Executive Functioning and Pediatric Neuropsychology

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What abilities and skills will people need to be successful in the 21st century?

1) Self-control

to resist temptations and not act impulsively

- thinking before you speak or act
  so you don't do something you'd regret or put your foot in your mouth
- to wait before making up your mind; not jumping to a conclusion or to an interpretation of what something meant or why it was done
- resist blurting out what first comes to mind
- resist 'tit for tat' (hurting someone because that person hurt you)

2) Discipline & Perseverance

Having the discipline to stay on task and complete it

- resisting the temptation to quit because you're frustrated, bored, or more fun things are calling
- continuing to work even though the reward may be a long time in coming (delaying gratification)

Evidence shows that discipline accounts for over twice as much variation in final grades as does IQ, even in college.

(Duckworth & Seligman, 2005)

3) Attentional Control

- Being able to concentrate,
- Pay attention, &
- Stay focused

even when the material is boring

4) Creativity in seeing connections between seemingly unconnected ideas or facts.

Playing with information and ideas in your mind, relating one to another, then dis-assembling those combinations and re-combining the elements in new ways.

Working memory involves holding information in mind and working with it.

5) Creativity in seeing familiar things in new ways / from different perspectives

If one way of solving a problem isn't working, can we conceive of the problem in a different way?

Can we think outside the box to come up with a different way of attacking the problem?

6) Flexibility

- Having the flexibility to take advantage of serendipity
- …to navigate around unforeseen obstacles, and
- …to admit you were wrong when you get more information

An example of poor cognitive flexibility:

When one door closes, another door opens;
but we often look so long and so regretfully upon the closed door, that we do not see the ones which open for us.

- Alexander Graham Bell

“Executive Functions”

is shorthand for

all of the abilities

I just mentioned.

The 3 core Executive Functions are:

- **Inhibitory Control**
  (which includes self-control, discipline, & attentional control)
- **Working Memory** (holding info in mind & MANIPULATING it; essential for reasoning)
- **Cognitive Flexibility** (including creative problem-solving & flexibility)

Higher-order Executive Functions are:

- Problem-solving
- Reasoning
- Planning

Inhibition can be critical in helping students to wait before speaking or acting

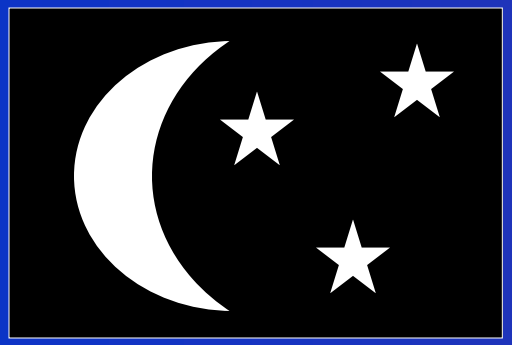
so that they think before they act instead of impulsively reacting, and

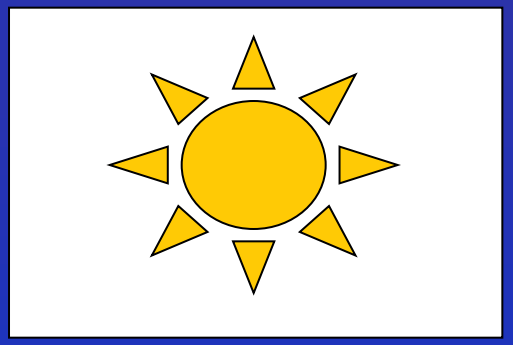
so that they resist the temptation to answer quickly, instead taking the time they need.

THE DAY-NIGHT TASK

(Gerstadt , Hong, & Diamond, 1994)

Semantically conflicting labels

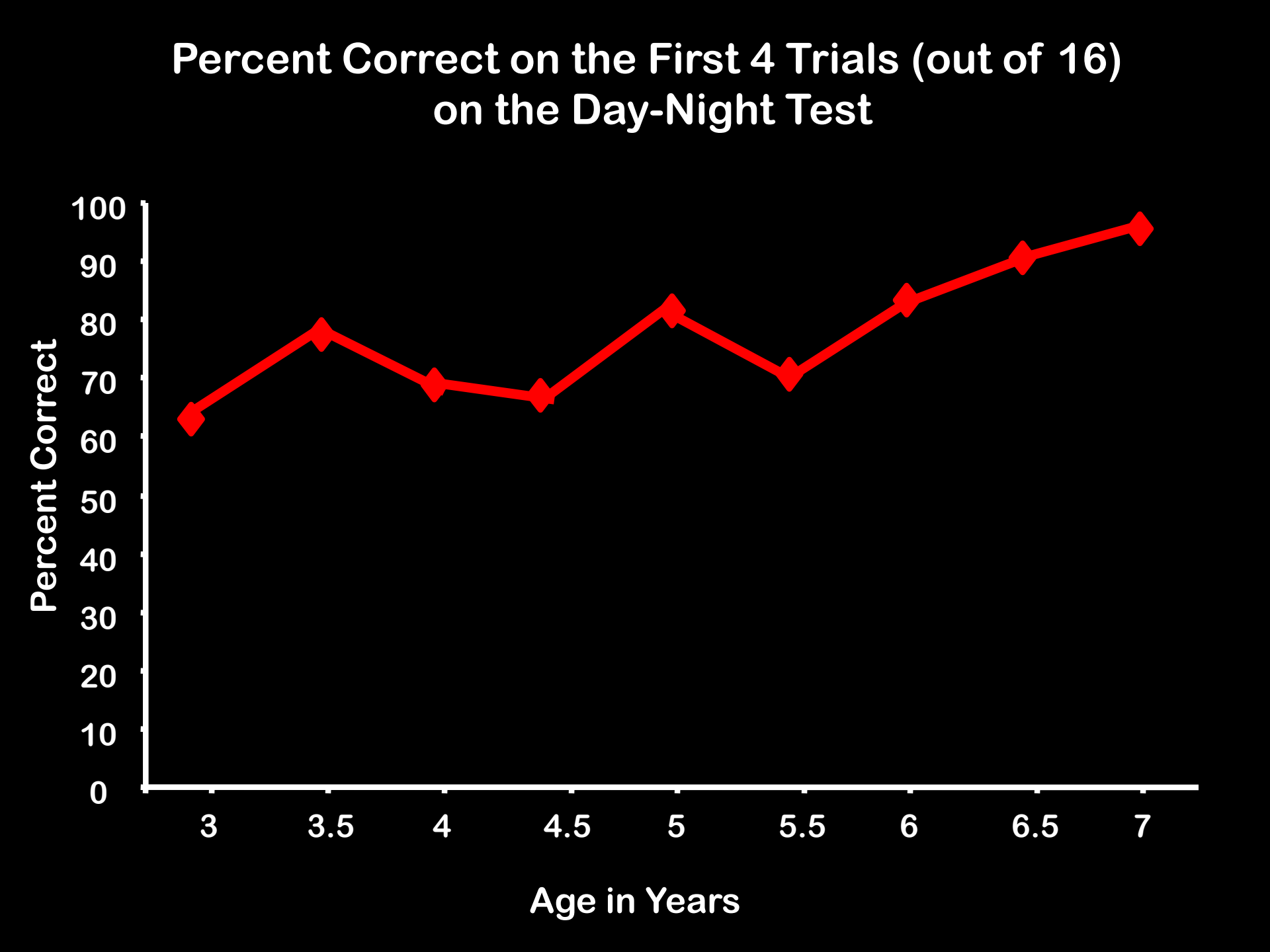


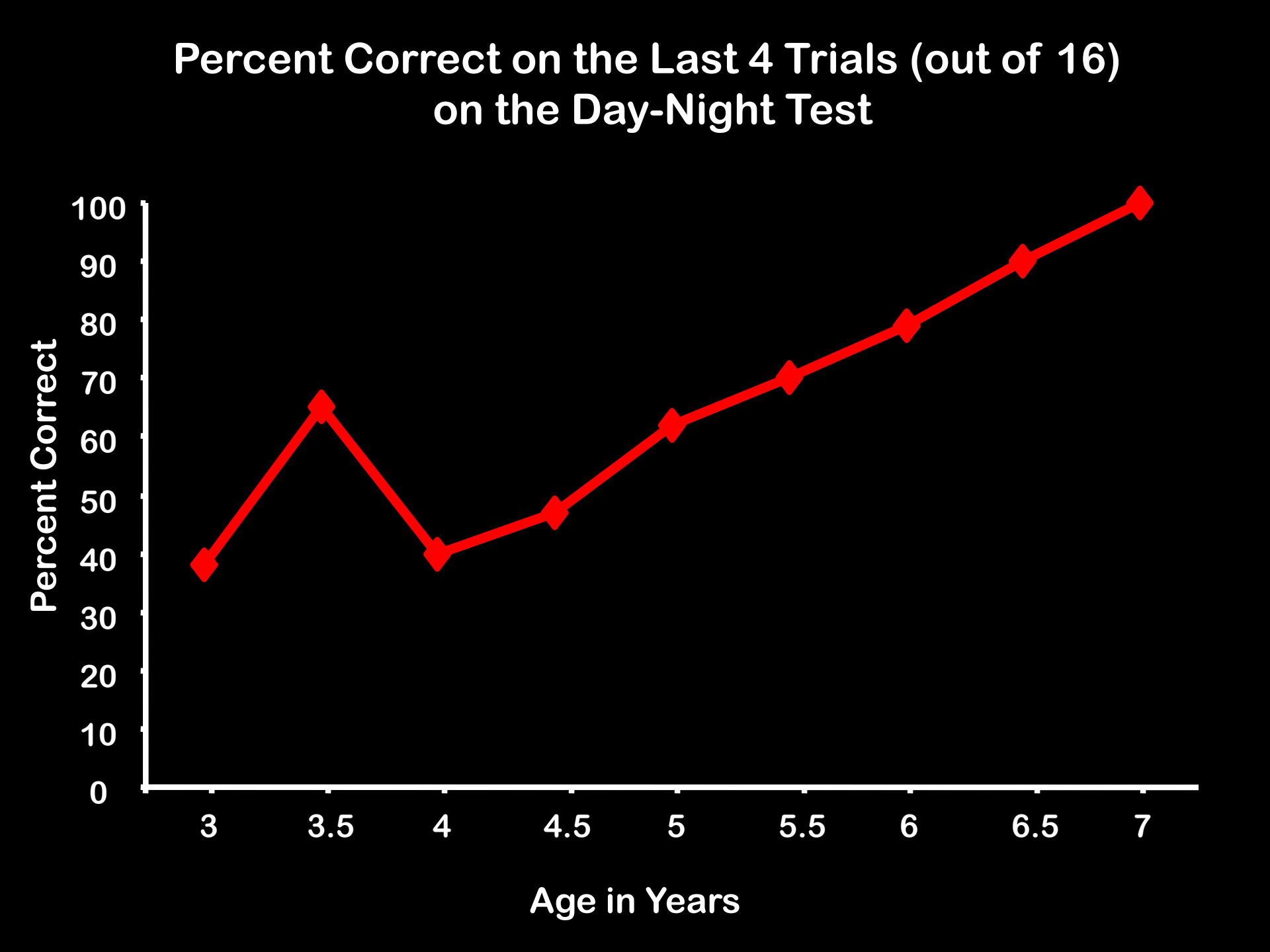


"Day"

"Night"

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


Percent Correct on the First 4 Trials (out of 16)
on the Day-Night Test
Percent Correct
100
90
80
70
60
50
40
30
20
10
0
3
3.5
4
4.5
5
5.5
6
6.5
7
Age in Years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100
90
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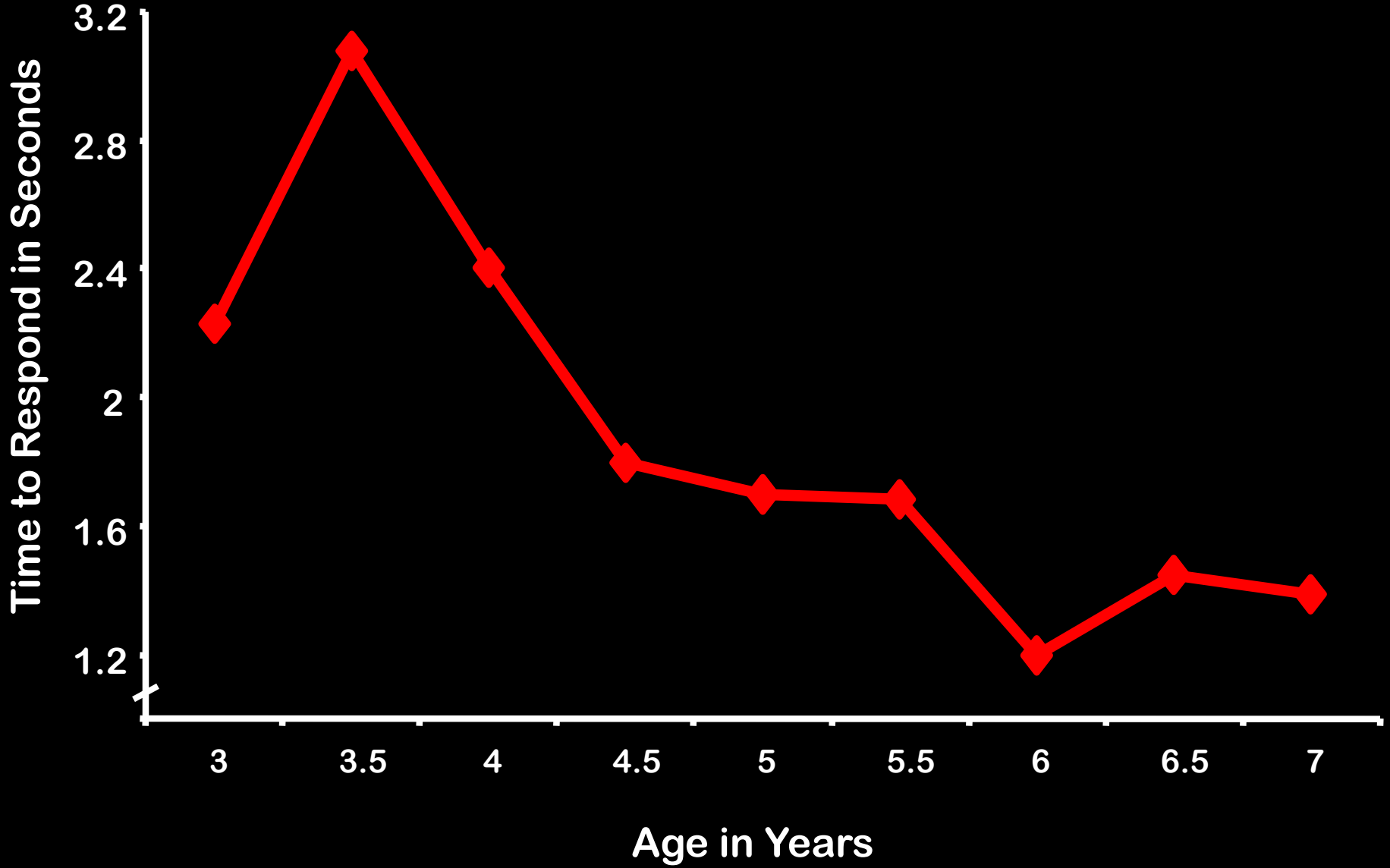
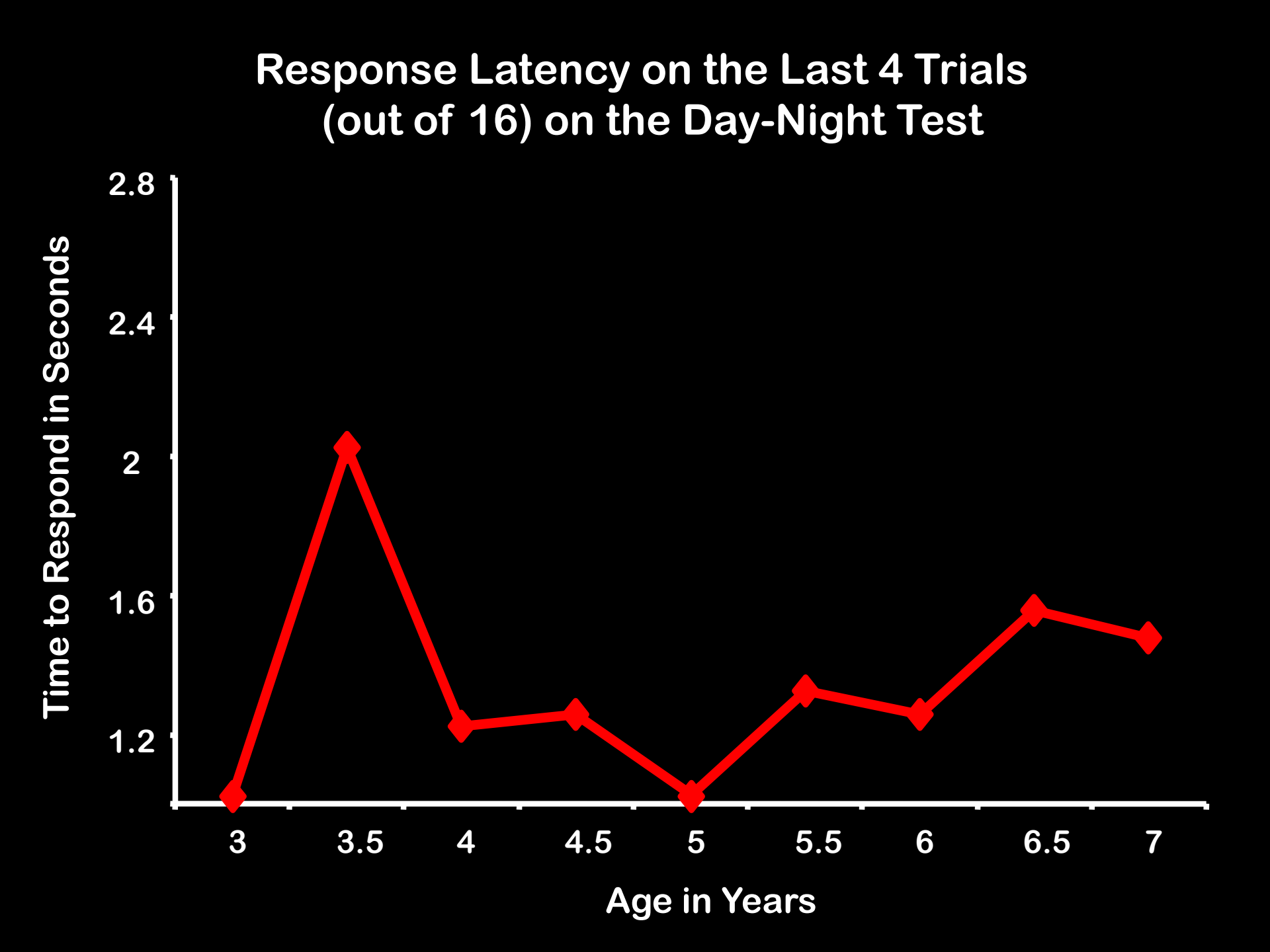
70
60
50
40
30
20
10
0
3
3.5
4
4.5
5
5.5
6
6.5
7
Age in Years

