Schizophrenia and Cognition

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UCLA

Disclosures

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Overview: Cognitive Deficits in Schizophrenia

- Severity?
- Domains affected and pattern of impairment: an introduction
- “Premorbid” function and course of cognitive deficits
- Putative mechanisms underlying cognitive impairment in schizophrenia

Severity of Deficits in Schizophrenia

- Heinrichs & Zakzanis 1998: d = .46-1.41
  - Meta-analysis
- CATIE Composite Score: d = 1.59
  - N = 1212, mean of 5 domains constructed from 19 variables
  - Relative to published norms
- First Episode Global Score: d = 1.53
  - N = 94, mean of 6 domains constructed from 46 variables
- Some studies suggest greater deficit (2-3SD) but likely psychometric challenges

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What are those domains?

- Debate: “g” vs “g_s”
- Between 5 and 12 different “factors” or constructs have been identified to underlie “global” cognitive ability
  - Q: What is intelligence?
  - A: What the intelligence test measures
- Different authors advocate different ways to slice the cognitive pie

The MATRICS Miracle!

- Consensus conferences and Rand Panel methods actually yielded consensus among neuropsychologists
- Agreement on cognitive domains to be assessed
- Some said it couldn't be done!
- Like herding sheep?

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Rare footage of consensus process

no animals were harmed in production of this slide

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Cognitive Domain Descriptions

- Existing literature can be confusing with respect to terminology if you're not familiar with the background…
- Particularly confusing are labels affixed to various measures of "attention", "executive function", "speed of processing", "reasoning and problem solving", "cognitive control", "working memory"
- There is NOT a simple one-to-one or part-whole correspondence between tests and domains

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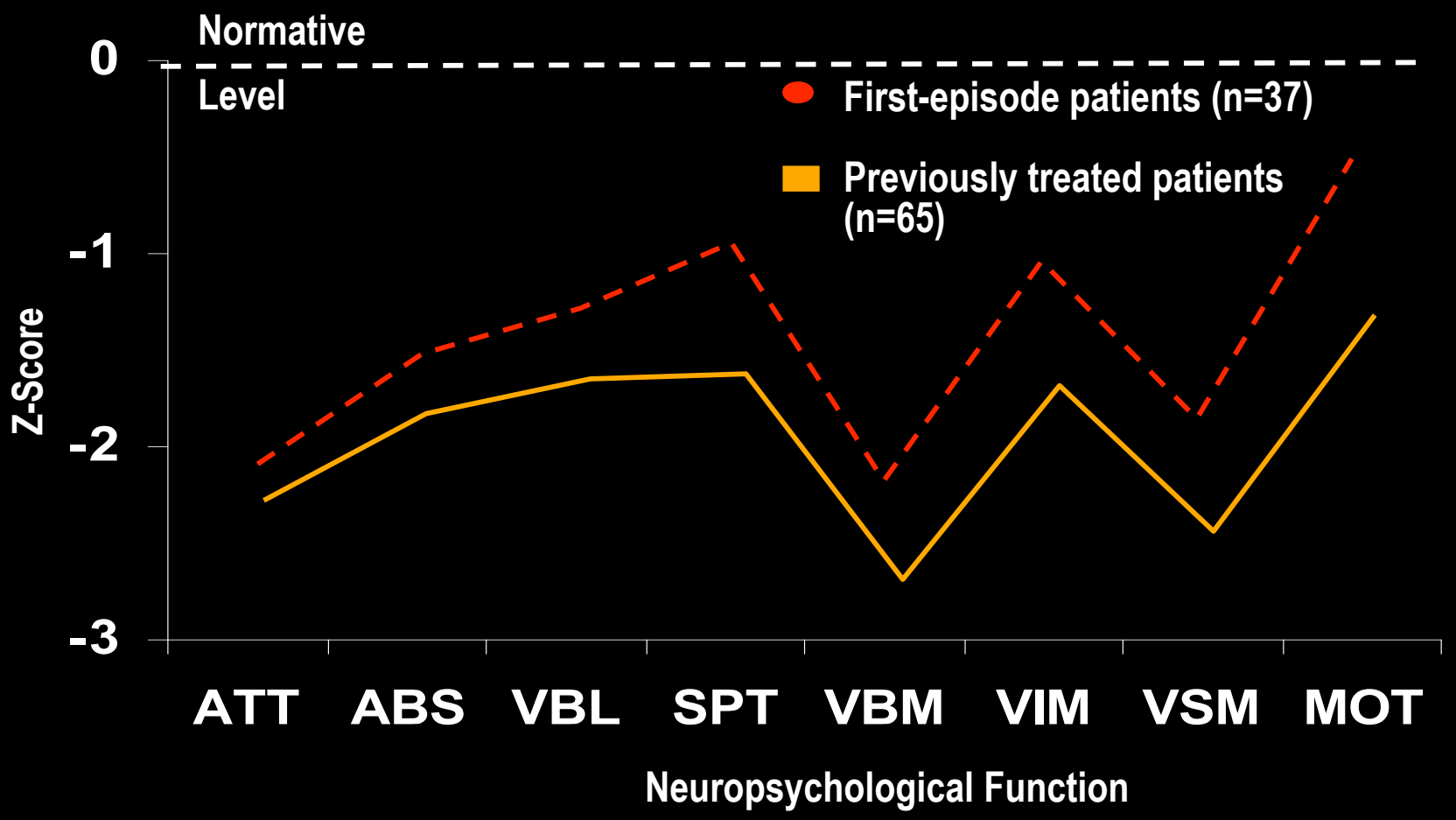
Saykin et al 1994



ATT=attention vigilance. ABS=abstraction-flexibility. VBL=verbal intelligence and language function. SPT=spatial organization. VBM=verbal memory and learning. VIM=visual memory. VSM=speeded visual-motor processing and attention. MOT=fine manual motor functions

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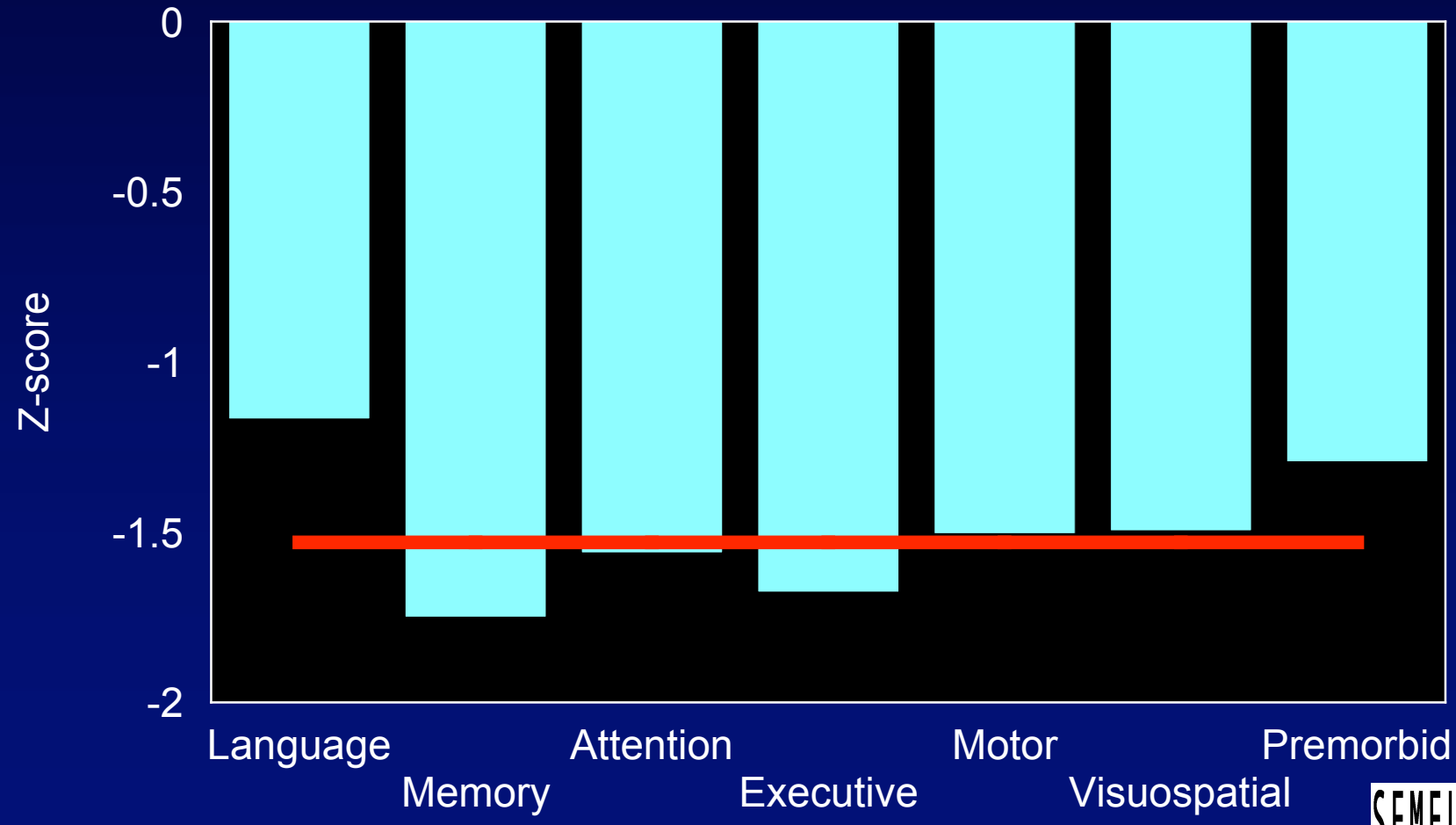
Profile of Neurocognitive Deficits in First Episode Schizophrenia: Stable Baseline



Bilder et al., Am J Psychiatry, 2000

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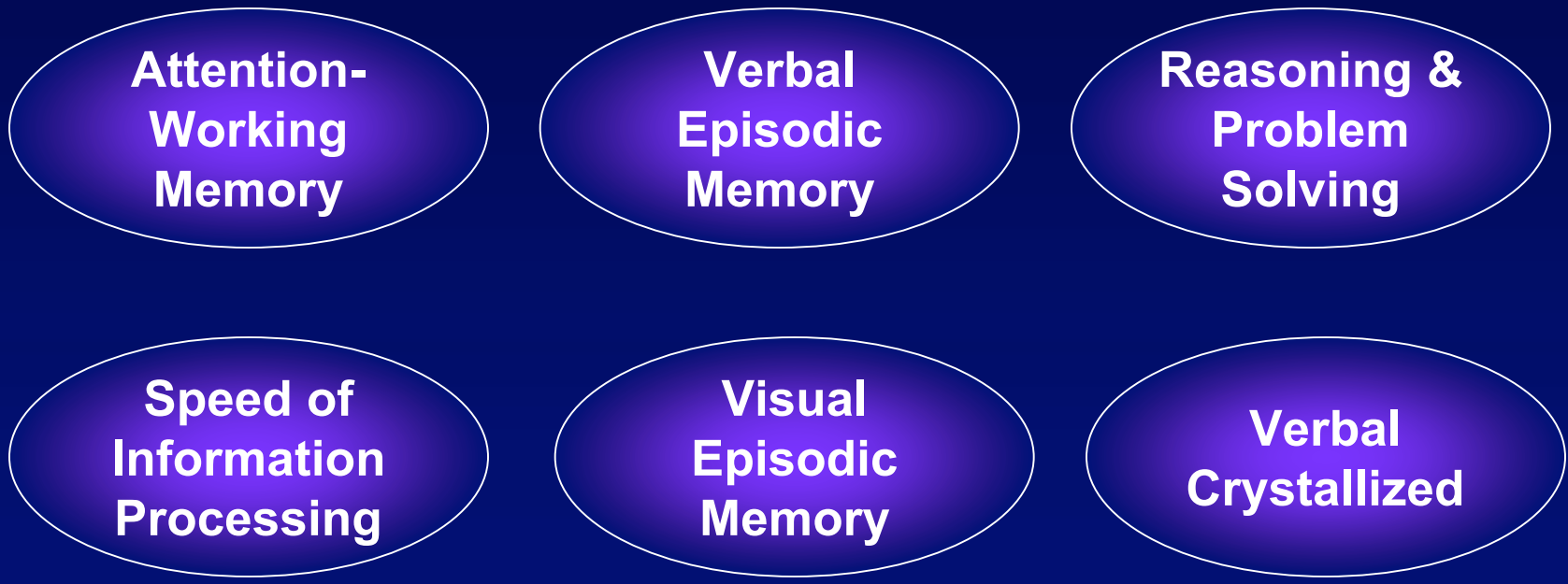
Domains in Schizophrenia: Glasdjo et al. 2004 CFA (based on 20 tests, 209 patients)



