Huttenlocher Award Lecture for the International Flux Society Annual Meeting

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Sept. 2022

I would like express my gratitude
for the award & my regret for not being
able to be there with you
and to acknowledge with gratitude and
respect that where I work is ancestral,
unceded territory of the wonderful
Coast Salish peoples (xʷməθkʷəy̓əm
[Musqueam], sḵwx̱wú7mesh [Squamish]
& səl̓ílw̓itulh [Tsleil-Waututh]).

Since I’ll be speaking quite quickly,

the text of much of what I’ll be say

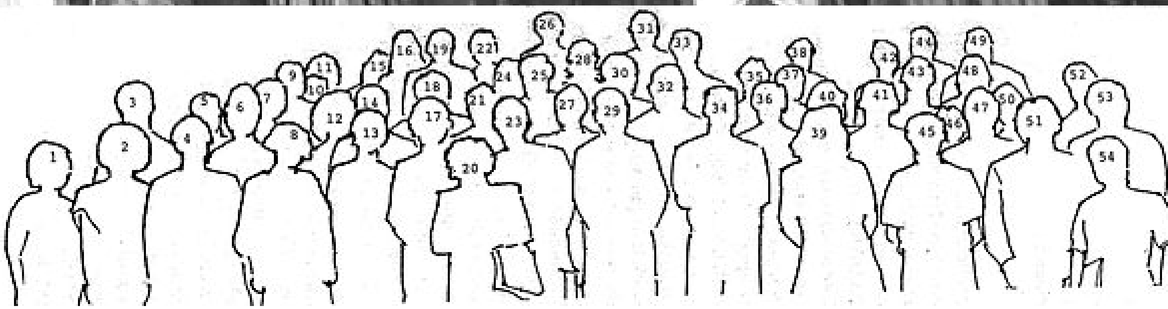
is on the slides,

to make it a little easier for

non-native English speakers

to follow along.

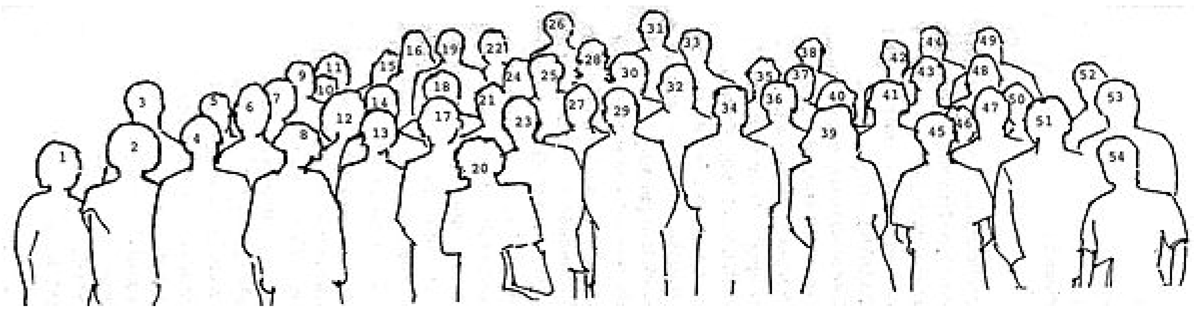
Birth of the field of Dev Cog Neuro



Conference in May 1989

1. Susan Rose, 2. Judy DeLoache, 3. William Overman, 4. Nathan Fox, 5. Kathryn Boyer, 6. Gerry Stefanatos, 7. Arthur Shimamura, 8. Nora Newcombe, 9. Stuart Zola-Morgan, 10. Judy Chasin, 11. Teresa Pantzer, 12. Barbara Malamut, 13. Adele Diamond, 14. Norman Krasnegor, 15. Marie Perri, 16. Jim Cummings, 17. Linda Acredolo, 18. Keith Nelson, 19. Barry Stein, 20. Rachel Clifton, 21. Richard Nakaniura, 22. Jackson Beatty, 23. Joseph Fagan, 24. Suzanne Craft, 25. Lewis Lipsitt, 26. Eric Knudsen, 27. Wendell Jeffrey, 28. Jonathan Cohen, 29. Joaquin Fuster, 30. Andrew Meltzoff, 31. Daniel Schacter, 32. Phillip Best, 33. Mark Stanton, 34. Douglas Frost, 35. Carolyn Rovee-Collier, 36. Paul Solomon, 37. Claire Kopp, 38. Lynn Nadel, 39. Helen Neville, 40. Emilie Marcus, 41. Richard Thompson, 42. Paula Tallal, 43. Robbie Case, 44. Henry Roediger III, 45. James Ranck Jr., 46. Ruth Colwill, 47. H. G. J. M. Kuypers, 48. Jocelyne Bachevalier, 49. Michael Noetzel, 50. Janet Werker, 51. Mike Richardson, 52. W. Stuart Millar, 53. Steven Keele, 54. Jean Mandler

Conference:
The Development & Neural Basis of Higher Cognitive Function



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Adele Diamond

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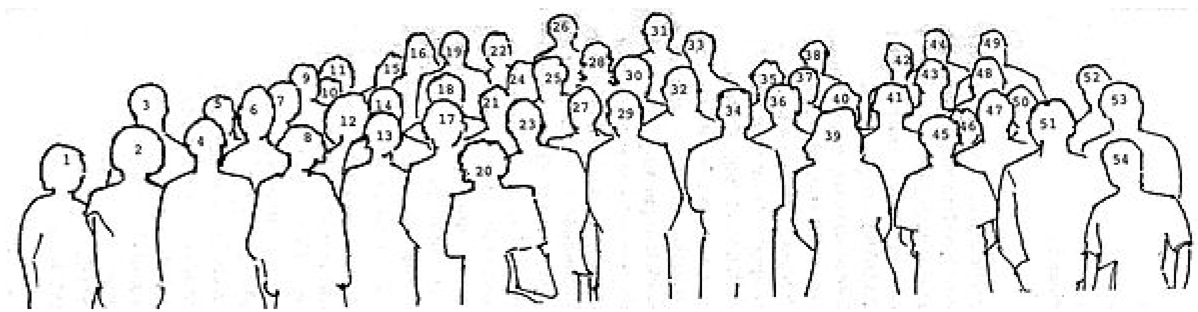

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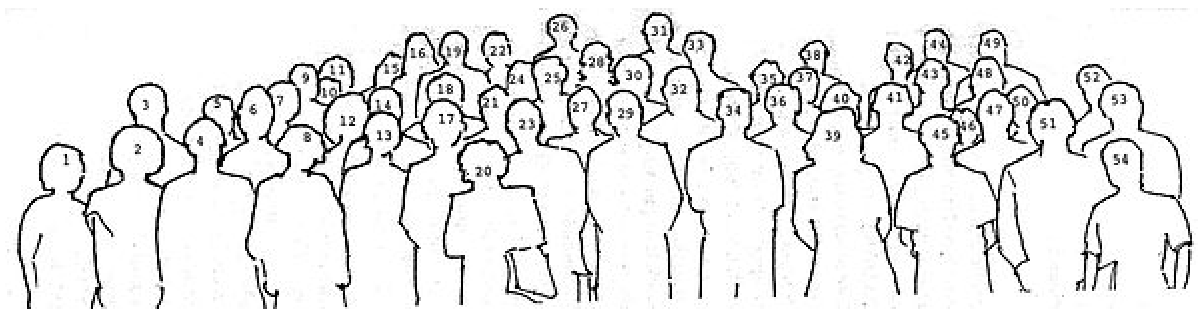

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To bridge the communication gaps, I invited researchers who were either using the same experimental paradigms to study the same behaviors or were investigating related scientific questions in complementary ways—though they were unaware of one another's work.

They used different words to talk about their work and had different ways of thinking about it, but the concrete, observable behaviors, and the precise experimental conditions under which those behaviors occurred, served to make translation possible.

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Saturday evening, May 20, 8:00 - 9:30

SPATIAL ORIENTATION, REPRESENTATION, & MAPPING

LINDA ACREDOLO: Behavioral Approaches to Spatial Orientation in Infancy

LYNN NADEL: Varieties of Spatial Cognition: Psychobiological Considerations

Sunday morning, May 21, 8:30 - 12:15

SENSORY INTEGRATION AND CROSS-MODAL MATCHING

ANDREW MELTZOFF: Cross-modal Perception, Memory, and the Control of Action: Infants' Reactions to Faces and Speech-Sounds

SUSAN ROSE: Cross-Modal Transfer in Human Infants: What is Being Transferred?

BARRY STEIN & M. ALEX MEREDITH: Multisensory Integration: Neural and Behaviora with Stimuli from Different Sensory Modalities

HELEN NEVILLE: Intermodal Competition and Compensation in Development: Evidence from Studies of the Visual System in Congenitally Deaf Adults

DOUGLAS FROST: Exuberant Cross-Modal Projections Very Early in Life

Tuesday morning, May 23, 8:45 - ~~12:30~~ 1:00

IMPLICIT & EXPLICIT MEMORY, I: VISUAL PAIRED COMPARISONS & DELAYED NON-MATCH TO SAMPLE

JOSEPH FAGAN: The Paired-Comparison Paradigm and Infant Intelligence

WILLIAM OVERMAN: Performance on Traditional Match-to-Sample, Non-Match-to-Sample, and and Object Discrimination Tasks by 12 to 32 Month-Old Children: A Developmental Progression

ADELE DIAMOND: Infants' and Young Children's Performance on Delayed Non-Match to Sample (direct and indirect) and Visual Paired Comparisons

STUART ZOLA-MORGAN: Performance of Amnesic Patients and Hippocampal Monkeys on Delayed Non-Match to Sample

JOCELYN BACHEVALIER: Ontogenetic Development of Habit and Memory Formation in Primates

Tuesday afternoon, May 23, ~~2:30~~ 3 - 5:00

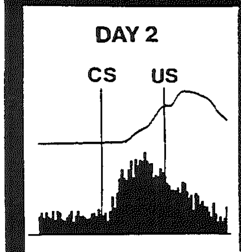
IMPLICIT & EXPLICIT MEMORY, II: PRIMING & REACTIVATION

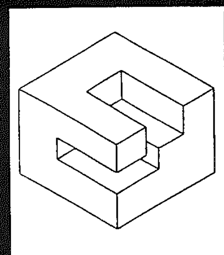
CAROLYN ROVEE-COLLIER: The "Memory System" of Prelinguistic Infants

DANIEL SCHACTER: Perceptual Representation Systems and Implicit Memory: Toward a Resolution of the Multiple Memory Systems Debate

HENRY ROEDIGER: Different Neural Systems May <u>Not</u> Underly Implicit Memory and Explicit Memory in Normal Adults, and Perhaps Not Even in Amnesic Patients

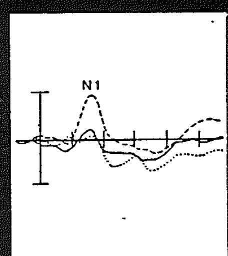
Acredolo Bachevalier Bell Best Carew Fagan Fox Frost Fuster
Ivry Keele Lipsitt Mandler Marcus Meltzoff Meredith Millar

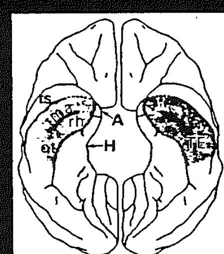




The Development and Neural Bases of Higher Cognitive Functions

Editor
Adele Diamond





Nadel Neville Overman Roediger Rose Rovee-Collier Schacter
Solomon Squire Stein Thompson Woodruf-Pak Zola-Morgan

Annals of the New York Academy of Sciences • Volume 608

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Volume 608

THE DEVELOPMENT AND NEURAL BASES OF HIGHER COGNITIVE FUNCTIONS

Edited by Adele Diamond

The New York Academy of Sciences
New York, New York
1990

At Harvard, was a member of the Whiting-LeVine training group in cross-cultural research, and thus got 3 years of dissertation funding:

1 year to prepare to go into the field

1 year to go anywhere in the world I wanted to go (was going to go to the S. Pacific because that seemed the most idyllic)

1 year to write it up

I GAVE THE MONEY BACK

So, I needed to come up with a dissertation topic.

Jerry Kagan: See the same cognitive changes in infants all over the world at roughly the same time in the 2nd half of the 1st year of life. Their experiences are so very different, can't just be learning; must be a maturational component. [Jumping up & down.]

Investigating that question is how I came to neuroscience.

MY HYPOTHESIS:

Maybe some of the cognitive advances in the 2nd half of the 1st year of life are made possible by maturational changes in prefrontal cortex.

One clue came from how similar a classic test for infants in the first year (A-not-B)

and a classic test for studying PFC in monkeys (delayed response) were

and that babies and monkeys fail these tasks in similar ways and under similar conditions.

Piaget, J. (1937). ***The Construction of Reality in the Child.*** **Original French Edition.**

Jacobsen, C.F. (1935). Functions of the Frontal Association Areas in Primates. ***Archives of Neurology & Psychiatry, 33.***

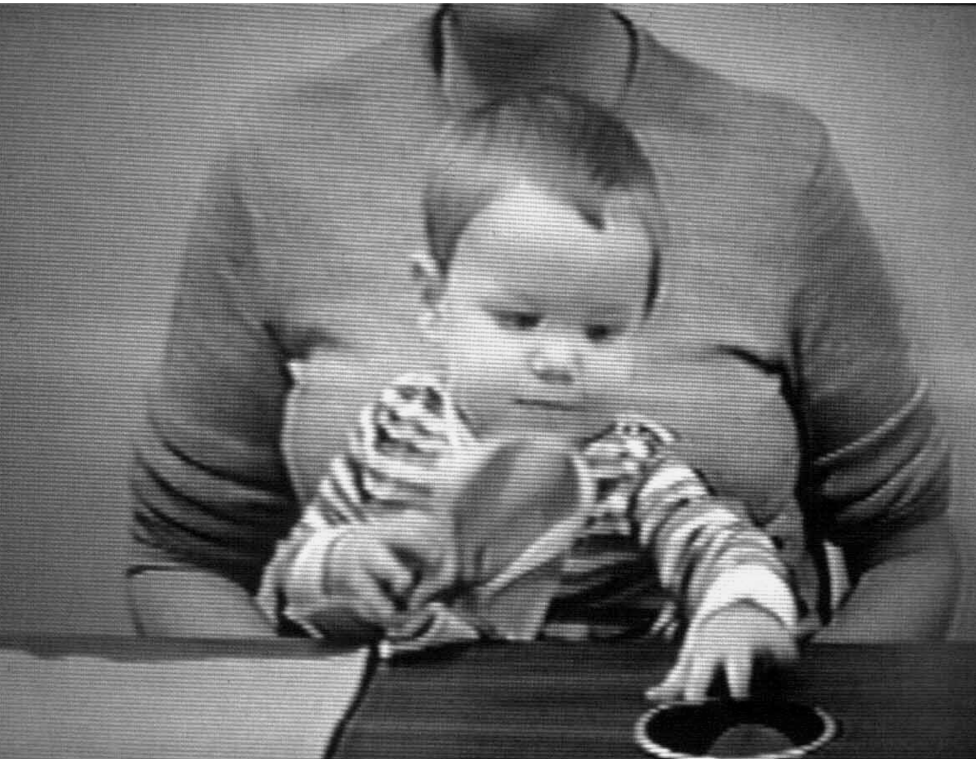
For almost 50 years,

DEVELOPMENTAL PSYCHOLOGISTS studying the A-not-B TASK with babies

and NEUROSCIENTISTS studying the DELAYED RESPONSE task with monkeys

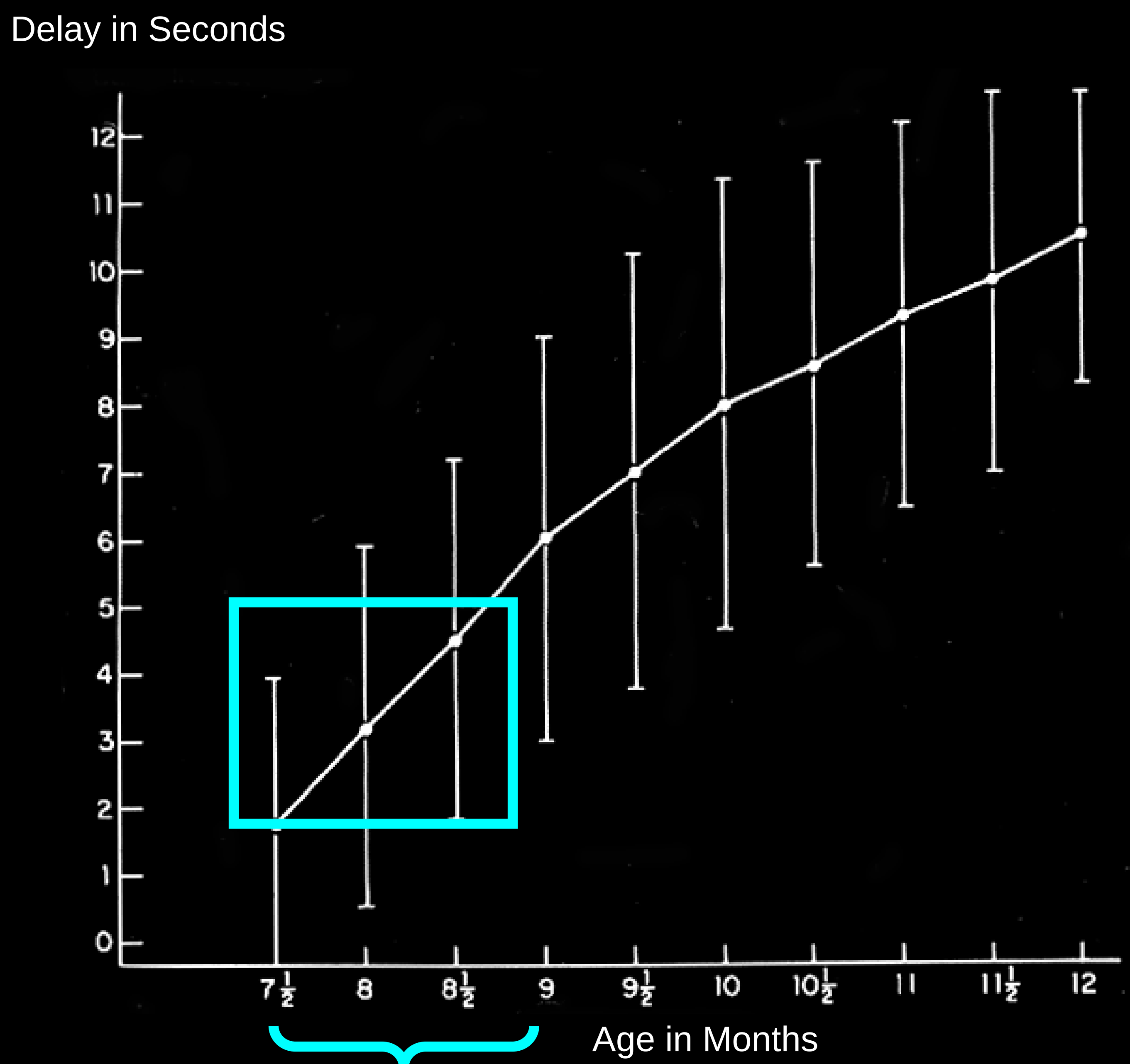
DID NOT KNOW they were studying the essentially SAME task

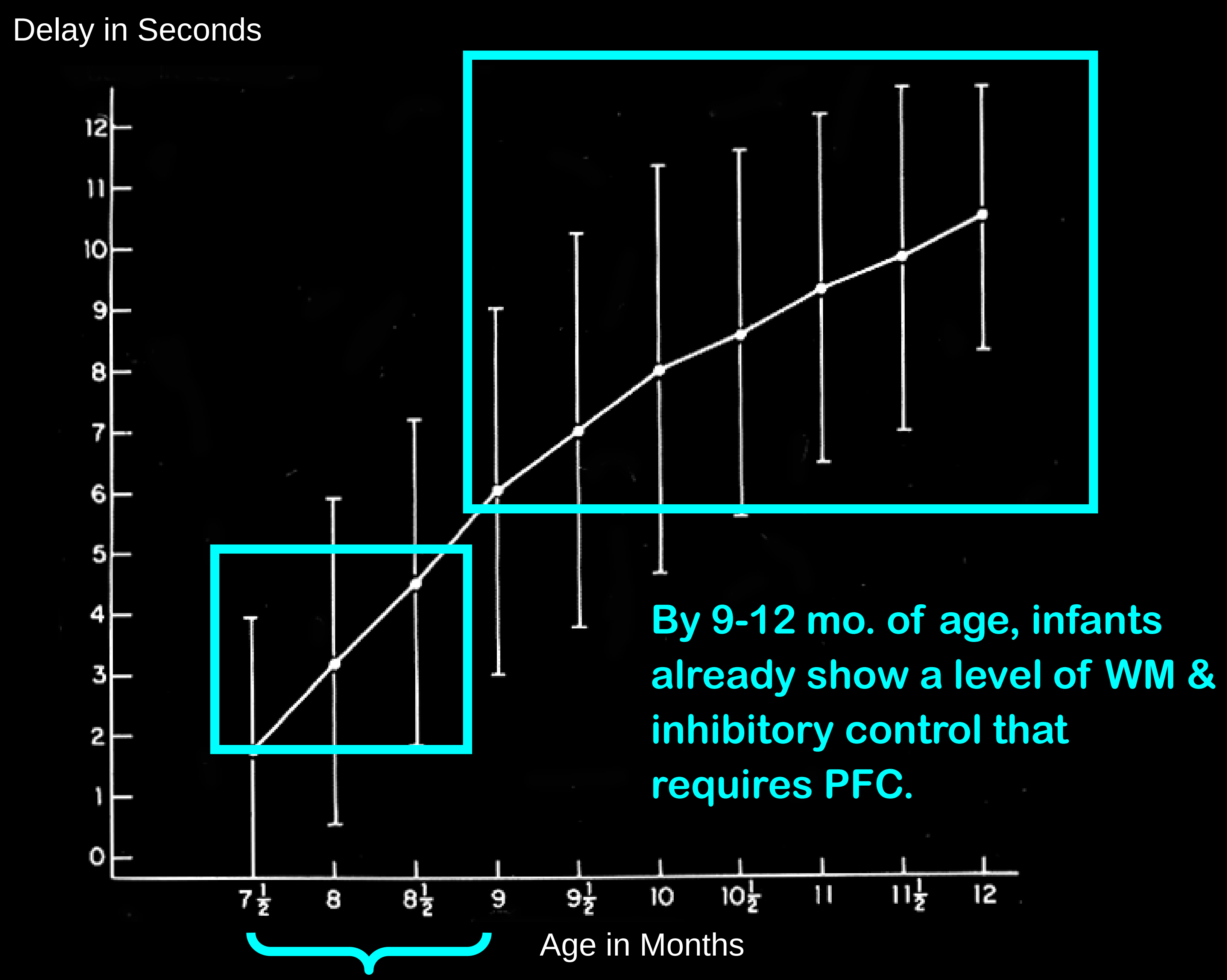
“A” Trial

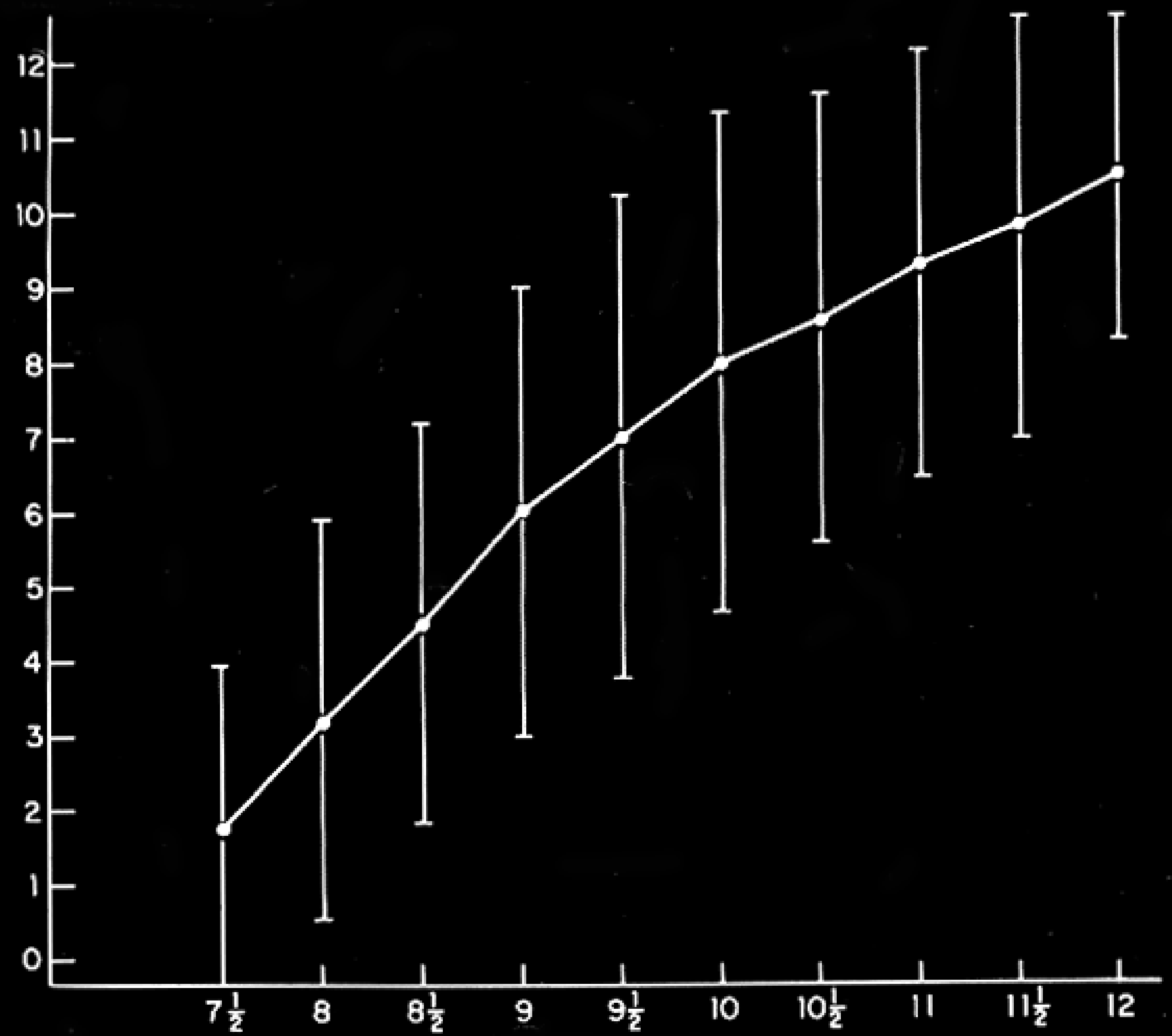


“B” Trial



Delay in Seconds
0
1
2
3
4
5
6
7
8
9
10
11
12
7½
8
8½
9
9½
10
10½
11
11½
12
Age in Months


Delay in Seconds
12
11
10
9
8
7
6
5
4
3
2
1
0
7½
8
8½
9
9½
10
10½
11
11½
12
Age in Months
By 9-12 mo. of age, infants already show a level of WM & inhibitory control that requires PFC.

Delay in Seconds at which
A-not-B error occurs



Age in Months


0:01:43:5


0:01:45:3


0:01:46:6


0:01:46:7


0:01:47:0

One Theme throughout my work:

Development proceeds not only by the acquisition of new knowledge, but also by the increasing ability to inhibit habitual or reflexive reactions that get in the way of demonstrating what is already known.

A child may know what he or she should do, and want to do that, but still not be able to act accordingly.

Moll, L., & Kuypers, H. G. J. M.

(1977)

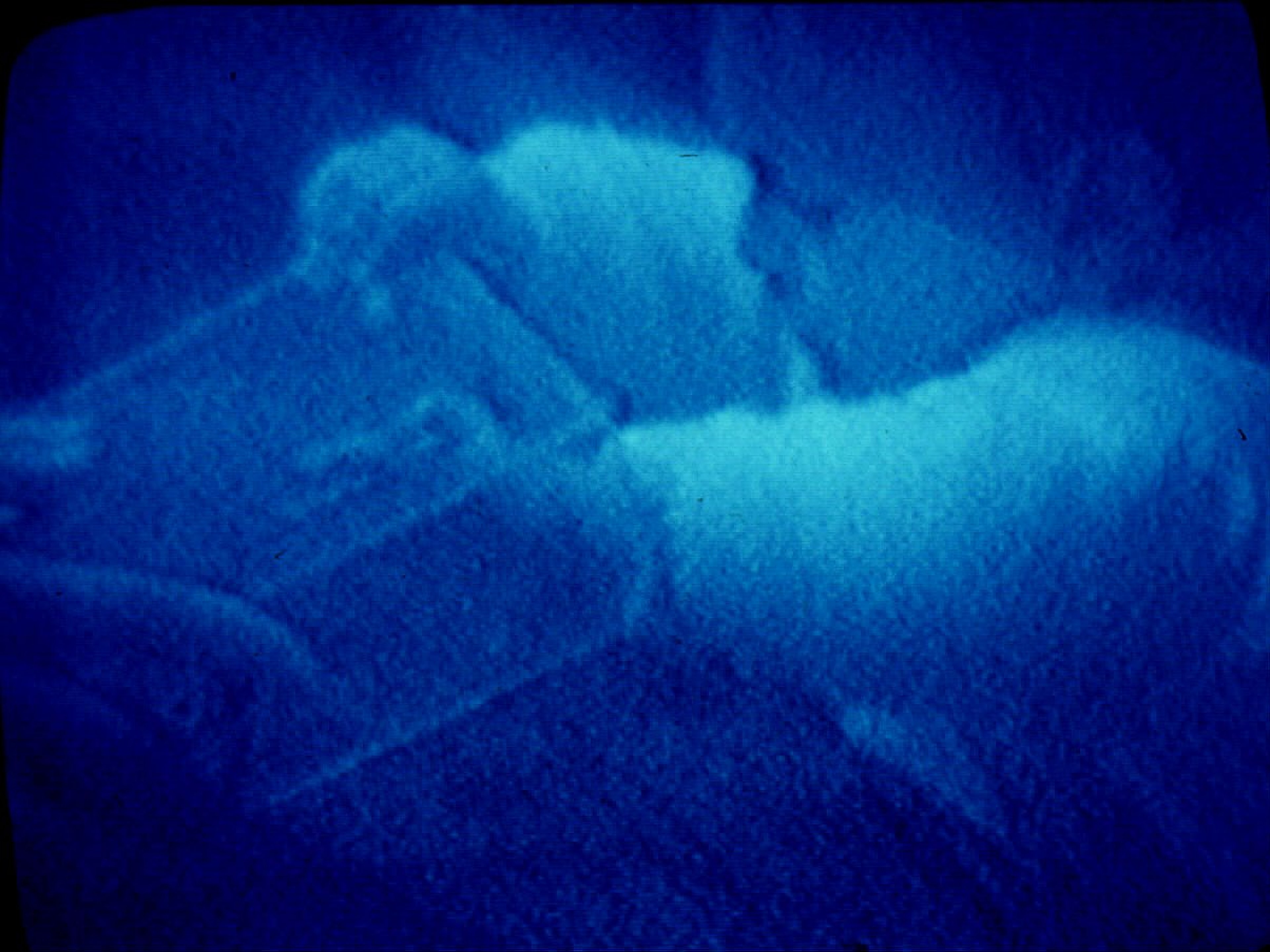
***Science*, *198*, 317-319**

Object Retrieval Task (6½-month-old)

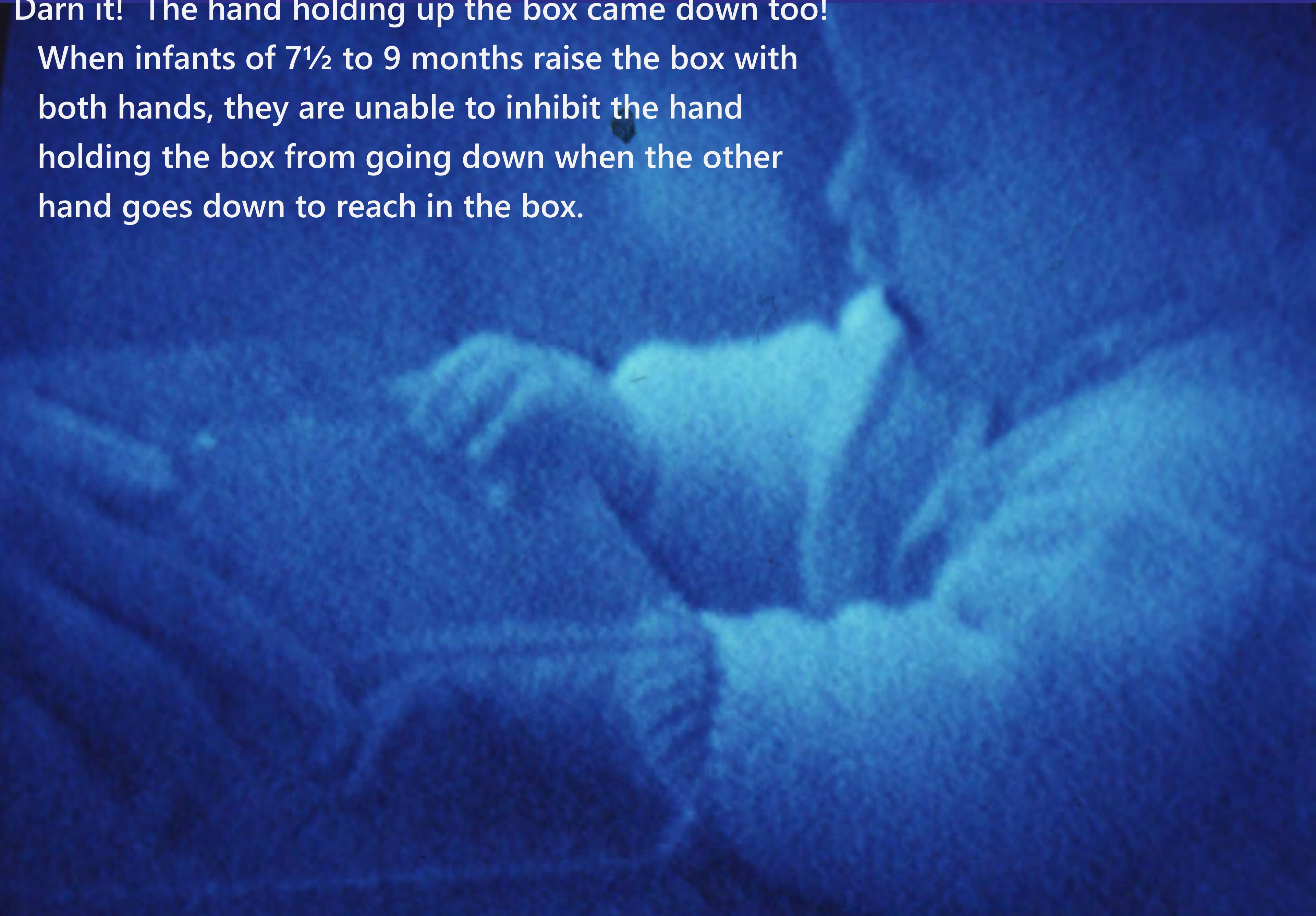
Mean Trial Duration for Same Size Transparent and Opaque Boxes on Left-Open Trials with Toy Deep in Box

Age in Months	Transparent Box	Opaque Box
7 ½	28.6	15.7
8	29.4	16.5
8 ½	24.9	14.0
9	16.7	11.3
9 ½	15.4	10.4
10	13.8	10.3
10 ½	13.3	9.8
11	11.4	11.2
11 ½	5.2	5.8
12	4.7	3.3


Object Retrieval Task
(7½-month-old)
Her pacifier is under the box



Darn it! The hand holding up the box came down too! When infants of 7½ to 9 months raise the box with both hands, they are unable to inhibit the hand holding the box from going down when the other hand goes down to reach in the box.



Percent of Trials on which Infants in Phase 1B Succeed

	Front of the Box is Open		
	Sees toy thru closed side throughout trial	"Show & Return" Sees toy thru opening & then closed side	Sees toy thru opening
Age in Months			
7 ½	2	15	100
8	2	20	100

Simultaneous integration of the movements of the 2 hands requires involvement of the Supplementary Motor Area (SMA) and inhibitory projections via the corpus callosum so that the tendency of one hand to do the same thing as the other hand can be suppressed.


Object Retrieval Task
(9-month-old)


For the 1st time, the memory of having looked along the line of reach is enough.

Working memory is needed to remember what they saw when they looked into the box opening

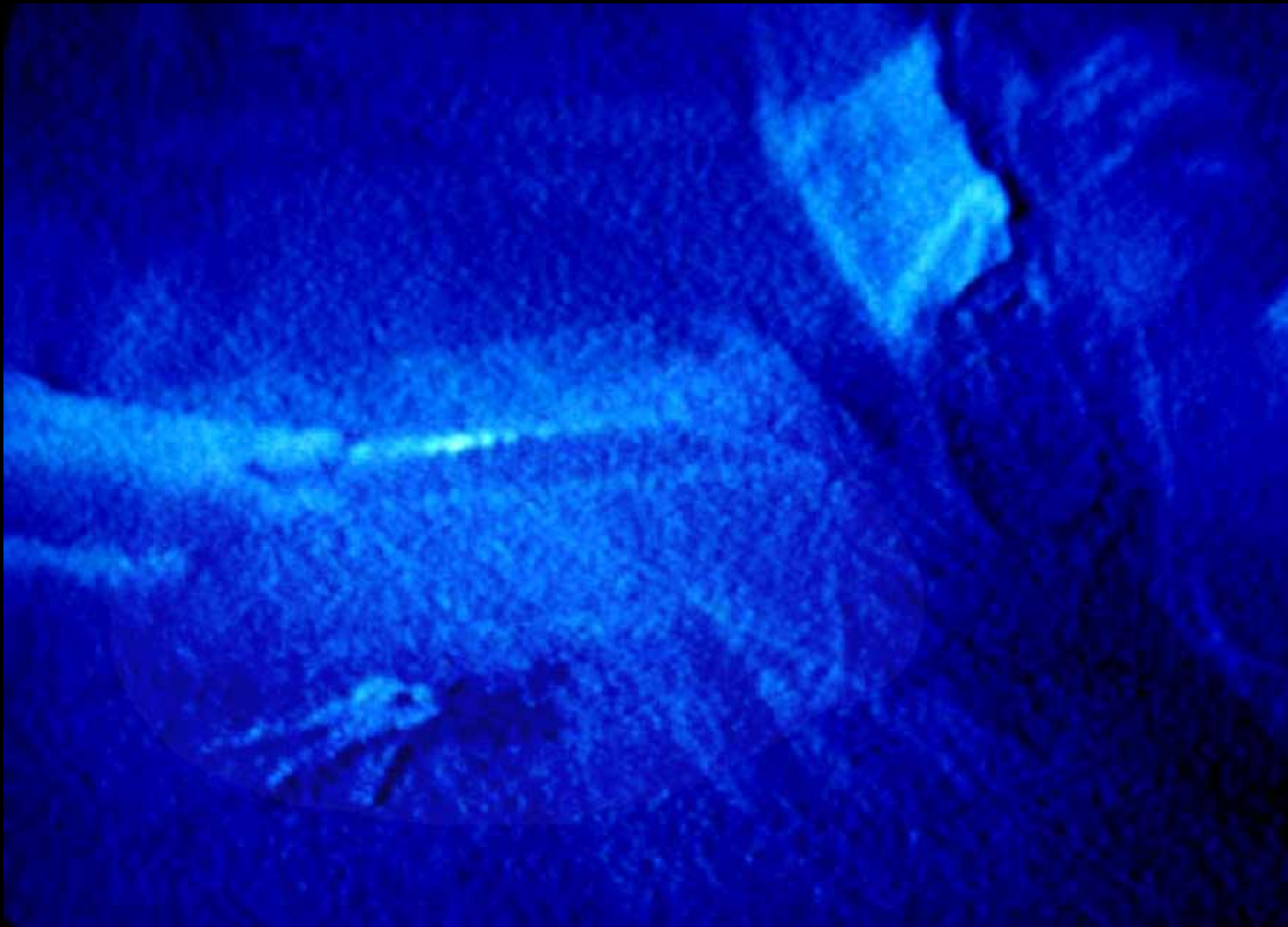
when they sit back up

and for integrating line of sight and line of reach.

