

Neuropsychological Function in Individuals with Phenylketonuria Treated with Kuvan®

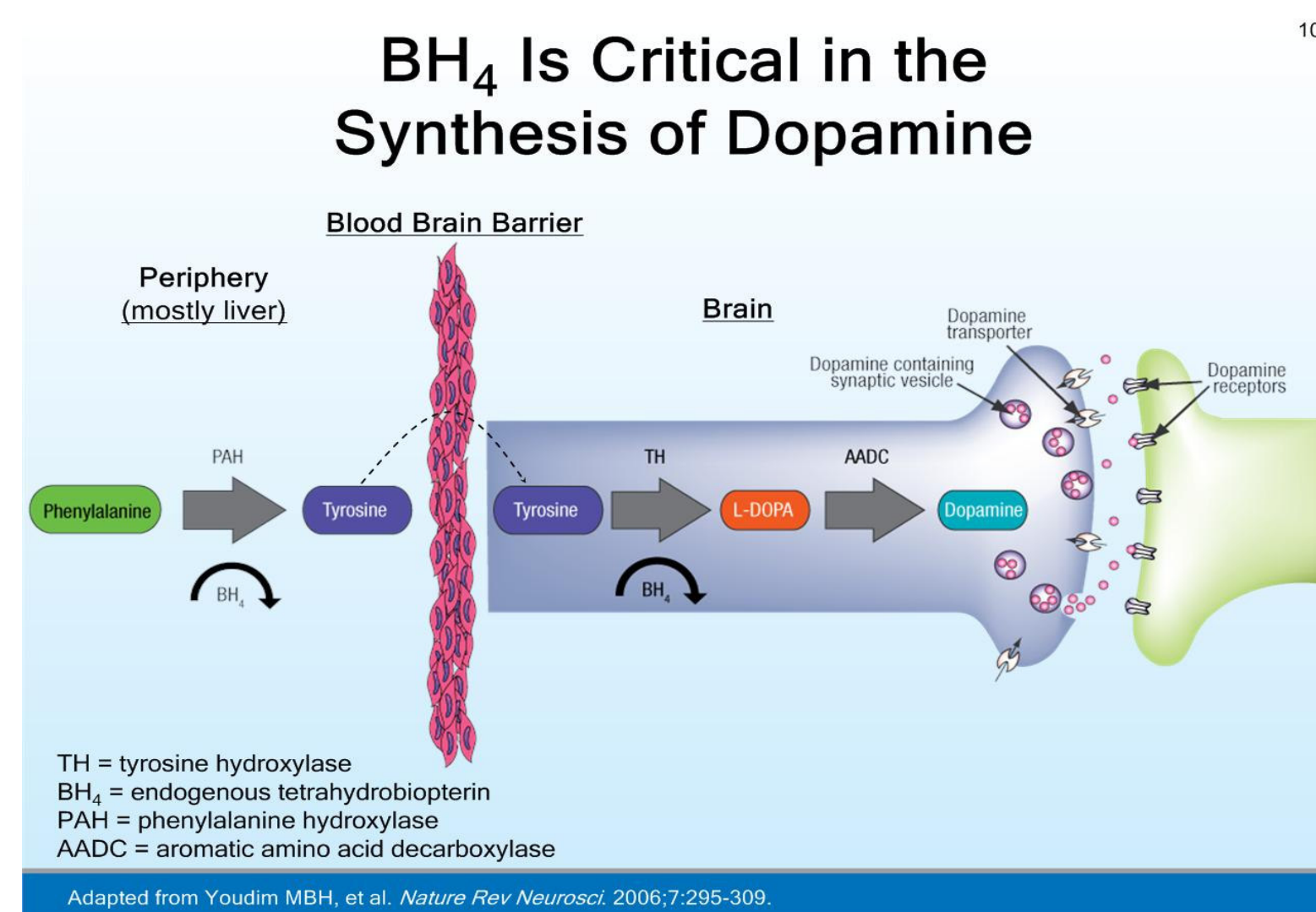
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INTRODUCTION

Phenylketonuria (PKU) is a hereditary disorder resulting in disrupted metabolism of Phenylalanine (Phe). The profound effects once associated with elevated Phe (e.g., mental retardation and seizures) have largely been eliminated through dietary restrictions. However, Phe remains elevated even in patients considered well treated by diet alone. Thus, although more subtle than in the past, PKU patients exhibit neurologic abnormalities and impaired cognition.

