

Neurocognitive and Behavioral Issues in PKU

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Educational Learning Objective

- **Describe the impact of elevated Phe on long-term patient outcomes**

KEY POINTS

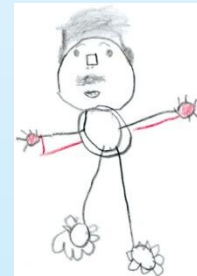
1. High Phenylalanine (Phe) levels harm the brain



2. Traditional therapies do not completely protect individuals with PKU



3. Neuropsychological follow-up is important in identifying deficits associated with even well-treated PKU



KEY POINT #1

High Phenylalanine (Phe) levels harm the brain.



1. Evidence
2. Dopamine hypothesis
3. White matter hypothesis

Blood Phe and IQ Are Correlated in Individuals With PKU

Observation period	Correlation between blood Phe and IQ	Lifetime IQ loss for each 100 $\mu\text{mol/L}$ (1.6 mg/dL) increase in blood Phe (IQ points)
Critical period (0–12 years old)	$r = -0.35^*$	1.3–3.1
Lifetime (all ages)	$r = -0.34^*$	1.9–4.1

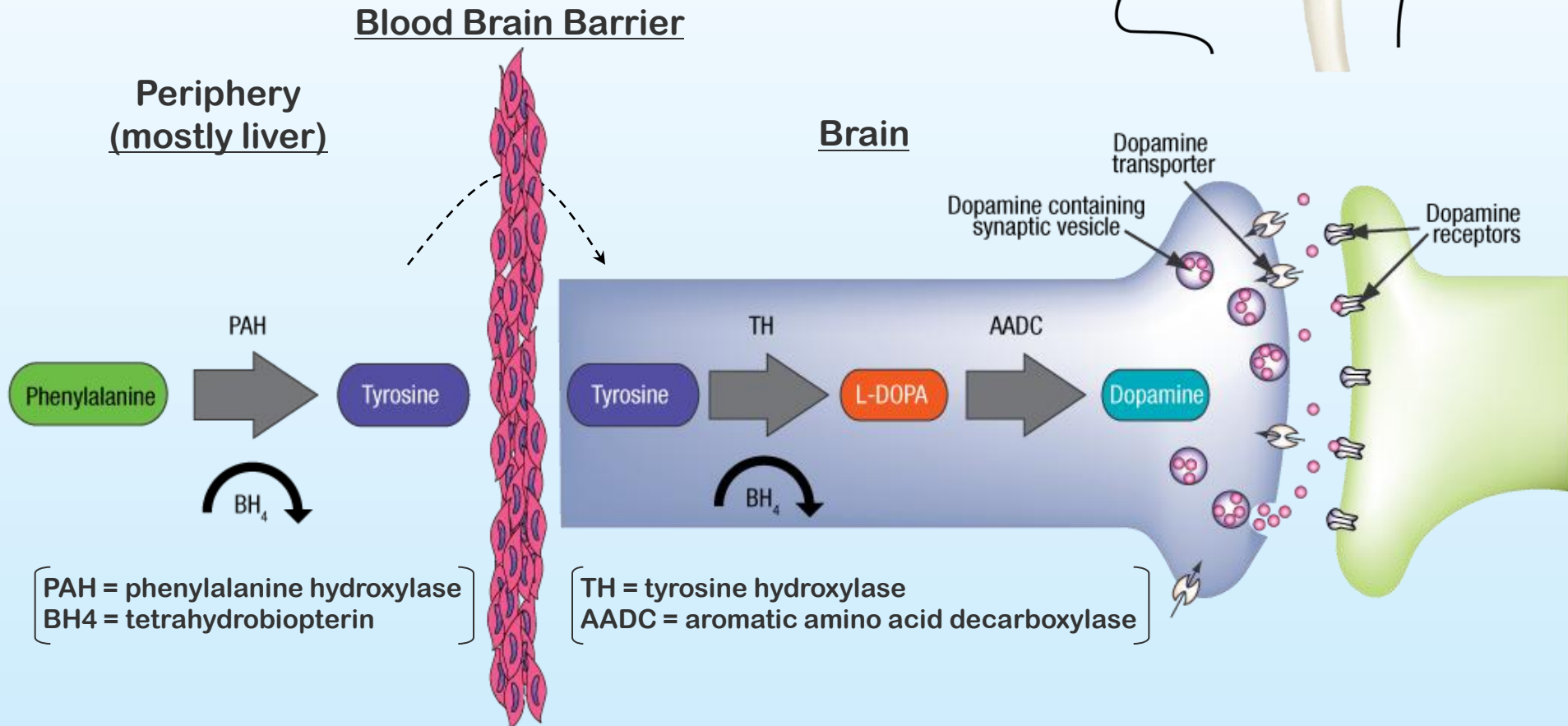
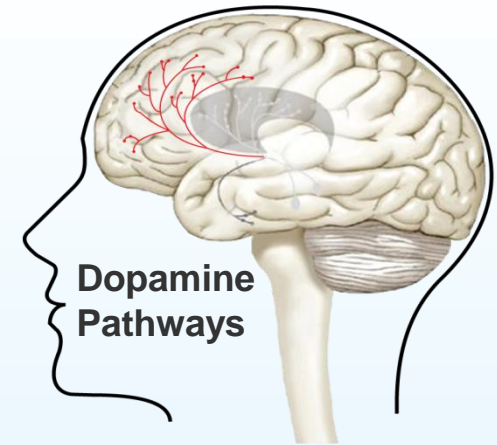
* $P < 0.05$

Outcomes for Adults with PKU Are Worse if Discontinue Diet

Outcome	Discontinued Diet	Continued Diet
Medical Problems	2.4 ± 1.8	0.9 ± 1.4
College Degree	32%	78%
Socioeconomic Class I or II*	19%	44%