Percent of Trials on which Infants in Phase 2 Succeed

	Front of the Box is Open		
Age in Months	Sees toy thru closed side throughout trial	"Show & Return" Sees toy thru opening & then closed side	Sees toy thru opening
8 ½	4	92	100
9	18	96	100

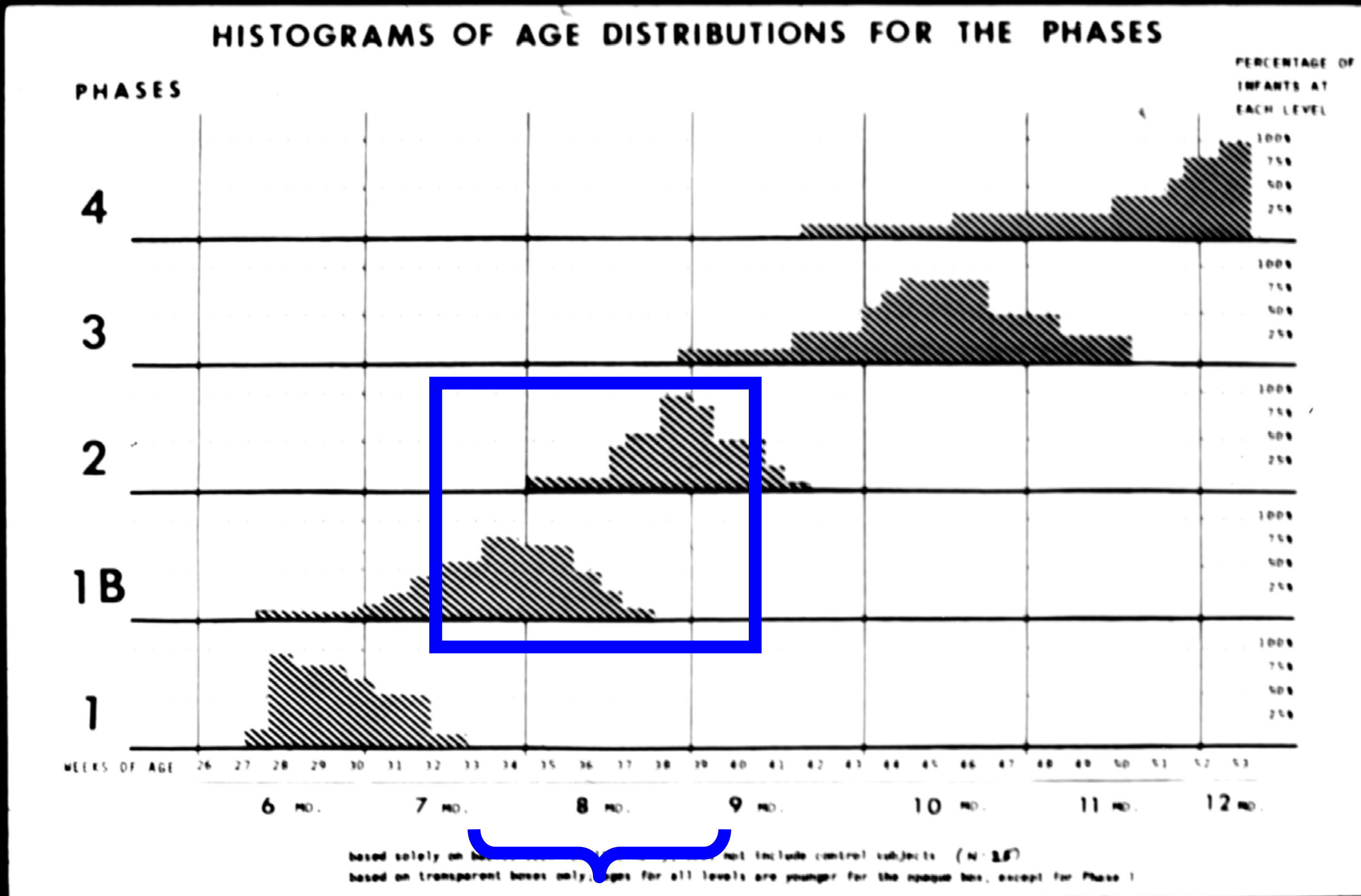
10-month-old infant



Remember

One Theme throughout my work:

Development proceeds not only by the acquisition of new knowledge, but also by the increasing ability to inhibit habitual or reflexive reactions that get in the way of demonstrating what is already known.


HISTOGRAMS OF AGE DISTRIBUTIONS FOR THE PHASES
PHASES
PERCENTAGE OF INFANTS AT EACH LEVEL
4
3
2
1B
1
100%
75%
50%
25%
WEEKS OF AGE
6 MO.
7 MO.
8 MO.
9 MO.
10 MO.
11 MO.
12 MO.
based solely on ... not include control subjects (N = 25)
based on transparent boxes only, ages for all levels are younger for the opaque box, except for Phase 1

Diamond, A. (1990). Developmental time course in human infants and infant monkeys, and the neural bases, of inhibitory control in reaching. In A. Diamond (Ed.), *The development and neural bases of higher cognitive functions* (pp. 637-676). *Annals of the New York Academy of Sciences, vol 608.*

Diamond, A. (1991). Neuropsychological insights into the meaning of object concept development. In S. Carey & R. Gelman (Eds.), *The epigenesis of mind: Essays on biology and knowledge* (pp. 67-110). Hillsdale, NJ: Lawrence Erlbaum Assoc.

Diamond, A. (1991). Frontal lobe involvement in cognitive changes during the first year of life. In K. R. Gibson & A. C. Petersen (Eds.), *Brain maturation and cognitive development: Comparative and cross-cultural perspectives* (pp. 127–180). NYC , NY: Aldine de Gruyter.

Diamond, A., Zola-Morgan, S., & Squire, L. R. (1989). Successful performance by monkeys with lesions of the hippocampal formation on A-not-B and object retrieval, two tasks that mark developmental changes in human infants. *Behavioral Neuroscience, 103,* 526–537.

Dorsolateral prefrontal cortex is required for tasks such as object retrieval, A-not-B, and delayed response,

where subjects must integrate information that is separated in space or time

and

must inhibit a predominant response.

	A-not-B	Delayed Response	Object Retrieval
Human infants show a clear developmental progression from 7½ -12 months.	Diamond, 1985	Diamond & Doar, 1988	Diamond, 1988
Adult monkeys with lesions of prefrontal cortex fail.	Diamond & Goldman-Rakic, 1989	Diamond & Goldman-Rakic, 1989	Diamond & Goldman-Rakic, 1985
Adult monkeys with lesions of parietal cortex succeed.	Diamond & Goldman-Rakic, 1989	Diamond & Goldman-Rakic, 1989	Diamond & Goldman-Rakic, 1985
Adult monkeys with lesions of the hippocampal formation succeed.	Diamond, Zola-Morgan, & Squire, 1989	Squire & Zola-Morgan, 1983	Diamond, Zola Morgan, & Squire, 1989
Infant monkeys show a clear developmental progression from 1½ - 4 months.	Diamond & Goldman-Rakic, 1986	Diamond & Goldman-Rakic, 1986	Diamond & Goldman-Rakic, 1986
5-month-old infant monkeys, who received lesions of prefrontal cortex at 4 months, fail.	Diamond & Goldman-Rakic, 1986	Diamond & Goldman-Rakic, 1986	

Having demonstrated that maturational changes in PFC might underlie some of the cognitive advances early in life, one of the next questions was,

"What was changing in PFC?"

One possibility was that the level of dopamine (DA) in PFC was increasing.

As a first pass way of looking at the role of dopamine in modulating cognitive functions dependent on PFC early in life in humans,

I decided to look at a group of children, who there was reason to believe, had lower levels of dopamine in PFC but otherwise basically normal brains:

Children treated early & continuously for PKU

Phenylketonuria (PKU) is a genetic disorder in the ability to metabolize one amino acid, phenylalanine (Phe), into another, tyrosine (Tyr).

Proteins in Diet → **Phenylalanine**

↓ ~~**phenylalanine hydroxylase**~~

Proteins in Diet → **Tyrosine**

↓ **tyrosine hydroxylase**

DOPA

↓ **DOPA decarboxylase**

Dopamine

Because of the problem in converting Phe to tyrosine,

- blood levels of Phe skyrocket, and
- the relative, and usually the absolute, levels of tyrosine fall.

The upshot is widespread brain damage and severe mental retardation – if untreated.

The treatment for PKU is to remove as much Phe from the diet as possible.

When that is begun early and consistently maintained, children with PKU are not mentally retarded and do not have gross brain damage.

However, there were reports of selective cognitive impairments in well-treated PKU children, reminiscent of deficits seen with PFC damage or dysfunction.

Those went largely ignored by physicians because no one could imagine a mechanism capable of producing that effect.

Phe and tyrosine compete to cross the blood-brain barrier.

If the bloodstream has mildly elevated levels of Phe & mildly reduced levels of Tyr,

the result is a mild reduction in the amount of tyrosine reaching the brain (the entire brain).

Most regions of the brain could care less if the amount of Tyr is slightly reduced.

For example, the striatum is insensitive to reductions in Tyr of even 50-60%.

But neuropharmacologists studying diabetic rats[1] had recently shown that if tyrosine is mildly reduced, PFC alone is affected.

I realized that this might provide a mechanism for selective EF deficits in treated PKU.

Bradberry, C. W., Karasic, D. H., Deutsch, A. Y., & Roth, R. H. (1989). Regionally-specific alterations in mesotelencephalic dopamine synthesis in diabetic rats: Associations with precursor tyrosine. *Journal of Neural Transmission, 78, 221-229.*

The dopamine neurons that project to prefrontal cortex differ from most other dopamine neurons in the brain in that...

- they fire faster, and
- turn over dopamine faster

This makes prefrontal cortex acutely sensitive to even a small reduction in tyrosine, while other brain areas are not.

Thierry, A.M., Tassin, J.P., Blanc, A., Stinus, L., Scatton, B., & Glowinski, J. (1977). Discovery of the mesocortical dopaminergic system: Some pharmacological and functional characteristics. *Advanced Biomedical Psychopharmacology*, *16*, 5-12.

Bannon, M.J., Bunney, E.B., & Roth, R.H. (1981). Mesocortical dopamine neurons: Rapid transmitter turnover compared to other brain systems. *Brain Research, 218,* 376-382.

Tam, S.Y., Elsworth, J.D., Bradberry, C.W., & Roth, R.H. (1991). Mesocortical dopamine neurons: High basal firing frequency predicts tyrosine dependence of dopamine synthesis. *Journal of Neural Transmission, 81*, 97-110.

Another recurring Theme in my work:

Unusual properties of the dopamine (DA) system in prefrontal cortex (PFC) contribute to PFC's vulnerability to environmental and genetic variations that have little effect elsewhere.

The special properties of the dopamine neurons that project to PFC provided a mechanism by which children treated for PKU might show effects limited to PFC.

To test that, I combined

longitudinal testing of infants and children on an extensive battery of neurocognitive tasks

with neurochemical and behavioral work in animals (creating the first animal model of treated PKU).

We found that children with PKU whose plasma Phe levels were 3-5 times normal (360-600 µmol/L) were impaired on all 6 tasks that required both...

working memory

and

inhibitory control

This deficit in the cognitive abilities dependent on DL-PFC was evident in all age ranges...

...infants (6-12 months old)

...toddlers (15-30 months old)

...young children (3½-7 years old).

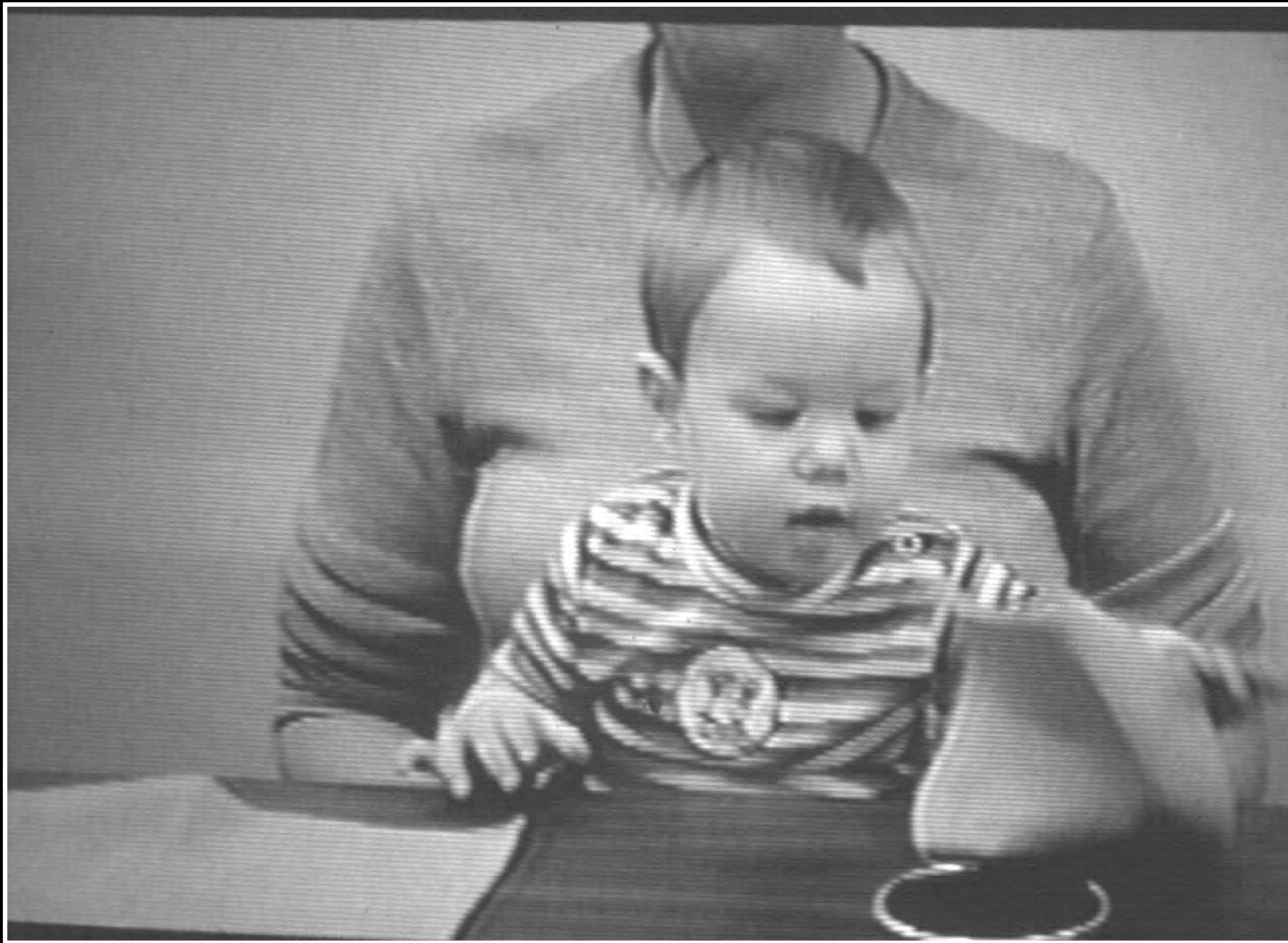
The deficit was clear whether the children were compared to...

...other PKU children with lower Phe levels,

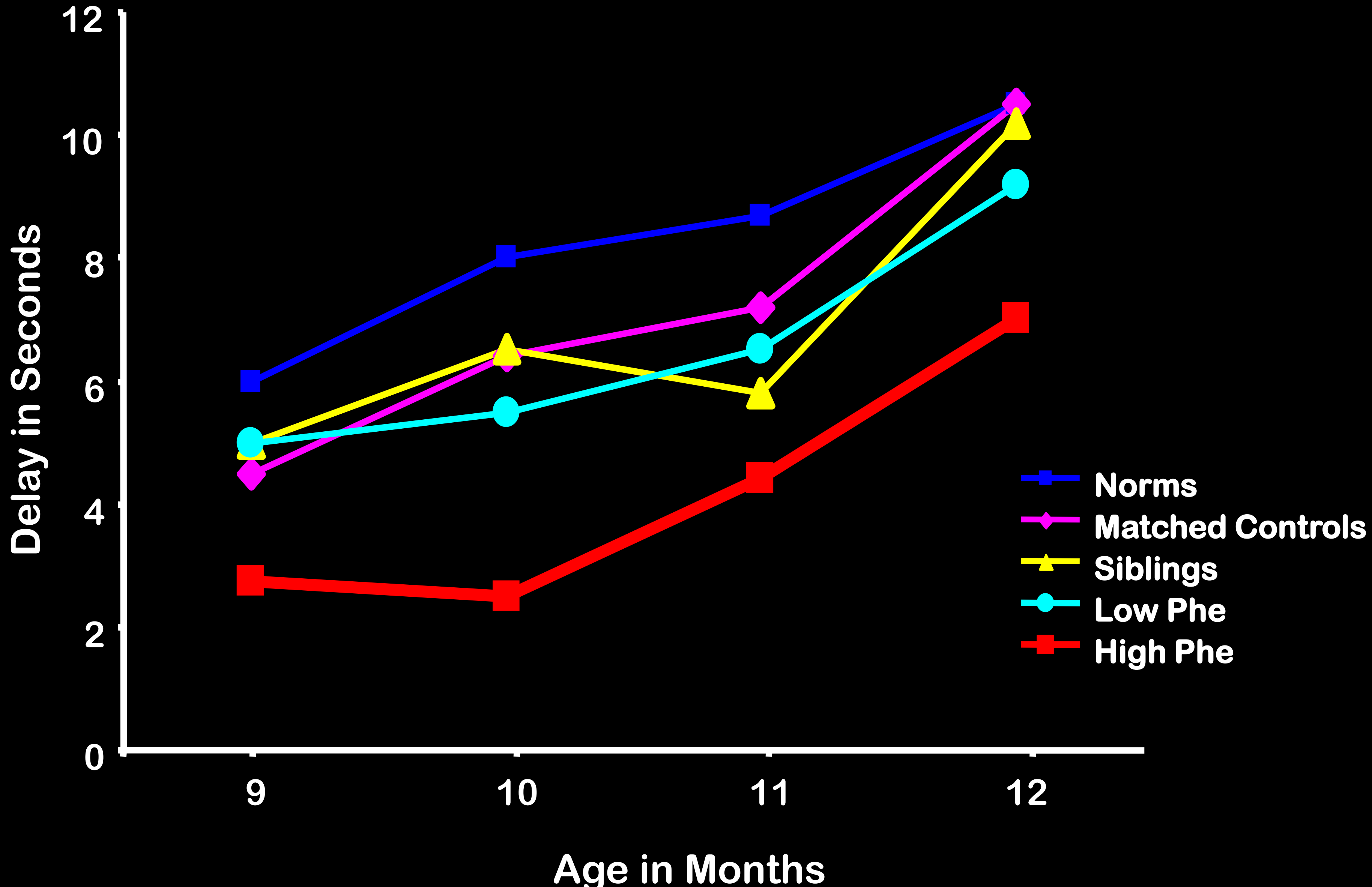
...their own siblings,

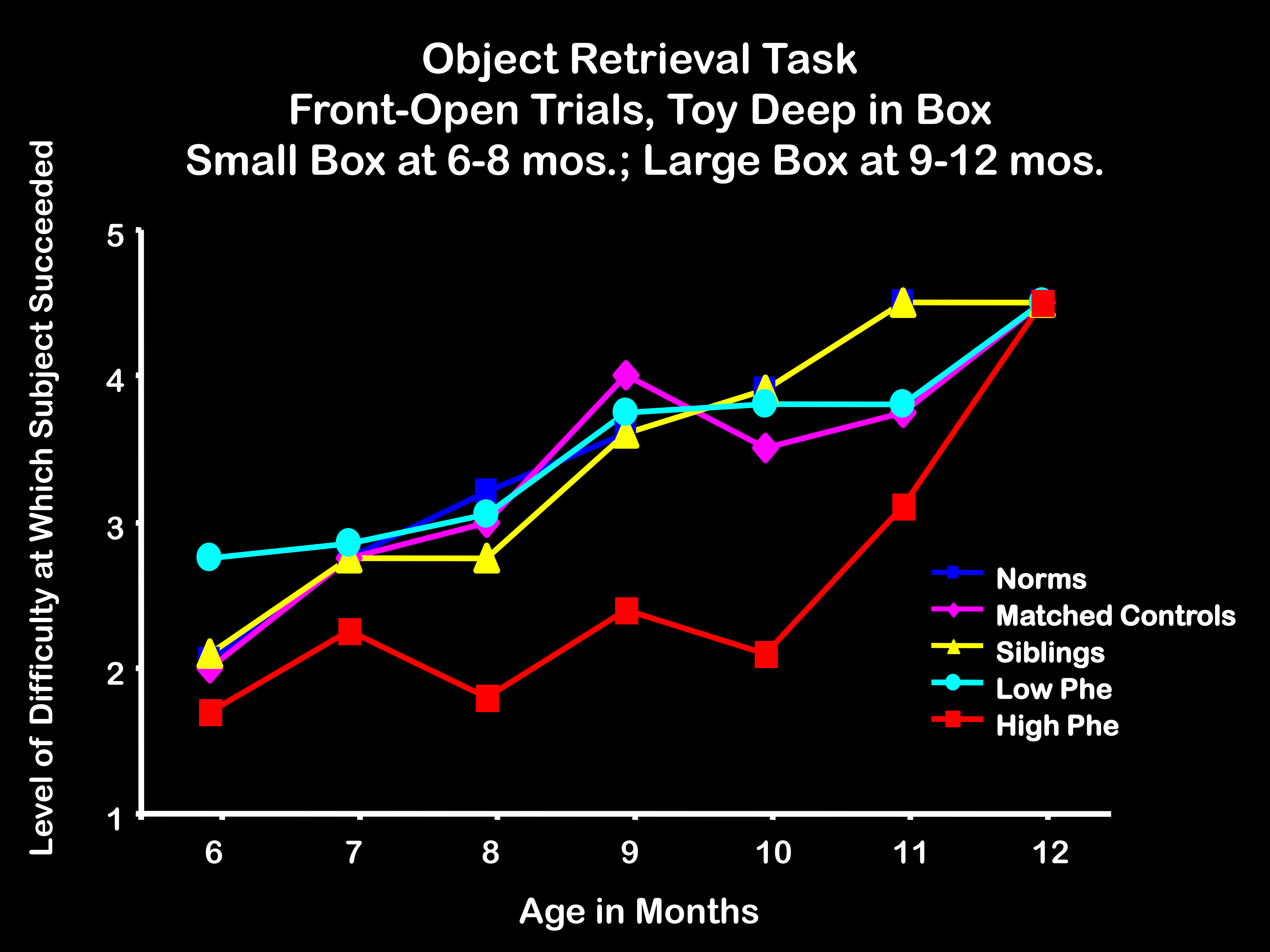
...matched controls, or

...children from the general population.



The A-not-B task

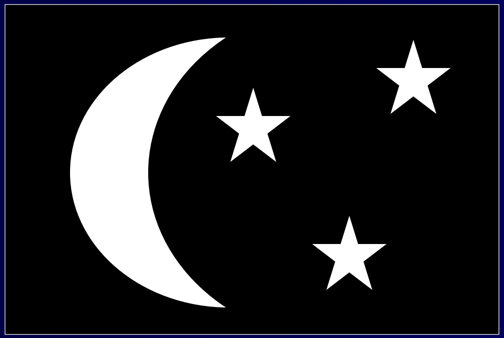



Object Retrieval Task
Front-Open Trials, Toy Deep in Box
Small Box at 6-8 mos.; Large Box at 9-12 mos.
Level of Difficulty at Which Subject Succeeded
1
2
3
4
5
6
7
8
9
10
11
12
Age in Months
Norms
Matched Controls
Siblings
Low Phe
High Phe

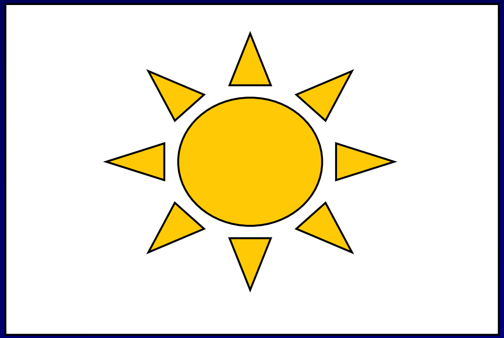
THE DAY-NIGHT TASK

(Gerstadt , Hong, & Diamond, 1994)

Semantically conflicting labels

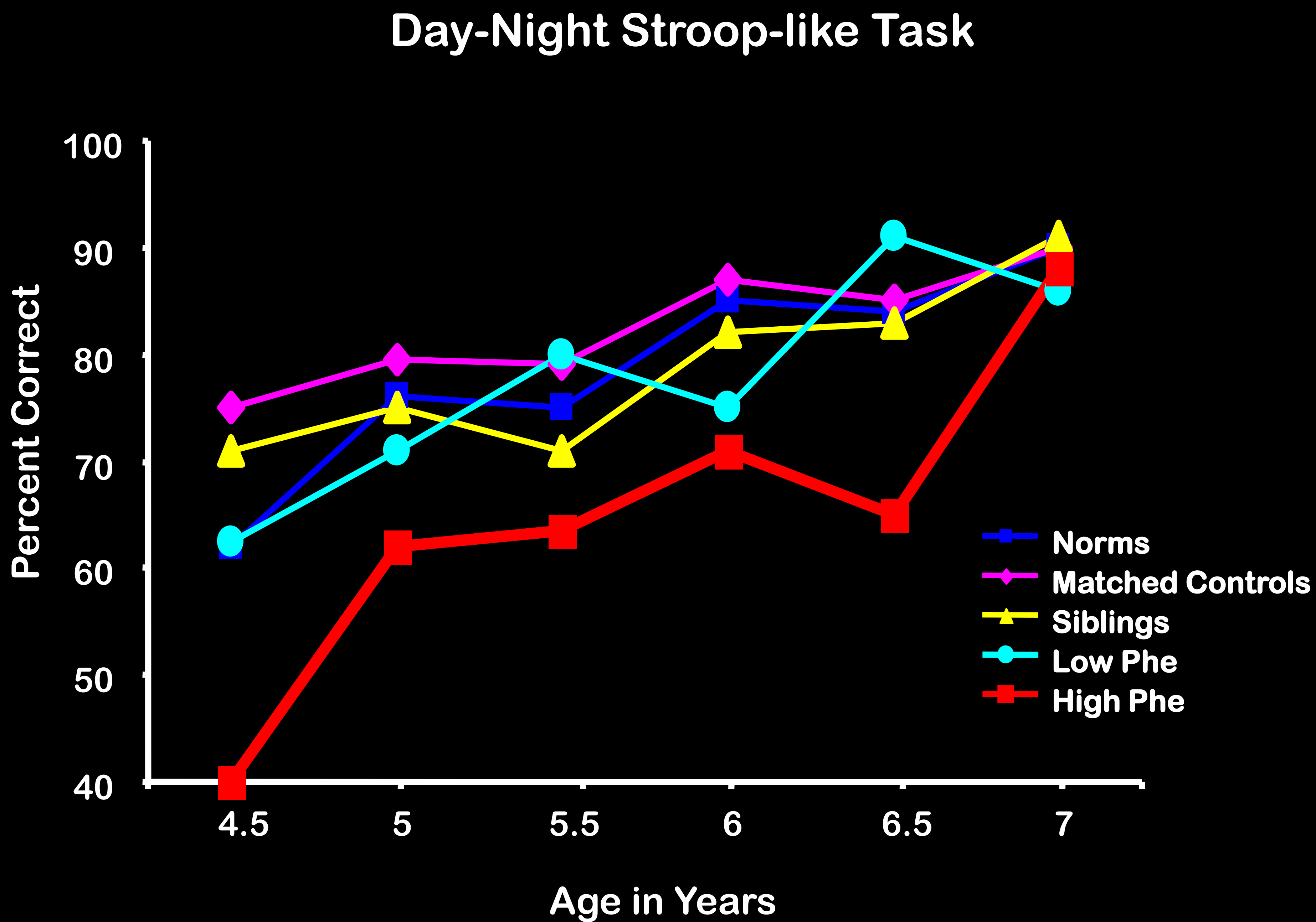


"Day"



"Night"

Requires holding 2 rules in mind, and inhibiting saying what the images really represent, saying the opposite instead.


Day-Night Stroop-like Task
Percent Correct
100
90
80
70
60
50
40
4.5
5
5.5
6
6.5
7
Age in Years
Norms
Matched Controls
Siblings
Low Phe
High Phe

The same children, who were impaired on the tasks dependent on prefrontal cortex, performed normally on all 10 control tasks.

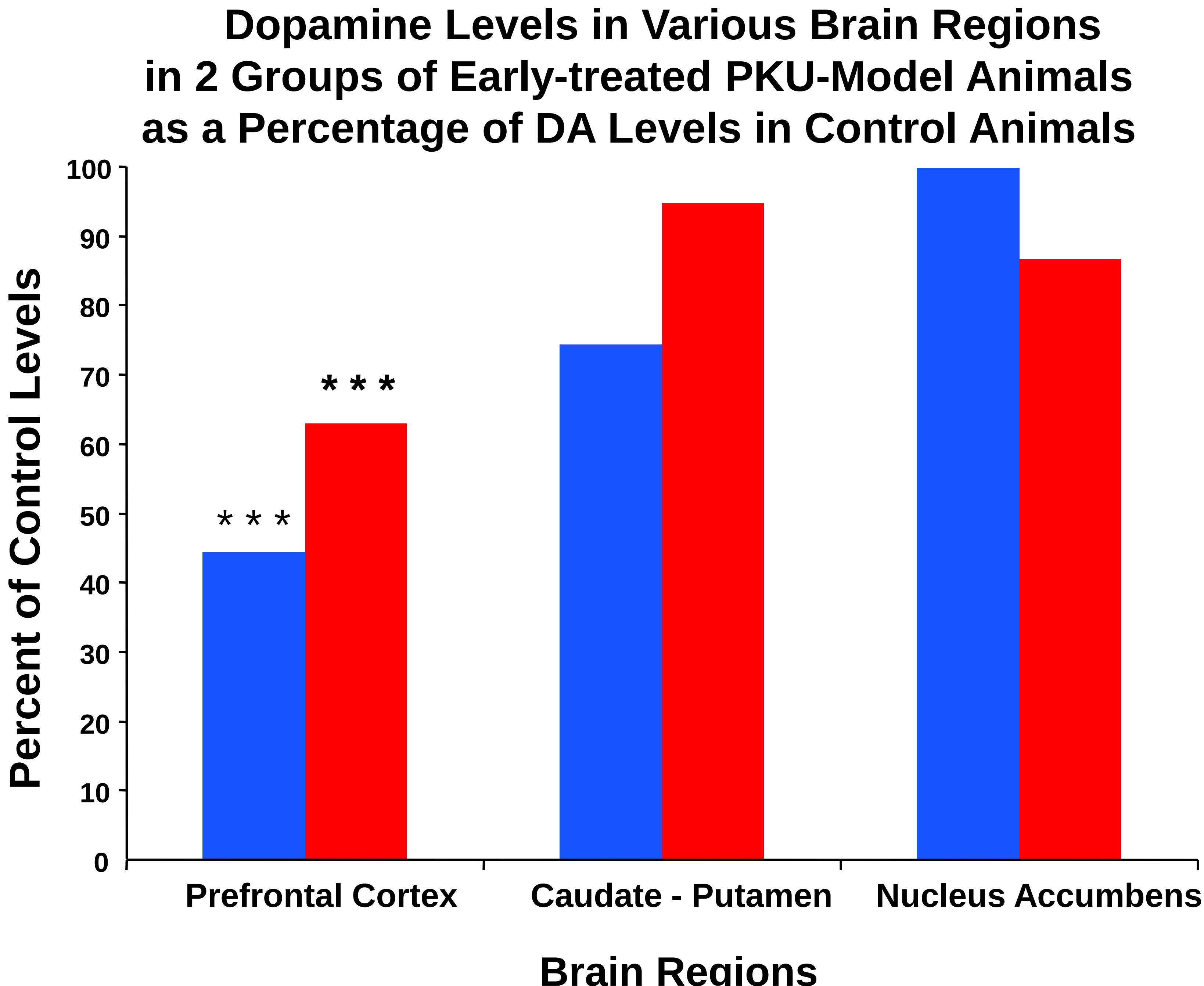
That suggests that the deficits were indeed selective (confined to one neural system). The functions of parietal cortex and of the medial temporal lobe appear to be spared.

Adele Diamond, Meredith Prevor, Glenda Callender, & Donald Druin

1997

Prefrontal Cortex Cognitive Deficits in Children Treated Early and Continuously for PKU

Monographs of the Society for Research in Child Development (Monograph # 252), 62 (4)


Dopamine Levels in Various Brain Regions
in 2 Groups of Early-treated PKU-Model Animals
as a Percentage of DA Levels in Control Animals
Percent of Control Levels
100
90
80
70
60
50
40
30
20
10
0
* * *
* * *
Prefrontal Cortex
Caudate - Putamen
Nucleus Accumbens
Brain Regions

There was almost no overlap between HVA levels in PFC of controls and experimental animals.

All but one control animal had higher HVA levels in PFC than *any* PKU-model animal.

A. Diamond, V. Ciaramitaro, E. Donner,
S. Djali & M. Robinson

(1994)

The first animal model of
early-treated PKU

Journal of Neuroscience
14, 3072-3082

Our work, building on that of others, led to a change in the guidelines for the treatment of PKU around the world:

the United Kingdom, Germany,
the Netherlands, Denmark,
France, Canada, & the United States

New guidelines: Phe levels should be kept between 120-360 μmol/L (2-6 mg/dL), rather than 120-600 μmol/L as recommended before.

Subsequent research has shown that this change has indeed improved children's lives (Stemerdink *et al.*, 1999; Huijbregts *et al.*, 2002).

While doing the longitudinal study I learned that there is another set of DA neurons that share all the same properties as the DA neurons that project to PFC:

the dopamine neurons in the retina

Retinal dopamine neurons also

- fire at a rapid rate
- have a high rate of dopamine turnover
- & are unusually sensitive to the level of available tyrosine.

Fernstrom, J. D., & Fernstrom, M. H. (1988)

Tyrosine availability and dopamine synthesis in the retina.

In I. Bodis-Wollner & M. Piccolino (Eds.), *Dopaminergic Mechanisms in Vision* (pp. 59-70). New York: Alan Liss

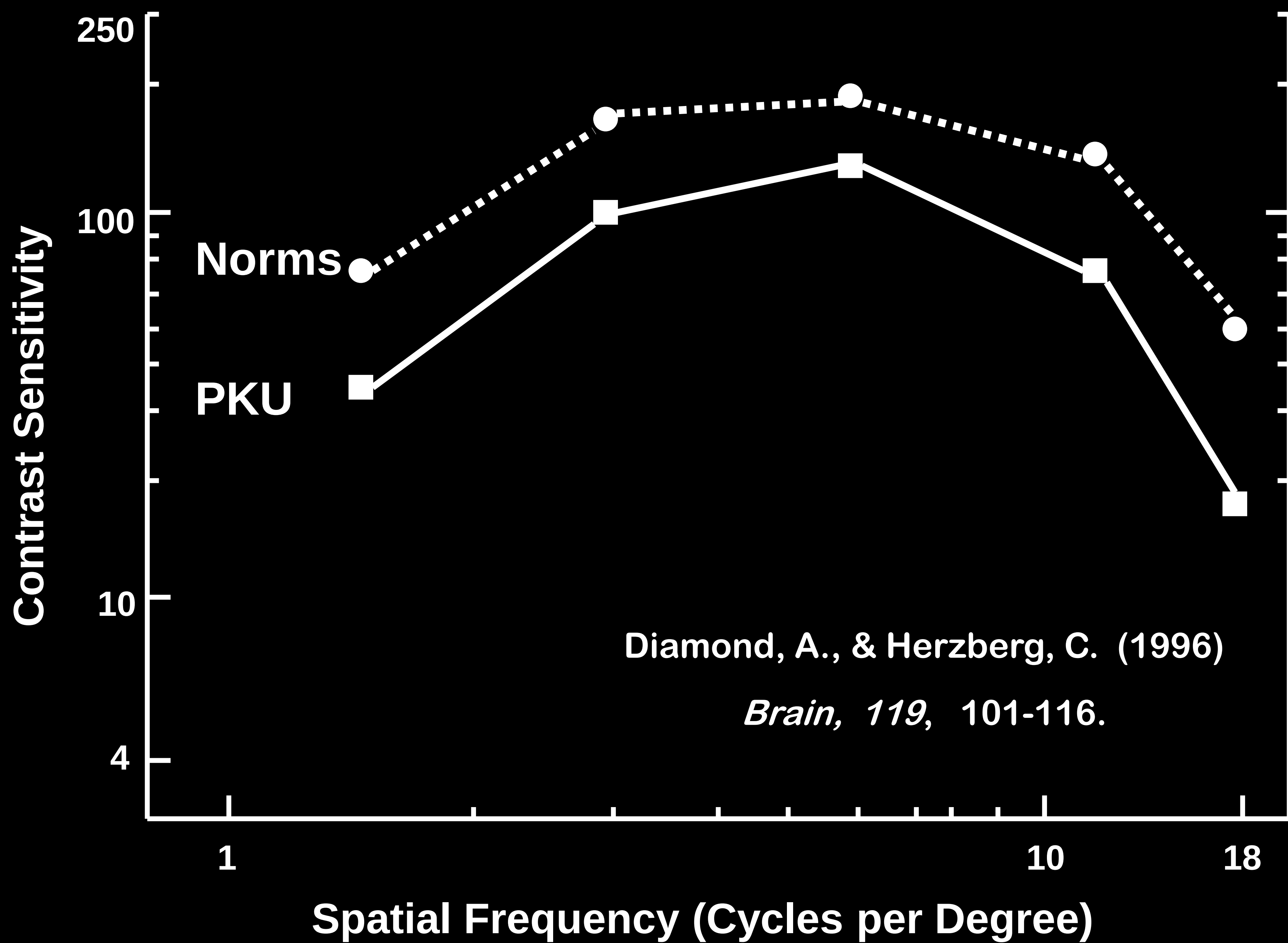
Iuvone, P. M., Tigges, M., Fernandes, A., & Tigges, J. (1989)

Dopamine synthesis and metabolism in rhesus monkey retina: Development, aging, and the effects of monocular visual deprivation. *Visual Neuroscience, 2*, 465-471.

To be consistent, I had to predict that retinal function should be affected as well in children treated PKU.

Dopamine in the retina is important for contrast sensitivity.

Patients with Parkinson’s disease, who have greatly reduced levels of dopamine, show impaired sensitivity to contrast.


250
100
10
4
Contrast Sensitivity
Norms
PKU
1
10
18
Spatial Frequency (Cycles per Degree)
Diamond, A., & Herzberg, C. (1996)
Brain, 119, 101-116.

We had found 2 different, superficially unrelated behavioral effects ---

- a selective deficit executive functions,

and

- a selective deficit in contrast sensitivity

both predicted based on the same underlying hypothesis.

But…while we had found a direct, inverse relationship between CURRENT Phe levels and performance on the COGNITIVE tasks requiring working memory + inhibition….

Contrast sensitivity was NOT related to current Phe levels.

It was related to Phe levels during the first month of life.

Perhaps that was because of the truncated range of current Phe levels in the vision study.

But, perhaps grossly elevated Phe levels during the first weeks of life, even if subsequently lowered and maintained at lower levels, cause irreparable damage to the visual system.

In order words, although it looked like we had beautifully converging evidence for our hypothesis, maybe the contrast sensitivity deficits were present for a DIFFERENT reason.