Kuvan® (sapropterin dihydrochloride/BH4) is a drug therapy that lowers Phe in BH4 responders and holds promise for improving brain function and cognition. In our study, brain and cognition are examined in PKU patients immediately prior to treatment with Kuvan (20mg/kg/day) using MRI and neuropsychological tests of intelligence (IQ), executive abilities, and reaction time (RT). For patients who respond to Kuvan® (i.e., reduction of $\geq 20\%$ in Phe within 4 weeks of treatment), brain and cognition are again examined after 6 months of Kuvan® therapy. We hypothesize that brain and cognition will be improved in Kuvan® responders. Here we report on baseline neuropsychological evaluation of the first 12 PKU patients enrolled and 3 patients returning for 6-month follow-up.



METHOD

SUBJECTS

	N	Age (yrs)	Phe
PKU	12	Range 8–20 (M= 12, SD=4)	$\geq 360 \mu\text{mol/L}$
CONTROL	8	Range 10 – 21 (M=16, SD=4)	---

MEASURES

INTELLIGENCE (IQ)	Wechsler Abbreviated Scale of Intelligence (WASI)
EXECUTIVE Working Memory	2-Back Letter & Spatial
EXECUTIVE Strategic Processing	Word List Learning
PROCESSING SPEED	Simple Reaction Time

RESULTS

BASELINE 1-tailed statistics (covarying age) reveals poorer performance for the **PKU** than **control** group on all measures.

Word List Learning

Stool	Chair	Foot
Pizza	Soup	Bed
Leg	Arm	Cheese
Sandwich	Egg	Knee
Table	Elbow	Sofa
Hand	Desk	Bread

2-Back Letter Condition

C +	+ F	P +	F +
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Spatial Condition

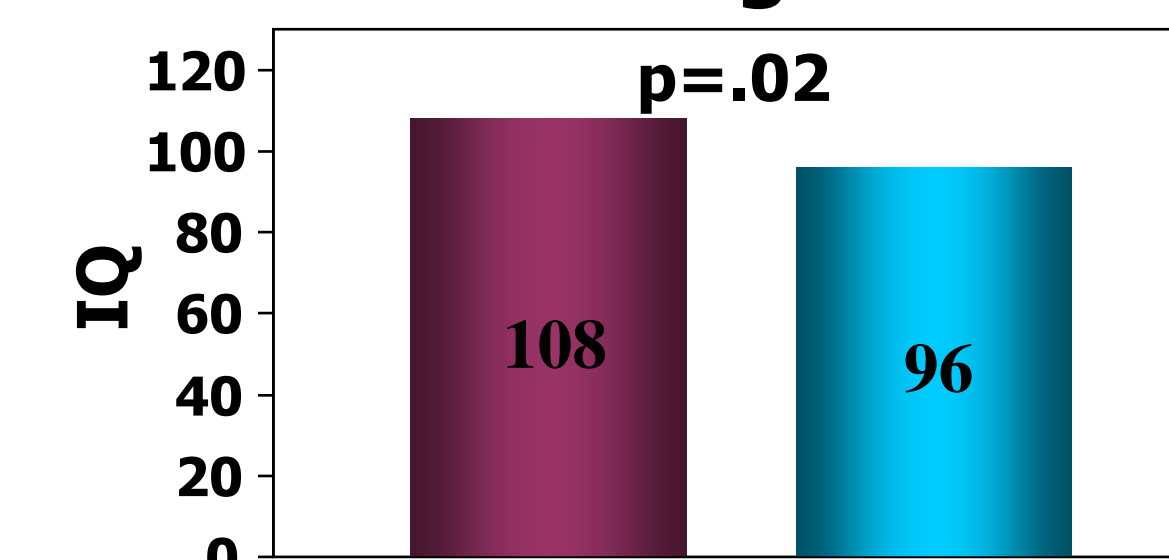
+ Q	C +	+ F	P +
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Simple Reaction Time