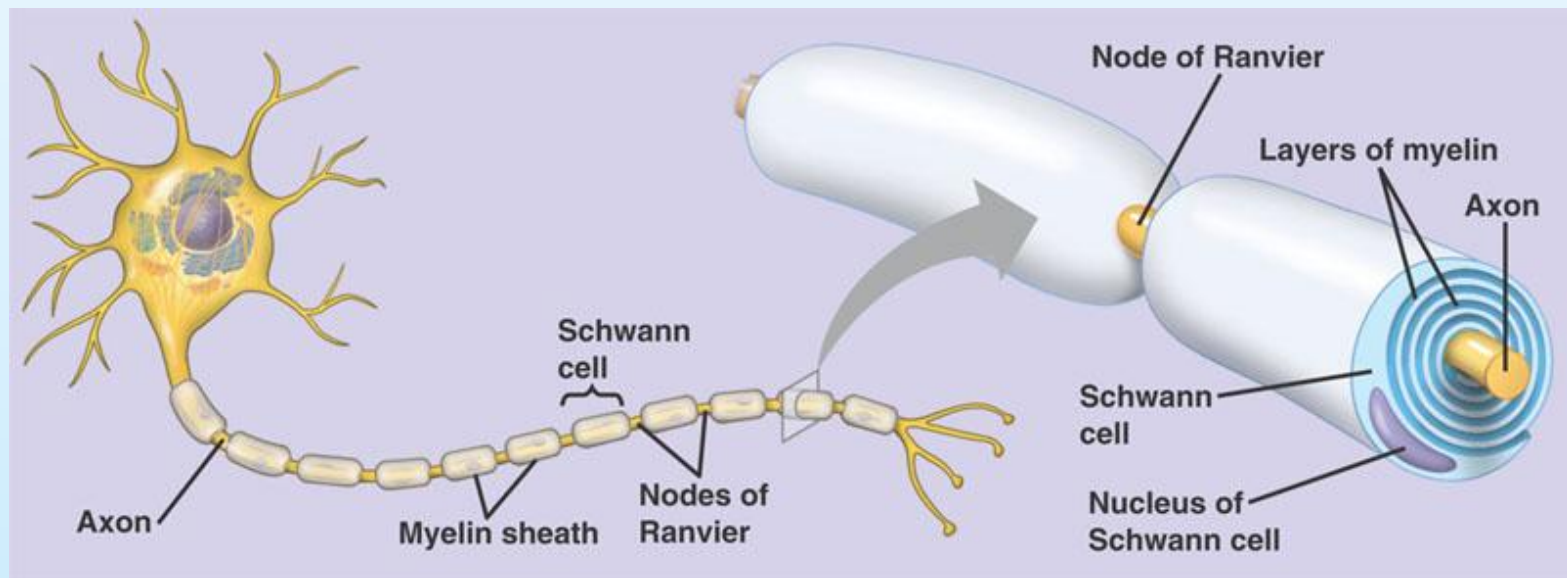
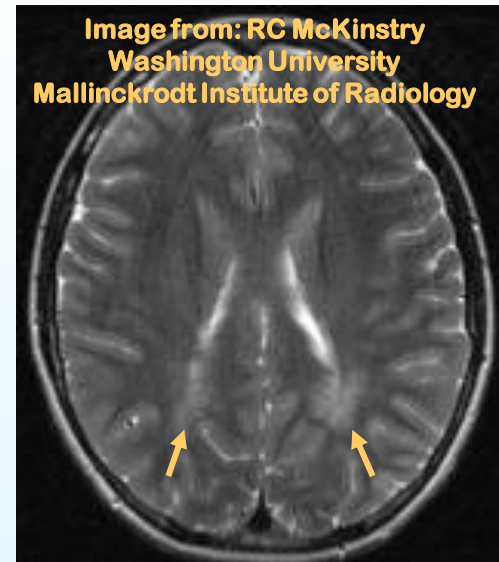
*Two highest socioeconomic classes in the Hollingshed classification system

Prefrontal Cortex Is Sensitive to Reductions in Dopamine



White Matter

Myelin insulates axons
to increase speed
of neural signal transmission



KEY POINT #2

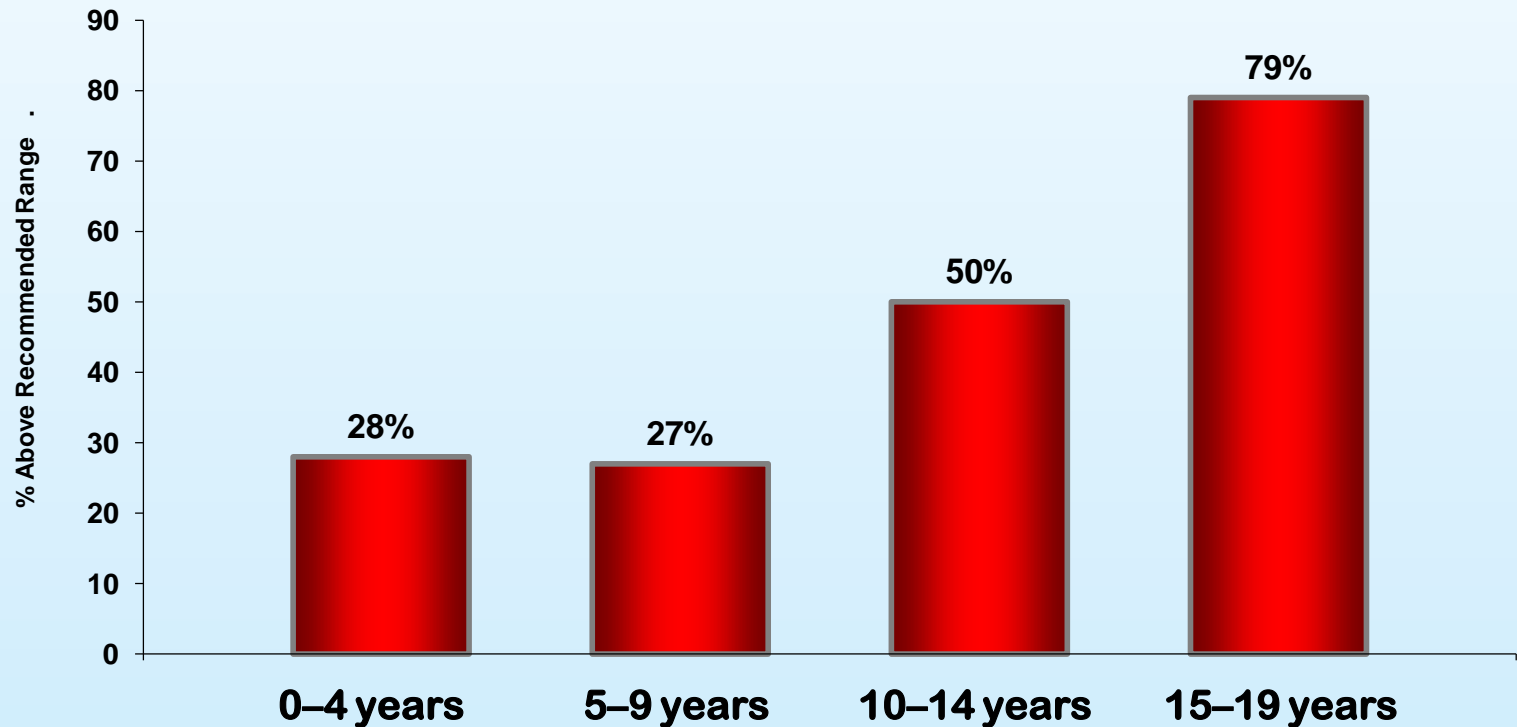
Traditional therapies do not completely protect individuals with PKU.



