UNIVERSITY of ROCHESTER MEDICAL CENTER

Age-Appropriate Endpoints to Assess Neurodevelopmental Outcomes

ADEPT-6
Pediatric Clinical Trial Endpoints for Rare Diseases with a Focus on Pediatric Patient Perspectives

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Disclosures (past 12 months)

Member, Medical Advisory Board

Batten Disease Support and Research Association

Research Support

- Abeona Therapeutics
- American University Centers on Disabilities
- Batten Research Alliance
- National Institutes of Health – NINDS; NIDDK

Consulting / Advisory Board Activities

- Amicus, Inc.
- Beyond Batten Disease Foundation (URBC)
- Neurogene (URBC)
- Taylor's Tale

Objectives

1. What is neurodevelopment? What are neurodevelopmental outcomes?
2. The patient perspective on ND outcomes – some considerations
3. Pediatric patient input on development and selection of ND outcome assessments
4. Relevance of neurodevelopment to non-neurodevelopmental outcomes
5. Some other considerations…

1. What is neurodevelopment?

Age dependent changes in the organization of the nervous system, especially early in life

Box 2. Structural architecture of the developing brain

The human brain undergoes dramatic changes in both its structural architecture and functional organization that reflect a dynamic interplay of simultaneously occurring progressive and regressive events. Although the total brain size is about 90% of adult size by age 6 years, the brain continues to undergo dynamic changes throughout adolescence and well into young adulthood [61]. Figure I illustrates some of these developmental changes, including proliferation and migration of cells mostly during fetal development [62,63], regional changes in synaptic density during postnatal development [11,12,64], and protracted development of myelination well into adulthood [65]. Current non-invasive neuroimaging methods do not have the resolution to delineate which of these processes underlies observed developmental changes beyond gray and white matter subcomponents.