… PKU siblings both between 6-16 years of age
(mean ages 9 and 11 years)

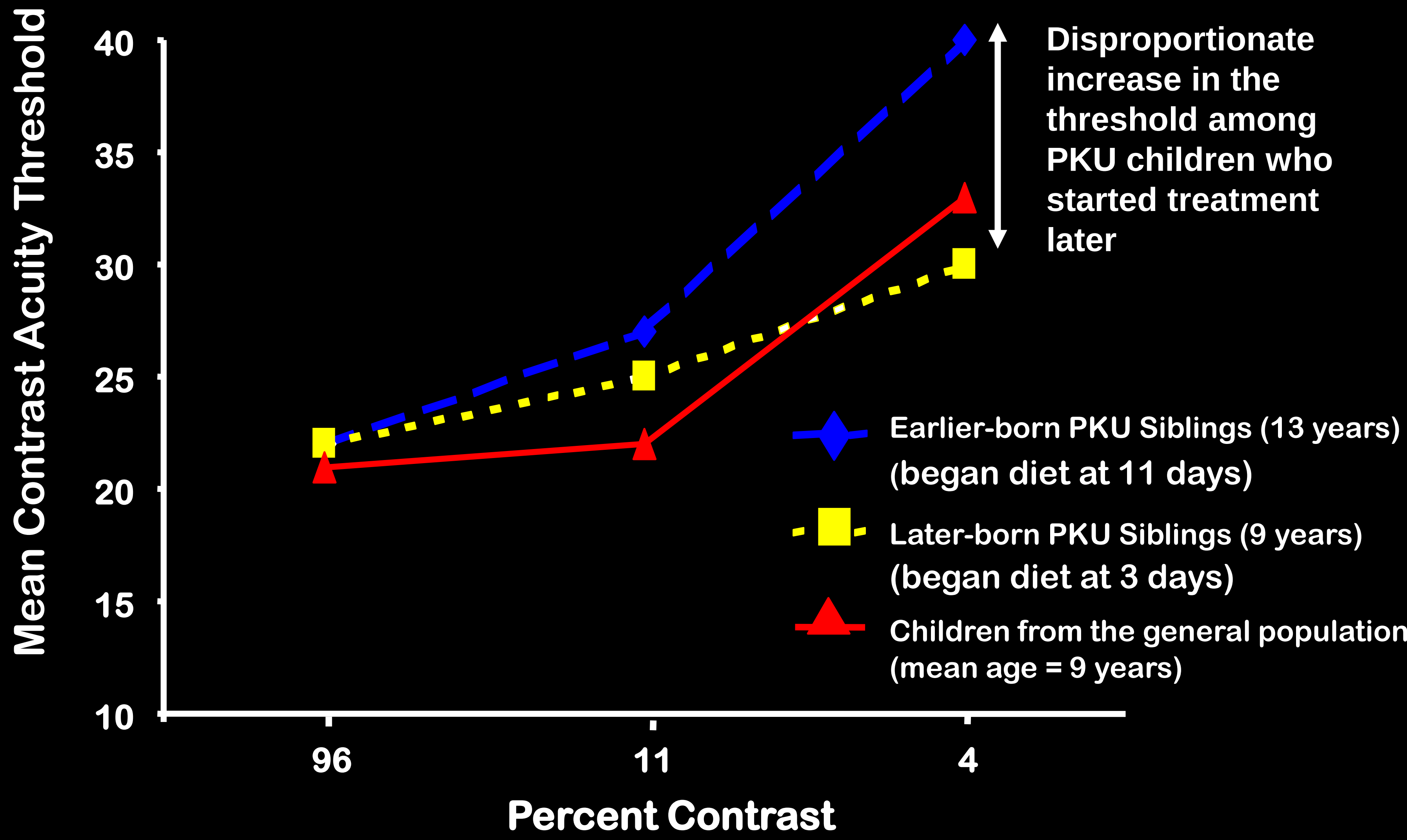
… one sibling started on the low-Phe diet at least 4 days earlier than the other

… both started on the diet before 21 days of age
(mean start: 3 and 11 days of age)

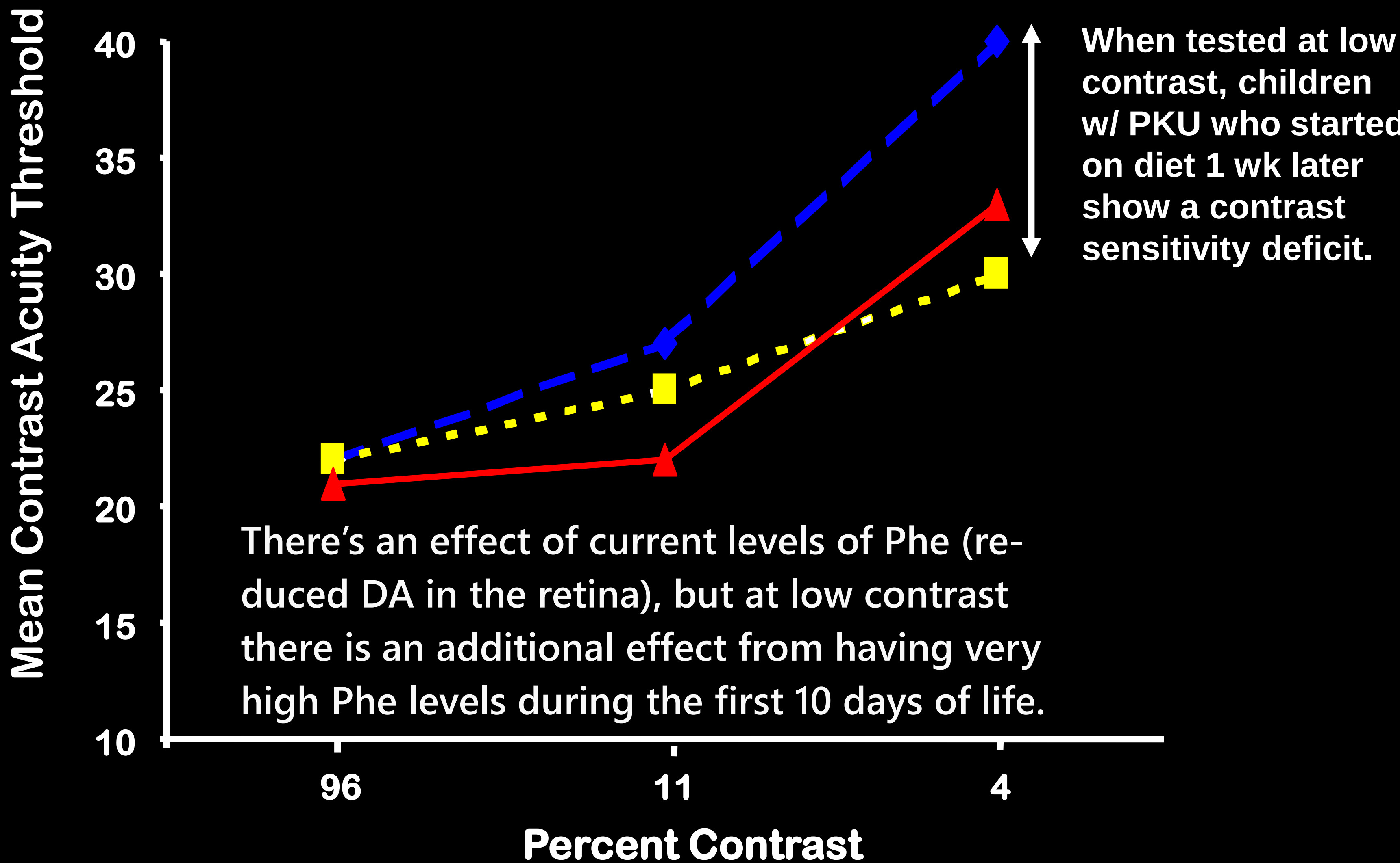
… both siblings had followed the low-Phe diet continuously since infancy

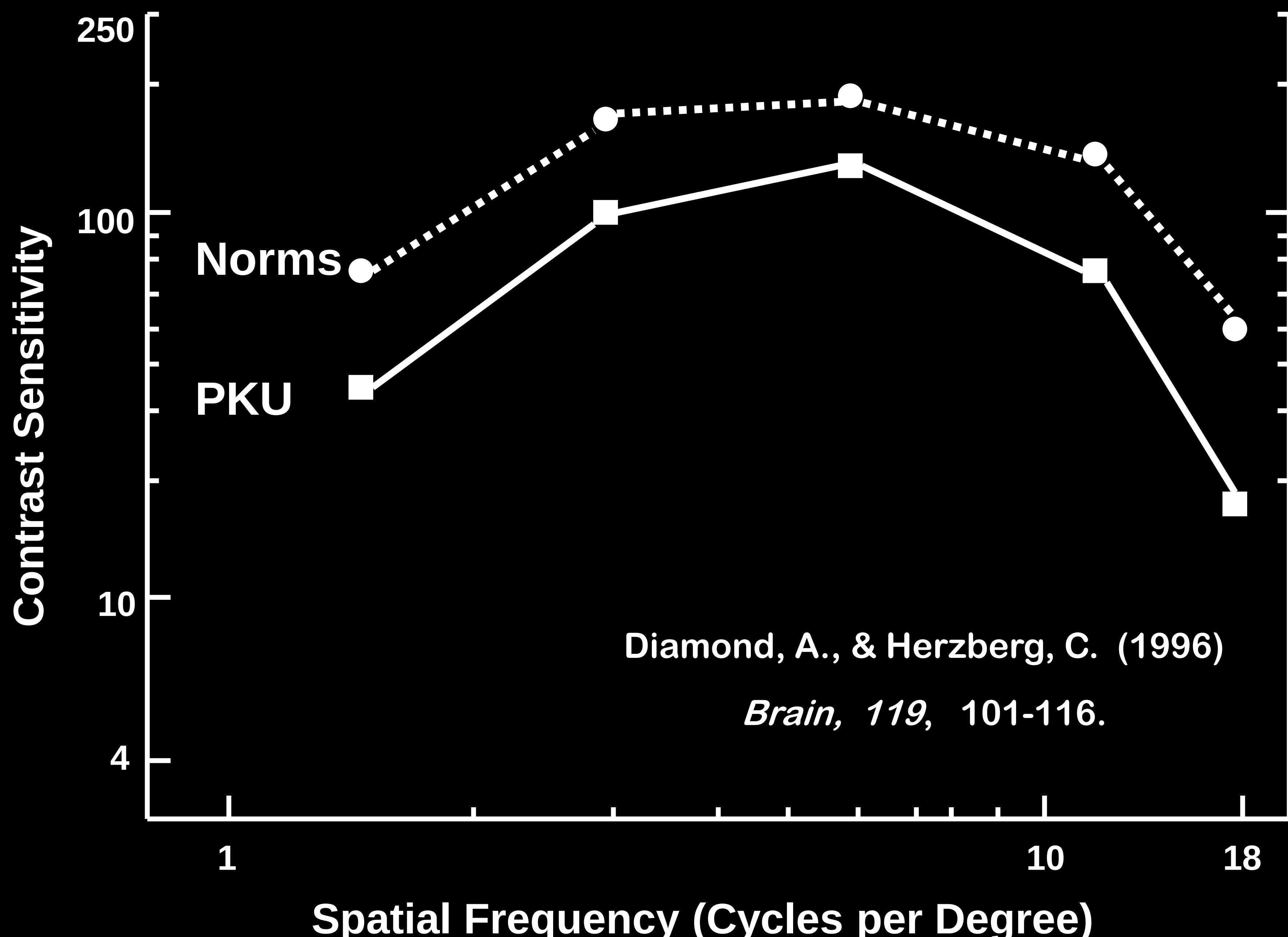
… both siblings were healthy, with normal IQs

Discrimination Performance of PKU children who Started Treatment Immediately After Birth or Roughly 10 Days Later & Same-Age Peers on the Regan Low Contrast Acuity Charts



Discrimination Performance of PKU children who Started Treatment Immediately After Birth or Roughly 10 Days Later & Same-Age Peers on the Regan Low Contrast Acuity Charts




250
100
10
4
Contrast Sensitivity
Norms
PKU
Diamond, A., & Herzberg, C. (1996)
Brain, 119, 101-116.
1
10
18
Spatial Frequency (Cycles per Degree)

Resulted in another change in the recommendations for the treatment guidelines for PKU:

Age for Diet Initiation

Treatment should be initiated as soon as possible, and no later than 7 - 10 days after birth.

National Institutes of Health
PKU Consensus Conference Statement, Oct. 2000

Maurer, D., & Lewis, T.L. (2001) Visual acuity: The role of visual input in inducing postnatal change. *Clinical Neuroscience Research,1,* 239-247.

Similarly report subtle deficits in CS evident many years later from visual deprivation (cataracts) right after birth.

It’s true that….

PKU children, whose Phe levels were 3-5 times normal, were impaired on all 6 prefrontal tasks requiring working memory + inhibition.

But the same children were NOT impaired on self-ordered pointing, which also relies on dorsolateral PFC.

I was wrong.

I had predicted that on <u>all</u> cognitive tasks dependent on DL-PFC would be impaired in children with PKU whose Phe levels were 2-5x normal.

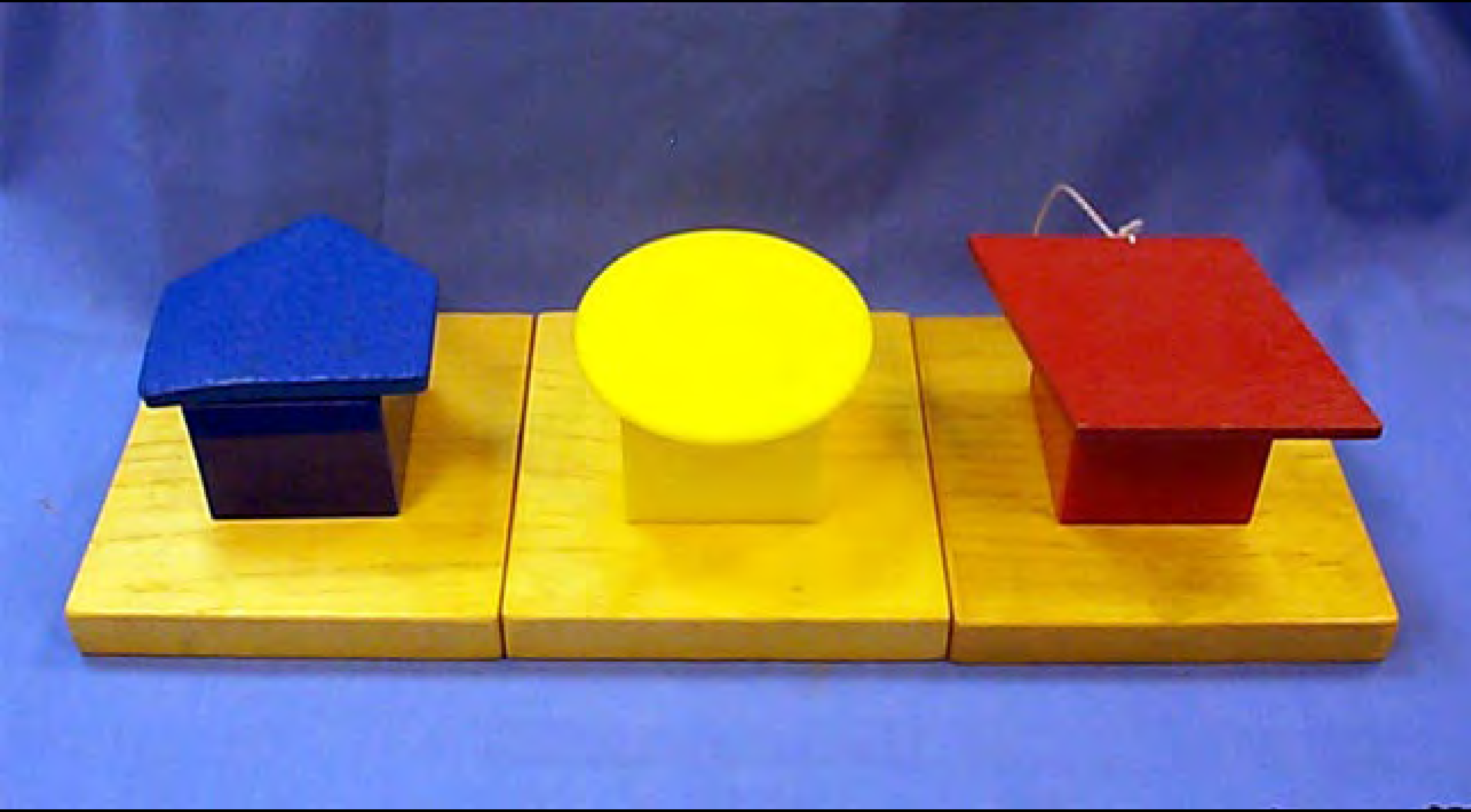
Performance on Self-Ordered Pointing has been linked specifically to dorsolateral PFC by work with….

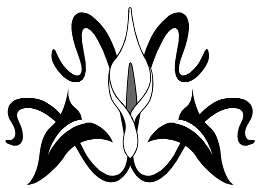
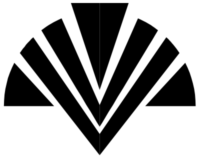
… lesioned monkeys

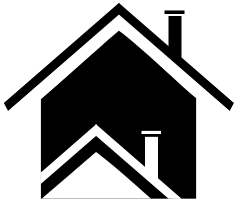
… brain-damaged patients

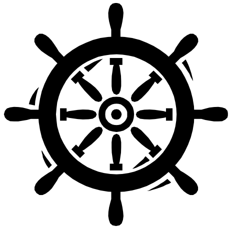
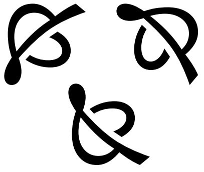
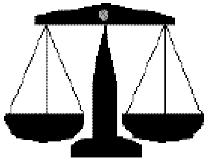
… functional neuroimaging in normal adults

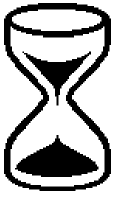
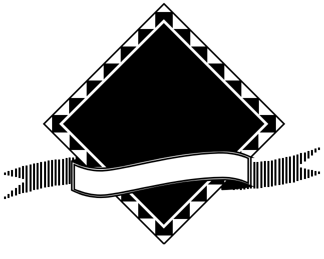
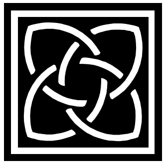

清香

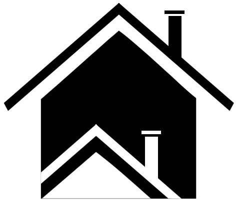
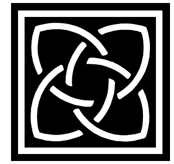
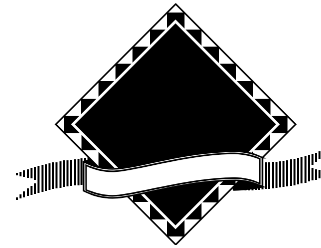
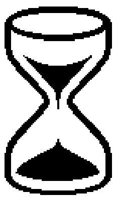
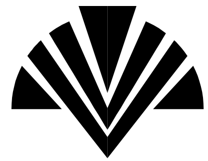


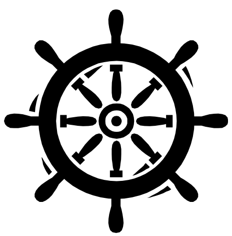
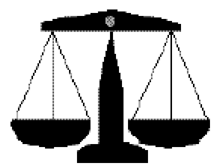
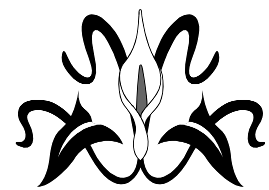



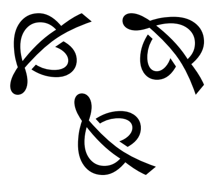





Why on earth didn’t we get deficits on Self-Ordered Pointing?

I didn’t have a clue.

Students in my lab,

and in most labs,

are always terribly disappointed

when they don't find

the effect they predicted.

But I tell them that they should rejoice!

“Now you have the opportunity to learn something you didn’t know before and perhaps no one knew before!”

Behavioral Task

Type of Lesion to Frontal Cortex	Delayed Response working memory + inhibition	Self-Ordered Pointing requires working memory
Excitotoxic **(cell bodies destroyed)**	**Performance IMPAIRED**	**Performance IMPAIRED**
6-OHDA **(dopamine depleted)**	**Performance IMPAIRED**	**Performance *SPARED***

Collins, Roberts, Dias, Everitt, & Robbins (1998). *Journal of Cognitive Neuroscience, 10*, 332-354

Type of Lesion to Frontal Cortex	Behavioral Task: Delayed Response working memory + inhibition	Behavioral Task: Self-Ordered Pointing requires working memory
Excitotoxic **(cell bodies destroyed)**	**Performance** **IMPAIRED**	**Performance** **IMPAIRED**
6-OHDA **(dopamine depleted)**	**Performance** **IMPAIRED**	**Performance** ***SPARED***

This is the pattern we saw in treated PKU children: Diamond, Prevor, Callender, & Druin (1997)

Then I learned there's a polymorphism of a gene that selectively affects DA levels in PFC.

That would let me test the hypothesis that Self-Ordered Pointing is insensitive to DA levels in PFC.

I predicted that polymorphisms of this gene

should affect performance on any of the 6 tasks that children treated for PKU were impaired on, or very similar ones,

but should not affect performance on self-ordered pointing.

Another unusual property of the dopamine system in PFC is a relative dearth of dopamine transporter.

The best mechanism for clearing away released dopamine is by dopamine transporter.

Dopamine transporter is abundant in the striatum & in most dopamine-containing brain regions but sparse in PFC.

So PFC is more dependent on

secondary mechanisms

for clearing away DA,

like the COMT [catechol-O-

methyltransferase] enzyme.

The COMT enzyme accounts for

> 60% of the DA clearance in PFC,

but < 15% in the striatum

Karoum et al. 1994; Männistö & Kaakkola 1999

The gene that codes for the

COMT enzyme

is called the

COMT Gene

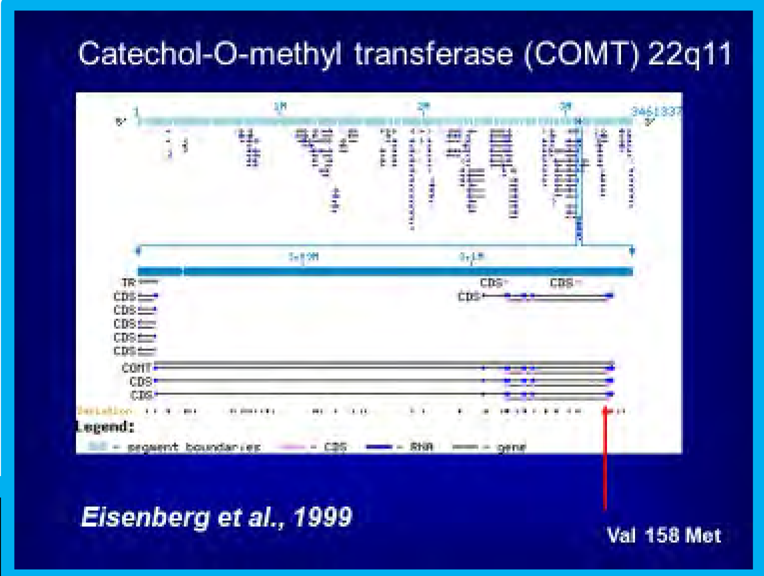
A common polymorphism of the COMT gene

consists of a simple substitution of

one amino acid, Methionine (Met), for

another, Valine (Val),

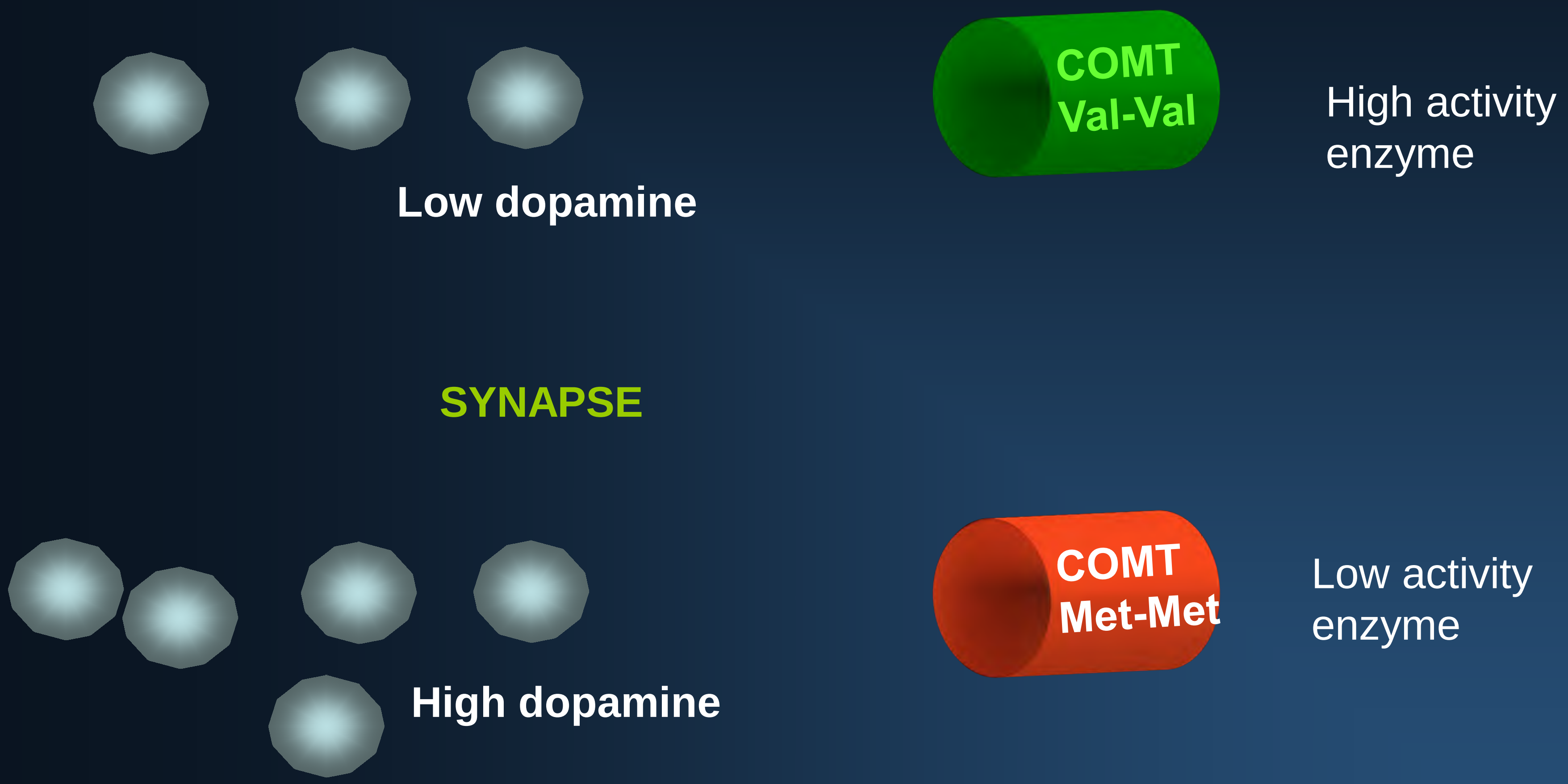
at codon 158



The Met variant of the COMT gene codes for a slower COMT enzyme, which leaves more DA around longer in PFC.

Boudikova et al. 1990; Chen et al. 2004; Lachman et al. 1996

Catechol-O-methyltransferase (COMT) Val158 Met



Zalsman et al.

The COMT enzyme is

25-33% less active in COMT-Met^{158} homozygotes than in COMT-Val^{158} homozygotes.

Boudikova et al. 1990; Chen et al., 2004

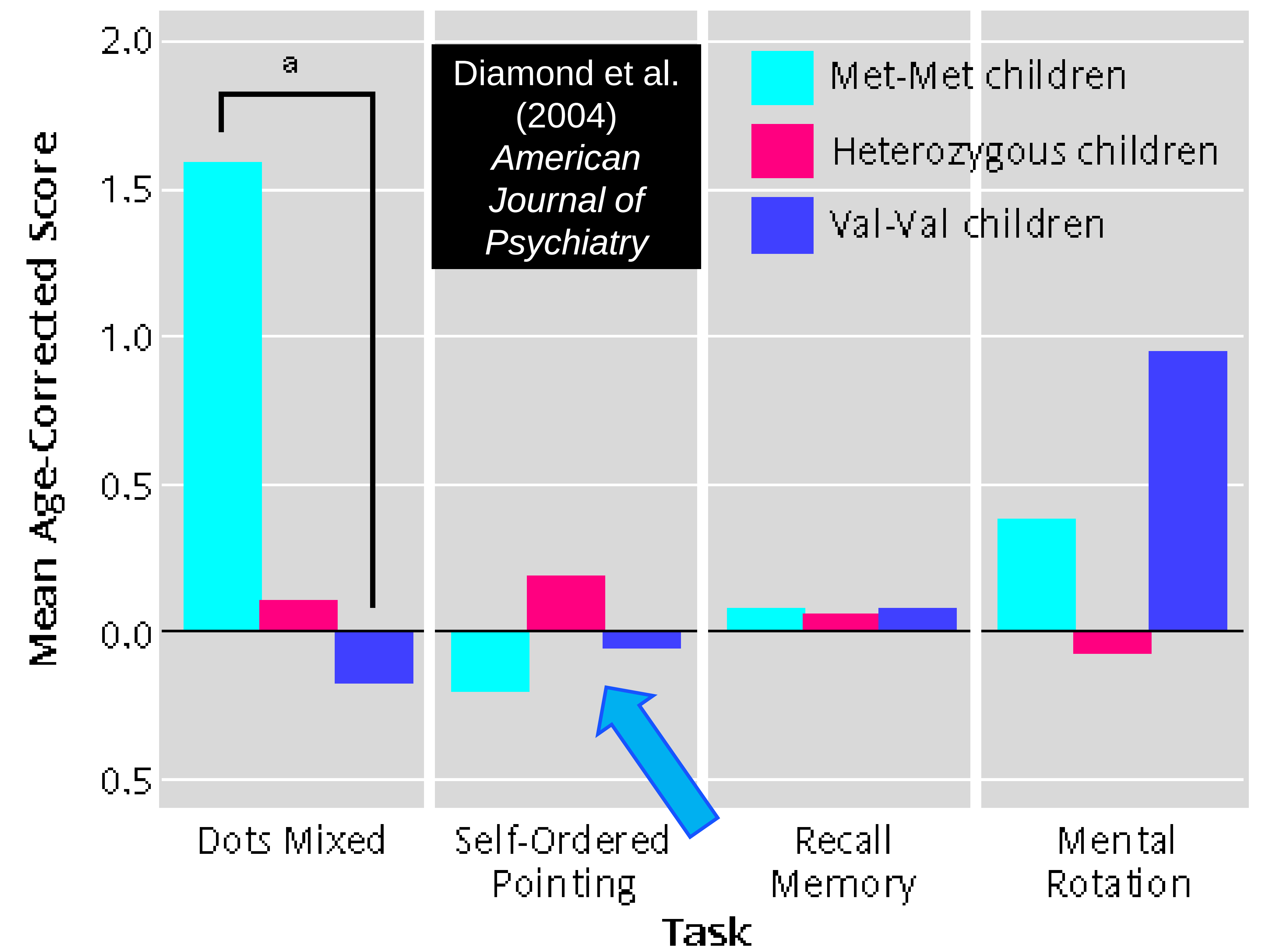
The Met variant of the COMT gene is also generally associated with better PFC function and better EFs.

Bruder et al. 2005; Diamond et al. 2004; Egan et al. 2001

Prediction: Those homozygous for the COMT-Met^{158} genotype, which leaves a little more DA in PFC,

- *should NOT* **differ** from COMT-Vals **on Self-ordered Pointing,**

  (i.e., no difference by COMT genotype on self-ordered pointing)


Diamond et al. (2004) *American Journal of Psychiatry*
Met-Met children
Heterozygous children
Val-Val children
a
2.0
1.5
1.0
0.5
0.0
0.5
Mean Age-Corrected Score
Dots Mixed
Self-Ordered Pointing
Recall Memory
Mental Rotation
Task

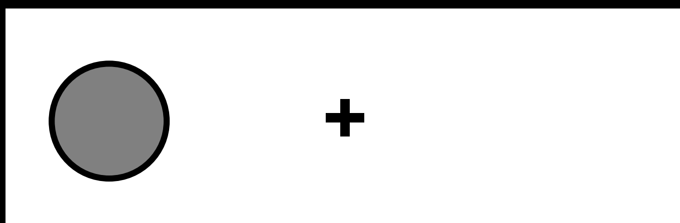
But on a task dependent on WM & inhibitory control,

we predicted that

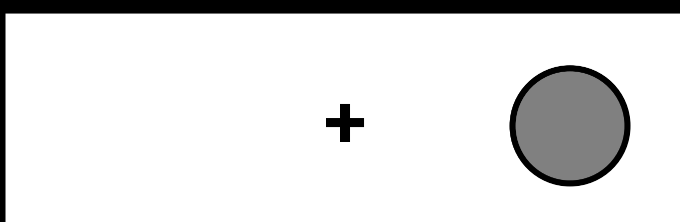
COMT-Mets would perform

better than COMT-Vals

Dots - Congruent

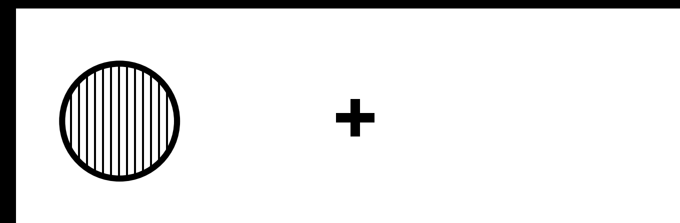


Push Left

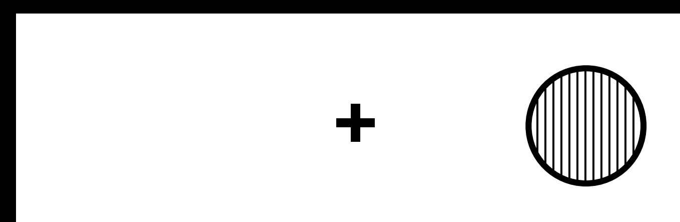


Push Right

Dots - Incongruent



Push Right

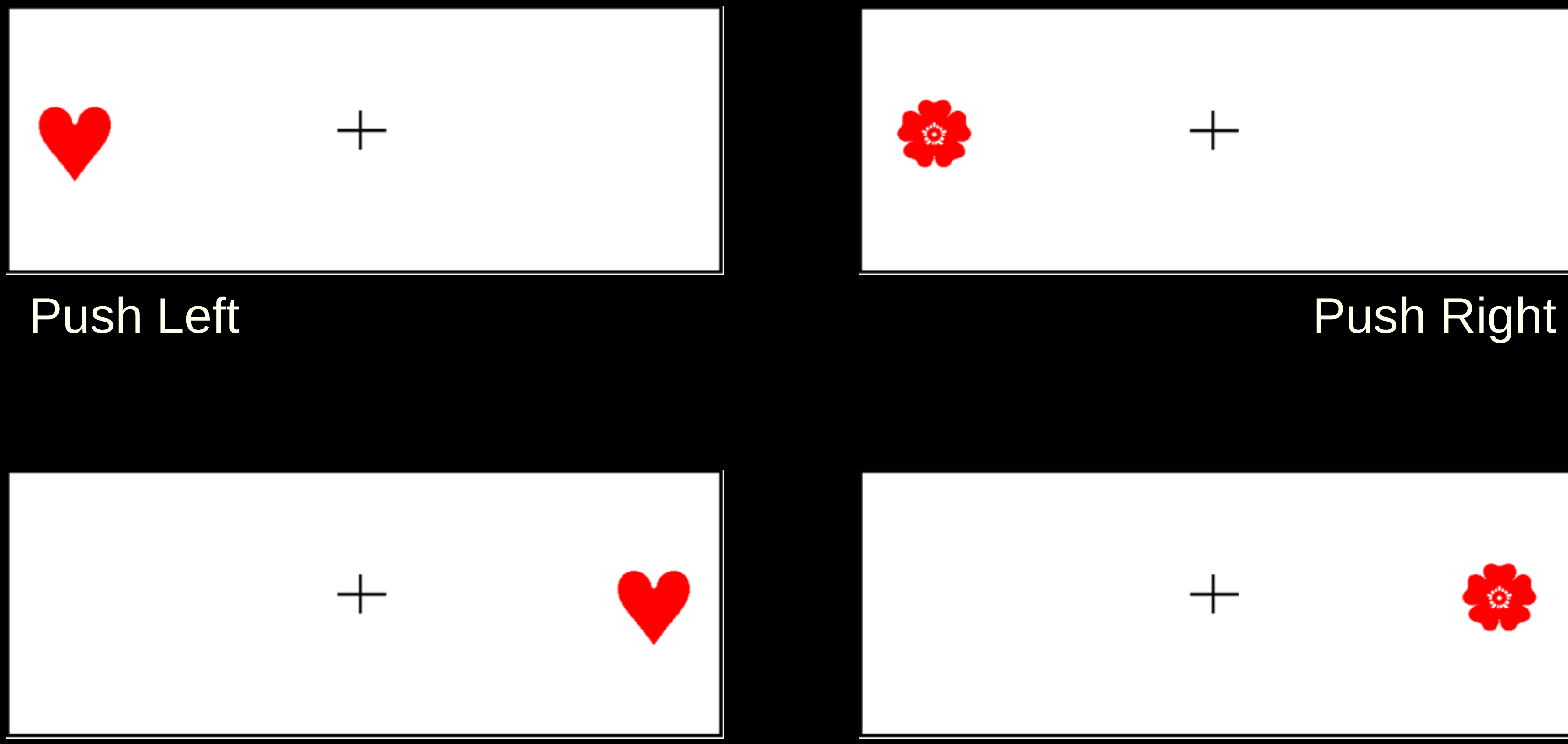


Push Left

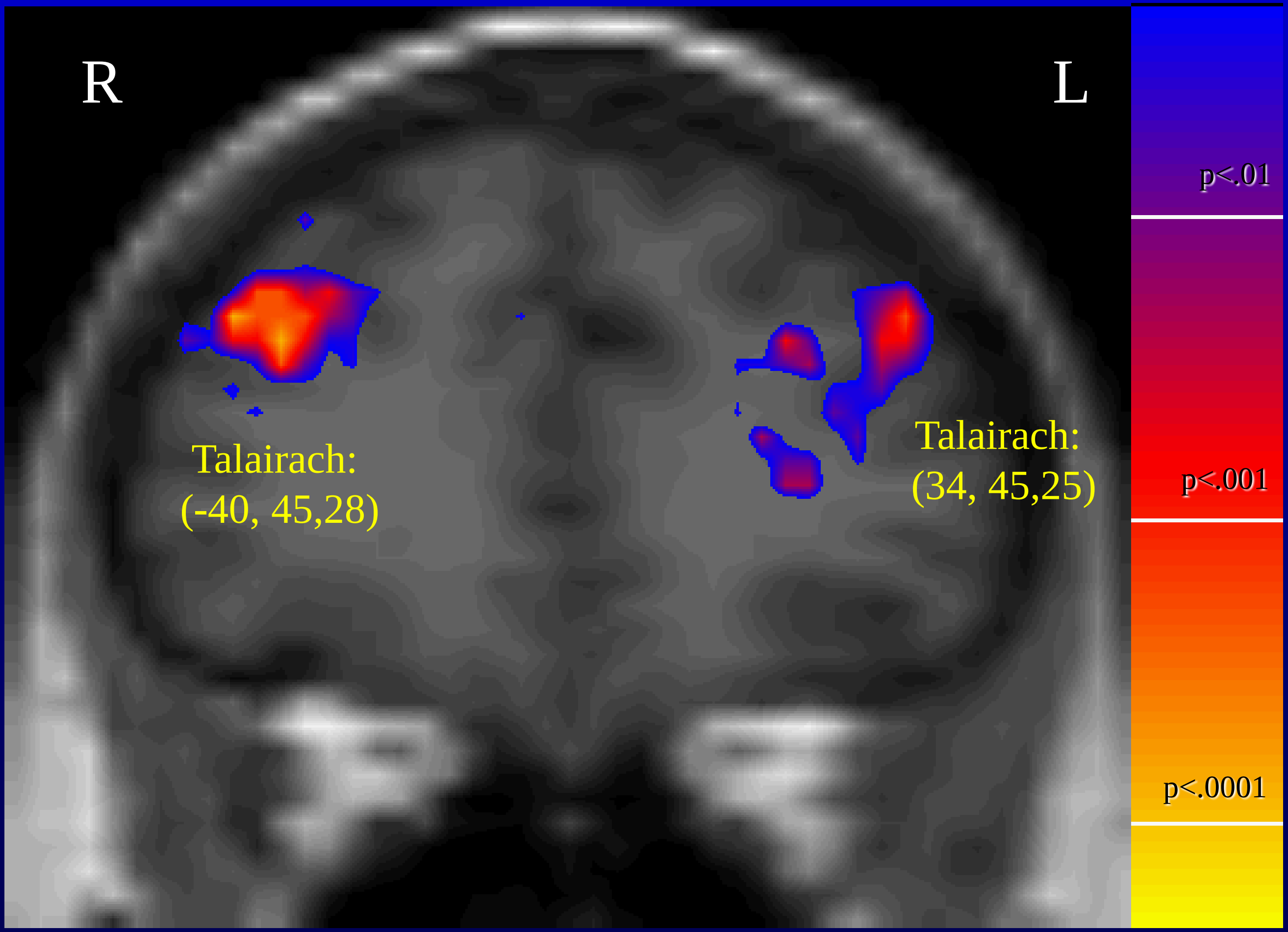
HEARTS & FLOWERS

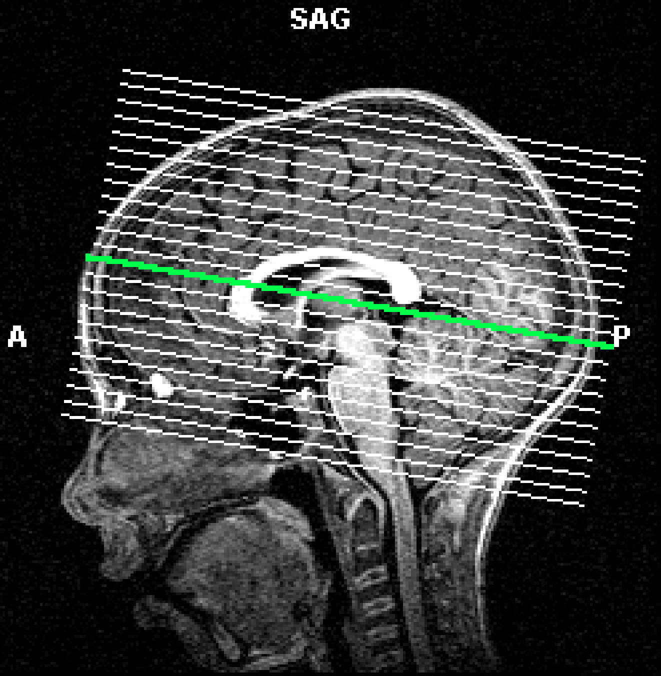
Congruent

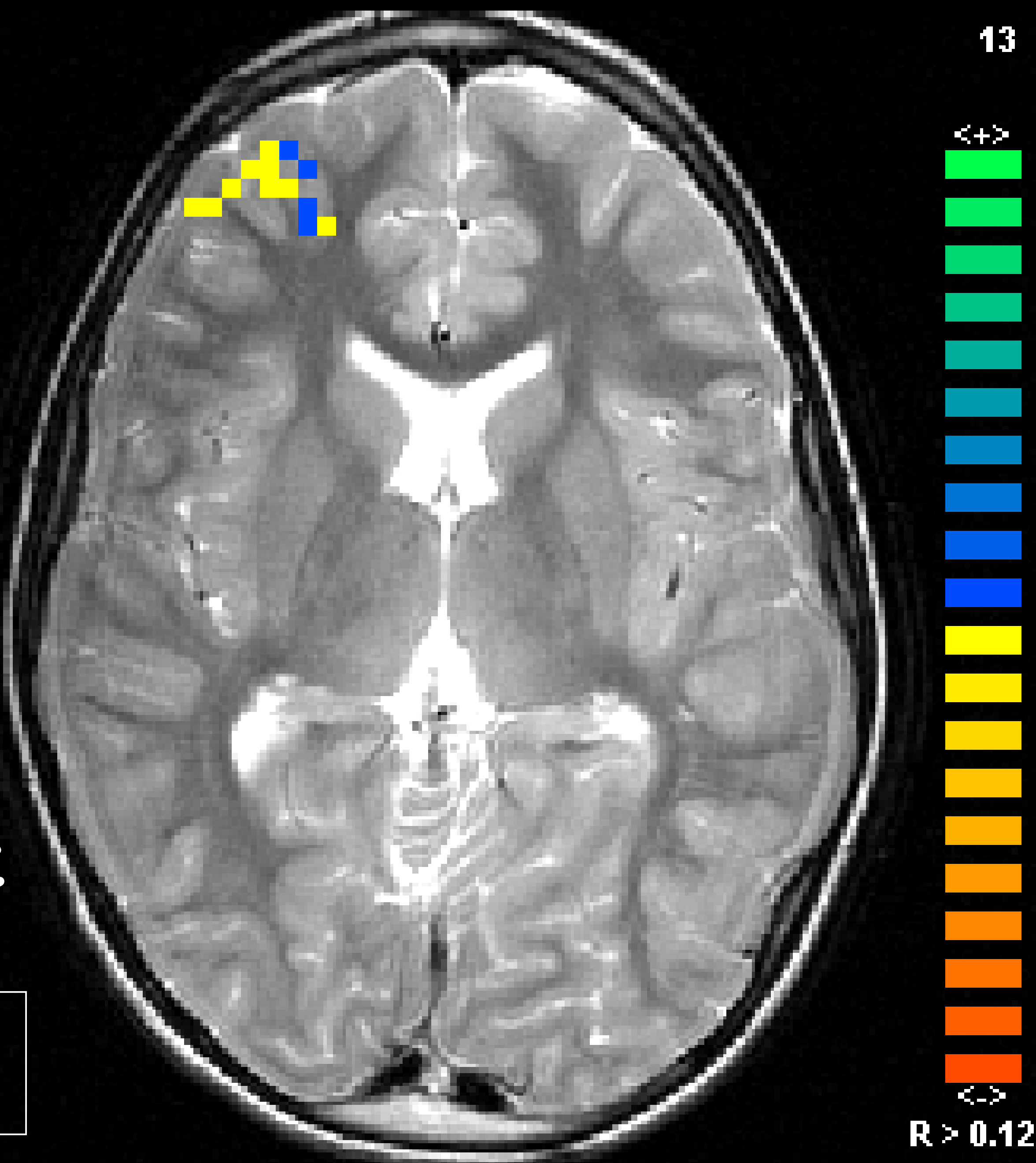
Incongruent



Increased Activation of Dorsolateral PFC (Area 46/9) Dots-Mixed minus Dots-Congruent