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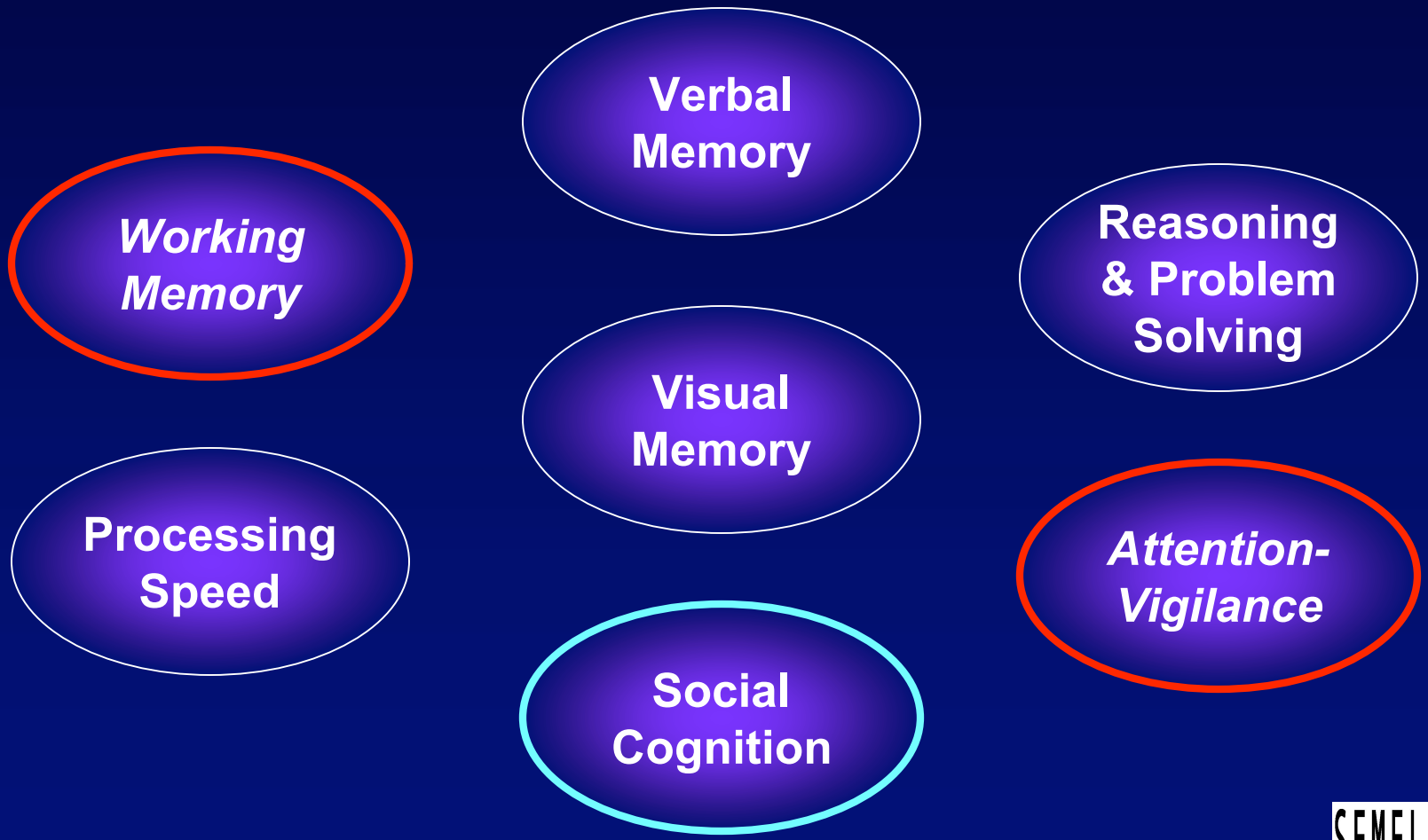
Domains Important in Schizophrenia: MATRICS Consensus



Nuechterlein et al 2004

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Speed of Processing

- Examples include (from MATRICS)
  - Category Fluency
  - Symbol-Coding
  - Trail Making A
- Emphasis: rapidity in execution of cognitive tests, usually demanding attention maintenance and flexibility, initiation of action
- Note: some literature might see fluency as “executive” or “language”, symbol coding and Trails A as “attentional”

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Attention/Vigilance

- Continuous Performance Tests
  - CPT-IP
  - 3-7 CPT
  - Degraded Stimulus CPT
- Sustained attention to rapidly presented target stimuli, variable degrees of working memory maintenance and perceptual demands
- Some studies saw other tests, like span, coding, as measures of ‘attention’

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Working Memory

  - Letter-Number Span/Sequencing (3)
  - WMS-III Spatial Span
  - Spatial Delayed Response Task
- Capacity to register and then maintain information on mind, update with new information, and/or manipulate that information to produce a response
- Note: some human tests (sequencing) emphasize “manipulation” more than maintenance that was central in monkey WM studies (Goldman-Rakic)

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Verbal, Visual Learning and Memory

- HVLT-R (list learning)
- NAB - Daily Living Memory
- BVMT-R (visual patterns)
- NAB - Shape Learning

- All require encoding of new material, recall and/or recognition after a delay

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Reasoning and Problem Solving

- NAB – Mazes
- WAIS-III Block Design
- BACS - Tower of London

- Require planning (strategy) to achieve a solution, and execution of the plan
- Note: this differs somewhat from other definitions of “executive” function, less emphasis on “switching” sets, response to conflict, or perseveration of previous response patterns (e.g., WCST, Trails B, resopnse inhibition tests [Stroop], etc.); no “abstraction” or conceptual categorization

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Social Cognition

  - MSCEIT - Managing Emotions
  - MSCEIT - Perceiving Emotions
- These are 2 of 4 branches of “emotional intelligence” (understanding emotions, facilitating thought are others)
- Some alternate concepts include “Theory of Mind”, emotional expression versus perception

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COURSE OF COGNITIVE DEFICITS IN SCHIZOPHRENA

When does it begin?

- During 2nd trimester of gestation?
  - Indirect evidence: conclusions from studies of neural migration deficits that have been difficult to replicate
- In the perinatal period
  - Direct evidence of increased obstetric complications in those who developed scz
- By one year of age
  - Direct evidence based on home movies comparing to-be ill with never-ill siblings, showing deficits of motor behavior and emotional expression

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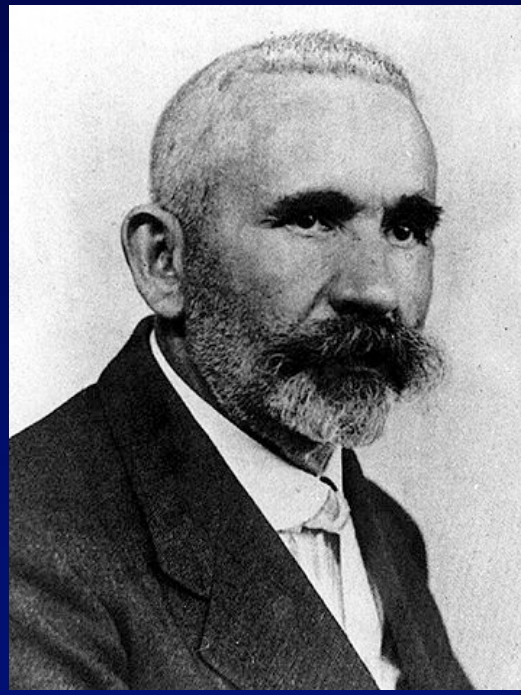
Dementia Praecox: The Old Clinical Evidence

- 10-15% of patients ⇒ 'defect state'
- Milder deterioration affecting up to 50%
  - Bleuler, 1972; Ciompi 1979, 1980; Huber et al., 1975
- Functional decline maximal in first 5 years
  - Abrahamson, 1983: Ciompi 1980; McGlashan, 1988; Williams et al., 1985



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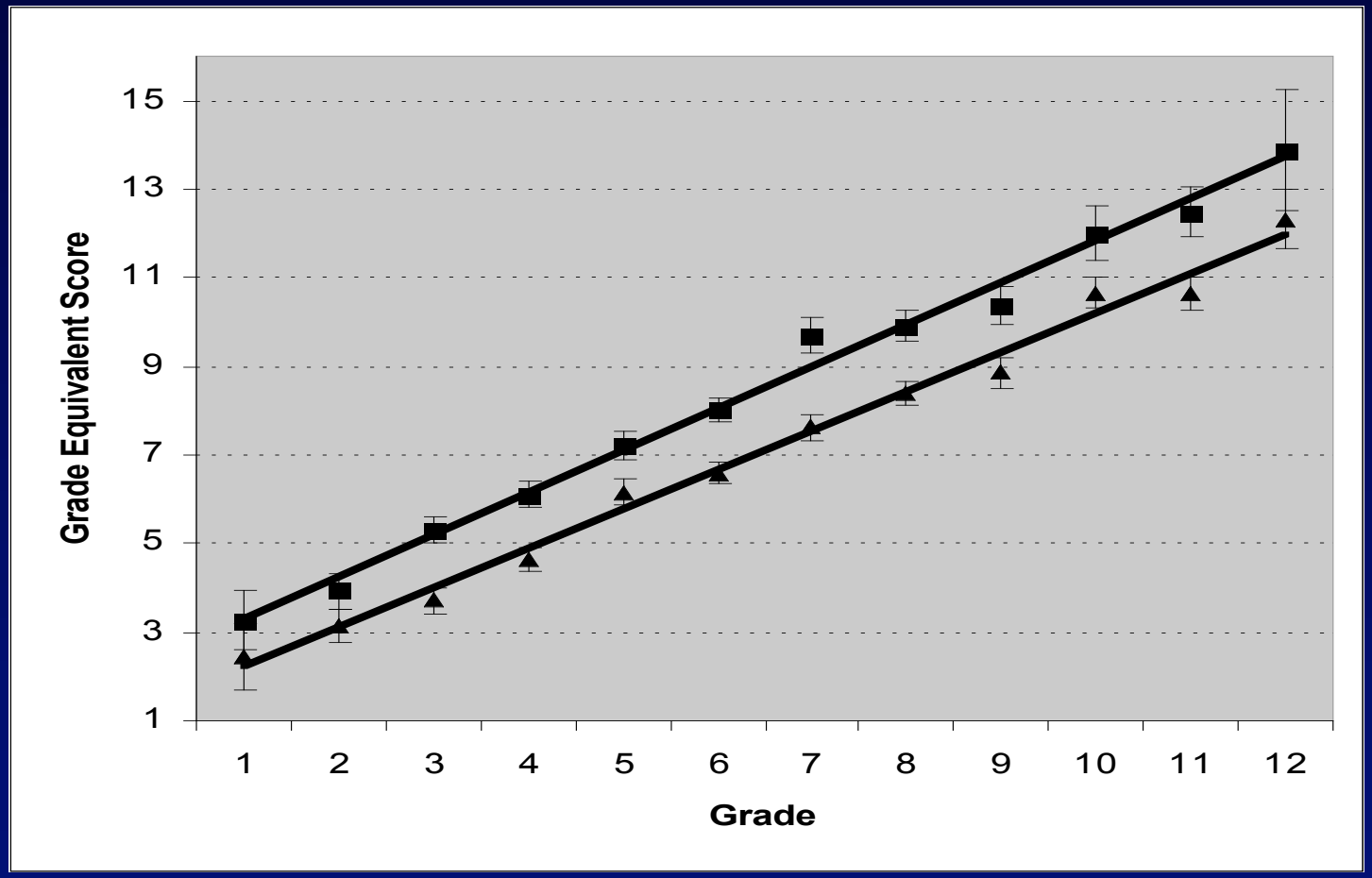
Achievement Test Scores from 1st to 12th Grades

Hillside Hospital Study of First Episode Schizophrenia



Bilder et al., JCEN, in press

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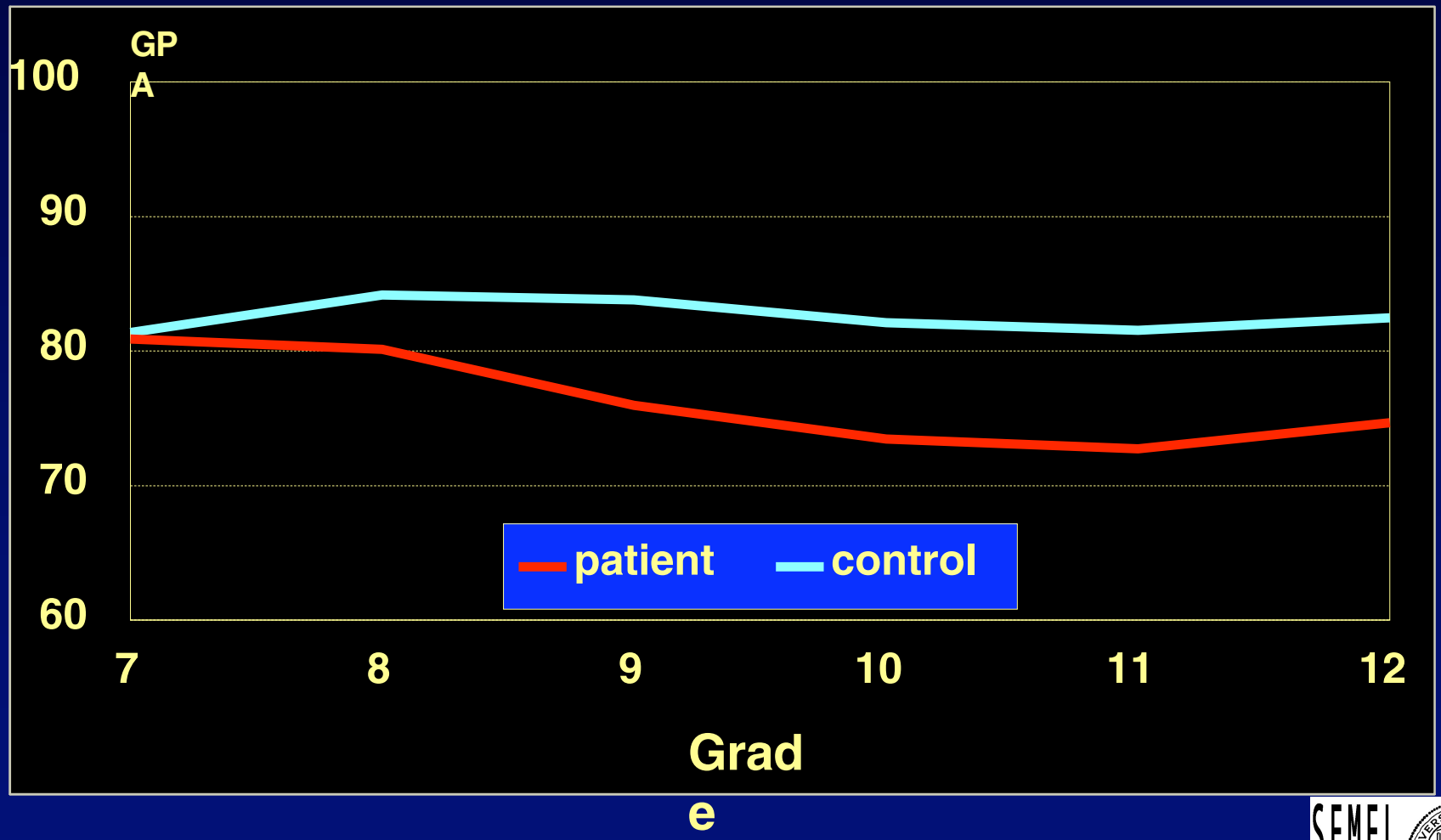
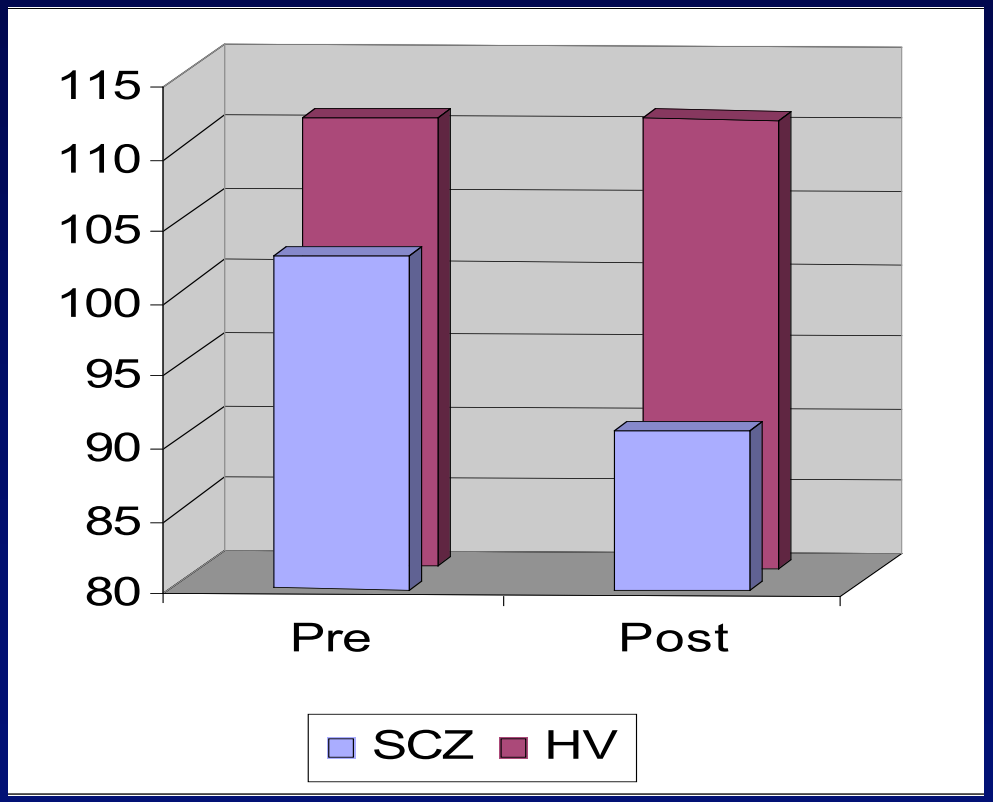
Grade Point Averages