Response Latency on First 4 Trials (out of 16) on the Day-Night Test




Response Latency on the Last 4 Trials
(out of 16) on the Day-Night Test
Time to Respond in Seconds
2.8
2.4
2
1.6
1.2
3
3.5
4
4.5
5
5.5
6
6.5
7
Age in Years

DITTY

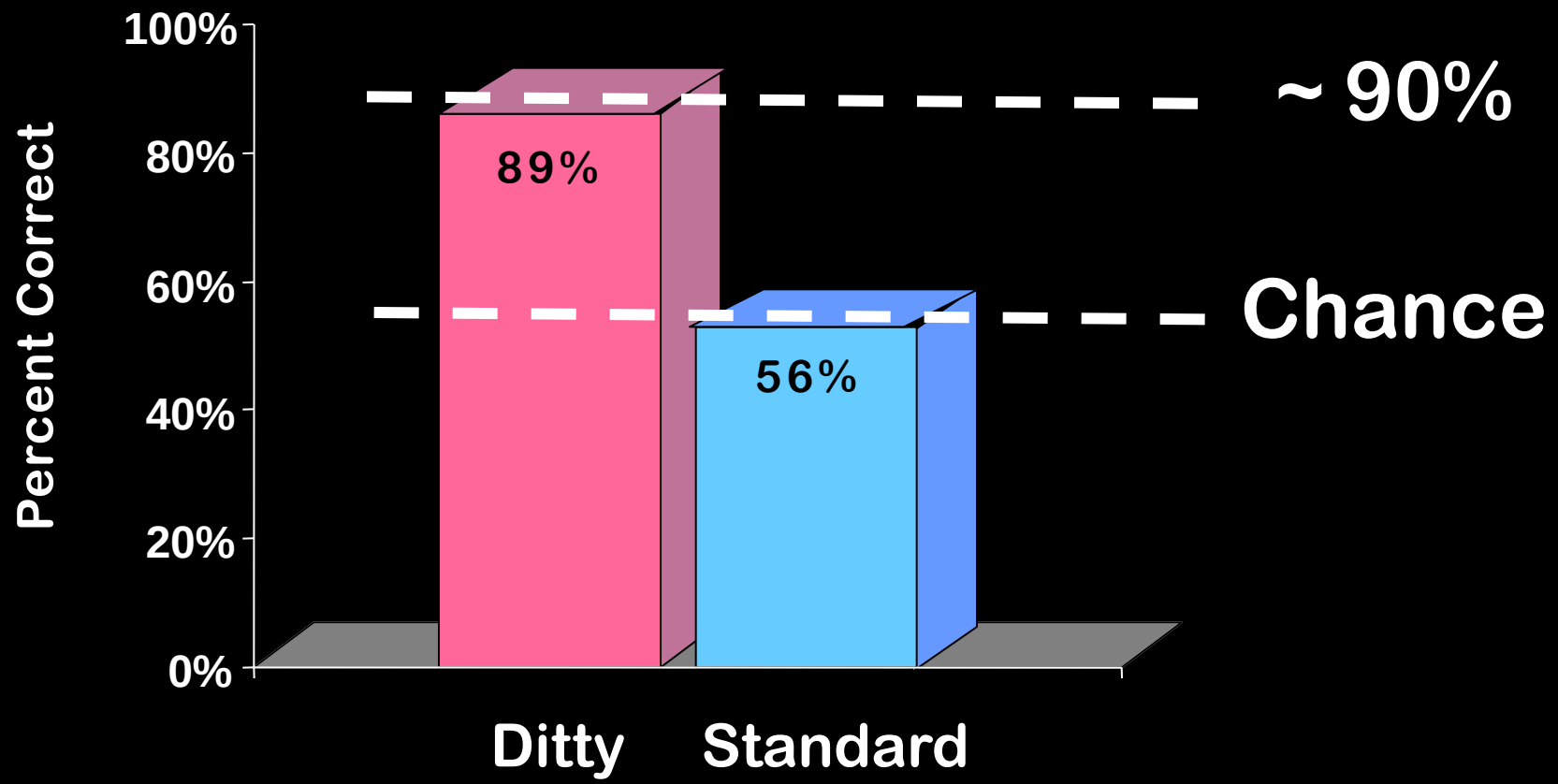
Experimenter sings a little ditty

♫ think about the answer, don't tell me ♫

before the child responds.

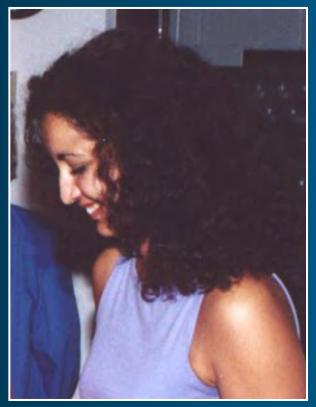
Imposes time between presentation of stimulus and response to make children take the time they need to 'compute' the answer

Percentage of Correct Responses by 4-Year-Old Children on the Ditty and Standard Conditions of the Day-Night Task

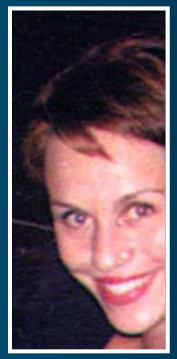


VIDEO

Conditions under which young children CAN hold two rules in mind and inhibit a prepotent response



Adele Diamond
Natasha Kirkham
& Dima Amso

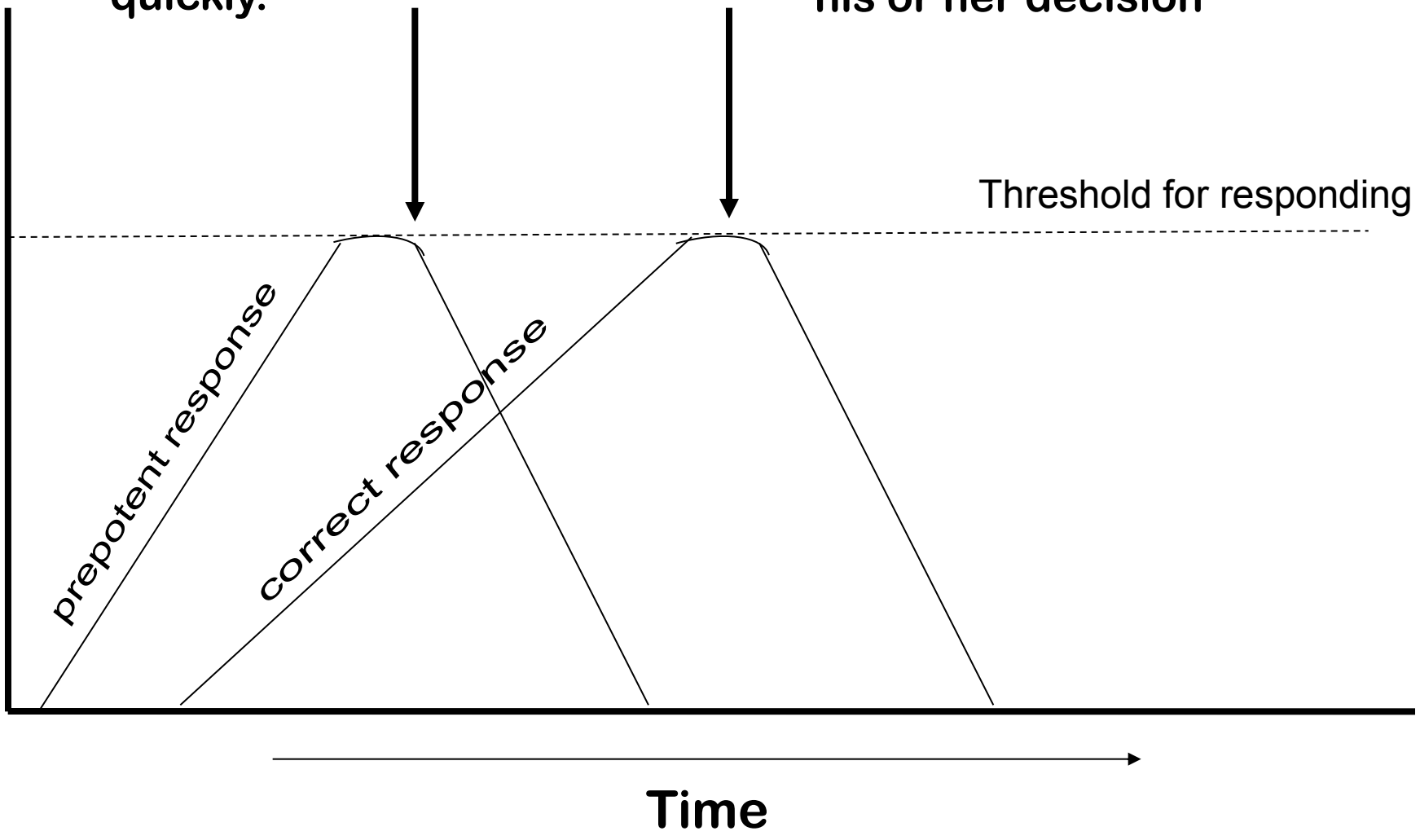


2002

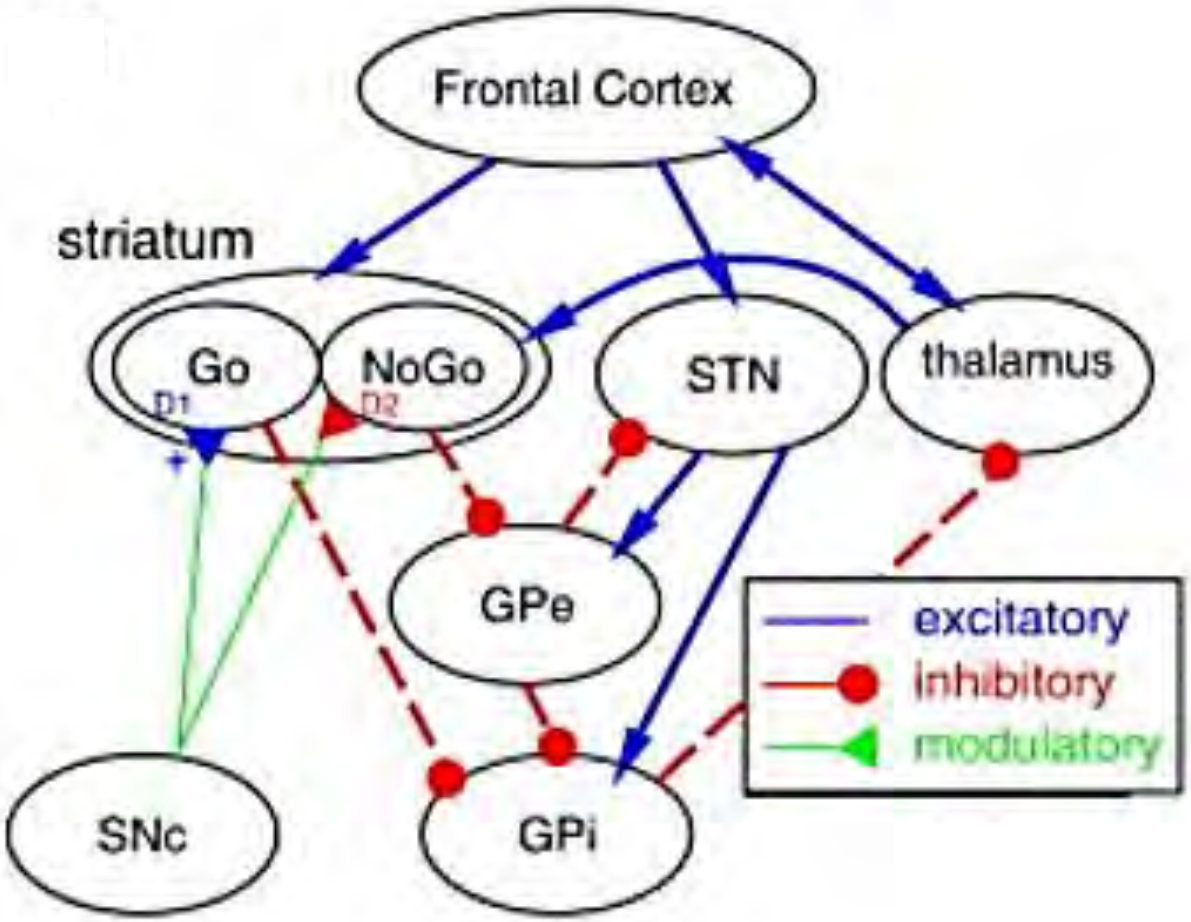
Developmental Psychology
vol. 38, p. 352–362

Prepotent, impulsive response 'wins' (gets emitted) if child is allowed to respond quickly.

Correct decision 'wins' if some way is found to delay when the child needs to indicate his or her decision



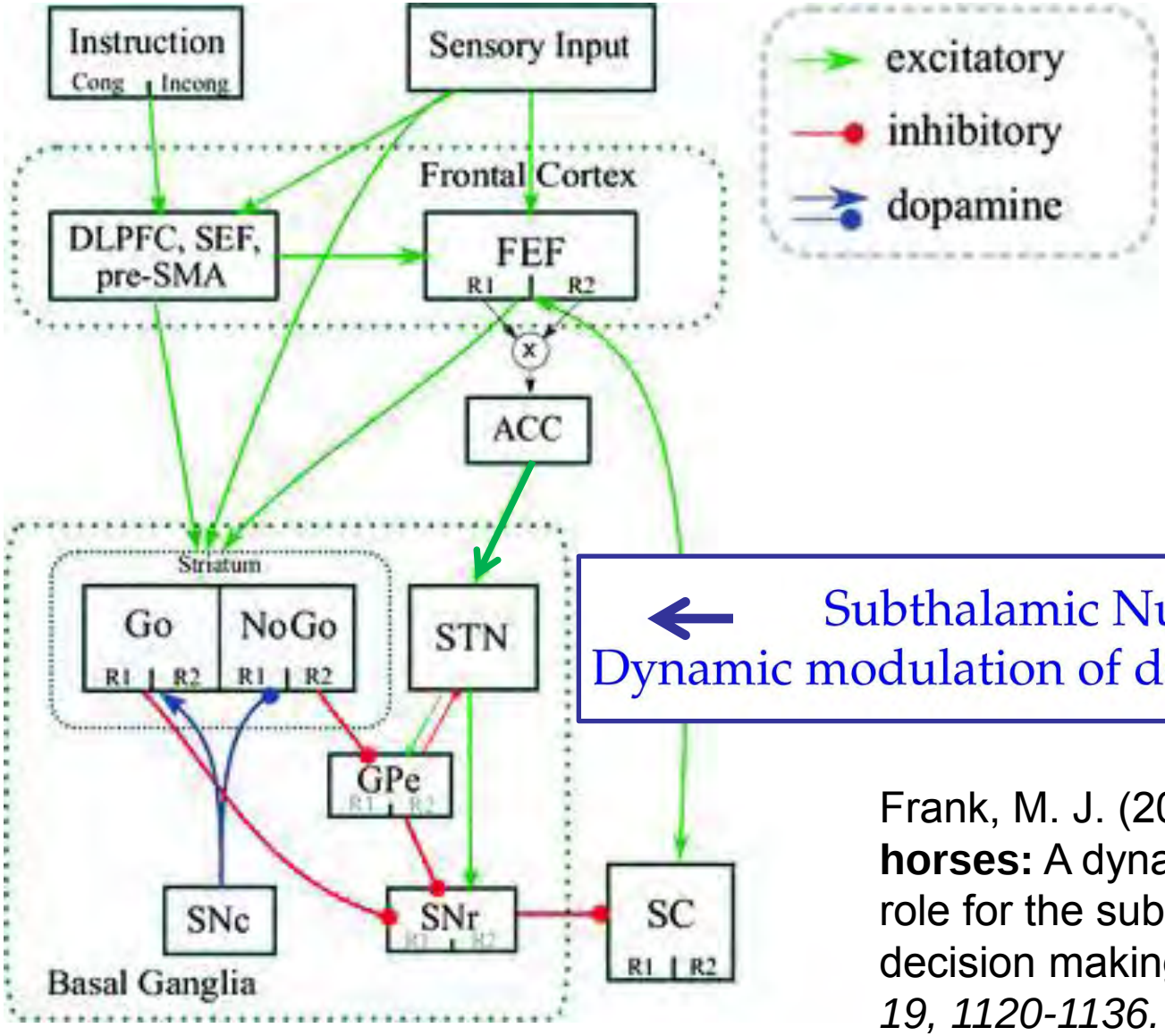
Subthalamic Nucleus:
Dynamic modulation of decision threshold



Michael Frank(2006). Hold your horses: A dynamic computational role for the subthalamic nucleus in decision making. *Neural Networks, 19, 1120-1136.*

Wiecki, T. V., & Frank, M. J. (2013). A computational model of inhibitory control in frontal cortex and basal ganglia.

***Psych. Rev.*, *120*, 329-355.**



← Subthalamic Nucleus: Dynamic modulation of decision threshold

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Without inhibitory control we'd be at the mercy of impulses, old habits of thought or action, and stimuli in the environment that pull us this way or that.

