS study: C4 gene in 28 K people with schizophrenia, and 36 K normals from 22 countries. From the genome data, they estimated people's C4 gene activity.
Higher the levels of C4 activity were, the greater a person's risk of developing schizophrenia was.

C4 immune protein (green) increases synaptic pruning



CUTTING CONNECTIONS C4 protein (green) is found on human nerve cells growing in a dish (cell bodies shown in blue). The protein may cause people with schizophrenia to lose nerve cell connections, researchers propose.

IMAGE COURTESY OF HEATHER DE RIVERA (MCCARROLL LAB)

Pruning in Schizophrenia

- During adolescence and early adulthood, synaptic pruning takes place primarily in the prefrontal cortex. People who carry genes that accelerate or intensify that pruning are at higher risk of developing schizophrenia than those who do not.

- Their prefrontal areas tended to have a diminished number of neural connections,

- People with schizophrenia have a MHC immune gene variant that apparently facilitates aggressive “tagging” of connections for pruning, in effect accelerating the process. Involve common variants of a gene called C4, and that those variants produced two kinds of proteins, C4-A and C4-B.

Aswin Sekar, et al., 2016

Pruning in Schizophrenia

- C4 is a critical component of the classical complement cascade, an innate-immune-system pathway that rapidly recognizes and eliminates pathogens and cellular debris.

- In mice, C4 mediated synapse elimination during postnatal development.

- C4 is expressed by neurons, localized to dendrites, axons, and synapses, and secreted; and that C4 promotes synapse elimination during the developmentally timed maturation of a neuronal circuit.

Pruning in Schizophrenia

- These results implicate excessive complement activity in the development of schizophrenia and may help explain the reduced numbers of synapses in the brains of individuals affected with schizophrenia.

- The team analyzed the genomes of more than 64,000 people and found that people with schizophrenia were more likely to have the overactive forms of C4-A than control subjects.

- “C4-A seemed to be the gene driving risk for schizophrenia.”

C4 Pruning in Schizophrenia

- Overactive C4-A gene leads to inappropriate pruning during this critical phase of development

- Would explain not only:
  - thinner prefrontal layers in schizophrenia,
  - but also the reason that the disorder most often shows itself in people's teenage years or early twenties.

- Possible biomarker for at risk adolescents

Choline in 2 schizophrenia studies

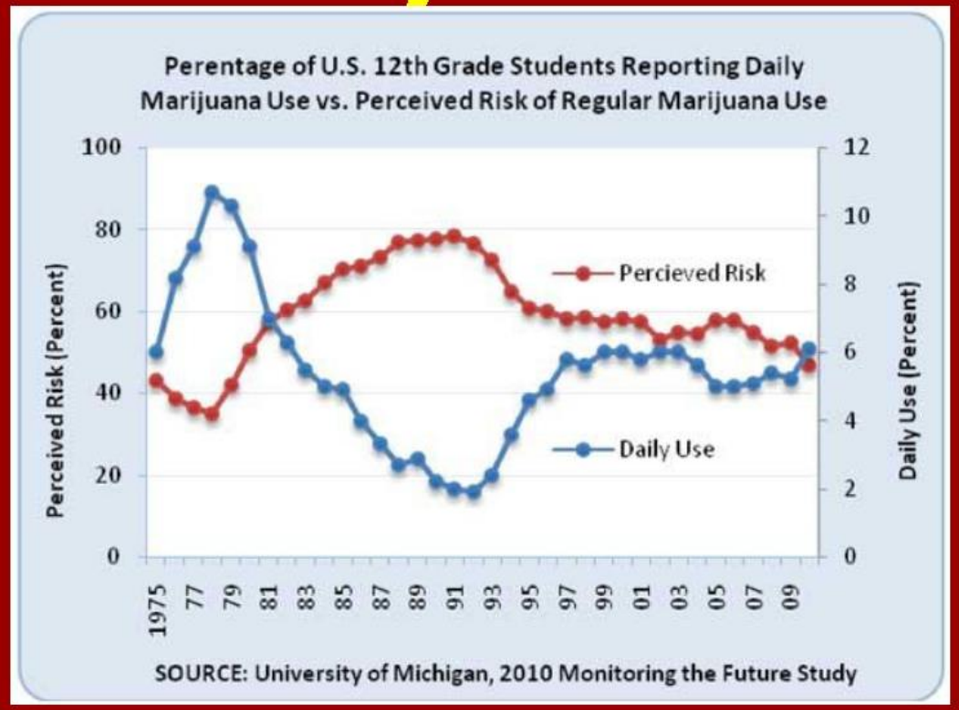
- Sharon K Hunter, et al., 2020 and 2021:
- Choline is an essential nutrient that can be found in foods such as milk (esp. breast milk), red meats (esp. liver), & egg yolks. Required for acetylcholine production, needed for neurodevelopment, immune response, epigenetic regulation.
- Based on previous studies of choline showing that it is vital for fetal neurodevelopment, including the development of inhibitory neurocircuits in the brain that are abnormal in individuals with schizophrenia and many of their family members, the group launched its first clinical trial in 2004.
- Low choline in pregnant women = prematurity. Black women at much higher rates for latter. Stress related.

Choline

- Choline supplementation (559 mg/day) reduces prematurity.
- Choline is critical for normal brain circuit development
- Choline affects immune response and nicotinic receptors (which control acetylcholine response).
- Famine, which affects many nutrients, is one cause of choline deficiency. Famines in both China and in Holland have been associated with increased risk for later schizophrenia in the offspring of women who were pregnant during the famines.
- Choline gene variation is associated with Nicotine Dependence; there is a genetically-determined deficiency in nicotinic receptors as a genetic factor in the onset and development of schizophrenia. Smoking activates these receptors.
- Prenatal marijuana use adversely affects fetal brain development and subsequent behavioral self-regulation in children. Supplemental choline in women who smoke marijuana during pregnancy reduces fetal brain development effects of marijuana (Hoffman et al., 2019)

2013: 61% of HS Seniors don't view MJ as harmful

Correlation of Perceived Risk and Marijuana abuse



2013

60.5% HS Seniors in 2013 Don't View regular Pot Use As Harmful & 6.5% use daily Monitoring the Future Survey 2013

In the U.S. marijuana use among high school seniors is more common than smoking cigarettes.

Statistics

- Teenagers and young adults are now using MJ more frequently than smoking cigarettes

- 1 in 6 (17%) teenagers who regularly smoke the drug become dependent

- It doubles the risk of developing psychotic disorders, including schizophrenia

- Cannabis users do worse academically.

- Heavy use in adolescence appears to create long term NP deficits

Statistics 2

- Driving after smoking cannabis doubles risk of having a car crash

- Smoking it while pregnant reduces the baby's birth weight

- MJ is addictive: heavy users experience a withdrawal syndrome as with alcohol and heroin.
-
- Rates of recovery among those seeking treatment are similar to those for alcohol (50%)

2016 study: MJ not associated with Anxiety

- 3-year prospective study
- Results indicate that cannabis use was not associated with increased incidence of any anxiety disorder