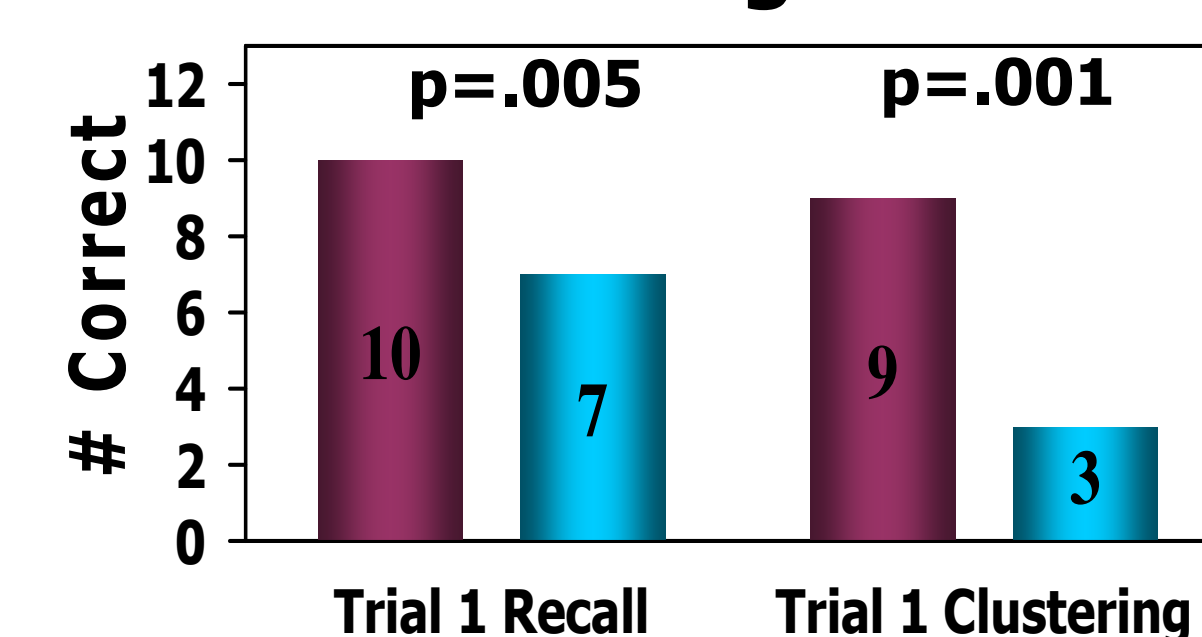
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6 MONTH FOLLOW-UP Data are currently available for only 3 subjects with PKU. Although precluding statistical comparison of **baseline** and **follow-up** performance, preliminary results on a case by case basis suggest that RT (simple RT task) decreased by $>13\%$ in 2 patients and number of errors (2-back working memory task) decreased by $>40\%$ in 2 patients (across letter and spatial conditions). These very preliminary results suggest that improvements in processing speed and executive working memory may occur after 6 months of Kuvan® treatment in Kuvan-responsive patients.