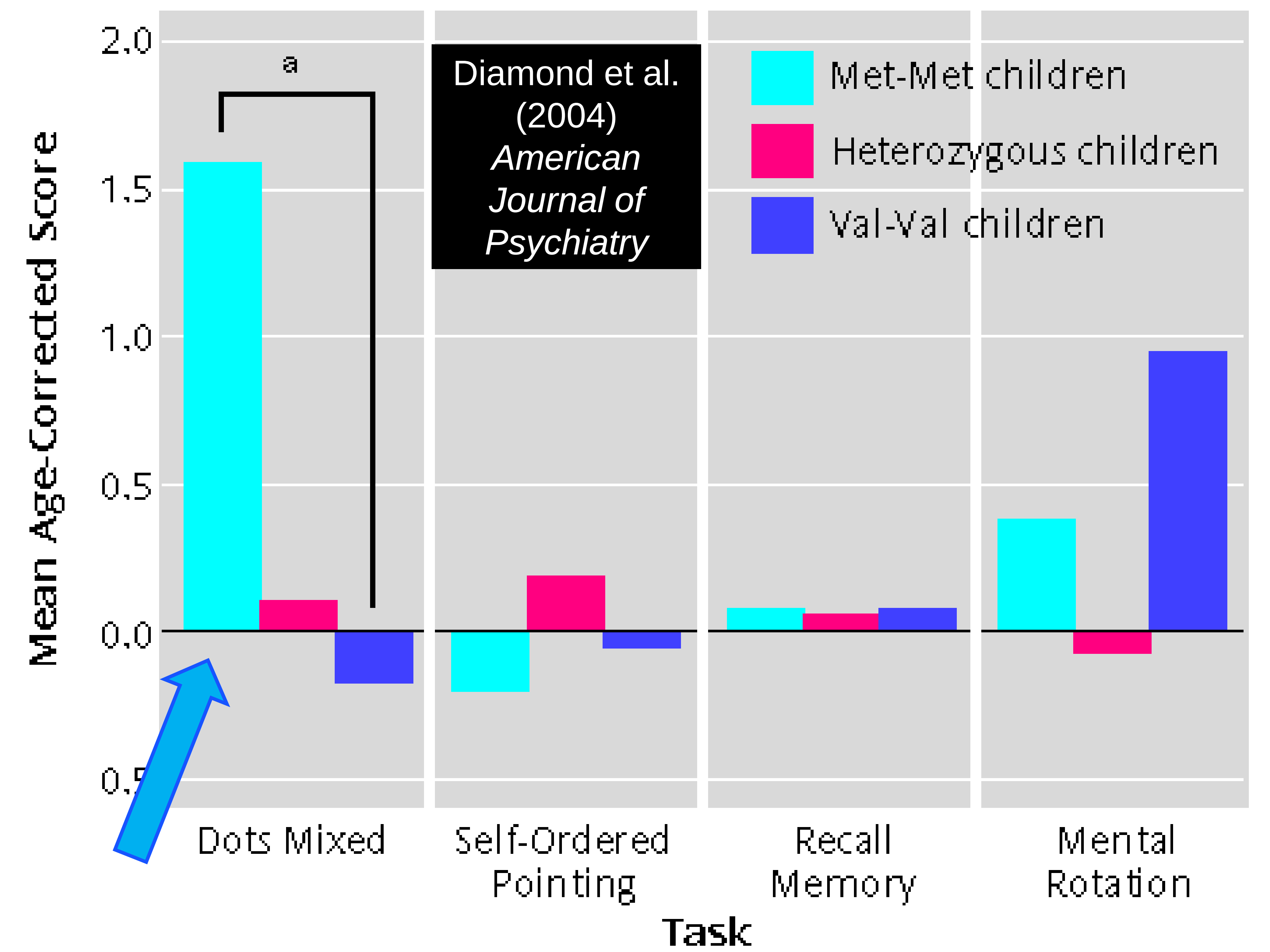






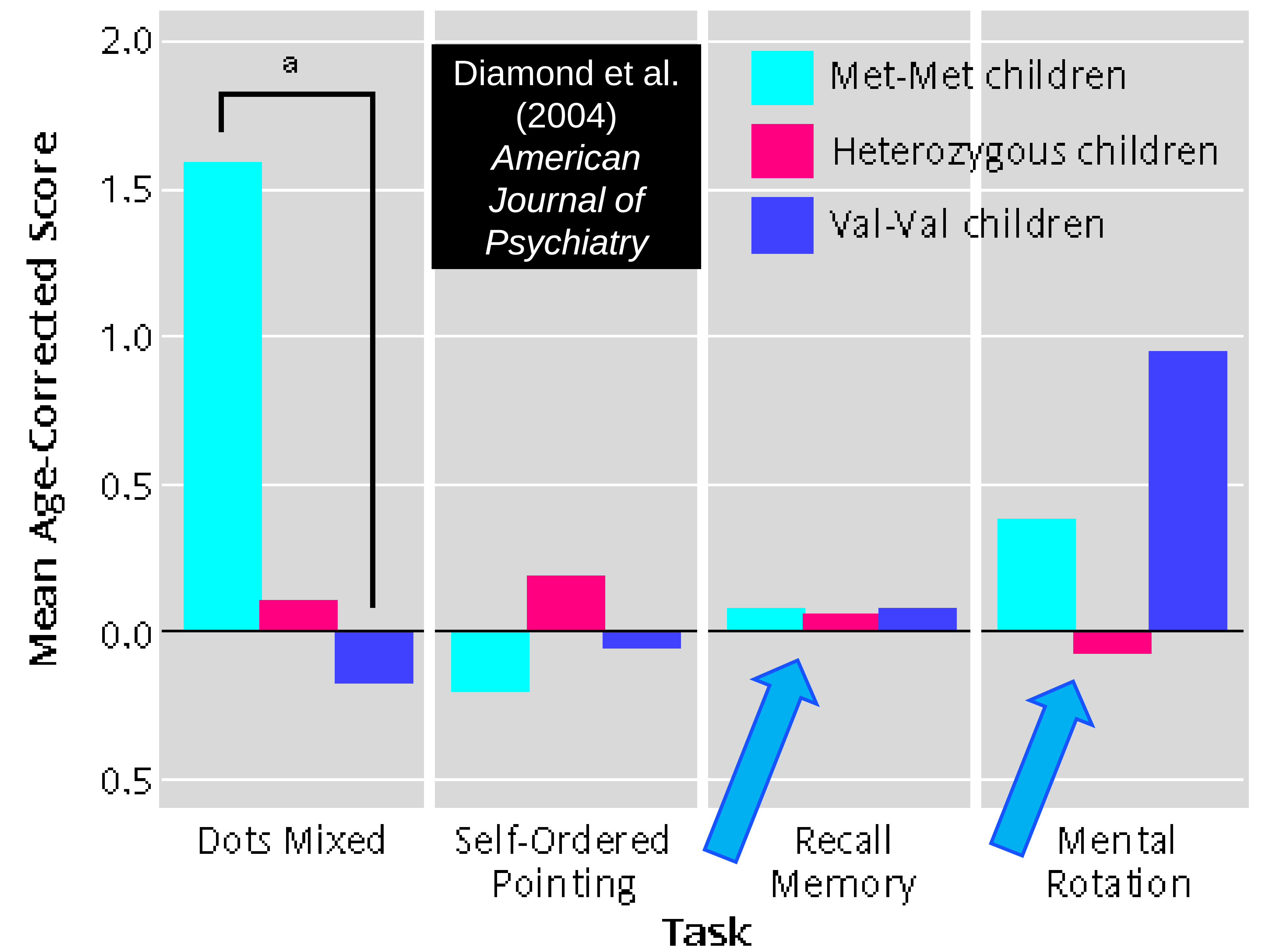
Dots-Mixed minus Dots-Congruent

10-year-olds


Diamond et al. (2004)
American Journal of Psychiatry
Met-Met children
Heterozygous children
Val-Val children
a
Mean Age-Corrected Score
2.0
1.5
1.0
0.5
0.0
Dots Mixed
Self-Ordered Pointing
Recall Memory
Mental Rotation
Task

This effect was specific to PFC function:

There was no relation between COMT genotype and non-PFC functions.



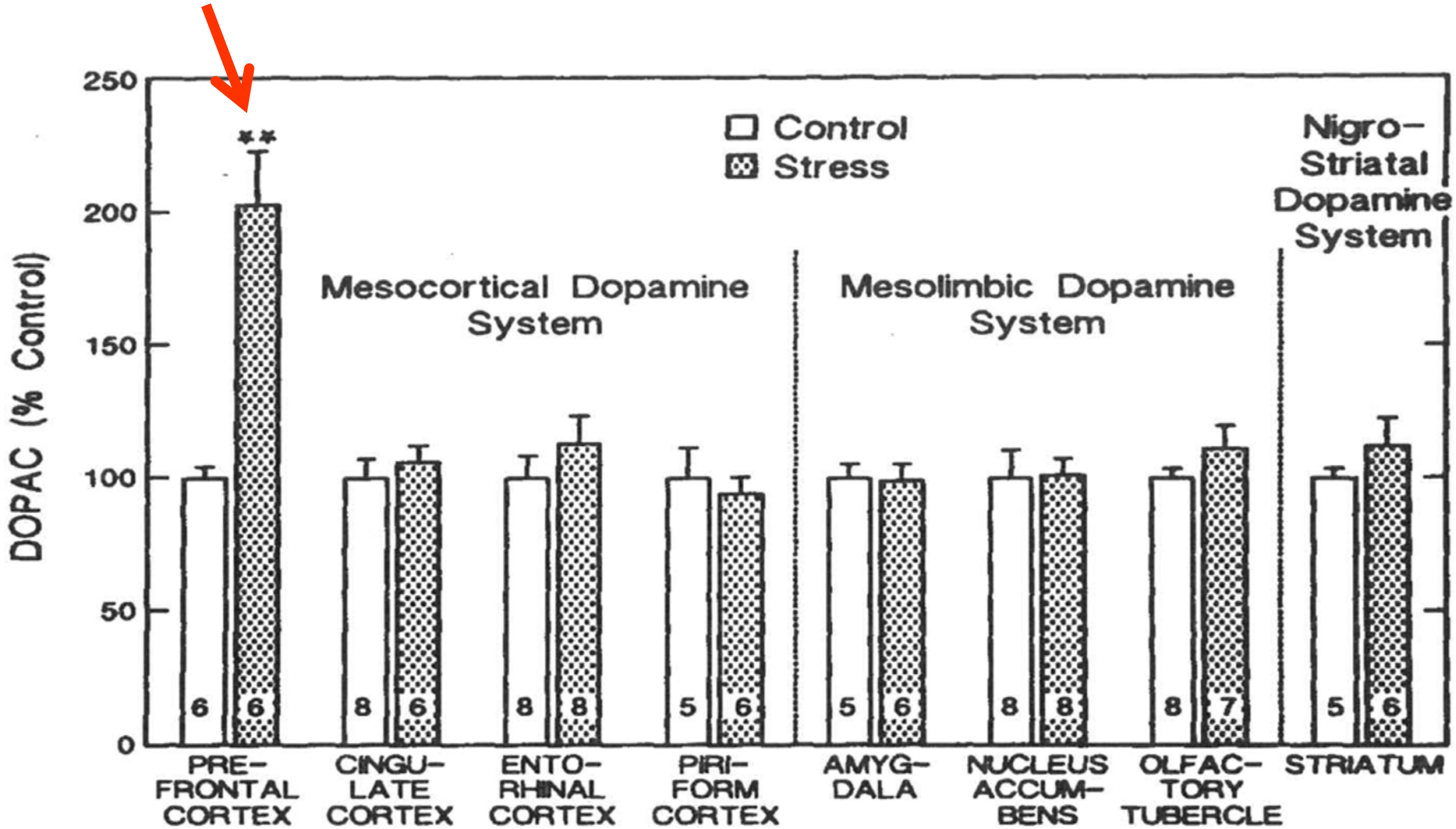
Diamond et al. (2004) American Journal of Psychiatry
Met-Met children
Heterozygous children
Val-Val children
Mean Age-Corrected Score
2.0
1.5
1.0
0.5
0.0
0.5
a
Dots Mixed
Self-Ordered Pointing
Recall Memory
Mental Rotation
Task

Yet another unusual property of the dopamine (DA) system in PFC is that even mild stress increases the level of DA in PFC.

Cerqueira et al. 2007; Lataster et al. 2011; Nagano-Saito et al. 2013; Roth et al. 1988

Stress and Prefrontal Cortex

Even mild stress increases DA release in PFC - but not elsewhere in the brain



(Roth et al., 1988)

Stress impairs EFs,

& prefrontal cortex on

which they depend,

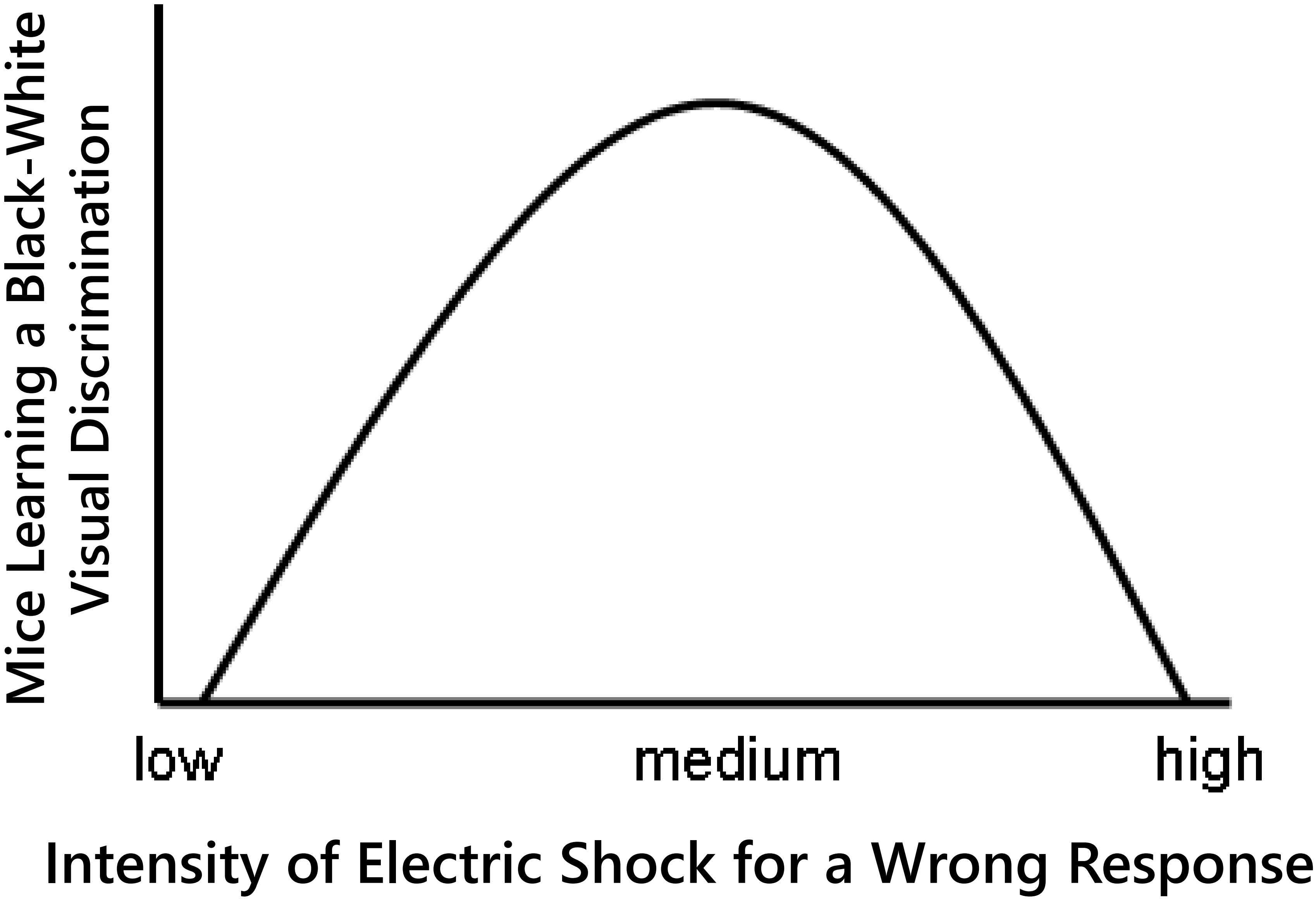
sooner

and more severely

than any other brain region.

Many of us were taught that people perform better on challenging cognitive tasks when they are slightly stressed / a bit on edge, rather than when calm.

Yerkes – Dodson Curve (1908)

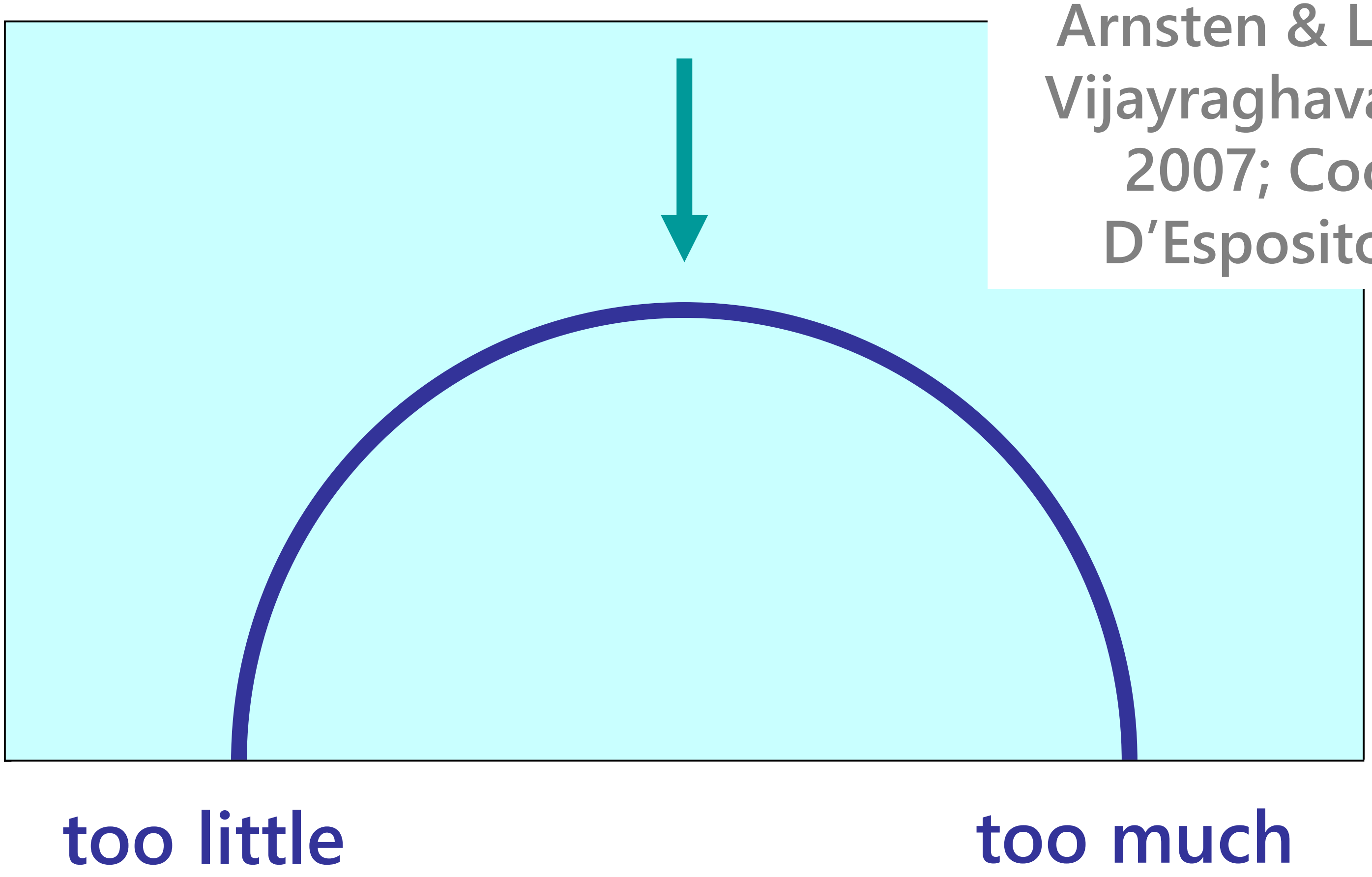


Is stress, even if mild, ever really good for higher cognitive functions?



The Optimum Level of Dopamine in PFC is an Intermediate Level

Arnsten & Li 2005; Vijayraghavan et al. 2007; Cools & D'Esposito 2011

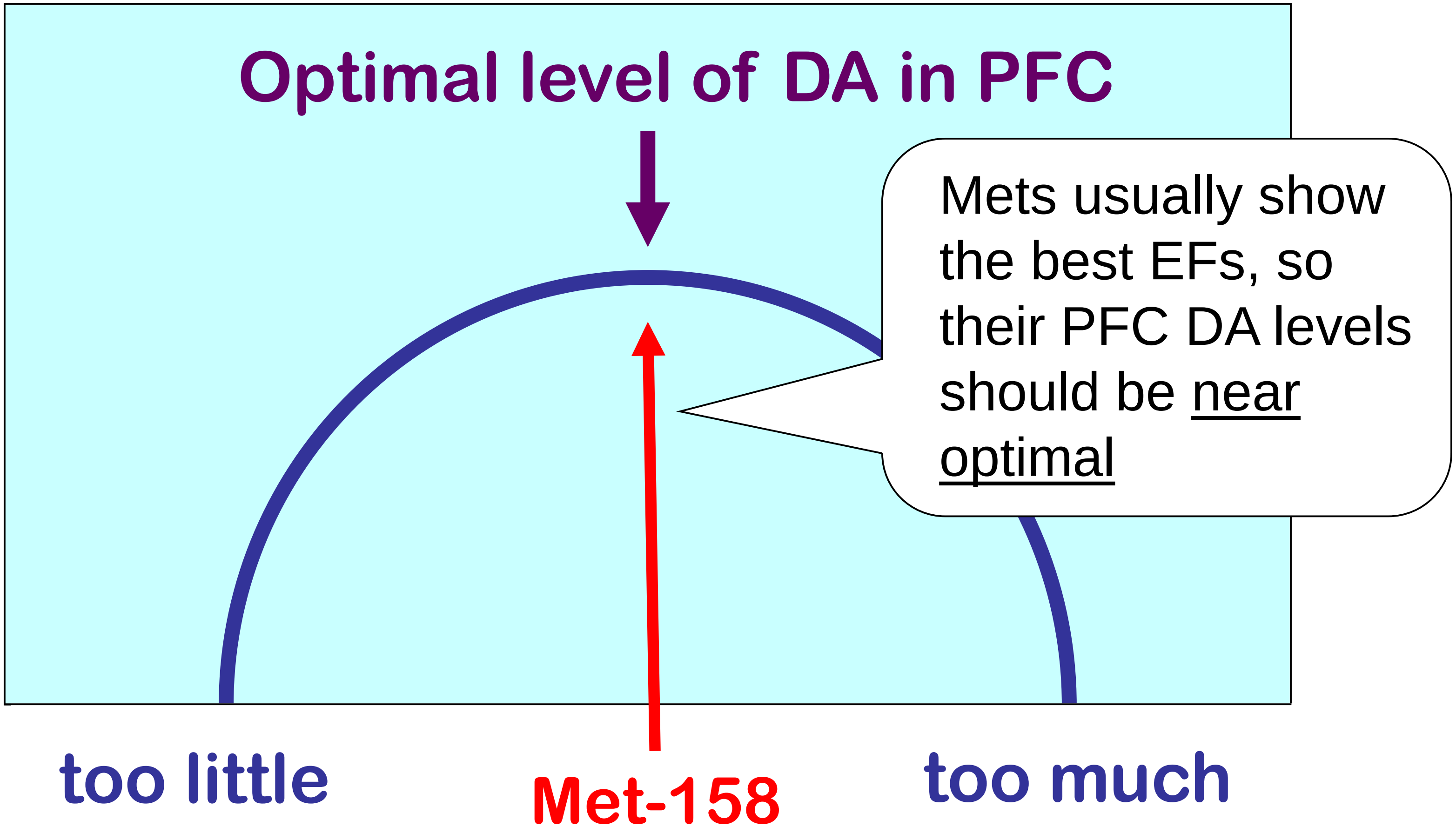


Remember

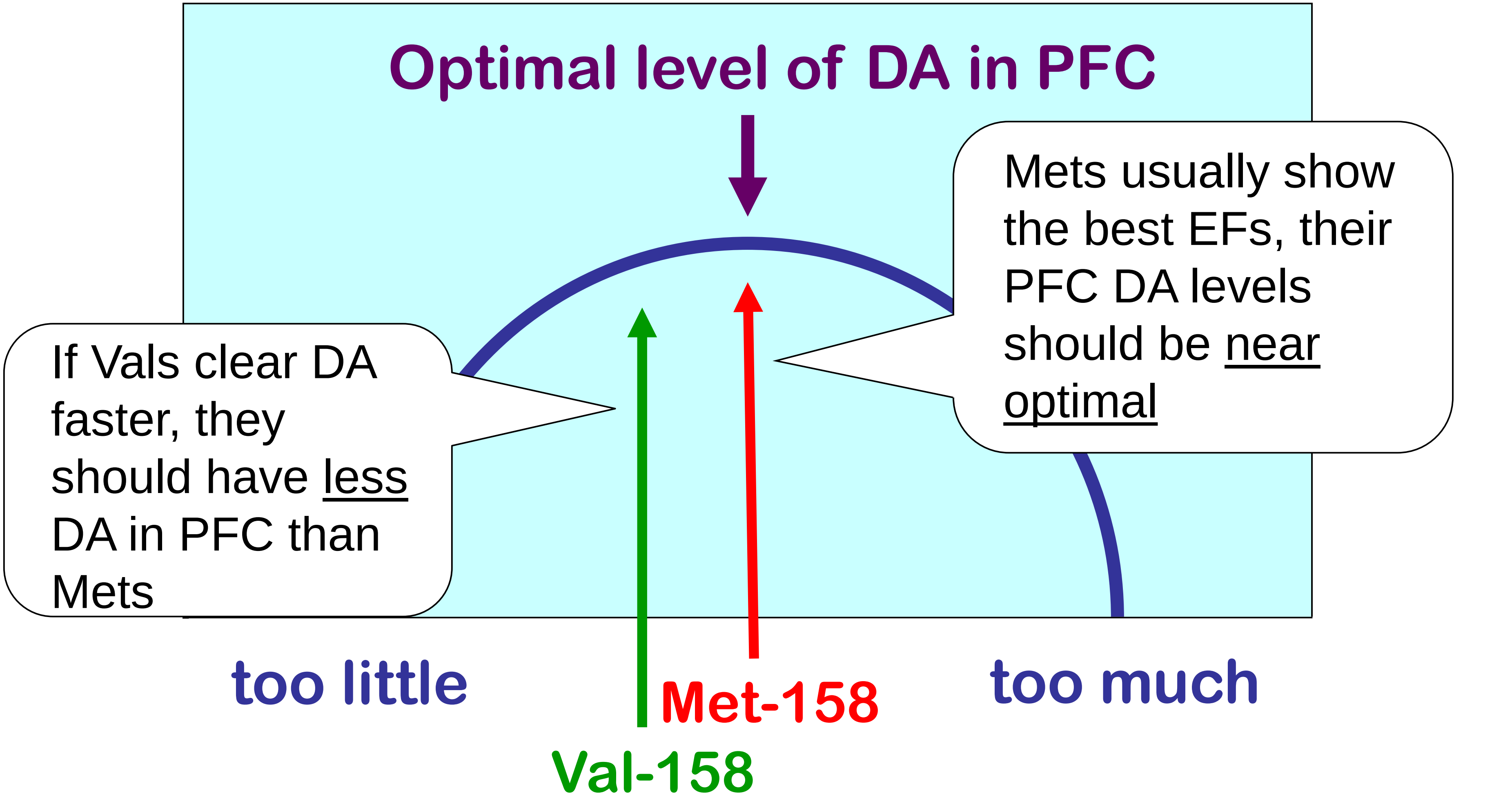
The Met variant of the COMT gene is also generally associated with better PFC function and better EFs.

Bruder et al. 2005; Diamond et al. 2004; Egan et al. 2001

Differences in COMT Genotype lead to Differences in PFC DA Levels



Differences in COMT Genotype lead to Differences in PFC DA Levels



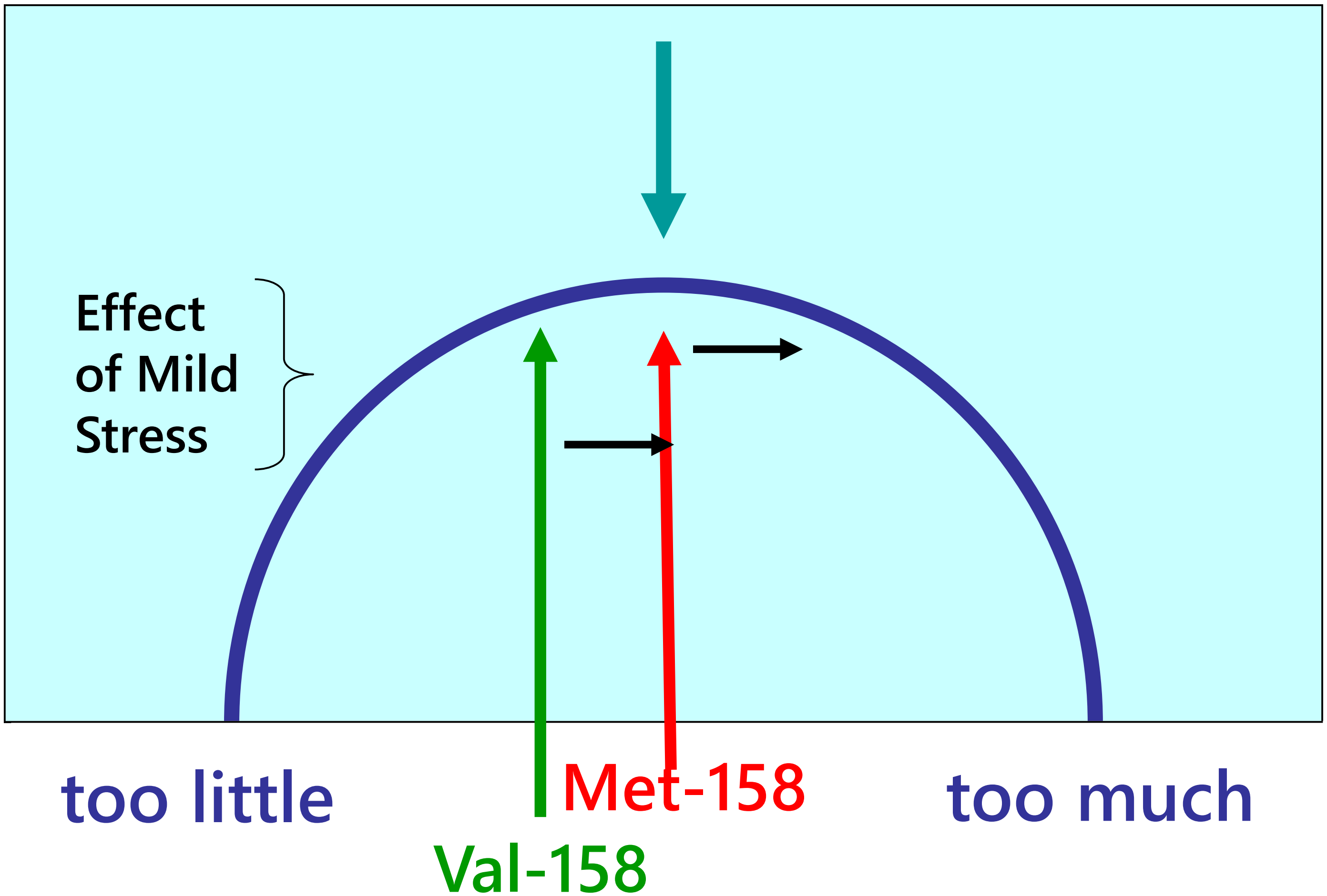
Remember:

Stress (even if mild)

Increases the level of

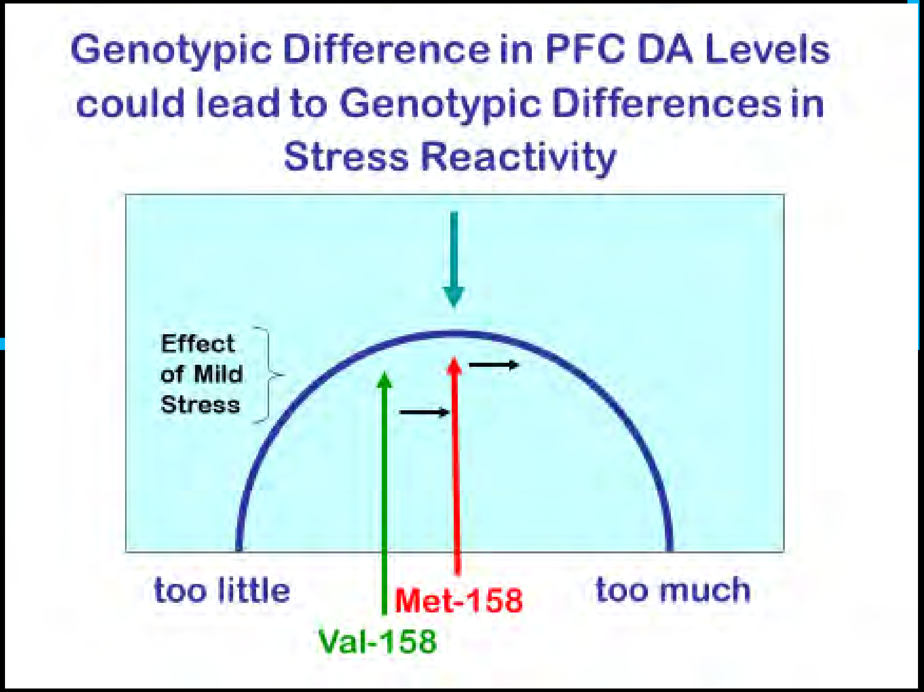
Dopamine in PFC

Genotypic Difference in PFC DA Levels can lead to Genotypic Differences in Stress Reactivity

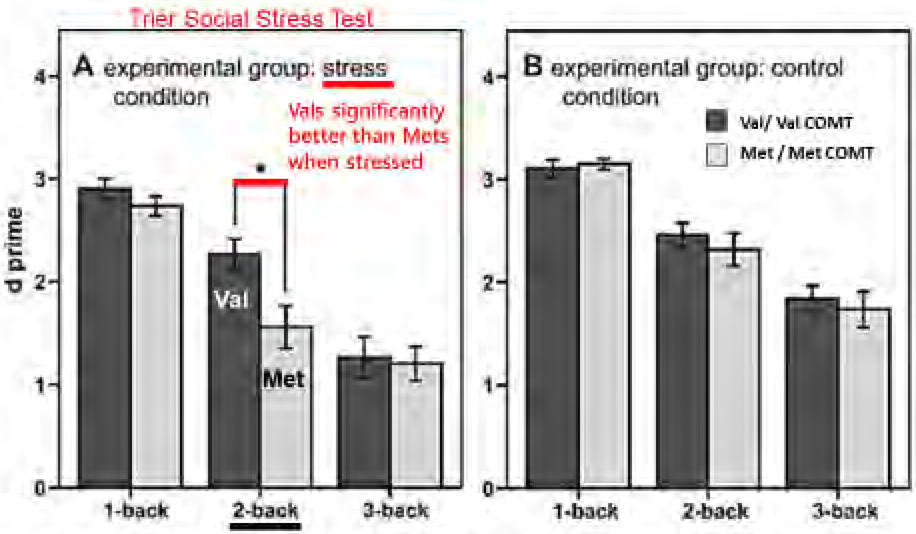


3 labs independently predicted that

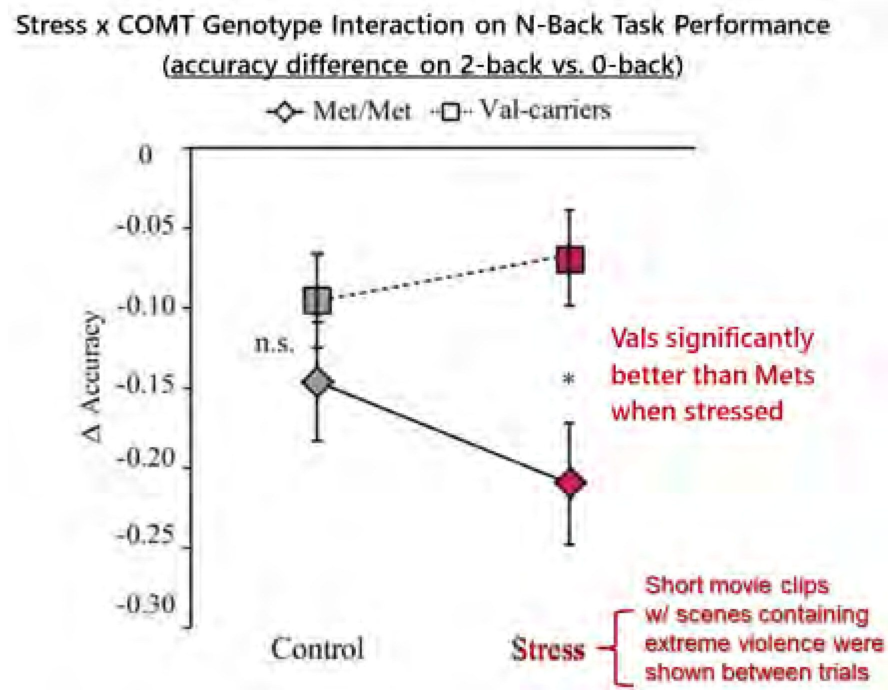
1. COMT-Mets would show worse EFs when mildly stressed
2. COMT-Vals would show better EFs when mildly stressed



Vals performed significantly better than Mets when stressed



Buckert et al. (2012): Under stress, young adults homozygous for COMT-Val158 showed ***better*** EF performance than young adults homozygous for COMT-Met158

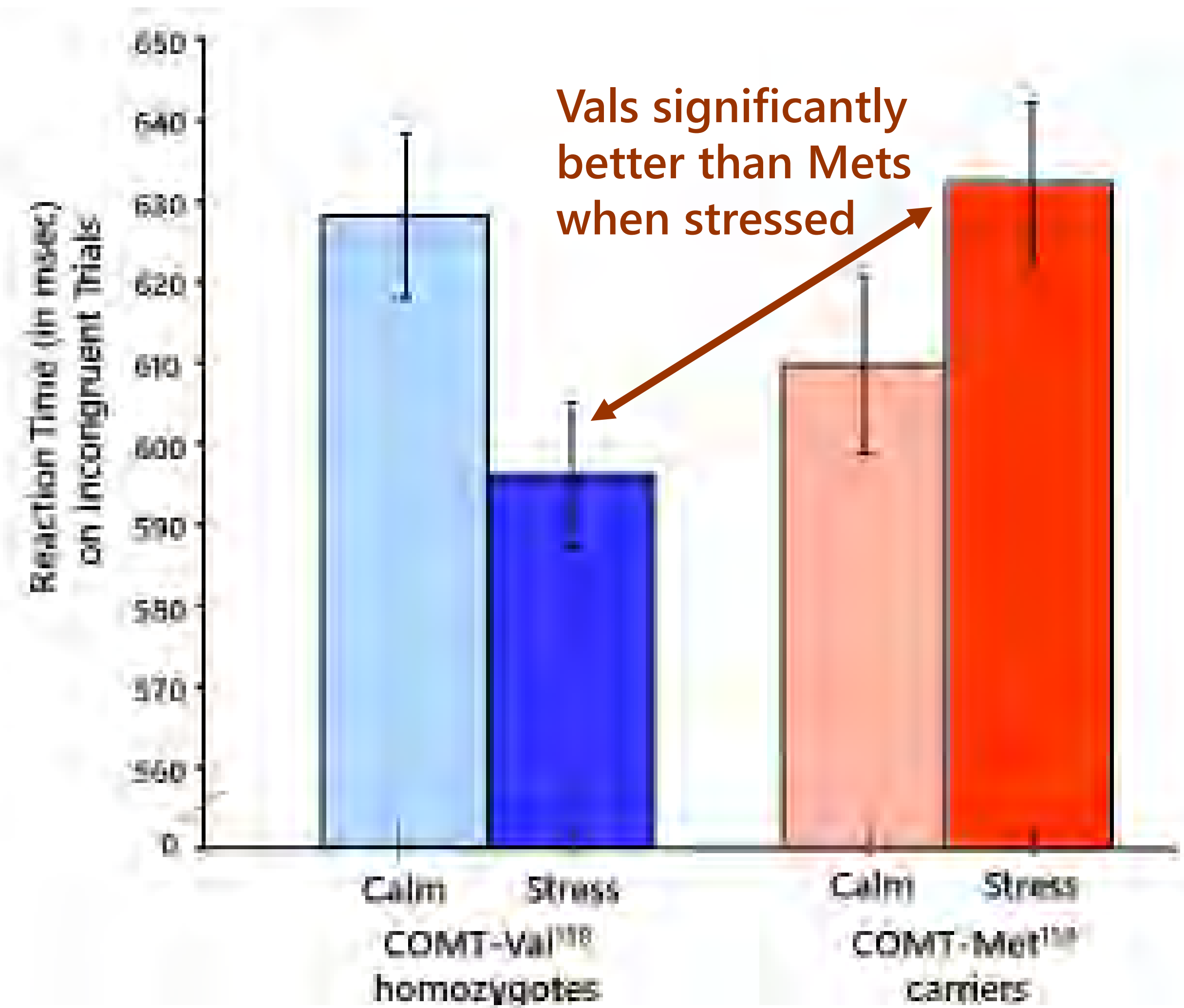


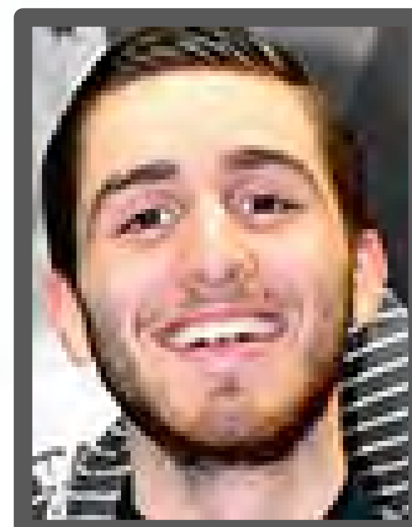
In my lab, we used a very, very mild psychosocial stressor (two research assistants looking over a participant's shoulder while that person was taking an EF test).