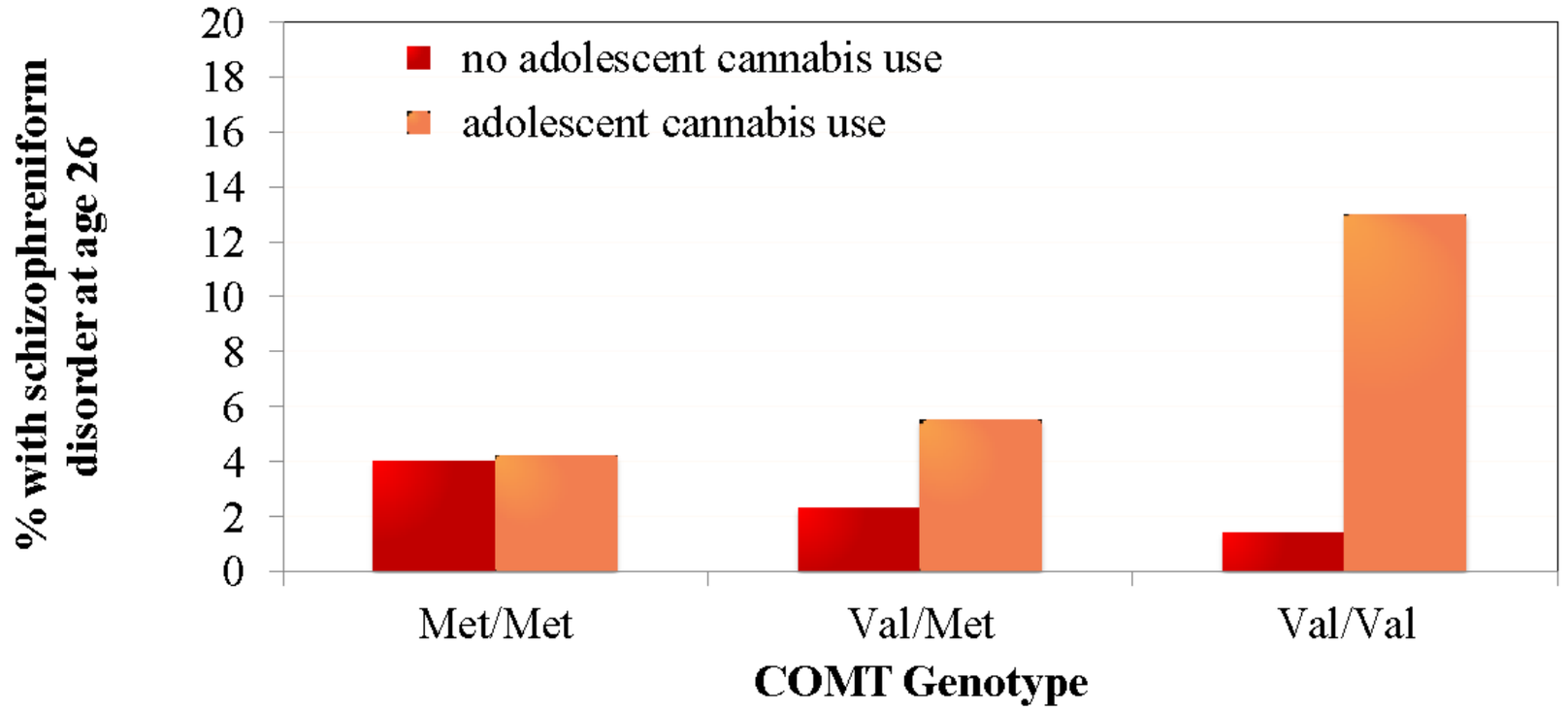
- Any baseline anxiety disorder was not associated with future initiation of cannabis use or onset of a CUD, yet individuals with baseline panic disorder were more prone to initiate cannabis use at follow-up possibly as a means of self-medication.

- Concluded that cannabis use and CUDs are not associated with increased incidence of most anxiety disorders and inversely, most anxiety disorders are not associated with increased incidence of cannabis use or CUDs.

Daniel Feingold, et al., 2016

Risk of Adult Psychosis

Adolescent Cannabis Use Increases the Risk for Adult Psychosis in Genetically Vulnerable Individuals



Source: Caspi, A. et al., Biol. Psychiatry, 57: 1117-1127; 2005.

Longitudinal studies:

- An increased risk of developing schizophrenia or mood disorders (depression) in adulthood if individuals regularly smoked marijuana during adolescence.

- Especially if any family history of mental illness (i.e., “genetics provided the loaded gun and marijuana pulled the trigger”). Also, mental illness, among those at risk, tended to show up earlier with marijuana use.

- Regular MJ use during adolescence found to increase risk 2 to 5 x of developing psychosis, schizophrenia, & depression in adulthood.

Malone DT et al., 2010

Cannabis and Schizophrenia

- 2017 study of 1200 schiz.: people who had consumed cannabis before age 18 developed schizophrenia approximately 10 years earlier than others.

- The higher the frequency of use, the earlier the age of schizophrenia onset. Cannabis use during puberty is a major risk factor for schizophrenia. The more [cannabis] you take—and the higher the potency—the greater the risk

- High-potency cannabis—approximately 16 % THC —was involved in 24 percent of all cases of a first episode of psychosis.

- 2021 review: cannabis-schizophrenia association is partially causal and also stems partly from shared familial/genetic risk factors

Moore TH, et al., 2007; Matthew Large, et al., 2011

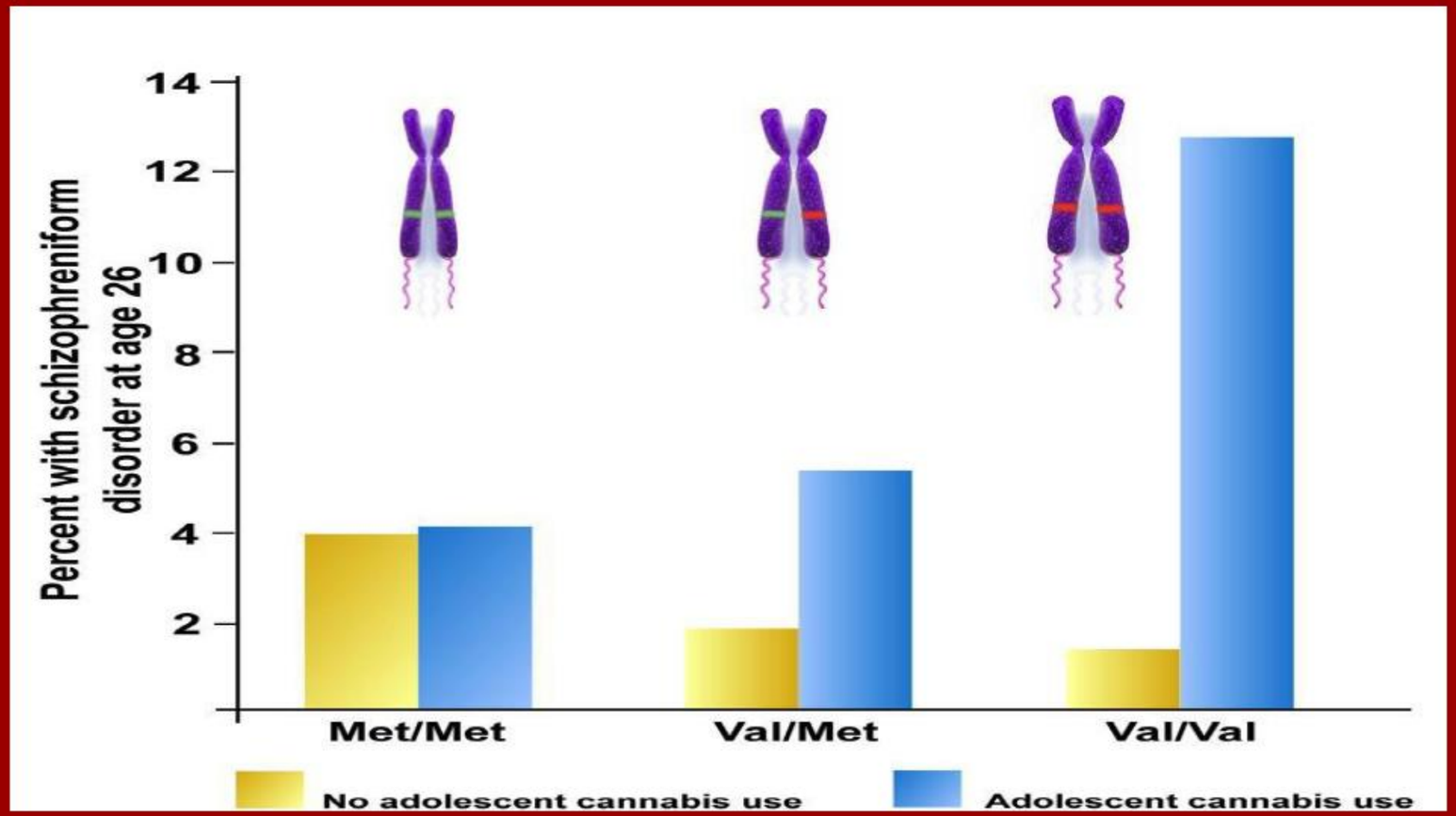
Schizophrenia

- Early and frequent cannabis use is a cause of psychosis, which interacts with other risk factors such as family history of psychosis, history of childhood abuse and expression of the COMT and AKT1 genes.

- THC effects neurodevelopment via immune processes; schizophrenia is now suspected of being due to immune driven synaptic over-pruning

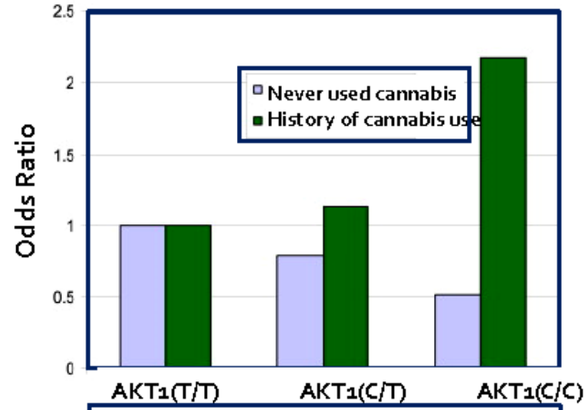
- There is a strong resemblance between the acute and transient effects of cannabis use and symptoms of psychosis, including impaired memory, cognition and processing of external stimuli.