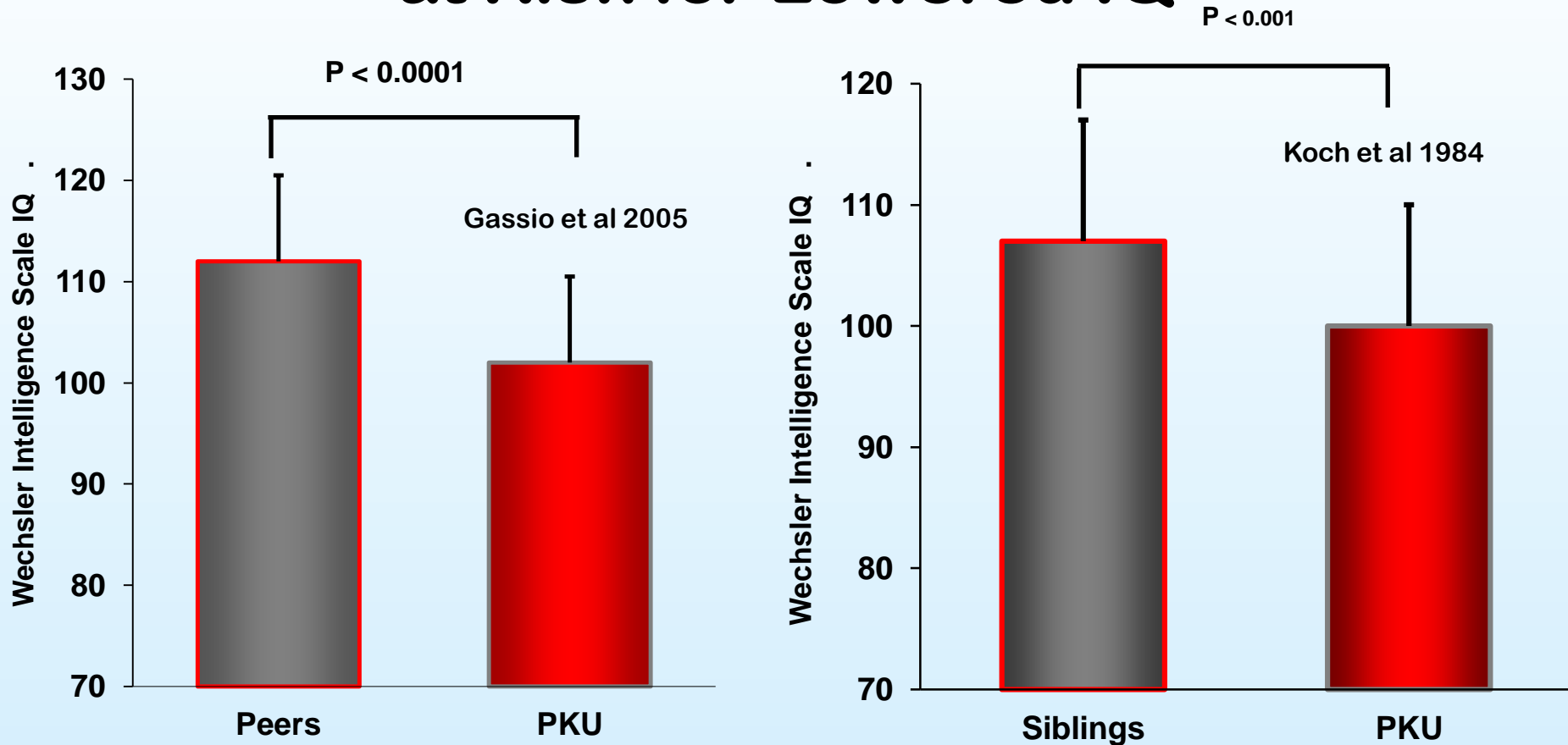
1. Adherence
2. Cognitive abilities
3. School achievement
4. Executive functioning
5. Processing speed
6. Emotional issues

Adherence to Diet Is Difficult

- ~1 in 3 children less than 10 years of age have blood Phe above recommended range
- Noncompliance increases in adolescence