Zareyan, Zhang, Wang, Song, Hampson, Abbott, & Diamond (2020)
First demonstration of double dissociation between COMT-Met158 and COMT-Val158 cognitive performance when stressed and when calmer.
Cerebral Cortex, xx, 1-16.
doi:10.1093/cercor/bhaa276 [Epub 30 Oct. 2020 ahead of print.]
http://www.devcogneuro.com/Publications/zareyan_2020_first_demonstration_of_double.pdf

Free download

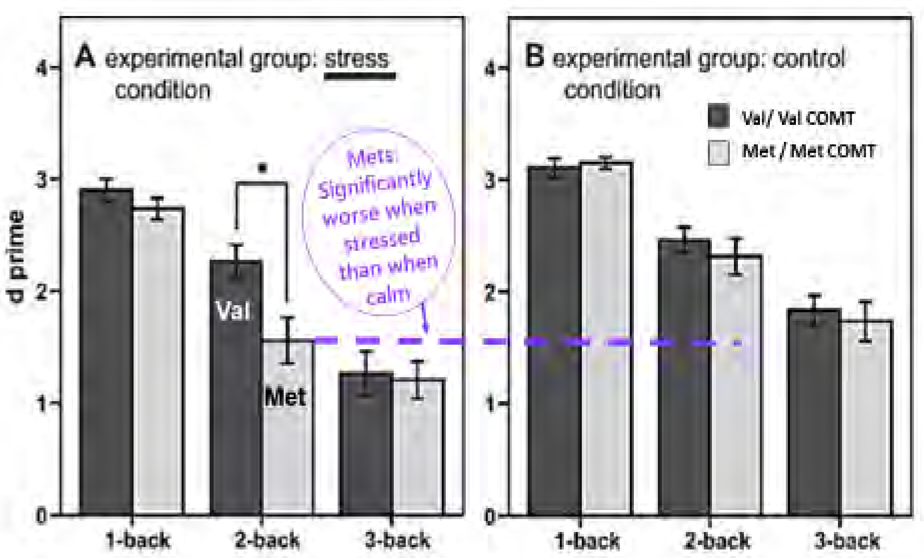
Speed on Incongruent Trials in the Flanker/Reverse Flanker Task

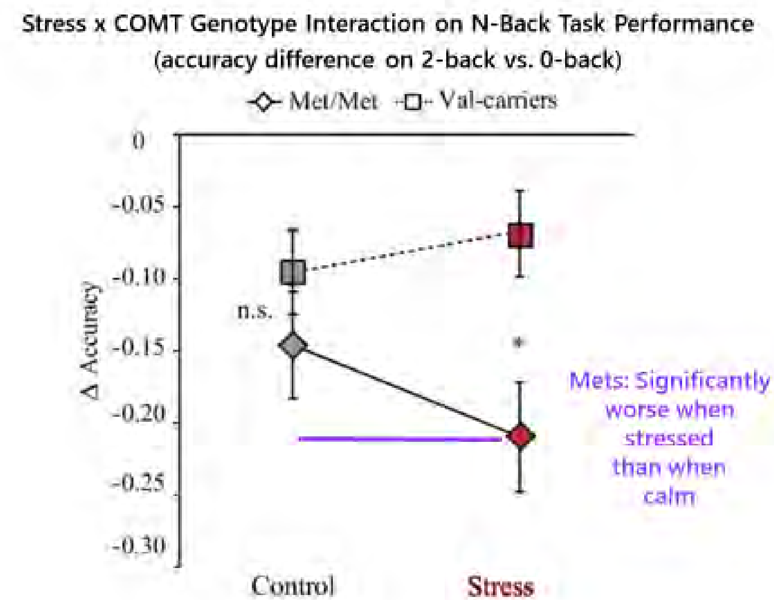




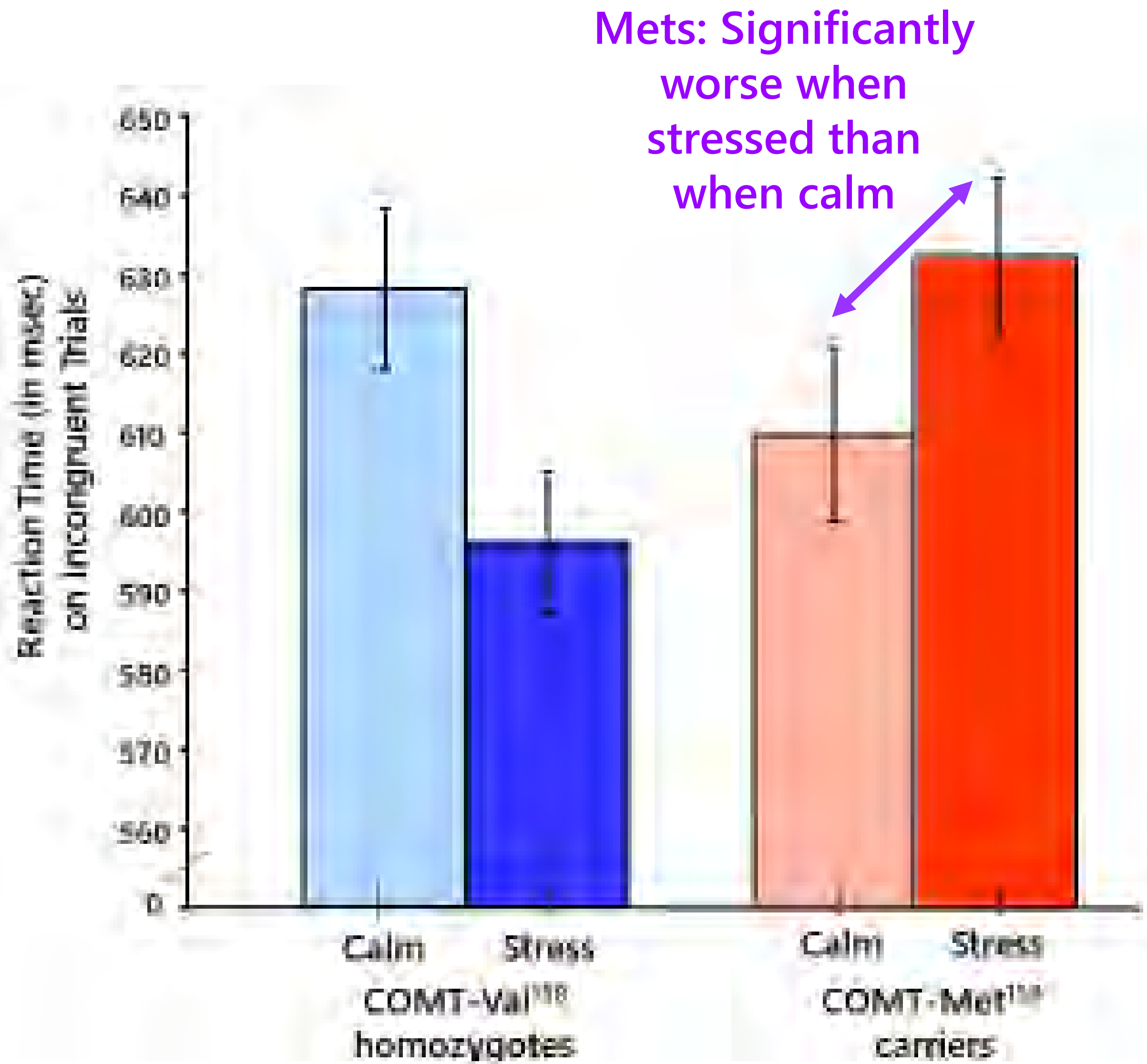
Shahab Zareyan

Mets performed significantly worse when stressed than when calm



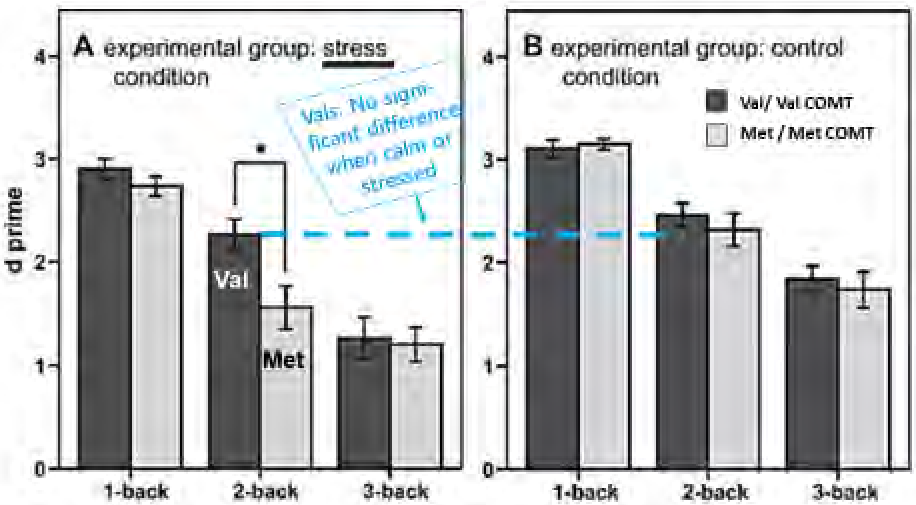


Speed on Incongruent Trials in the Flanker/Reverse Flanker Task

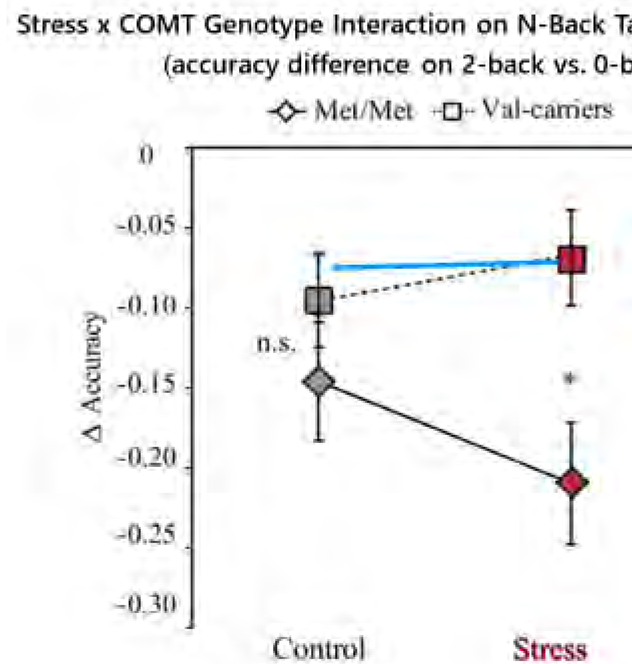


Zareyan, Zhang, Wang, Song, Hampson, Abbott, & Diamond (2020). *Cerebral Cortex* doi:10.1093/cercor/bhaa276 [Epub 30 Oct. 2020 ahead of print.]

BUT, Vals did NOT perform significantly better when stressed than when calm



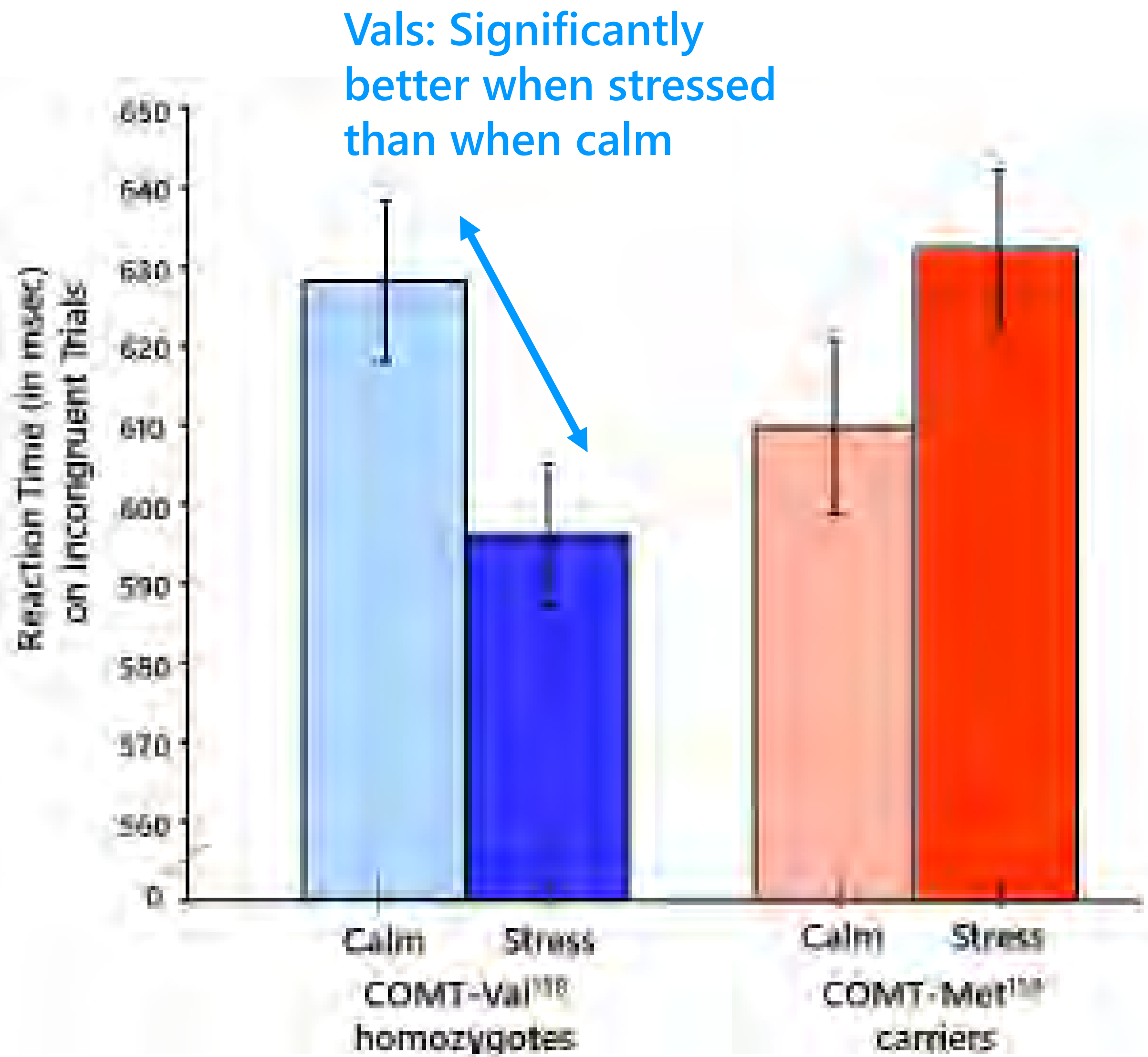
Buckert, M., Kudielka, B. M., Reuter, M., & Fiebach, C. J. (2012). The COMT Val158Met polymorphism modulates working memory performance under acute stress. *Psychoneuroendocrinology, 37*, 1810-1821. doi:10.1016/j.psyneuen.2012.03.014



Vals: no significant difference when calm or stressed

Qin, Cousijn, Rijpkema, Luo, Franke, Hermans, & Fernández (2012) *Frontiers in Integrative Neuroscience vol 6*

Speed on Incongruent Trials in the Flanker/Reverse Flanker Task



Zareyan, Zhang, Wang, Song, Hampson, Abbott, & Diamond (2020). *Cerebral Cortex* doi:10.1093/cercor/bhaa276 [Epub 30 Oct. 2020 ahead of print.]

Take home message from the 3 studies of the effect of stress on EFs:

Stress and anxiety,

even if quite mild,

only help a few

and impair the

performance of many

Even stress that is quite mild hurts the EFs of <u>most</u> people

(COMT-Mets & heterozygotes – i.e., any COMT-Met carrier)

Some (COMT-Vals) are better able to tolerate it, but they are <u>not</u> helped by it unless it is <u>VERY</u> mild

By the way,

estrogen down-regulates COMT gene transcription (Ho, 2008)

COMT enzyme activity is 30% lower in women than men (Chen et al., 2004)

Thus estrogen acts to

increase the level of

dopamine in PFC.

So during the portion of the menstrual

cycle when E2 are most elevated,

women are more sensitive to stress,

esp. if they have a COMT-Met allele.

Jeanette Evans

Evans, J. W., Fossella, J., Hampson, E., Kirschbaum, C., & Diamond, A. (2009). *Gender differences in the cognitive functions sensitive to the level of dopamine in prefrontal cortex.* Presented at the Assoc. for Psychological Science (APS) Annual Meeting, San Francisco, CA

Haolu Zhang

Zhang, H. (2017). *Estrogen-mediated sex differences in the effects of social evaluative stress on executive functions*. Master's Thesis in Neuroscience, University of British Columbia.

CAVEAT:

Our results may be specific to social evaluative stress.

There are many different kinds of stress; the effects & time courses might well differ by type of stress.

But certainly, feeling stressed
because you're worried about
what others might think of you
or might think of your performance
(social evaluative stress)
is not beneficial
for Executive Functions.

Performance

Anxiety

is not beneficial

Arousal ≠ Stress

There's a difference between the excitement and exhilaration of being challenged,

and the anxiety of feeling stressed.

Joy &

the Challenge of

Pushing One's Limits

are better motivators

than Fear or Anxiety

Indeed, there's a

downside of the

Met variant

of the COMT gene

Persons homozygous for COMT-Met^{158} tend to

- be more sensitive to **stress**

  Armbuster et al. 2012

- have higher **anxiety**

  Olsson et al. 2005

- and have heightened **pain stress responses**

  Zubieta et al., 2003
  Diatchenko et al., 2005

It has long been known that some of the brightest people also have the most fragile personalities and are highly reactive to stress.

Here is a possible mechanism for why the two might go together.

re: dandelion & orchid children

‘Dandelions’ are children who do okay wherever they are planted.

They are often seen as models of resilience.

Perhaps children homozygous for COMT-Val^{158} are the dandelions; they do okay even in a stressful environment.

The COMT Met-158 genotype, which confers risk on individuals when they are in adverse, stressful circumstances, holds out promise of extraordinary potential if only the right fit of circumstances can be found.

Someone who is not doing well in one environment, or with a particular instructional style, might shine in another environment or with a different instructional approach.

Indeed, the EF performance of those with better WM capacity is more adversely affected by social presence or social evaluation than is the EF performance of those with not as good WM ability.

E.g., social presence more negatively affects performance on the Simon task (Belletier et al. 2015) and on a visual search task (Wühr and Huestegge 2010) for those with better WM capacity.

And, those with better WM capacity are more likely to fail under pressure (Beilock & Carr, 2005).

This means that it is exactly those with presumably the greatest potential for success (those with the best WM capacity) whose performance on demanding cognitive tasks is most adversely affected by stress.

On the other hand, a professor might think a particular student is amazing,

but a student who had not looked particularly impressive

might be the one better able to function under pressure or in emergency situations;

that COMT-Val student might end up being the real hero or heroine.

Exactly those who perhaps didn't look so impressive in the regular day-to-day (e.g., COMT-Val homozygotes) might be indispensable exactly when needed most – when a sudden emergency requires quick, clear, creative thinking.

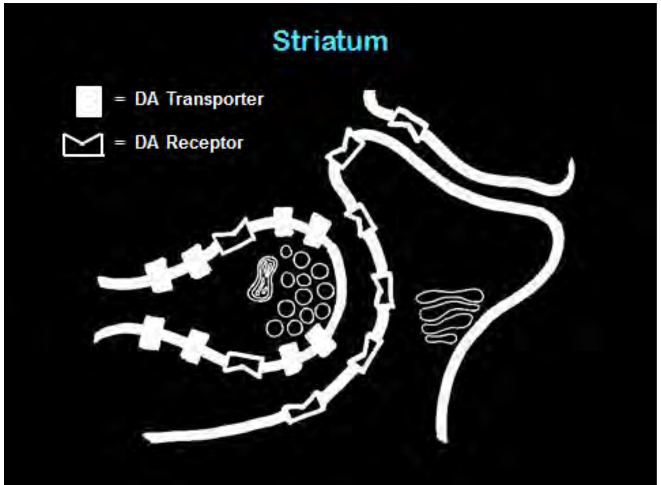
Turning now to one way that an unusual property of the DA system in PFC is important re: ADHD

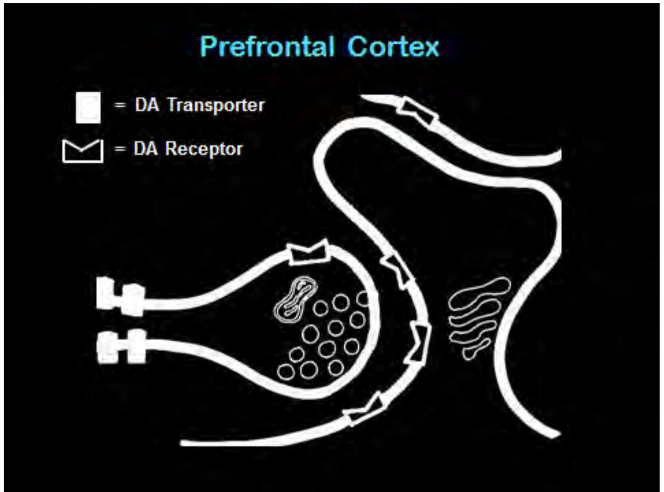
Remember:

The best mechanism for clearing away released dopamine is by dopamine transporter.

Remember:

Dopamine transporter is abundant in the striatum but sparse in prefrontal cortex.





Since there's lots of DAT in the striatum, polymorphisms of the dopamine transporter (DAT1) gene should be important for the striatum.

The striatum is implicated most in the impulsive and hyperactive aspects of ADHD.

PFC is implicated most in the cognitive deficits.

Indeed, levels of hyperactive-impulsive symptoms are correlated with the number of DAT1 high-risk alleles, but levels of inattentive symptoms are not.

Waldman *et al.*, 1998

DAT binding has been found to be related to motor hyperactivity but ***not*** to inattentive symptoms.

Jucaite *et al.*, 2005

Medications that affect the dopamine transporter should

be important for the striatum

and for the ADHD symptoms most closely linked to the striatum (hyperactivity and impulsivity).

At moderate to high doses

stimulants (like methylphenidate [MPH])

act on the dopamine transporter,

inhibiting re-uptake of dopamine.

Indeed, at moderate to high doses

MPH successfully treats

hyperactive & impulsive symptoms

(which are linked to the striatum).

Barkley et al. 1991; Barkley 2001;
Milich et al. 2001; Weiss et al. 2003

But those doses

yield much less benefit

for PFC

because PFC has little DAT.

On the other hand, a significant percentage of children with ADHD-IA are not helped by methylphenidate and those who are helped often do best at low doses.

Barkley et al., 1991; Barkley, 2001; Milich et al., 2001; Weiss et al., 2003

The mode of action of stimulants (like MPH) is **different at low doses.**

Berridge et al. 2006;
Devilbiss & Berridge 2008;
Schmeichel & Berridge 2013;
Spencer et al. 2012, 2015

At low doses, stimulants preferentially increase dopamine release in PFC and preferentially enhance signal processing in PFC.

We hypothesized that, by basing the decision about dose on children's behavior (rather than their cognition), many children with ADHD might be receiving too high a dose of stimulant for optimal performance in school.

Our ADHD Study

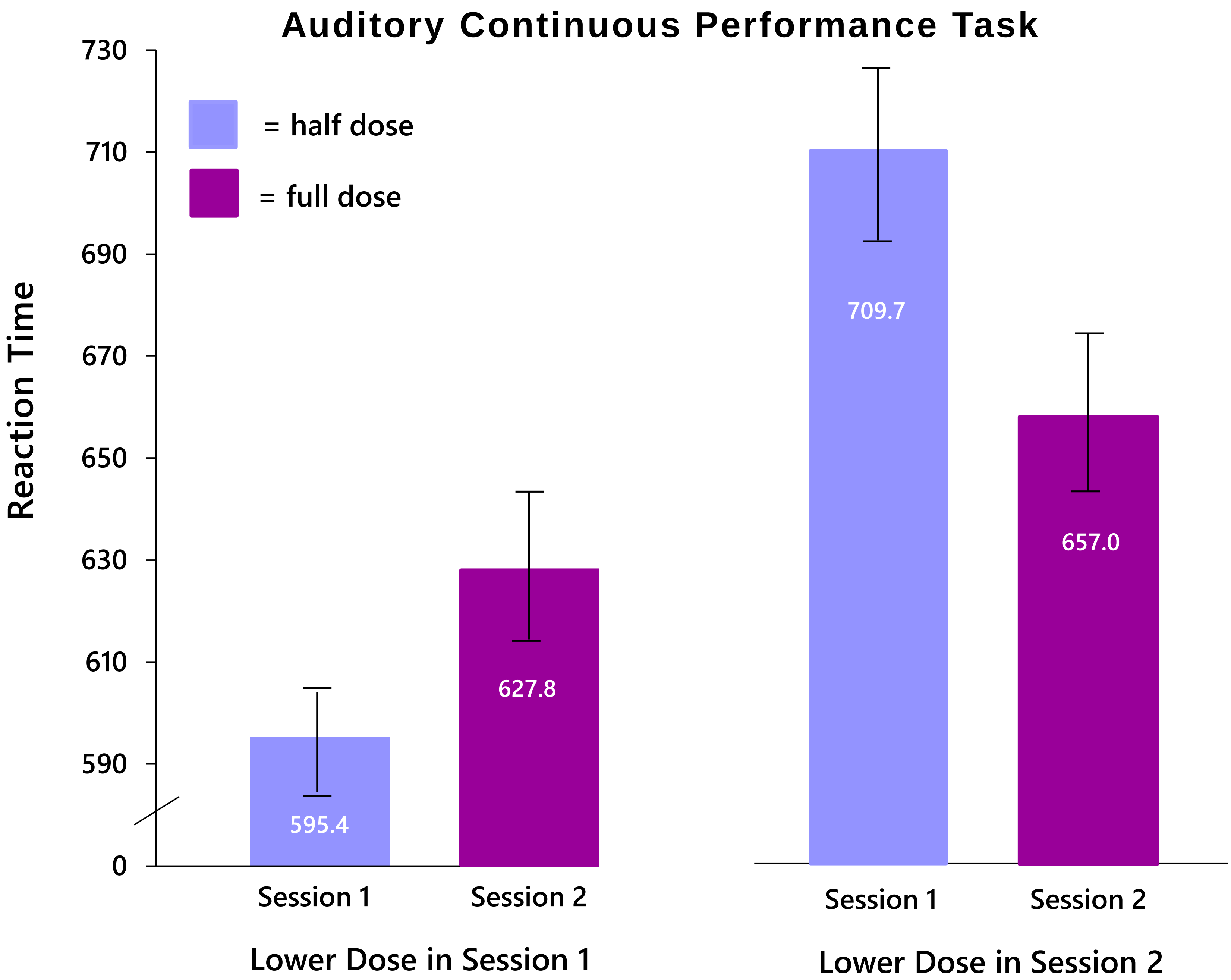
Double-blind, Crossover Design

	Session 1	Session 2
Half:	½ their usual dose of meds	their regular dose of meds
Half:	their regular dose of meds	½ their usual dose of meds

We found

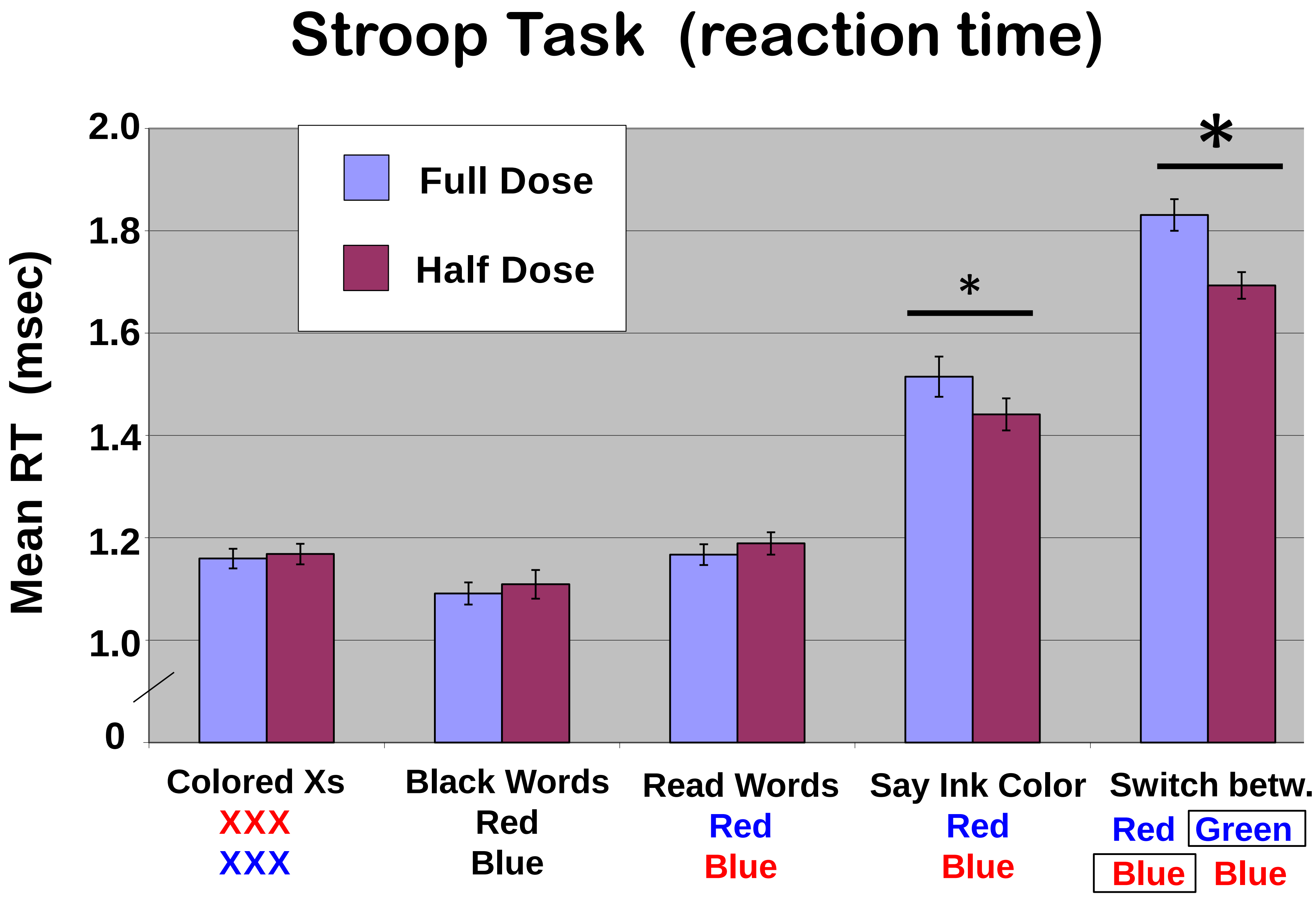
auditory sustained attention

was better on ½ the prescribed dose:



Auditory Continuous Performance Task
Reaction Time
730
710
690
670
650
630
610
590
0
= half dose
= full dose
595.4
627.8
709.7
657.0
Session 1
Session 2
Session 1
Session 2
Lower Dose in Session 1
Lower Dose in Session 2

We also found that inhibitory control and cognitive flexibility were better on ½ the prescribed dose:



Stroop Task (reaction time)
Mean RT (msec)
2.0
1.8
1.6
1.4
1.2
1.0
0
Full Dose
Half Dose
*
*
Colored Xs
XXX
XXX
Black Words
Red
Blue
Read Words
Red
Blue
Say Ink Color
Red
Blue
Switch betw.
Red
Green
Blue
Blue

Thus, the best doses of MPH for controlling behavioral problems

are probably too high for providing the best aid for cognitive problems.

It is likely that many children with ADHD are being prescribed too high a dose of psychostimulant for optimal performance in school.

The higher dose of stimulant might actually be *impairing* children's ability to get as much out of class as they could without medication.

Indeed, the higher dose might make children less able to concentrate & attend (more in a daze).

When cognitive development is perturbed,

as in a neurodevelopmental disorder,

motor development is often adversely affected as well.

At least half of all children with ADHD have

poor motor coordination

& fit the diagnosis for

developmental coordination disorder.

Children with ADHD show more sway when tested for balance than control children.

Either with eyes closed (no visual input), or when on a foam pad (reduced proprioceptive input).

They have problems particularly when they need to rely on vestibular input.

Zang et al. (2002)
Chinese J of Clinical Rehabilitation

Bittmann et al. (2005)

On the Functional Relationship between Postural Motor Balance and Performance at School

Deutsche Zeitschrift Für Sportmedizin, 56 (10)

found highly significant differences in balance regulation between better and worse students.

They were able to discriminate good students from poor ones with 80% accuracy based on their balance skills.

Research shows that much of balance

(especially when there's reduced sensory input [e.g., eyes closed] or a reduced base of support [e.g., feet together or one leg raised])

requires PFC

Bauby & Kuo, 2000; Karim et al., 2014; Kwag & Zijlstra, 2022; Mihara et al., 2008; Rydalch et al., 2019; St George et al., 2021

It's well-established that the cerebellum is critical for motor learning and balance

(Glickstein & Yeo, 1990; Morton & Bastian, 2004).

Less well known is that cerebellum also plays an important role in EFs

(Diamond, 2000; Koziol et al., 2014; Schmahmann, 2004, 2019; Stoodley, 2014; Stoodley et al., 2012; Strick et al., 2009).

Given that balance appears to tax EFs and require PFC

and given that the cerebellum (which is imp. for balance) is also imp. for EFs,

we are now testing the hypothesis that training balance will improve not only balance, but also EFs.

Another recurring Theme in my work:

Motor development and cognitive development appear to be fundamentally intertwined.

Diamond, A. (2000)

Close Interrelation of
Motor Development and Cognitive Development and
of the Cerebellum and Prefrontal Cortex

Child Development, 71, 44-56

thanks for listening

adele.diamond@ubc.ca

My thanks to the NIH (NIMH, NICHD, & NIDA), which has continuously funded our work since 1986,
& also to the Bezos Family Fdn, Spencer Fdn, CFI, CRC, NSERC, & IES for supporting our work - & especially to all the members of my lab.

Motor development and cognitive development appear to be fundamentally intertwined.

Diamond, A. (2000)

Close Interrelation of
Motor Development and Cognitive Development and
of the Cerebellum and Prefrontal Cortex

Child Development, 71, 44-56

To some extent the cognitive competencies are there early, but the control of action comes in late.

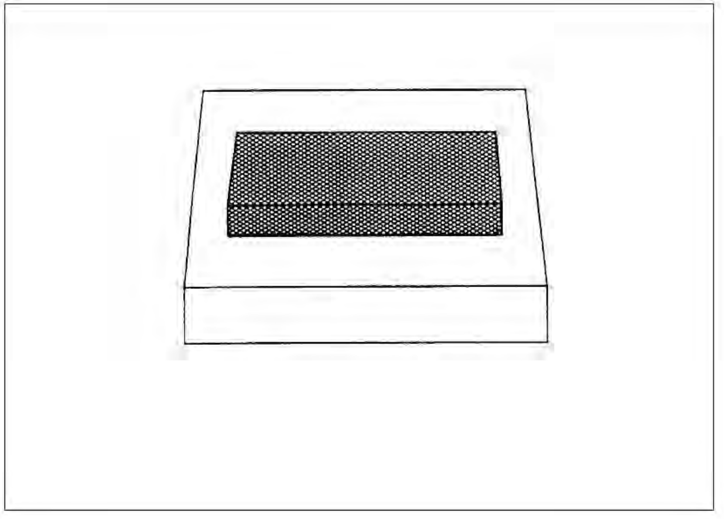
Young children understand some things quite early, but cannot demonstrate this until much later because imprecise execution of motor actions (reaching) and because of their inability to inhibit reflexive or habitual reactions.

Piaget theorized that infants 5 to 6 months old do not understand the concept of contiguity, i.e., they do not realize “that two objects can be independent of each other when the first is placed upon the second” (Piaget, 1937/1954, p. 177).

The behavioral observation on which this was based was that although infants can retrieve a small free-standing object, they fail to retrieve that same object if it is placed on top of a slightly larger object.

At first we couldn’t replicate Piaget’s observation that infants of 5-6 months can’t retrieve a matchbox placed on top of a book.

We used a smaller rectangular block placed on top of a larger rectangular block.



Whatever one may think of Piaget's theorizing, he was an excellent and accurate observer of children's behavior.

If we couldn't replicate what Piaget had observed, *we* were doing something wrong.

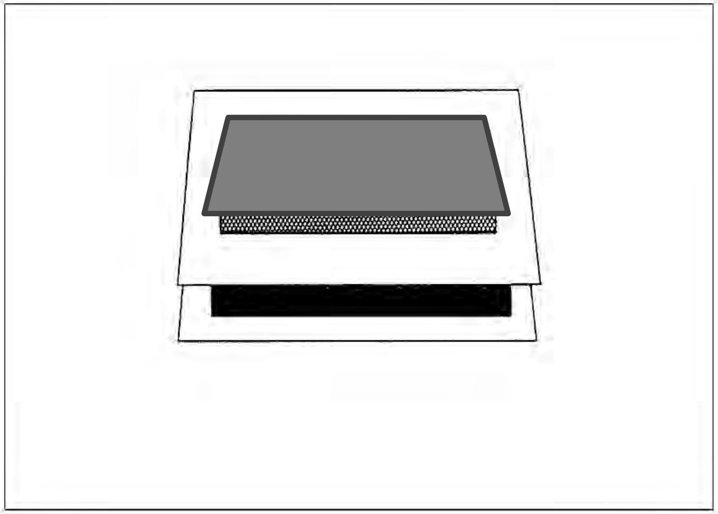
It dawned on me,

we were simulating presenting a matchbox on a book with the binding side of the book facing the child.

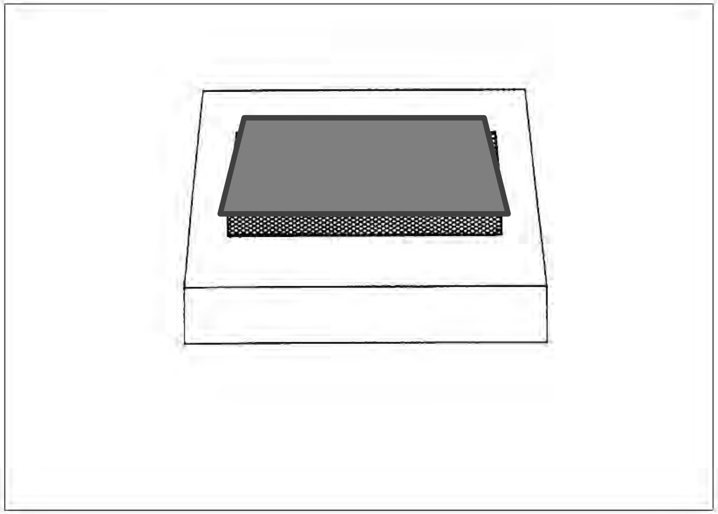
Maybe Piaget had presented the matchbox on a book, with the pages facing the child.

(Piaget never mentioned the orientation of the book).

Sure enough. We replicated Piaget's observation with the larger block shaped like this (the 'pages side' facing the child):



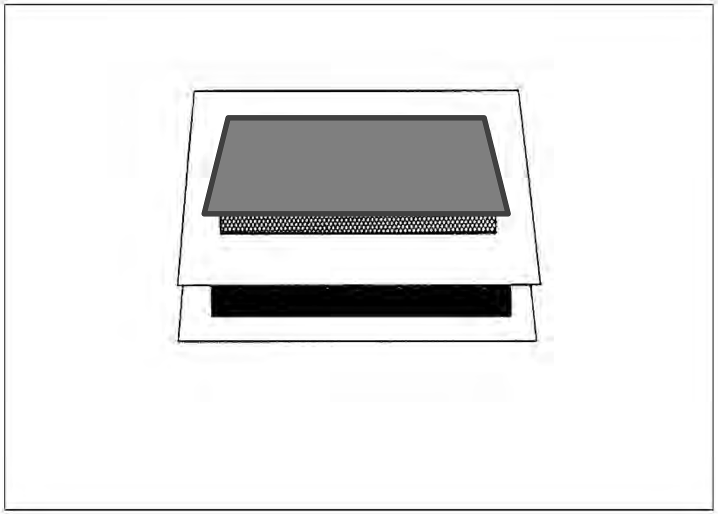
But not when it was shaped like this (the 'binding side' facing the child):



Why would the orientation of the book matter?

The bottom block here presents an easily graspable edge for an infant.