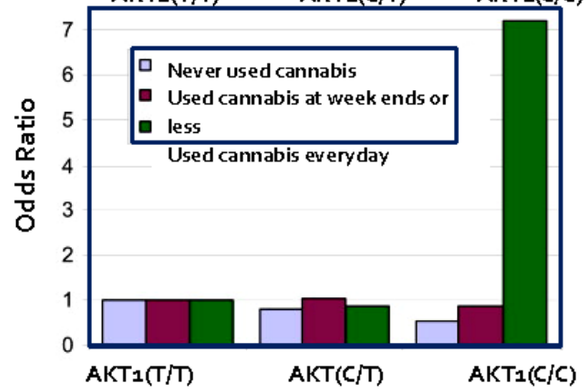
Adolescents who Smoke Cannabis have Increased Risk of Schizophreniform Disorder, Depending on the COMT Gene



Caspi et al., 2005

Regular Cannabis Use Increases Schizophrenia Risk in those with AKT1 rs2494732 genotype

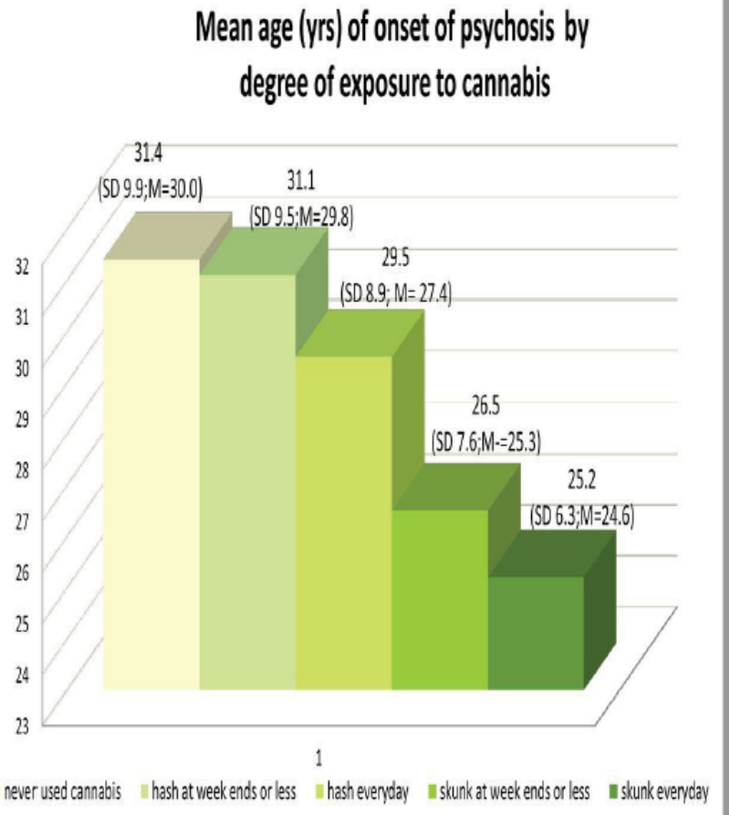




AKT1 genotype does not predict History of Cannabis use (p=0.772) GXE multiplicative model: p*=0.014

Di Forti et al., Biological Psychiatry, 2012.

High Potency Cannabis and Earlier Onset of Psychosis



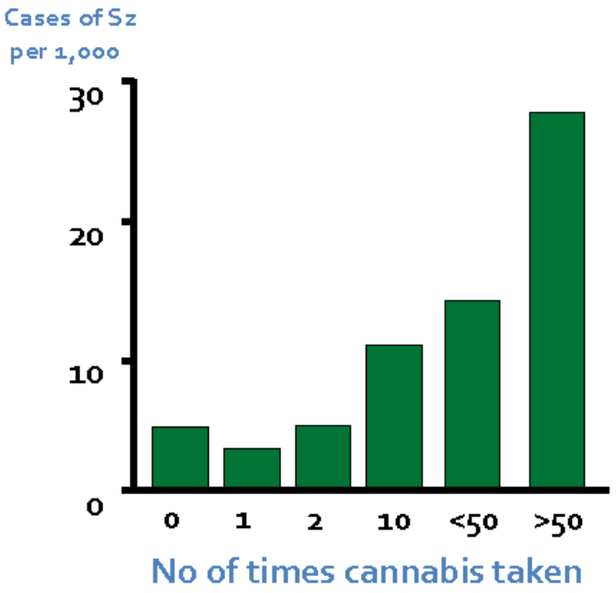
Di Forti M et al. Schizophr Bull 2013;schbul.sbt181

DiForti, M, et al. (2013) – 6 year earlier onset of psychosis if daily use started age 15 or less

Cannabis-Associated Psychosis

CANNABIS AND SCHIZOPHRENIA

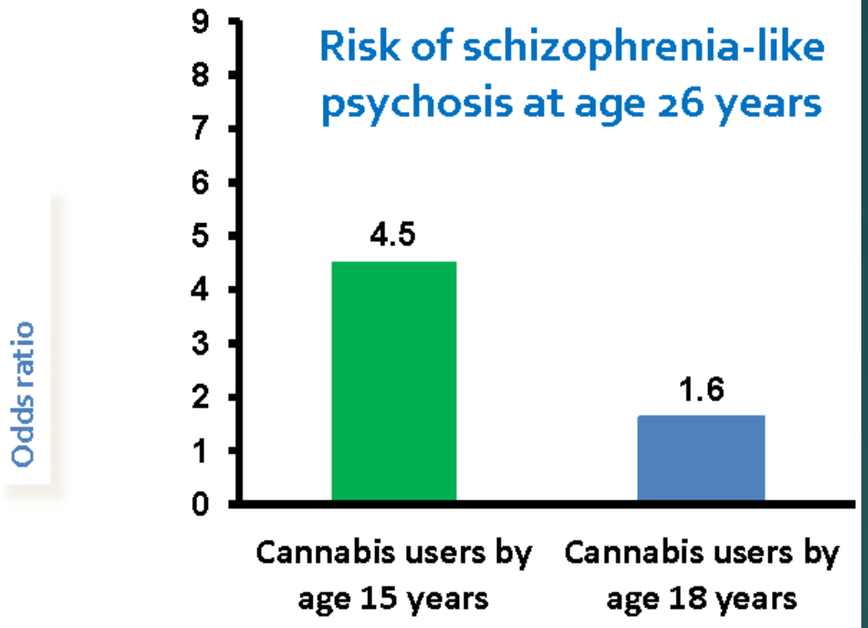
Study of Swedish Conscripts (n=45570)



Andréasson et al Lancet, 1987.

CANNABIS AND SCHIZOPHRENIA-Like

Longitudinal prospective Dunedin study (n=1037)



Arseneault et al BMJ 2002

Increased frequency of use

Early use onset

Skunk & earlier Psychosis onset

- "Skunk" (16% THC) Marijuana and Risk of Psychosis
- DiForti, M, et al. (2013) – 6 year earlier onset of psychosis if daily use started age 15 or less
- Di Forti, M et al. (2015): English "Skunk" pot is high potency pot ~ 16% THC, low CBD
- N = 410 first episode psychosis, 370 controls:
  - Occasional or weekend use increased psychosis risk 3X more than non users
  - Daily use increased risk is 5X more than non users
- Welch, KA, et al (2010) – increased ventricular volume associated with marijuana use in 16-25 yo

Schizophrenia and Cannabis

- We also know that cannabis use by people with established psychotic disorder can exacerbate symptoms.
- Overall, the evidence suggests cannabis use will bring forward diagnosis of psychosis by an average of 2.7 years.
- The risk of developing schizophrenia increases with the duration and dose of cannabis use.
- Regular cannabis users have double the schiz risk of non-users.
- Those who have used cannabis at some point in their life have a 40% increased risk compared with non-users.

Normal cannabinoid receptors in the brain

- An important function of cannabinoid receptors is the regulation of GABA, an inhibitory neurotransmitter.
- Depression of GABA release impacts plasticity In the hippocampus, anxiety & aggression in the amygdala, motor function in the basal ganglia; pain processing in the hindbrain.
- Endocannabinoid-dependent long-term depression (LTD) in the striatum and nucleus accumbens is involved in habit learning and addiction

THC messes up dendrites (neuron receptors)

- In rats, adolescent THC exposure results in distinct proximate and long-term alterations of dendritic architecture.

