The Practical Constraints of Clinical Trials

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Potential Conflicts of Interest

Consulting/Advisory Board:

Abbott, Astra-Zeneca, Bristol Myers Squibb, Cephalon, Dainippon Sumitomo, Eli Lilly Laboratories, Johnson & Johnson, Lundbeck/ Solvay/ Wyeth, Memory, Merck, Pfizer, Saegis, Sanofi/Aventis,

Research Funding:

Astra-Zeneca, Bristol-Myers Squibb, Johnson and Johnson, Pfizer

Potential Conflicts of Interest

Royalties Received:

Brief Assessment of Cognition (BACS)

MATRICS Battery (BACS Symbol Coding)

Likely Characteristics of Multisite Clinical Tri

- Variability in data quality
  - Site feasibility evaluation required
    - Past history with task or similar
    - Evidence that current situation is adequate
  - Tester screening required
    - What are the minimal educational and experience requirements for the specific tas

Rater Training and Certification: Trust No

- Humans will demonstrate their worst characteristics when confronted with the prospect of estab inter-rater reliability
- Sponsors
  - Have had tremendous difficulty organizing training based upon the primary outcome measure (e.g. 6 hou PANSS training; 2 hours of cognitive training for a cognition trial).
  - Companies have repeatedly reverted to old strategies for confronting these new challenges
- PI's
  - Will delay the identification of testers indefinitely if not forced to choose (e.g., on the plane to the investiga meeting), and will change their minds frequently if they are unaware of the training process
- Testers
  - Will frequently exaggerate their experience to their PI's and the central coordinating center
  - Will claim to have performed necessary pre-meeting training
  - Will claim that they were not told they needed to be prepared
  - Will try to get the sponsor to undermine the certification process
- Professional clinical-trials sites may not have sufficient expertise to run sophisticated cognitive neuroscience tasks, however some of them are eager and easily coached, and have large samp
- Academic sites will have fewer patients, slower IRB processes, and greater expertise, which ca problem. Rowers all need to row the same way. Being 'better' is *worse* for the reliability of the g There is no "I" in inter-rater reliability. OK, there are four, but none of them are capitalized.

How to Love Those You Cannot Trust

- Sponsors
  - Give sponsors ample warning of the training and certification processes that will be required for establishi reliability
  - Be prepared to teach them what reliability is and why low reliability is bad (costs money)
  - Have a budget ready
  - Be prepared to cancel involvement in a trial if procedures for adequate reliability are not established. I ha wasted so many months following compromised reliability procedures that resulted in useless data.
- PI's
  - Identify testers early
  - Once testers are chosen, they should be changed only in extreme circumstances
  - Keep PI's aware of training process so that they do not inadvertently sabotage it
- Testers
  - Screen them prior to allowing them to be identified as the site tester
  - Training materials must be prepared and sent to sites well ahead of investigators meeting (one month is i give ample time for inexperienced testers to learn and practice
  - Have a personal "look them in the eye" telephone CONVERSATION with each potential tester: "I will be certifying you at the meeting, so be sure that you are prepared to show me that you are doing the tests correctly." Be clear that procedures will be certification and not "getting to know you".
  - Central coordinating center MUST evaluate performance and have power to reject testers

Data Review Processes

- The larger the number of sites, the less any individual site feels responsible for assuring the quality of the data (don't let Kitty Genovese die again!)
- Large multi-site studies may require ongoing data quality review every data point
- Catastrophic continuing inaccuracies can be avoided by reviewi data immediately after test administration
- Ongoing conference calls for testers to describe problems and h they responded to them are tremendously helpful
- Smaller studies with select sites that have academic reputations lose may require less review from a central site, but it is importa to have ongoing checks that data quality procedures are adequa at each site. Random test review from central site keeps everyo honest. Remember that we academic researchers only pretend live at the top of Maslow's moral pyramid. Accountability is necessary.

Practical Constraints Will Require Decisions A
Task Duration and Complexity

- Can the construct be measured in a simpler, cheaper, more parsimonious manner?
- Is the cognitive construct really as specific as assumed
- Easily administered tasks have reduced confusion amo testers, patients, PIs and readers
- Does increased task complexity lead to greater missing data?
- Does the size or specificity of the effect outweigh the practical constraints, both financial and scientific?

Responding to Inevitable Crises

- Low enrollment leads to additional sites
  - Need to have plan for mobile evaluation of new sites and test
- Personnel changes
  - Adding testers to a site with experience can be less demandi than to a new site
    - Deputizing certified testers as trainers
    - Final approval of testers should be central
- Some sites may not be capable of participating
  - "*Nothing gets people's attention like a hanging*" – Joe McEvo CATIE Schizophrenia Trial Strongman

Lessons from Clinically-Oriented Cognitive Batteries

- Shorter is better if it tests the same thi with equal reliability
- This may be a big ‘if’ for cognitive neuroscience tasks, but cognitive neuroscientists might not be accustomed to sacrificing theory for brevity and practicality, which clinical trials *require*

CATIE Schizophrenia Neurocognitive Test Battery

- Wide Range Achievement Test (WRAT-III)–Readin Test (1 visit only)
- Verbal Fluency
  - Controlled Oral Word Association Test (COWAT)
  - Category Instances
- Wechsler Intelligence Scale for Children (WISC-III) Mazes
- Hopkins Verbal Learning Test (HVLT)
- Facial Emotion Discrimination Task (FEDT)

CATIE Schizophrenia Neurocognitive Test Battery (cont.)