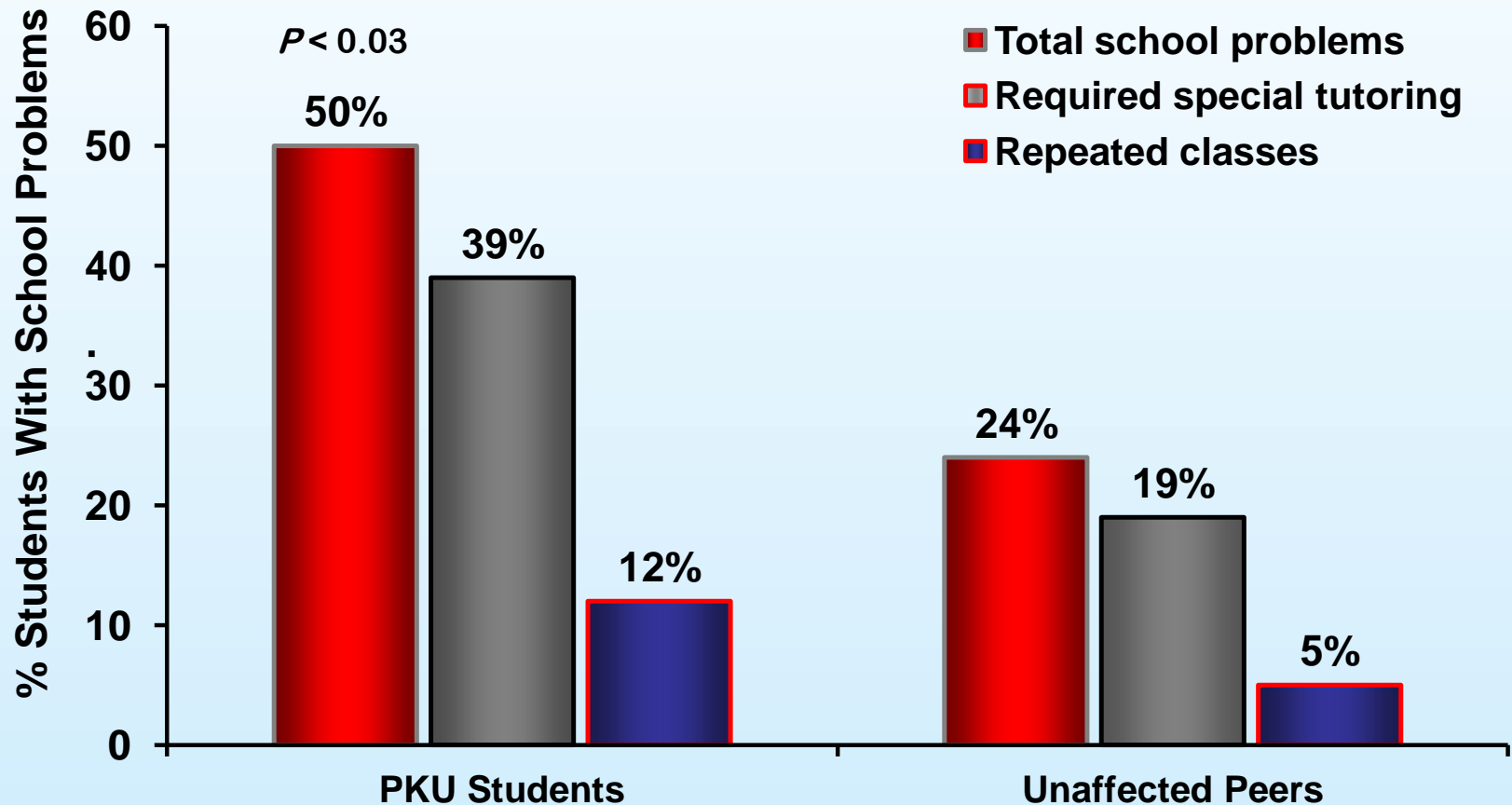


Children with PKU on Diet Are at Risk for Lowered IQ



- **Blood Phe and IQ are correlated** Waisbren et al 2007
- **Variability in Blood Phe may be important** Anastasoiaie et al 2008

