Multi-Center Research: Cognitive Data in the SEARCH for Diabetes in Youth Study using the NIH Toolbox

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Here, it's different.

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Disclosures:

There are no disclosures to report

overview

- Cognitive assessment in multisite clinical empirical studies
- SEARCH4 study
- NIH Toolbox
- Challenges, progress and impressions

Multi-site studies in pediatrics

- COG (CCSG) neurocognitive studies successful in demonstrating the deleterious effects of CRT in ALL (Long term event free survival in ALL now about 85% despite move from use of CRT in average risk ALL) but more recent studies have had less successful retention:
  - Long batteries, hard for ill children
  - Requirement for trained personnel
- Urea cycle longitudinal study
  - Different batteries across different ages
  - Locally developed measures
  - Long protocol resulting incomplete batteries, inconsistent data
  - Weak retention
  - Requirement for trained personnel

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And

DIRECT COGNITIVE ASSESSMENT IS OFTEN EXCLUDED FROM CLINICAL STUDIES

SEARCH; a surveillance study, capturing the natural history, quality of care and outcome of children and adolescents with diabetes mellitus

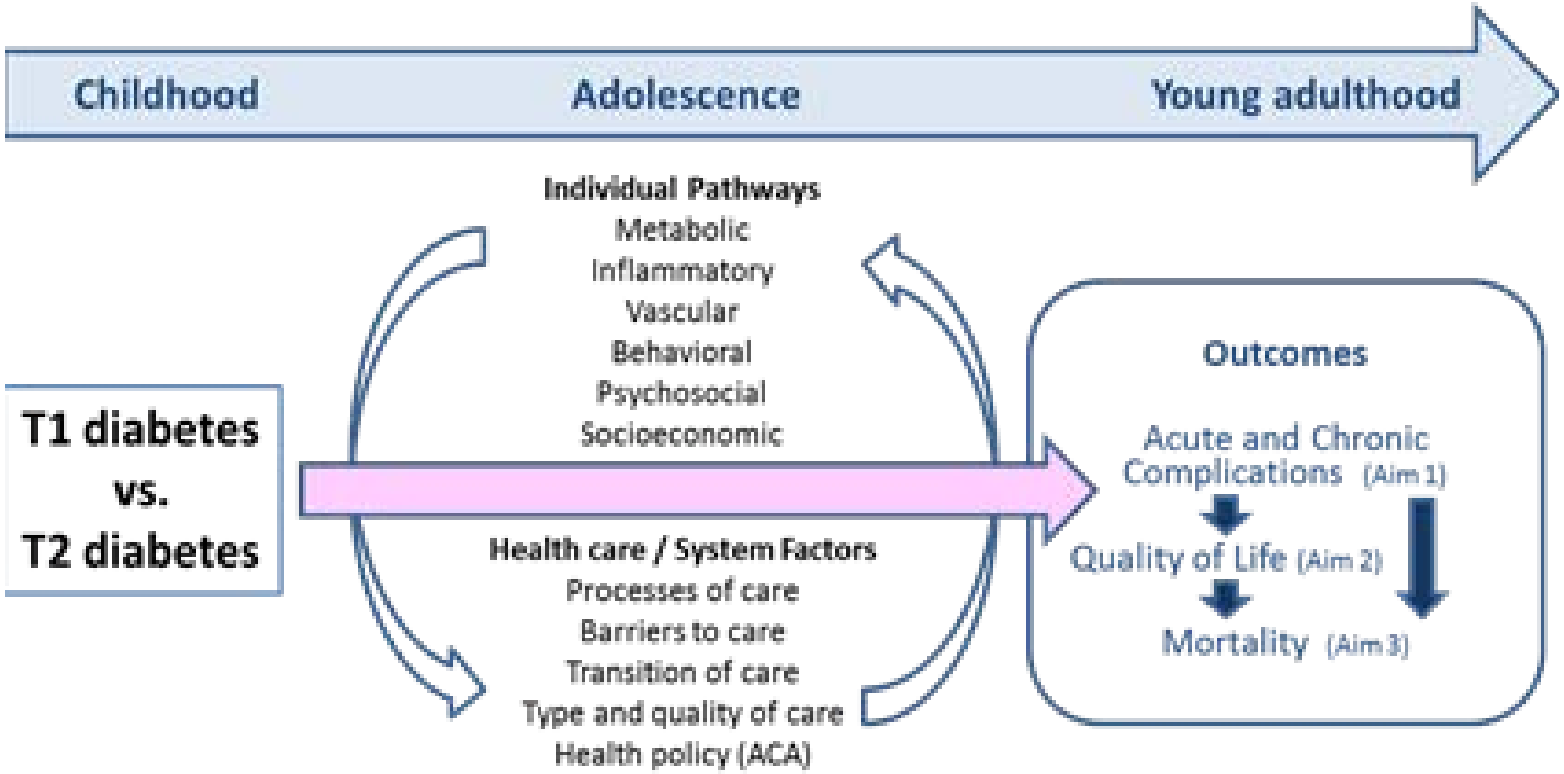
- multi-center population-based study of youth with diabetes (T1D and T2D) initiated in 2000