Inhibition allows us a measure of control over our attention and our actions, rather than simply being controlled ***by*** external stimuli, our emotions, or old habits of mind or behavior.

Thus it helps make it possible for us to change & to CHOOSE how we react and how we behave rather than being "unthinking" creatures of habit. It doesn't make overriding habits or automatic responses easy, but it creates the possibility.

Children with better inhibitory control (i.e., children who were more persistent, less impulsive, and had better attention regulation) as adults 30 years later have…

- better health
- higher incomes and better jobs
- fewer run-ins with the law
- a better quality of life (happier)

than those with worse inhibitory control as young children,

controlling for IQ, gender, social class, & home lives & family circumstances growing up

across diverse measures of self control.

That's based on a study of 1,000 children born in the same city in the same year followed for 32 years with a 96% retention rate.

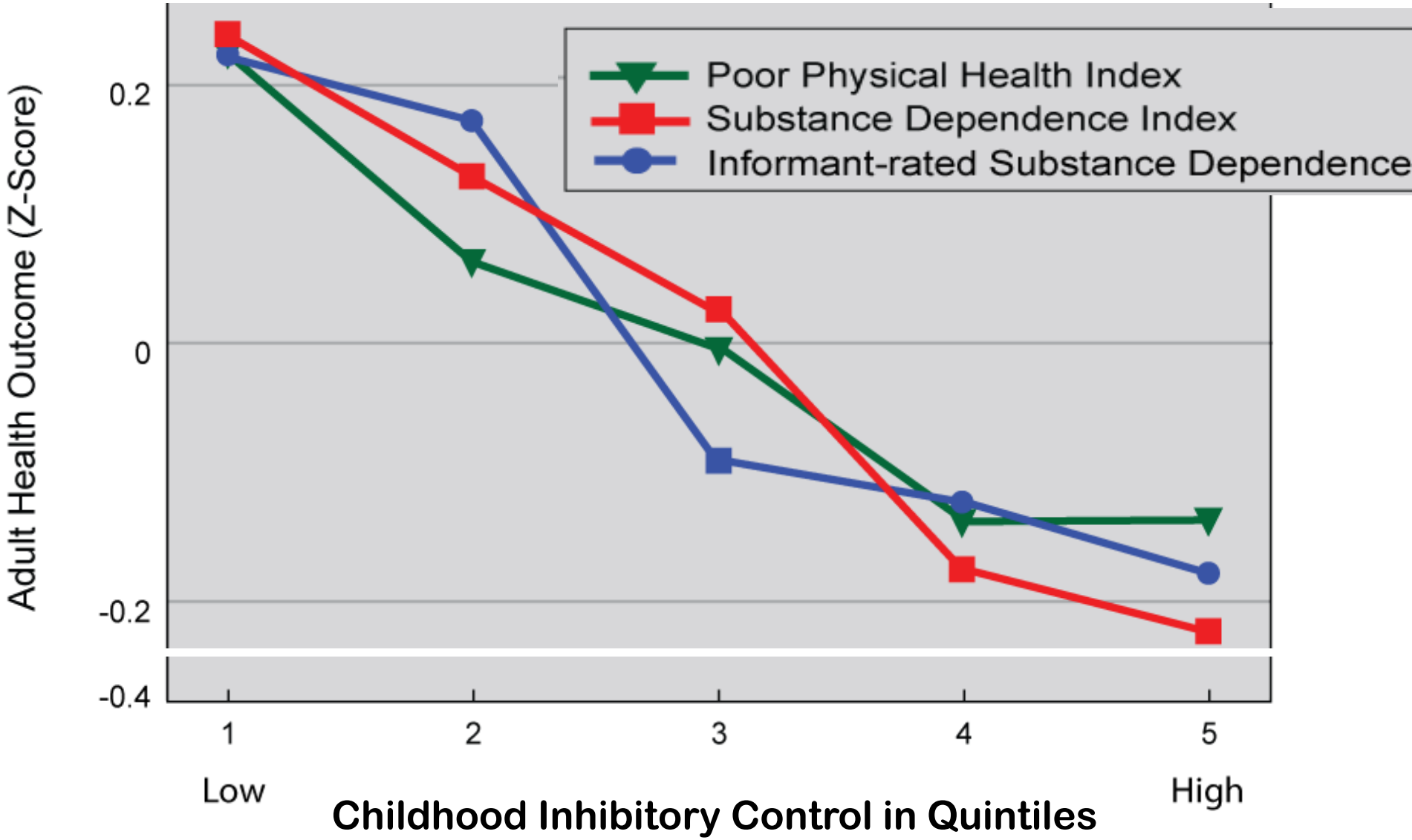
by Terrie Moffitt et al. (2011)
Proceedings of the Nat'l Academy of Sci.

"Interventions that achieve even small improvements in [inhibitory control] for individuals could shift the entire distribution of outcomes in a salutary direction and yield large improvements in health, wealth, and crime rate for a nation."

Nowhere in their data, did Moffitt et al. find any hint of a discontinuity or cutoff between those clinically diagnosed with a self-control impairment (like ADHD) and everyone else. For wealth, health, and crime the gradients are linear and continuous.

Those ADULTS, who as children had worse inhibitory control, have worse HEALTH

Moffitt et al., 2011



The 3 core Executive Functions are:

- **Inhibitory Control**
  (which includes self-control & discipline, also selective attention)
- **Working Memory** (holding info in mind & MANIPULATING it; essential for reasoning)
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Higher-order Executive Functions are:

- Problem-solving
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Working memory is critical for making sense of anything that unfolds over time, for that always requires holding in mind what happened earlier & relating that to what is happening now.

- relating one idea to another
- relating what you read (or learned / heard) earlier to what you are reading (learning / hearing) now
- mental math calculations
- understanding cause and effect
- remembering multi-step instructions & executing them in the correct order

Reasoning would not be possible without working memory, for reasoning requires holding bits of information in mind and seeing how they relate. Working memory enables us to consider the past and possible future in making plans and decisions.

What some people call "working memory" could also be termed:

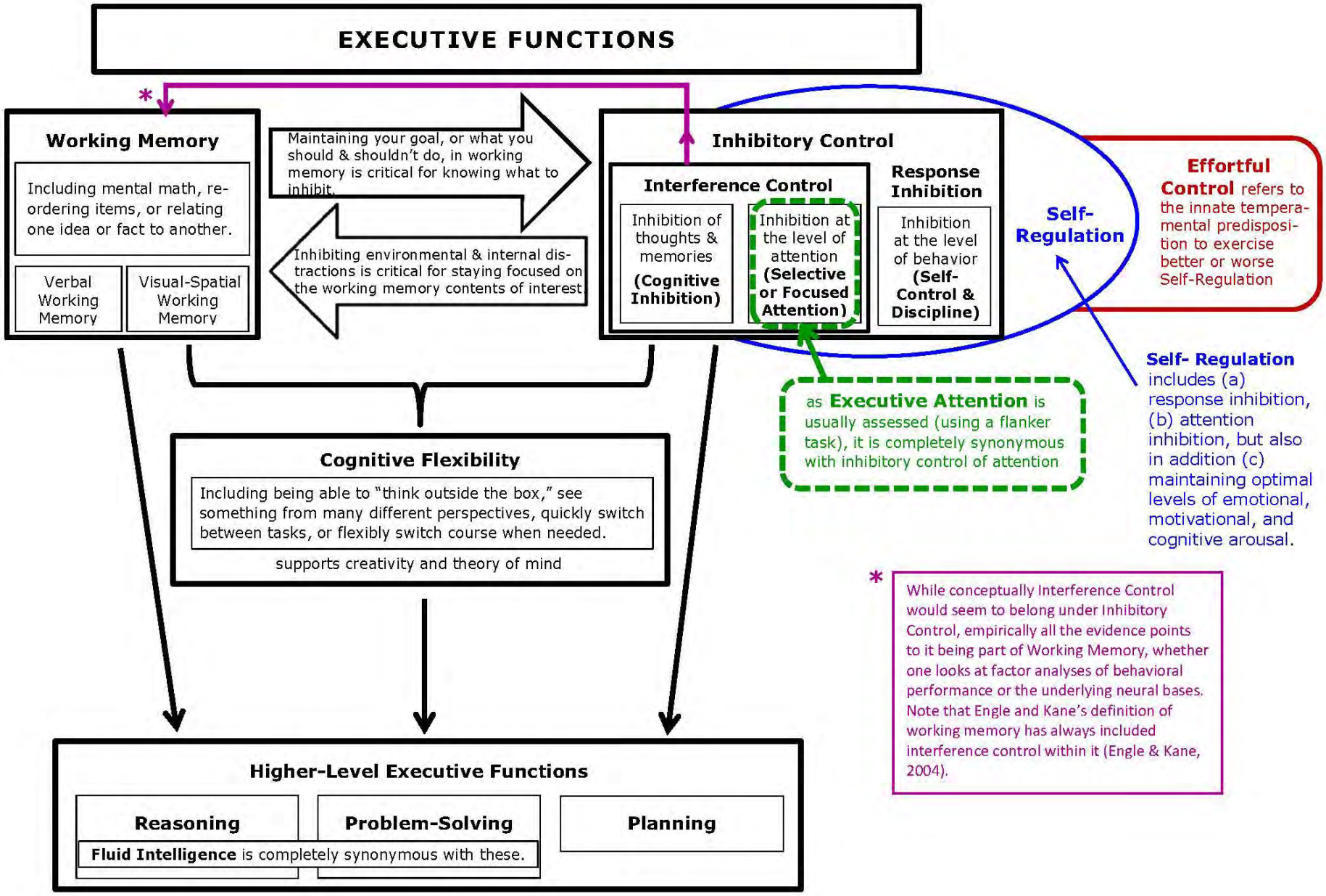
Keeping your ATTENTION focused on specific mental contents while mentally working with them

The distinction between attention and working memory may be arbitrary.

They appear to be similar in many ways, including neural basis.

Empirically, selective attention and working memory are very tightly linked.

The same prefrontal system that helps us selectively attend to stimuli in our environment also helps us selectively keep our mind focused on the information we want to hold in mind in working memory (e.g., Ed Awh; Adam Gazzaley).


EXECUTIVE FUNCTIONS
*
Working Memory
Including mental math, re-ordering items, or relating one idea or fact to another.
Verbal Working Memory
Visual-Spatial Working Memory
Maintaining your goal, or what you should & shouldn't do, in working memory is critical for knowing what to inhibit.
Inhibiting environmental & internal distractions is critical for staying focused on the working memory contents of interest
Inhibitory Control
Interference Control
Inhibition of thoughts & memories (Cognitive Inhibition)
Inhibition at the level of attention (Selective or Focused Attention)
Response Inhibition
Inhibition at the level of behavior (Self-Control & Discipline)
Self-Regulation
Effortful Control refers to the innate temperamental predisposition to exercise better or worse Self-Regulation
as Executive Attention is usually assessed (using a flanker task), it is completely synonymous with inhibitory control of attention
Self- Regulation includes (a) response inhibition, (b) attention inhibition, but also in addition (c) maintaining optimal levels of emotional, motivational, and cognitive arousal.
Cognitive Flexibility
Including being able to "think outside the box," see something from many different perspectives, quickly switch between tasks, or flexibly switch course when needed.
supports creativity and theory of mind
Higher-Level Executive Functions
Reasoning
Problem-Solving
Planning
Fluid Intelligence is completely synonymous with these.
* While conceptually Interference Control would seem to belong under Inhibitory Control, empirically all the evidence points to it being part of Working Memory, whether one looks at factor analyses of behavioral performance or the underlying neural bases. Note that Engle and Kane's definition of working memory has always included interference control within it (Engle & Kane, 2004).

Engle & Kane define WM as the ability to (a) maintain selected information in an active, easily retrievable state while (b) blocking or inhibiting other information from entering that active state (i.e., memory maintenance + interference control).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Storytelling requires and invites a child's rapt attention for extended periods (sustained, focused attention), and, **working memory** to hold hold in mind all that has happened thus far, different characters' identities, and to relate that to the new info being revealed - **without visual aids.**

A researcher (Gallets, 2005) randomly assigned children in Kindergarten & Grade 1 to storytelling or story-reading -- 2x a week for 12 weeks.

Recall improved more in the children assigned to storytelling than in children assigned to story-reading.

Children in the storytelling condition recalled more story characters & more story episodes than did children in story-reading.

Maybe one reason is that when you are reading to, or with, a child you are looking down at the page.

But when you are telling a story you are looking directly at the children & interacting more.

You probably think, “Oh what a wonderful scene!”

I would like to suggest that young children also need this: STORYTELLING, where only the teller sees the pages in the book.

Without the visual aids of pictures or puppets, children need to work harder to sustain their attention and to remember the details of the story and who's who in the story.

The more interaction, the more conversation between someone relating a story (thru reading or storytelling) & the children, the more actively engaged the children are, the more their vocabulary improves.

The conversation that takes place in the context of reading seems to have more benefit than the reading itself.

Working Memory & just holding information in mind (Short-Term Memory) are distinct.

Working Memory & just holding information in mind

- cluster onto separate factors in factor analyses of children & of adolescents & adults (Alloway et al., 2004; Gathercole et al., 2004).
- WM is more linked to DL-PFC while maintenance more linked to VL-PFC (D'Esposito; Smith & Jonides, 1999; Owen)

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How can we stop ourselves from get really upset when a child misbehaves? What we usually get upset about is the intent we think is behind an action.

Could use Cognitive Flexibility to re-frame:

A child might be acting in the most awful manner because he has been terribly hurt and is afraid of being hurt again, so he will push you away before you have a chance to reject him or he will test you to see if are *really* someone he can feel safe with.

If we see the misbehavior as coming from hurt, we can react completely differently.

Say the color of the ink that each set of X's is printed in as fast as you can.

XXX XXX XXX XXX XXX

XXX XXX XXX XXX XXX

Read the words below as quickly as you can.

green blue green red blue

green blue red green green

Say the color of the ink in which each word is written as fast as you can.

red blue green green blue

blue red green red blue

Say the color of the ink in which each word is written as fast as you can EXCEPT when there is a box around the word. When there's a box around the word, read what the word says as fast as you can.

green blue green red blue green

red blue green green blue red

To see a full-blown Stroop Effect compare performance on color-naming trials in a mixed block to performance on word-reading trials in a single-task block:

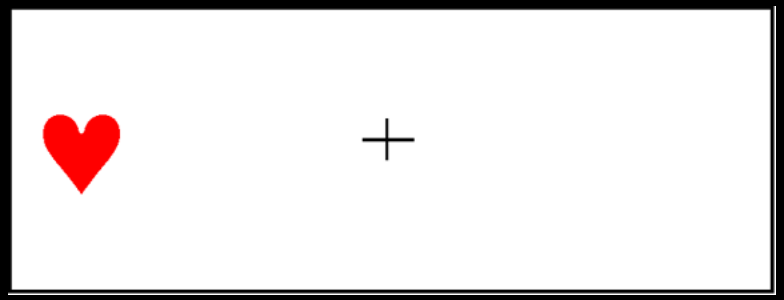
green blue green red blue green

blue red red

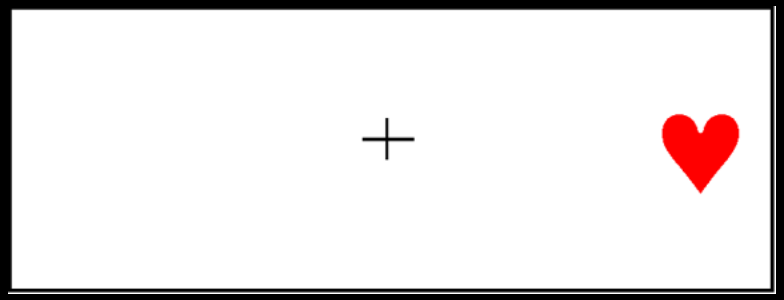
re: Delis-Kaplan battery

HEARTS & FLOWERS

Congruent

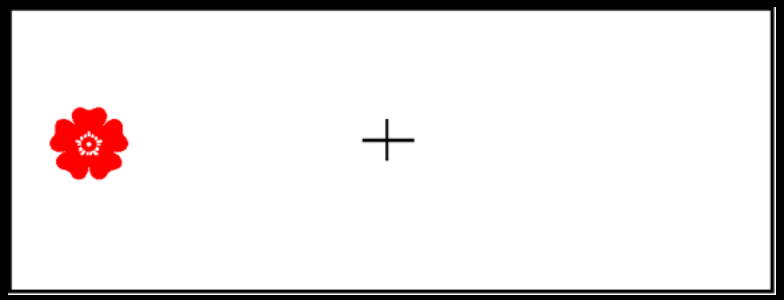


Push Left

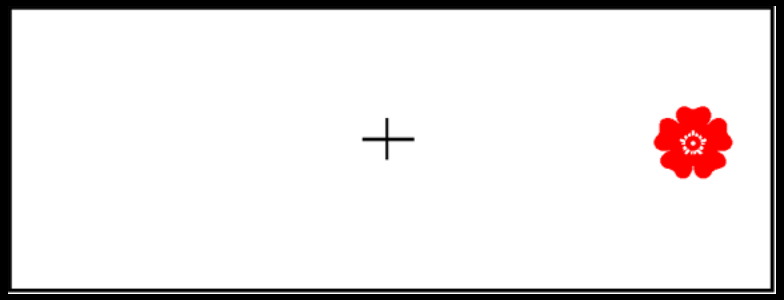


Push Right

Incongruent



Push Right



Push Left

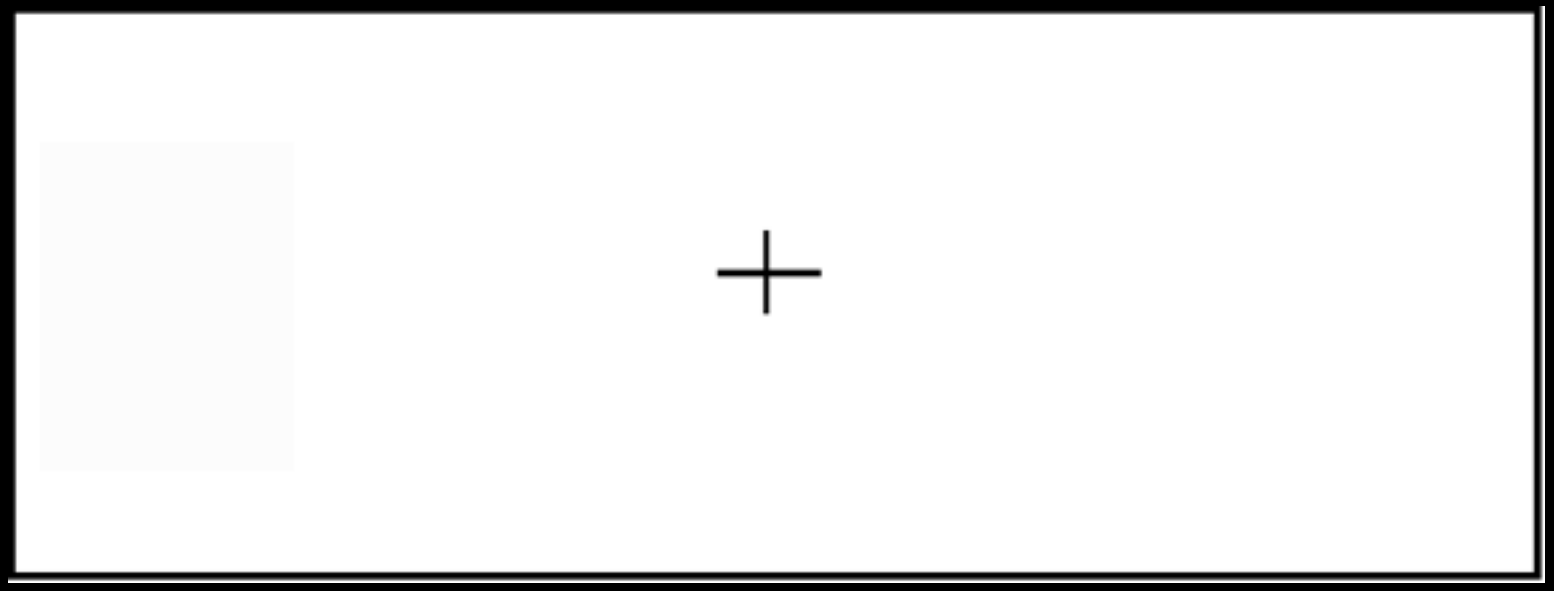
HEARTS – CONGRUENT

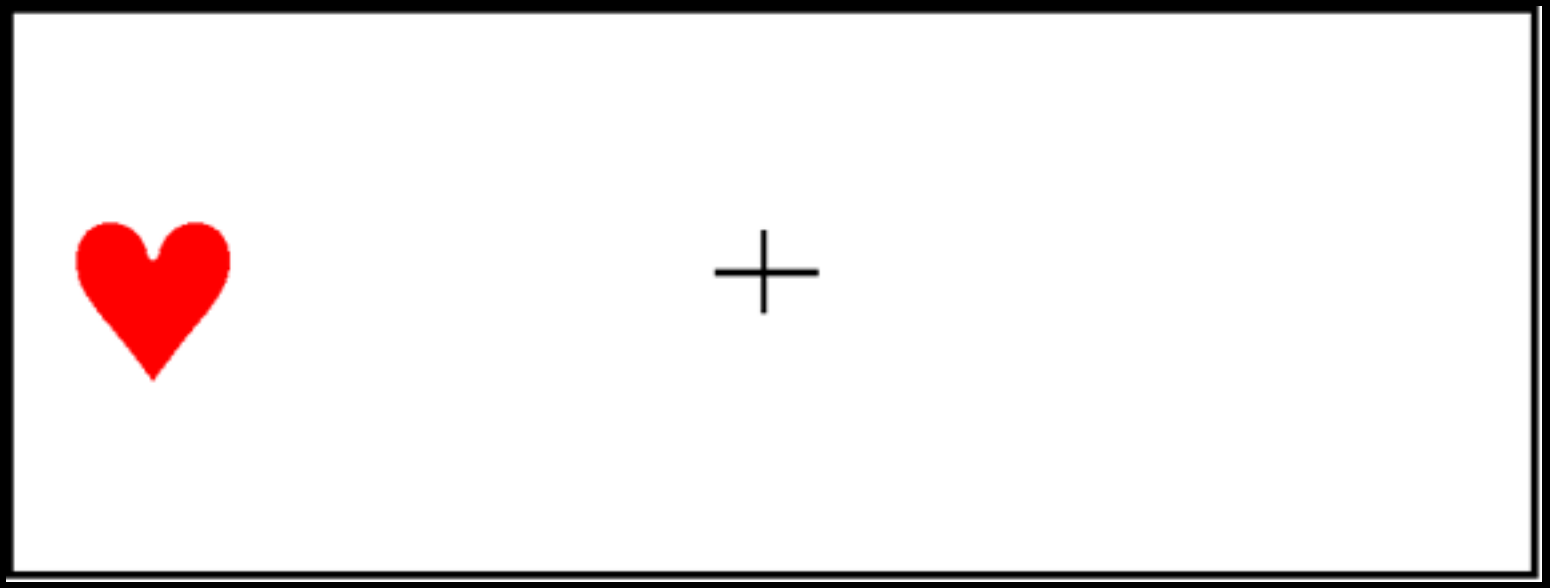
Each time you see a HEART, press with the thumb or forefinger on the SAME side as the stimulus.

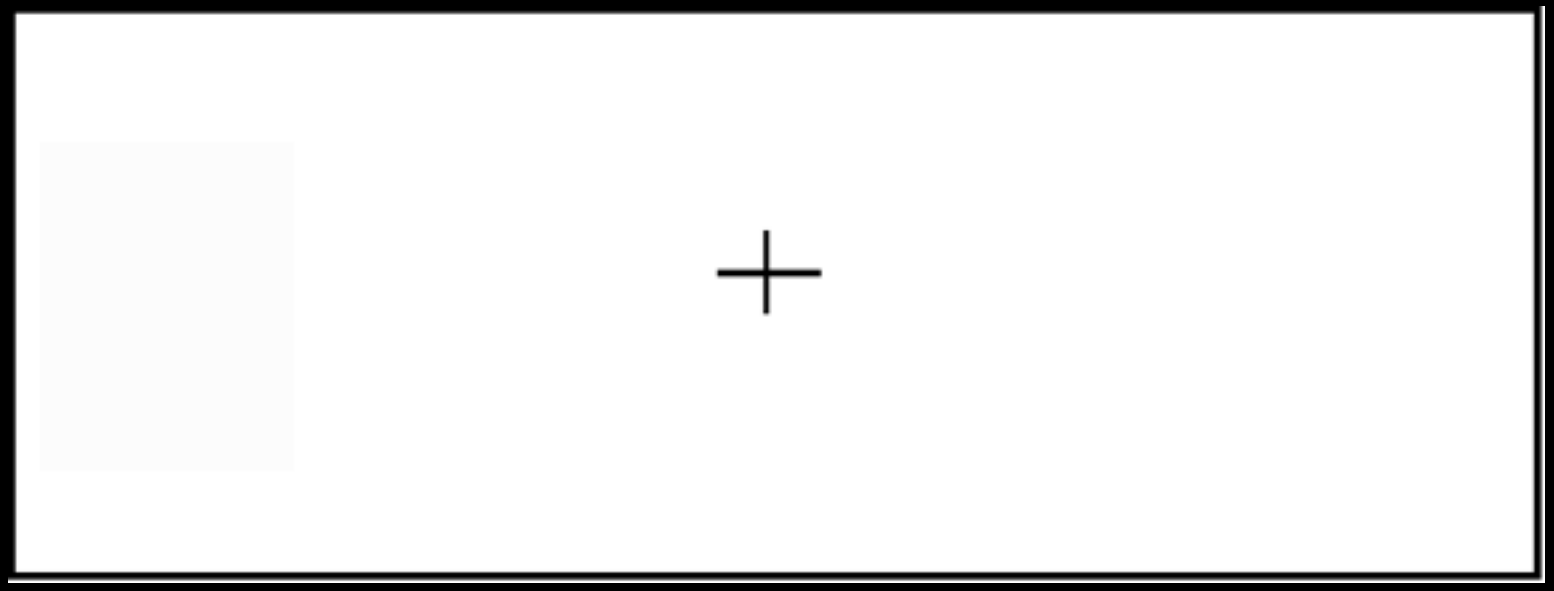
For example, if the heart appears on the left, press with your left hand.

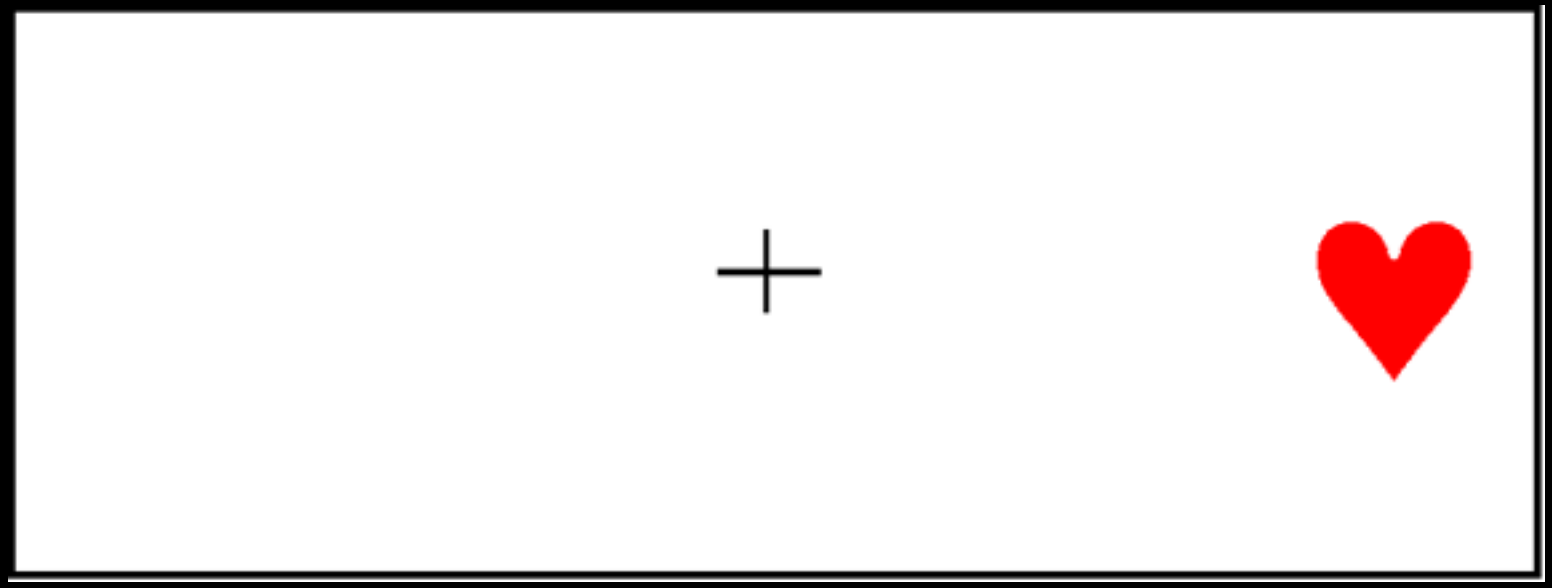
Remember:

PRESS ON THE SAME SIDE AS THE HEART









FLOWERS - INCONGRUENT

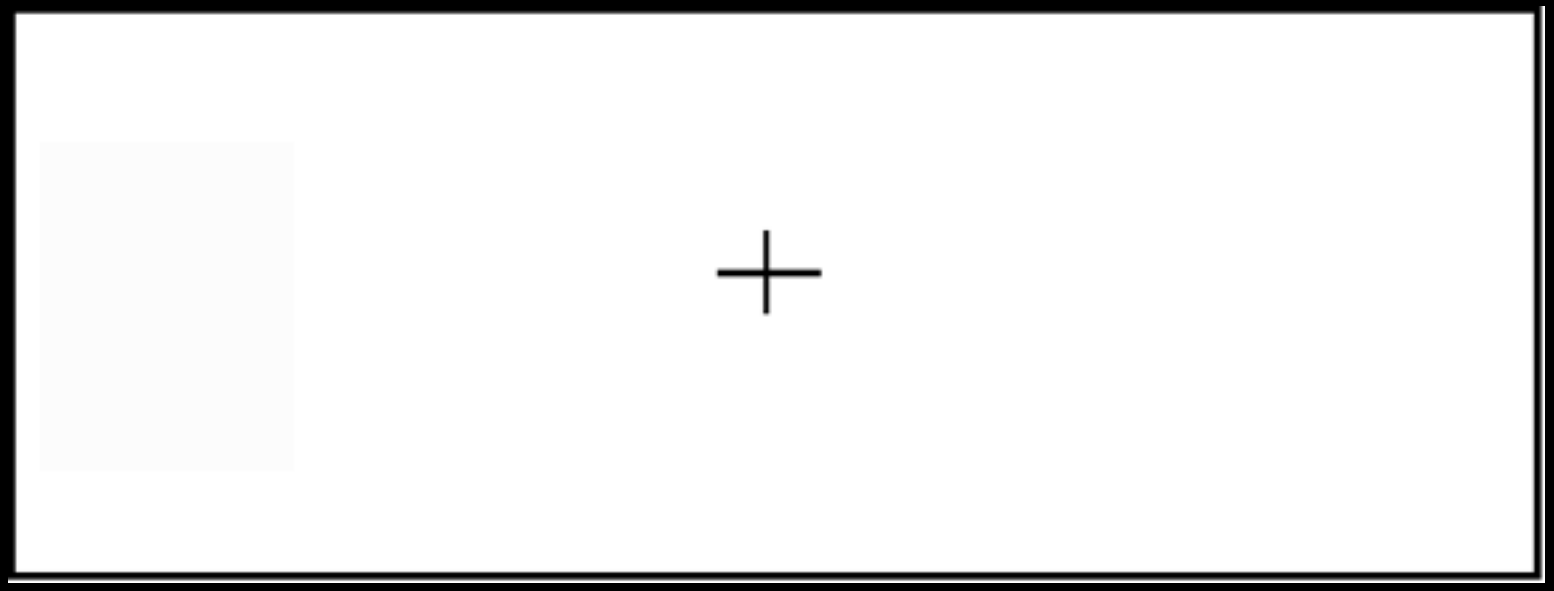
Now you'll see a flower. Press on the side OPPOSITE the flower.

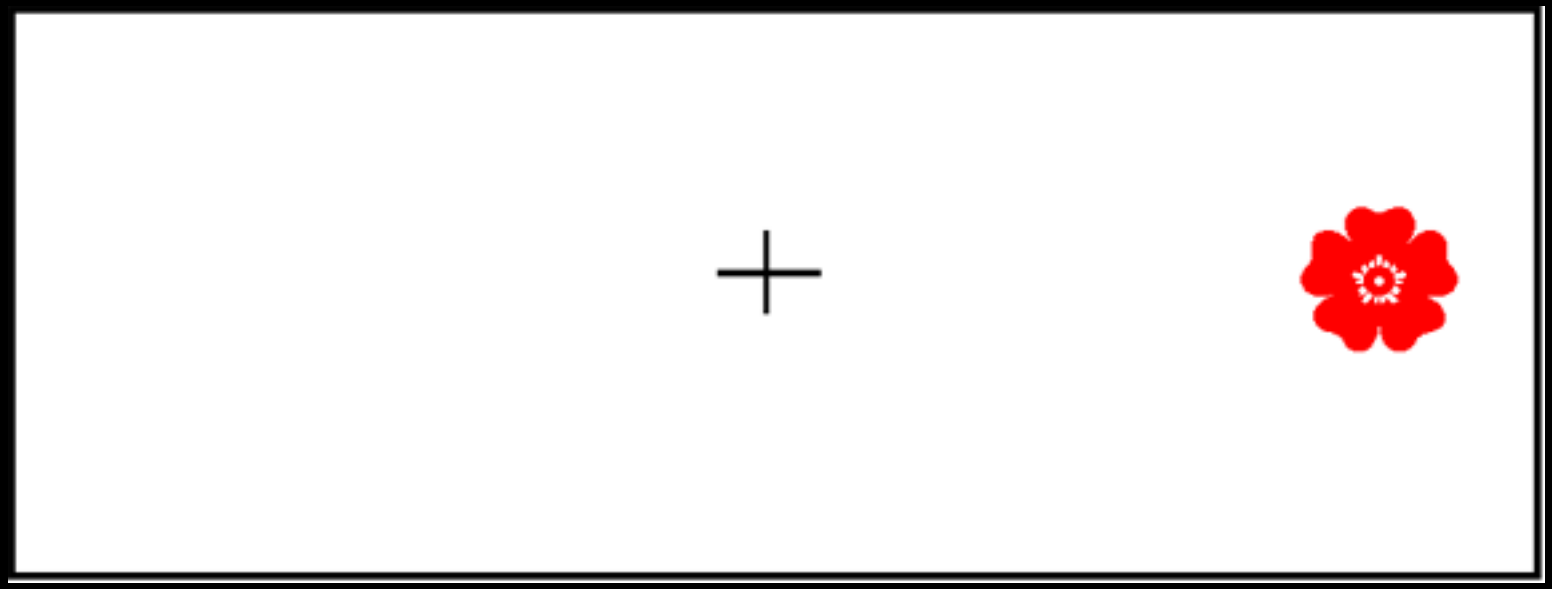
For example, if a flower appears on the left, press with your right hand.