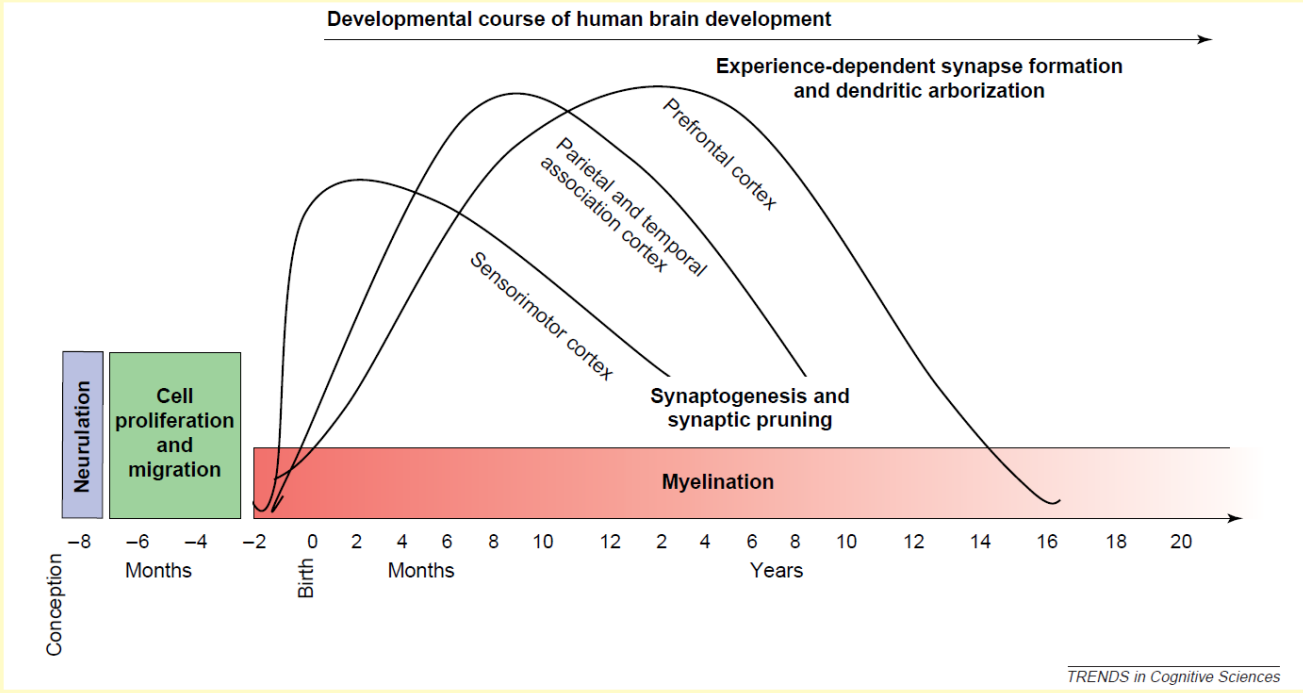
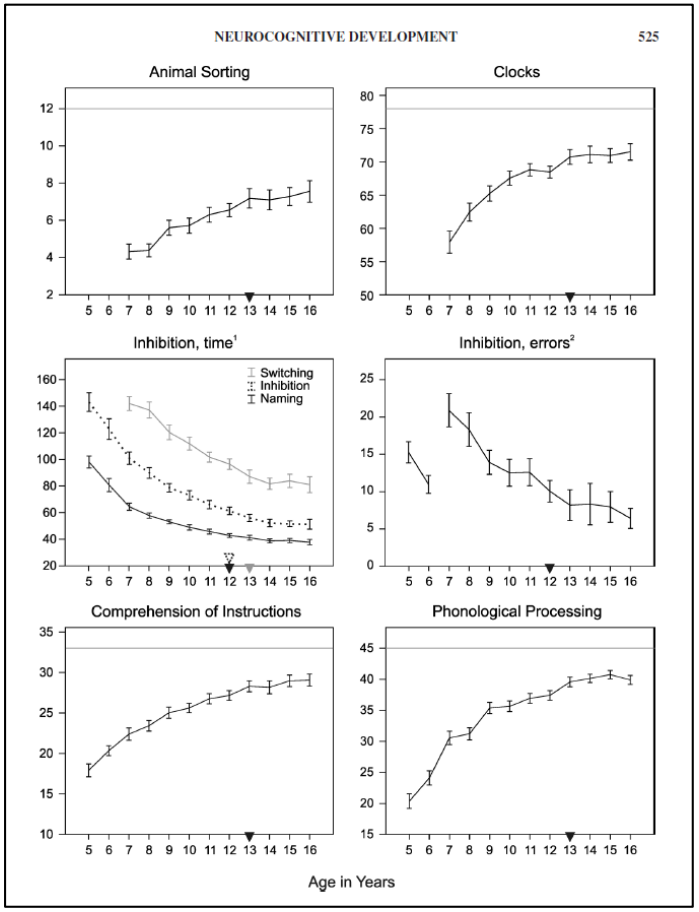
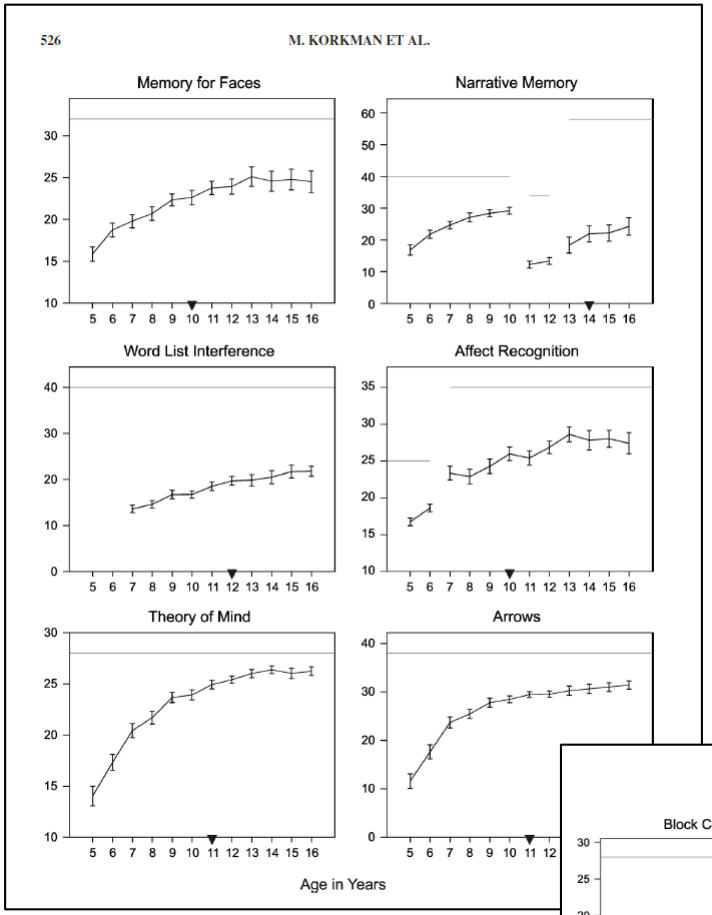


Figure I. See text for details. Adapted with permission from Ref. [66].