- Specifically, THC exposure disrupted normal neurodevelopmental processes by inducing premature pruning of dendritic spines and atrophy of dendritic arbors in early adulthood.

- In human adolescents, Cannabis use has been linked to enduring impairments of executive functioning and impulse control.

2021 study: cannabis use in adolescence

Matthew D. Albaugh, et al., 2021

- Total of 799 school survey study participants were identified who reported being cannabis naive at study baseline and had behavioral and neuroimaging data available at baseline and 5-year follow-up.

- Using 1598 magnetic resonance images from 799 participants revealed that cannabis use was associated with accelerated age-related cortical thinning from 14 to 19 years of age in predominantly prefrontal regions.

- Baseline cortical thickness was not associated with lifetime cannabis use at 5-year follow-up, suggesting that the observed neuroanatomical associations with lifetime cannabis use were not associated with preexisting differences in brain structure.

2021 study: cannabis use in adolescence

- At 5 year follow-up, cannabis use (from 0 to >40 uses) was negatively associated with thickness in left and right prefrontal areas;

- Cannabis use in a dose-dependent fashion such that greater use, from baseline to follow-up, was associated with increased thinning; thinning in right prefrontal cortices, from baseline to follow-up, was associated with attentional impulsiveness at follow-up.

- Cannabis use during middle to late adolescence may be associated with altered cerebral cortical development, particularly in regions rich in cannabinoid 1 receptors.

Depression vs. NCD

Test Feature	Depression	NCD
Frequent task reminder	Unusual	Needed
Memory complaint	Extreme *	Infrequent
Rate of forgetting	Normal	Rapid
Incidental Memory	Intact	Impaired
Task effort	Poor *	Good
Memory cueing	Helpful	Unhelpful
“Don’t Know” comment	Usual *	Unusual
Recognition Memory	Intact	Impaired
Digit Span	>5	<5

What works in treating cognitive deficits?

Omega 3 prevents the onset of psychotic disorder and reduced rates of non-psychotic Axis I disorders

- 12 week course of Omega-3 significantly reduced the risk of progression to psychotic disorder during a 7 year follow-up period.
- Significantly reduced rate of prescription of antipsychotic medication.
- The majority of the individuals from the omega-3 group did not show severe functional impairment, were employed full-time, and no longer experienced attenuated psychotic symptoms at follow-up
- Other studies are inconsistent.

Mei-Chi Hsu, et al., 2020

Do Antipsychotics Affect Cognition?

- Typical Antipsychotics: Possible improvement
  - attention on CPT – sx reduction effect?
- No effect or possibly worsen
  - WCST
  - Trails
  - Simple reaction time
  - Manual motor tests
- Meta-analysis by Woodward, Purdon, Meltzer & Zald (2005): Atypicals (Clozapine, Olanzapine, Seroquel, Risperidone) may have a mild cognitive remediation effect & are superior to typicals in improving cognition: Learning and Processing Speed ↑↑
- But no compelling evidence of benefit

Early CBT Reduces Psychosis

- For young people who are at high risk of developing psychosis: significantly reduce their chances of going on to develop a full-blown psychotic illness by getting early access to cognitive behavioral therapy (CBT)

- The risk of developing psychosis was more than halved for those receiving CBT at six, 12 and 18-24 months after treatment started.

- CBT for psychosis prevention places a heavy emphasis on ‘normalizing’ and de-stigmatizing experiences such as hearing voices or having paranoid thoughts.

CBTp: Cognitive Behavioral Therapy for Psychosis

- Cognitive behavioral therapy for psychosis (CBTp):
  - shows reduction in brain response to social threat,
  - increased connectivity between dorsolateral prefrontal cortex (DLPFC) and amygdala following CBTp

CogSmart: Cognitive Training

- Cognitive Training has been used for many years in the field of TBI

- CogSmart (UCSD, E. Twamley):
- 12-week, group-based, manualized, compensatory cognitive training intervention
- Targeting prospective memory, attention, learning/memory, and executive functioning.
- The intervention focused on compensatory strategies, such as calendar use, self-talk, note taking, and a 6-step problem-solving method
- Does not require computers

CogSmart Manuals are available:

- Cognitive Training (both group and individual formats)

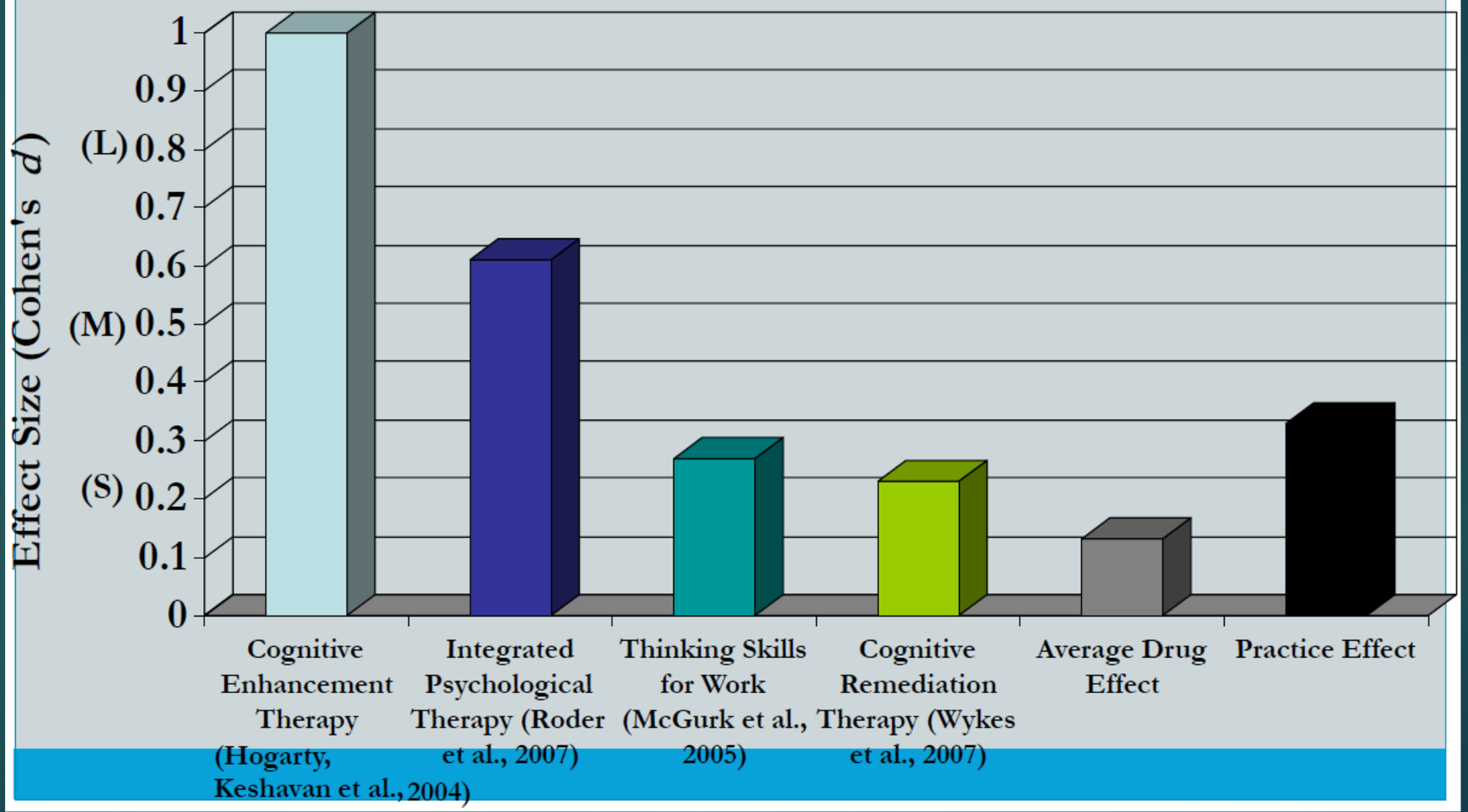
- Cognitive Symptom Management & Rehabilitation Therapy for mild to moderate TBI

- Contact: etwamley@ucsd.edu

www.charlesjvellaphd.com:

- Vella Executive Functioning Questionnaire (unnormed)
- Executive Skills & Metacognitive Therapy (87 pp; based on Twamley)