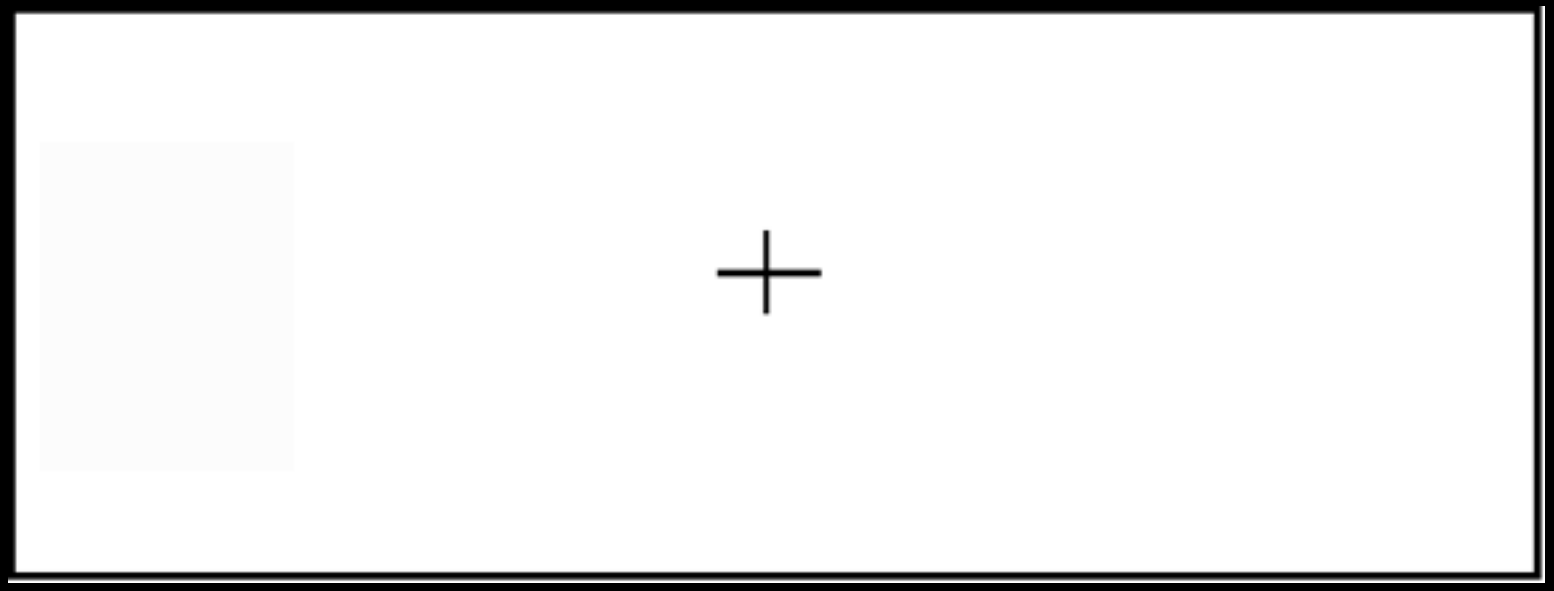
(Here, you'll need to inhibit on every trial the natural tendency to respond on the same side as the stimulus)

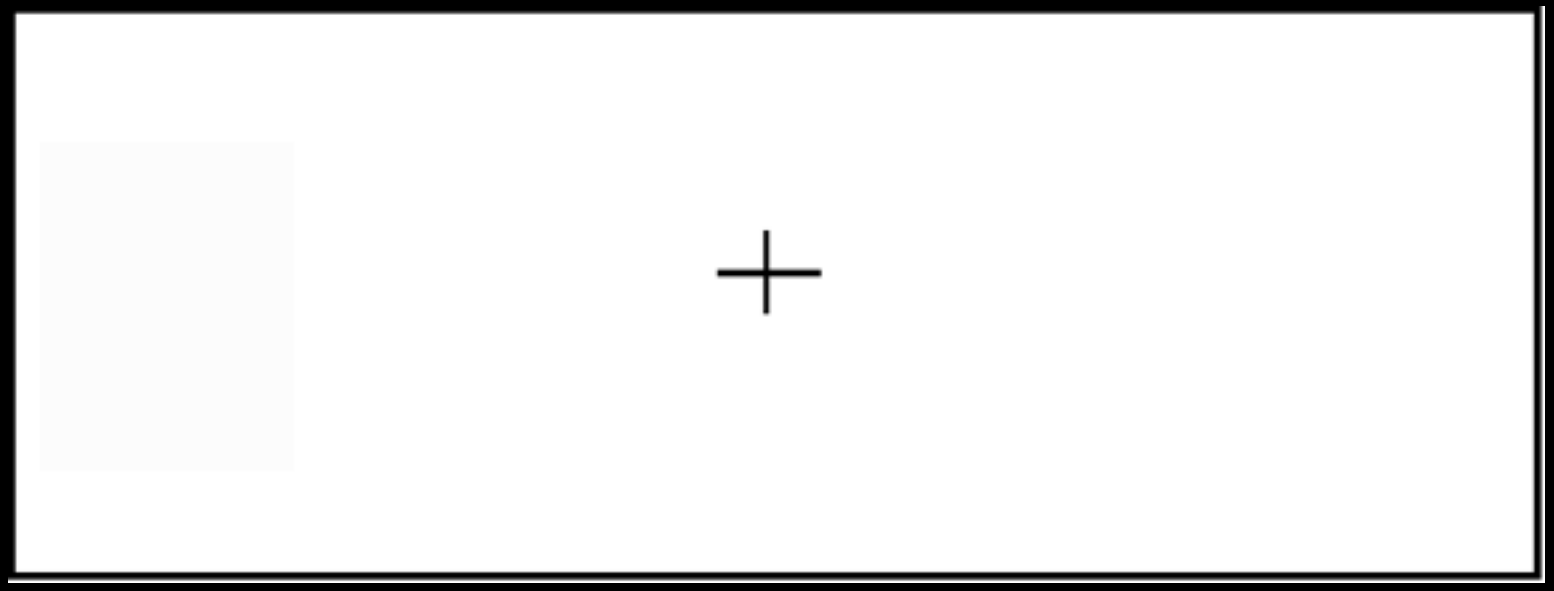
Remember:

PRESS ON THE SIDE <u>OPPOSITE</u> THE FLOWER









HEARTS & FLOWERS-MIXED: Now you will sometimes see a heart and sometimes a flower.

On only half the trials will you have to inhibit the tendency to press on the same side as the stimulus, BUT you'll have to switch between the same-side and opposite-side rules.

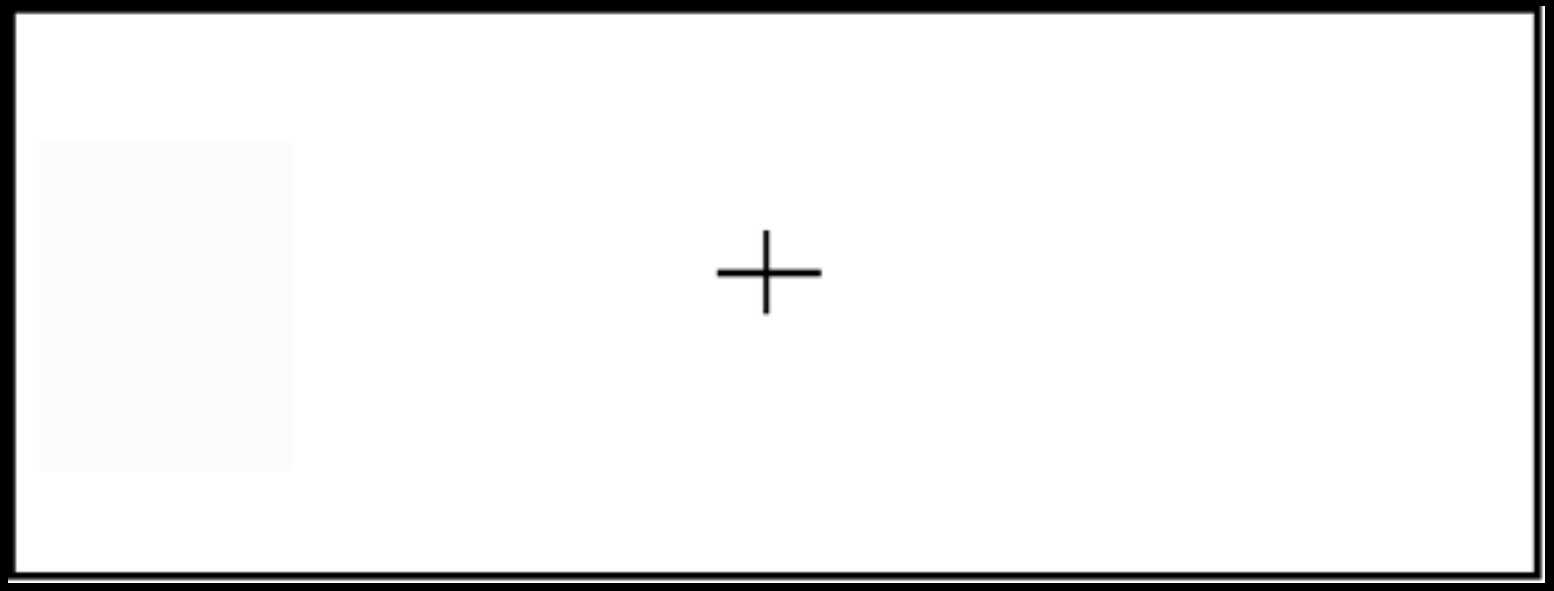
The rules stay the same:

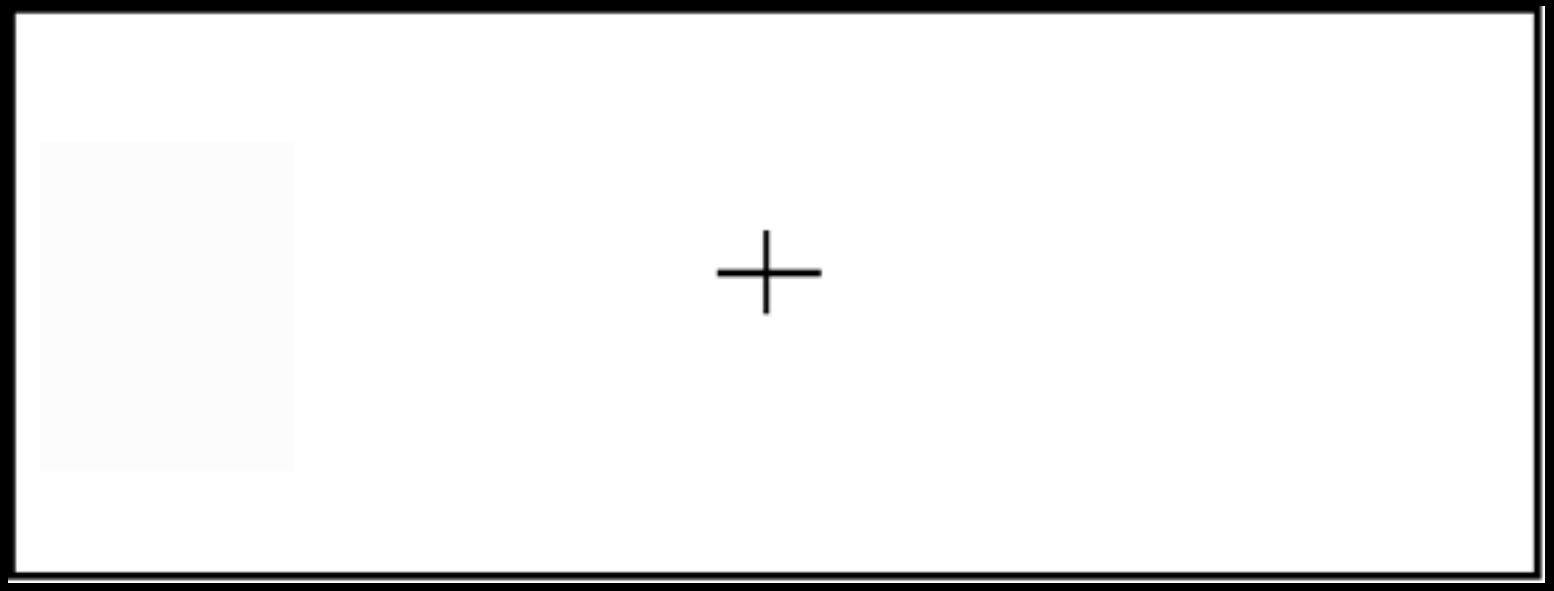
For HEARTS, press on the SAME side.

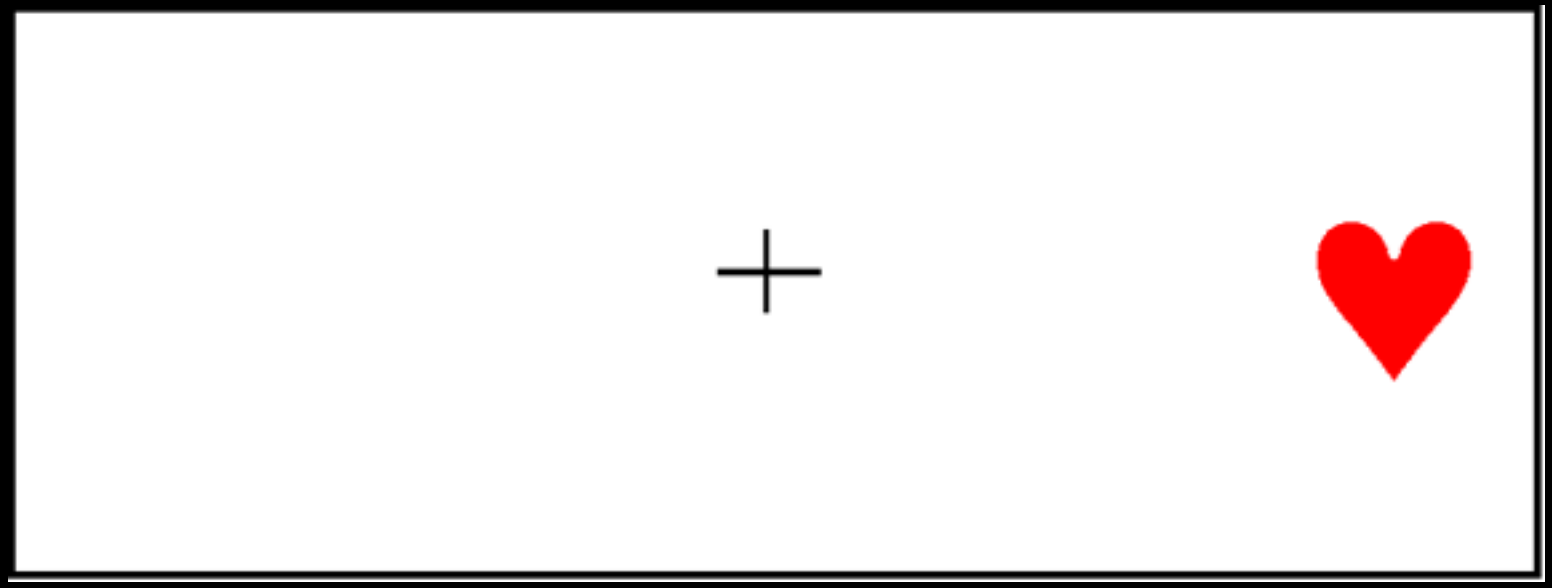
For FLOWERS, press on the OPPOSITE side.