[1]Casey, et al., 2005





Age-related changes in cognitive test performance

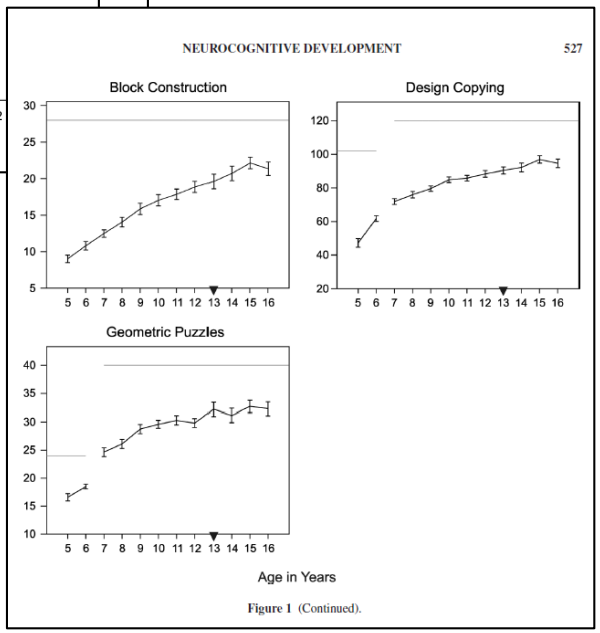


Figure 1 Means with 95% confidence interval of subtest raw scores in different age groups. The gray horizontal line indicates the maximum score for the specific age-range and black inverted triangle the age of subtest mastery. [1]Time is indicated separately for three conditions: Naming, Inhibition, and Switching. [2]Errors are presented as total number of errors: in two conditions for 5- to 6-year-olds (Naming and Inhibition) and in three conditions for 7- to 16-year-olds (Naming, Inhibition, and Switching). Standardization data from the NEPSY-II copyright © 2007 NCS Pearson, Inc. Used with permission. All rights reserved.

[2]Korkman, et al.

What are ND Outcome Measures?

Behavioral measures that reflect age dependent changes in the organization and function of the nervous system

"Behavior" is defined broadly – any function that can be experienced or observed

Many different methods available to us, to measure behavior

- Self report (e.g., questionnaires about mood, quality of life)
- Proxy report, such as parent or teacher (e.g., behavior rating scales)
- Clinician-based assessment (e.g., disease-severity rating scale; range of motion assessment)
- Performance-based assessments (e.g., neuropsychological tests; test of grip strength)

2. The patient perspective on ND outcomes - some considerations

Age and developmental level of child

- can the child self-report on their experience?
- at what level of detail?
- time frame for reflecting on symptoms and function?
- ability to connect events / experiences to how they feel/function?

Fig. 1 – Good research practices discussed in this Task Force Report. PRO, patient-reported outcome.

Good Research Practices	Comments and Recommendations
1. Consider Developmental Differences and Determine Age-Based Criteria for PRO Administration	• Four age groups are discussed. These age groups should be used as a starting point when making decisions. It is not possible to provide age cutoffs that will fit every situation. Specific age cutoffs should be determined individually for each PRO instrument and tested with cognitive interviews in each new target population. • Less than 5 years old: No clear evidence of reliability or validity of child-report measures • 5 to 7 years old: Child-report is possible, but reliability and validity are often questionable • 8 to 11 years old: Reliability and validity of child-report improves • 12 to 18 years old: Self-report is preferred
2. Establish Content Validity of Pediatric PRO Instruments	• Children and adolescents can be effective content experts. • In most cases, children should be included in qualitative research performed to establish content validity of pediatric PROs. • Cognitive interviews should be conducted with the intended respondent. Children should be interviewed for child-report instruments, and parents should be interviewed for parent-report instruments. • Content validity should be demonstrated within narrow age groupings.