First Episode Schizophrenia vs Controls



Estimated IQ Before and After the First Episode of Schizophrenia (based on SAT scores, FSIQ)



Bilder et al., JCEN, in press

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Prospective Longitudinal Neurocognitive Assessment Results in FES

- Stony Brook: overall stability; lack of normal improvement in memory
- Penn: little overall change (corrs with structure change)
- Iowa: mild improvement
- Hillside: mild improvement ~3 IQ points (corrs with structure change)

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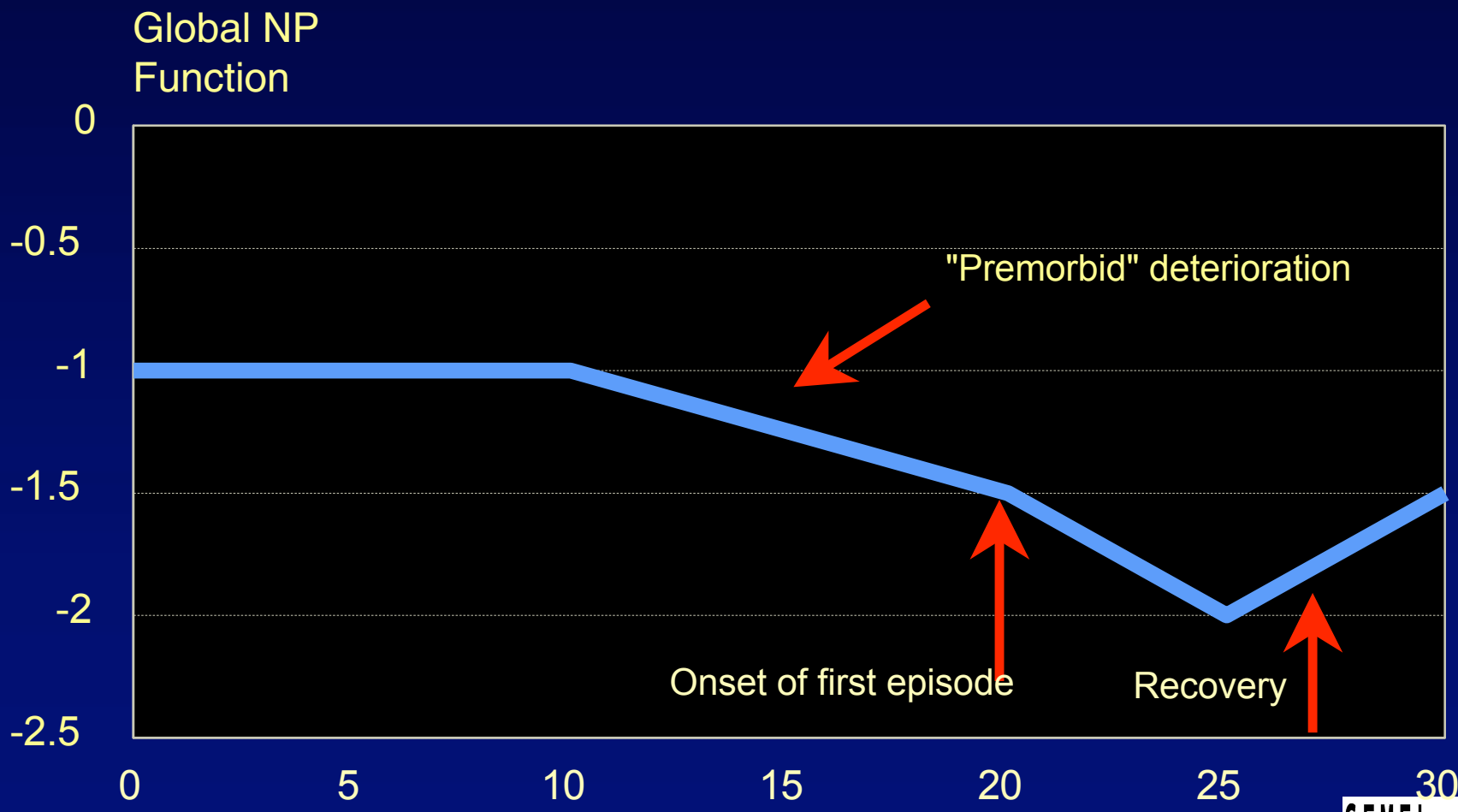
Course of NP Deficit in Schizophrenia

Composite Speculation Based on FES Sample



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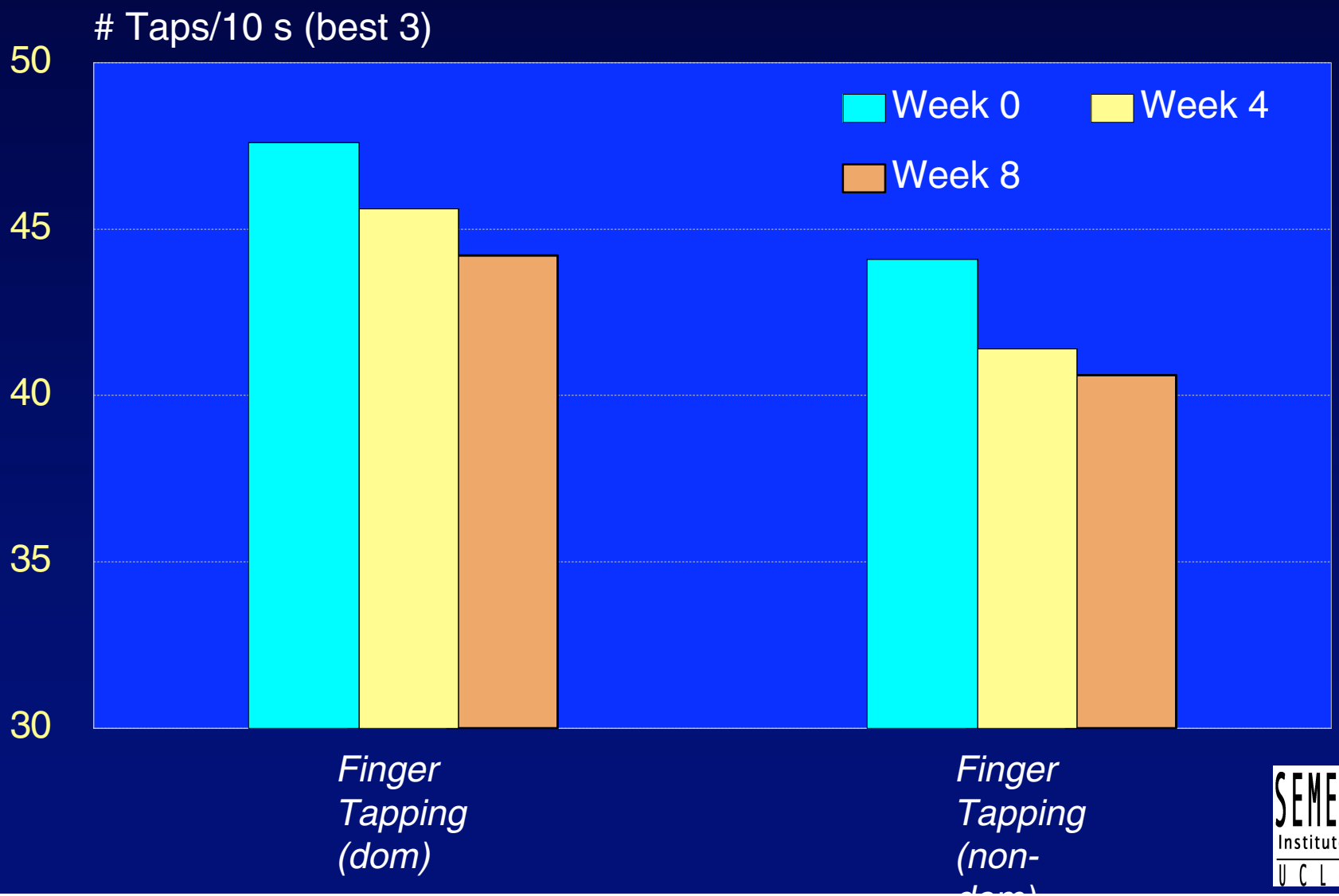
Treatment Effects?

- First-generation studies – using conventional antipsychotics, at doses possibly considered high by today's standards
- Second-generation studies – using novel antipsychotics

Tapping Speed Decreases During Early Treatment in First Episode Schizophrenia



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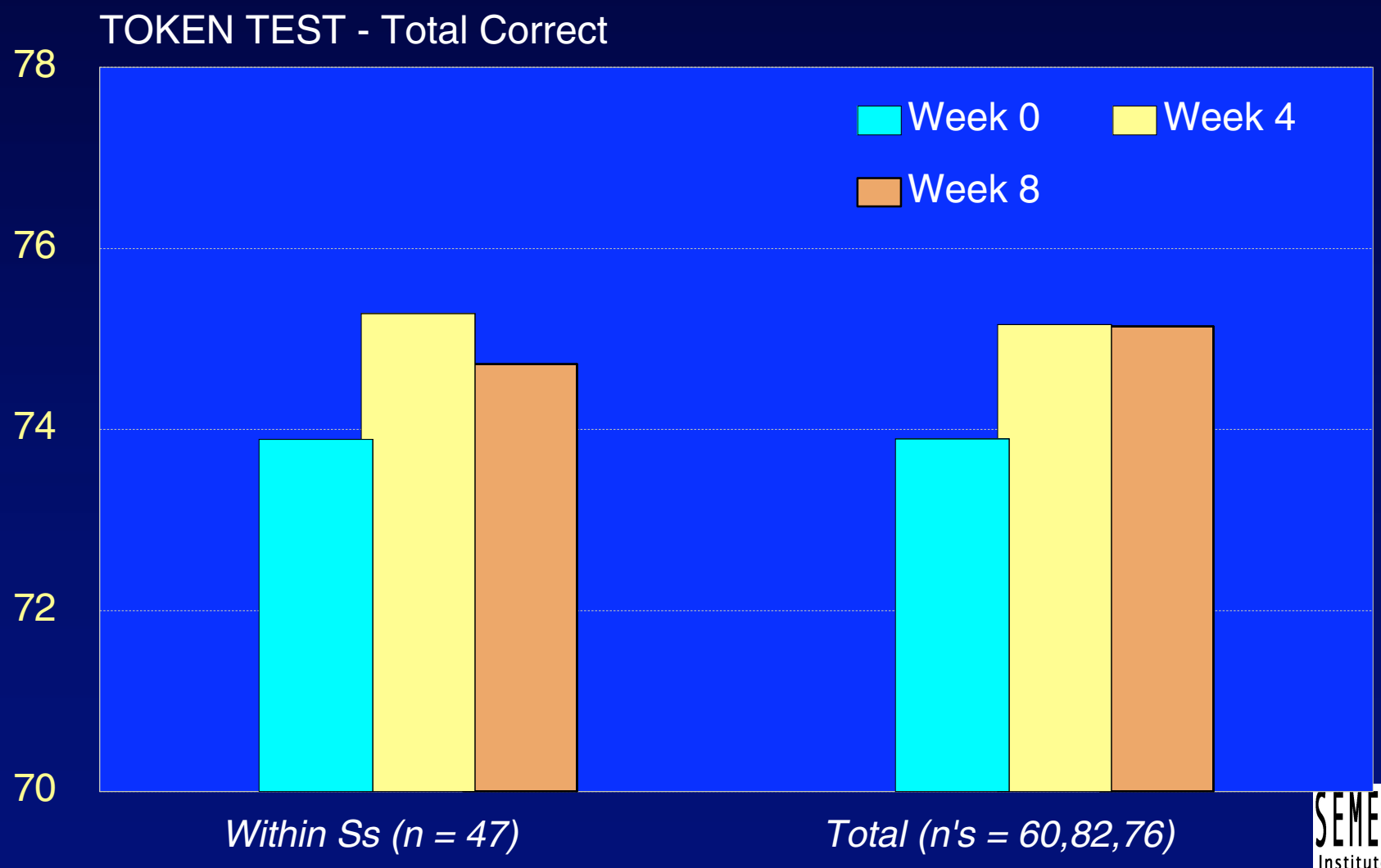
Auditory Verbal Comprehension Improves During Early Treatment in First Episode Schizophrenia



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Conventional Antipsychotic Treatment Effects on Cognitive Function in First Episode Schizophrenia

- Adverse effects on motor function: speed and dexterity (normalized with continued treatment)
- Beneficial effects (limited normalization) on some attentional and receptive language measures
- What about the new antipsychotics?