- SEARCH 4, current study, opened 2016

Primary aims of initial (2000) SEARCH protocol

- Estimate of the population prevalence and incidence of T1D, T2D, and other types of diabetes by age, gender and race/ethnicity
- Develop efficient and practical approaches to the classification of diabetes type for prevalent and incident cases
- Describe and compare clinical presentation and course of T1D, T2D and other types of diabetes

SEARCH4


Childhood
Adolescence
Young adulthood
Individual Pathways
Metabolic
Inflammatory
Vascular
Behavioral
Psychosocial
Socioeconomic
T1 diabetes
vs.
T2 diabetes
Health care / System Factors
Processes of care
Barriers to care
Transition of care
Type and quality of care
Health policy (ACA)
Outcomes
Acute and Chronic Complications (Aim 1)
Quality of Life (Aim 2)
Mortality (Aim 3)

SEARCH 4 Aim 1 (2016)

- Determine the prevalence and incidence of acute complications (severe hypoglycemia and diabetic ketoacidosis)
- To determine the burden (prevalence, incidence and progression) and clustering of diabetes-related acute and chronic complications
  - Retinopathy
  - Nephropathy
  - Autonomic neuropathy
  - Peripheral neuropathy
  - Arterial stiffness
- To determine the prevalence of
  - Cardiac damage
  - Pregnancy outcomes
  - **Neurocognitive outcomes**

- 2015 asked to design a cognitive component to the study

Registry and cohort components- Who is enrolled in cohort study?

- Individuals with T1 or T2 diabetes,
  - Diagnosis confirmed by physician
  - Less than 20 years of age at time of dx

Table 4. Sampling plan for visit C_2			
Sample	**NHW**	**Minority**	**Total**
All T2D	64	318	382
All minority T1D	0	764	764
700 NHW T1D*	700	0	700
Total	764	1,082	1,846
* 300 onset age < 10; 400 onset age ≥ 10			

  - N ≈ 1800
- Multiple sites

Ohio	8 urban and suburban counties encompassing and surrounding Cincinnati
Washington	5 urban counties encompassing and surrounding Seattle
South Carolina	selected counties in 2001, all counties in subsequent years
Colorado	selected counties in 2001, all counties in subsequent years
California	health care plan enrollees
Indian Health Service beneficiaries	Arizona /New Mexico (sometimes grouped in CO cohort)

Challenges in planning cognitive assessment

- no prior attempt at collecting cognitive data in this large, distributed and diverse population
  - mean age of eligible S's is 21.9 years, 12-35 years of age
  - Racial, ethnic and educational diversity
  - No substantial language diversity was identified
- Assessment to be completed by PRA's across the country, none with prior training in psychological assessment
- Cognitive assessment to be completed as part of a lengthy visit that starts with participants fasting
- No internet at some sites

Data Collected on Cohort Study Participants	SEARCH 4
Surveys:	
Employment, education: parent or youth > 18 years	X
Pubertal status, co-morbidities; family history	X
Pregnancy outcomes in females	X
Medication: Diabetes & related conditions	X
Behavioral: Diet, physical activity, alcohol use	X
Marijuana, other substance use	X
Processes of care/quality of care	X
Health care costs	X
Psychosocial: Depression (CES-D)	X
Family conflict; fear of hypoglycemia	X
Transitions of care	X
Food security and assistance	X
Stressors; work ability index; stigma/discrimination	X

Laboratory measures (blood):	
Fasting glucose, cystatin C, serum creatinine, fasting C-peptide, lipid profile, inflammatory markers (CRP, IL6), A1c, AGE (CML), DNA, miRNA extraction	X
URINE: albumin, creatinine (first morning void)	X
Stored Samples: DNA, miRNA, serum, plasma, urine	X
Outcome(s):	
Cardiovascular: Arterial stiffness (PWV, AiX)	X
Cardiac echocardiography: LV mass, systolic & diastolic function	X
Neuropathy: heart rate variability; peripheral neuropathy	X
Retinopathy Retinal photos, vessel caliber	X
Nephropathy: Albuminuria	X
Cystatin C	X
Neurocognitive tests: NIH Toolbox.	X
Acute complications: DKA, hypoglycemia	X
Quality of life (Peds QL3.2 Diabetes Module)	X
Mortality surveillance (NDI)	X

NIH Toolbox – cognitive measures

- Designed for longitudinal assessment, with the tests consistent across ages
- Designed to be administered non-psychologists
  - Limited decision making required, termination rules built in
  - Instructions often recorded, or read from the screen
- Substantially shorter then traditional assessment
- With iPad administration internet access is not required at the time of administration
- Scoring is generally automatic
- Fully adjusted standard scores available to accommodate diverse populations
- Integrated system for communicating data to the coordinating center

What cognitive skills are assessed?