- Revised Wechsler Adult Intelligence Scale (WAIS-R) Digit Symbol Test
- Letter-Number Test of Auditory Working Memory
- Grooved Pegboard
- Continuous Performance Test (CPT), Identical Pairs Versions (2, 3, and 4 digits)
- Computerised Visuospatial Working Memory Test
- Computerised WCST

Stepwise Multiple Regression Predicting Unweighted Mean of Variables in CATIE

Variable Entry Based On Administration Time	Total R^2	R^2 Change	Est. time
WAIS-R Digit Symbol	.610	.610	3.1
HVLT Verbal Memory	.722	.112	4.1
Grooved Pegboard	.790	.068	5.0
U. Maryland LN Seq	.868	.078	5.9
Verbal Fluency	.889	.021	8.0
WISC-R Mazes	.935	.046	11.2
CPT-IP	.957	.022	13.4
Visuospatial WM Test	.978	.022	16.2
WCST-64	1.000	.022	more

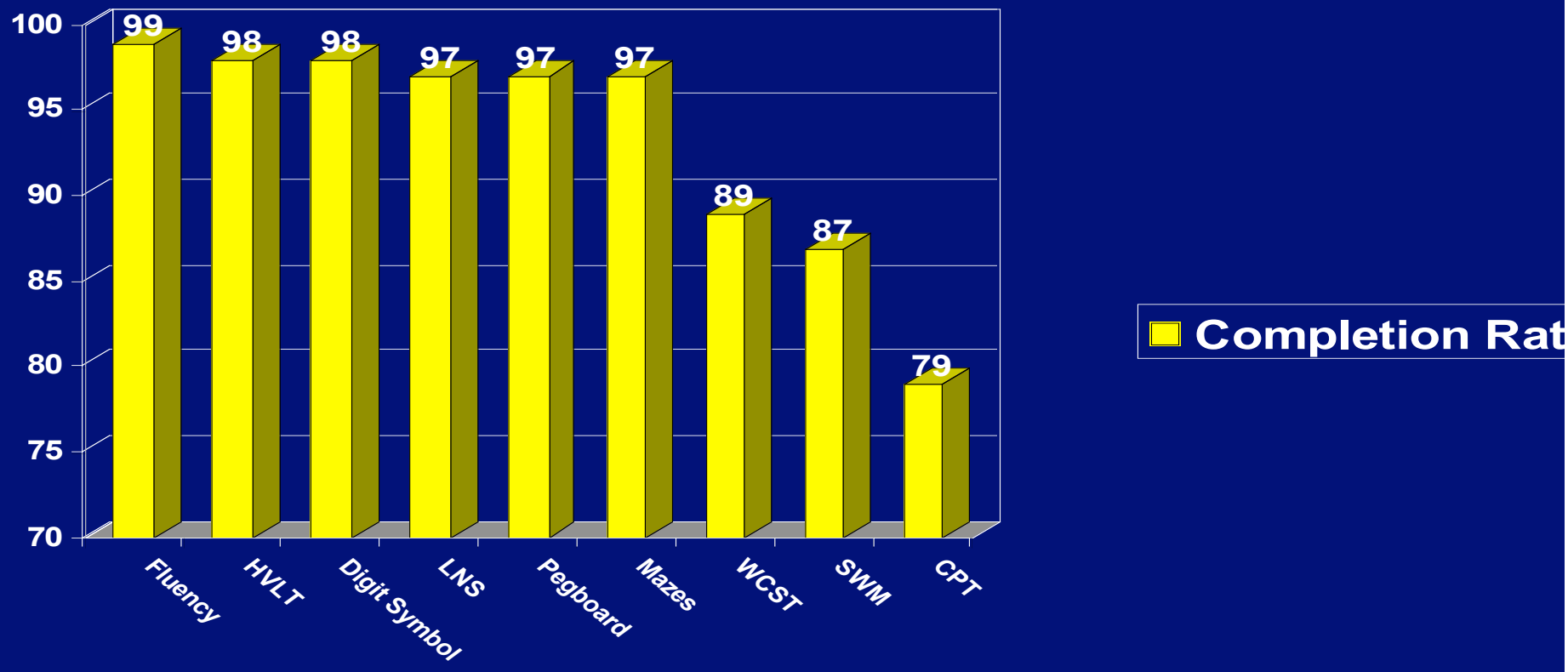
F-statistic for all steps was greater than 193.0; all P-values <.0001; N=1035

WAIS-R=Wechsler Adult Intelligence Test, Revised; HVLT=Hopkins Verbal Learning Test; WISC-III=Wechsler Intelligence Test for Children, 3rd ed; WCST=Wisconsin Card Sorting Test