Children with PKU on Diet Present More School Problems than Unaffected Peers



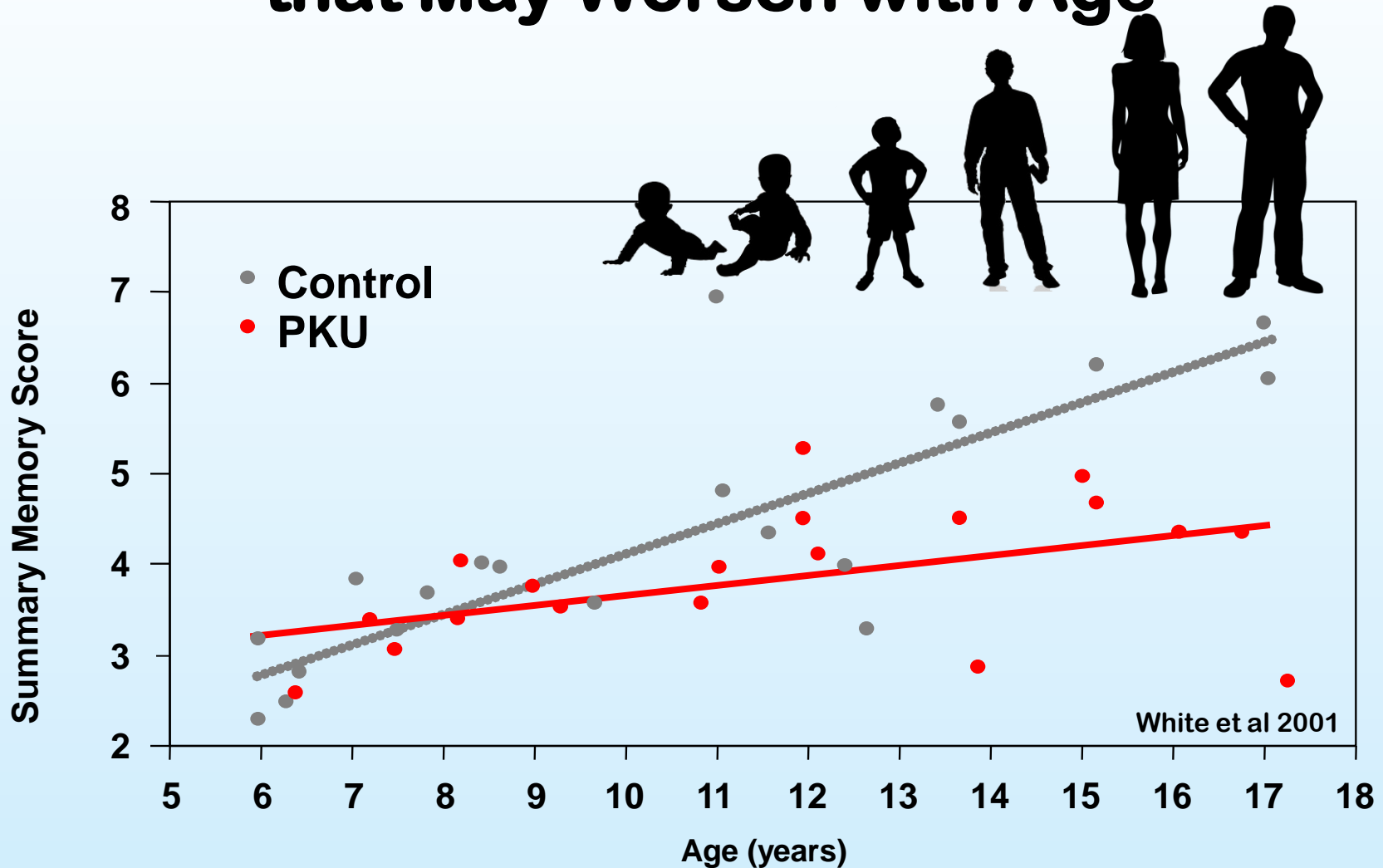
Executive Functioning Deficits

- We don't know if he's missing or just lost under all that paper!



- Planning
- Organization
- Working memory
- Initiation
- Inhibition of usual response
- Cognitive flexibility

Executive Deficits Across the Lifespan that May Worsen with Age



Diamond A, et al. *Monogr Soc Res Child Dev.* 1997;62:1-208.

Huijbregts SC, et al. *Neuropsychology.* 2003;17:369-379.

Channon S, et al. *Neuropsychology.* 2004;4:613-620.

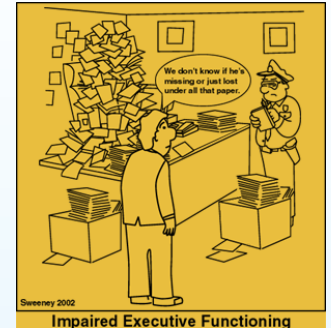
White DA, et al. *J Int Neuropsychol Soc.* 2002;8:1-11.

Araujo GC, et al. *Neuropsychology.* 2009;23:130-134.

VanZutphen KH, et al. *Clin Genet.* 2007;72:13-18.

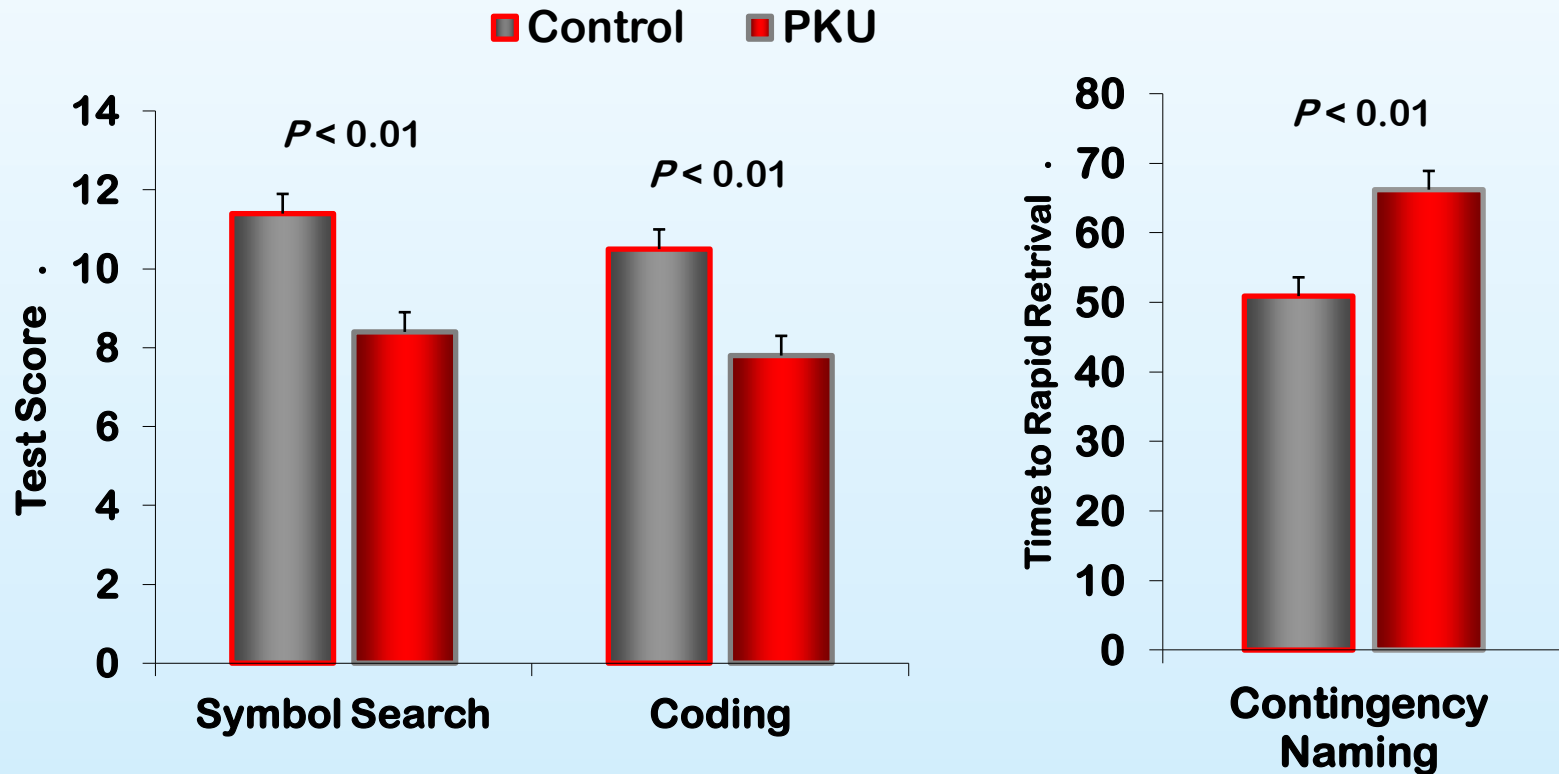
White DA, et al. *Neuropsychology.* 2001;15(2):221-229.