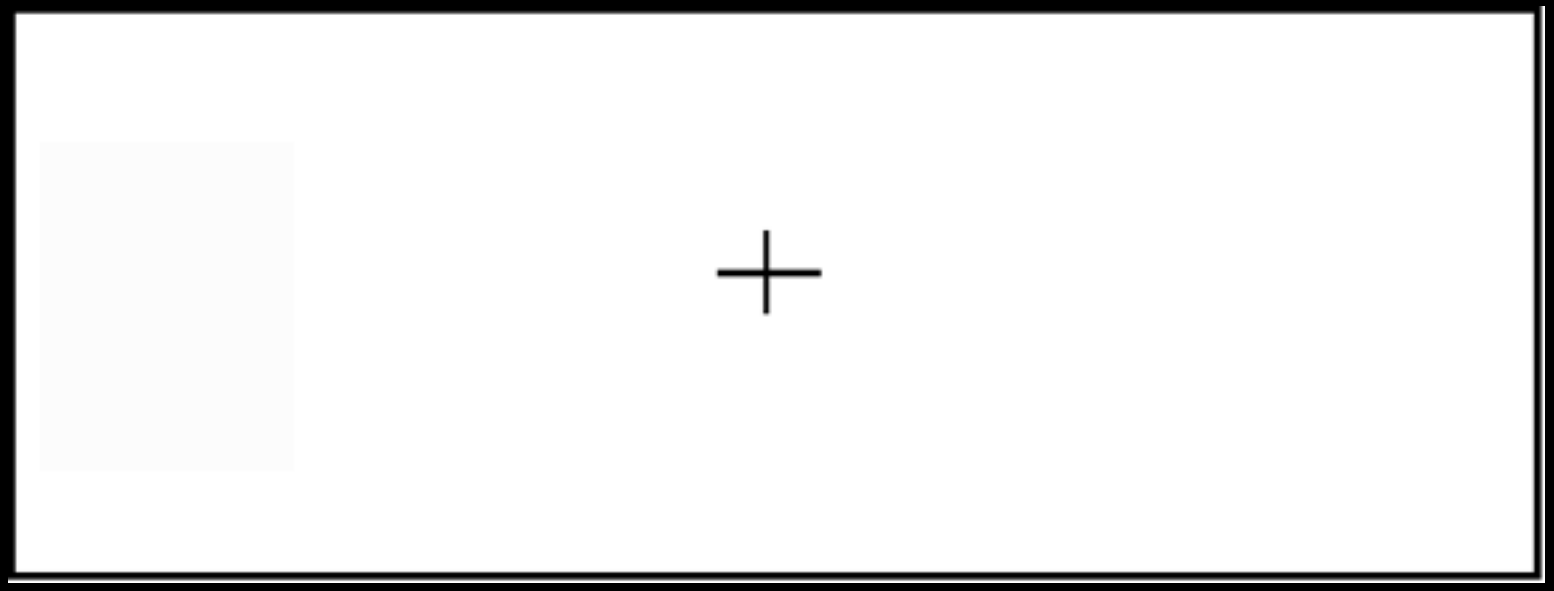
HEARTS – SAME SIDE

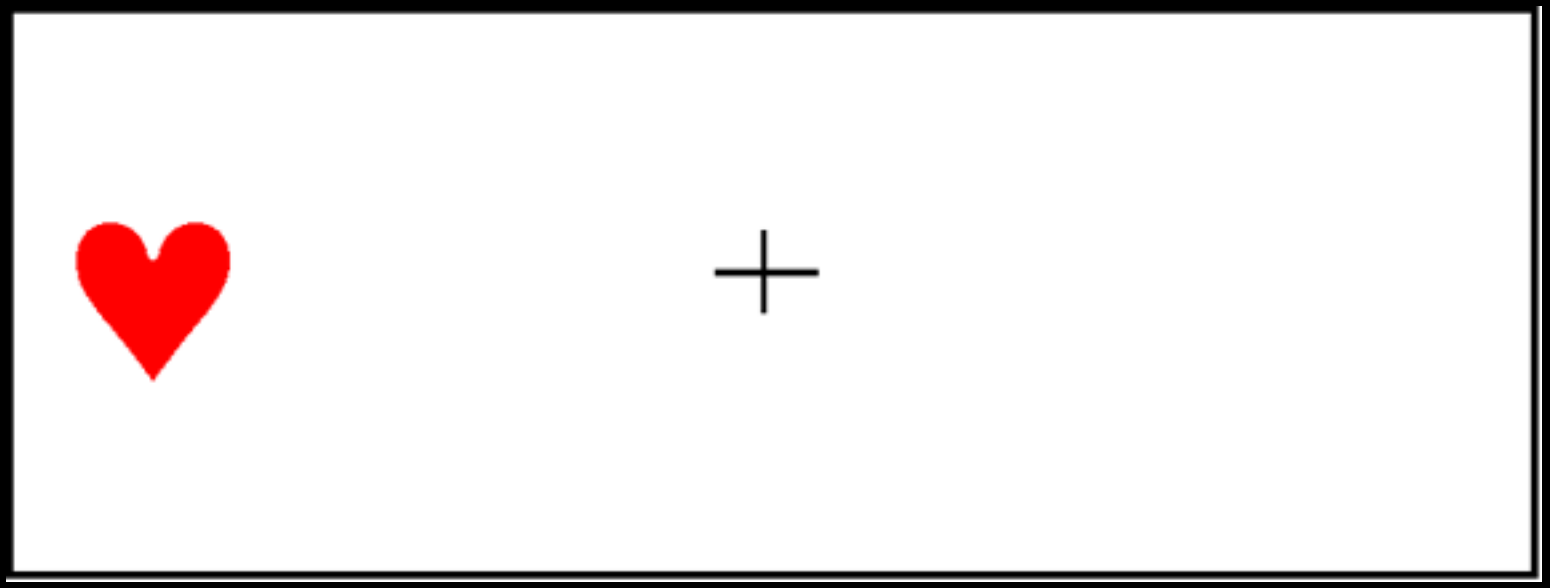
FLOWERS – OPPOSITE SIDE









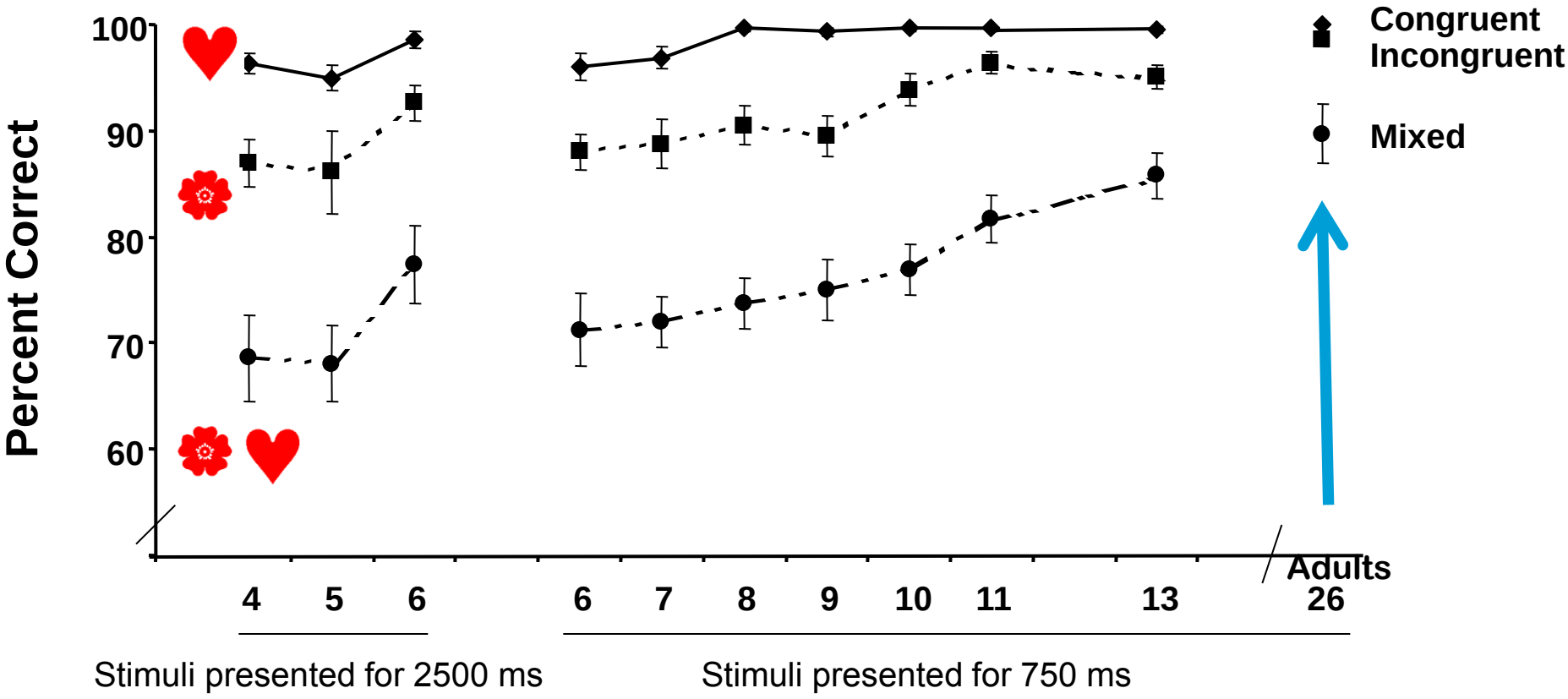


It is *not* that children forget the rules.

Indeed, children often call out the correct higher-order rule on trials in the mixed condition (e.g., “same,” “opposite,” “opposite,” “same”) even as they are making errors.

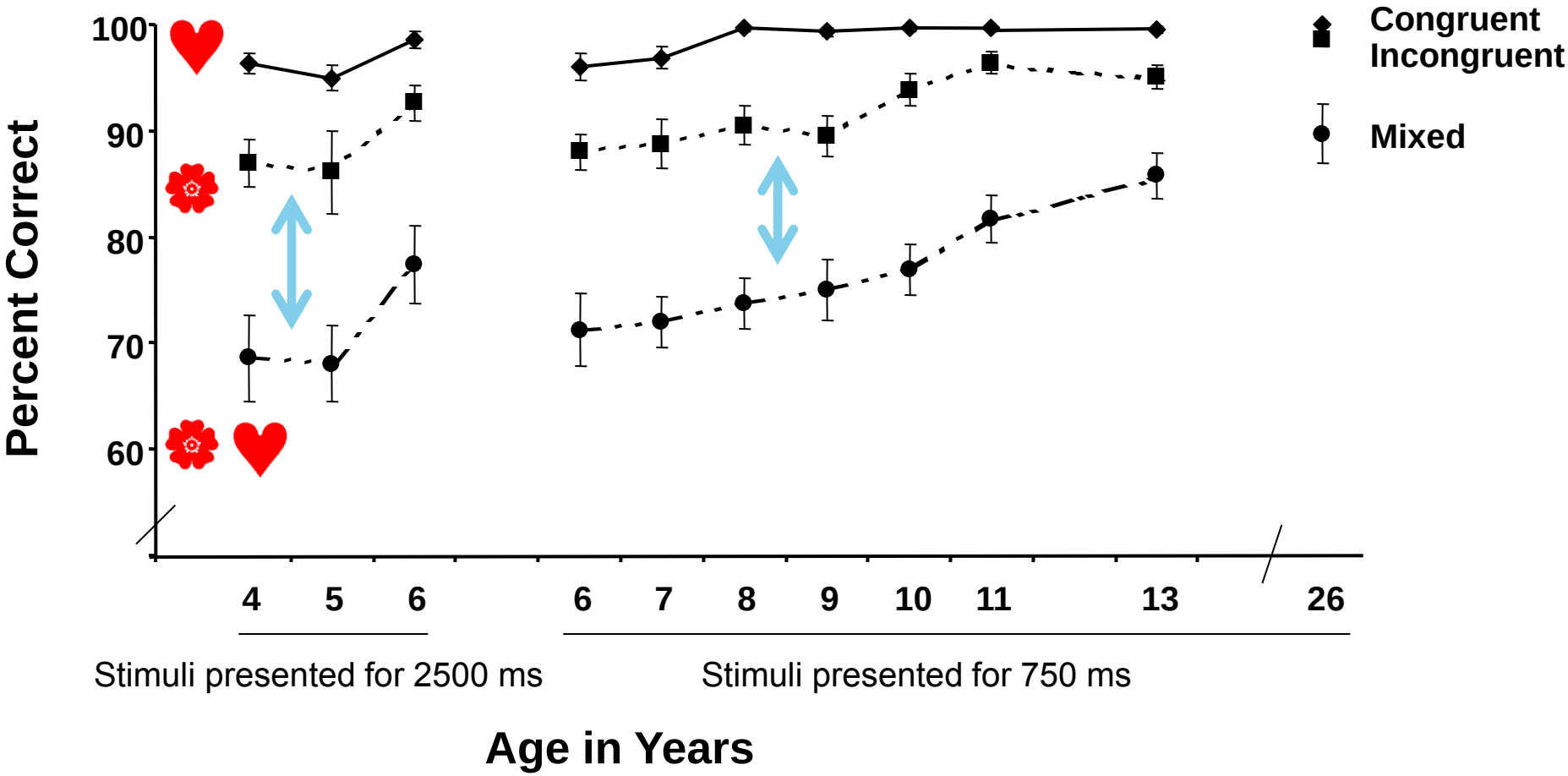
The problem seems to be in quickly translating the rule into the correct response.

Hearts and Flowers Task: Accuracy



Davidson et al. (2006). Neuropsychologia, 44, 2037 - 2078

Dots Conditions: Accuracy



Davidson et al. (2006). Neuropsychologia, 44, 2037 - 2078

Even inhibiting a prepotent response

e.g., responding on the opposite side from a stimulus (inhibiting the tendency to respond on the same side as the stimulus)

or saying the color of the ink (inhibiting the tendency to read the words)

is not that hard if you are to keep doing it.

What's hard is to flip back and forth between doing one thing and another.

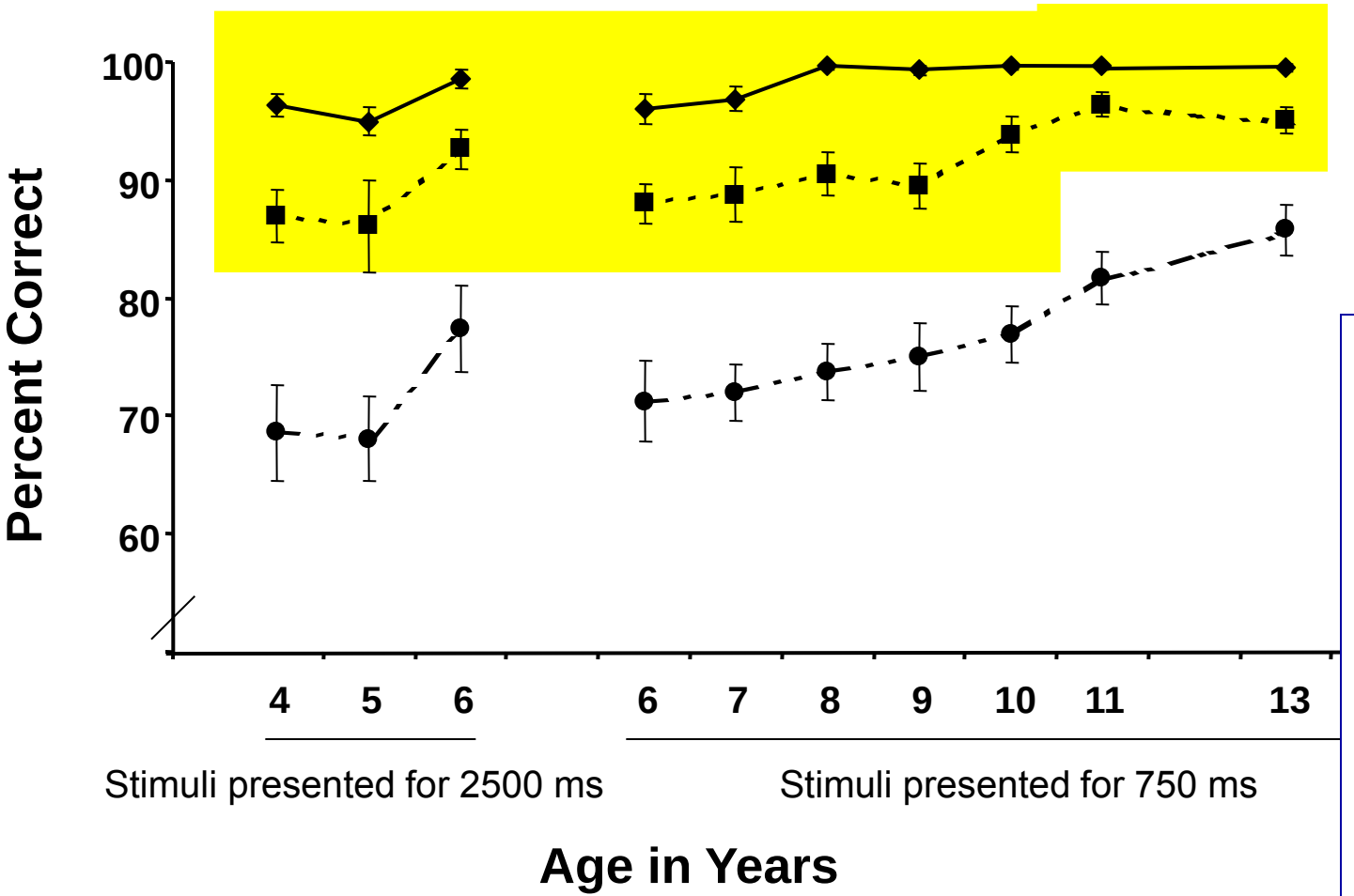
Inhibiting a prepotent tendency *some* of the time (Mixed blocks) is *more* difficult than inhibiting a prepotent tendency *all* the time (Incongruent blocks).

It is SWITCHING (Cog. Flex.) –

re-setting one's attentional focus,
re-orienting one's mindset --

that is most difficult & when DL-PFC is most critically required.

Hearts and Flowers Task: Accuracy

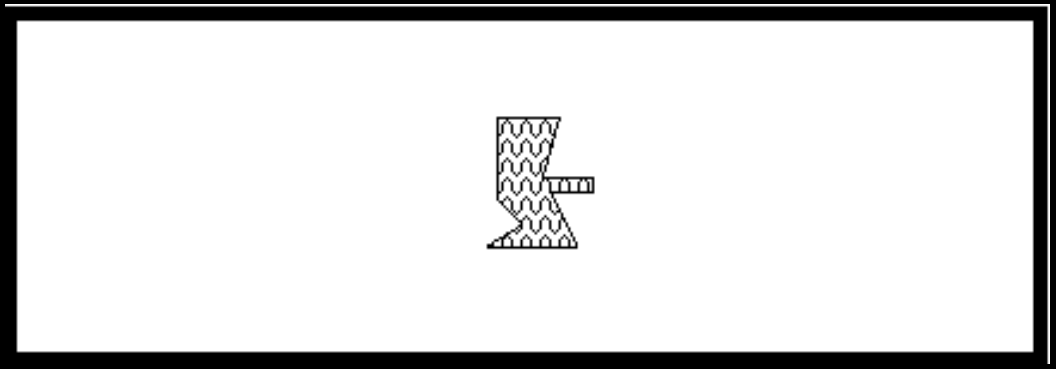


At every age studied, children were slower & less accurate on the Flower block than on the Heart block.

That effect is *completely* absent in adults.

Even very young children have excellent memories. Inhibition is a far greater challenge for them than holding information in mind.

Abstract Figures - Center Presentation



Push Left

Push Right

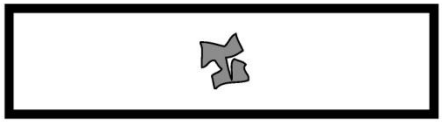
ABSTRACT SHAPES TEST:
A MEMORY LOAD TASK

Press Left

Press Right

Press Right

Press Right



Press Left

Press Left

Increasing demands on INHIBITION (the Flower block vs. the Heart block) are more difficult for young children (ages 4-9 years) than increasing demands on how much information they must hold in mind (2 to 6 items).

The opposite is true for us adults:

Increasing MEMORY demands is *far* more difficult for us than increasing demands on inhibition.

The costs associated with increasing MEMORY demands are greater for adults,

the costs associated with increasing INHIBITORY demands are greater for young children.

We adults may not appreciate how inordinately difficult inhibition is for young children because it is so much less taxing for us.

Development from 4-13 Years of Cognitive Control and Executive Functions:

Evidence from Manipulations of Memory Load, Inhibition, and Task Switching

← Matthew Davidson

Loren Cruess Anderson →

← Dima Amso

& Adele Diamond

published in Neuropsychologia

vol 44, pages *2037 - 2078*

Wright, A. & Diamond, A. (2014). An effect of inhibitory load in children while keeping working memory load constant. *Frontiers in Psychology, 5*, 1-9. (Special issue on Development of Executive Function during Childhood).

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Zaitchik, D., Iqbal, Y., & Carey, S. (2014). The effect of executive function on biological reasoning in young children: An individual differences study. *Child Development, 85*, 160-175.