Keefe et al, *Neuropsychopharmacology*, 2006

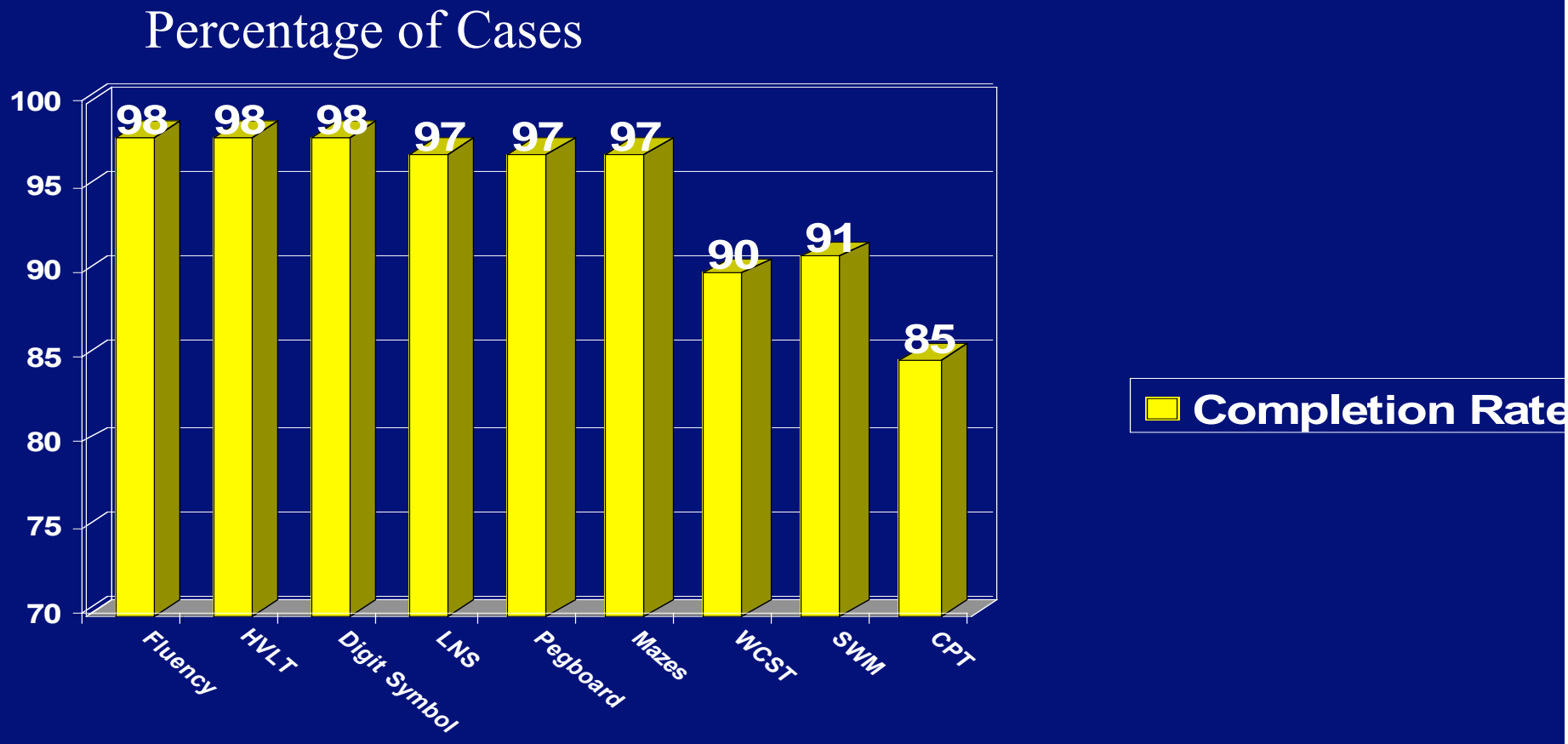
Baseline Completion Rates

Percentage of Cases



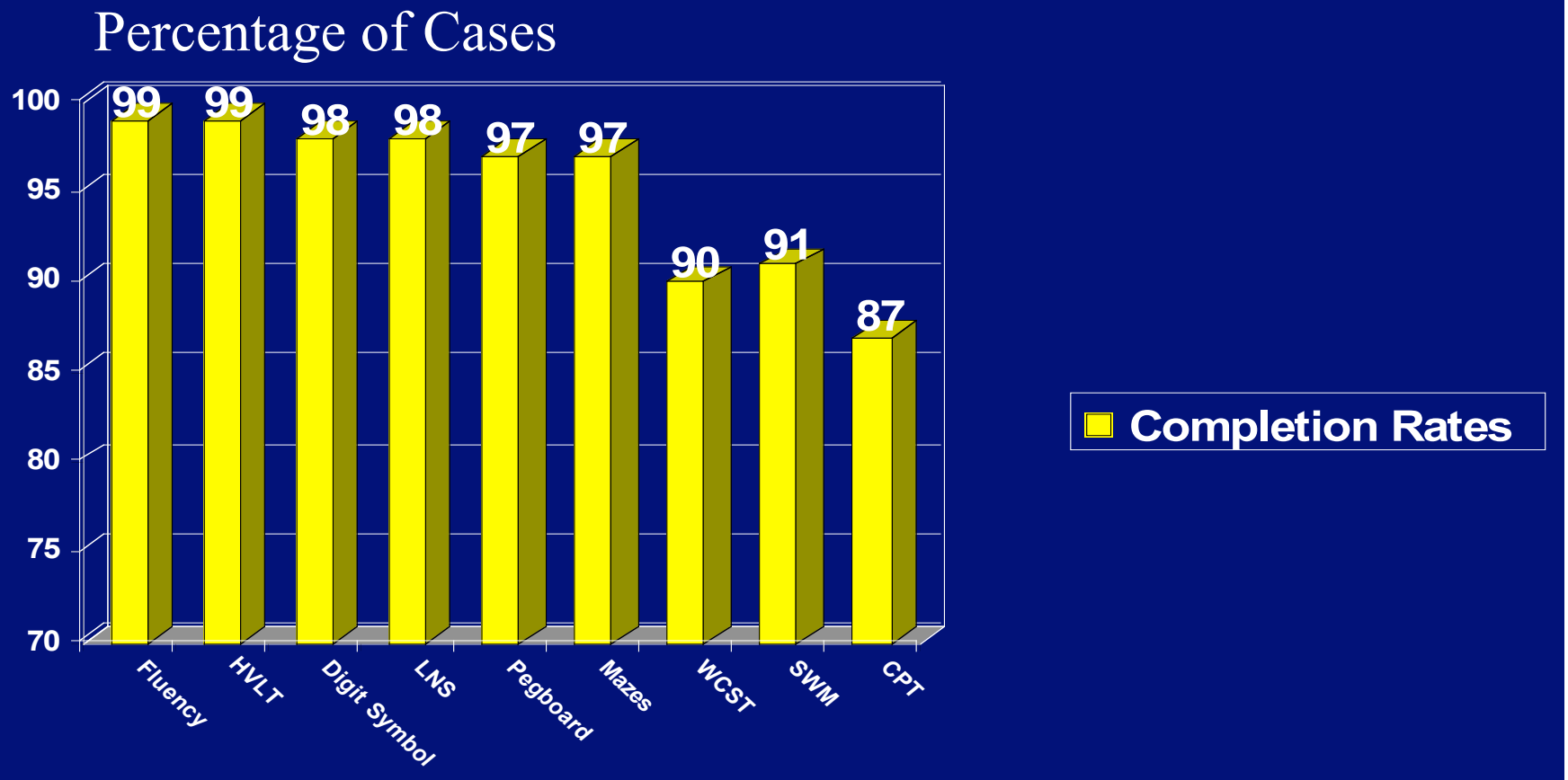
Keefe et al., *Neuropsychopharmacology*, 2006; total n=1427