If you combine imperfect precision in reaching with the grasp reflex, you are likely to find infants grasping the bottom block (i.e., the book)



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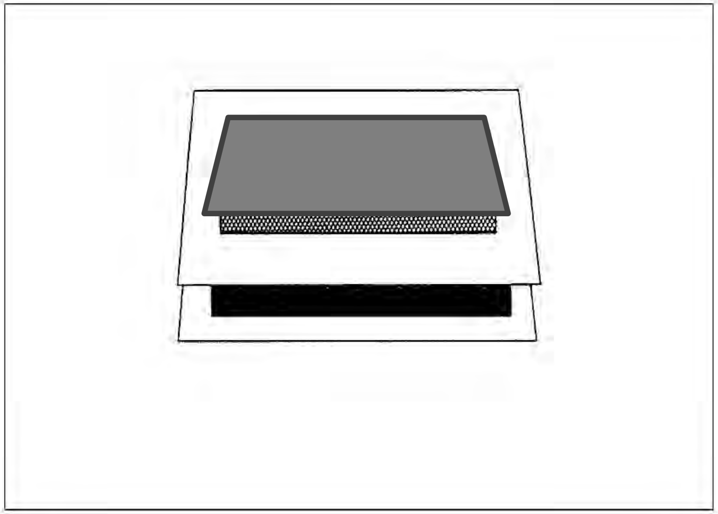
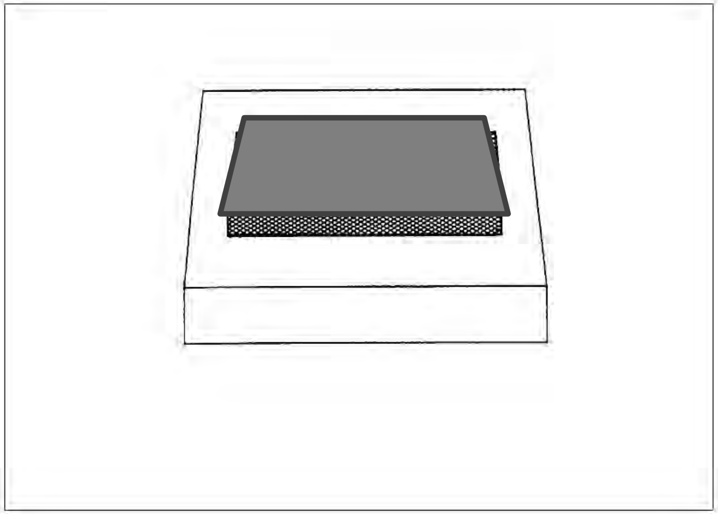
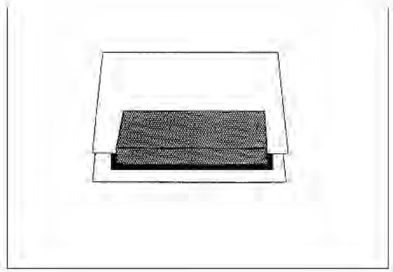
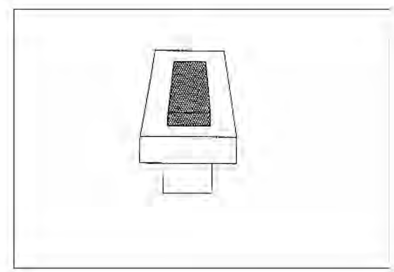
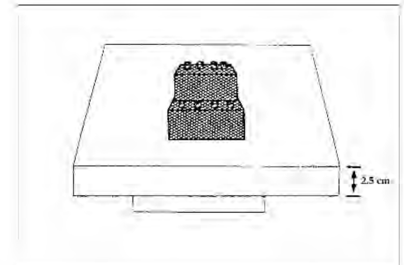


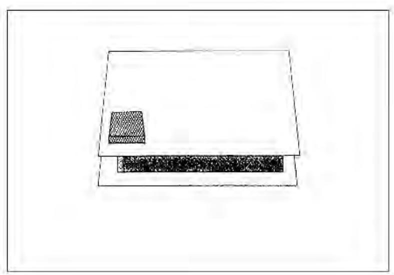
Here, even if infants accidental-ly graze the edge of the bottom block en route to the top block, they can't grasp it.

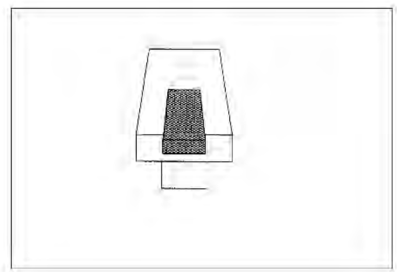


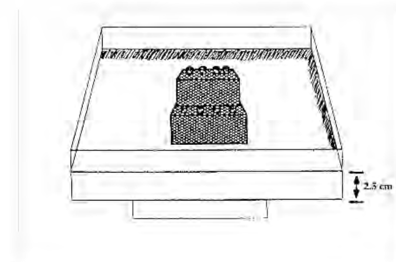


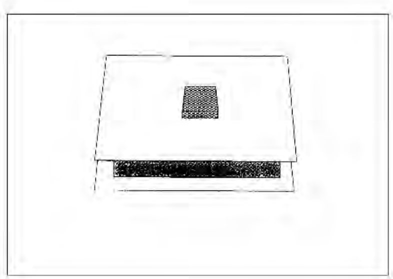












Diamond, A. & Lee, E.-Y. (2000) Inability of 5-month-old infants to retrieve a contiguous object: A failure of conceptual understanding or of control of action? *Child Development, 71,* 1477-1494.

So, Piaget's observations were absolutely correct, but his conclusion was not.

The problem is not conceptual, as Piaget thought. Babies understand perfectly well that 2 objects continue to exist independently when they share a border with one another.

Babies' problem here is motor – with precision reaching and inhibiting the grasp reflex.

Infants' problem consists of lack of precision in visually guided reaching and lack of ability to inhibit reflexive reactions to touch.

More 5-month-olds succeeded, in less time, and with fewer touches to an edge of the base, on trials more forgiving of an imprecise reach than on less forgiving trials.

Success in retrieving objects close in size and fully contiguous with their bases was seen even at 5 months when the demands on skill in reaching were reduced.

Bower (1974) demonstrated that infants fail to retrieve an object if it is placed directly behind a slightly larger object.

For example, infants will retrieve a small object if it is several inches behind a screen,

but not if it is directly behind the screen.

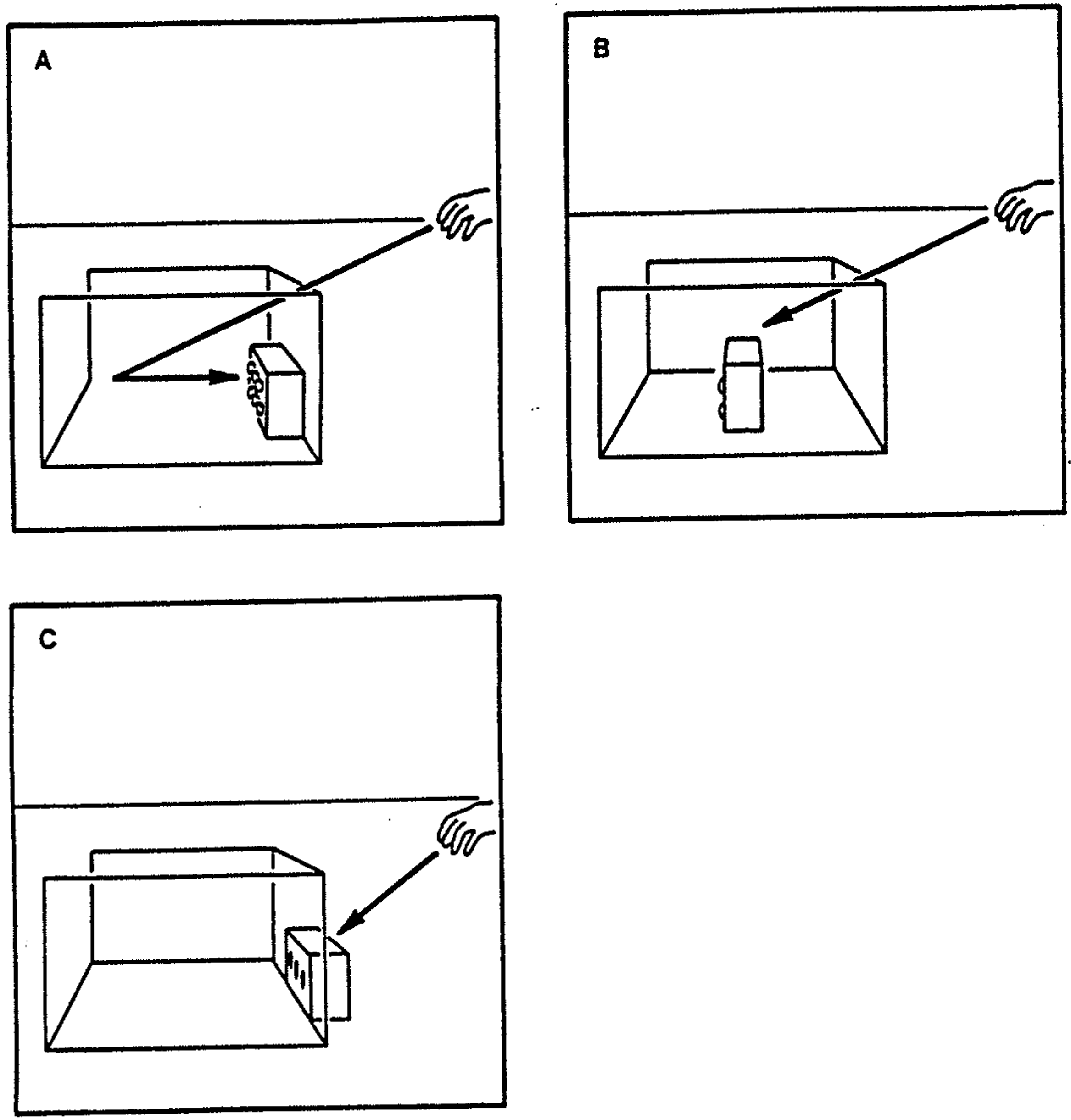
Bower (1977) concluded: "It seems that what the baby doesn't understand is that two objects can be in a spatial relationship to one another, so that they share a common boundary. Evidently it is the common boundary that is critical" (pp. 116-117).

7-month-old reaching for a Lego inside our box


0-04:28:6

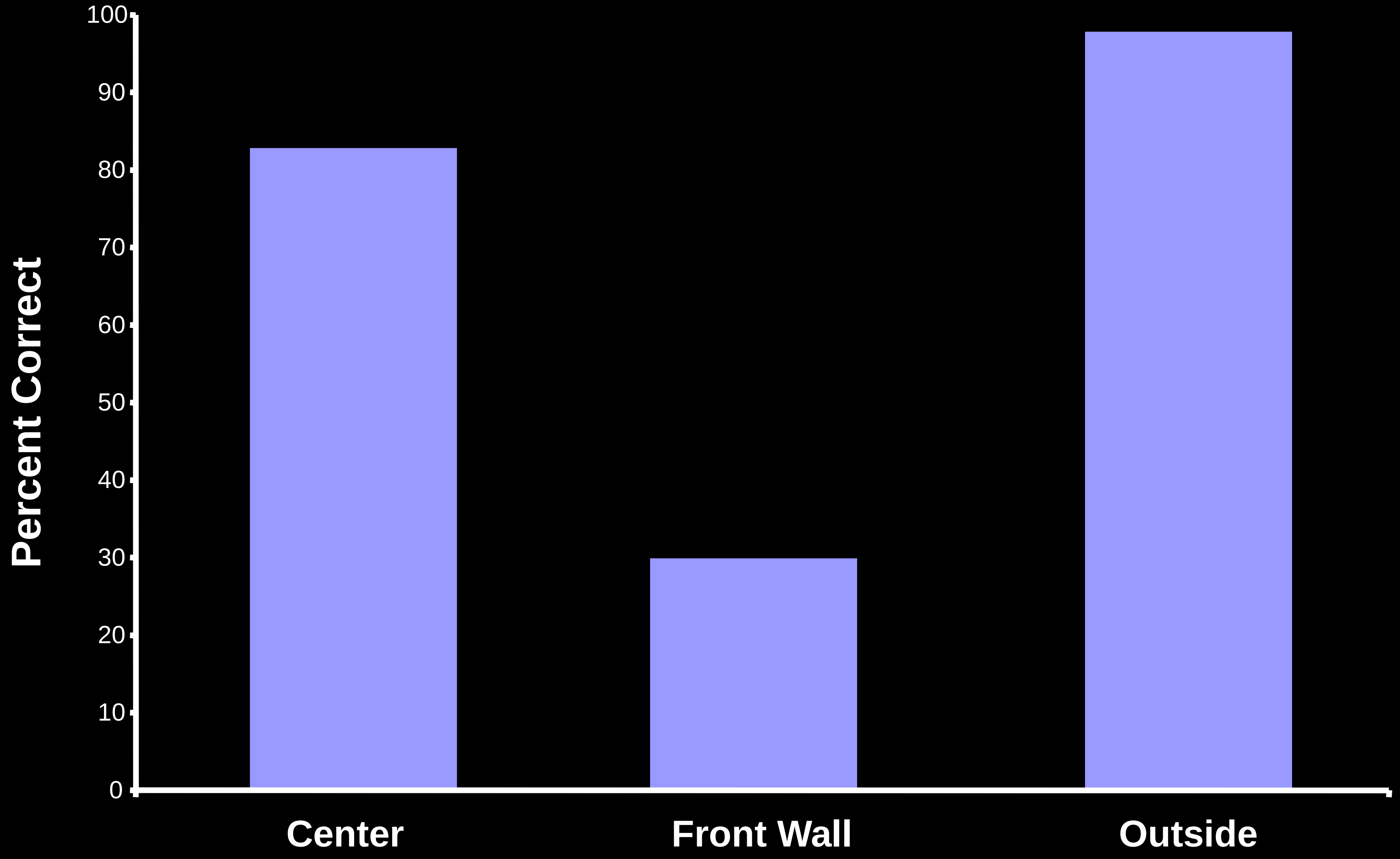
Same infant, same session, different camera angle

7-month-old fails to retrieve Lego inside our box
when it is against the front wall


A
B
C


0:05:01:2


0:05:05:6



Percent Correct
100
90
80
70
60
50
40
30
20
10
0
Center
Front Wall
Outside


0:06:09:9

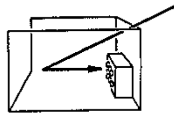

0:06:21:7


DDDDDDDDDD
0:03:39:5


0:03:43:5

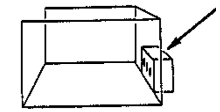
Infants of 7 Months Fail

need a bi-directional reach

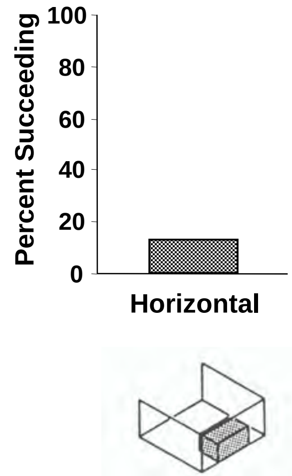


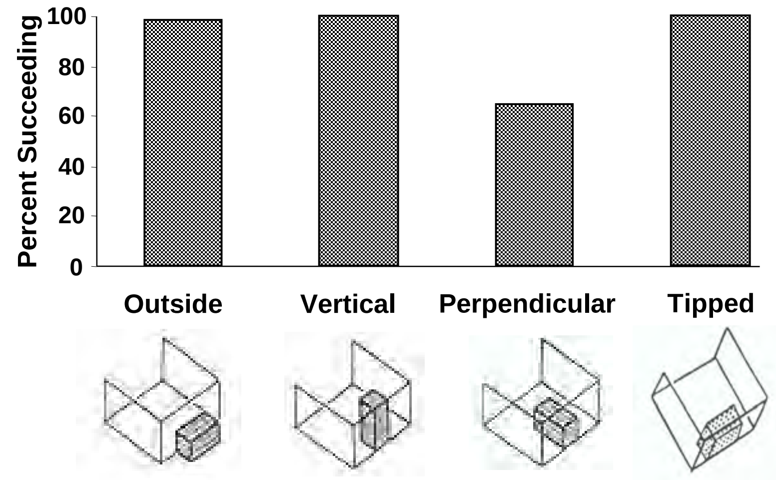
Infants of 7 Months Succeed

can reach on a simple straight line

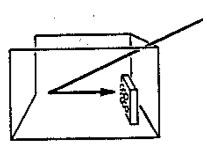


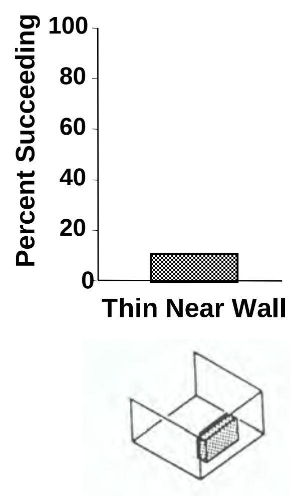
Toy Contiguous
with Front Wall
of Box

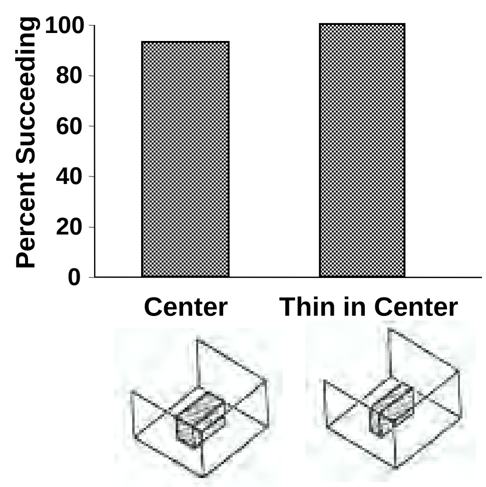




**Toy *not* Contiguous
with Front Wall
of Box**





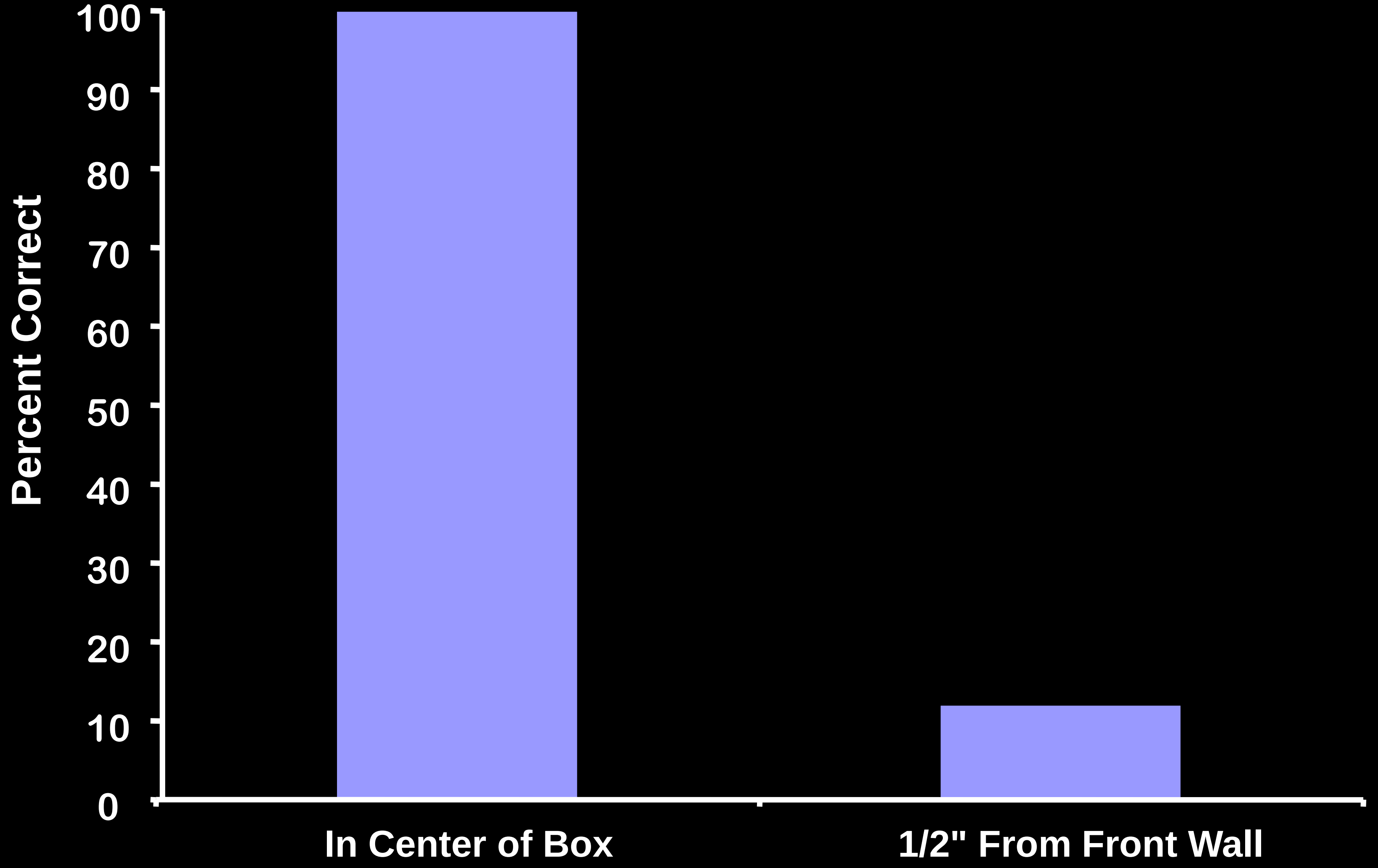



DDDDDDDDDD
0:03:01:5


0:03:02:0


DDDDDDDDDD
0:03:21:7


0-03:23:0


Percent Correct
100
90
80
70
60
50
40
30
20
10
0
In Center of Box
1/2" From Front Wall

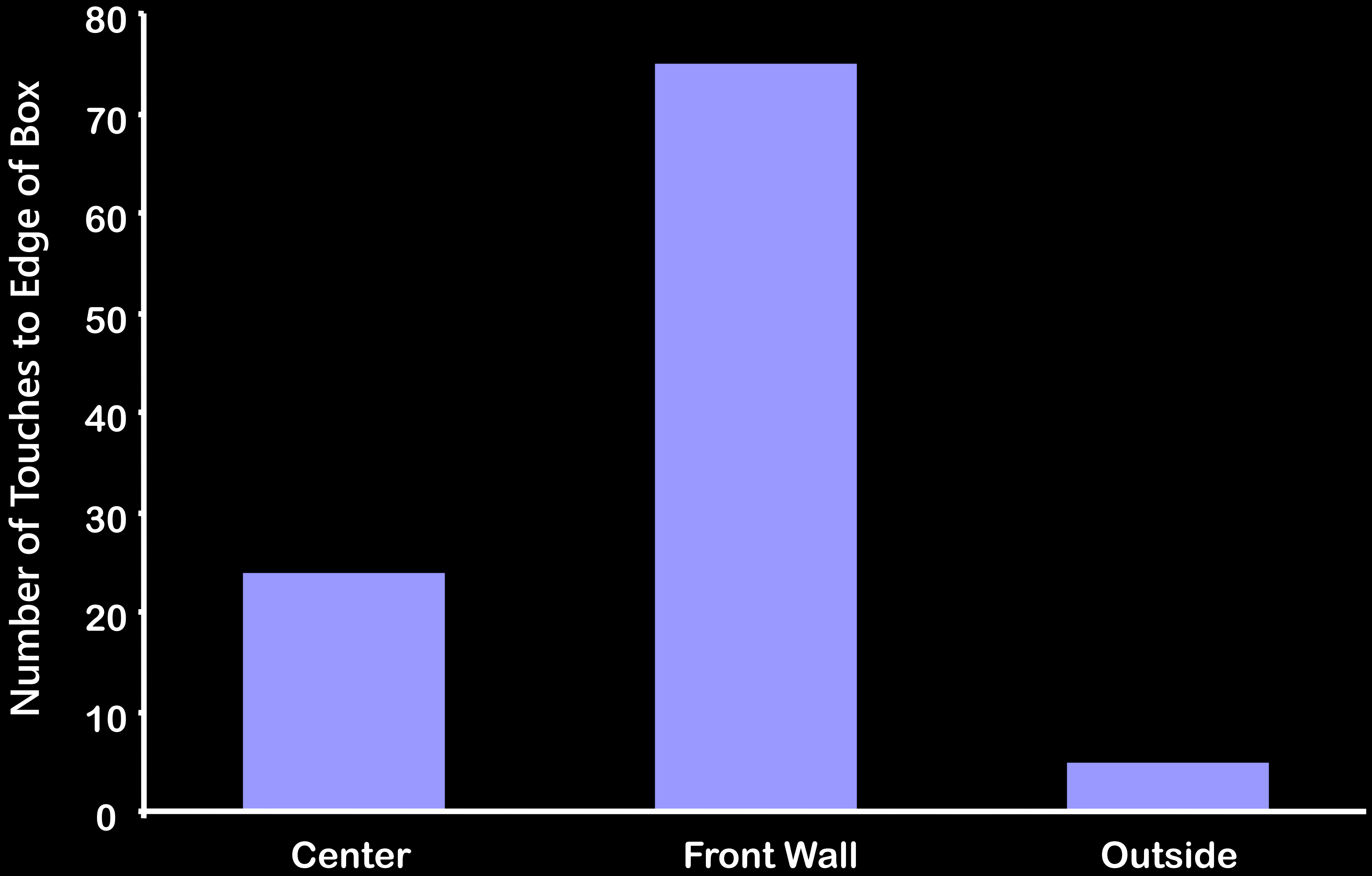

0:05 42:6


0:05:43:0

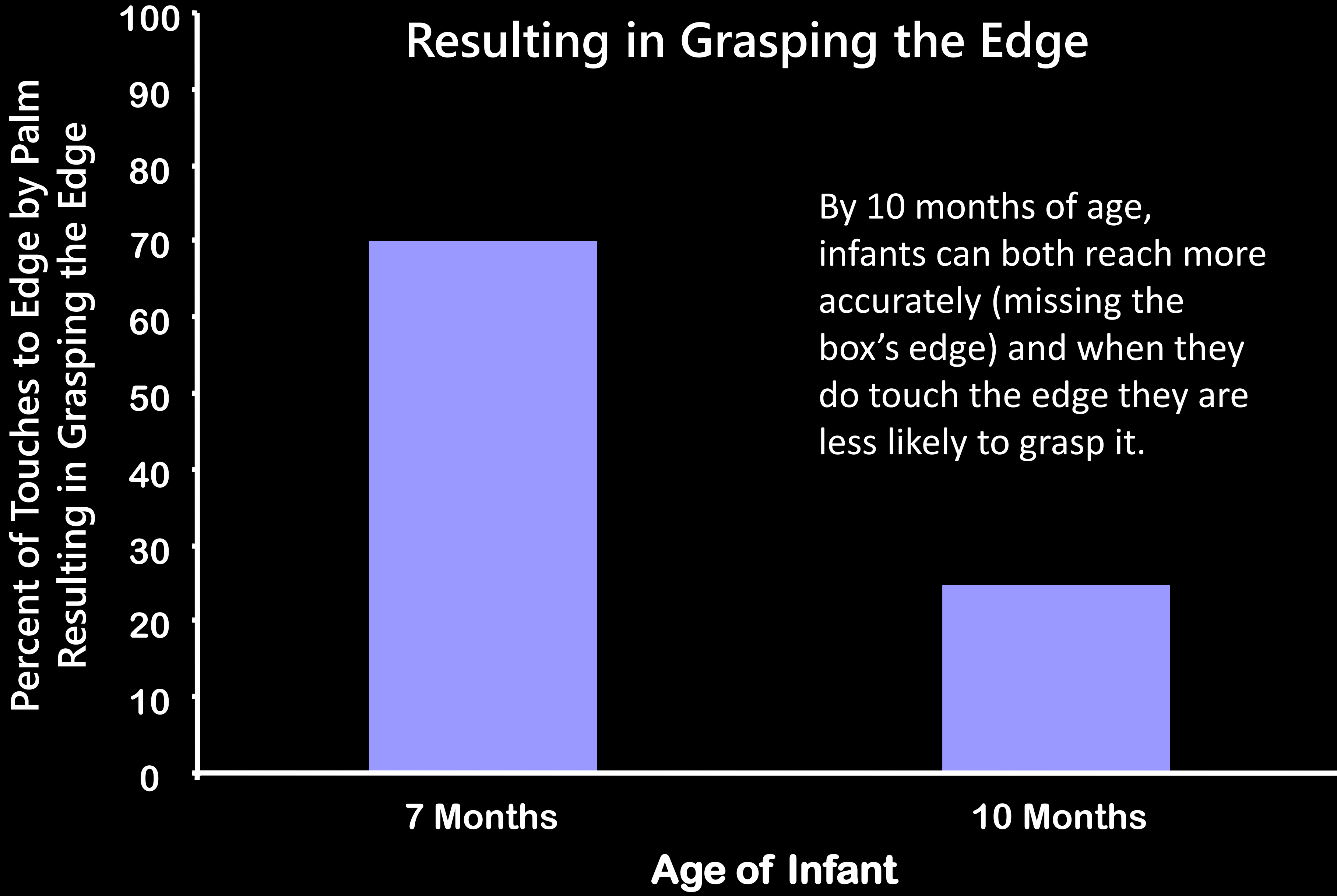

0:05:43:2


0:05:46:8

Number of Touches to Front Edge of the Box



Percent of Touches to Edge by Palm Resulting in Grasping the Edge



Infants of 7 months typically reacted to touching the edge of the box by reflexively grasping the box (68% of the time) or reflexively withdrawing their hand (15% of the time).

They rarely continued a reach despite grazing the edge of box and rarely continued a reach after grasping the box. Instead, they pulled their hand back and began the reach again from the starting position.

Infants of 10 months, on the other hand, were much less likely to react reflexively when they touched the box (grasping the edge only 25% of the time and almost never reflexively pulling their hand back) and were much more likely to continue their reach despite contacting the box.

Infants of 7 months thus seem to understand the concept that an object continues to exist as a separate entity when it shares a boundary with another object.

Their behavior often fails to reflect this understanding, however, because of their imperfect control of their hands.

By at least l0 months of age, and perhaps earlier, infants have sufficient control of their actions to enable them to demonstrate in their behavior the conceptual understanding that seems to be present much earlier.

Diamond, A. & Gilbert, J. (1989)
Development as progressive inhibitory control of action:
Retrieval of a contiguous object.
Cognitive Development, 4, 223-249.

Diamond, A. (1991)
Neuropsychological insights into the meaning of object
concept development. In S. Carey & R. Gelman (Eds.),
The epigenesis of mind: Essays on biology and knowledge (pp.
67-110). Hillsdale, NJ: Lawrence Erlbaum Assoc.

Delayed Non-Matching to Sample is a classic task for studying visual recognition memory dependent on the medial temporal lobe

also replicated in amnesic adults and in infant monkeys

Success on Delayed Nonmatching to Sample appears very **LATE** in Development

Humans	Infants do not reliably choose the novel stimulus until 21 months of age with delays of only 5 sec.
Monkeys	Infant monkeys do not reliably choose the novel stimulus until 4 months of age at delays of 10 sec.

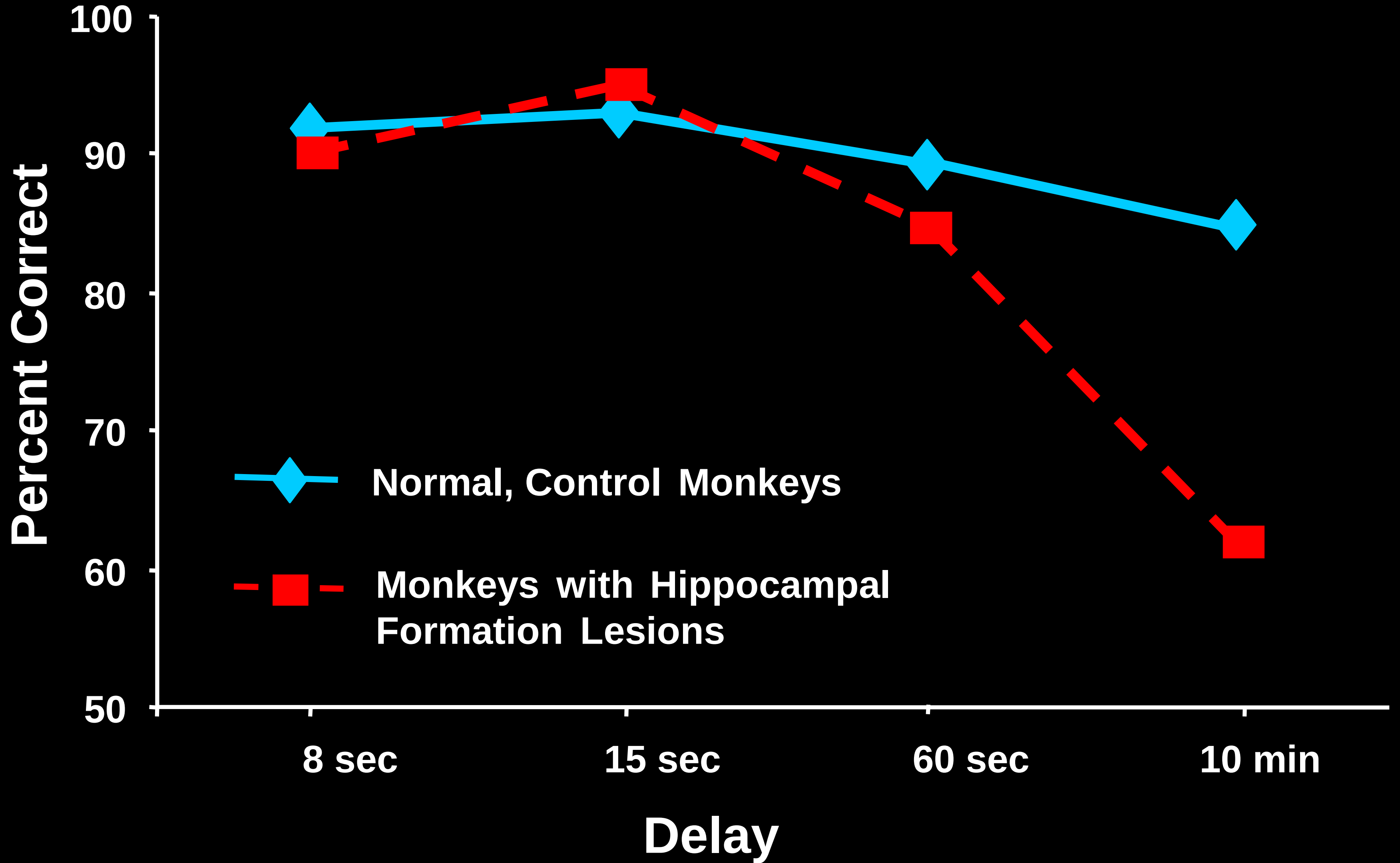
An Early and a Late Developing System for Learning and Retention in Infant Monkeys

Behavioral Neuroscience

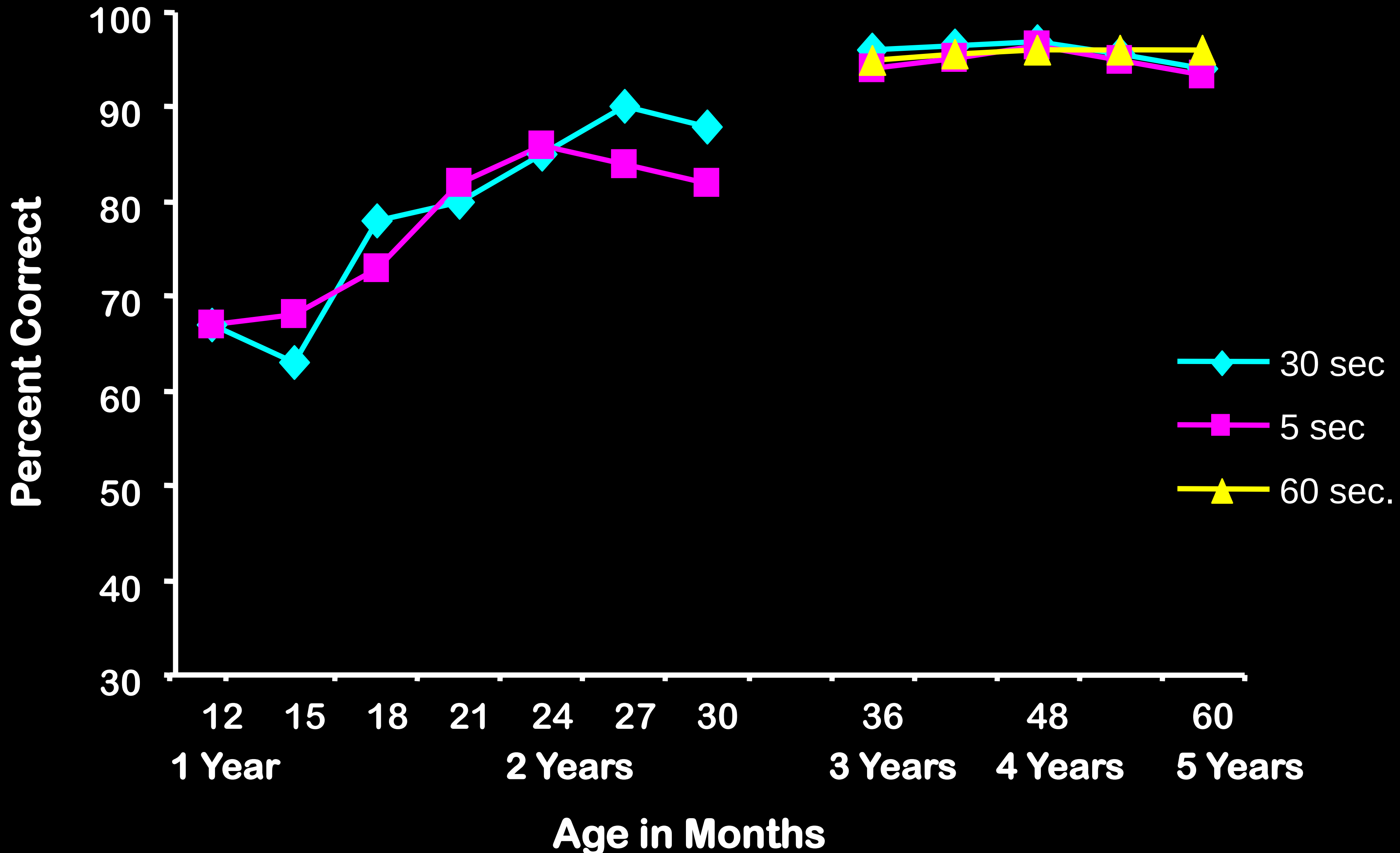
1984

On the evidence that memory formation and habit formation represent two qualitatively different learning processes based on separate neural mechanisms, the functional development of these two processes was followed ontogenetically. Separate groups of rhesus monkeys of different ages were tested in delayed nonmatching-to-sample and 24-hr concurrent discrimination learning, considered to be measures of recognition memory and discrimination habit formation, respectively. The youngest group of infant monkeys failed to learn the nonmatching task until they were approximately 4 months old. With further maturation, learning ability on…

Performance on the Delayed Nonmatching to Sample Task

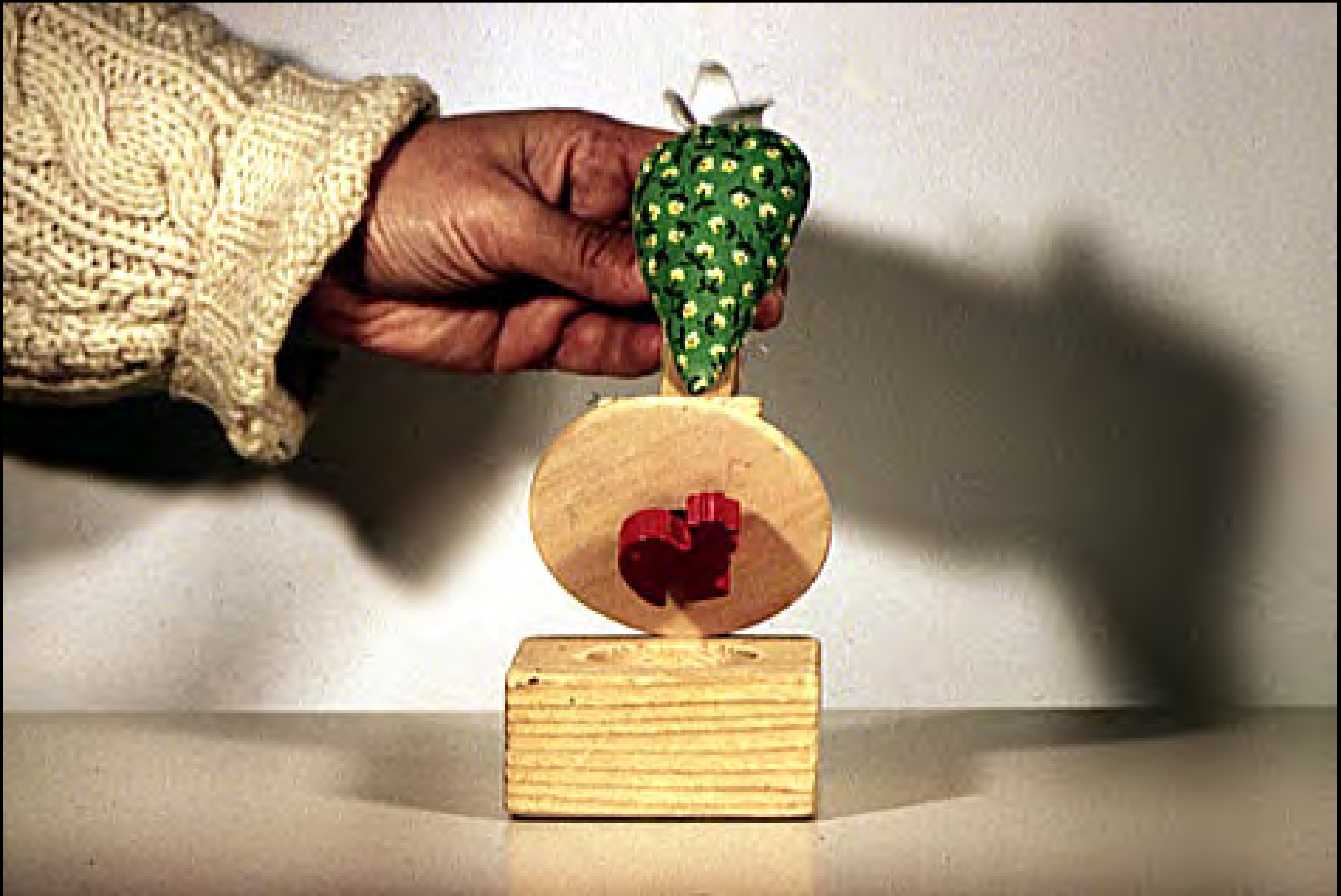


Percent Correct at Delays of 5, 30, & 60 Sec

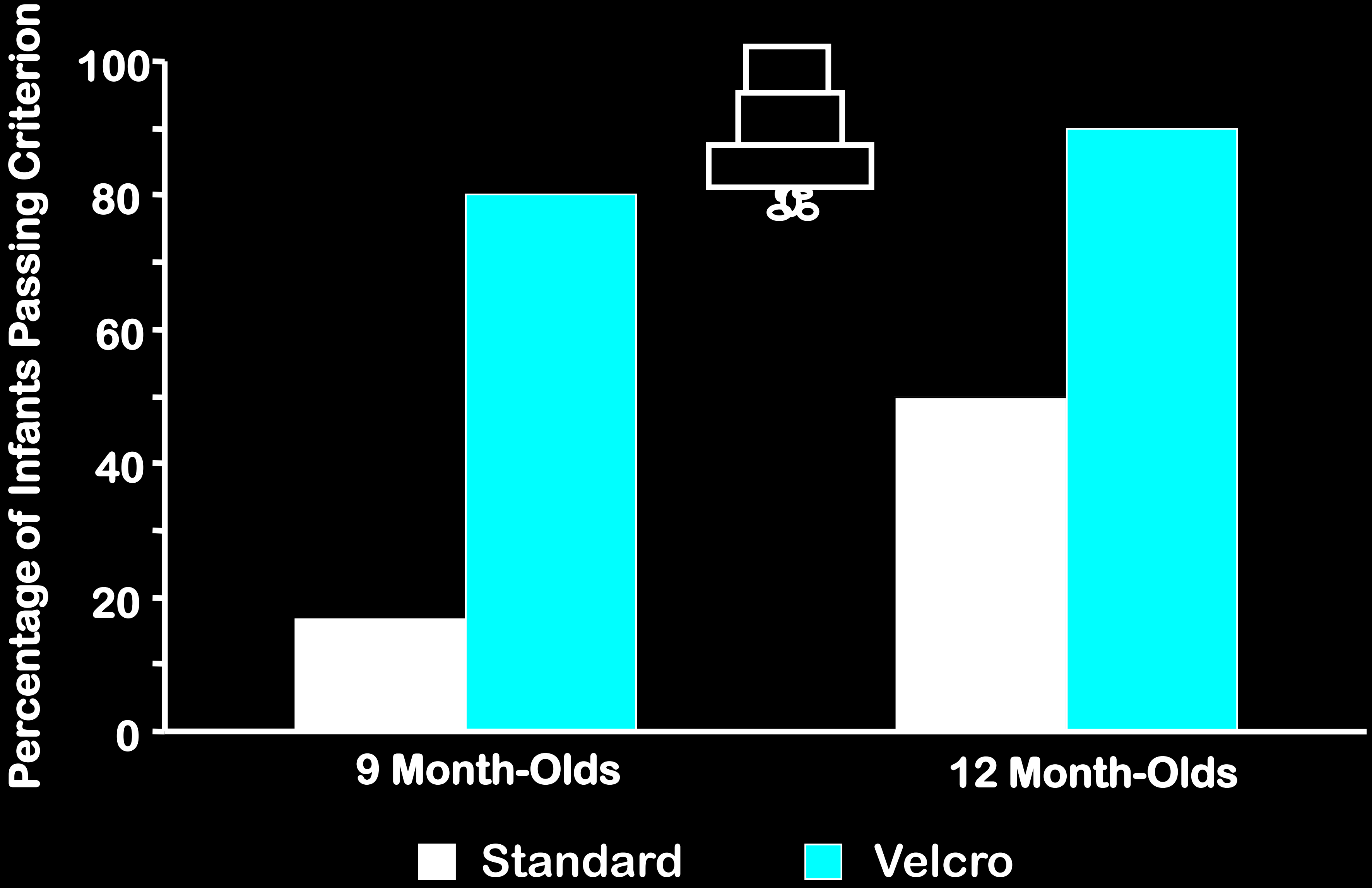


Velcro Condition

Reward contiguous with
& physically connected to,
though detachable from,
the stimulus



Percentage of Infants Passing Criterion at the 5-Sec Delay in the VELCRO Condition of DNMS



When the reward and stimulus were physically connected, when the reward moved with the stimulus as the infant displaced the stimulus, the task was easy.