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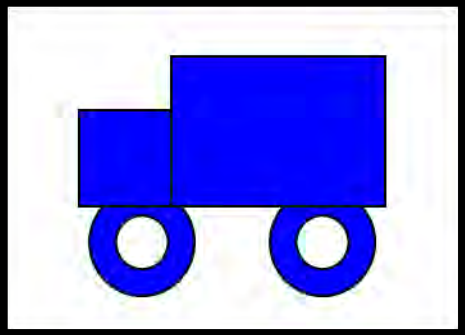
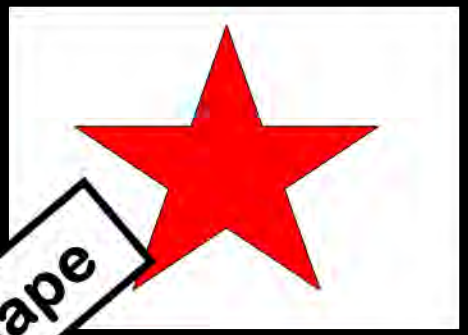
Diamond, A., Barnett, W. S., Thomas, J., & Munro, S. (2007). Preschool program improves cognitive control. *Science, 318*, 1387-1388.

Dimensional Change Card Sort

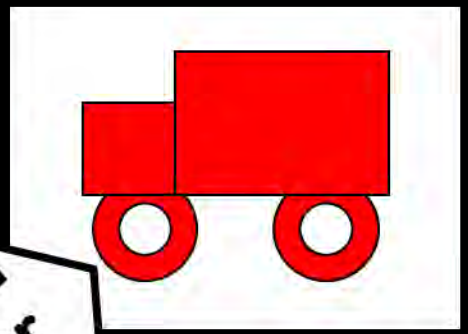
(Zelazo, Frye, & Rapus, 1996)

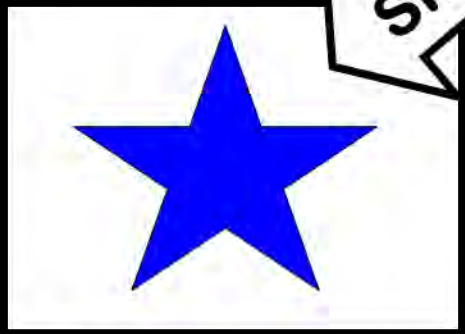


Target Cards

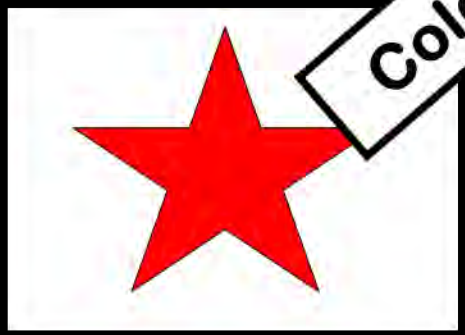


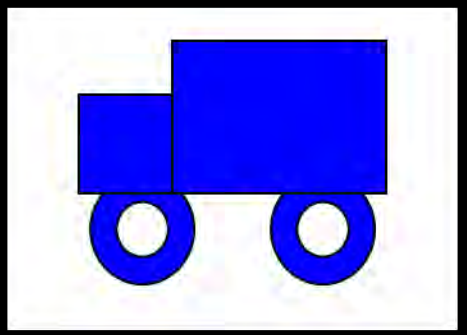
Shape





Color

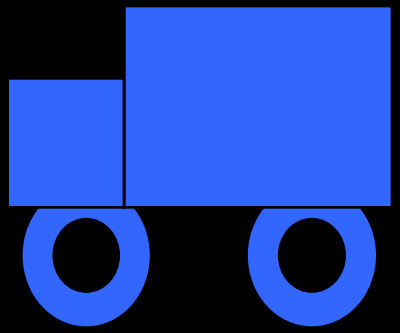




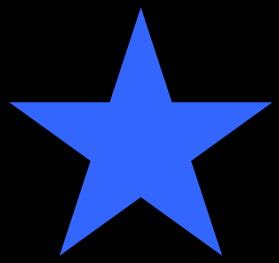
Holding two rules in mind, and inhibiting the tendency to continue sorting by the first dimension

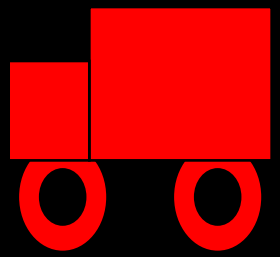
When sorting by COLOR, Correct Response is the Blue Star.

Card to be sorted:



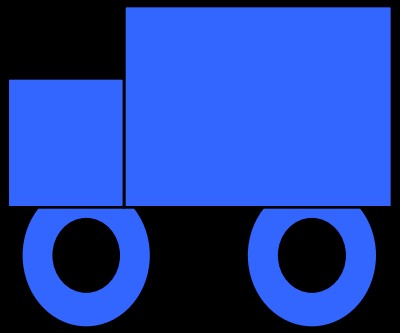
Model Cards:



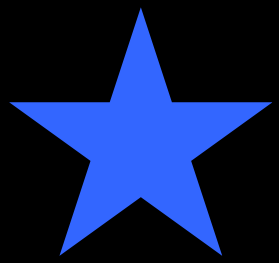


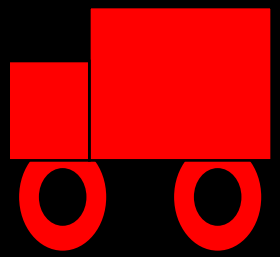
When sorting by SHAPE, Correct Response is the Red Truck.

Card to be sorted:



Model Cards:



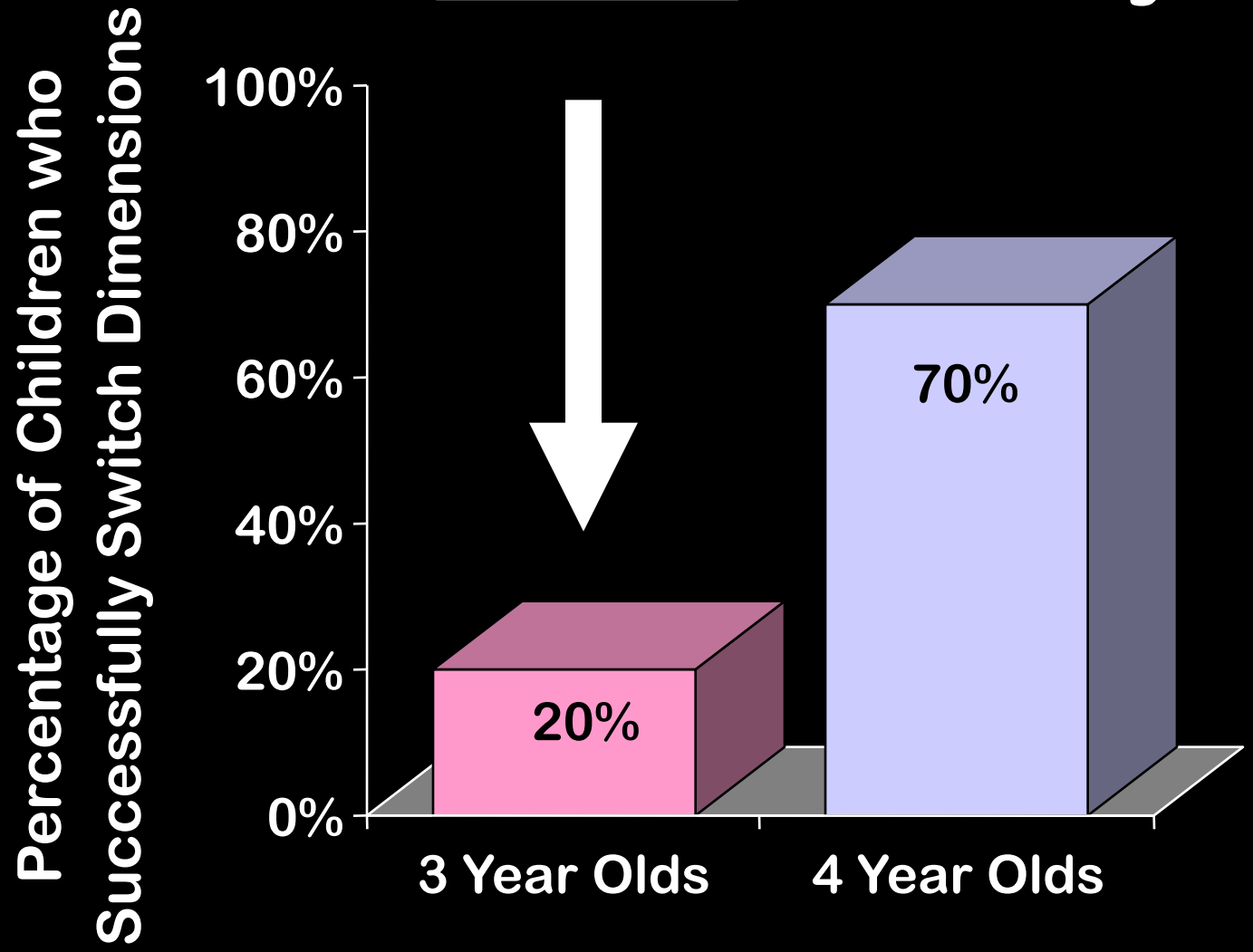


3-year-olds sort the cards perfectly

by either

color or shape

but, very few 3-yr-olds can switch how they sort



www.devcogneuro.com/videos/cardsort.mpg

video

http://www.devcogneuro.com/videos/cardsort_failedswitch.wmv

The child has clearly in mind what the new sorting criterion is and the appropriate rules for that dimension.

BEFORE the stimulus appears the child is all set to perform correctly.

Then a stimulus appears that is relevant to both tasks, in incompatible ways.

That CREATES a problem, triggering the mindset the child is trying to inhibit.

The core problem for 3-year-olds in switching appears to be:

Attentional Inertia

Once they have focused their attention on a dimension, their attention gets STUCK there. They need to disengage from, or inhibit, their previous way of thinking about the stimuli.

Helping Children Apply their Knowledge to their Behavior on a Dimension-Switching Task

Natasha Kirkham, Loren Cruess & Adele Diamond

Developmental Science
2003
vol 6, pages 449-467

It is not enough to know something or remember it;

you must get that knowledge into your behavior.

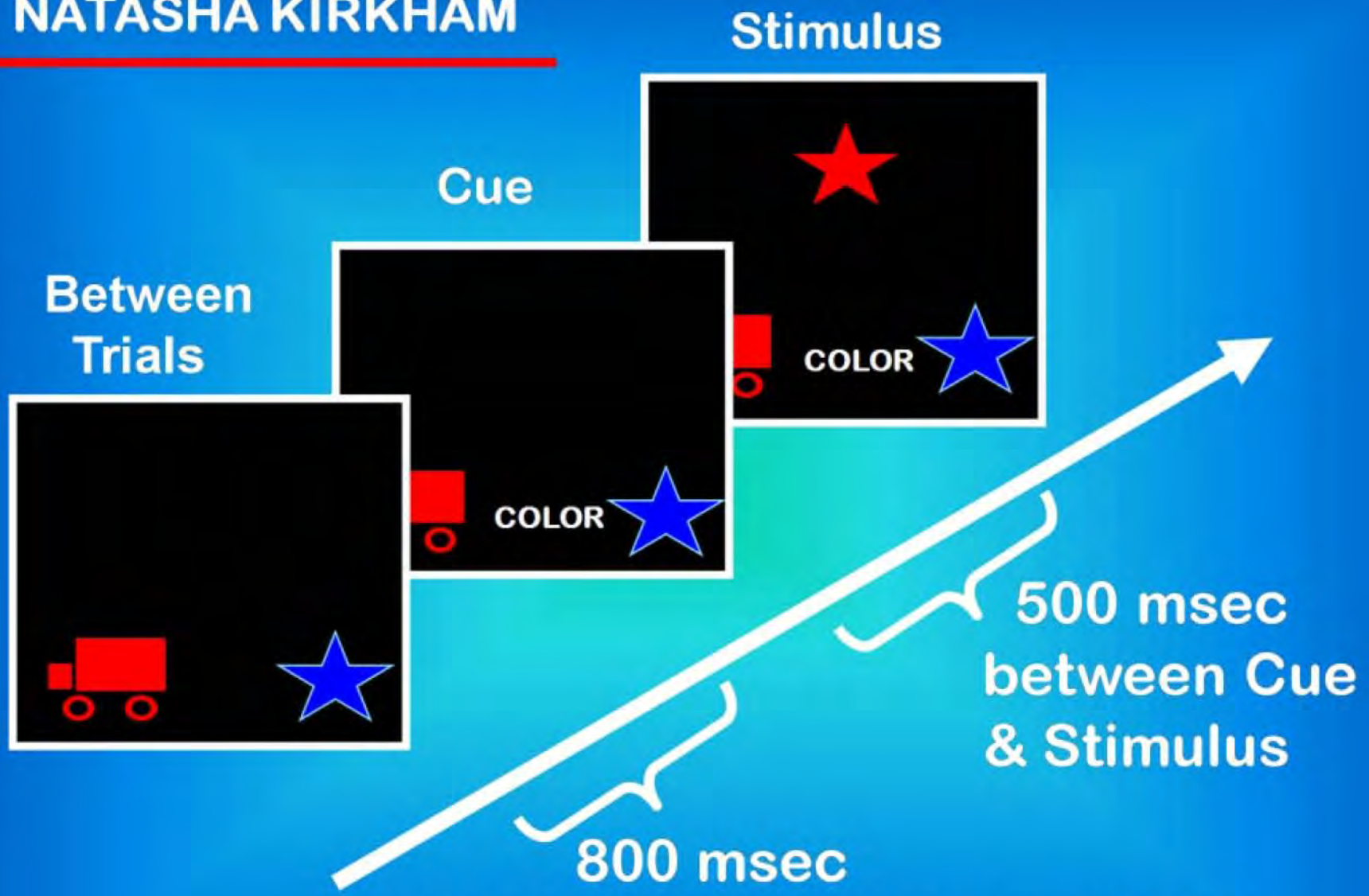
People have assumed that if children knew what they should do, they would do it. (If they did not, they were intentionally misbehaving.)

But, between knowing and implementing, another step, long ignored, is often needed. When there's a strong competing response, that response must be inhibited. And young children may not be able to do that.

Development proceeds by BOTH the acquisition of knowledge and skills and by the increasing ability to inhibit inappropriate reactions that get in the way of demonstrating what is already known.

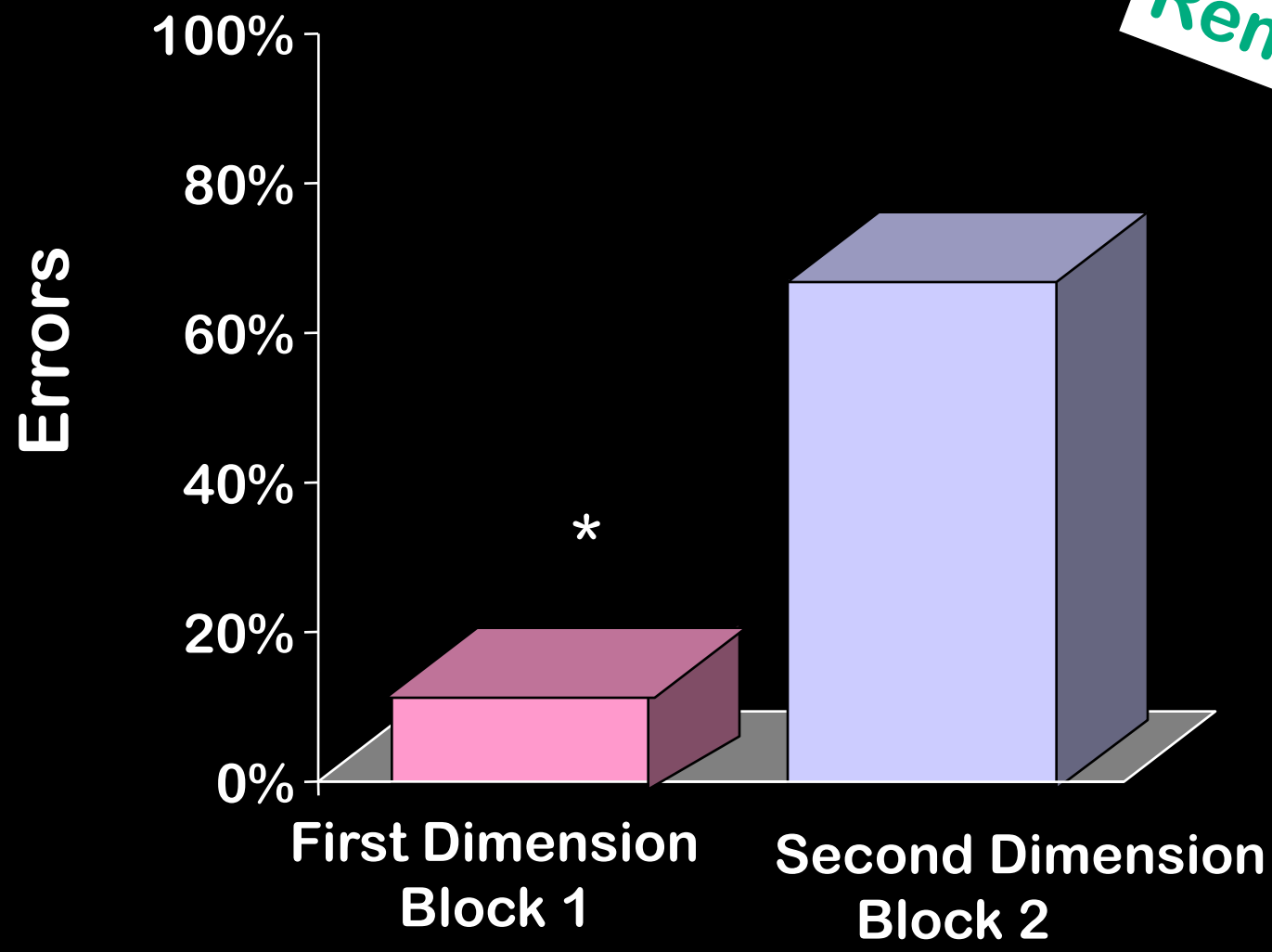
A child may know what he or she should do, and want to do that, but still not be able to act accordingly.