- Crystallized skills
  - Picture Vocabulary
  - Oral Reading Recognition (omitted from the final battery; time, examiner concerns about local dialect and ability to rapidly score)
- Fluid reasoning skills
  - Pattern Comparison Processing Speed Test
  - List Sorting Working Memory Test
  - Flanker Inhibitory Control and Attention Test
  - Dimensional Change Card Sort Test
  - Picture Sequence Memory Test

Empirically based areas of concern for individuals with diabetes

T1D – subtle deficits in

- Speed of information processing
- Psychomotor efficiency
- Attention
- Visuo-construction
- Mental flexibility

T2D – more consistent deficits in

- Memory
- Psychomotor speed
- Tasks of executive functioning
  - Planning
  - Attention
  - Mental flexibility
  - Judgment
  - Organization

Areas of concern assessed and not assessed by NIH toolbox

Addressed

- Speed of processing
- Memory
- Mental flexibility
- Attention
- Judgment – response inhibition

Not addressed

- Visuo-construction
- Organization

Assessment was introduced Fall, 2015

- Areas that would not be assessed
- How PRA's would accommodate to completing cognitive assessment
- How participants would accept cognitive assessment
- Additional time required
- Toolbox platform had just migrated to iPad administration
- Concern about recognition of safety issues

Use of NIH Toolbox in multi-center clinical studies

- Searched NIH Toolbox web site, Ovid and Google, updated September, 2017
  - From 2008 on
  - Search term “NIH Toolbox”, reviewed identified studies
    - Focused upon cognitive performance (e.g. not grip strength)
    - Not part of the standardization or validation process for the NIH toolbox
    - Answered a clinical question, i.e. not a study of normal development
    - Multi-centered; not the same city
- Multiple studies from the development and standardization studies
- 14 empirical multi-site studies non-standardization studies published from 2008- September, 2017
  - 2 **clinical**, empirical, multi-site non-standardization/validation studies

Process: Training and monitoring

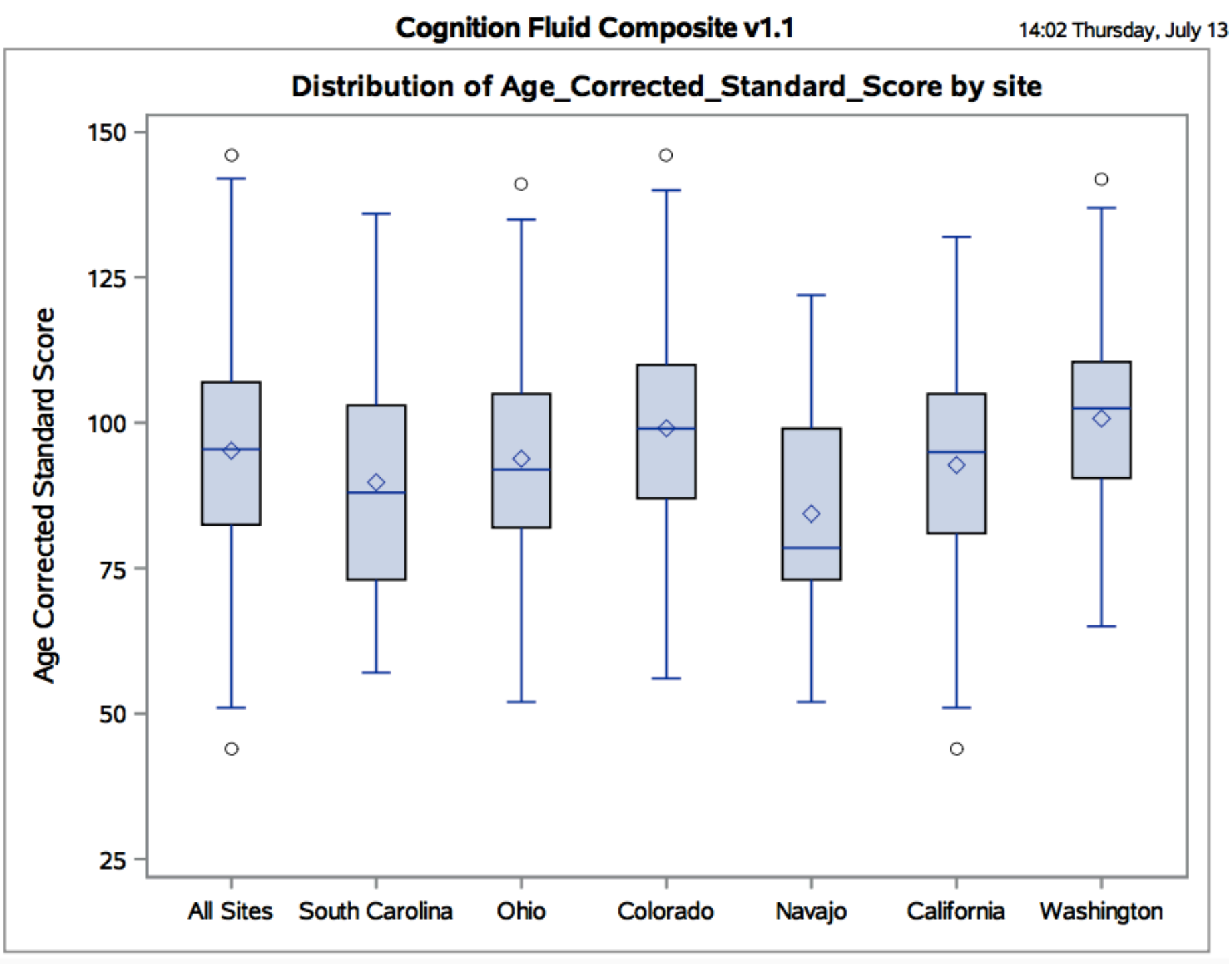
- 2 day face-to-face training with PRA's
- Assessment of PRA's
    - Knowledge of testing requirements
    - Observed administration of measures
- Added assessment of quality of performance/variants to MOP to data capture system
- Added "script" for PRA's to introduce the Toolbox to participants
- Repeated assessment of knowledge base of PRA's
- Data monitoring with follow-up retraining
    - unusual numbers of outliers
- Small groups phone calls to review administration and insure adherence to standardization procedures
- Repeat face-to-face training and observation scheduled next month