Effects of Cognitive Remediation on Cognition in Schizophrenia



Cognitive Enhancement Therapy (G. Hogarty)

Principles in CET:

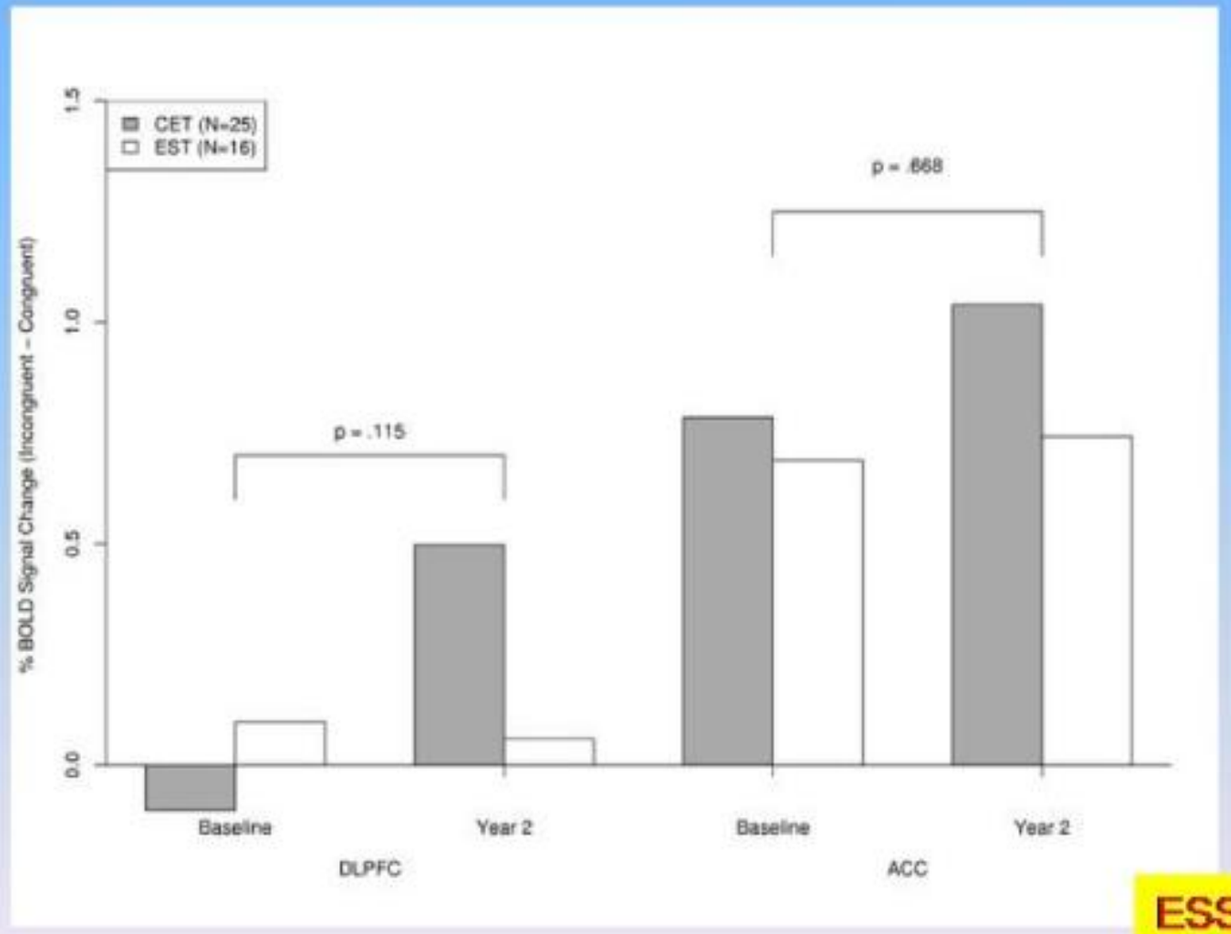
- **Repetitive, individualized** to patient s cognitive style, ability and progress

  - **Bottom-up** (non-social followed by social cognition) and Top-down approaches in parallel

  - **Multi-modal:** judicious combination of cognitive remediation with motivation enhancement, CBT, individual support, psycho ed and stress- management (the cadillac approach)

Increased DLPFC and cingulate activation with a cognitive control task after CET

Cho, Eack and Keshavan
In preparation



ESSENCE study

Does CET change brain function?

Currently available Cognitive Rehab for Schizophrenia Programs

- CET: Cognitive Enhancement Therapy;
- NET: Neurocognitive Enhancement Therapy; WT: Work Therapy;
- TCT: Target Cognitive Training; PSG: Problem Solving Group;
- MTG: Memory Training Group;
- CRT: Cognitive Remediation Therapy;
- EG: Experimental Group;
- CNR: Computer-aided Neurocognitive Remediation;
- IT: Immediate Treatment;
- EST: Enriched Supportive Therapy;
- CR: Cognitive Remediation;
- CAT: Computer Assisted Training;
- CDg: Cognitive Differentiation Program Group Condition; Cdi: Individual Condition

A Meta-Analysis of Cognitive Remediation for Schizophrenia

- The 2011 meta-analysis (2,104 participants) of 40 studies yielded durable effects on global cognition and functioning
- Cognitive remediation therapy was more effective when patients were clinically stable.
- Almost all cognitive domains demonstrated significant effect sizes from 0.25 to 0.65.

Til Wykes, et al., *Am J Psychiatry 2011*

A. Vita, et al. 2021: Effectiveness of Cognitive Remediation in Schizophrenia

- Comprehensive review of 130 research studies from 2011-2020 of cognitive remediation in Schizophrenia

- CR is an evidence-based intervention that is effective – small-moderate effect size; given
  - An active and trained therapist,
  - structured development of cognitive strategies,
  - integration with psychosocial rehabilitation were crucial ingredients of efficacy.

Effectiveness of Cognitive Remediation in Schizophrenia

- Results revealed a significant role of education, premorbid IQ, and symptom severity, indicating that patients who are clinically compromised are valid candidates for CR.
- The effectiveness of CR does not appear to be overly influenced by patient-associated characteristics, suggesting that it is a viable option for most individuals with a diagnosis of schizophrenia.

- Conclusions: These findings show that CR is an evidence-based intervention that should be included consistently into clinical guidelines for the treatment of individuals with schizophrenia and implemented more widely in clinical practice.

Multifamily Psychoeducation Groups (MFG)

- William R. McFarlane:
  - Multifamily groups in the Treatment of Severe Psychiatric Disorders

- This TX is an elaboration of models developed by Anderson, Falloon, McFarlane, Goldstein and others.

- Outcome studies report a reduction in annual relapse rates for medicated, community-based people of as much as 75% by using a variety of educational, supportive, and behavioral techniques.

Other Programs

- LEAP® Course - Dr. Xavier Amador: Listen, empathize, agree, partner
- Cognitive Behavior Therapy for Psychosis
- Metacognitive training (MCT) for delusions
- Social Cognitive Training

- National Alliance on Mental Illness (NAMI)

Clinical Implications of Neuropsychological Deficits

- Cognitive deficits underlie adaptive behavior deficits which medications cannot improve
- Improvement in cognition may improve social skills, work skills, etc.
- Cognitive domains of executive functioning, verbal fluency and verbal working memory correlate with recovery from schizophrenia
- Cognitive deficits are related to insight; insight related to treatment compliance
- Cognitive deficits that are related to social perception interfere with learning so that patients cannot benefit from traditional rehab approaches

Take Home Points

- What are cognitive deficits in schizophrenia and bipolar disorder?

  Cognitive deficits are a core feature of both Schiz and BD. They involve Speed, Memory, Attention, Reasoning, & Tact.

- Do they precede the illness, persist and/or progress?

  Cognitive deficits are pervasive, precede and persist over the course of the illness, predict outcome, and progress early in the illness.

- What causes the deficits?