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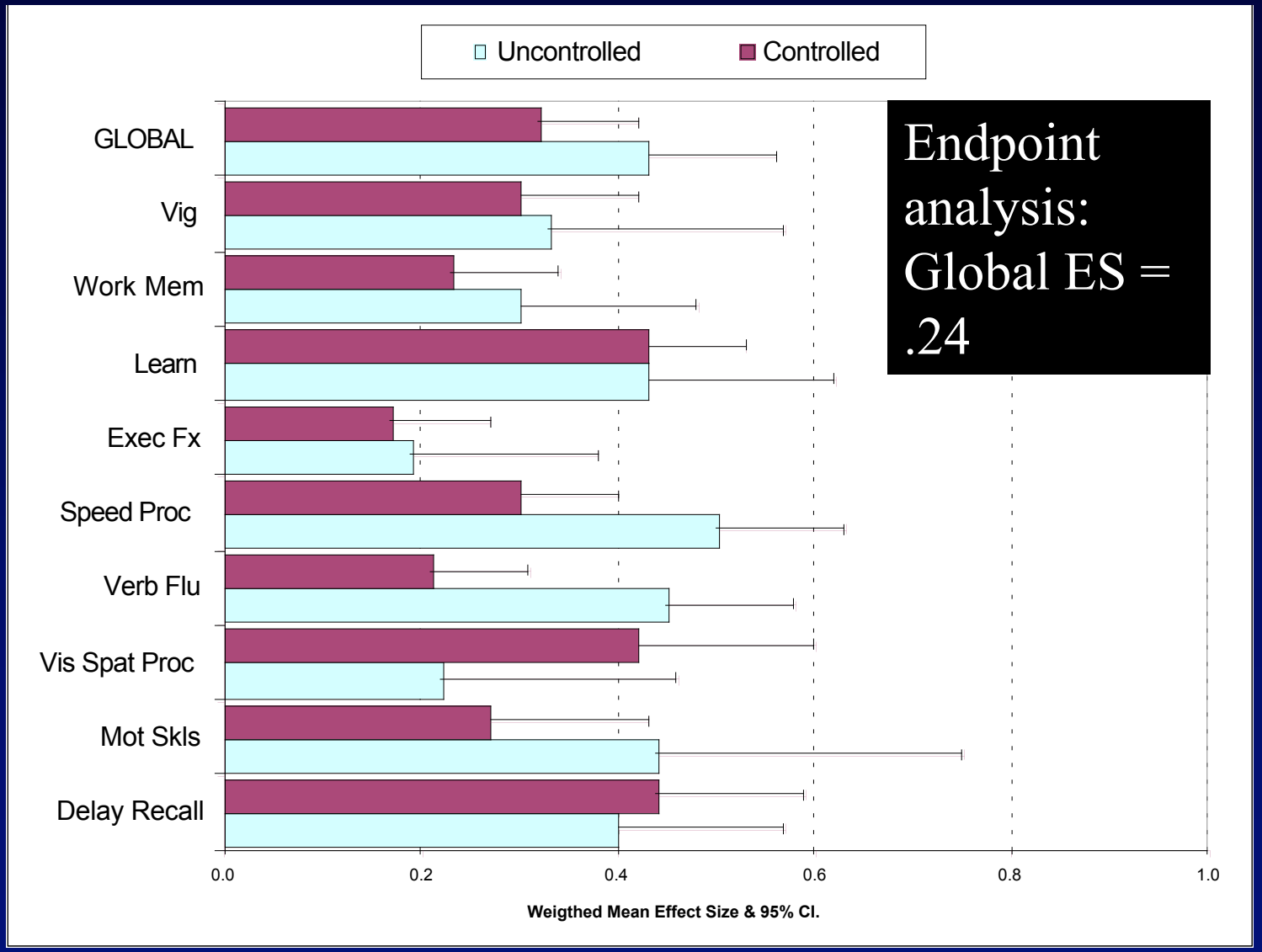
Meta-analysis of novel antipsychotic effects on cognition (Woodward et al.)



Int J Neuropsychopharmacol. 2005 Sep;8(3):457-72

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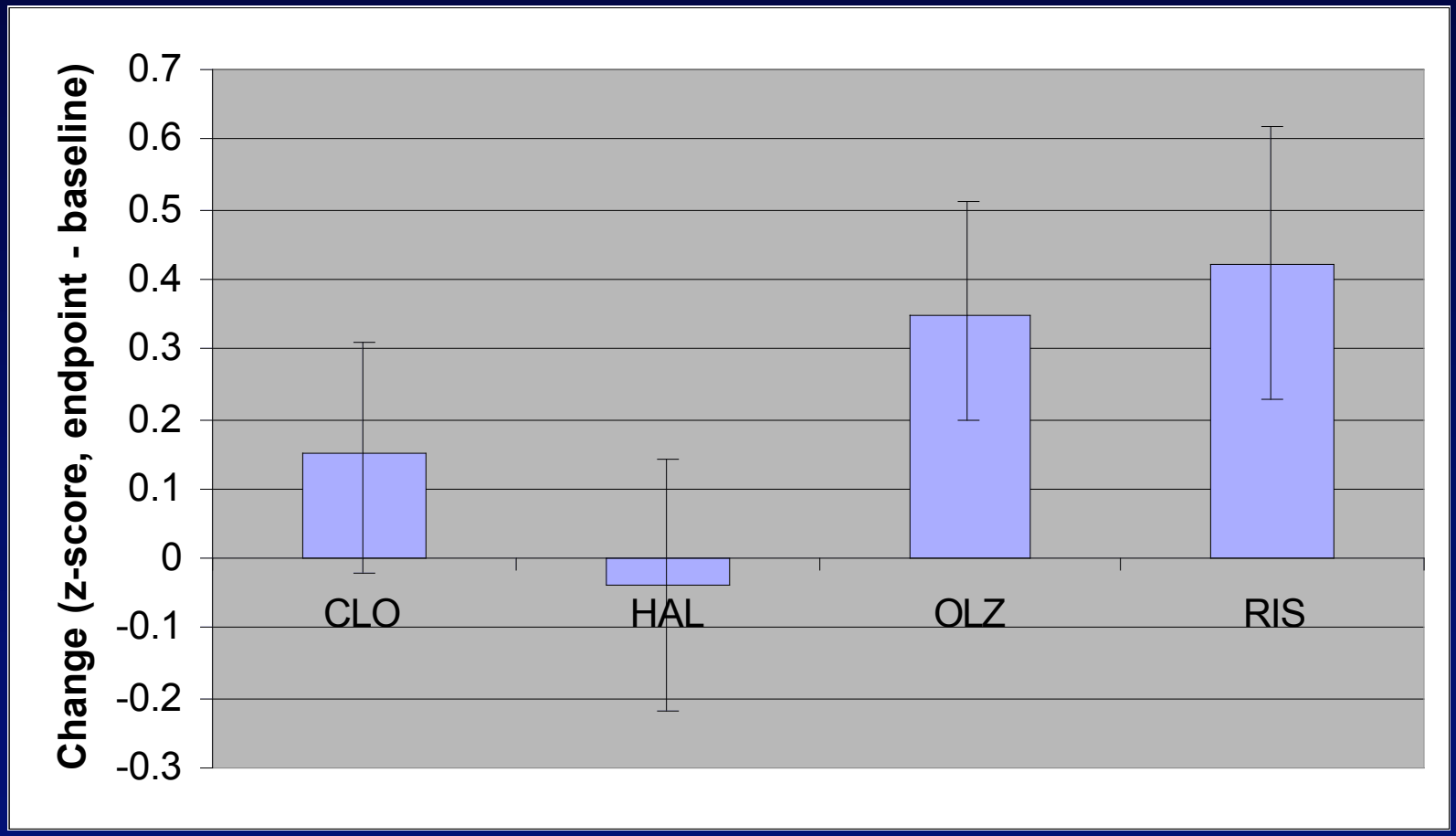
Fig 1. Global Scale

(mean of 16 test variables)

Change Scores (± 95% confidence intervals)



Time effect: F(1, 97) = 24.33, p<.0001; Time X Group: F(3,97) = 4.96, p<.003; Post-hoc tests: OLZ and RIS improve; OLZ > HAL; RIS > HAL [from Bilder et al., AJP, 2002]

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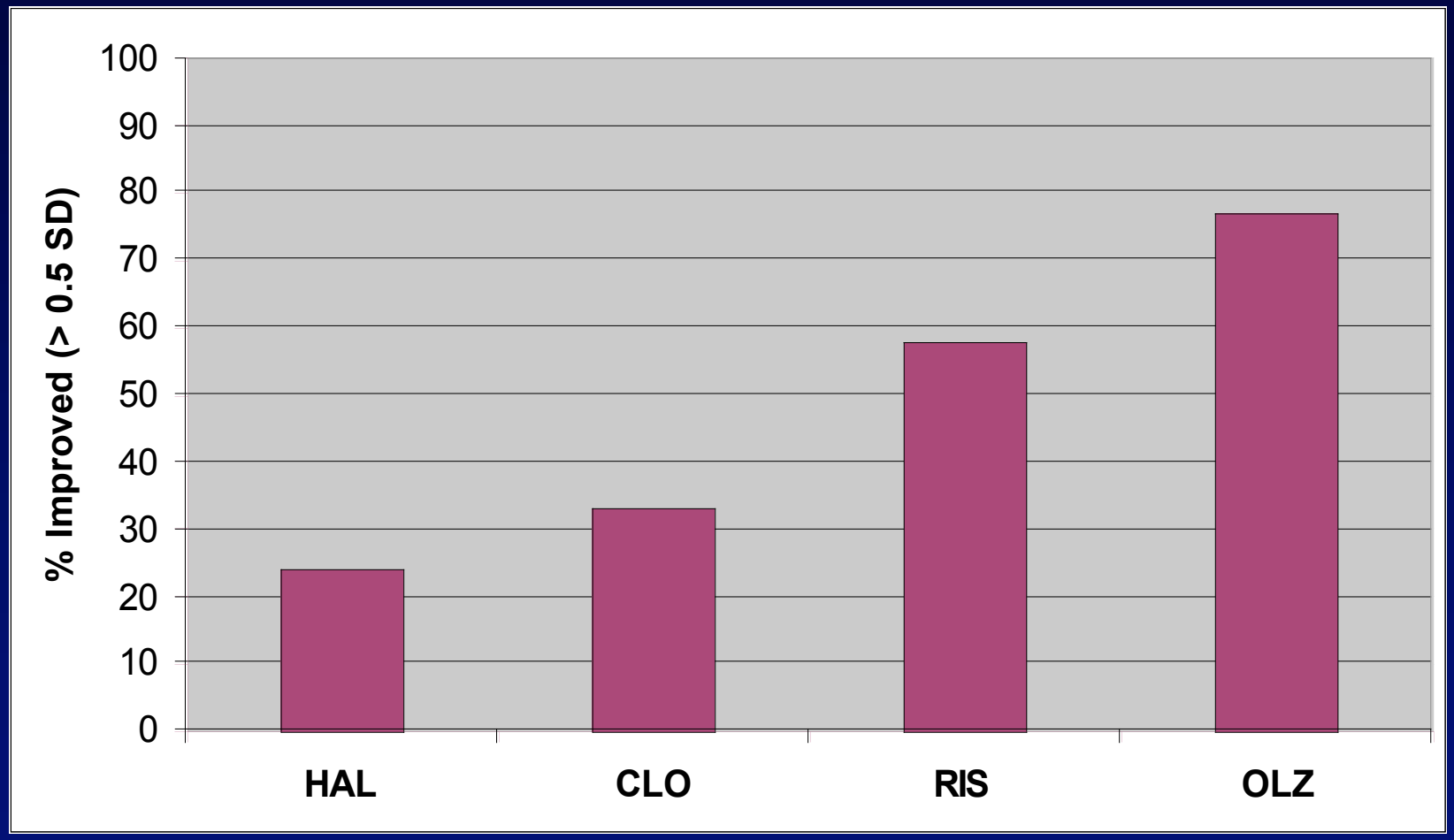
"Clinically Meaningful" Changes

(operational definition: gain of more than 0.5 SD relative to baseline)



Groups differ overall: χ^2=17.5, df = 3, p < .0006

Pair-wise comparisons: OLZ>HAL, OLZ>CLO, RIS>HAL

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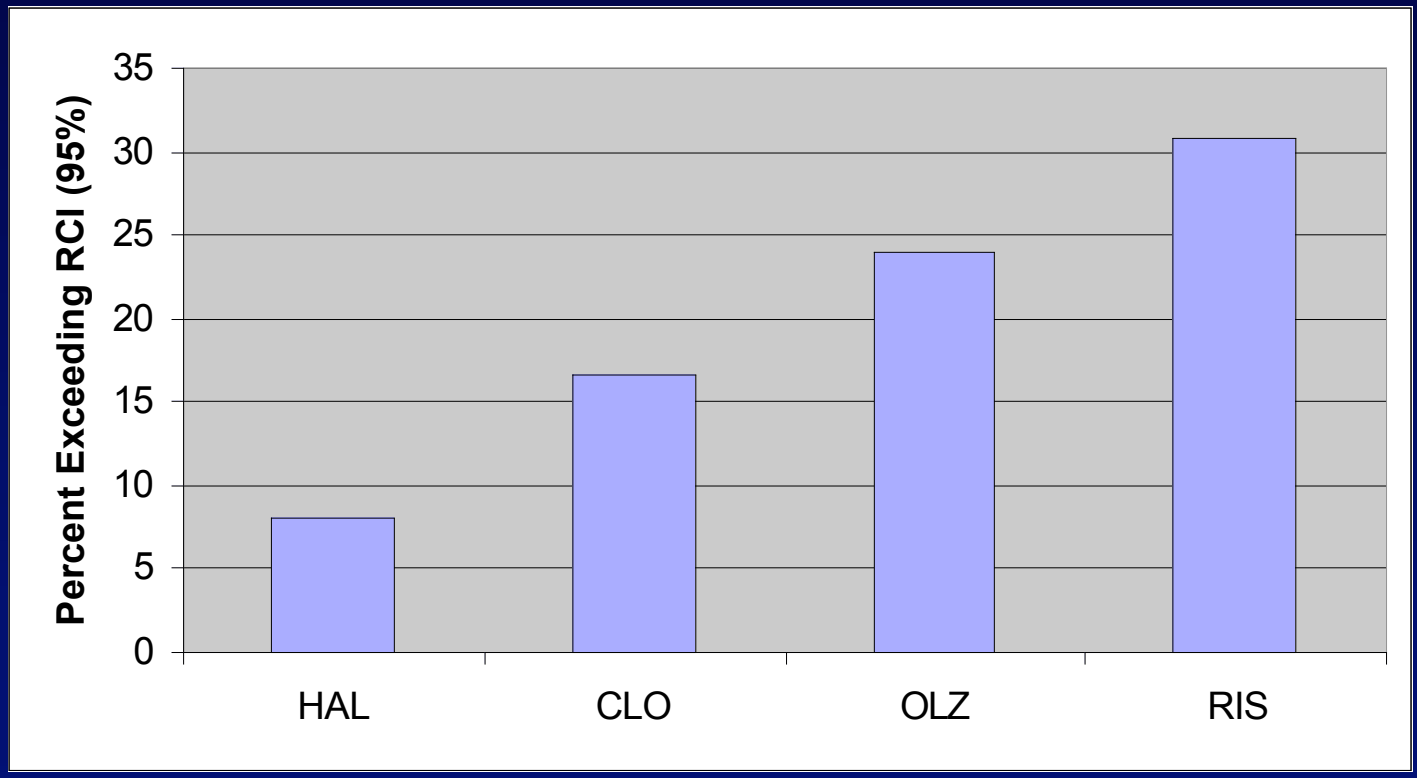
Reliable Changes Using RCI

N = 100; test-retest r_{xx} = .70; SE = .36

requires changes of 1.64 SE or .593 units, which is ~ 1 SD)



Adapted from Bilder et al., AJP 2002

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But what about the brain?