First Reassessment Completion Rates



Keefe et al., 2007; total n=967

Second Reassessment Completion Rate

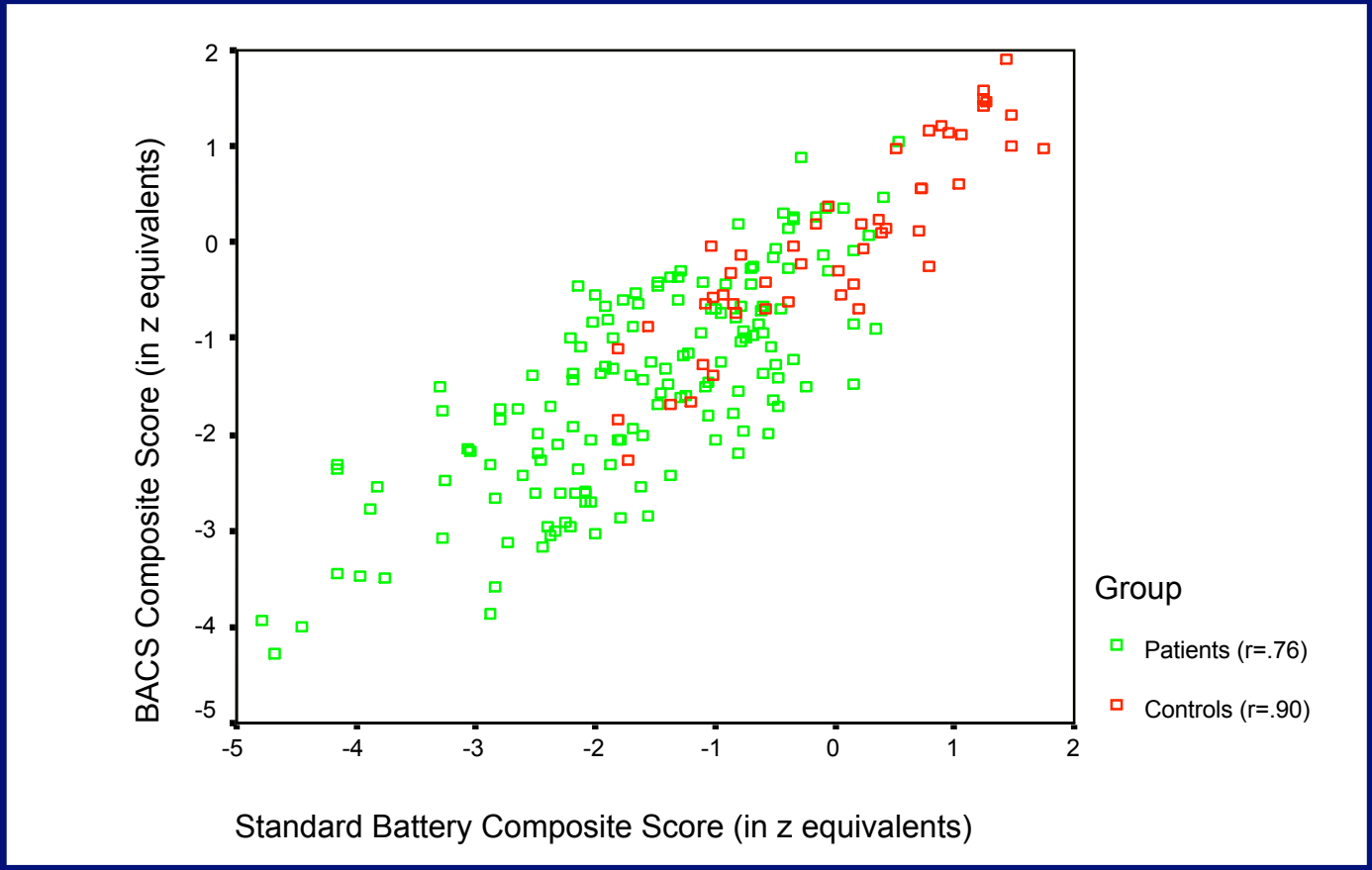


Keefe et al., 2007; total n=825

Preliminary Conclusions

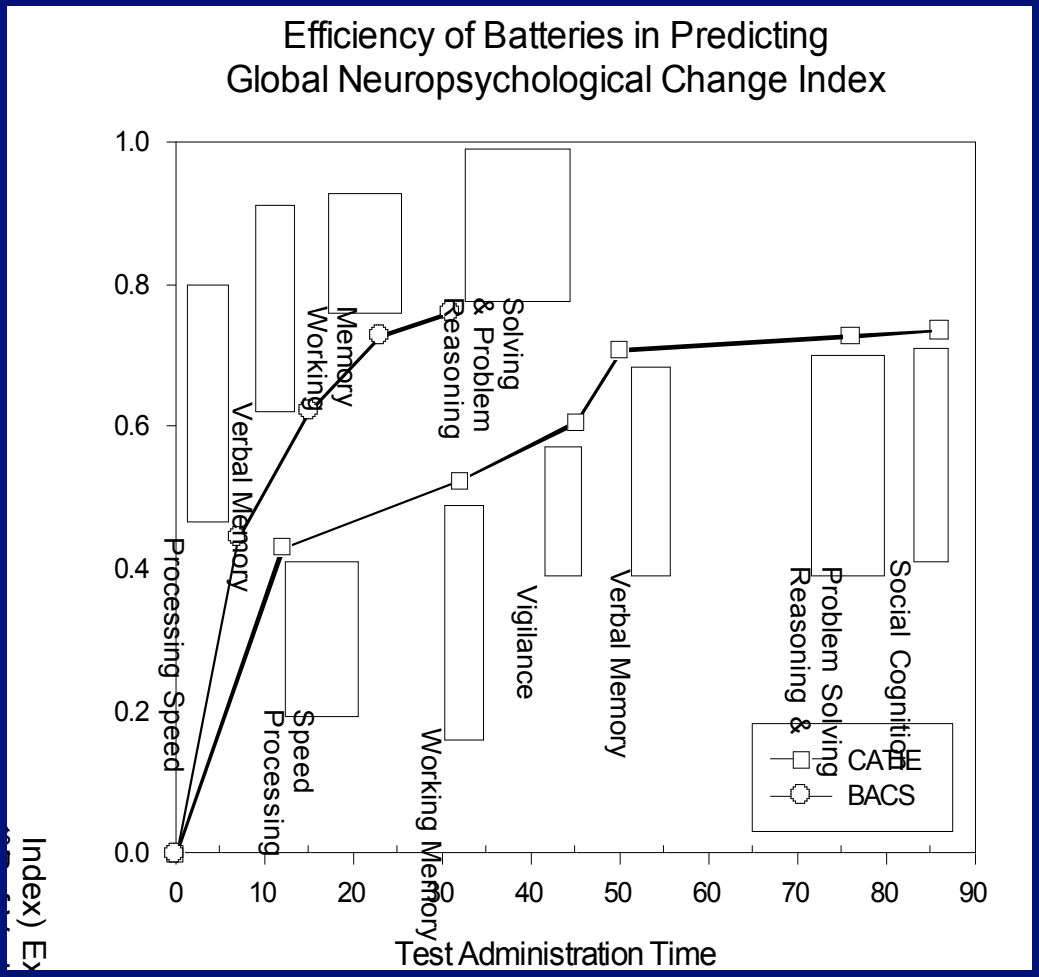
- Computerized tests look like they have considerably lower completion rates
- By the time you get to assessment 3, you have 40 cases who are not evaluable (because of current or prior missing data) on the HVLT, 407 on the CPT and 336 on the WCST

BACS and Standard Battery Composite Scores fo Patients and Controls



Keefe et al, *Schizophrenia Research*, 2004; 68: 283-297

Efficiency of Cognitive Measures in First Epis Psychosis Patients (N=216)