[3]Matza, et al. 2013

Fig. 1 – Good research practices discussed in this Task Force Report. PRO, patient-reported outcome.

3. Determine Whether an Informant-Reported Outcome Instrument is Necessary	• Informant-reported outcomes include both proxy and observational measures. • When children in the target age range are capable of completing a PRO instrument independently, a child-reported measure should be used. • Second, when children in the target age range are not capable of completing a PRO measure, an informant-reported measure may be used. • Informant-reported measures should assess observable content as much as possible.
4. Ensure that the Instrument is Designed and Formatted Appropriately for the Target Age Group	• Health-related vocabulary and reading level • Response scale • Recall period • Length of instrument • Pictorial representations • Formatting • Administration approaches • Electronic data collection (ePRO)
5. Consider Cross-Cultural Issues	• Content validity and measurement approach of a pediatric PRO instrument will need to be re-examined within each new culture.

2. The patient perspective on ND outcomes - some considerations

What ND outcomes might or might not be amenable to assessment with patient-reported outcome measures?

- Sensory function / sensation

  Example: Diabetic Peripheral Neuropathy symptoms ([4]Moser, et al. 2017)

- Motor function

  Example: PROMIS Mobility , child self-report ([5]Kratz, et al. 2013)

- *Cognition*
  - *Attention*
  - *Memory*
  - *Executive Function*
  - *Language*
  - *Visual-spatial skills*

Self-reporting on one's own cognition is sometimes tricky, and may be impacted by some aspects of cognition (e.g., executive function; general intellectual level) or mood

- *Mood and Behavior*

A child's view of their cognition[6-8]

J Clin Exp Neuropsychol. 2005 April ; 27(3): 255–277. doi:10.1080/13803390490515478.

Development and Validation of the Subjective Awareness of Neuropsychological Deficits Questionnaire for Children (SAND-C)

BRADLEY J. HUFFORD[1,2] and **PHILIP S. FASTENAU**[3,4]

Factor structure varied by age

- 9-12 yrs: [1] General cognition; [2] Attention; [3] Self-monitoring of behavior
- 13-16 yrs: [1] Executive/attention; [2] Impulse control; [3] Lanuage; [4] Fine motor control; [5] Memory and gross motor; [6] Visual spatial function

Arthritis Care & Research
Vol. 66, No. 6, June 2014, pp 943–948
DOI 10.1002/acr.22247

BRIEF REPORT

Value of Questionnaire-Based Screening as a Proxy for Neurocognitive Testing in Childhood-Onset Systemic Lupus Erythematosus

PATRICIA VEGA-FERNANDEZ,[1] FRANK A. ZELKO,[2] MARISA KLEIN-GITELMAN,[2] JIHA LEE,[1] JESSICA HUMMEL,[1] SHANNEN NELSON,[1] ERIN C. THOMAS,[2] JUN YING,[3] DEAN W. BEEBE,[4] AND HERMINE I. BRUNNER[1]

Do Self- and Proxy Reports of Cognitive Problems Reflect Intellectual Functioning in Children and Adolescents with Congenital Heart Defects?

Sandra Buratti[1,2], Carmen Ryberg[1,2], Malin Broberg[2] and Jan Sunnegårdh[1]*

[1] Department of Pediatric Cardiology, The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg, Sweden, [2] Department of Psychology, University of Gothenburg, Gothenburg, Sweden

3. Pediatric patient input on ND outcome assessment measures

Defining & Describing the Concept of Interest

[9]HIV-Associated Neurocognitive Disorders in Zambia (HANDZ) study; PI: David R Bearden

Example: **Zambia Depression Assessment – Pediatrics (ZDAP)**

CONSTRUCT / CONCEPT OF INTEREST: SAD MOOD – ***sample questions***

1. What does the term “feeling sad” mean to you?
2. If you were going to ask a patient whether or not he or she was sad, how would you go about asking this?
3. If you were going to ask one of your friends this question, what would be the best way to ask it, to make sure they understood?
4. When someone is sad, what do they look like or do that is different, compared to a person who is not sad?

3. Pediatric patient input on ND outcome assessment measures

How the measure is administered?