Executive Deficits Make Diet Adherence Difficult

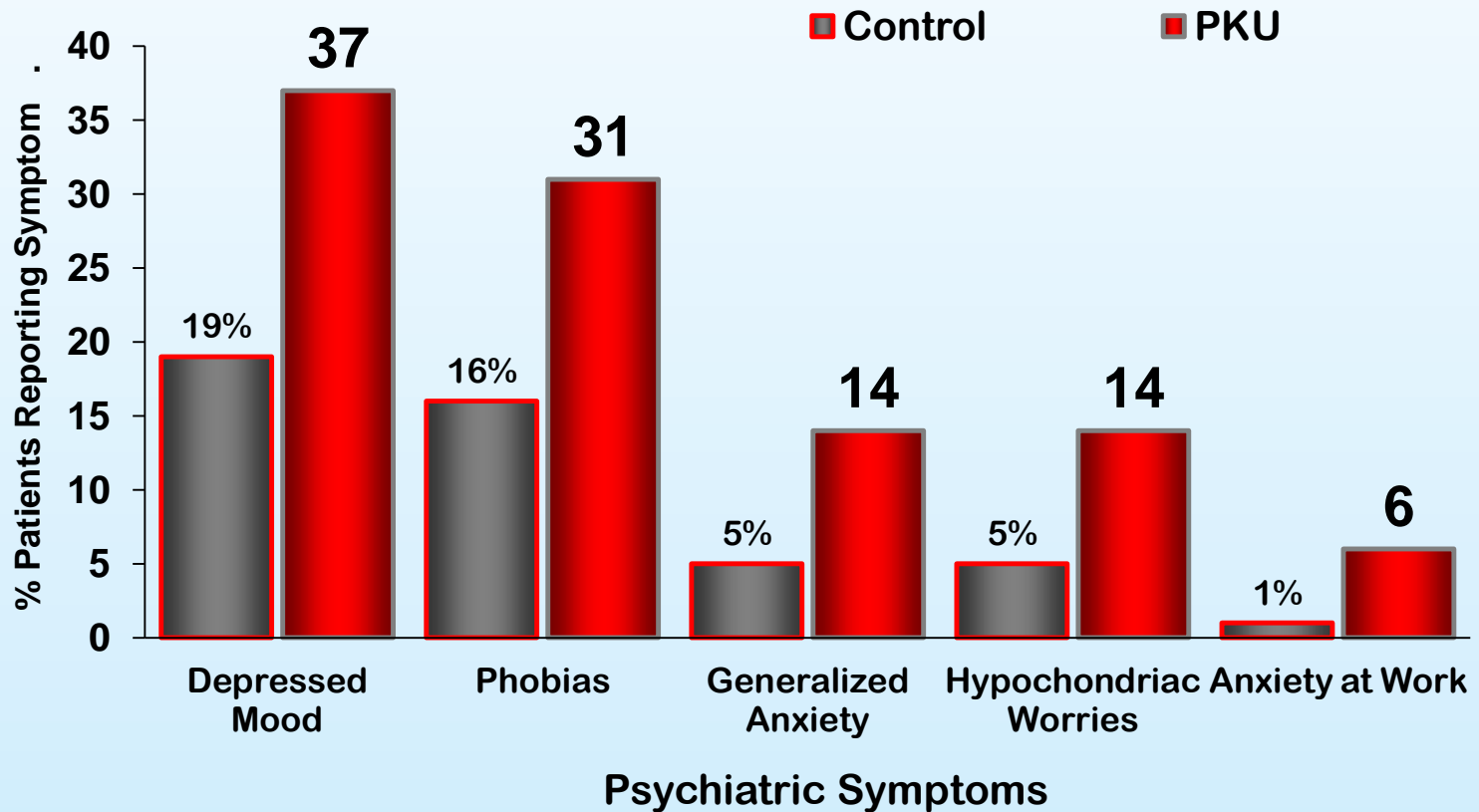


- Planning diet
- Remembering Phe intake for records
- Remembering to take formula
- Inhibiting impulse to eat foods not allowed on diet
- Maintaining medical food supplies
- Monitoring blood Phe and making appropriate adjustments in intake

Speed of Processing Is Reduced in Children with PKU



Adults with PKU Demonstrate Increase in Psychiatric Symptoms



* $P < 0.05$ compared with 18-year-old controls

KEY POINT #3

Neuropsychological follow-up is important in identifying subtle deficits associated with even well treated PKU.



1. Case study
2. Screening by non-psychologists
3. The Genetics and Metabolism Psychology Network

Case Study: A.D.