Hill et al, *JINS* (in press)

CATIE and BACS scores correlated 0.84 at baseline, 0.90 after one year of treatment.

Both the CATIE and Brief Assessment of Cognition (BACS) batteries had similar levels of information efficiency in aggregate (CATIE: R2=.736, F=98.68, df=6,212, p<.001; BACS: R2=.760, F=169.12, df=4,214, p<.001), yet the BACS achieved this in a much shorter period of time

And it is much more complicated than th

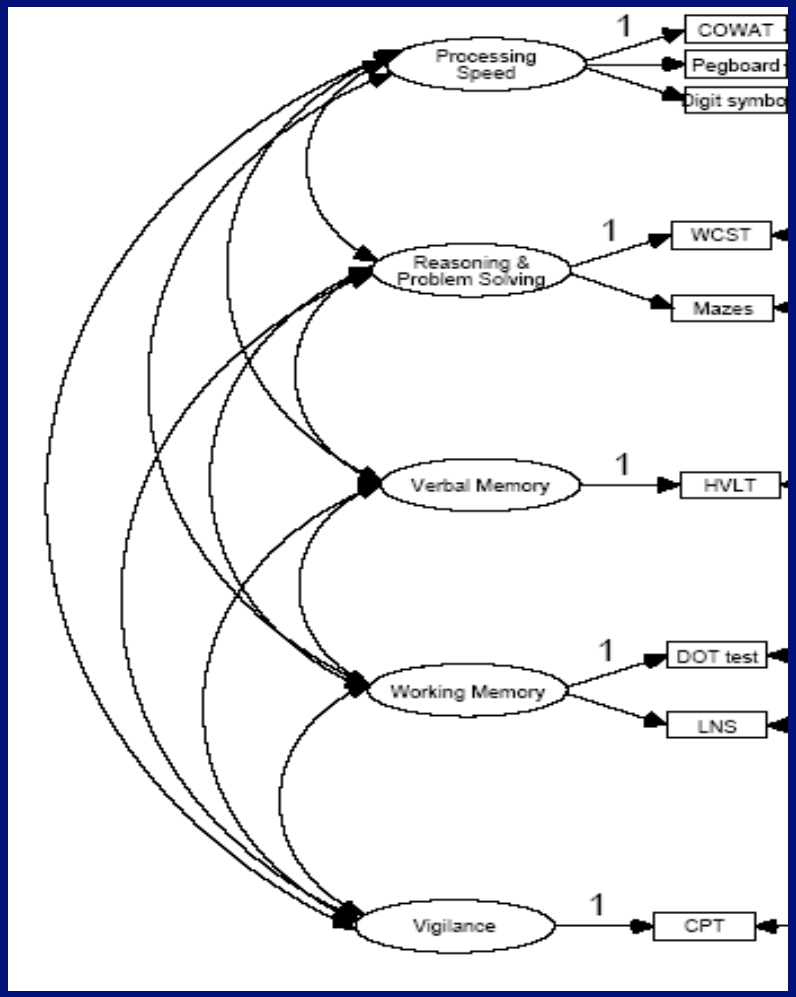
- Prediction of things other than global N score may result in different subsets o abbreviated assessments
- Prediction of Global NP Score, Genera Deficit Score (GDS), UPSA Score, SSPA Score, Every day outcomes
- N=246