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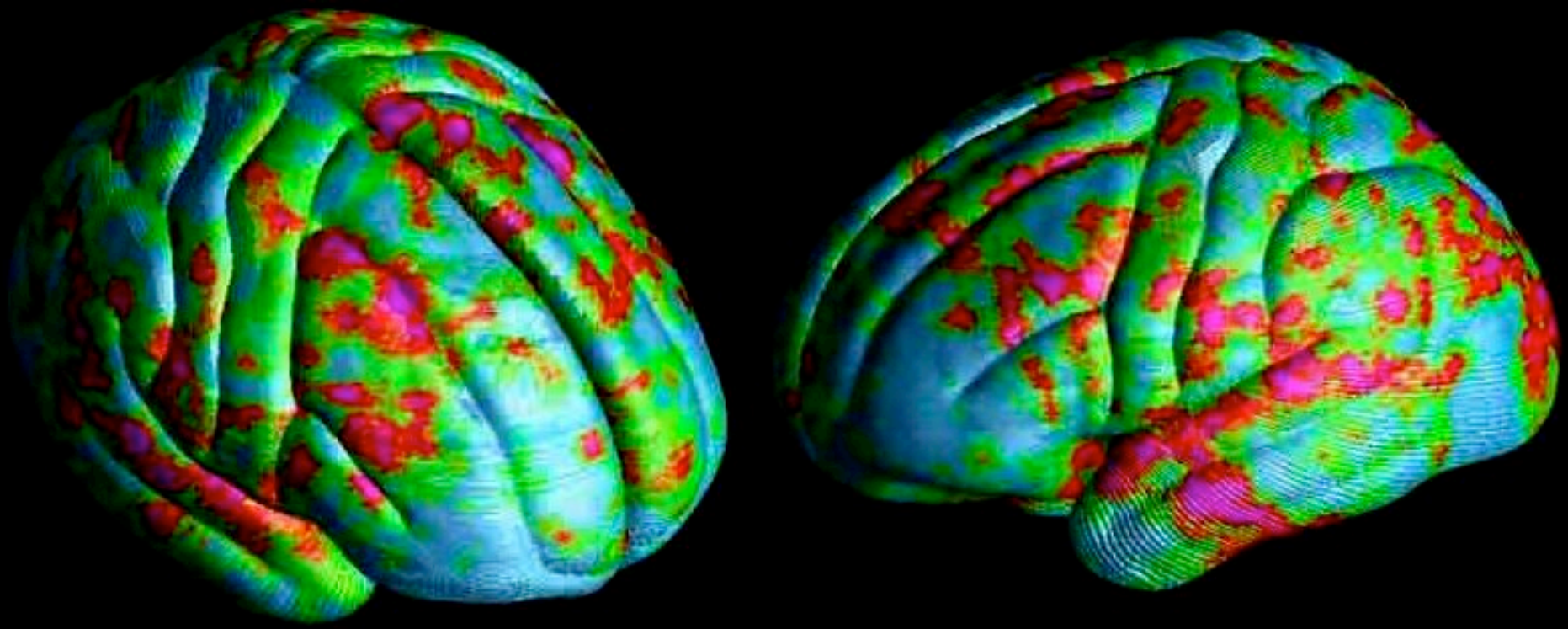
Hypotheses about cognitive impairment in schizophrenia

- Regional or lateralized deficits:
  - Left lateralized fronto-temporal
  - Left lateralized superior temporal gyrus
  - Dorsolateral prefrontal cortex
  - Hippocampal formation
- Dysconnectivity
  - Fronto-striato-pallido-thalamic
  - Fronto-striato-cerebellar
  - Subiculo-accumbens
- Widespread, heteromodal or panmodal neuronal dysfunction

Widespread Cortical Gray Matter Deficit in FES



Narr, Bilder, Toga et al., *Cerebral Cortex*, 2004

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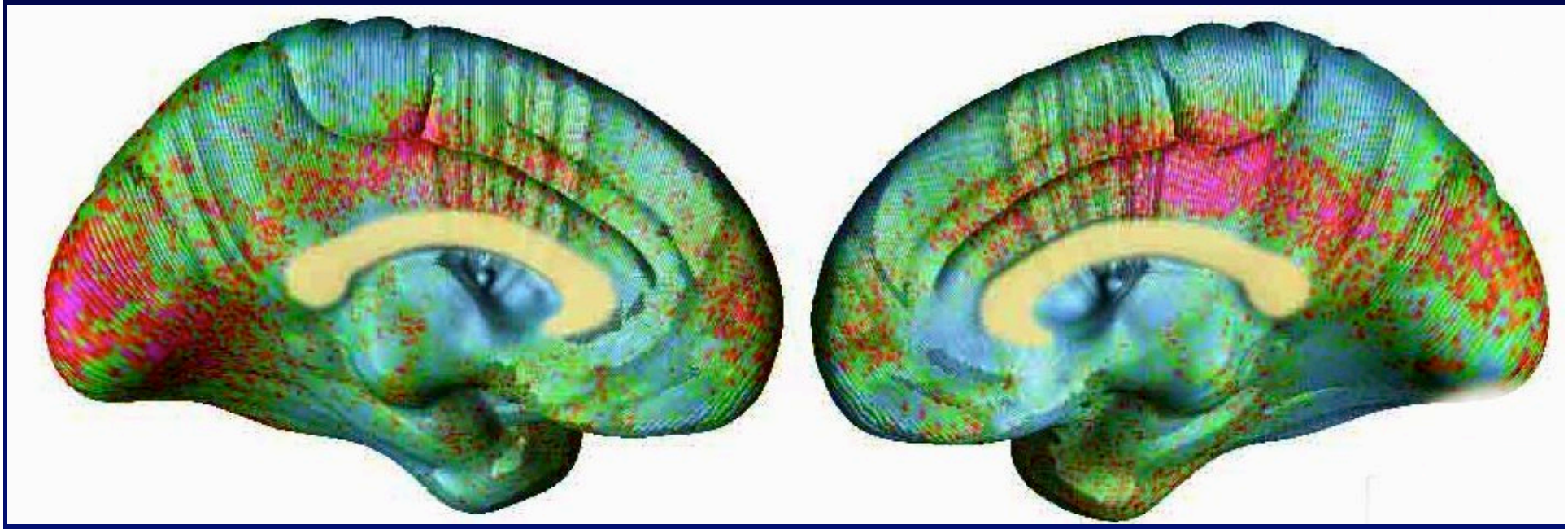
Cortical Thickness Deficit on Medial Surface - FES



Narr et al., *Biological Psychiatry*, 2005

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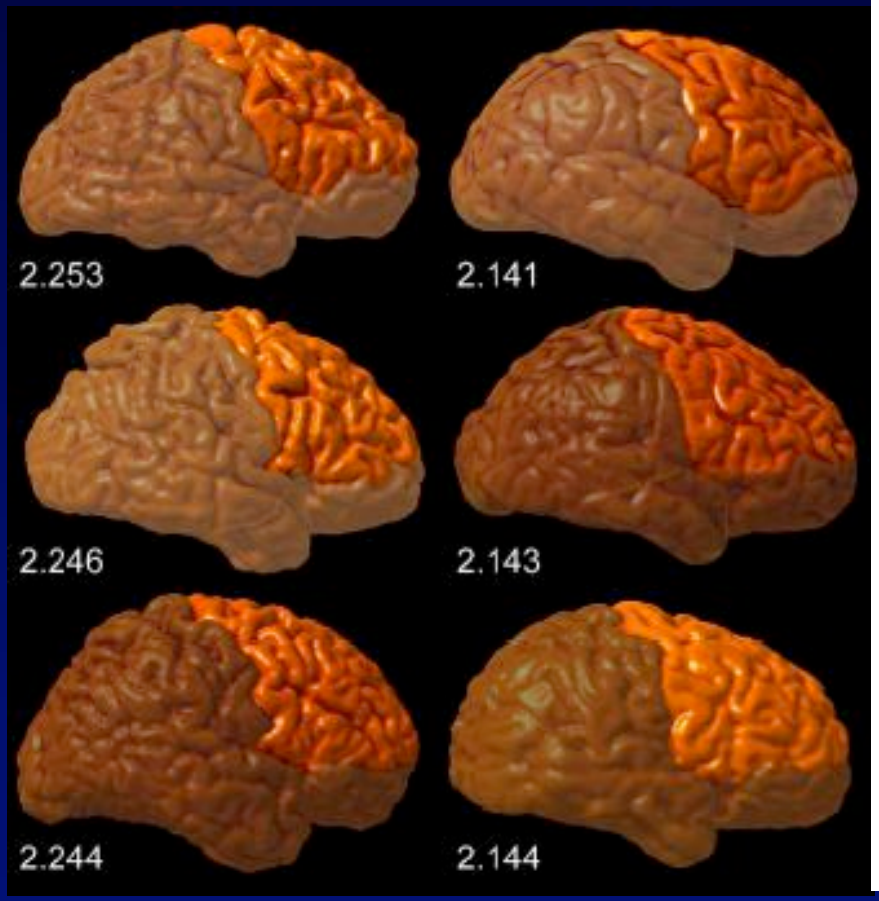
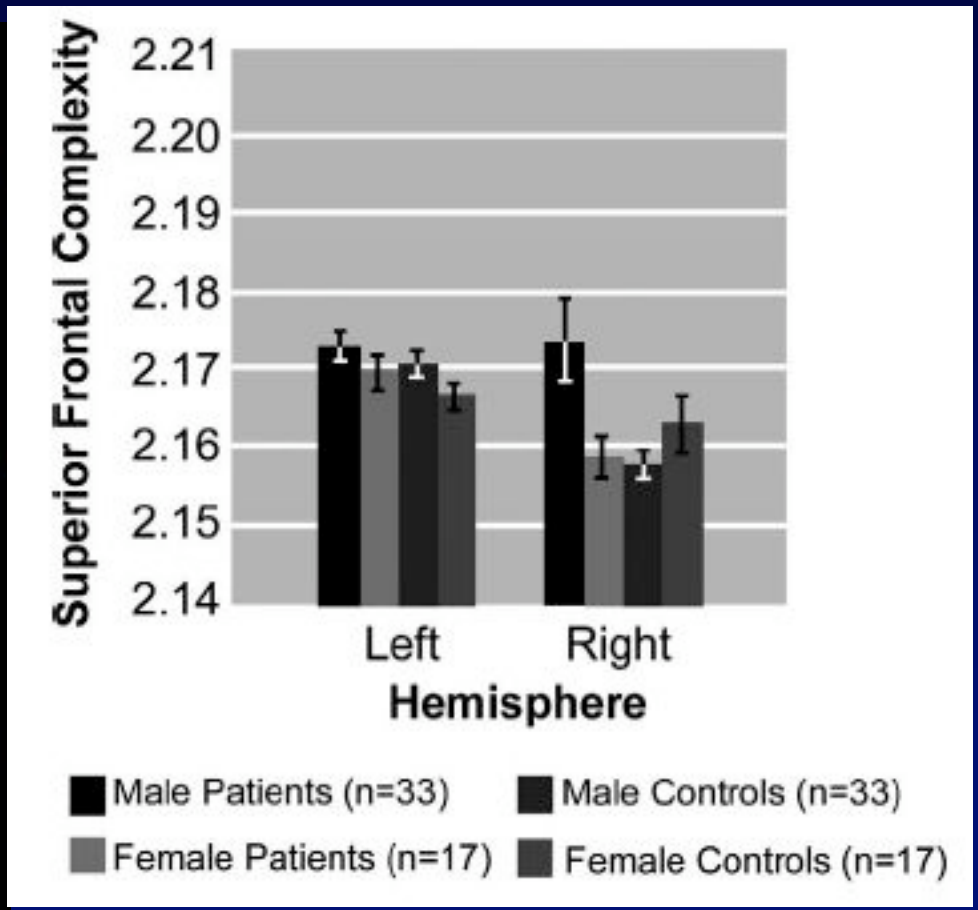
Increased R Frontal Gyrification in FES