Issues

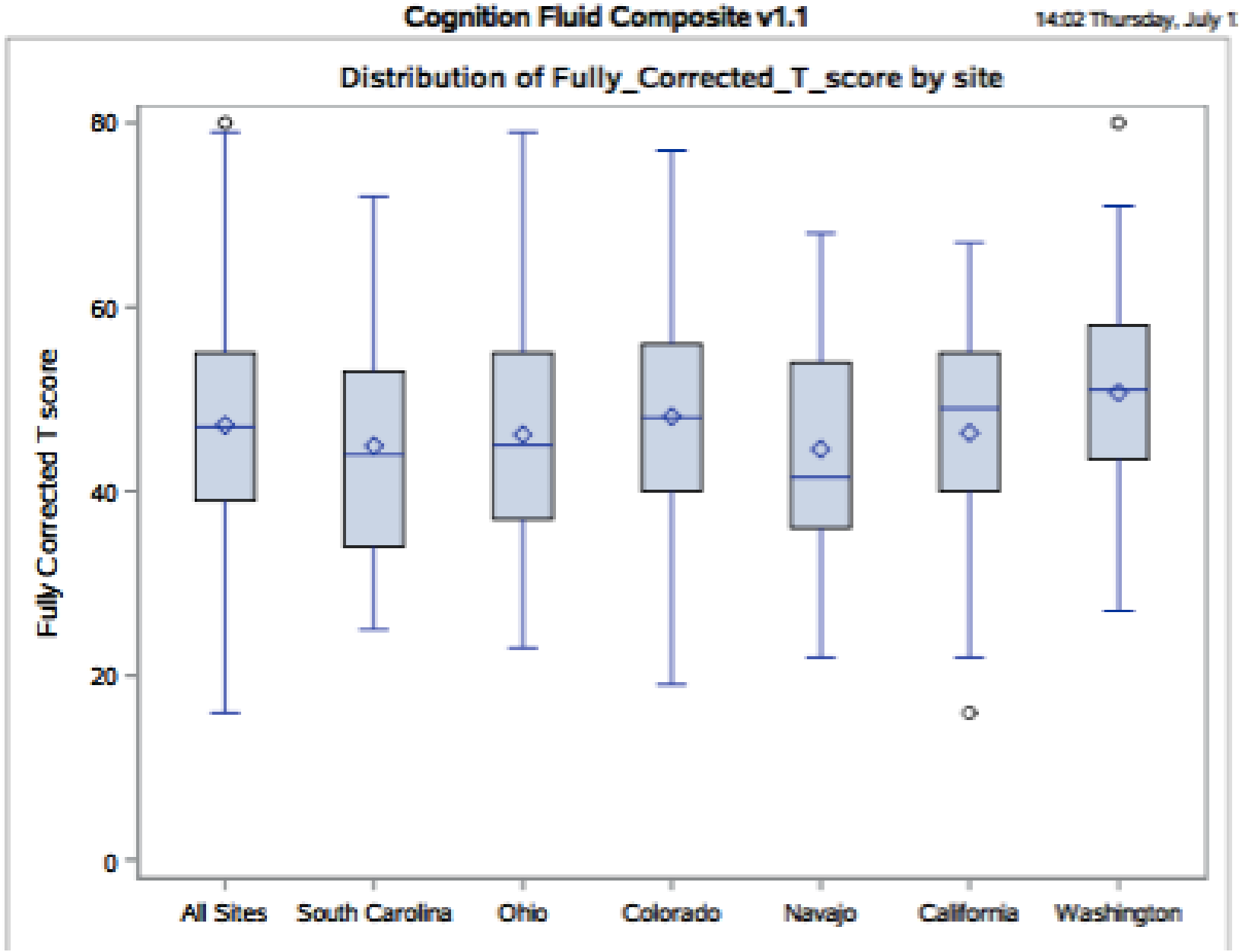
- One (of 15) original PRA's could not demonstrate reliable administration of Toolbox; reading inadequate
- Personnel changes
- Atypical participants
  - Vision difficulties
  - Previously diagnosed disability (autism, ID)
  - Recent health issues (hospitalizations)
- Changes in test
  - Updates of iPad version
  - Difficulties with uploading results

Progress to date, July 13, 2017

	Participants with neurocognitive data				Discrepancy with expected neurocognitive data	
Site	Total	Age 10-11	Age 12+	# with all 7 measures (t-score)	Clinic forms but no neurocognitive data	No clinic forms, have neurocognitive data
All Sites	553	6	547	517 (93.5%)	8	3
South Carolina	106	0	106	103 (97.2%)	6	0
Ohio	100	0	100	98 (98.0%)	0	0
Colorado	159	3	156	157 (98.7%)	0	0
Navajo	14	0	14	14 (100.0%)	1	0
California	88	1	87	65 (73.9%)	1	0



Colorado compared to Navajo
p <0.001



Colorado compared to Navajo
$p < 0.3$

Trends in data (not divided into T1D and T2D)