- Paper & pencil vs. screen-based
- Listening vs. 'hands-on' participation
- Style of questions (yes/no vs. open-ended); vocabulary level

Face validity of the measure?

HIV-Associated Neurocognitive Disorders in Zambia (HANDZ) study; PI: David R Bearden

<u>Pilot-testing NIH Toolbox – Cognition Battery tests</u>

- Cognitive interviewing to evaluate face validity of the measures

Examples:

Picture Vocabulary: "to see if I know words" ; "to see if I am intelligent"

Auditory Verbal Learning: "my memory"; "learning"; "if I can remember"

Oral Symbol Digit Test: "my speed" ; "if I know the symbols [numbers]"

3. Pediatric patient input on ND outcome assessment measures

Is the measure "kid-friendly"?

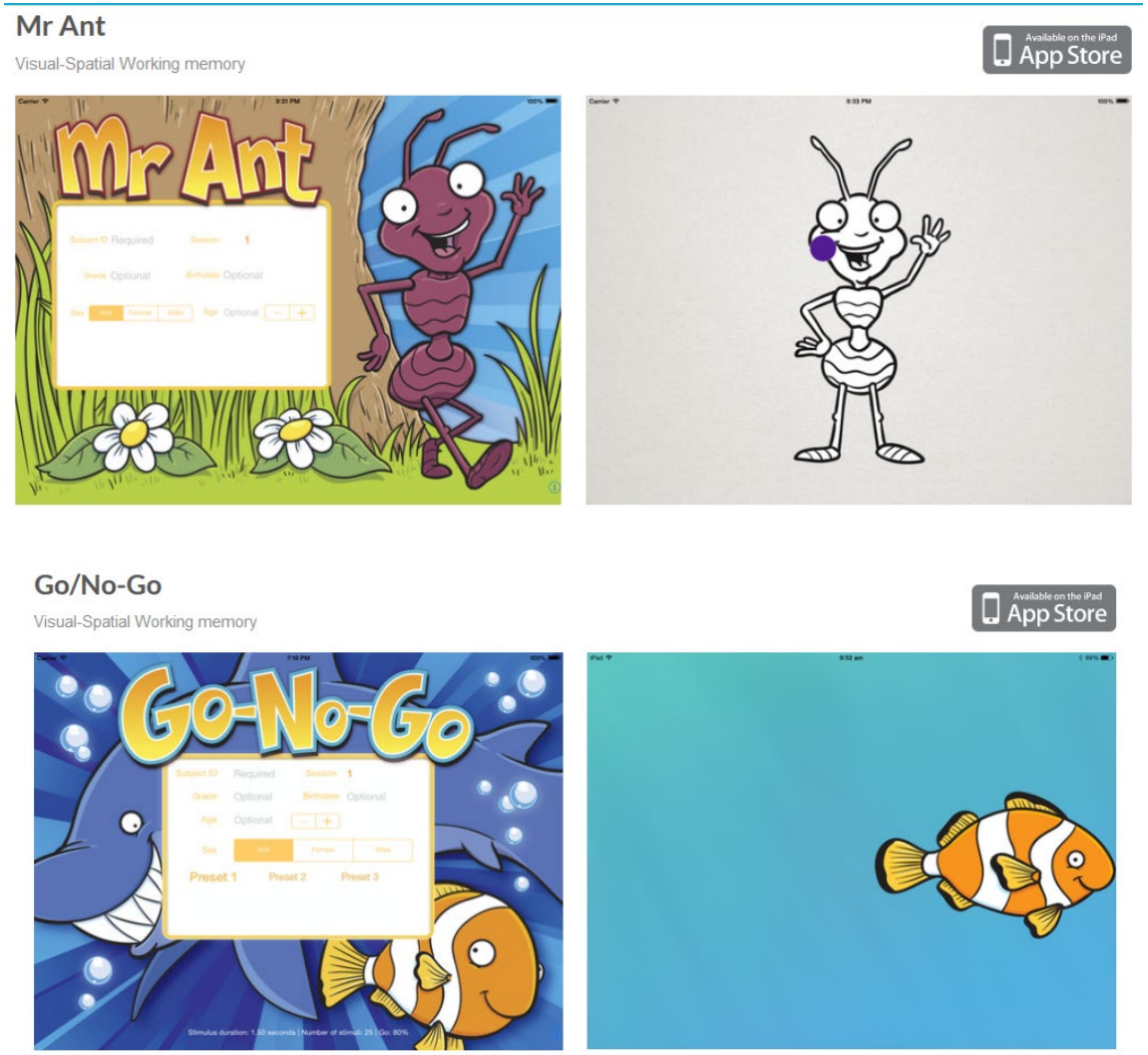
Can the outcome assessment be designed to optimize a child's orientation / attention to the task?