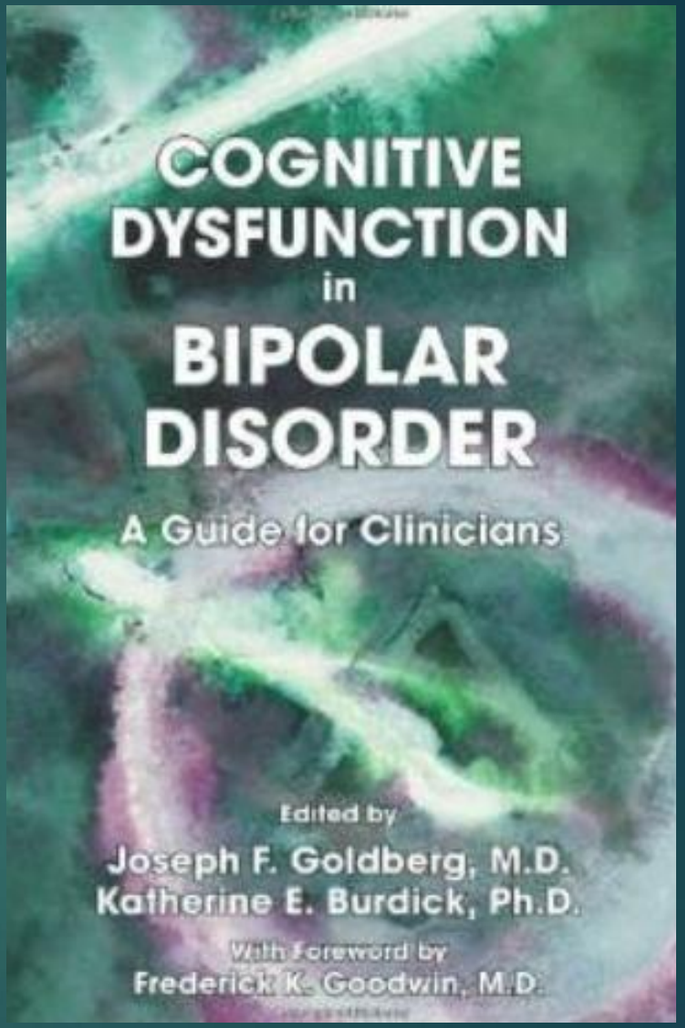
  Cognitive deficits are caused by altered brain anatomy & function, esp. in frontal and limbic areas.

- What works in treating the cognitive deficits?

  Cognitive deficits may be improved with cognitive remediation; but more research needed.

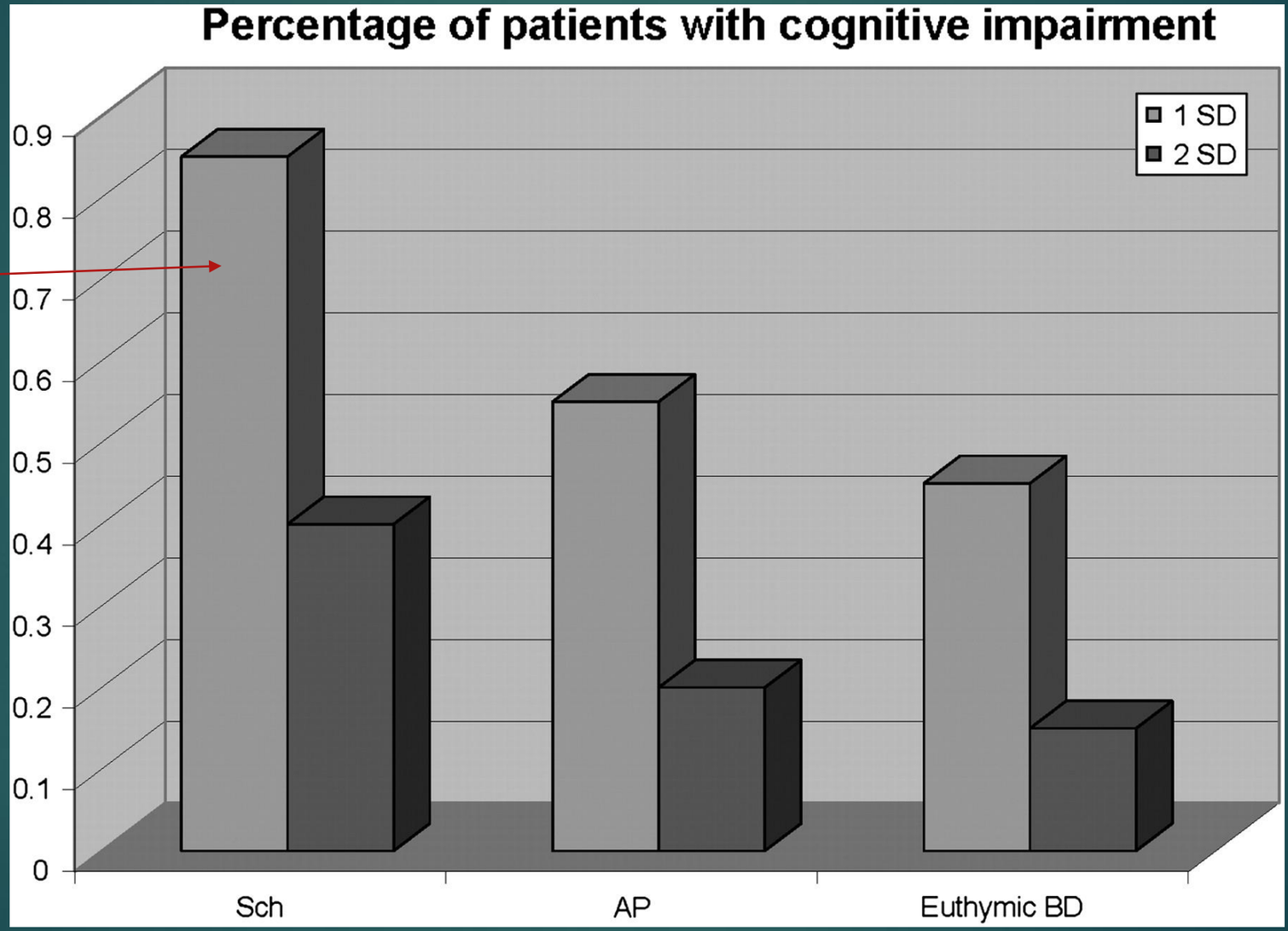
Bipolar Disorder: The Book

- **Cognitive Dysfunction in Bipolar Disorder: A Guide for Clinicians by** Joseph F. Goldberg & Katherine E. Burdick, 2008



Prevalence of Cognitive Impairment in Schizophrenia, Affective Psychoses, & Euthymic BD.

2 sd



Bora E et al. Schizophr Bull 2009;36:36-42

Bipolar: Three times more days depressed than manic or hypomanic

- Depression represents the predominant abnormal mood state for treated outpatient bipolars.

- Percentages of time spent ill for bipolar I versus II patients were:
  - euthymia 48% versus 50%;
  - depression 36% versus 37%;
  - hypomania 12% versus 10%;
  - mania 1% versus 0.2%;
  - cycling 4% versus 3%.

- A 13 year study found that people with bipolar disorder spend an average of one-third of the weeks of their lives in states of depression (Judd et al. 2002.)

Kupka RW, et al. 2007

Bipolar Genetics

- Genetic factor
  - 10x more likely to have Bipolar if you have a close relative that does
  - Concordance rate is 69% in identical twins and 13% in fraternal twins: Same if reared together as if reared apart
  - Evidence of minor EF deficits in first degree relatives
  - Structural brain abnormalities (ventricular enlargement)

Early Onset Bipolar = neurotoxic

- Patients with early-onset bipolar disorder are at risk for a host of poor outcomes:
  - notably rapid cycling,
  - lengthy episodes,
  - polarity switches,
  - deteriorations in functioning.
- There are neurotoxic effects of repeated episodes on the developing juvenile brain
- Clearly need to reduce number of manic episodes to preserve the brain.

Bipolar Disorder

- Depression represents the predominant abnormal mood state for treated outpatient bipolars. 3x more depression than mania
- Highly genetic: 69% in identical twins; minor EF deficits in first degree relatives
- There are neurotoxic effects of repeated episodes on the developing juvenile brain
- Diffuse cognitive dysfunction during the acute phases of bipolar illness; cognitive deficits seem to remit during periods of euthymia,
  - bipolar depression = psychomotor slowing and impairment of memory;
  - hypomania = frontal-executive deficits
  - euthymia = a milder disturbance of attention, memory and executive function.