The critical late-maturing competence is the ability to grasp the relation between stimulus and reward, to understand the role of the stimulus as a marker or symbol for the reward's location

Murray Jarvik

(1956)

Simple color discrimination in chimpanzees: Effect of varying contiguity between cue and incentive.

***Journal of Comparative and Physiological Psychology, 49*, 492-495.**

Judy DeLoache

(1995)

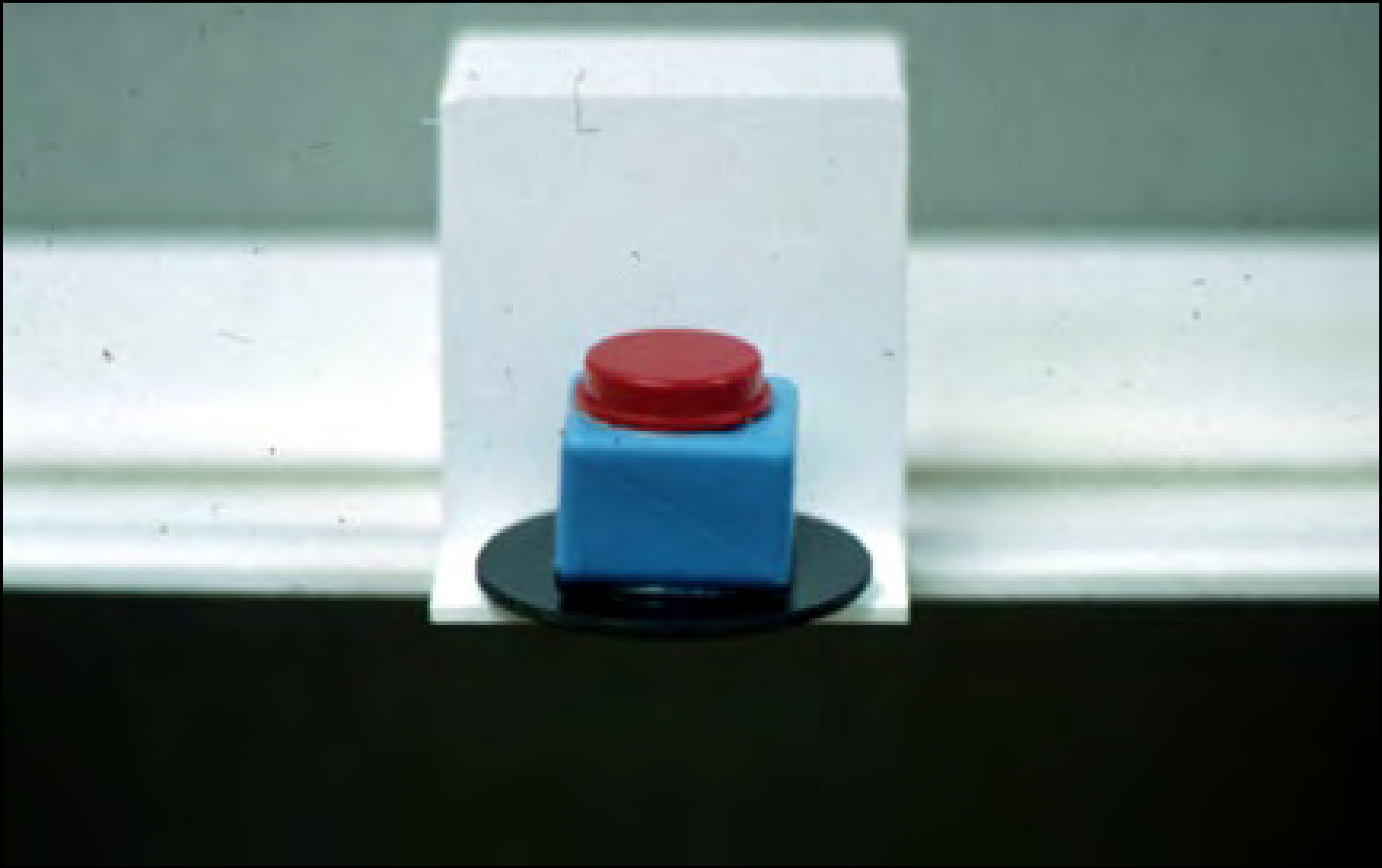
Early understanding and use of symbols: The model model.

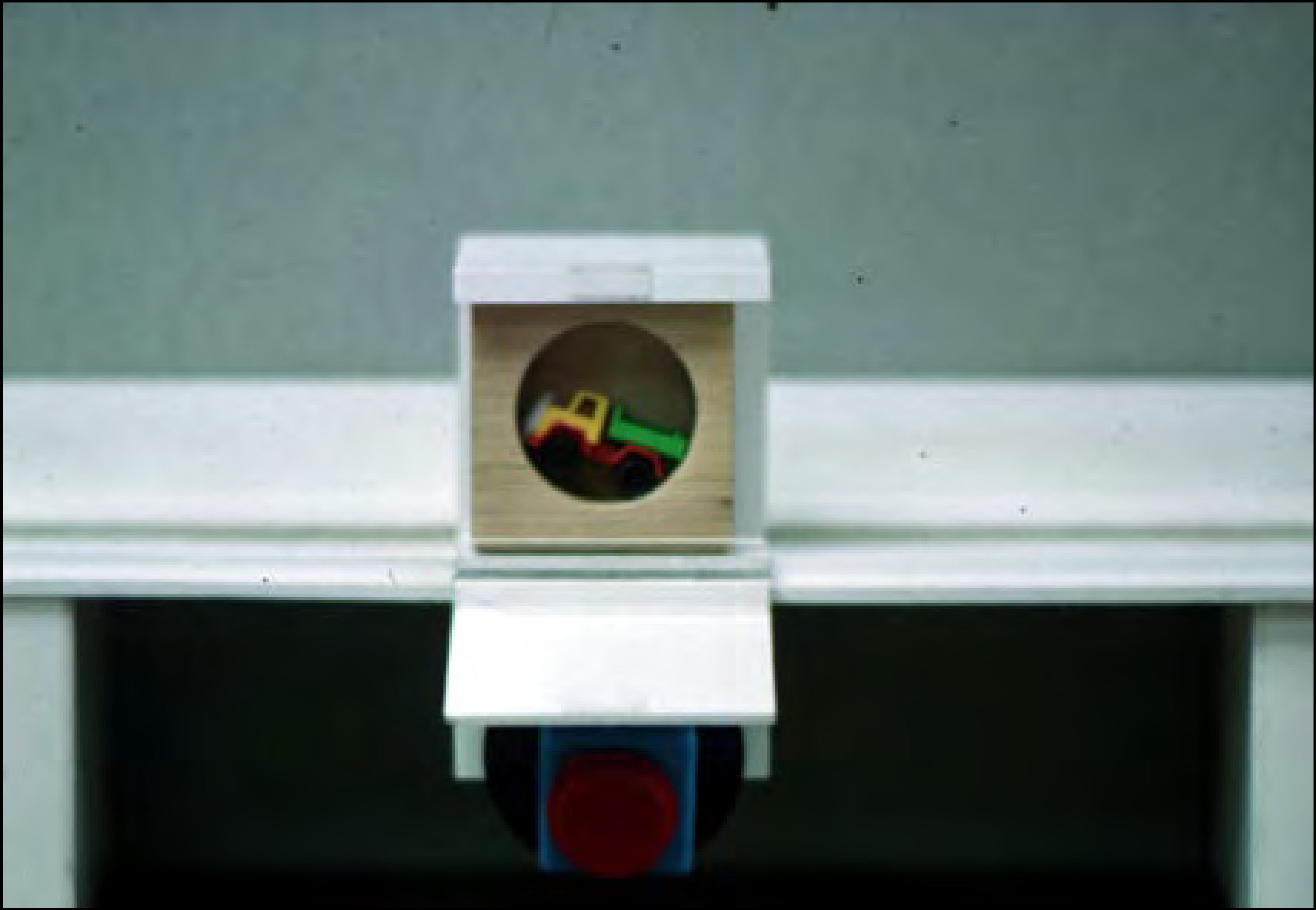
***Current Directions in Psychological Science, 4*, 109-113.**

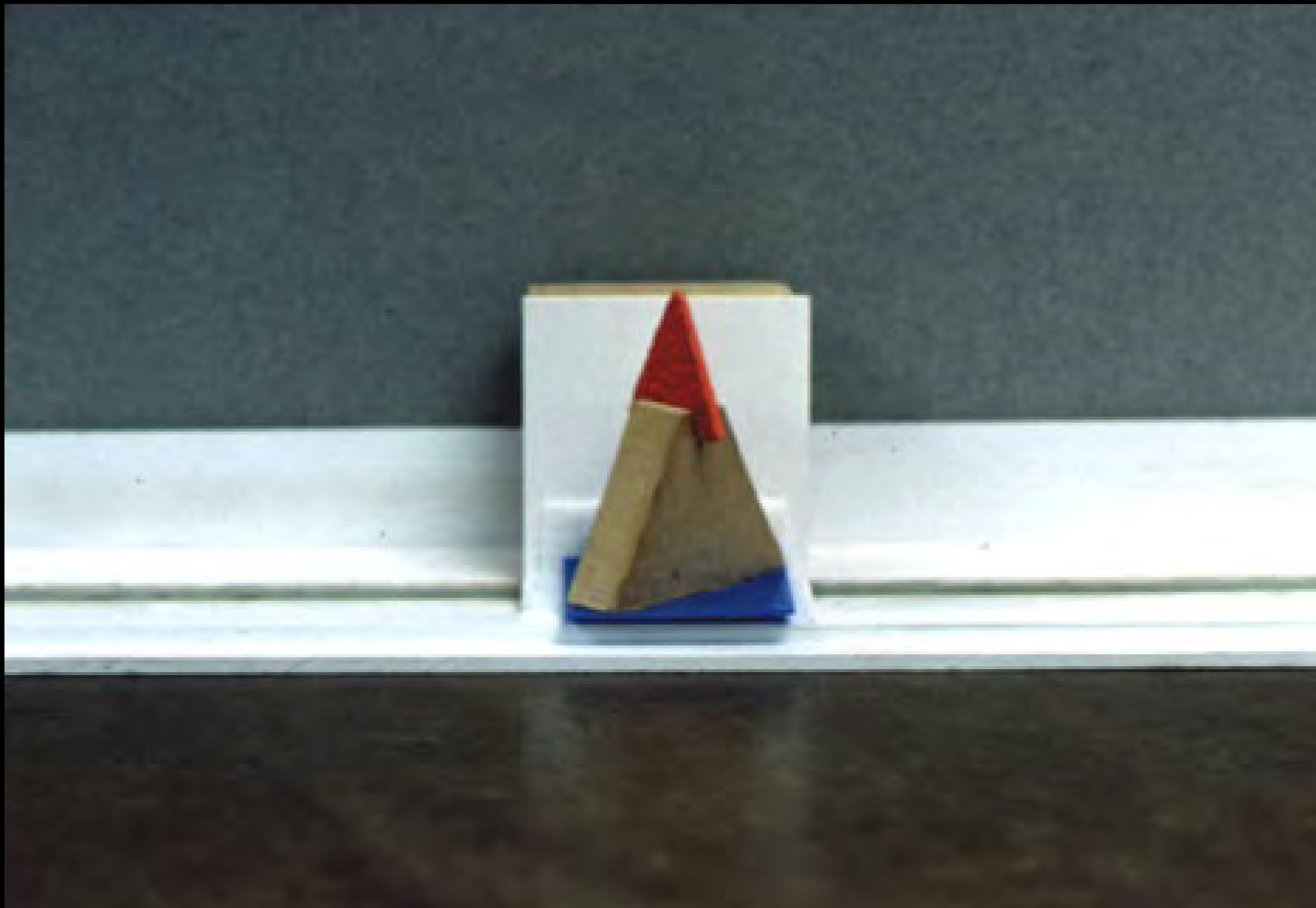
Is it SPATIAL proximity, TEMPORAL proximity, or PHYSICAL CONNECTION, that makes the difference in infants’ performance?

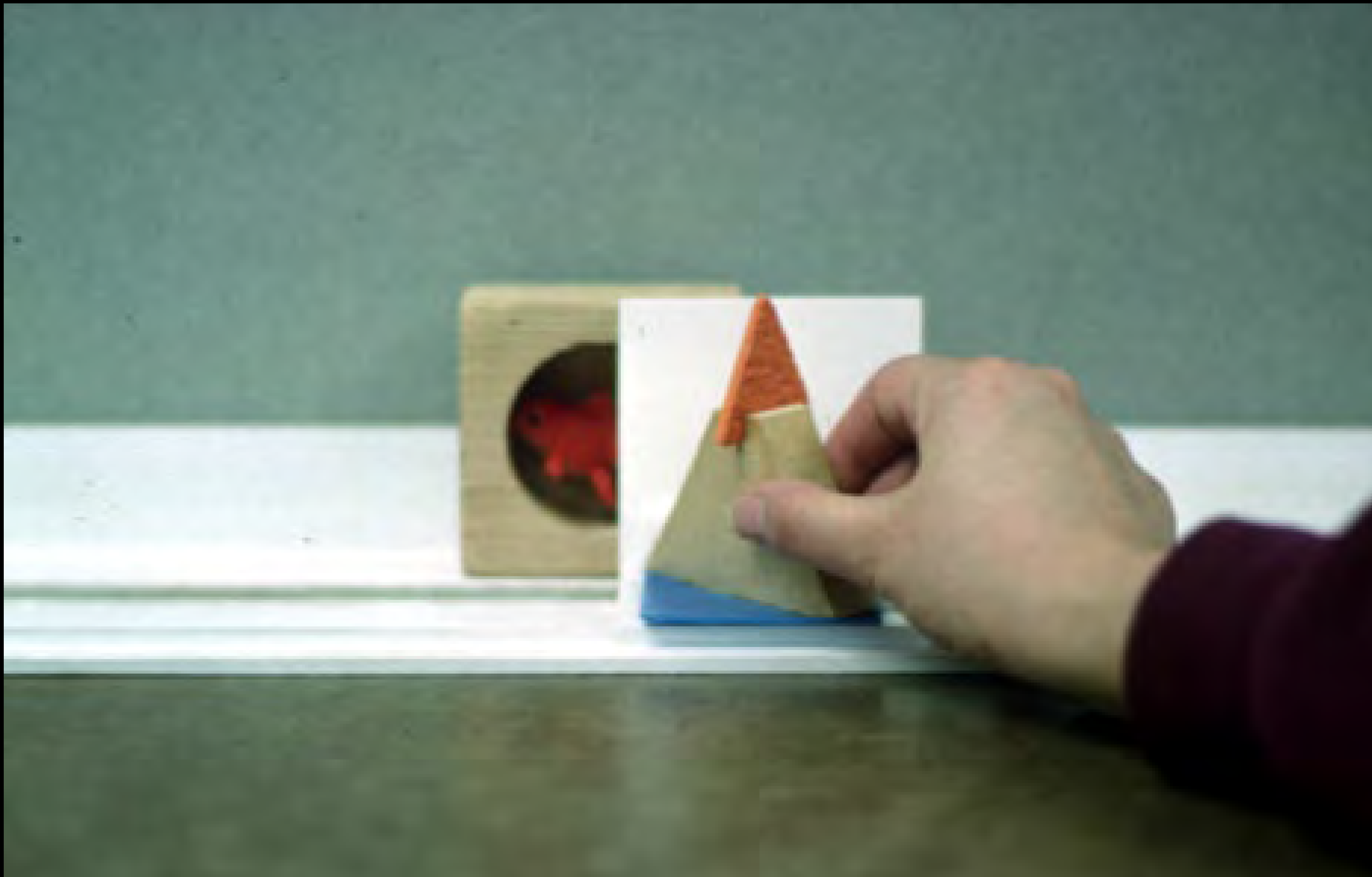
Behind Condition

Reward seen immediately when stimulus is moved, but stimulus and reward clearly share no physical connection.



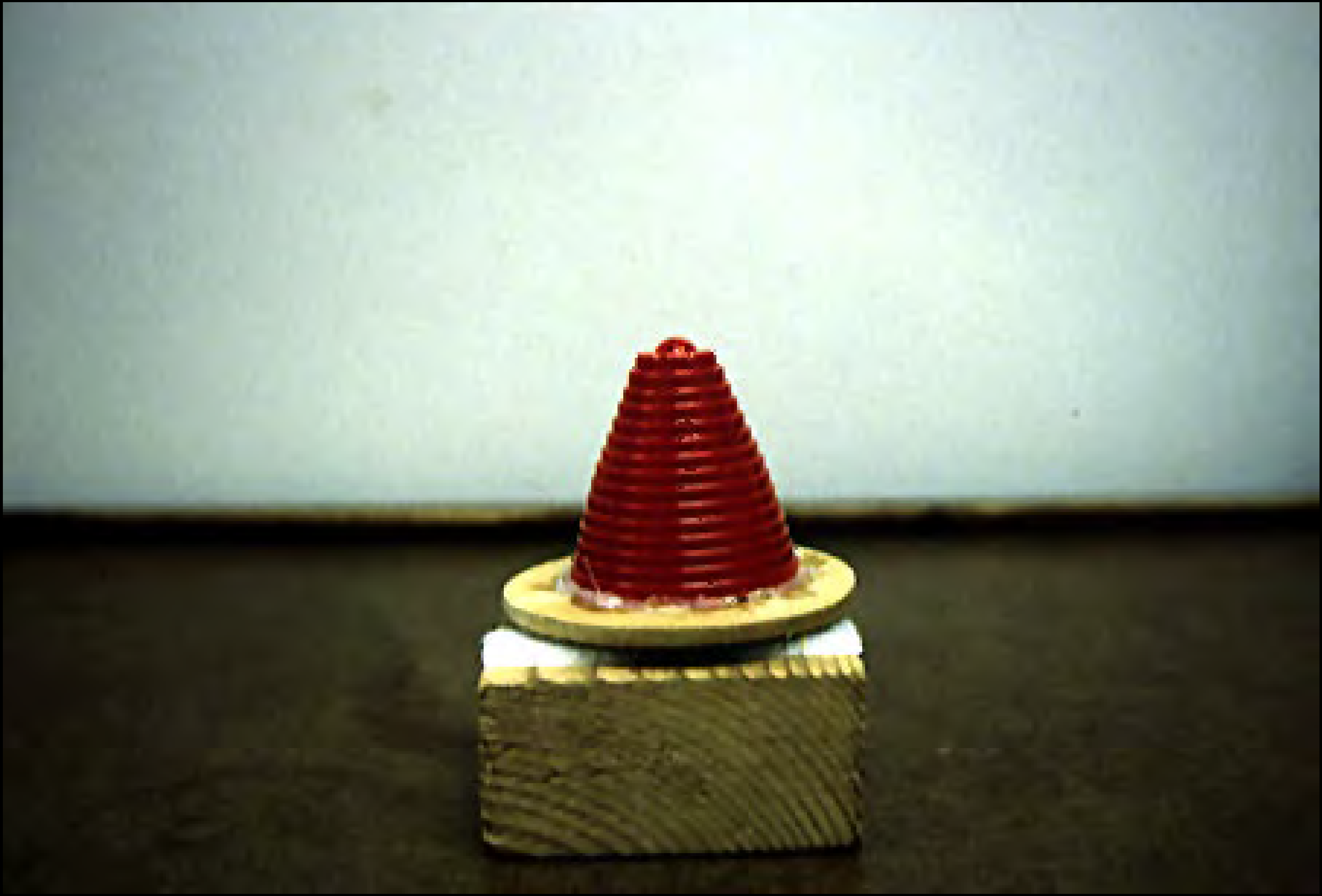




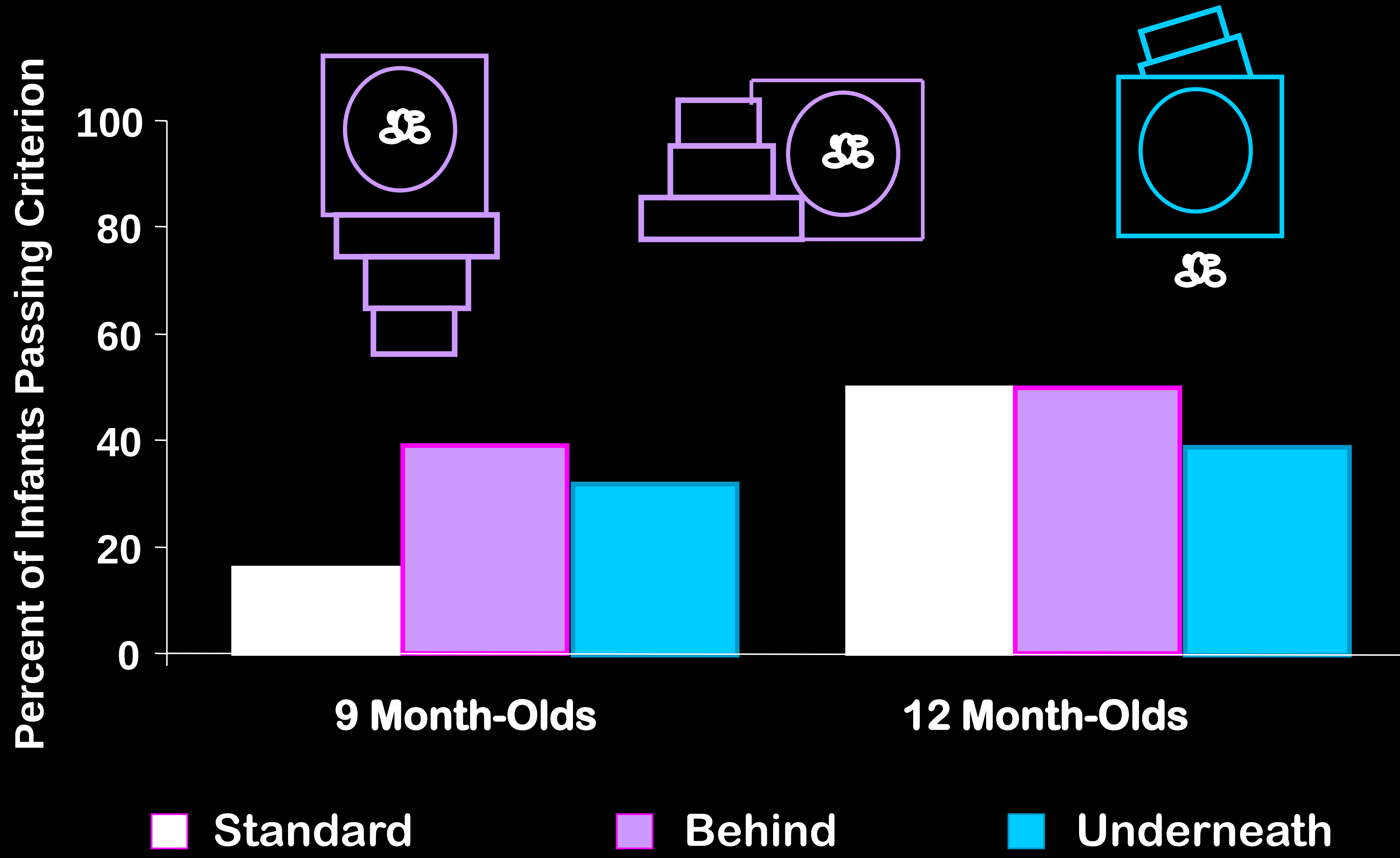


Underneath Condition

Reward seen immediately when stimulus is moved, but stimulus and reward clearly share no physical connection.



Percentage of Infants Passing Criterion at the 5-Sec Delay in the BEHIND & UNDERNEATH Conditions of DNMS



Grasping that One Thing is Related to Another: Contributions of Spatial Contiguity, Temporal Proximity, and Physical Connection

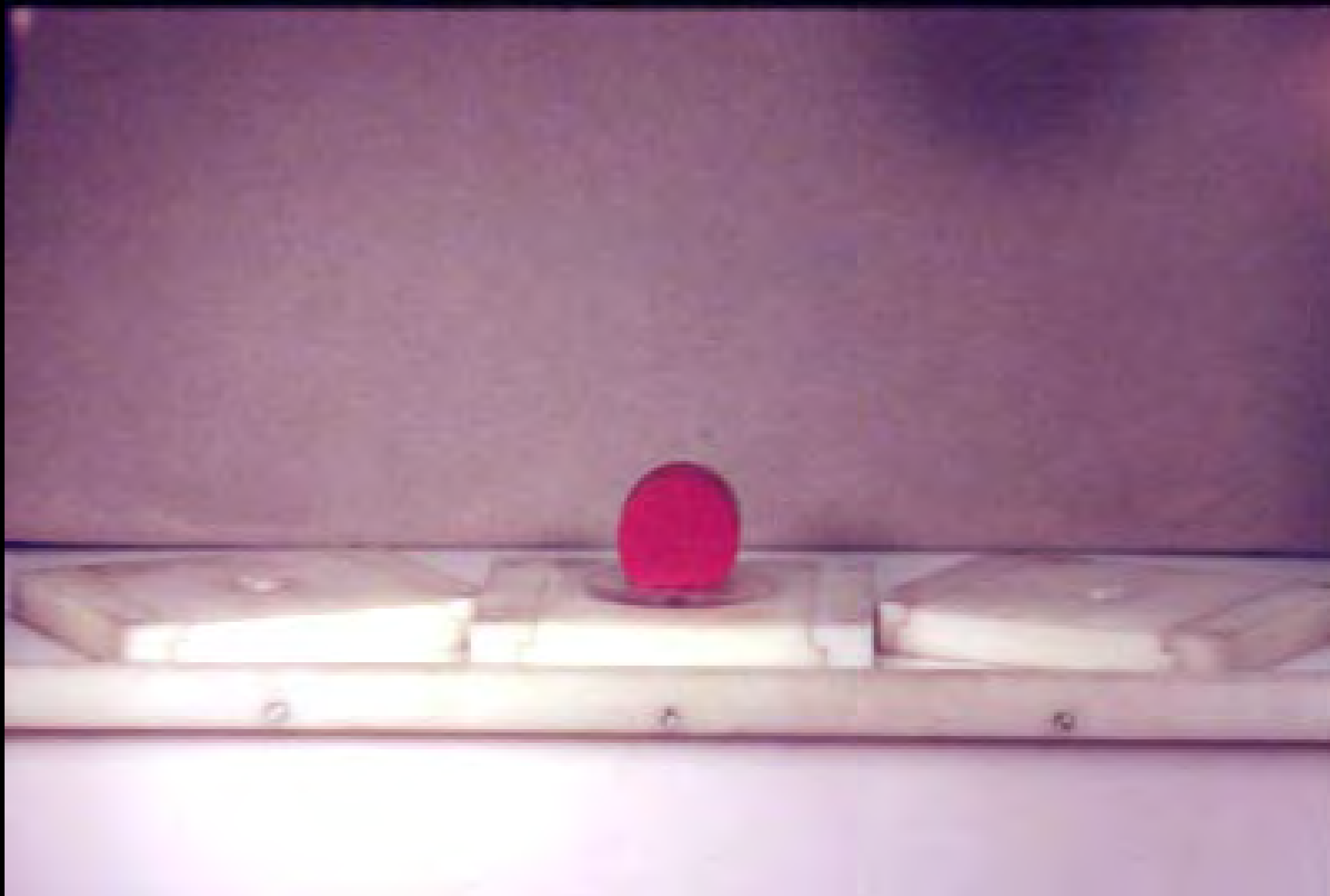
Kristin Shutts, Erin Ross, Michael Hayden, & Adele Diamond

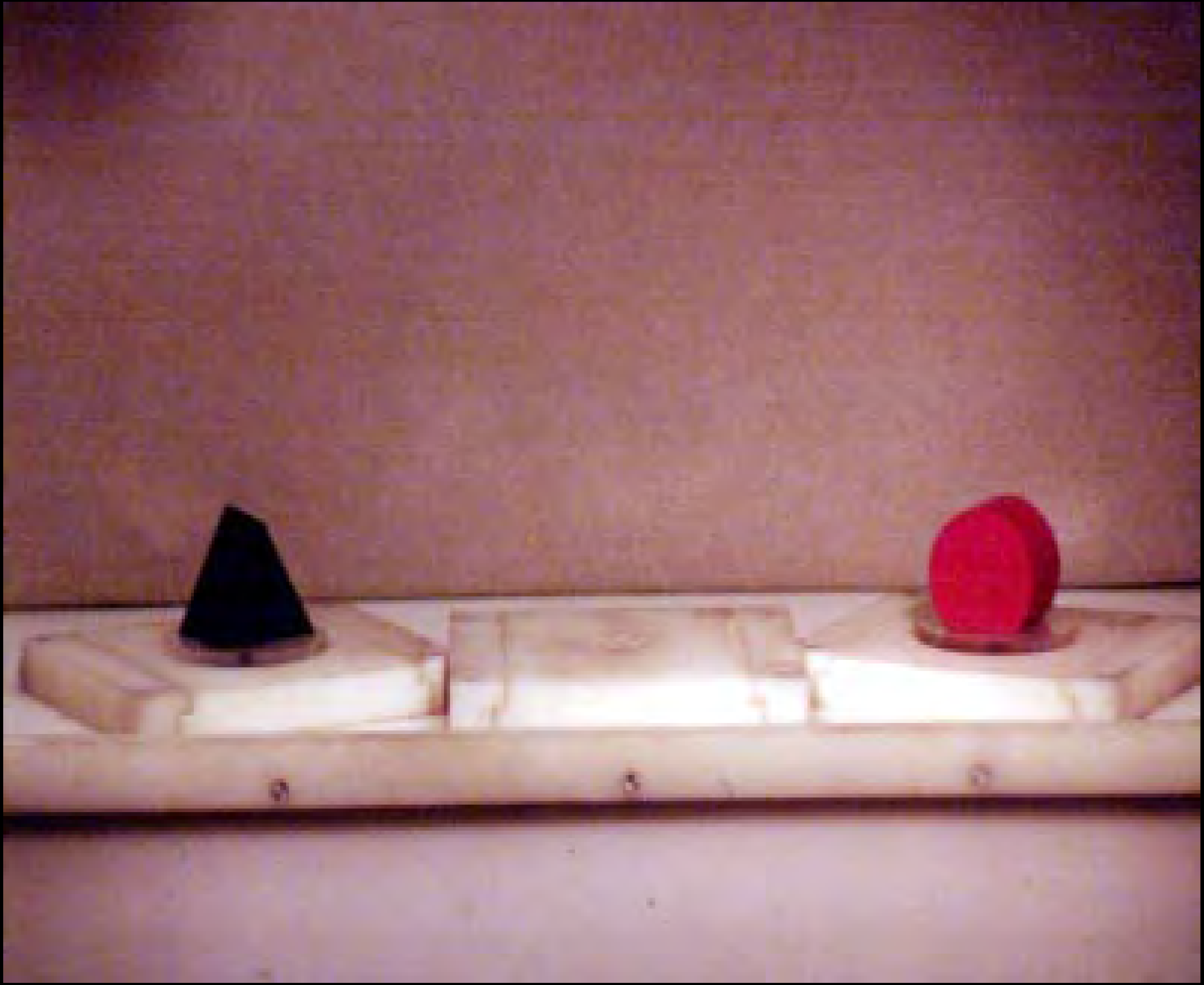
2001

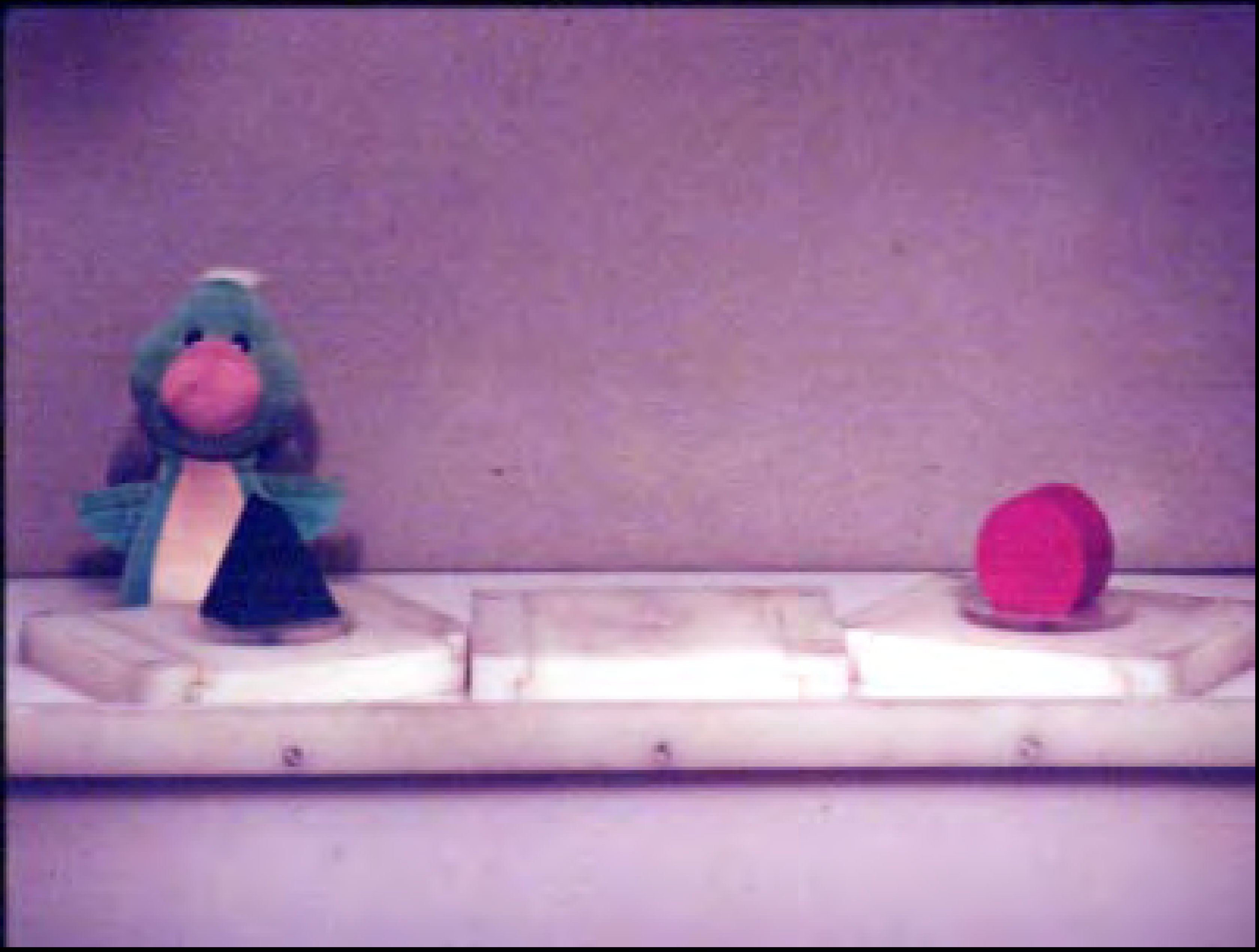
Presented at the Society for Research in Child Development Biennial Meeting

Jack-in-the-Box Condition:

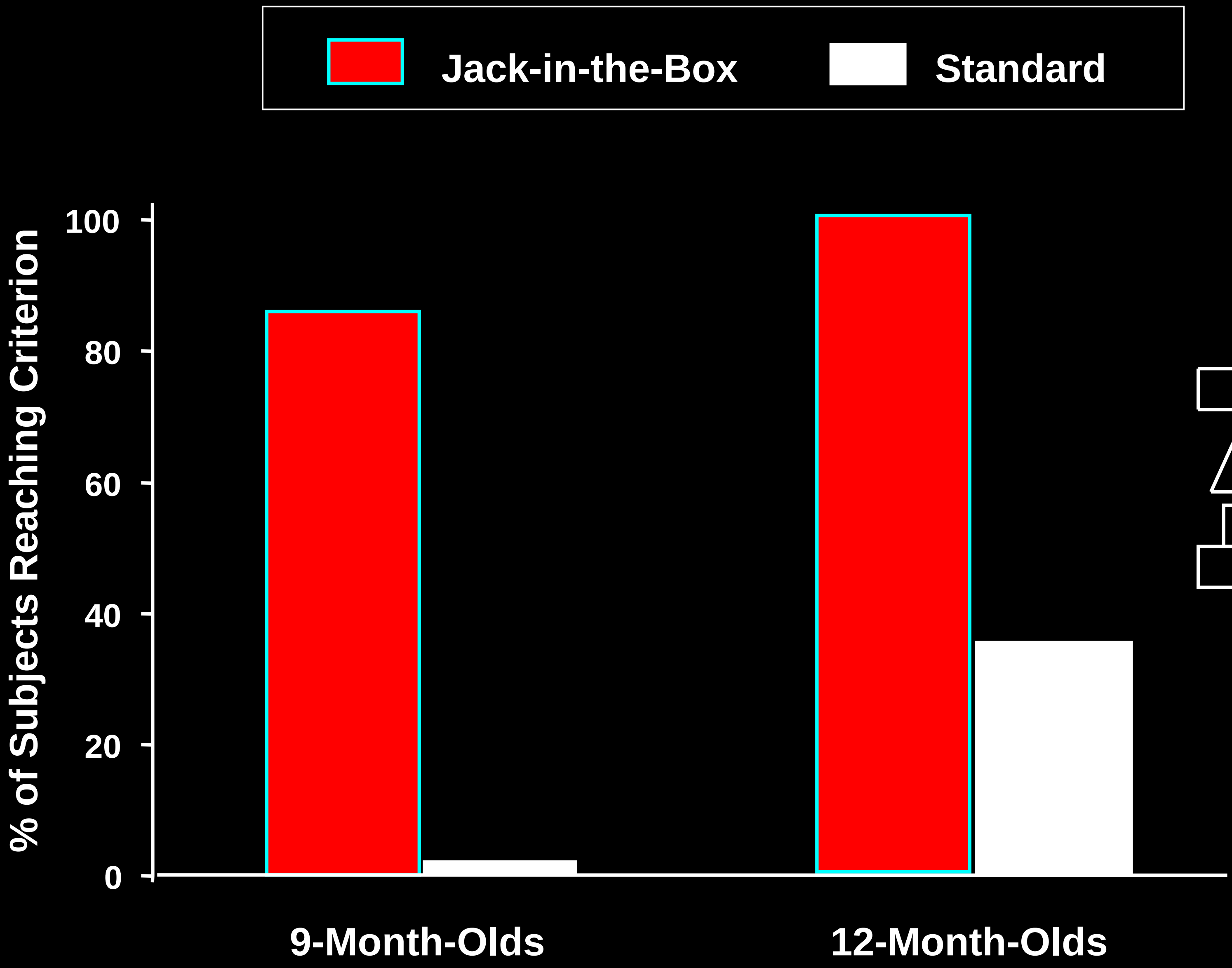
The reward is temporally close to the stimulus, but not spatially close.