Early Years Toolbox[10]

http://www.eytoolbox.com.au/

Ages 2:6-5:11 (Expressive Vocabulary)

Ages 3:0-5:11 (Executive Function tasks)



3. Pediatric patient input on assessment of endpoints[11-12]

What is the perceived burden associated with participation in the outcome assessment?

Open Access Protocol

BMJ Open

Hearing the voices of children: self-reported information on children's experiences during research procedures: a study protocol

Mira S Staphorst,[1] Jo
Johannes B van Gou

Staphorst *et al. BMC Pediatrics* (2017) 17:199
DOI 10.1186/s12887-017-0949-y

BMC Pediatrics

RESEARCH ARTICLE Open Access

The development of the DISCO-RC for measuring children's discomfort during research procedures

Mira S. Staphorst[1], Reinier Timman[1*], Jan Passchier[2], Jan J. V. Busschbach[1], Johannes B. van Goudoever[3,4] and Joke A. M. Hunfeld[1]

4. *Relevance of neurodevelopment to non-ND outcome assessments and endpoints*

- Can the child describe or answer questions about how they feel / function?
- Can the child identify priorities for health and well-being?
- Are outcome assessments (*and their instructions)* designed to be accessible? understandable ? kid-friendly?

Good Research Practices	Comments and Recommendations
1. Consider Developmental Differences and Determine Age-Based Criteria for PRO Administration	• Four age groups are discussed. These age groups should be used as a starting point when making decisions. It is not possible to provide age cutoffs that will fit every situation. Specific age cutoffs should be determined individually for each PRO instrument and tested with cognitive interviews in each new target population. • Less than 5 years old: No clear evidence of reliability or validity of child-report measures • 5 to 7 years old: Child-report is possible, but reliability and validity are often questionable • 8 to 11 years old: Reliability and validity of child-report improves • 12 to 18 years old: Self-report is preferred

5. Some other considerations

- Cognition and developmental level inform the ability to provide accurate and/or detailed information on other outcomes of interest

- Sensory and motor function may inform design of some measures to ensure accessibility

  EXAMPLE – CLN3 (juvenile) Batten disease *(Adams et al, 2013)*
  - *Children experience vision loss (onset between ~ 4-7 yrs. of age)*
  - *Assessment of cognition involves only verbally-mediated tasks*

- "Age-appropriate" may not always be disease appropriate….

  EXAMPLE – Sanfilippo Syndrome / MPS-IIIA *(Delaney et al., 2013)*
  - *Often, mismatch between chronological & developmental age*
  - *Vineland Adaptive Behavior Scales informs selection of cognitive assessment*

5. Some other considerations

- Would some outcome assessments need to vary, within trial, across the range of ages and developmental levels of patients who are included?

  EXAMPLE – MPSIIIA *(Delaney et al., 2013; Ghosh et al., 2017)*
  - *Choice of ND outcome assessment used, to assess cognitive endpoint, is guided by developmental level of the child*

- *Using our ND Crystal Ball….*

Within a trial, must anticipate age-expected changes in neurodevelopment and have outcome assessments that are sensitive to that change

Will children "grow into" areas of strength or difficulty, as neurodevelopment continues beyond the time-span of the trial?