Best Two NP Predictors/ Variance Accounted

Outcome	Predictors	% Variance
Global NP	TMT B, RAVLT	64%
GDS	TMTB, Digit Sym	72%
UPSA	Digit Sym, Bos Name	40%
SSPA	DS Backward, TMT A	32%
SLOF Functional	TMT A, Animal FL	24%

Harvey et al., submitted

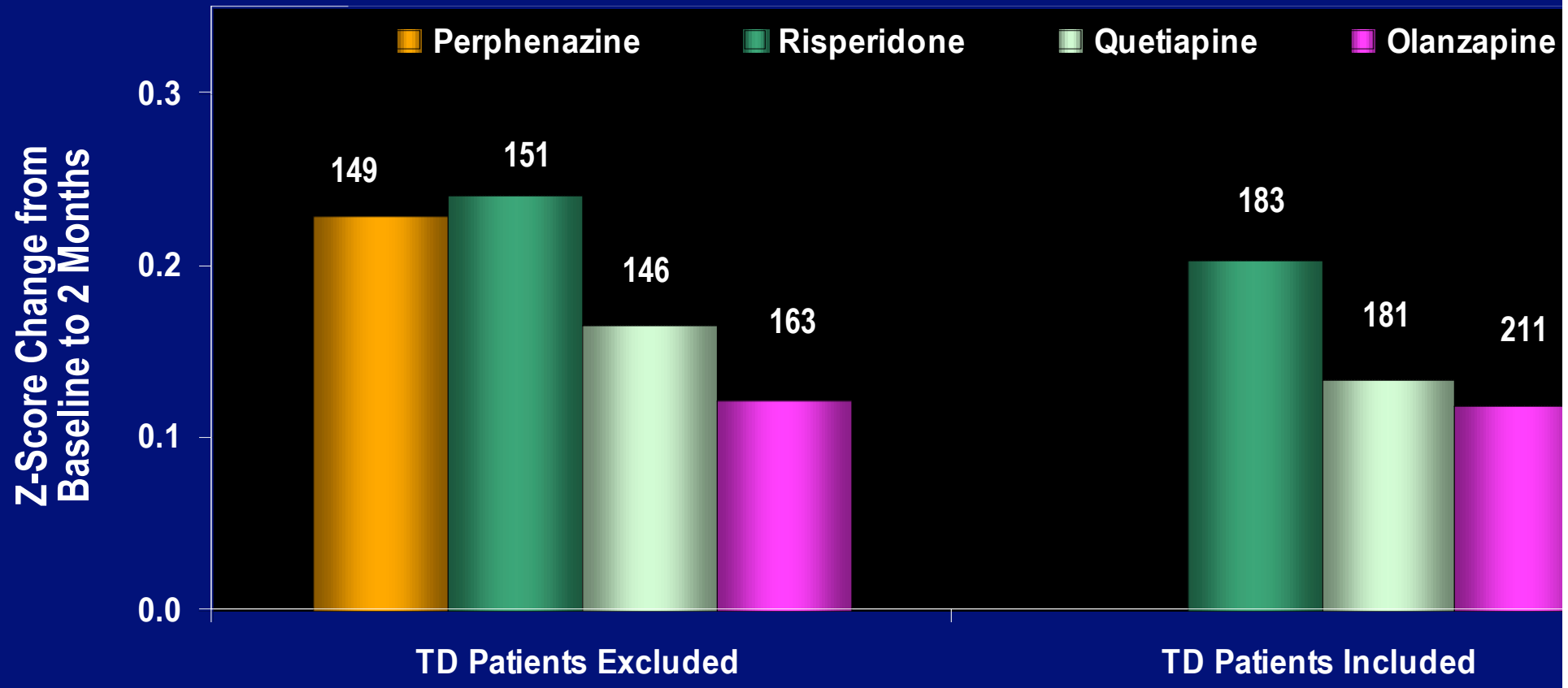
Structural Equation Modeling Analyses on CATIE Baseline Data (N=1331)



- Null model failed to fit the data
- A unifactorial model based on the ni tests was an improvement in fit; χ 2(27)=192.18, p<0.001; CFI=.94, GFI= RMSEA=.077
- A unifactorial model including the fi pre-defined domain scores was a considerable improvement in fit ove unifactorial model from the nine test (22)= 152.27, p<.001; CFI=.98, GFI=.9 RMSEA=.080 .
- A five-factor model that included the tests from each of the five cognitive domains as separate factors was a significantly poorer fit compared to unifactorial model from the five pre-defined domain scores χ2(14)=78.04 p<.001.