History

- Male with PKU, now age 11 years
 - Newborn screening level 30 mg/dL
- Over-treated until 17 months
 - Failure to thrive and mild microcephaly
- Poor metabolic control from ages 2–4 years, until g-tube placed for intake of formula
- Levels varied until age 10 years
 - 3.6–16.9 mg/dL
- ADHD medication required
- IQ = 81 (100 is average)



Case Study

Recent and Current

- Began treatment with sapropterin at age 10
- Blood Phe steady at 5.4 mg/dL
- No longer needs ADHD medication
- Height 5th percentile; weight 2nd percentile
- IQ = 105 (Increase of 24 points)



Case Study

Current

- 11-year-old boy in 4th grade
- Continues with g-tube
- Eczema and bedwetting
- Receives occupational therapy
- Has attention problems and requires one-on-one aide in classroom
- Kind, imaginative, eager to please
- Enjoys socializing, video games, sports



Assessment Observations

- Polite, cheerful, talkative
- Concentrated fairly well, but hummed as worked

Enjoyed relating facts about spiders

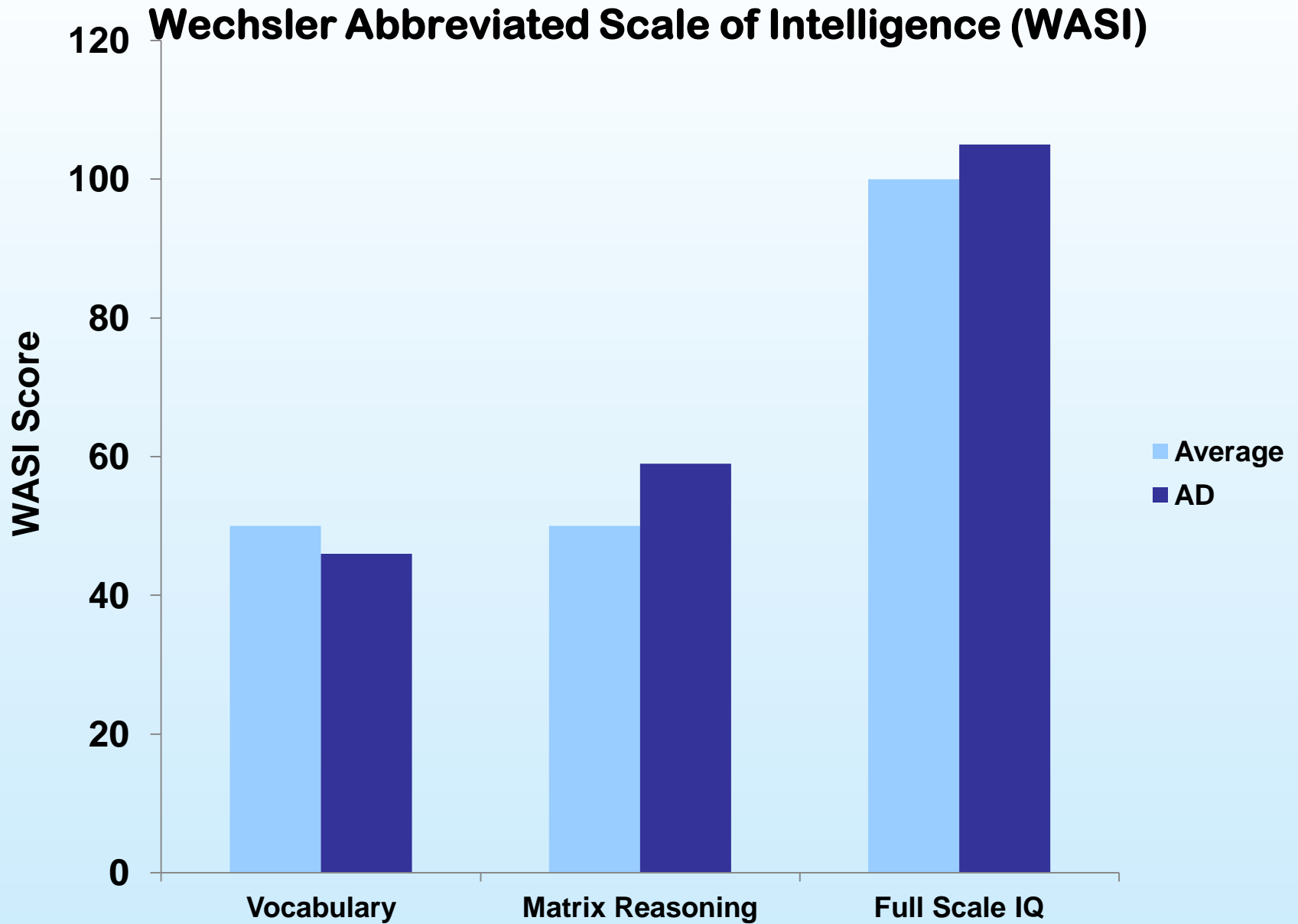


Told far-fetched stories about school and home, stating these capture interest of other children

- Did not appear to believe stories, but rather to intentionally elaborate



Intellectual Performance



Executive Functioning

- **Example List**

- Carrot
- Taxi
- Elephant
- Car
- Airplane
- Lettuce
- Cat
- Potato
- Butterfly
- Spinach
- Boat
- Tiger
- Scooter
- Squash
- Parrot

California Verbal Learning Test

Trial 1: 4 words

Trial 5: 9 words

(Used categories)