- Anticipated outcomes
  - Normal fluid cognition composite
  - Normal language, (crystallized skill)
  - Difficulties with inhibitory control
  - Difficulties with attention
  - Difficulties with working memory
- Unanticipated outcomes
  - Normal speed of processing
  - Adequate mental flexibility
  - Adequate semantic memory

Impressions, Conclusions

- Cognitive assessment as part multi-site study with geographically and ethnically diverse populations is possible using the NIH Toolbox
  - Only 1% of the participants seen are not completing the Toolbox
  - We are successfully completing assessment of most patients (94% have all scores)
  - Fully corrected scores appear to address SES/education issues allowing us to look at disease related variables
- Non-psychologists can successfully administer the Toolbox to a clinical population
- Cognitive evaluations are being completed without increased study costs
- Initial, unanalyzed cognitive data appears to mirror to the anticipated pattern of performance

To the developers of the NIH Toolbox
To the meeting planners
To you for your attention and interest
To the PRA's at the multiple sites who have been so diligent and have gracefully taken countless quizzes

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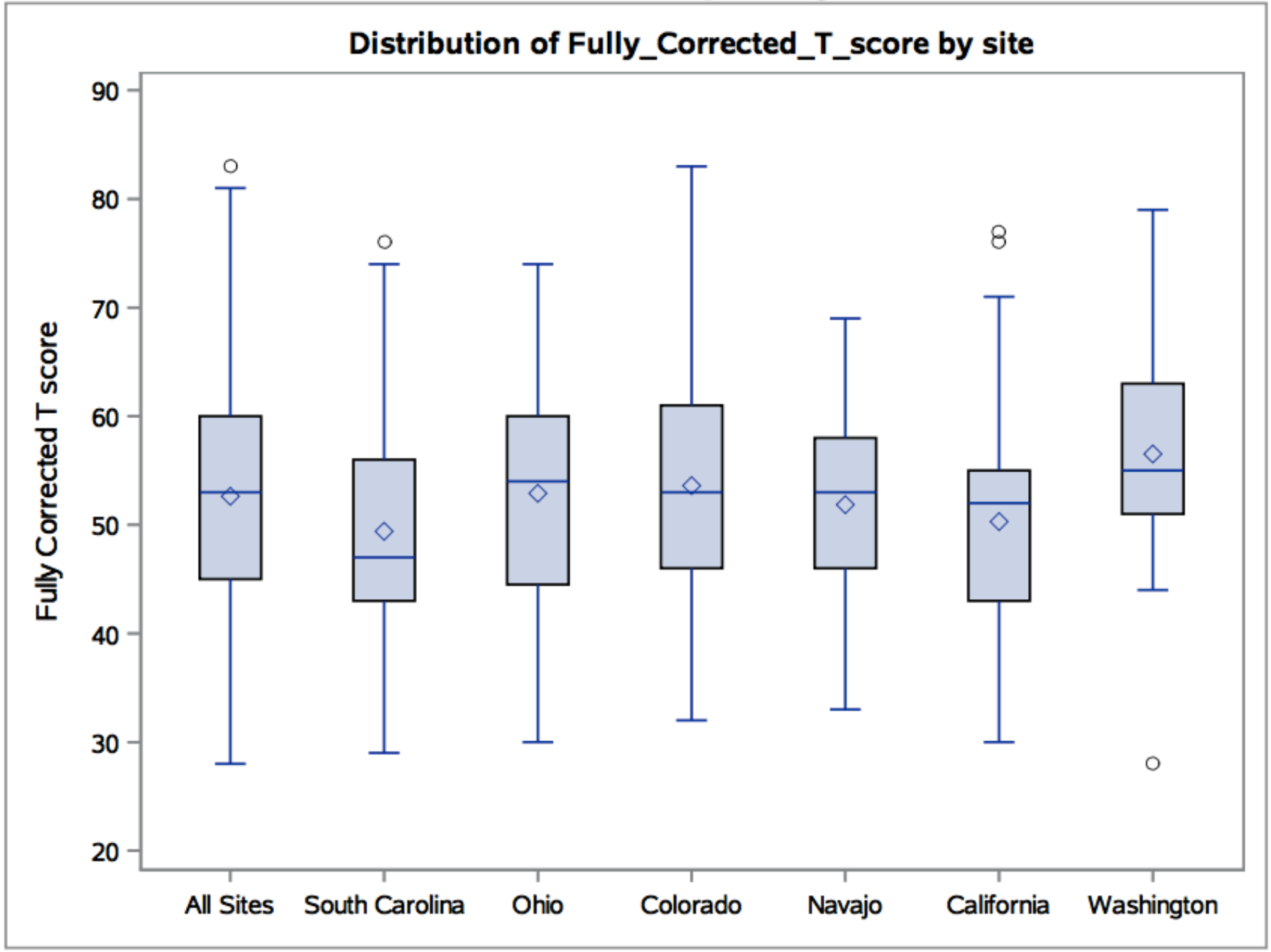
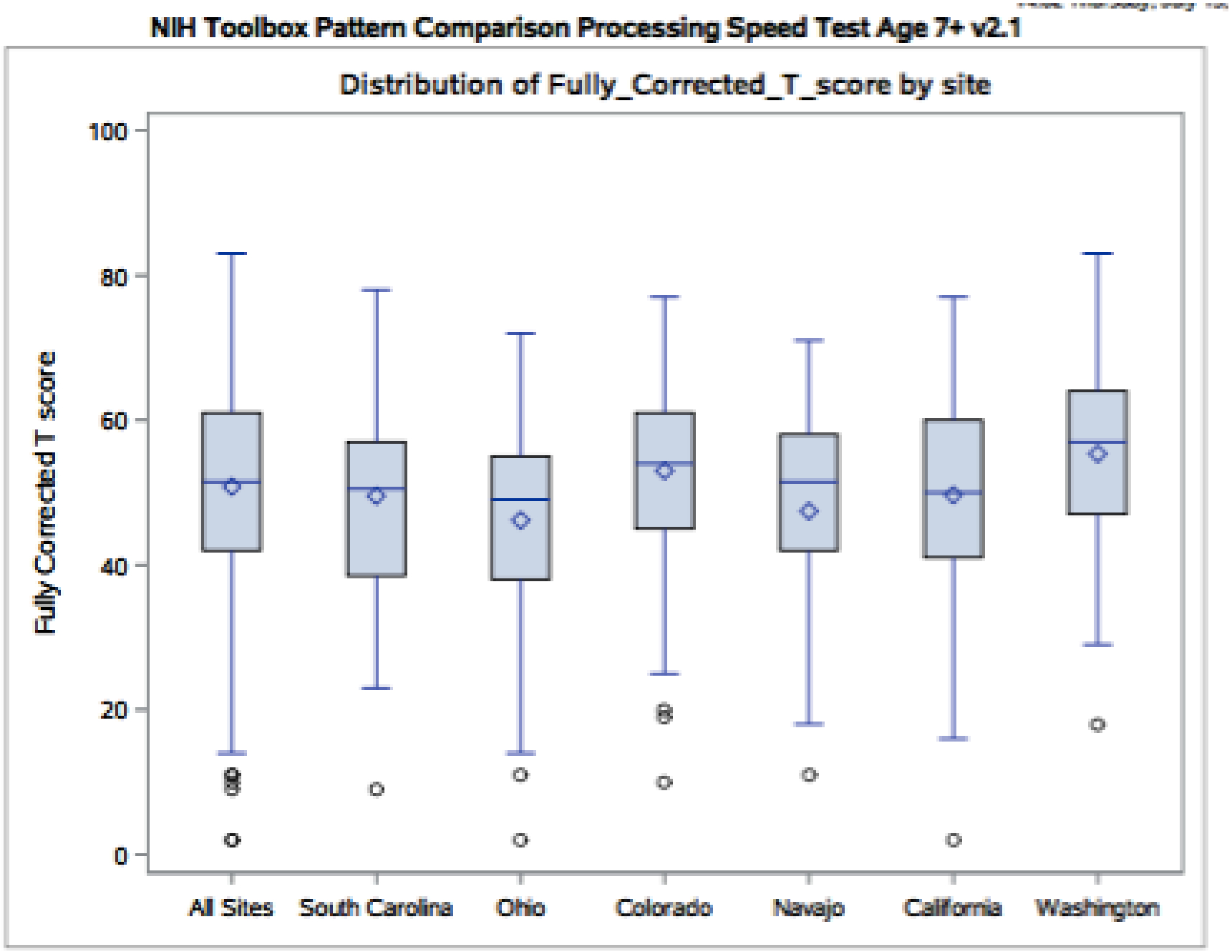