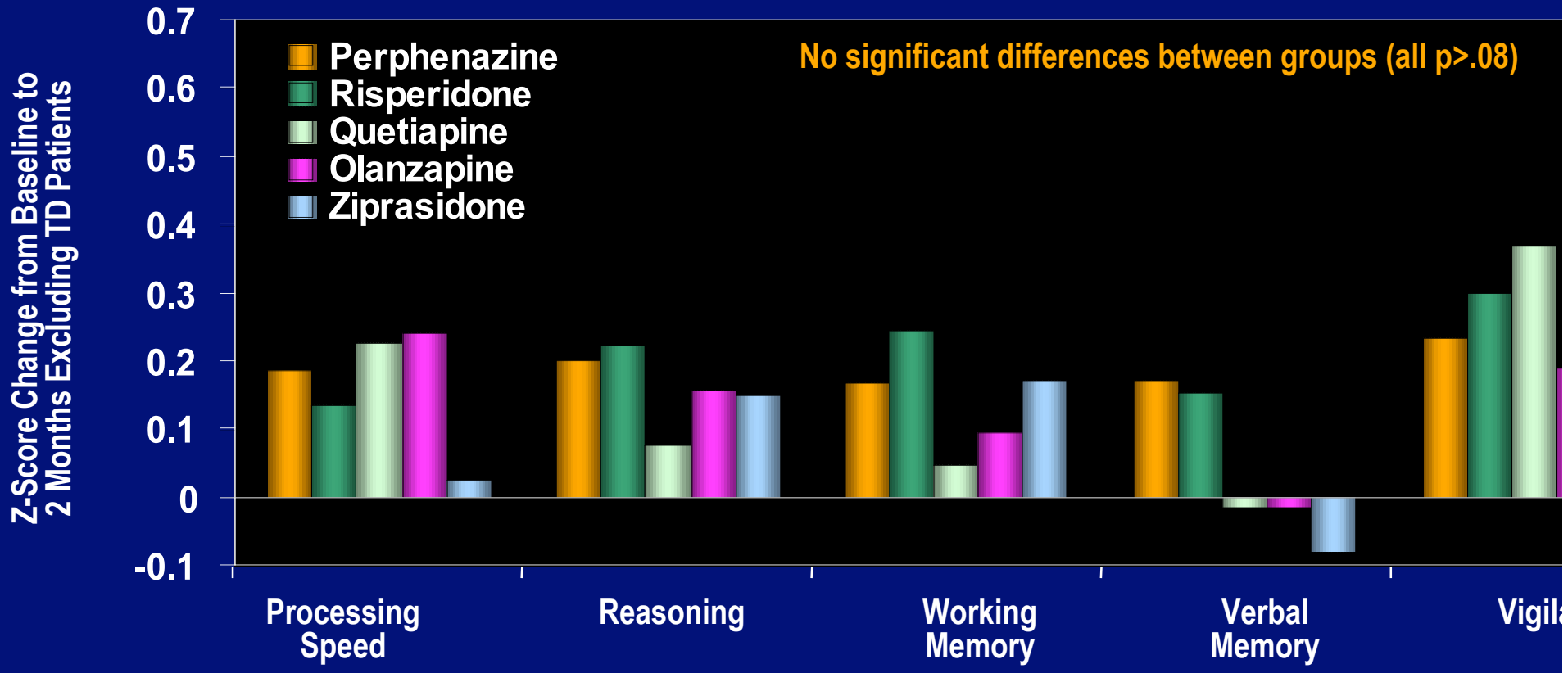
Keefe et al, *Neuropsychopharmacology*, 2006

Change in Neurocognitive Composite Sco After 2 Months of Treatment



N above histogram. No significant differences between treatments (p=.20). TD=tardive dyskinesia.
Keefe RSE, et al *Arch Gen Psychiatry* (2007).

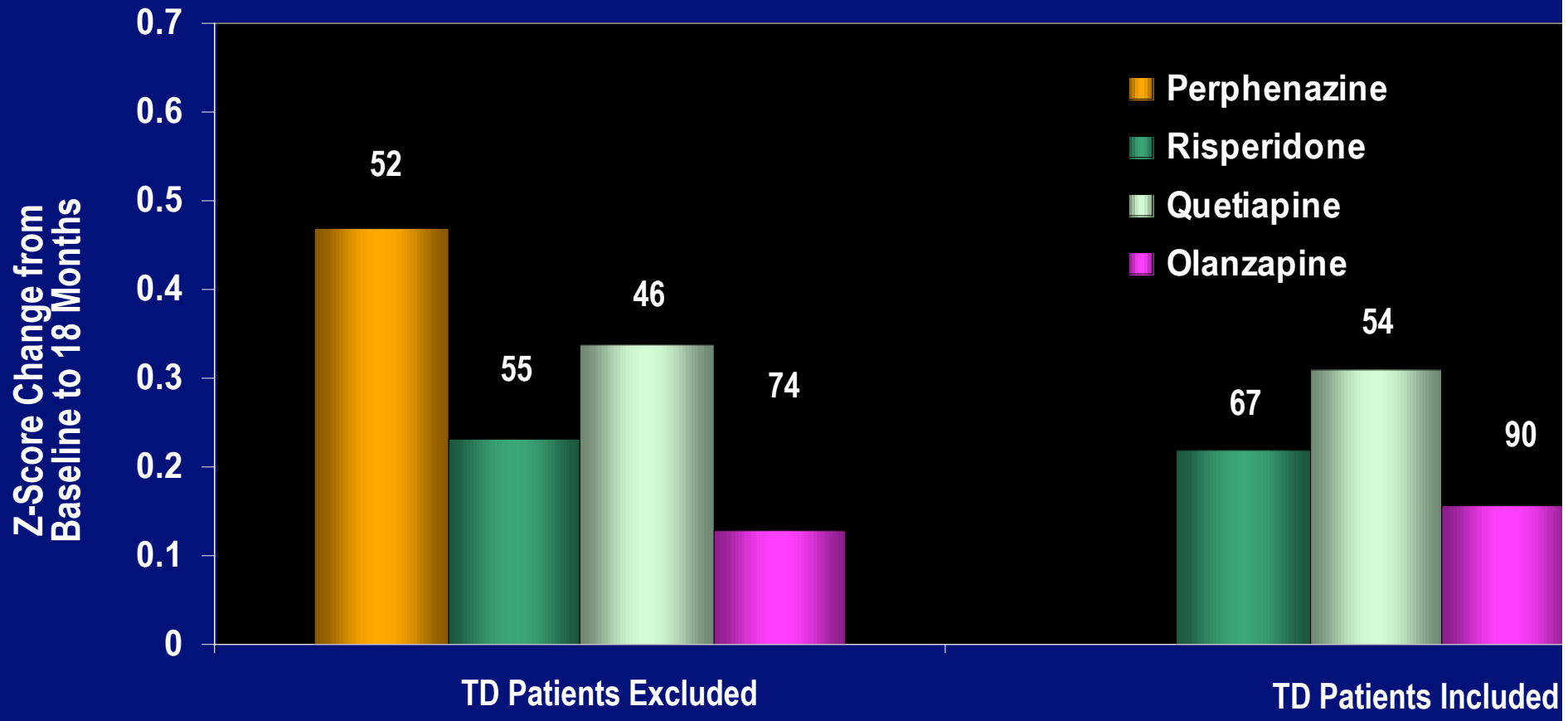
Change in Neurocognitive Domains After Months of Treatment