Narr et al., *Biological Psychiatry*, 2004

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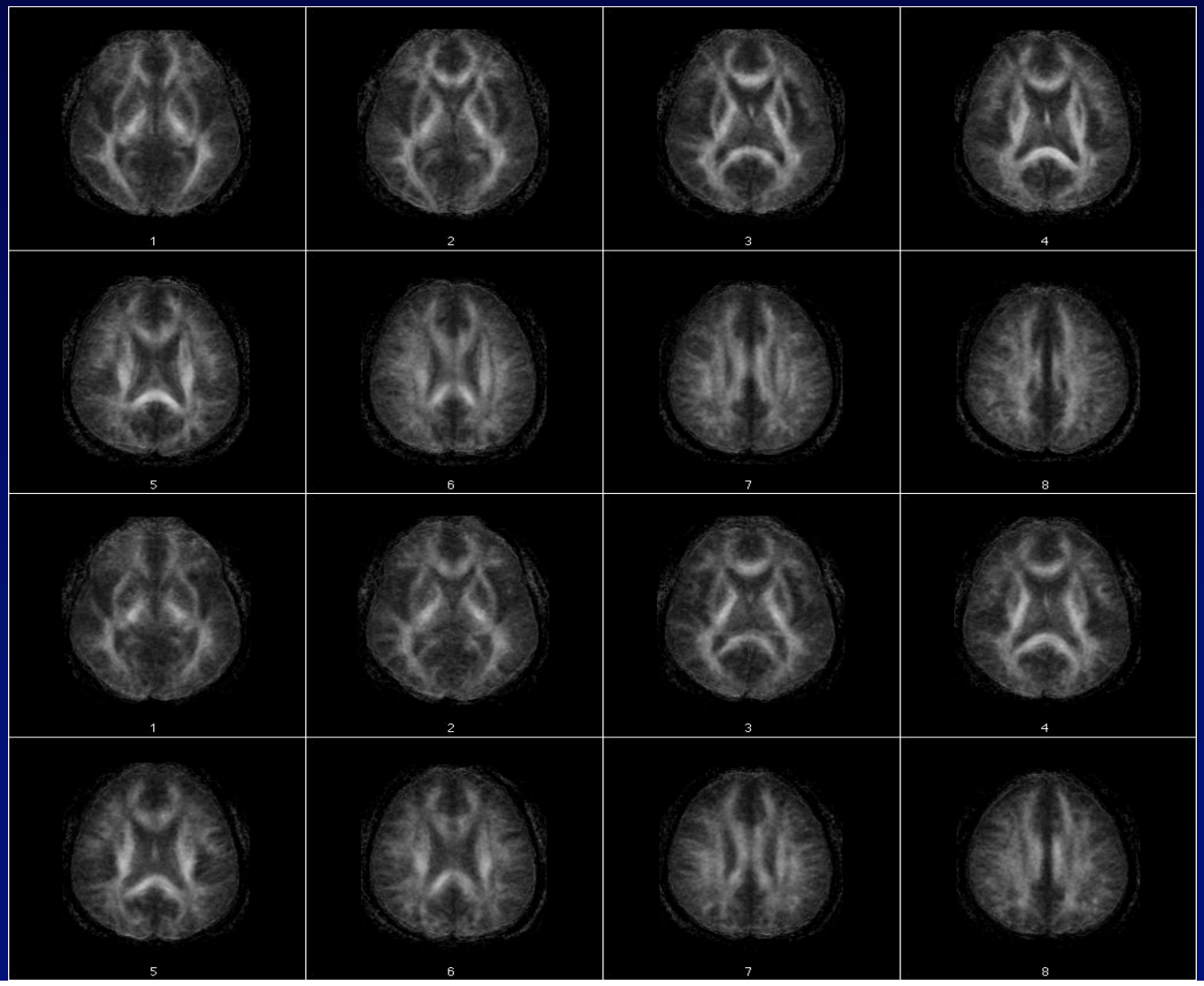
FA Maps for FES Patients and Healthy Volunteers

A



B

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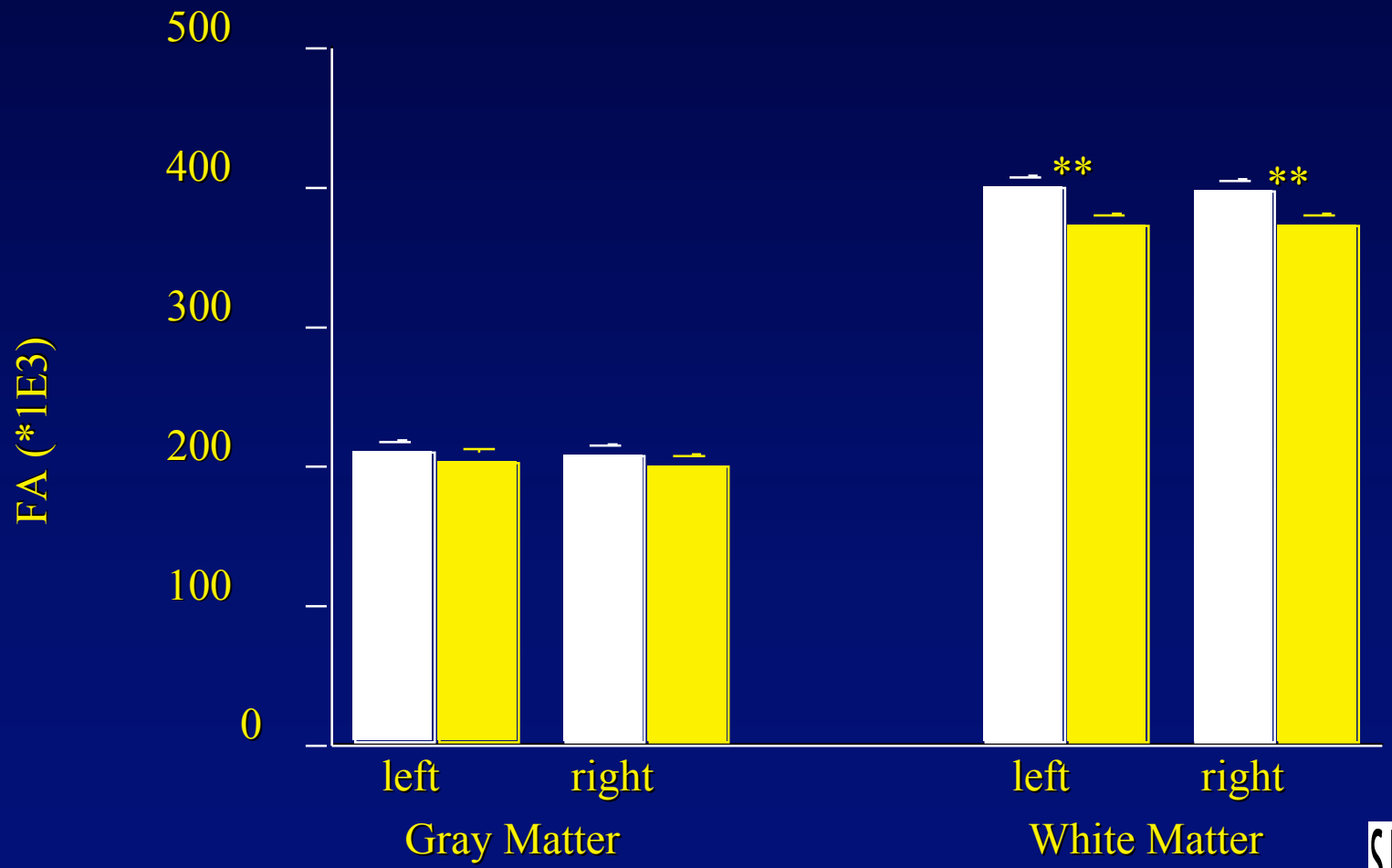
FES DTI-FA Findings



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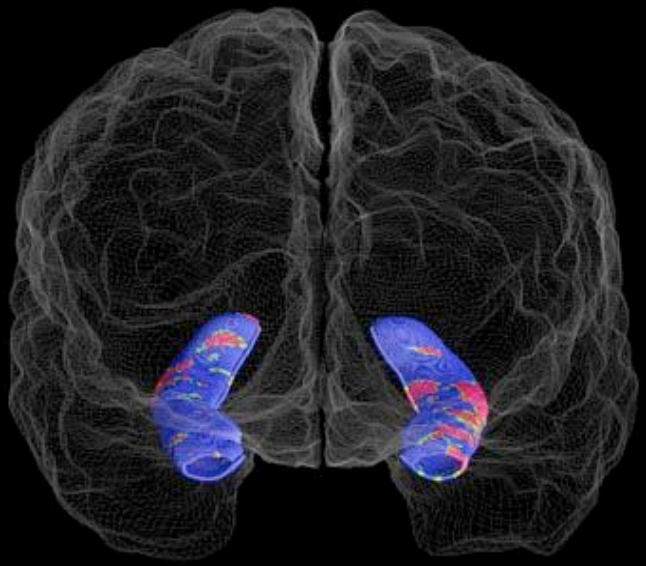
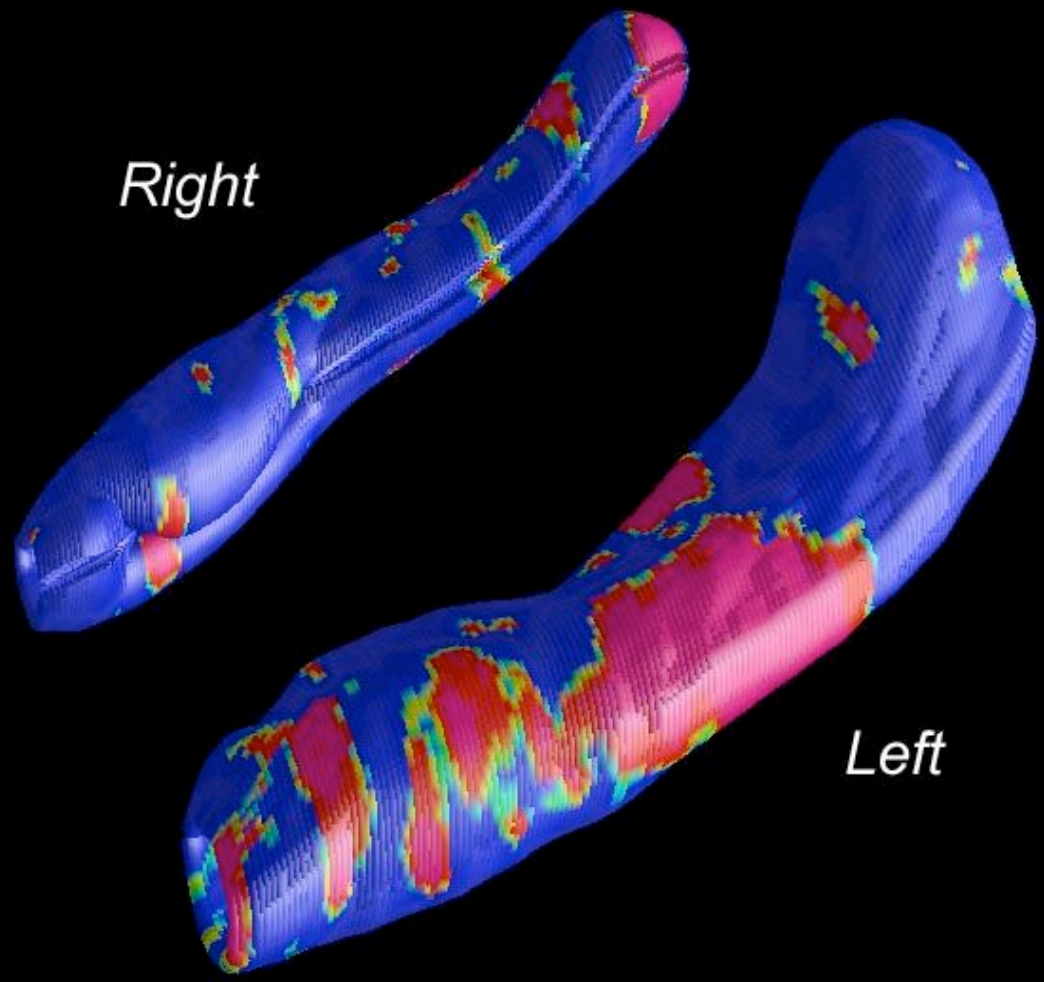
Volume Reductions in FE Schizophrenia

Atlas Space

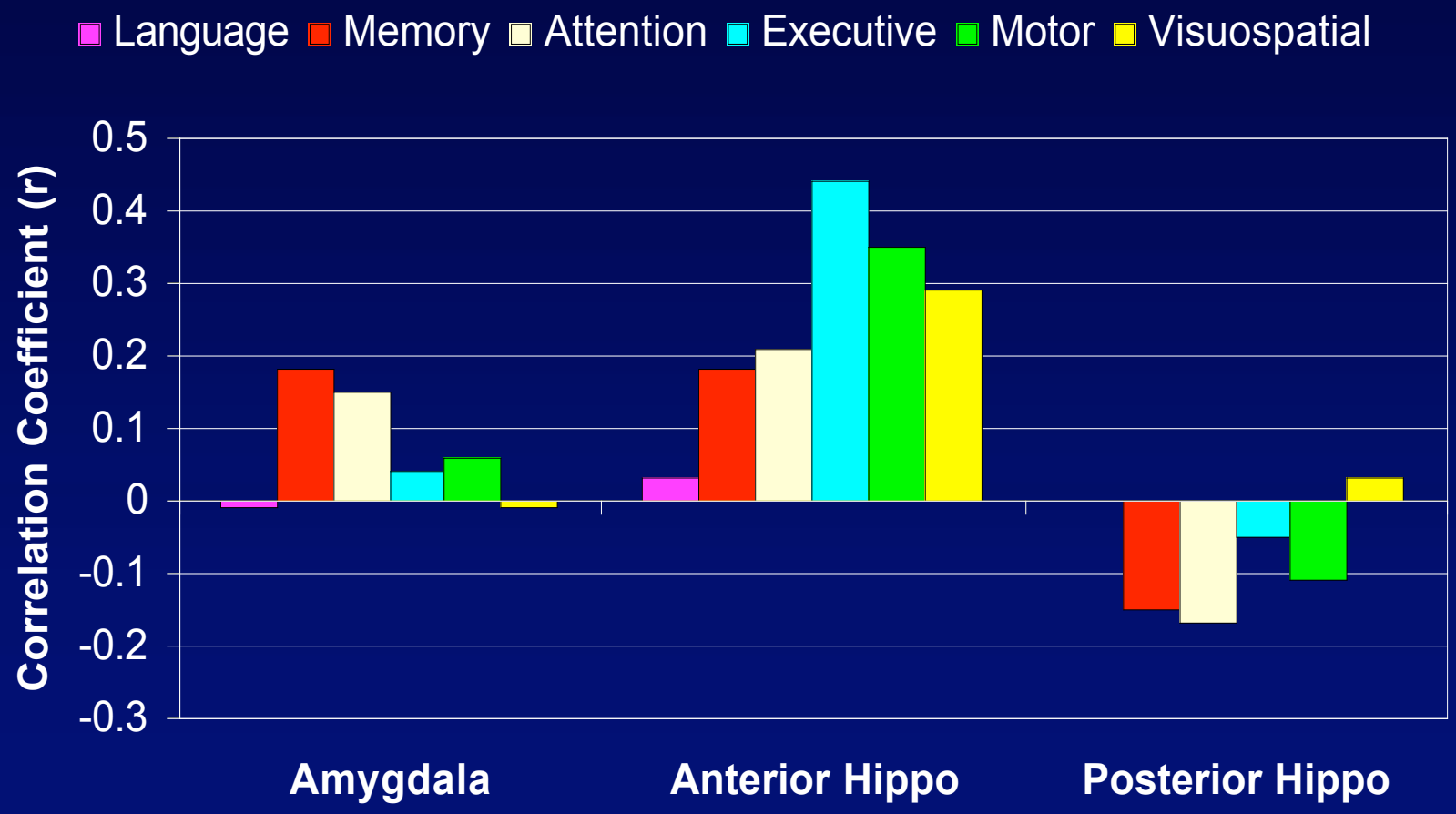




P-value

Anterior Hippocampal Volumes Correlated with "Frontal Lobe" Functions in Schizophrenia