Previous Year

Trial 1: 3 words

Trial 5: 5 words

Processing Speed

Example of a Symbol Search Task

€ £

€

≠

¥

§

YES

NO

ø *f*

√

‡

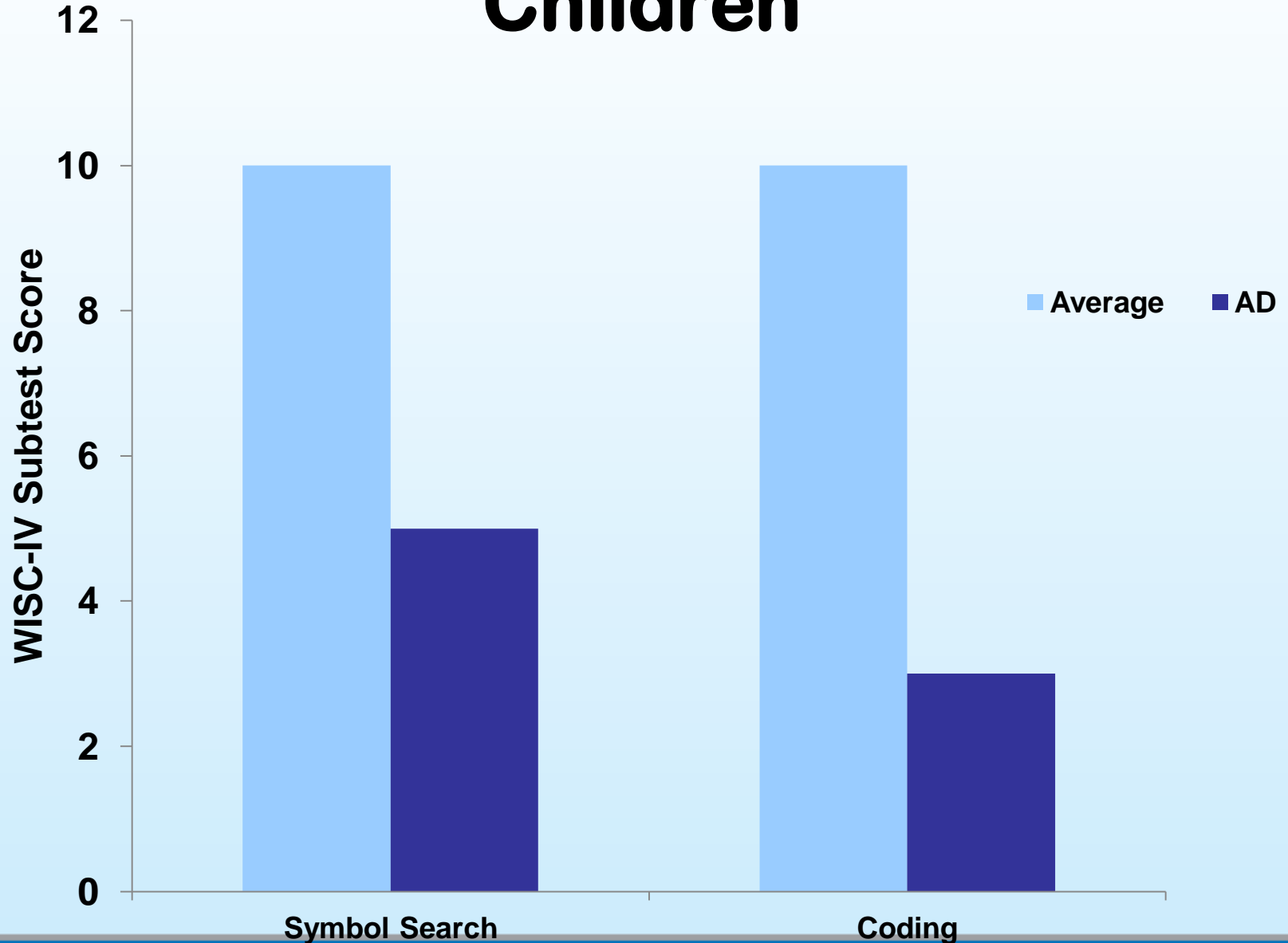
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◇

YES

NO

Wechsler Intelligence Scale for Children



Academic Achievement (WIAT)



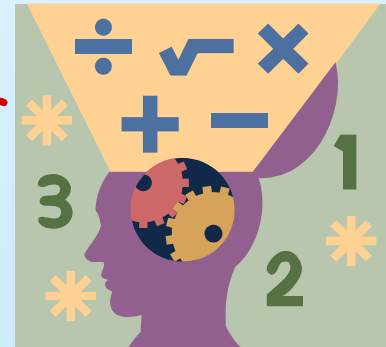
Reading Recognition: 5th grade level

Reading increased 1 grade in last year

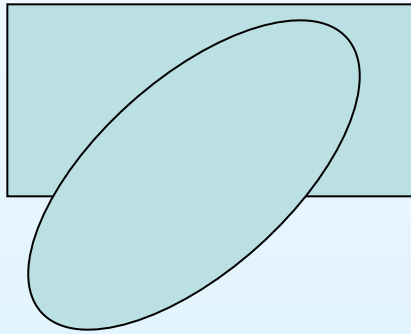
Numerical Operations: 3rd grade level

Careless errors, could not borrow or carry, did not attempt adding long columns of numbers

Math increased 1/2 grade in last year



Visual Motor Integration



Berry Visual Motor Integration Test (VMI): Standard Score = 70 (100 is average) Drew with confidence, but poor organization so details misplaced.

Same score as last year.

Recommendations

- Continue with extra help and occupational therapy
- Teach compensatory strategies in arithmetic
- Psychological counseling
- Behavioral therapy for weaning from g-tube
- Medical evaluation for eczema and bedwetting
- Re-evaluation in one year

Screening Tests That Can Be Administered by Non-Psychologists

PSYCHOLOGICAL REALM	TEST
Adaptive Functioning	Adaptive Behavior Assessment System (ABAS-II)
Behavior	Behavior Assessment System for Children (BASC-II)
Executive Functioning	Behavior Rating Inventory of Executive Function (BRIEF)

Abbreviations & Sources

- **ABAS-II: Adaptive Behavior Assessment System-Second Edition (Harrison, Oakland 2003)**
- **BRIEF: Behavior Rating Inventory of Executive Function (Gioia, Isquith, Guy, Kenworthy, 2000)**
- **BASC-II: Behavior Assessment System for Children-Second Edition (Reynolds, Kamphus, 2004)**
- **BAI: Beck Anxiety Inventory (Beck, Steer, 1993)**
- **BDI-II: Beck Depression Inventory-Second Edition (Beck, Steer, Brown, 1996)**

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This is an exciting time for the fields of genetics, metabolism, and psychology. With advances in identification and treatment of rare genetic and metabolic conditions comes a responsibility to add our voices to discussions regarding policy, research, and distribution of resources. The time has come for a Genetics and Metabolism Psychology Network so that we may take full advantage of our experiences and expertise.

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KEY POINTS

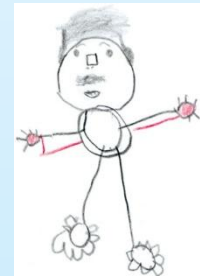
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Questions & Answers