TD=tardive dyskinesia.

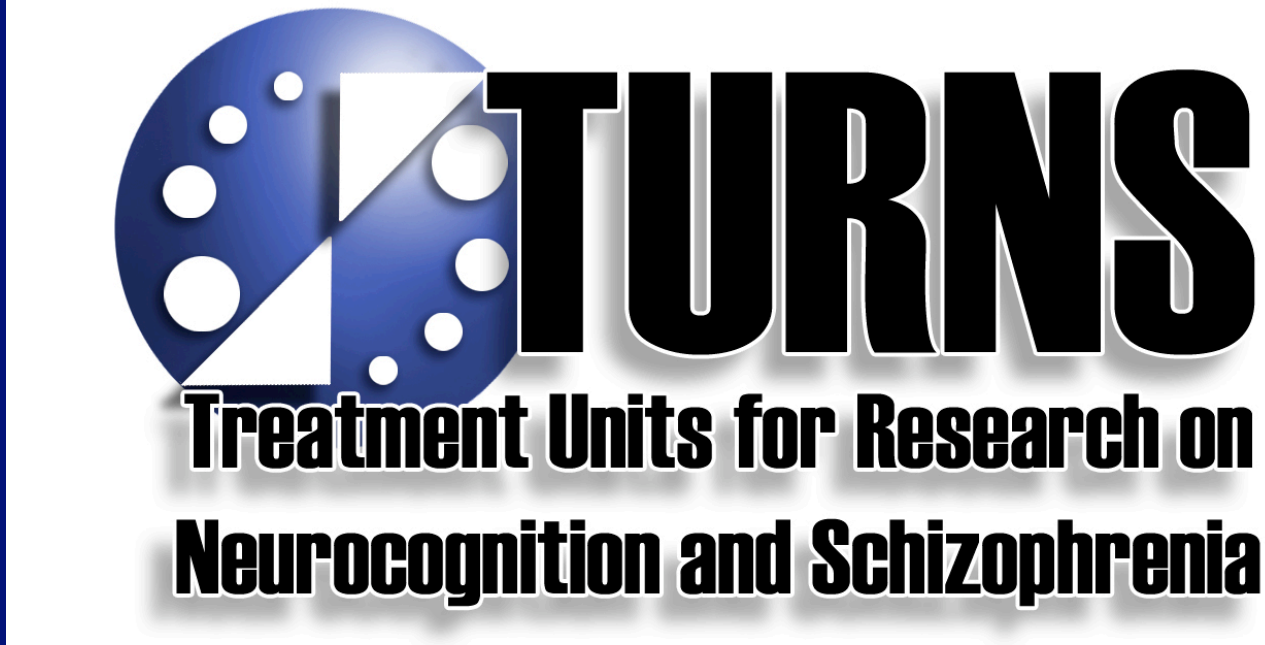
Keefe RSE, et al *Arch Gen Psychiatry* (2007).

Change in Neurocognitive Composite Sco After 18 Months of Treatment



N above histogram. TD=tardive dyskinesia. Overall differences between treatments ($p<.05$).
Keefe RSE, et al, *Arch Gen Psych* (2007).

TURNS


TURNS
Treatment Units for Research on
Neurocognition and Schizophrenia

TURNS Schedule of Cognitive Assessme

|----------Double-blind treatment---------|------Follow-u

Measure	Baseline	Week 4	Week 8	Week
MATRICS battery	Org/MK	Org/MK	Org/MK	
Ancillary Cognitive Measures	Org/MK	Org/MK	Org/MK	
SCoRS	Org/MK	Org/MK	Org/MK	Org
UPSA	Org/MK	Org/MK	Org/MK	

Org = Organon 24448 (faramptor) Study; MK= Merck 0777; SCoRS = Schizophrenia Cognition Rating Scale; UPSA = UCSD Performance-based Skills Assessment

Collaborators

Duke

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