Bilder et al., 1995; Szeszko et al., 2002



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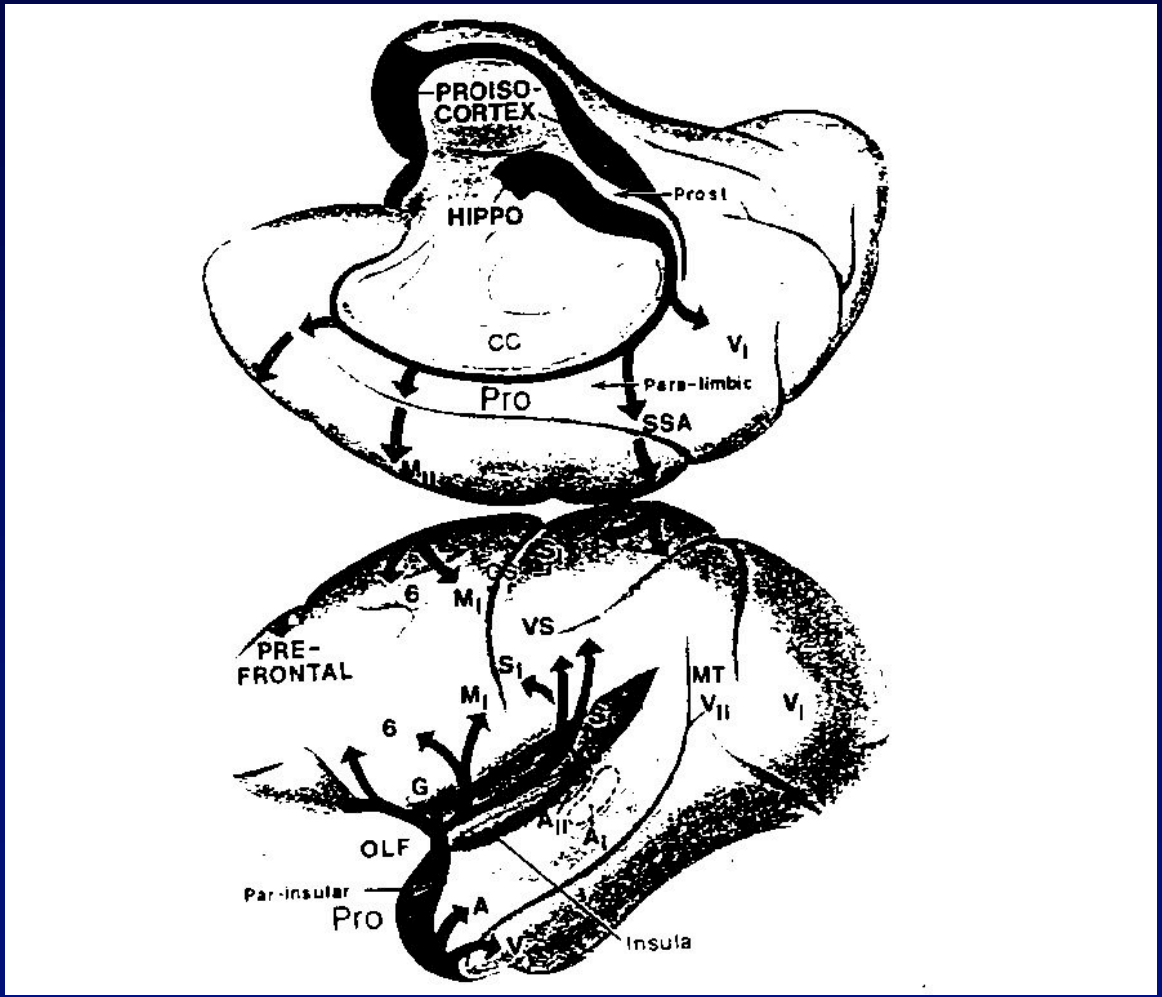
Dual Trends: Overview for the Spatially Gifted



From Pandya, 1999

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Schizophrenia as a frontolimbic disorder

- "Hypofrontality" and task failure across broad range of tasks
- Metachromatic leukodystrophy as a model of frontohippocampal disconnection
- Correlations of anterior hippocampal volume with frontal dysfunction (human data, animal model [neonatal VH lesion])
- Failures on tasks involving conflict, need to incorporate novel action into established behavioral programs; BOTH perseveration and excessive distractibility

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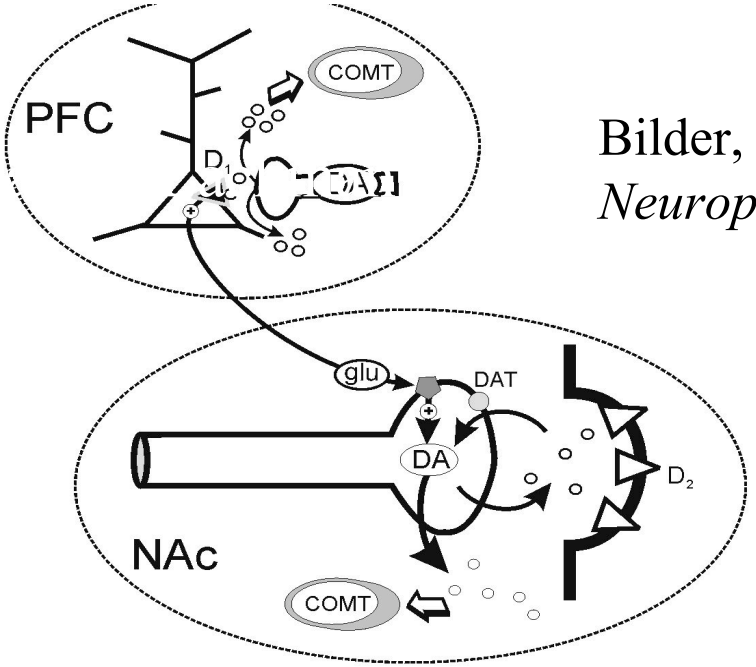
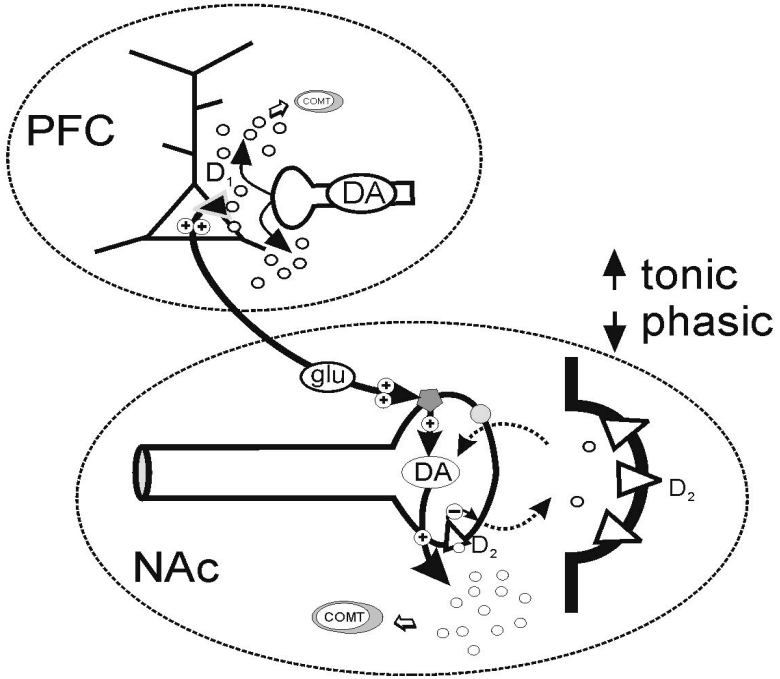
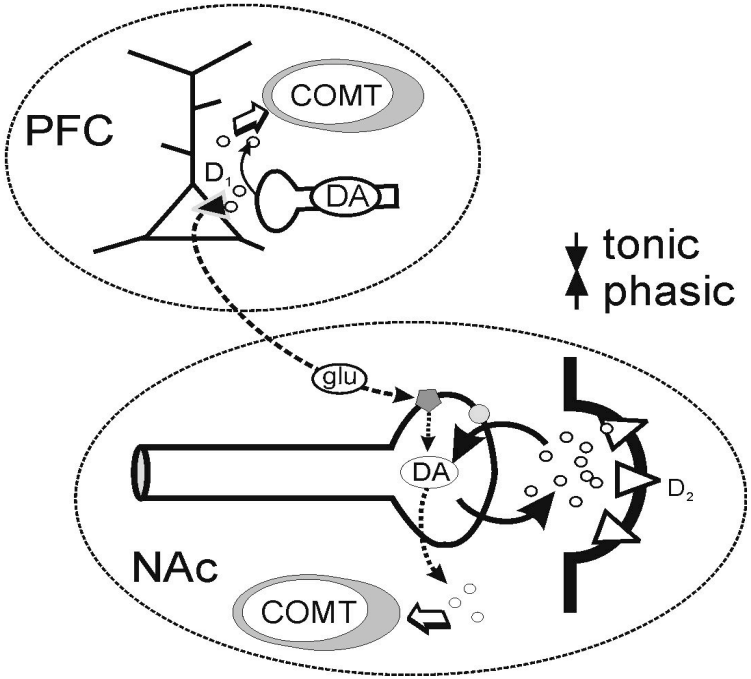


Bilder, Volavka, Lachman, & Grace, *Neuropsychopharmacology*, 2004

Met allele
(decrease COMT activity)



Val allele
(increase COMT activity)



PCP/NMDA Model of Schizophrenia

- Original (ca. 1960): PCP and other dissociative anesthetics (e.g., ketamine) induce psychotic symptoms that closely resemble schizophrenia
- Mechanism of action (ca. 1980): Dissociative anesthetics mediate their effects by blockade of N-methyl-D-aspartate (NMDA) type glutamate receptors
- Implication (ca. 2000): Dysfunction of NMDA receptors and/or glutamatergic systems may be critical to the pathophysiology of schizophrenia, may offer a treatment target

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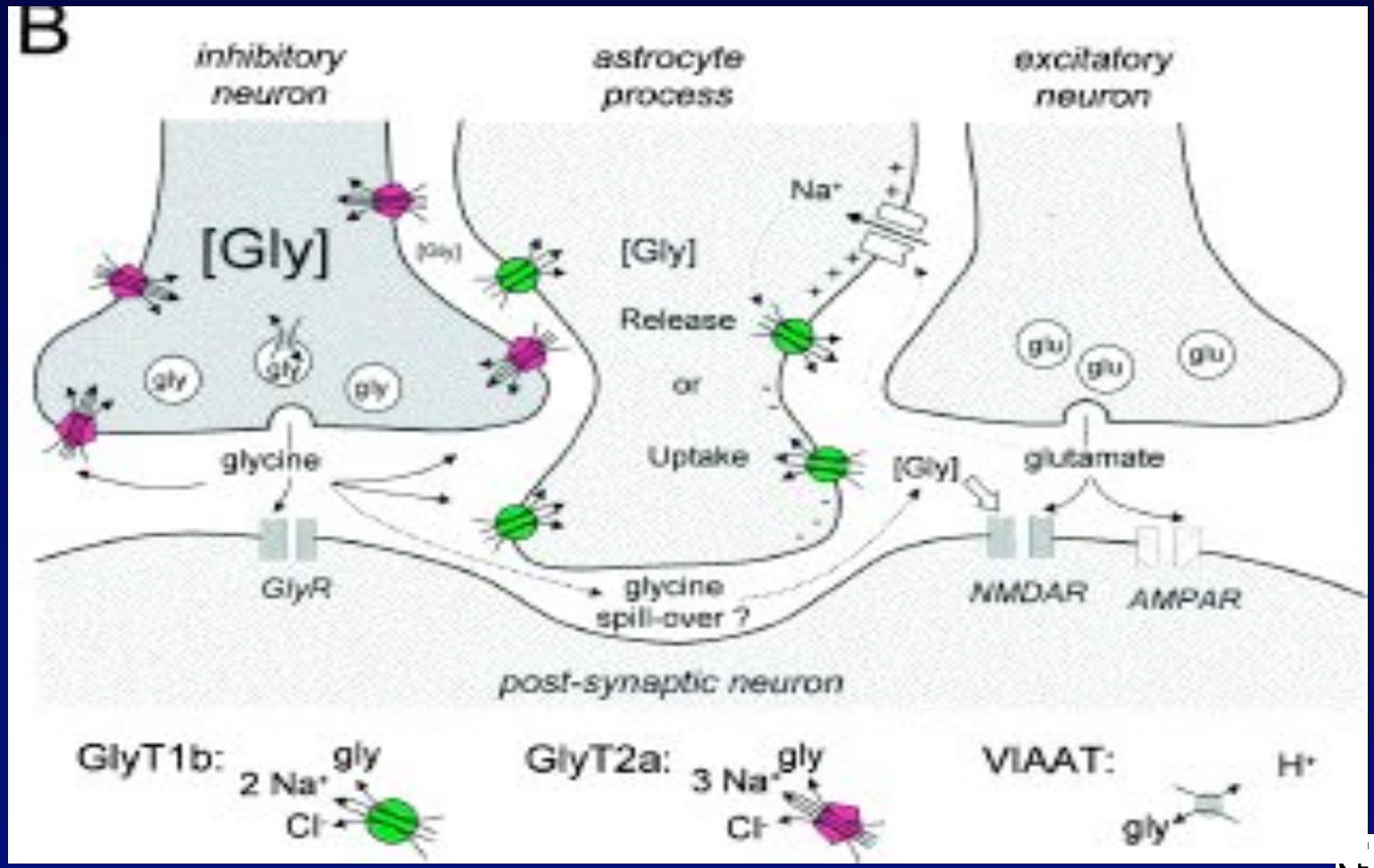
New Directions in Glycinergic Therapies?