Distribution of Fully_Corrected_T_score by site
Fully Corrected T score
90
80
70
60
50
40
30
20
All Sites
South Carolina
Ohio
Colorado
Navajo
California
Washington


NIH Toolbox Pattern Comparison Processing Speed Test Age 7+ v2.1
Distribution of Fully_Corrected_T_score by site
Fully Corrected T score
100
80
60
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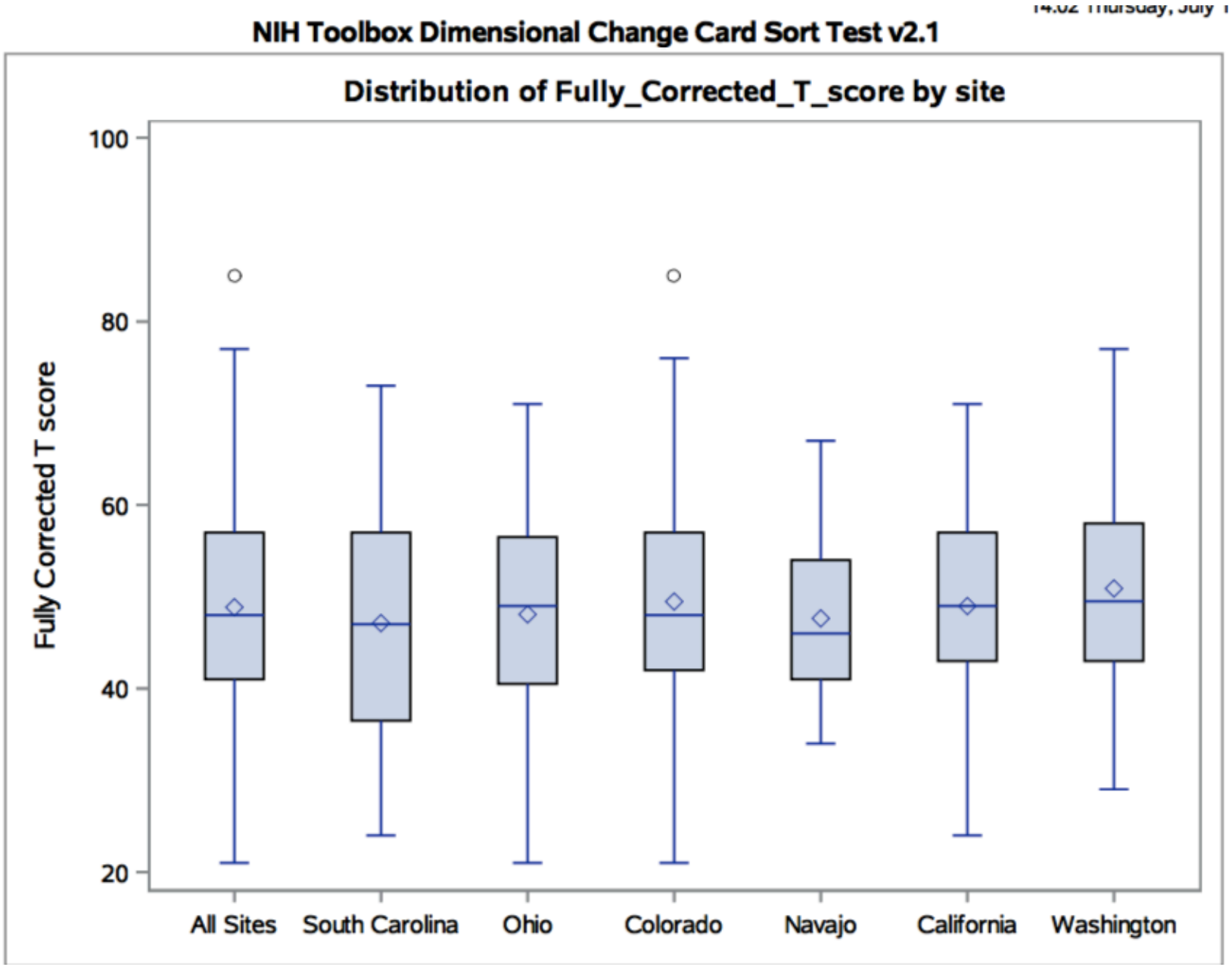
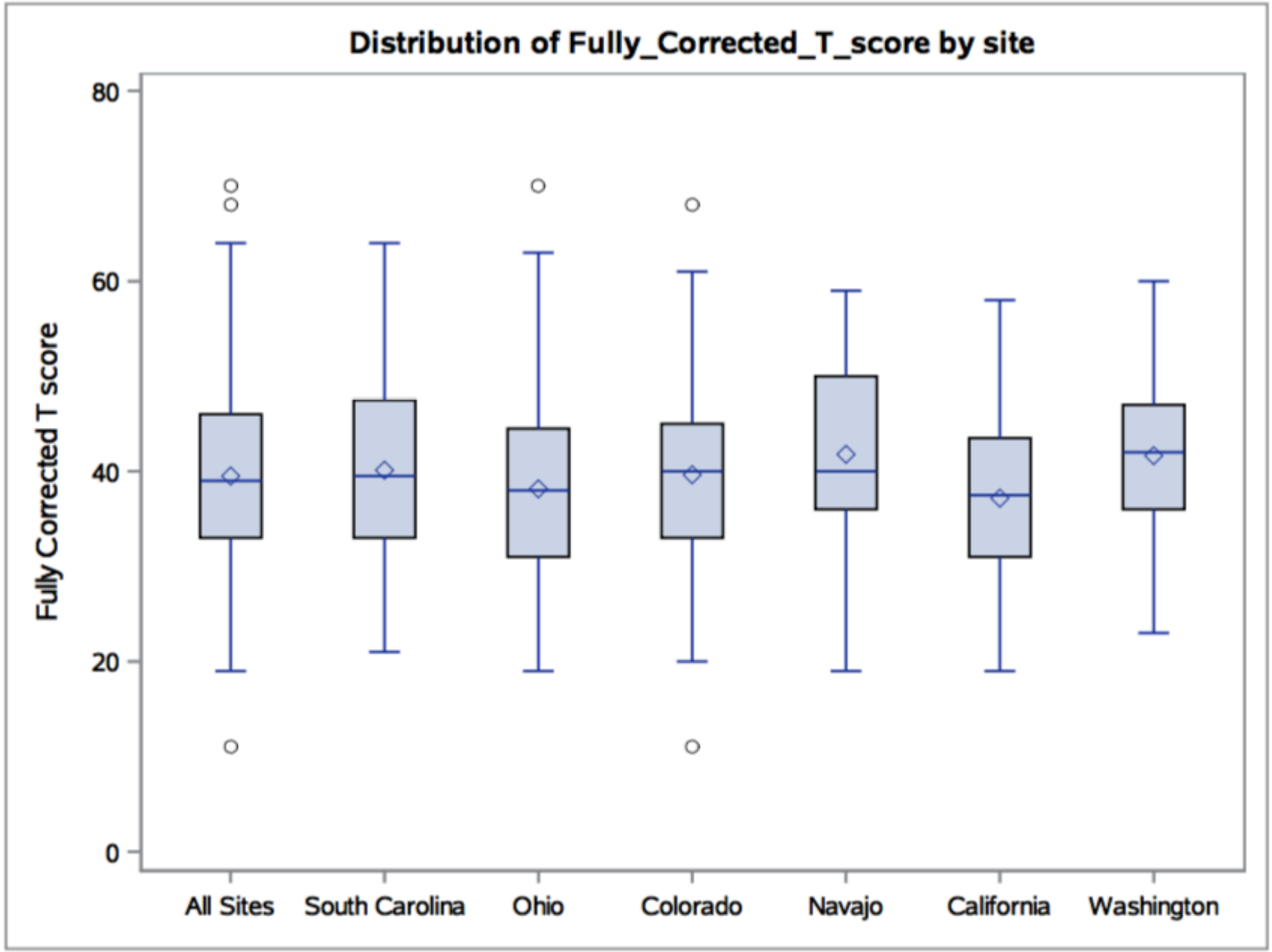
20
0
All Sites
South Carolina
Ohio
Colorado
Navajo
California
Washington