Neurocognitive Deficits in Bipolar Disorder

- Bipolar disorder produces cognitive deficits, even during periods of symptom remission:
  - Marked deficits in executive-function and verbal learning
  - Worse the more intense the disease process
  - Are persistent, despite psychiatric symptom reduction
- Significantly affect psychosocial functioning

Major Deficit in Bipolar disorder: Executive Functioning

- Executive dysfunction is the main long-term neuropsychological deficit of bipolar disorder.
- All aspects of executive function (planning, abstract concept formation, set shifting) were impaired in symptomatic BD patients.
- May be normal in fully recovered patients with uncomplicated BD.
- Frontal and subcortical hypometabolism in bipolar illness

NP deficits predict Social & Vocational Functioning

- Verbal memory impairments and/or executive dysfunction are associated with:
  - reduced social and vocational functioning in patients with bipolar disorder,
  - even in the absence of manic or depressive symptoms

Martinez-Aran et al., 2004; Dickerson et at., 2004

Meta-Analysis of BD I: Enlarged ventricles & WM Hyperintensities

- N = 98 MRI studies

- Increase size in bilateral ventricles & increased WM hyperintensities (2 most replicated BD1 finding) – mostly in frontal & parietal in deep white
- Increased amygdala volume is prototypical of BD I
- Abnormalities in cerebellum
  - Reduced frontal glial cell count

Kempton, et al., 2008

Schizophrenia and Bipolar Disorder

- Epidemiological, genetic and neuroimaging studies show cognitive deficit similarities between bipolar disorder (BD) and schizophrenia (SZ).

- BD patients show cognitive deficits that are milder but qualitatively similar to those of patients with schizophrenia.

- Remitted BD patients out-performed stable schizophrenia pts. on most cognitive measures but this advantage disappeared when they were acutely symptomatic.

Cognitive Deficits 2

- Most studies point at the presence of diffuse cognitive dysfunction during the acute phases of bipolar illness.
- Most of these cognitive deficits seem to remit during periods of euthymia,
- but some of them may persist in approximately one third of bipolar patients.

Euthymia: normal non-depressed, reasonably positive mood

- BP patients routinely complain of neuropsychological difficulties.
- Euthymia (neutral mood in absence of a depressive or manic cycle) does not equal normal NP function
- Each phase has a characteristic pattern of deficits with disturbance in attention and memory being common across all phases of the illness:
  - bipolar depression = psychomotor slowing and impairment of memory;
  - hypomania = frontal-executive deficits
  - Euthymia = a milder disturbance of attention, memory and executive function.

Euthymia

- 75% of asymptomatic bipolar patients scored:
  - more than one standard deviation below healthy comparison subjects
  - on at least four cognitive measures,
  - suggesting widespread, but relatively mild, neuropsychological dysfunction in euthymic bipolar disorder.

Glahn et al., 2007

Tip #3: Need for NP screening or testing

- Given the known NP deficits in Bipolar disorder, clinicians should routinely do mental status testing (MOCAs) with newly stabilized Bipolar pts and schizophrenia pts.

- Those that have more serious deficits (esp. EF), should receive NP evaluation.

Meta-analytic Study of Manic vs. Euthymic States

- Moderate impairments were evident across a variety of neurocognitive measures in manic BP, including:
  - sustained attention,
  - working memory,
  - language,
  - psychomotor speed,
  - executive-function.

- Euthymic Bipolar disorder characterized by generalized moderate level of neuropsychological impairment with particular marked impairment in verbal learning and memory.

Cognitive deficits not due to psychotropic medications

- Data from neurocognitive performance in unmedicated bipolar patients:
  - Cognitive deficits and underlying abnormalities in neuronal activation in patients with bipolar illness are not primarily attributable to the use of psychotropic medications
  - But Bipolar federal bank examiner on 2000 mg Lithium had severe EF deficit

Bearden et al 2006

Core Feature: Sustained Attention Deficit

- Attention: attentional abnormalities were seen in symptomatic BD patients and persisted in remission in measures of sustained attention and inhibitory control.

- **Conclusions:** Sustained attention deficit may represent a neuropsychological vulnerability marker for bipolar disorder.

L. Clark, *The British Journal of Psychiatry* (2002)

Memory

- Verbal memory is impaired even in euthymic patients

- Visuo-spatial memory deficits were variable depending on the tasks used.

Quraishi S, Frangou S, 2002

Conclusions: Cognition in Bipolar

- Poorer learning and memory, executive functions, psychomotor speed
- Manic state – greatest deficits
- Euthymic State – least deficits
  - Greater deficits on measures of executive function and memory than on measures of attention and speed
- Positive correlation between number of manic episodes and verbal memory, memory retention, and executive functions.

Cognitive Deficits 2

- Diffuse cognitive dysfunction during the acute phases of bipolar illness.
- Deficit levels seem to remit during periods of euthymia
- Some deficits may persist in approximately one third of bipolar patients.

Social Cognitive Deficits in BD

- BD 1 pts have significant impairments in:
  - Identification of primary facial emotions
  - Social perception
  - Mirror neuron firings

Bipolar Course: Mania is bad for your brain

- No cognitive deficit prior to illness onset of BPD
- Evidence of minor EF deficits in first degree relatives
- Positive correlation between number of manic episodes and verbal memory, memory retention, and executive functions.
- Toxic to Brain: Deleterious effects of repeated manic episodes and psychotropic medication on cognitive performance

G. Goodwin, et al., Europ Neuropharm, 2007

BPD is a cognitive disorder with poor functional outcome

- Despite its absence in DSM-5 criteria, neurocognitive dysfunction is a core symptom of bipolar disorder.
- Cognitive deficits are present in BPD during both manic and depressive episodes; they are also present in euthymic pts. These deficits include memory, executive functioning, sustained attention.
- These deficits result in functional decline (diminished occupational, educational, psychosocial, & residential functioning) that persists long past symptomatic recovery in a significant portion of BPD pts.
- 28% are unable to work; 27% live in supervised settings; 30-60% fail to regain full functioning in occupational and social domains.

Good clinical but low functional recovery

- More than 97% of bipolar patients appear to recover clinically within 2 years
- But only 37% recover functionally during the same time period.
- A significant contributor to the substantial difference is residual cognitive dysfunction.

Statistics

- Only about 40% of patients are fully adherent with medication regimens in the year following an episode. EF dysfunction.

- While antidepressants may be effective in some individuals with bipolar disorder, they can precipitate a rapid mood switch from depression to mania, a phenomenon also known as treatment-emergent mania (5-20%).

Lithium reduces AD Risk and increases REST Protein

- Bipolar disorder is associated with increased risk for NCD.
- Lithium treatment reduces the prevalence of Alzheimer's disease in patients with bipolar disorder to levels in the general elderly population.
- Lithium increases REST protein, which is one of the biological bases of Cognitive Reserve

Antidepressants: Increase Hippocampal Volume

Neurogenesis in mood disorders

- Psychotropic medications used in treating those disorders are neuroprotective and induce neurogenesis
- All antidepressant drugs and ECT increase neurogenesis & BDNF.
- Mood stabilizers such as lithium and valproate increase neurogenesis.

H. Nasrallah, 2008; Reif, et. al., 2006

Statistics 4

- Stressful life events and high levels of familial expressed emotion are robust predictors of mood recurrences and delayed episode recovery in bipolar illness.

- Individual, family, group, and systematic care treatments are effective in combination with pharmacotherapy in delaying relapses, stabilizing episodes, and reducing episode length.

Conclusions: Neurocognitive Deficits in Bipolar Disorder

- Individuals with bipolar affective disorder have cognitive impairments, even during periods of symptom remission (euthymic state).
- While these cognitive impairments are typically less pronounced than those found in other psychiatric (e.g. schizophrenia) or neurological (e.g. Alzheimer's dementia) illnesses.
- Reduced neuropsychological ability significantly affects bipolar patients' psychosocial functioning
- Acute manic phases have most impaired NP deficits

NP testing in Major Depression

- Effort abnormal: Fail effort measures; NP is normal if pass effort measures
- Processing speed, attention↓↓
- Recognition memory normal
- Normal confrontation naming and fluency; conversation fluid
- Variable and inconsistent performance
- Tearfulness & affect; not apathy
- Frequent “I don’t know”

Schizophrenia vs Psychotic Bipolar

Margo W.Menkes, et al., 2018

- Neuropsychological impairment in the early stage of psychosis is more severe in schizophrenia.

- Psychotic bipolar disorder: not greater cognitive decline between illness stages.

- Schizophrenia is associated with relatively greater neurodevelopmental involvement,

Schizophrenia vs Psychotic Bipolar

- Main role of speed-dependent neurocognitive functioning: Speed of processing and psychomotor coordination are impaired.

- Episodic memory deficits are consistently documented as a core aspect of cognitive dysfunction in schizophrenia, present from the onset of the illness and strongly associated with functional disability.

- There is a central deficit in dorsolateral prefrontal cortex (DLPFC) function.

Schizophrenia vs Bipolar

- Cognitive impairment is reliably present in the majority of patients, independent of such positive symptoms as delusions and hallucinations, and a major cause of poor social and vocational outcome.