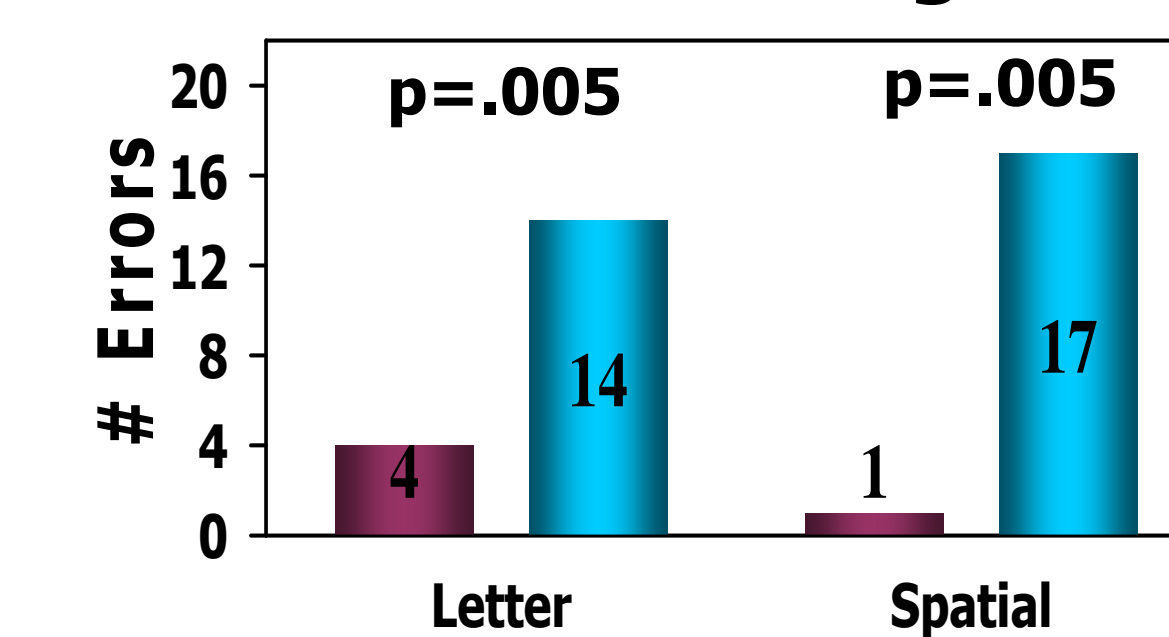
Intelligence



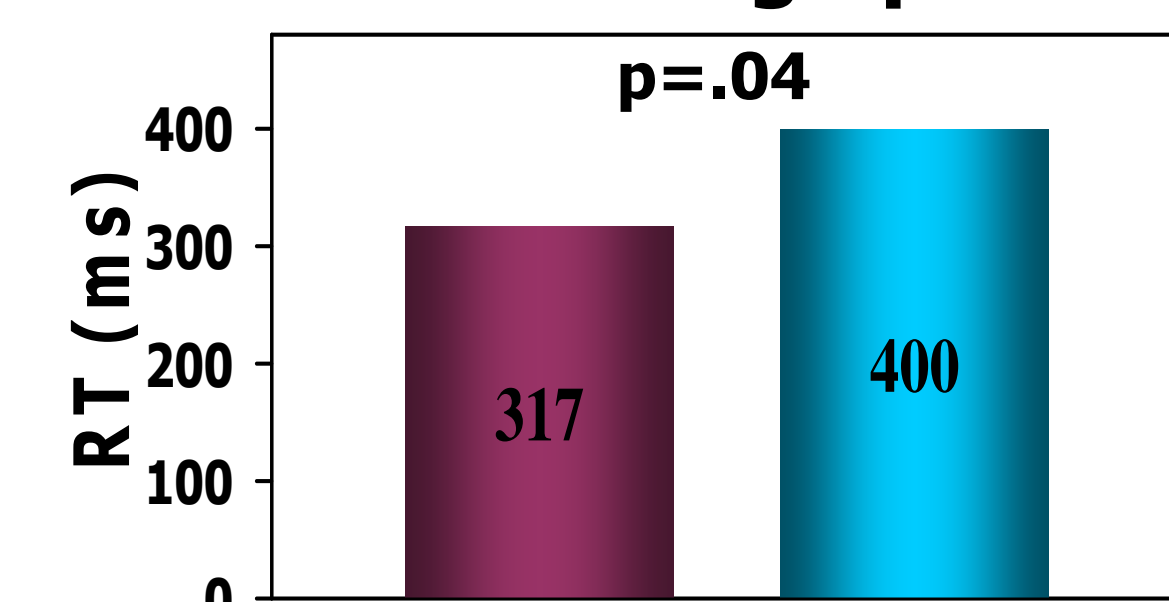
Executive: Strategic Processing



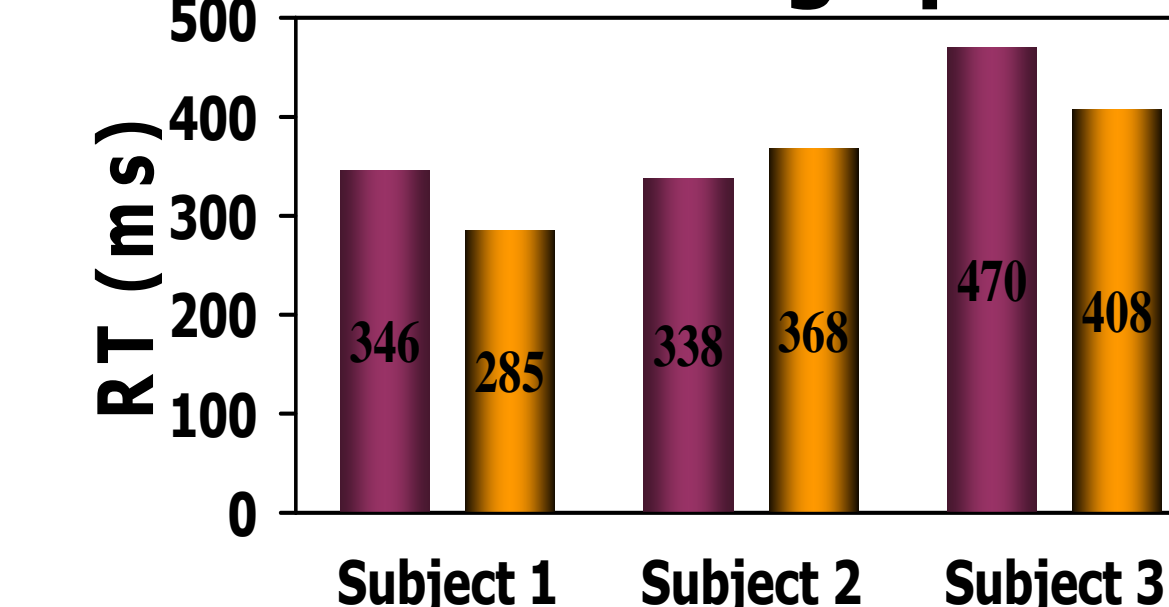