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REVIEW ARTICLE

Neurocognitive Outcomes and Interventions in Long-Term Survivors of Childhood Cancer

Kevin R. Krull, Kristina K. Hardy, Lisa S. Kahalley, Ilse Schuitema, and Shelli R. Kesler

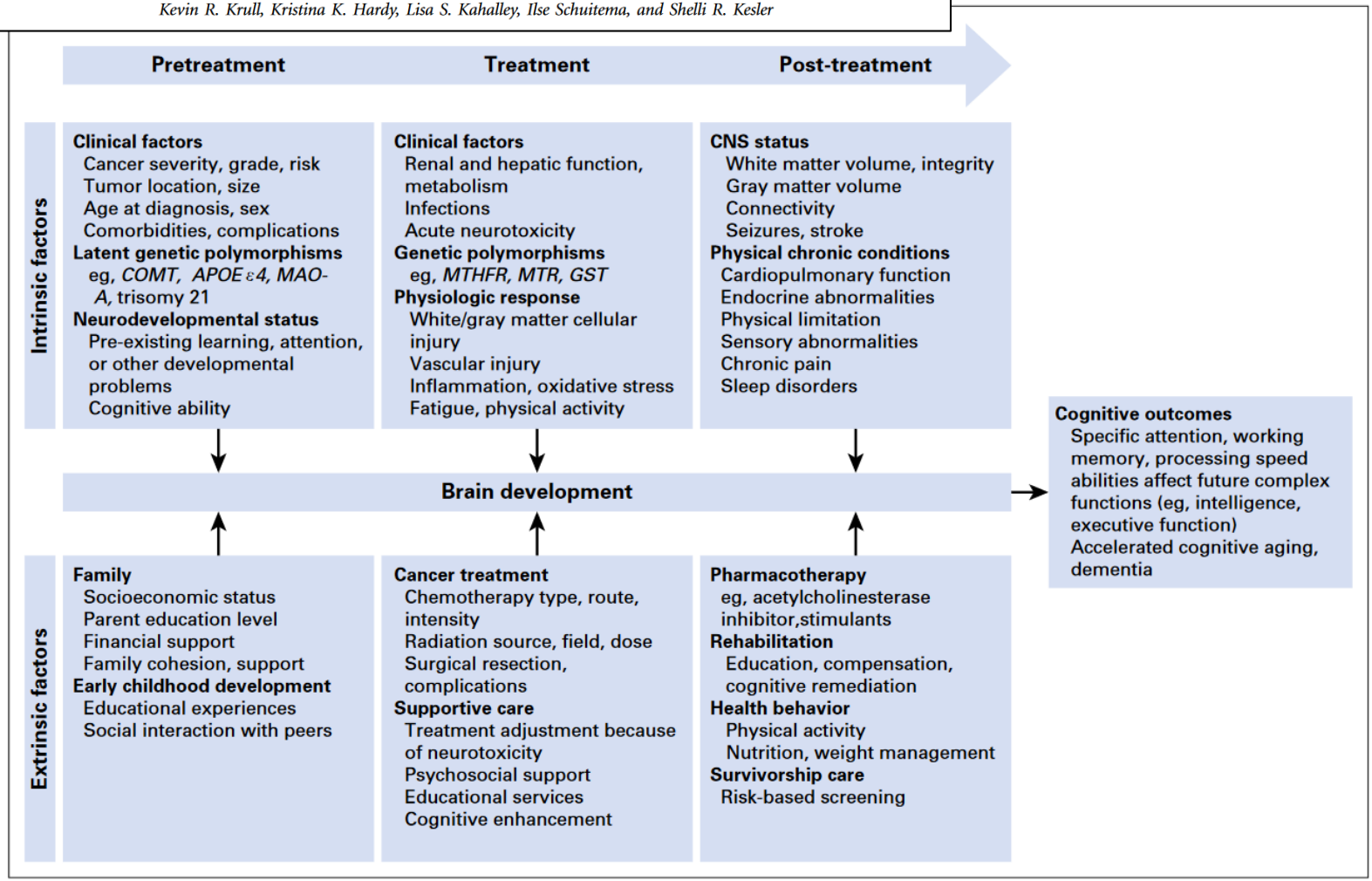

Fig 1. Model of biobehavioral impact of cancer and cancer therapy on brain development and neurocognitive outcomes in long-term survivors of childhood cancer.

Closing Thoughts

Age-dependent changes in cognition, motor, and sensory function will likely impact selection of

- Endpoint focus
- Selection of tools (outcome assessment measures) to measure endpoints

Pediatric patients can offer input on ND endpoint definition, development of ND outcome assessments, and/or support direct measurement of an endpoint (i.e., patient-reported outcome measures). This may depend upon…

- Age / developmental level
- Concept of interest
- Impact of symptoms upon ND function

So… *"No size fits all", or …. "One size fits one…" ?*

"Begin with the end in mind…."

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