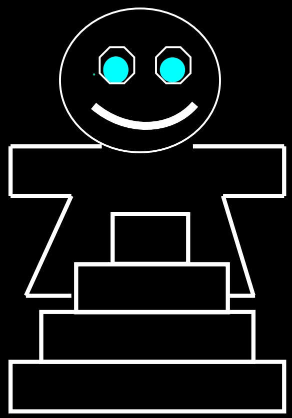






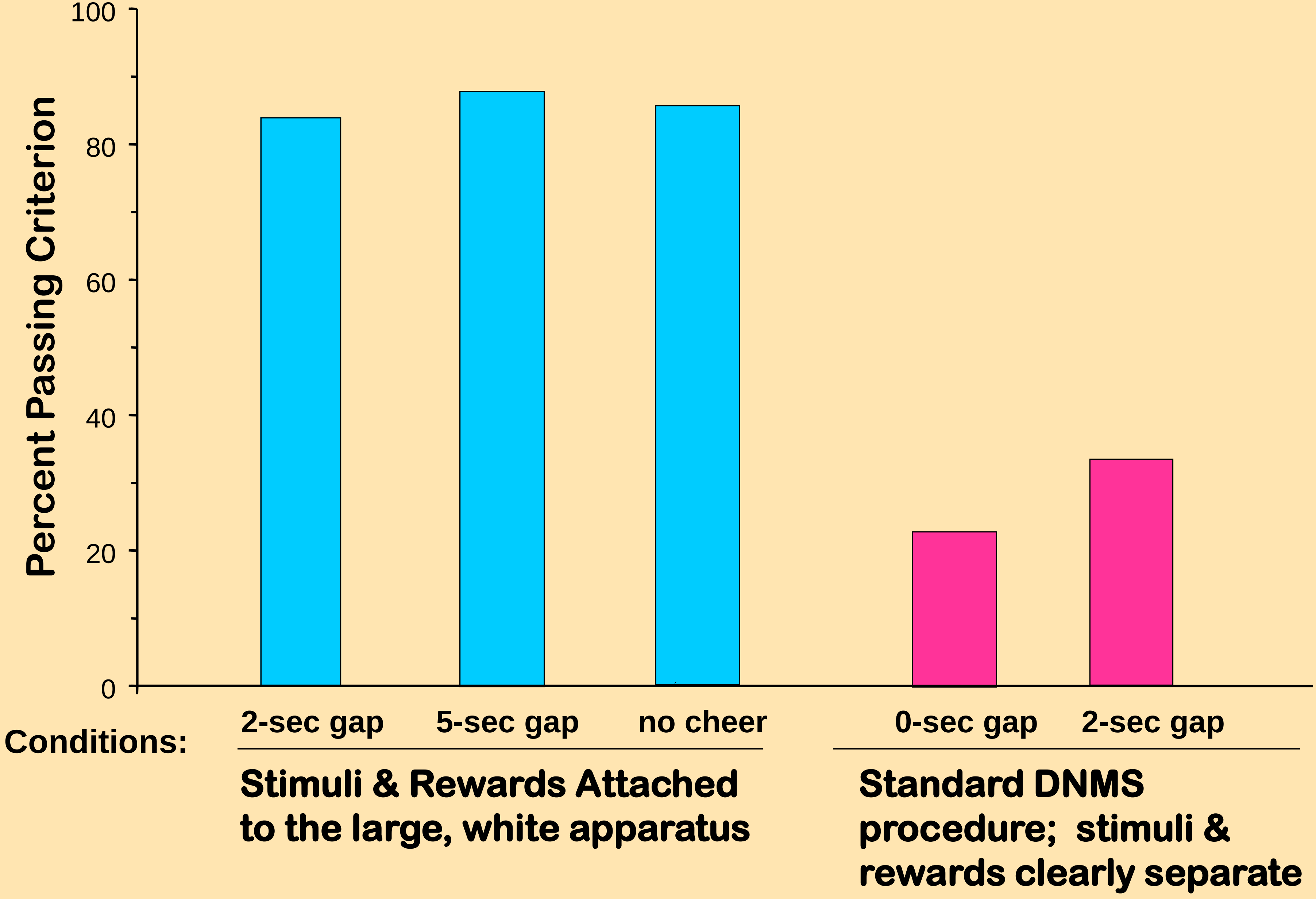
Performance of 9- and 12-Month-Old Infants in the JACK-IN-THE-BOX and STANDARD Conditions

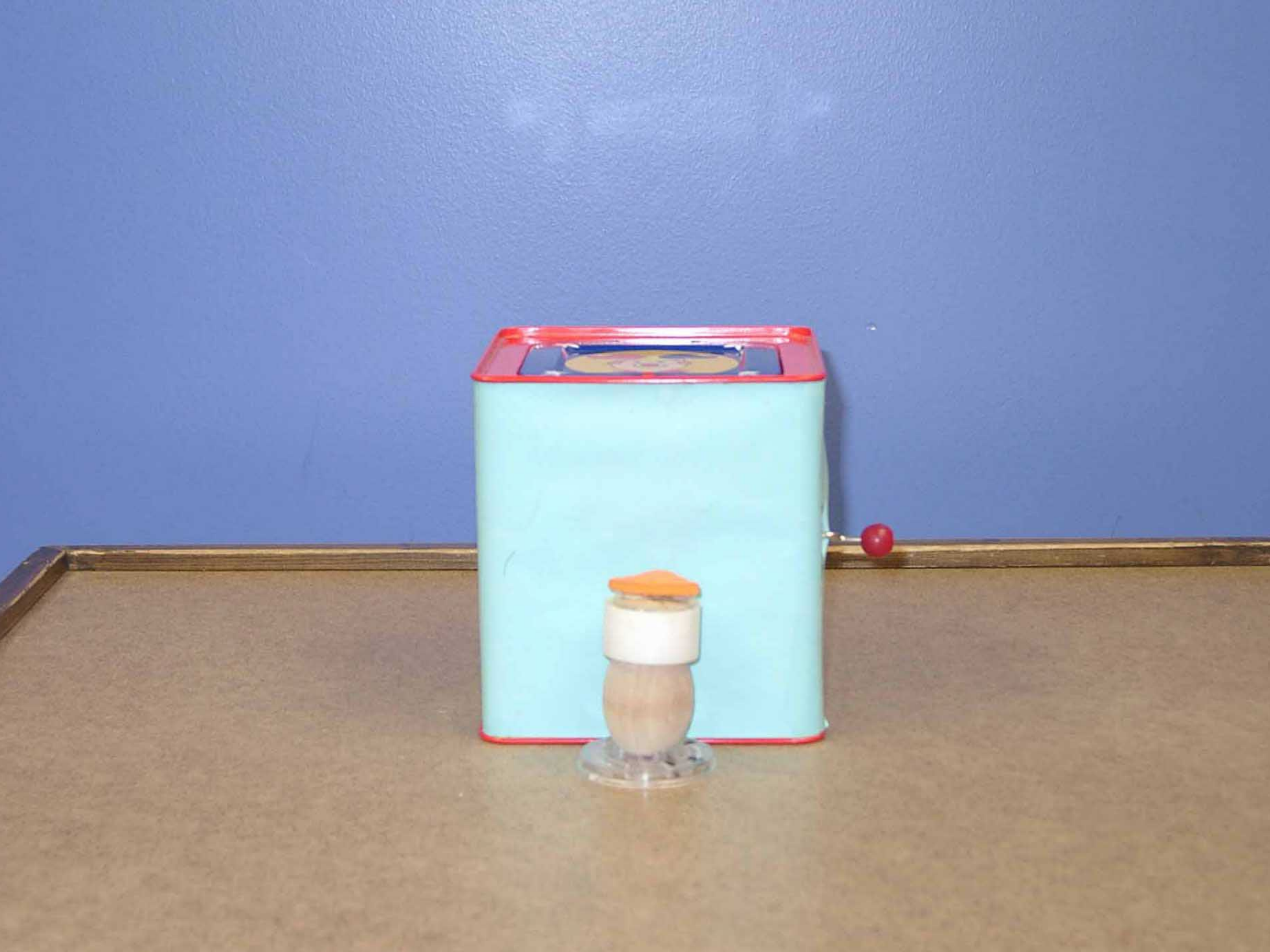


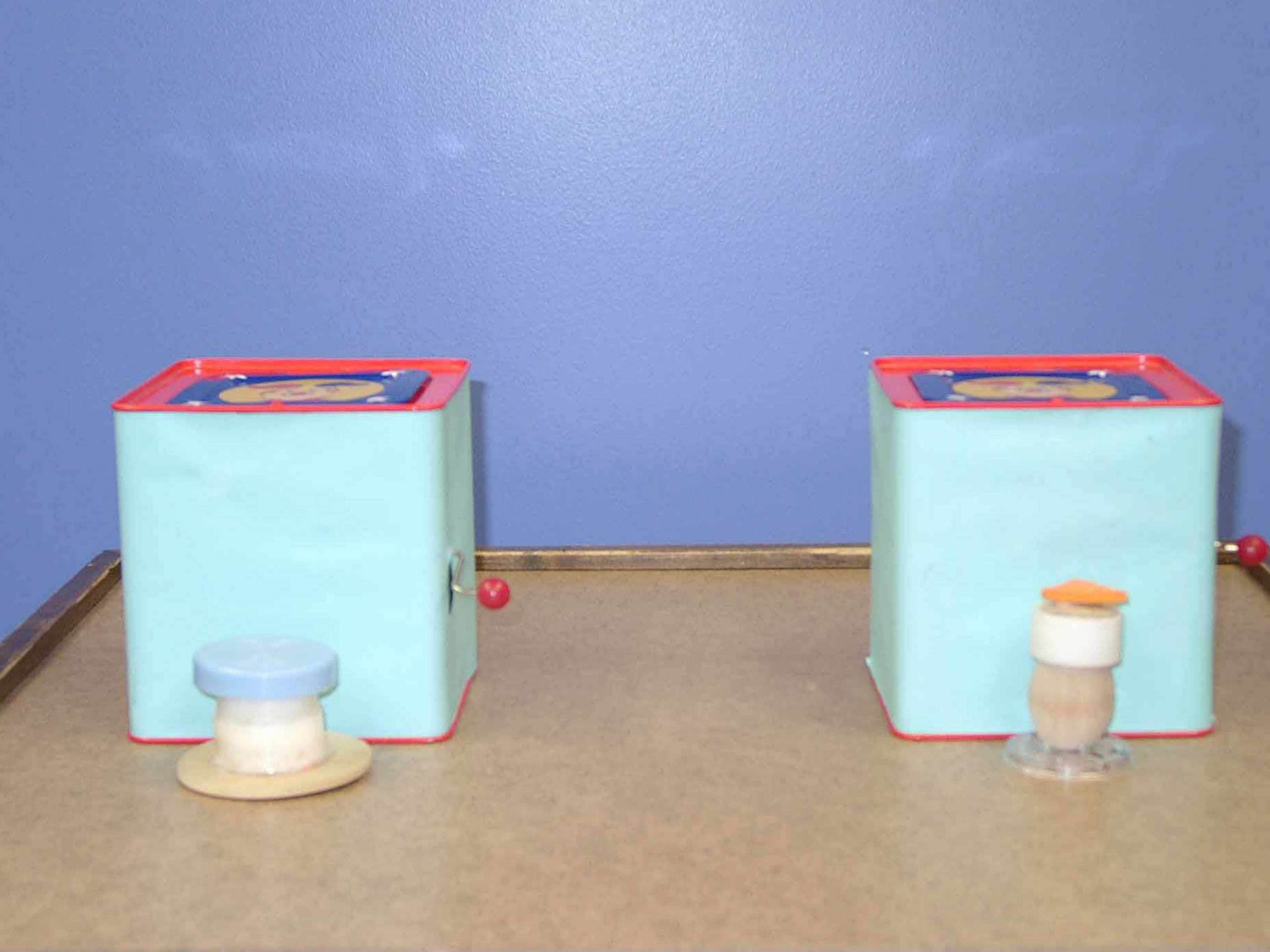


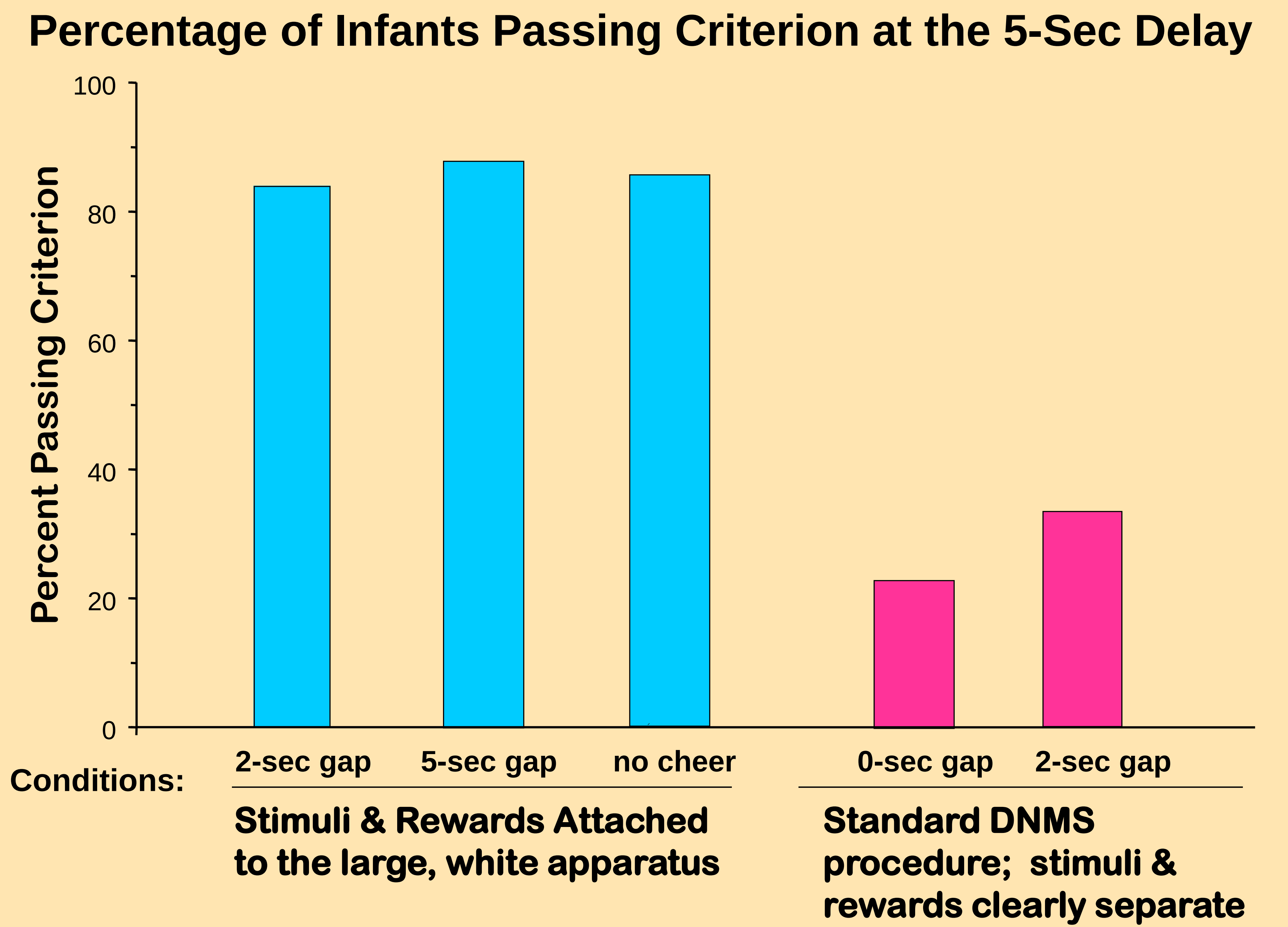
When infants displace the stimulus and the puppet pops up, the stimulus may appear to act as a lever causing the puppet to pop up. Perhaps infants perceive the stimulus and reward as physically connected even though they are not spatially close.

Percentage of Infants Passing Criterion at the 5-Sec Delay








Percentage of Infants Passing Criterion at the 5-Sec Delay
Percent Passing Criterion
100
80
60
40
20
0
Conditions:
2-sec gap
5-sec gap
no cheer
0-sec gap
2-sec gap
Stimuli & Rewards Attached to the large, white apparatus
Standard DNMS procedure; stimuli & rewards clearly separate

It turns out that it does NOT matter whether the 2 objects are physically close or not,

OR how soon the reward is received (or appears) after the infant acts on the stimulus.

Even if the stimulus is directly in front of the reward or directly on top of it, and the reward pops up the instant the infant *grasps* the stimulus, infants don't *get* it.

PHYSICAL CONNECTION, even if indirect, appears to be key.

Even if stimulus & reward are some DISTANCE from one another,
with no direct connection to one another,
and the reward doesn't appear until 5 seconds AFTER acting on the stimulus,

AS LONG AS both are connected to the same single piece of apparatus, infants succeed.

In the absence of physical connection, even close spatial AND temporal proximity are insufficient.

In the presence of physical connection, neither close spatial nor close temporal proximity is needed.

Early Success on the Delayed Nonmatching to Sample task when Stimulus and Reward appear to be part of a Single Apparatus but Not when they are clearly Two Separate Objects.

Adele Diamond, A., Eun Young Lee, Michael Hayden
(*submitted*)

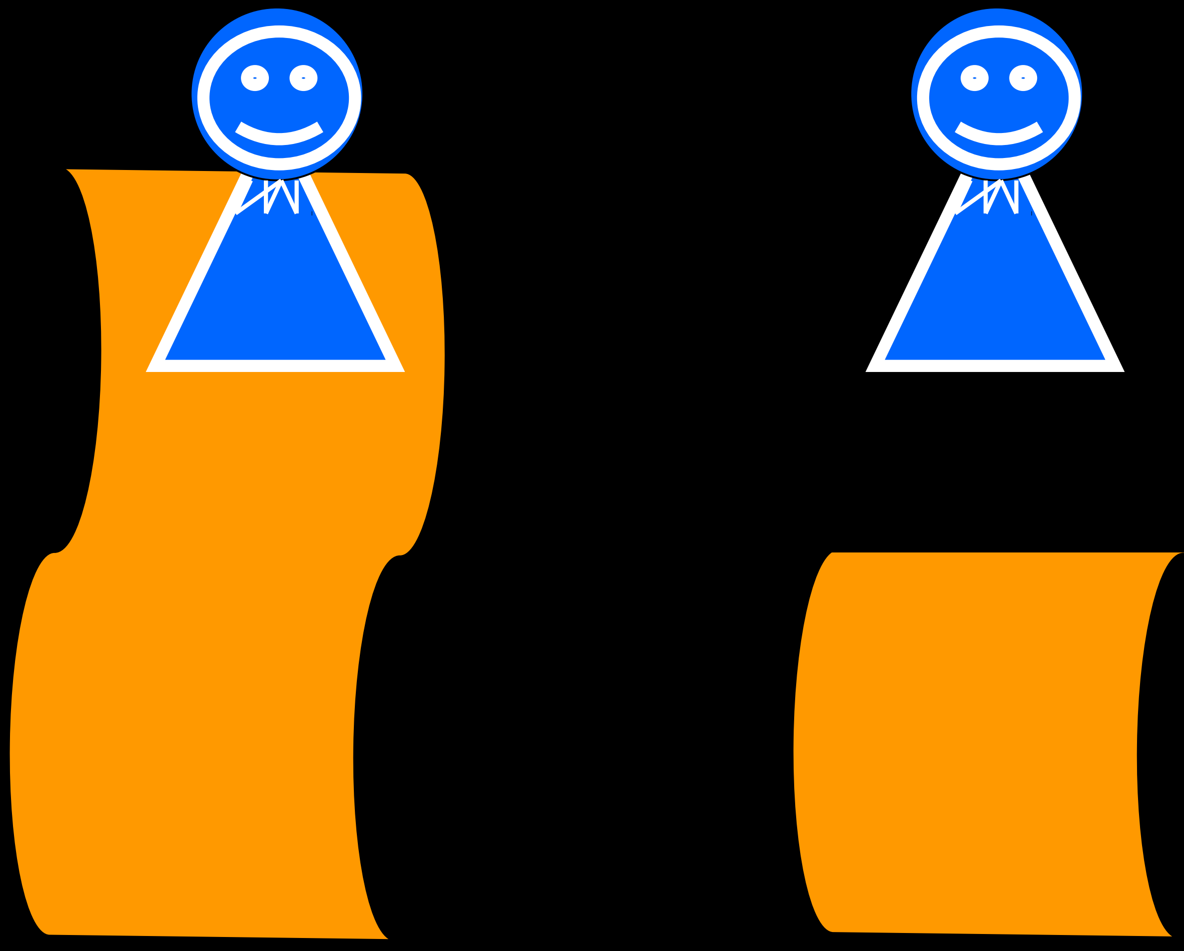
Andrea Aguiar &

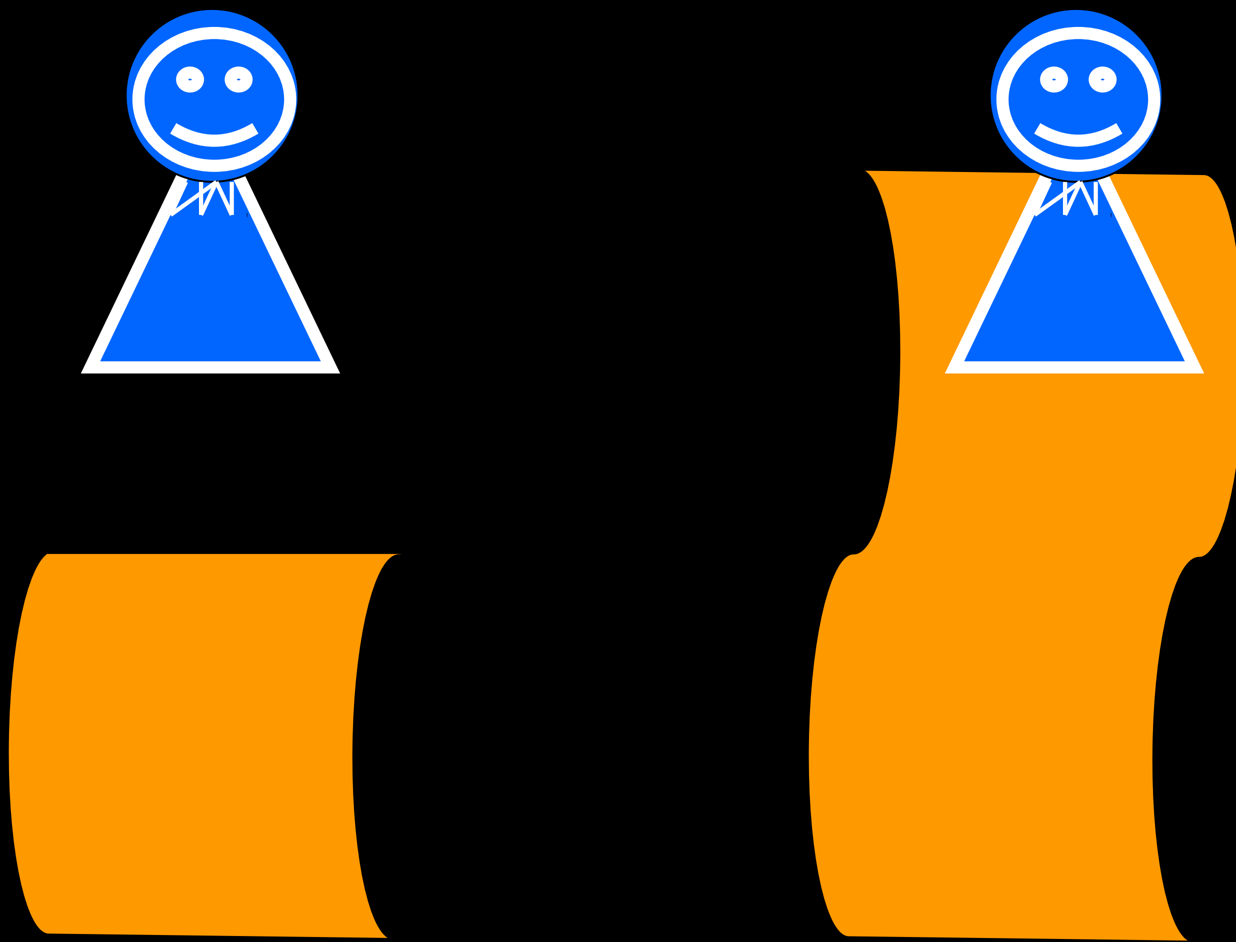
Renee Baillargeon

(2000)

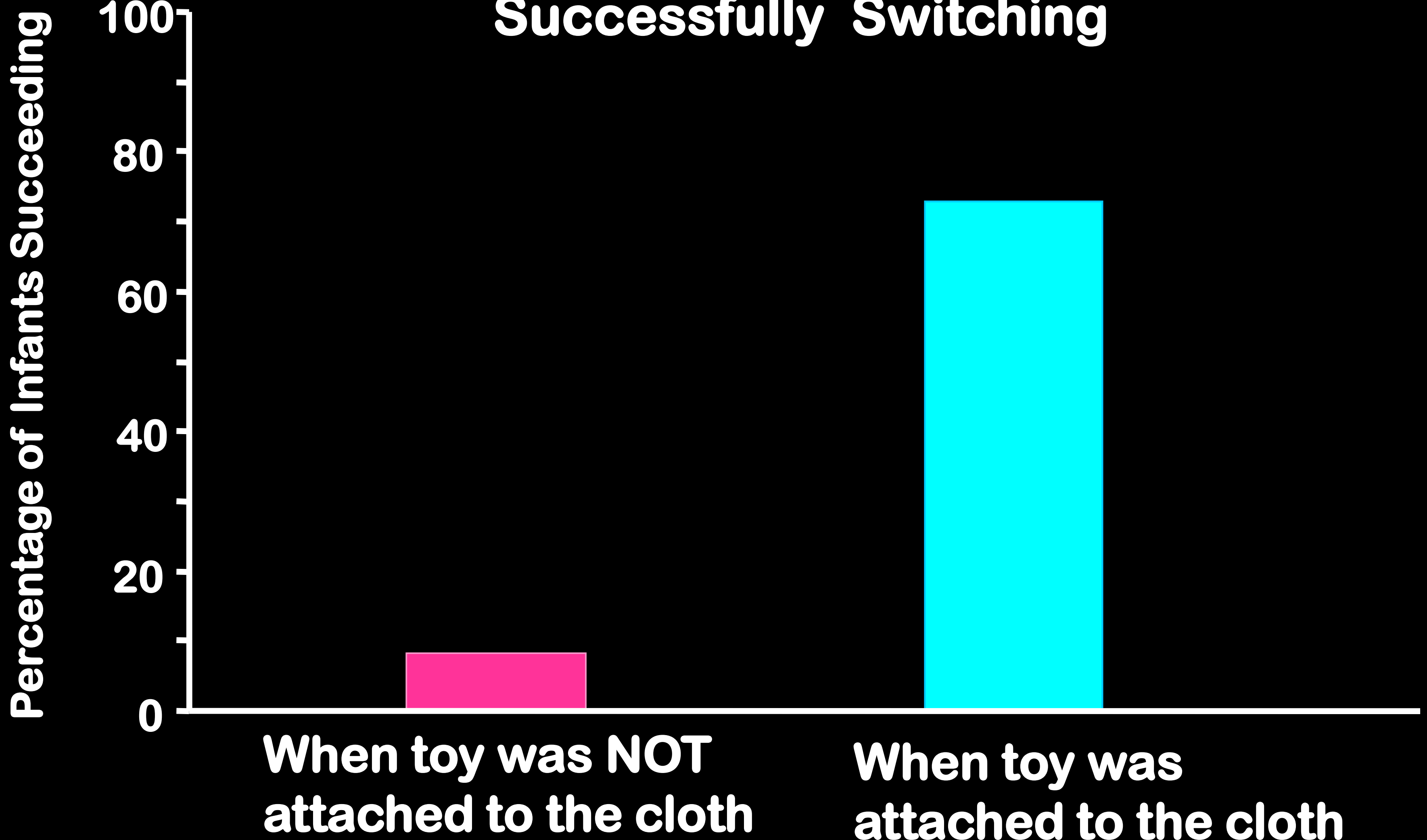
Perseveration and Problem Solving in Infancy

In H.W. Reese (Ed). ***Advances in child development and behavior, Vol. 27*****. (pp. 135-180). San Diego: Academic Press**





Percentage of 9-month-olds Successfully Switching



In BOTH instances the toy sat on the cloth.

Murray Jarvik

(1953)

Discrimination of colored food and food signs by primates.

Journal of Comparative and Physiological Psychology

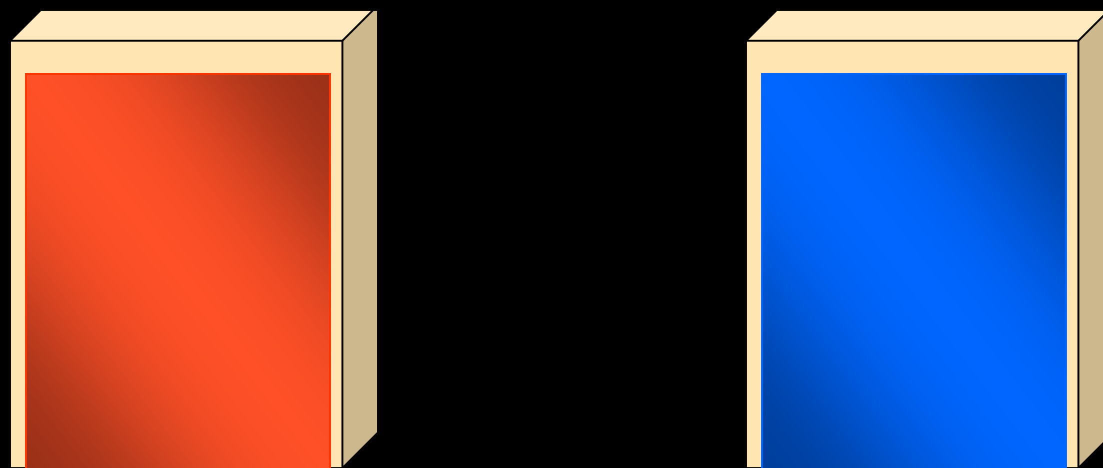
vol 46, pages 390-392

Jarvik -

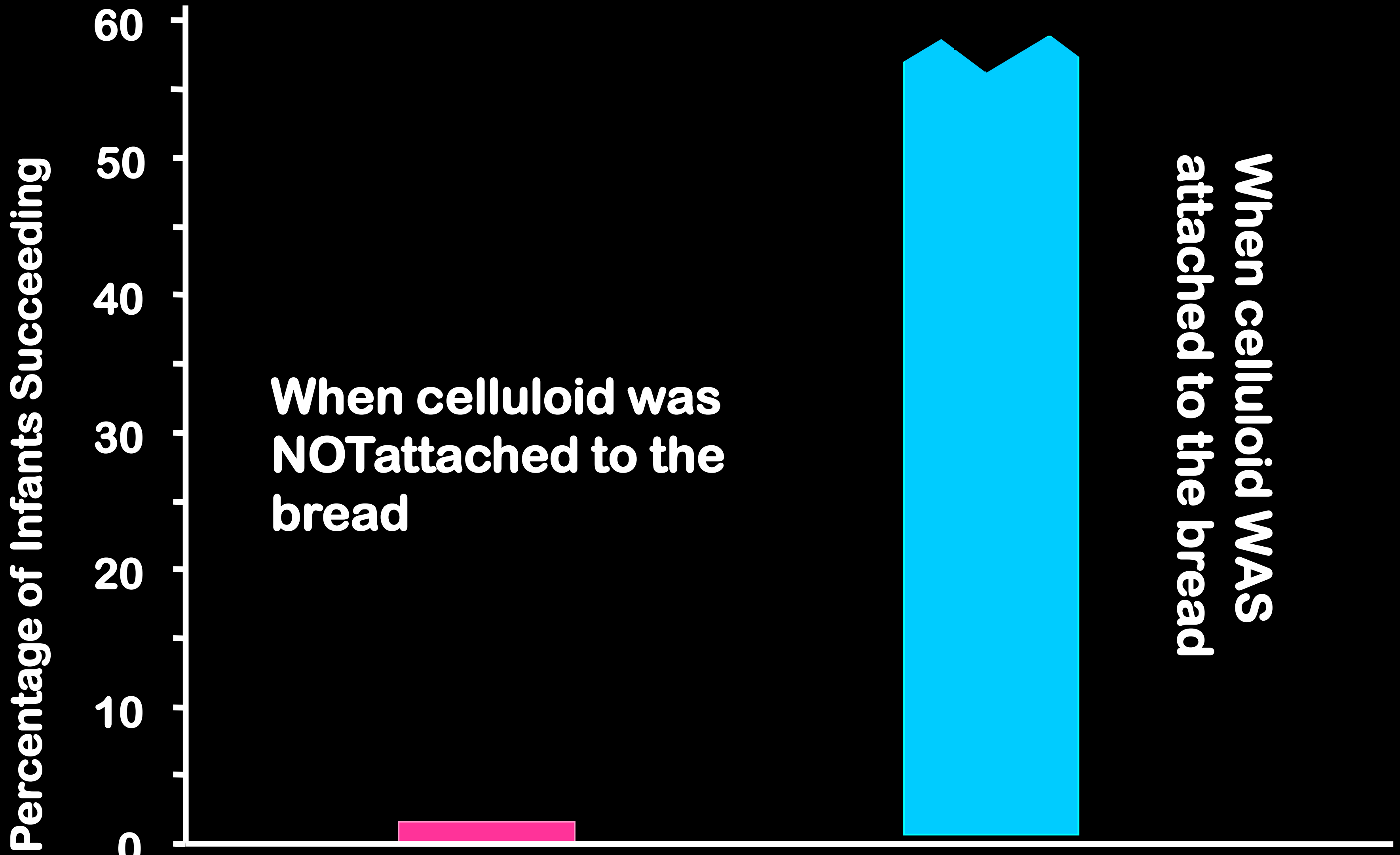
transcluent celluloid on top of bread reward

Condition 1: laid on top

Condition 2: pasted on top



Trials to Criterion on Color Discrimination

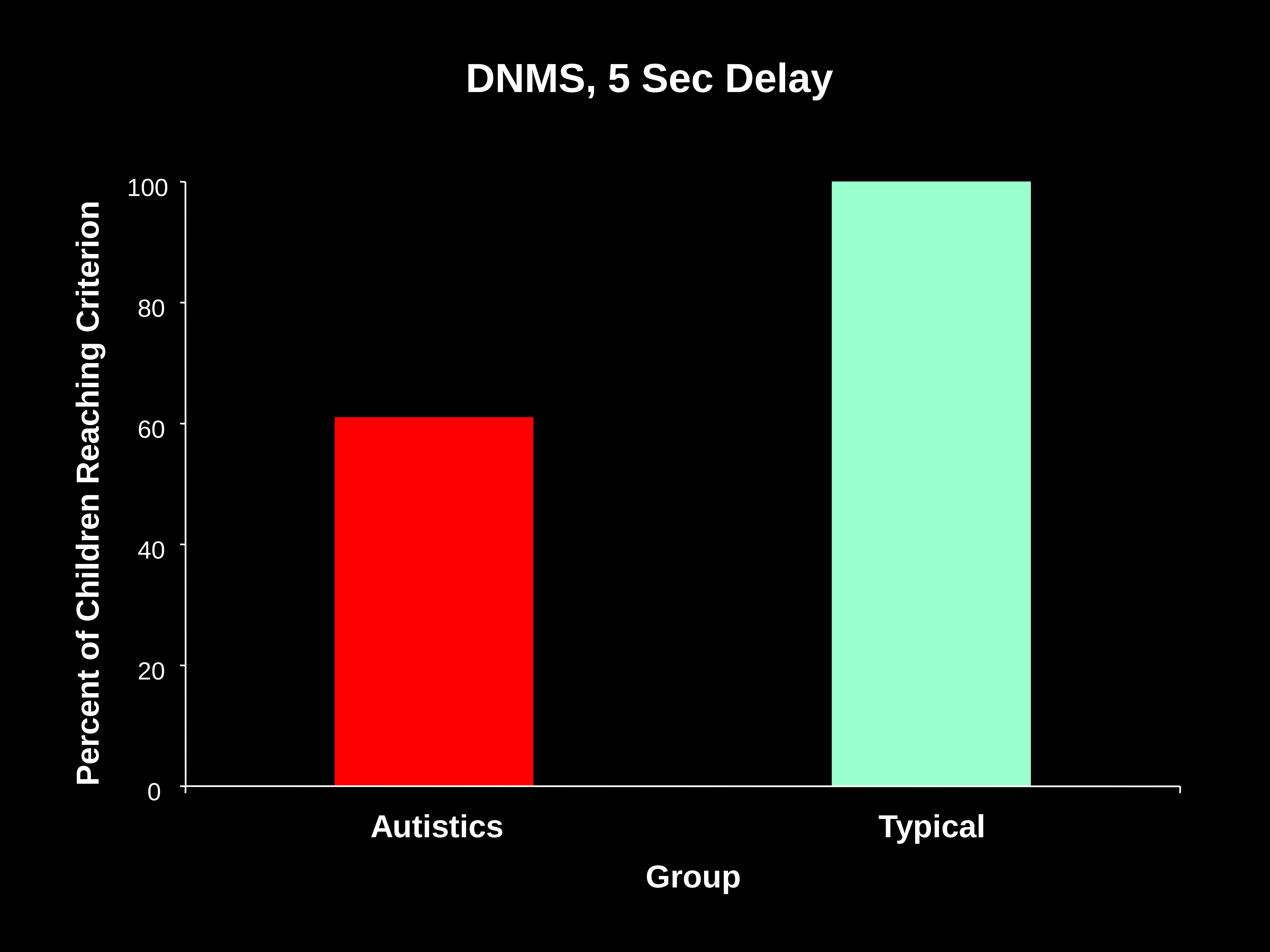


In BOTH instances the celluloid sat on top of the bread.

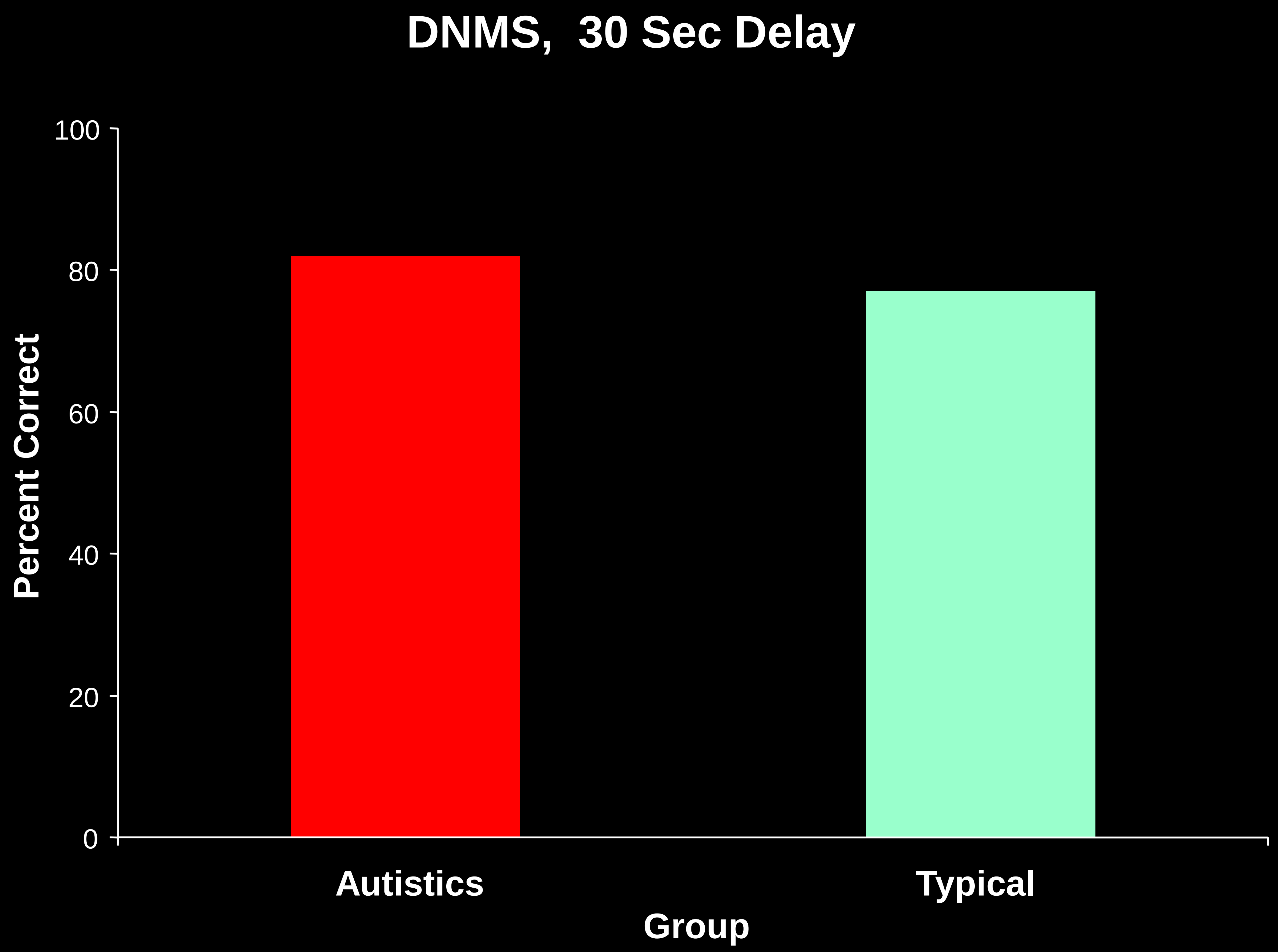
Children with autism fail the DNMS task under the same conditions as do 9-12 month old infants.

Perhaps they are failing for the same reasons.

If so, then they should succeed in the Velcro condition and in the single apparatus Jack-in-the-Box condition.



DNMS, 5 Sec Delay
Percent of Children Reaching Criterion
100
80
60
40
20
0
Autistics
Typical
Group


DNMS, 30 Sec Delay
100
80
60
40
20
0
Percent Correct
Autistics
Typical
Group