Executive: Working Memory



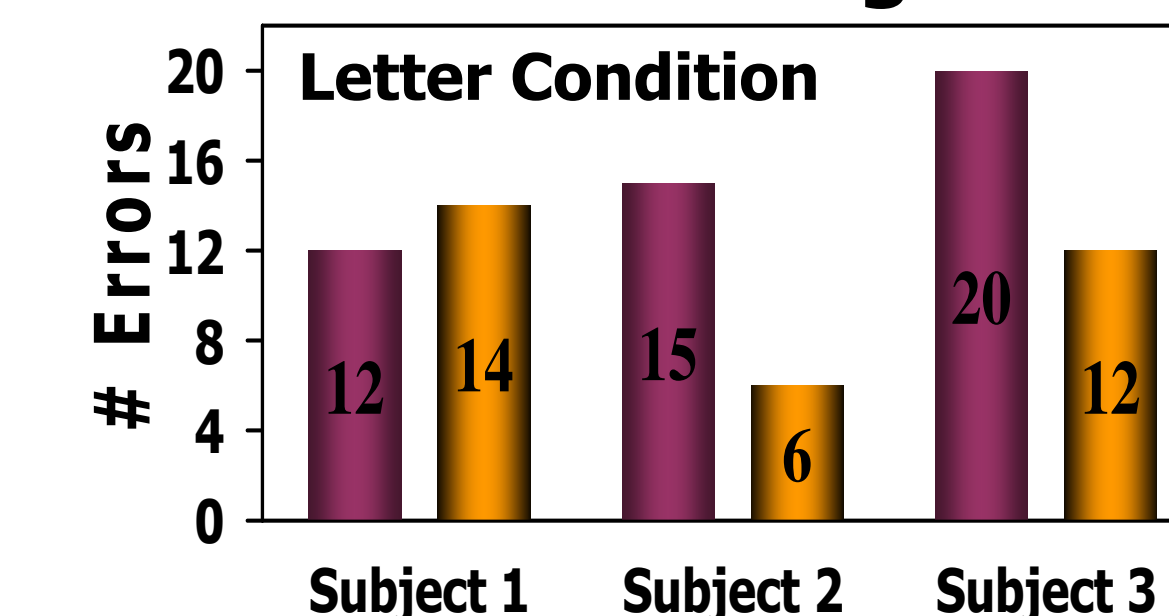
Processing Speed



Processing Speed



Executive: Working Memory



Executive: Working Memory