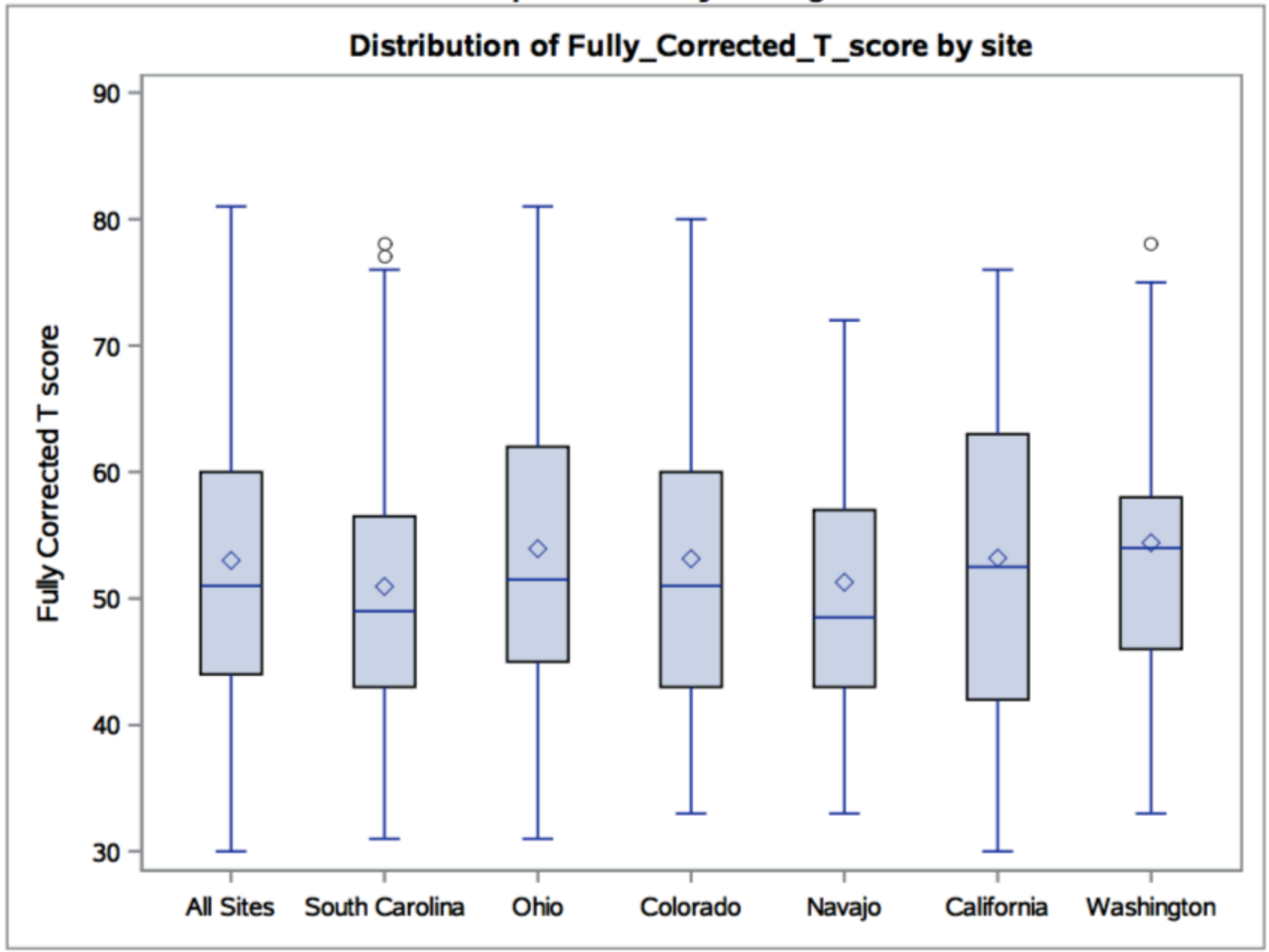
Mental flexibility- DCCS



NIH Toolbox Flanker Inhibitory Control and Attention Test v2.1



NIH Toolbox Picture Sequence Memory Test Age 8+ Form A v2.1



NIH Toolbox List Sorting Working Memory Test Age 7+ v2.1