- Cognitive impairments in schizophrenia are not epiphenomena. That is, they are not secondary to psychological issues that involve delusions, distracting effects of hallucinations, or gross motivational defects.

- Presence of lack of awareness of illness (anosognosia).

Schizophrenia vs Bipolar

- First, correlations between psych. symptoms and cognition are weak in schizophrenia and very strong in bipolar disorder.

- Second, critical impairments in working memory and executive functions in schizophrenia do not respond to teaching or cognitive rehabilitation to a marked degree.

- Psych. symptoms and cognition are dissociated: A study of clozapine has found that while symptoms showed significant improvement over a one-year interval, cognitive impairment remained stable and marked.

Schizophrenia vs Bipolar

- Bipolar: Is more state-like and thus most likely to be present when psychiatric symptoms are in evidence (e.g., dysphoria, anhedonia, anergia in depression, grandiosity, expansiveness, pressured speech, racing thoughts, gross overactivity in mania). Cognition waxes and wanes in concert with the clinical symptoms of bipolar disorder.

- Cognitive impairment in schizophrenia: more trait-like: stable and lifelong. It does not remit, even if other symptoms like hallucinations and delusions are significantly reduced.

- Schizophrenia: cognitive deficits in EF & attention prior to the onset of the disorder. These become pronounced around the time the illness commences, after which they remain stable over many years.

Schizophrenia vs Bipolar

- Long-term memory involving the acquisition and recall of new information may be impaired at relatively severe levels. Patients with schizophrenia also show reduced mental speed and reaction time.
- This pattern of deficits implicates frontal-temporal regions and their Schiz interconnectivity. Working memory may be the core deficit in schizophrenia in that it is present irrespective of whether IQ is compromised or preserved
- Exhibit a 10-point decline of intelligence once their illness begins. They have normal or near normal IQ?s premorbidly but, even during the early phases of their illness, exhibit a marked reduction in intellectual function. Bipolars maintain their IQ level
- Vocational Rehab only works for 27% of individuals with schizophrenia, and of the remaining, only 30-50% of those who were ‘successes’ are working two years later.
- Vocational rehabilitation as “prosthesis for the frontal lobe”,

Schizophrenia vs Bipolar

- Executive Function deficit is the most important factor in determining how well someone functions in the community.

- People with schizophrenia and people with social anhedonia exhibit decreased anticipatory pleasure and have similar difficulties in projecting themselves into the future (prospection).

- Premorbid generalized cognitive impairment in schizophrenia that worsens throughout development, and stabilizes by the first-episode of psychosis, suggesting a neurodevelopmental course

Schizophrenia vs Bipolar

- Cognitive impairments are most severe in schizophrenia, intermediate in bipolar disorder, and the least severe in psychotic depression. In all groups, cognitive deficits are associated with poorer functional outcome.

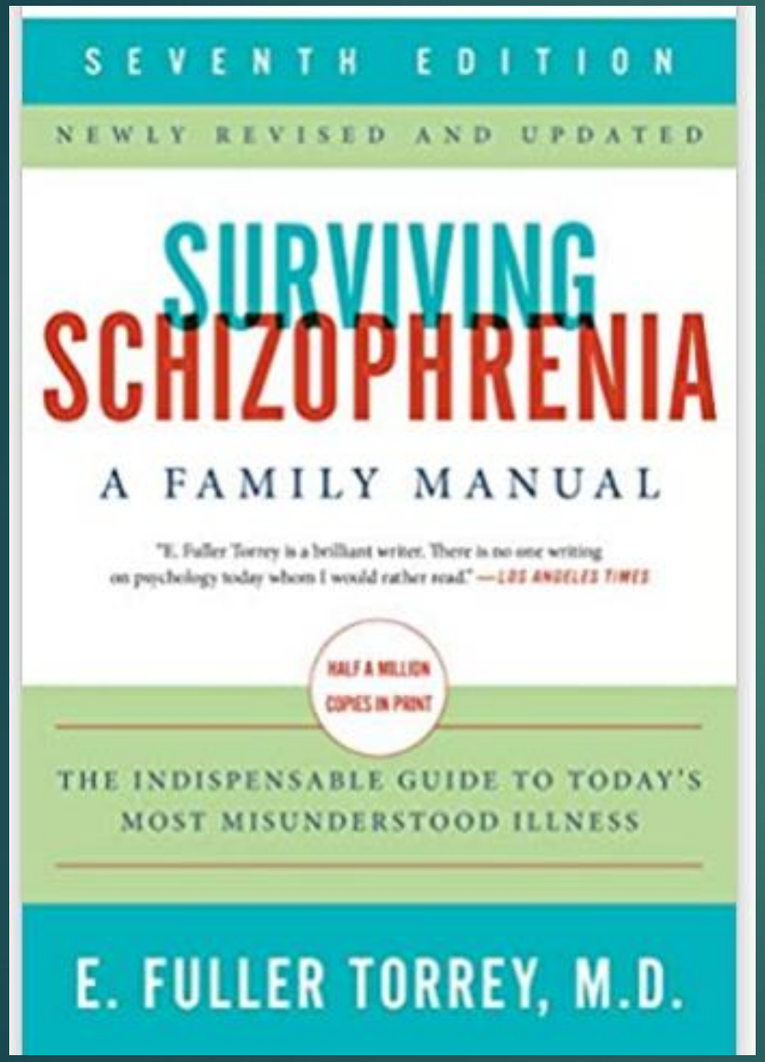
- The generalized deficit is the clearest and most reliable signal, data suggests specific deficits in verbal memory across all groups, specific processing speed impairments in schizophrenia and executive functioning impairments in bipolar disorder.

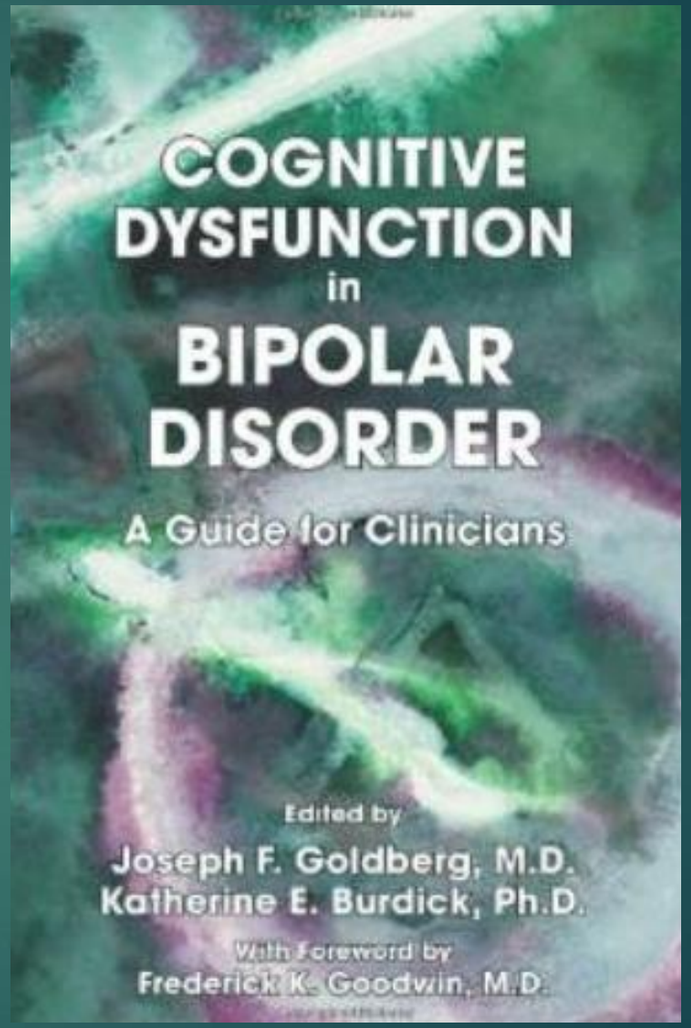
- Volumes of the DLPFC, Inferior frontal gyrus, hippocampus, and white matter are associated with the global cognitive impairment seen in schizophrenia

Tip #4: NP recommendations:
Schiz & BP pts are not Cognitively Normal

- Once symptomatically stable, all Schiz and BP pts. should receive a MoCA (http://www.mocatest.org).
- If MoCA (especially Executive Functioning (EF) items) are impaired (<25), then refer for fuller NP assessment.
- If Schiz & BP pts. have significantly impaired EF, then need more supervision recommendations
- Psychiatry departments should have Cognitive Rehabilitation groups; most significant psychiatric conditions (Schz, BP, MDD, BPD, ADHD) have impaired EF; meds do not improve EF

Required reading





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