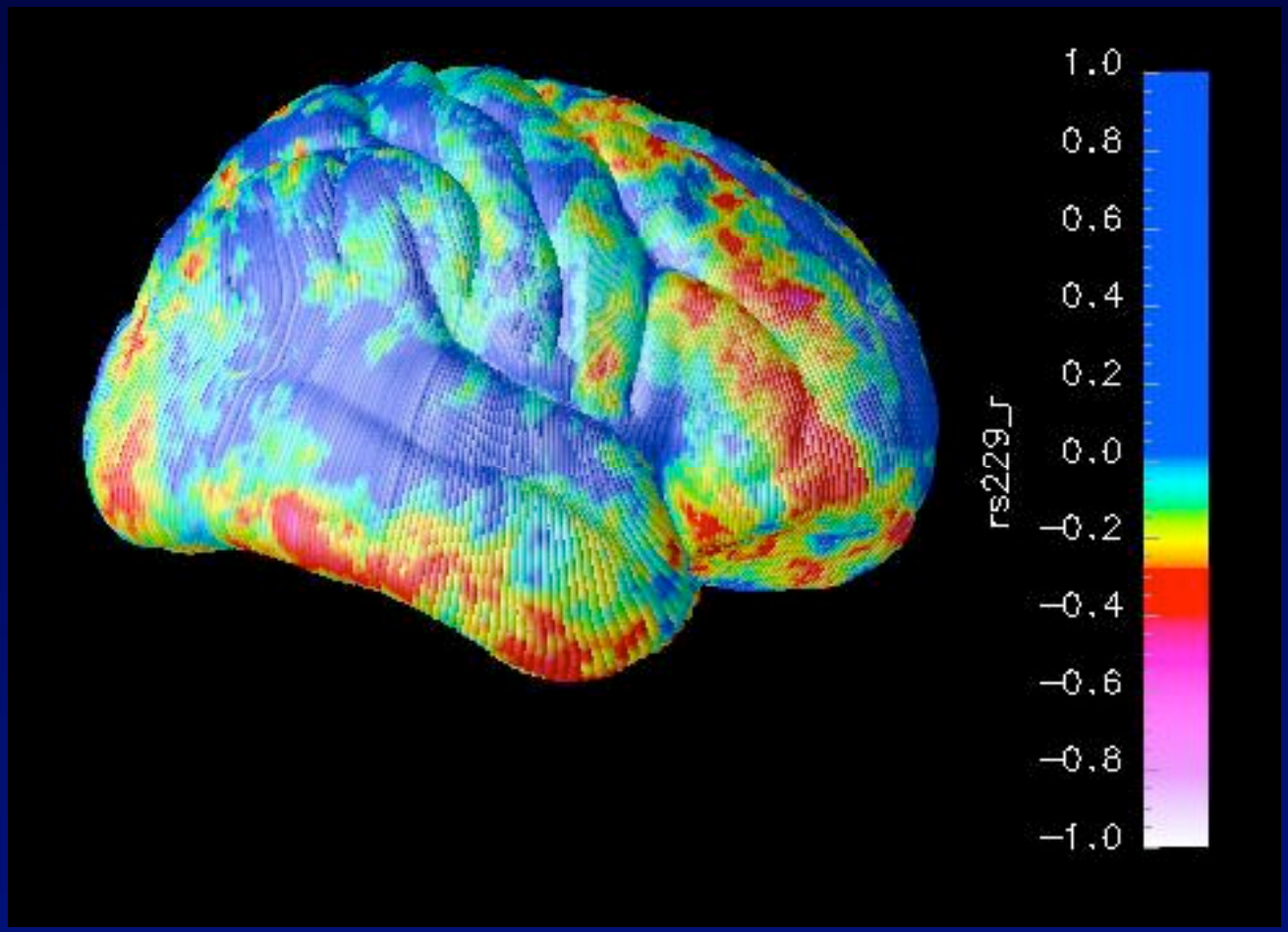


Clues from Genetics?

- Many candidates, few strong single gene effects capable of explaining "schizophrenia" as a phenotype
- Some good candidates for intermediate cognitive phenotypes
  - CHRNA7, DISC1, DTNBP1, BDNF, COMT… (201 'hits' for 'schizophrenia' in EntrezGene as of 8/21/05)

Voxelwise Linkage Analysis: Disc1

Correlation of intrapair differences in gray matter density with DISC1 SNP alleles shared IBD in DZ twins discordant for schizophrenia



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Nelson Freimer on Candidate Gene Research

Q: Why does the drunk search for his keys under the streetlamp, even though he lost them in the bushes?
A: “That’s where the light is!”

Likelihood of false positive errors may be very high, and likelihood that gene “of interest” is the actual gene involved (rather than in LD) may be small

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CCP Multi-Level Knowledge Traversal: Example Data Sources for Different Levels

DSM-IV-TR hierarchy (diagnosis level)	Syndrome
DSM-IV-TR hierarchy (symptom level)	Symptoms
DARPA class hierarchy of cognitive concepts	Cognitive Phenotypes
Foundational Model of Anatomy; imaging db's; SFN db's	Neural System Models
Neurotransmitter lists; signalling pathways; SFN db's	Cellular System Models & Signalling Pathways
Entrez-Protein; Structure; Conserved Domains; 3D Domains, etc.	Proteins
Gene, SNP, OMIM, etc.	Genes

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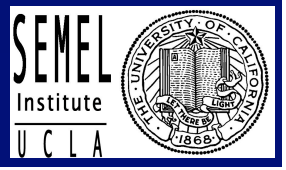
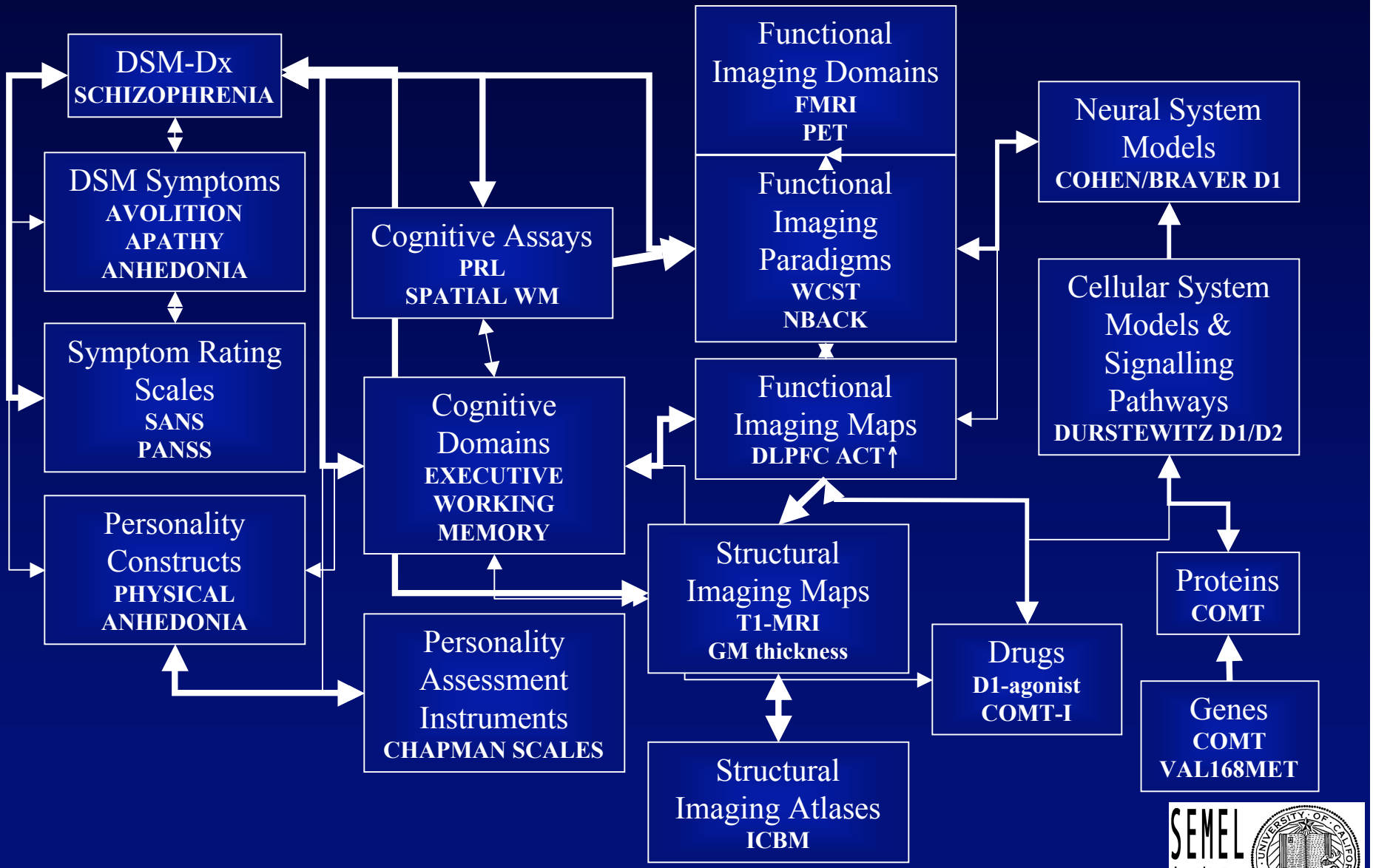
CCP Multi-Level Knowledge Traversal: "COMT" Hypothesis of Cognitive Deficits in Schizophrenia

Schizophrenia	Syndrome
Negative Symptoms	Symptoms
Working Memory	Cognitive Phenotypes
DLPFC, fronto-striatal function	Neural System Models
D1, "tonic" DA transmission	Cellular System Models & Signalling Pathways
COMT	Proteins
COMT Val168Met polymorphism	Genes



Sample Relationships with Weights for the Hypothesis: "COMT polymorphism effects in schizophrenia"



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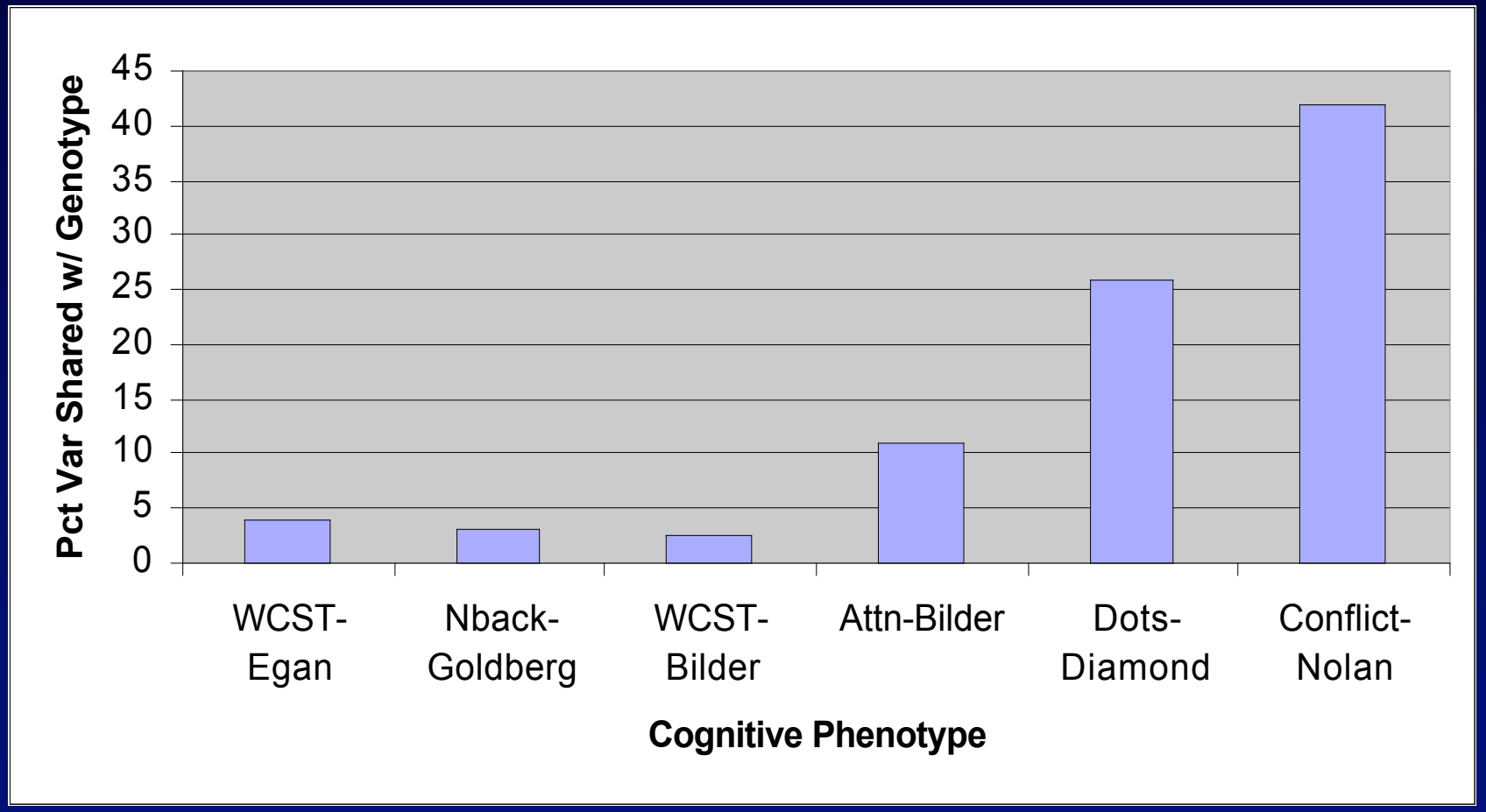
Variance Shared by COMT Genotype and Cognitive Phenotypes



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Cognition in Schizophrenia: Conclusions

- Deficits severe, pervasive; limit function
- Neurodevelopmental origins, with subsequent modulation
- Unitary models of pathology unlikely
- Advances in therapeutics for these complex systems disorders will require convergence of approaches from molecular through syndromal, with improved definitions of the target phenotypes

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- ICSTM slides.keefe.ppt

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