NATASHA KIRKHAM

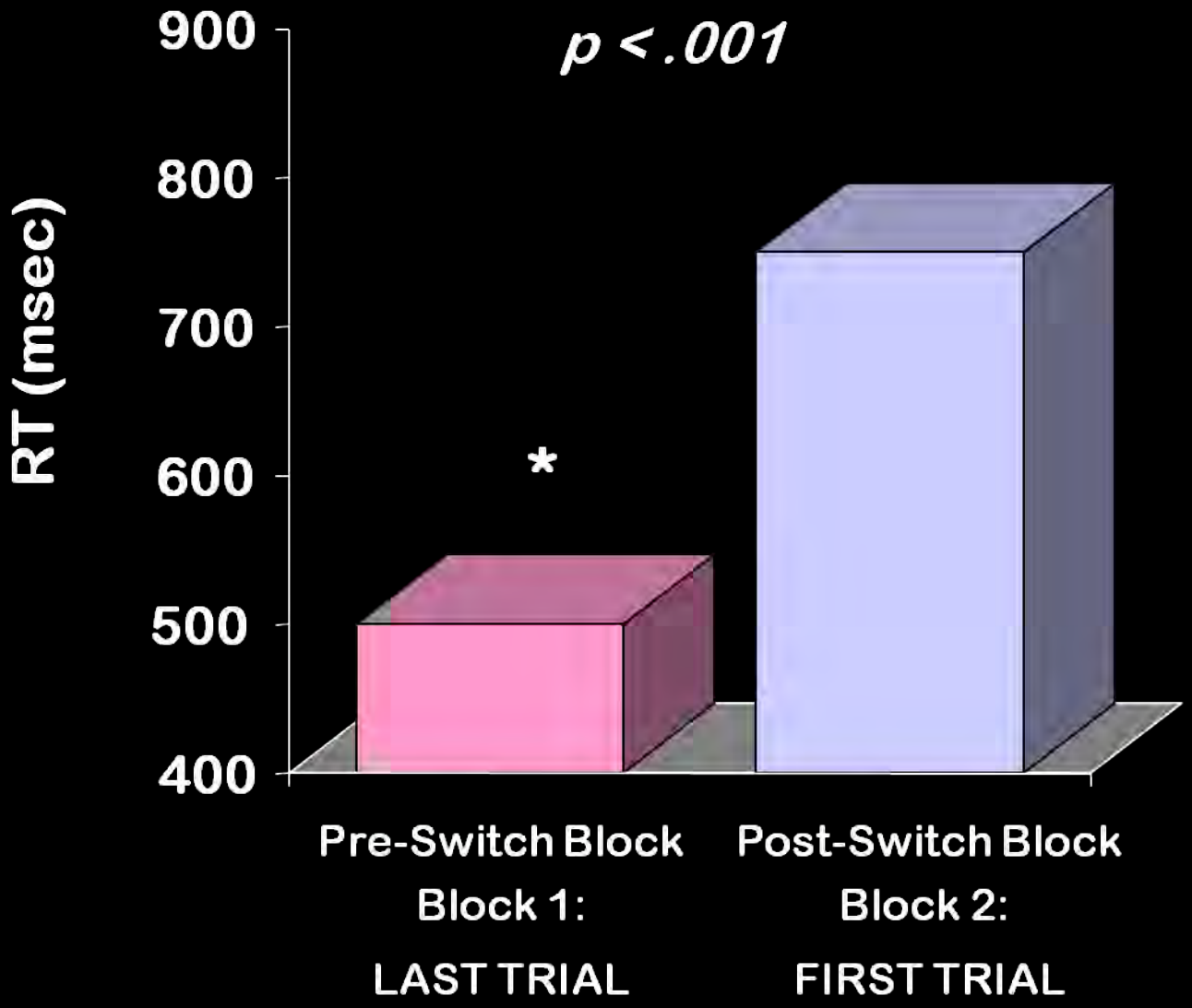


Percentage of Errors by Children of 3 Years on the First and Second Dimension

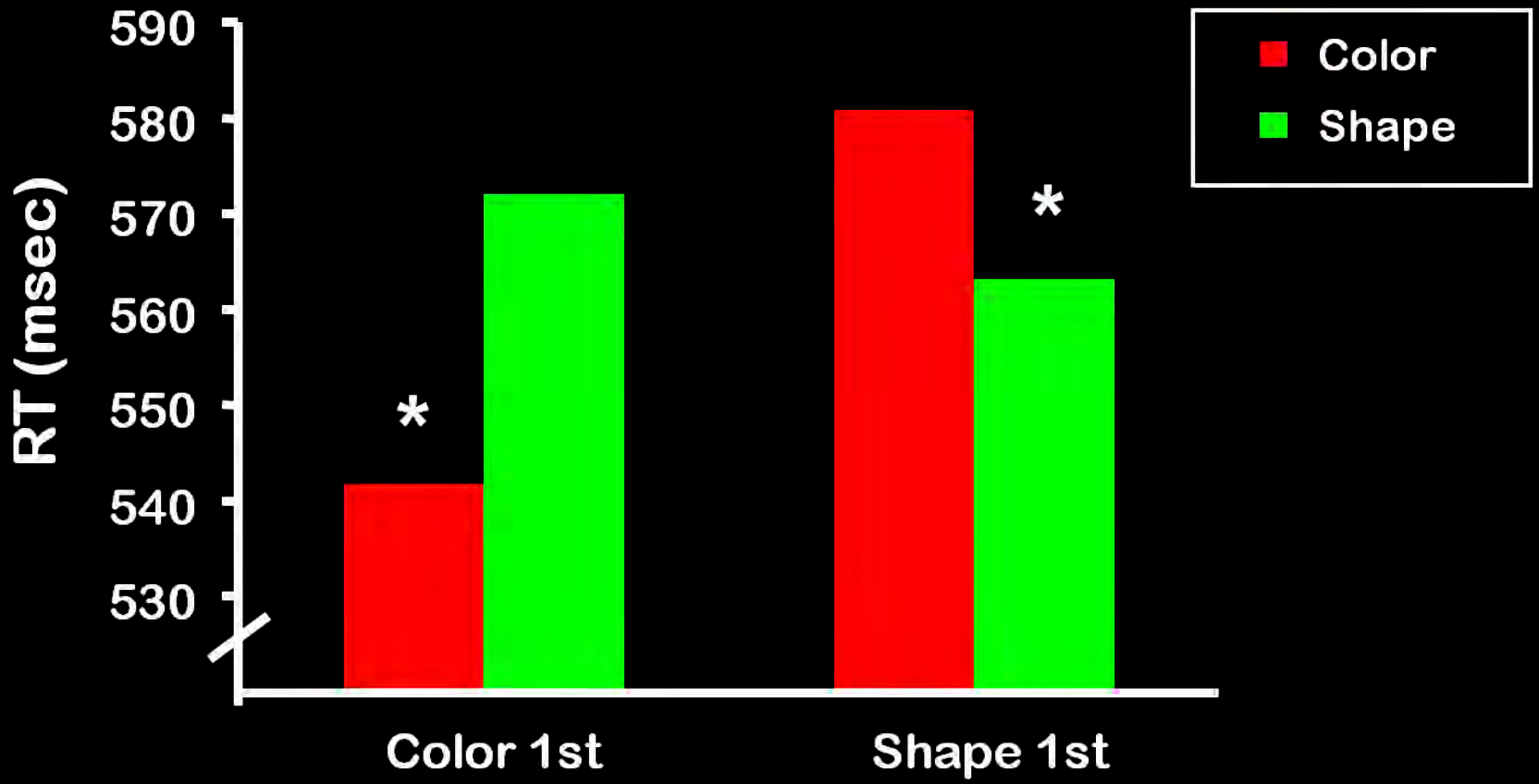
Remember



ADULTS
Last Trial in Block 1 vs. First Trial in Block 2



Effect of First Dimension Sorted on Performance throughout the Entire Session



The first dimension sorted effects performance over all blocks. E.g., If you started with Color, you are Faster on Color for the rest of the session, and Slower on Shape than if you had started with Shape first.

Adults show the same cognitive biases that characterize infants and young children.

Though, in adults, these biases are more subtle and held more in check. We are able to inhibit them.

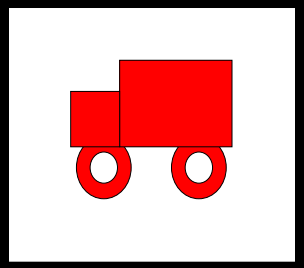
Adele Diamond & Natasha Kirkham

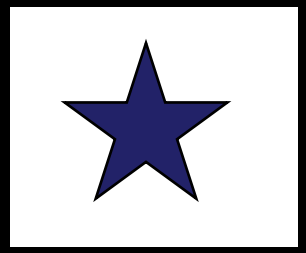
(2005)

Not quite as grown-up as we like to think: Parallels between cognition in childhood and adulthood.

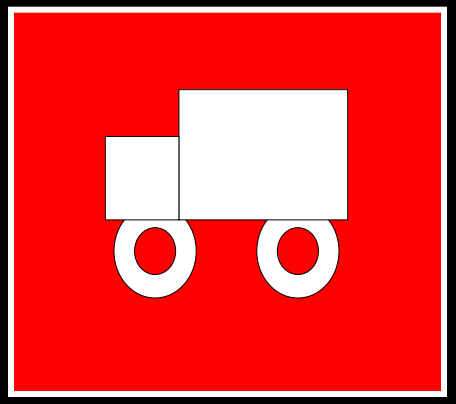
Psychological Science
vol 16, 291-297

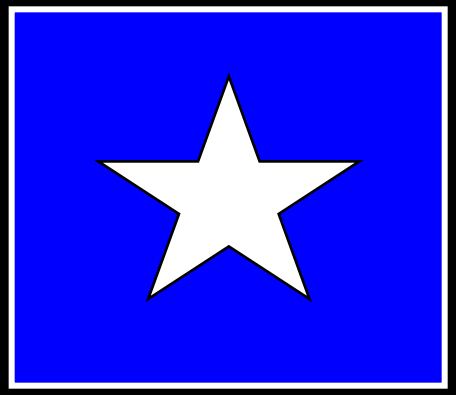
Each dimension is an intrinsic part of the stimulus object.

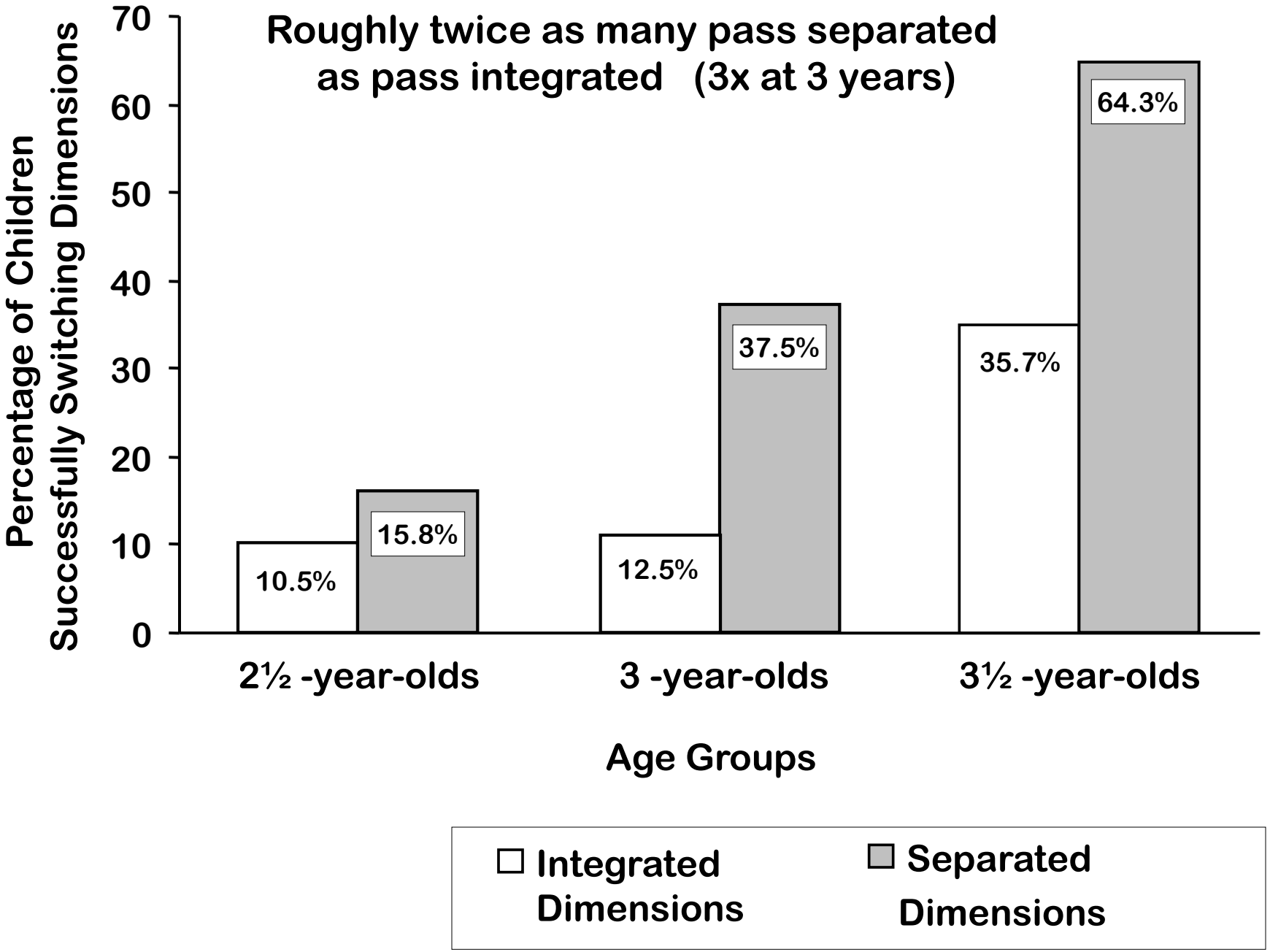


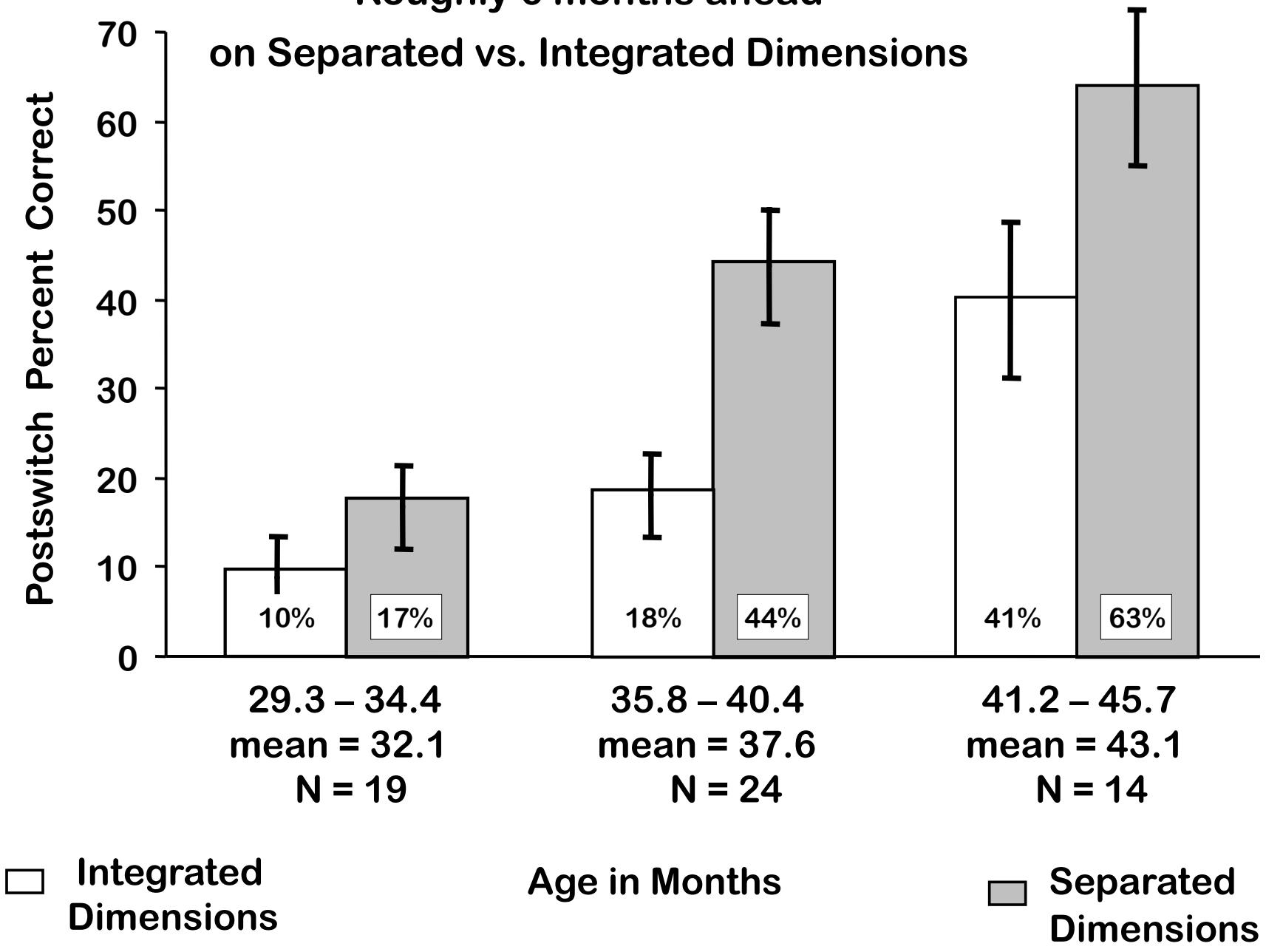


What if both dimensions are not properties of the stimulus?





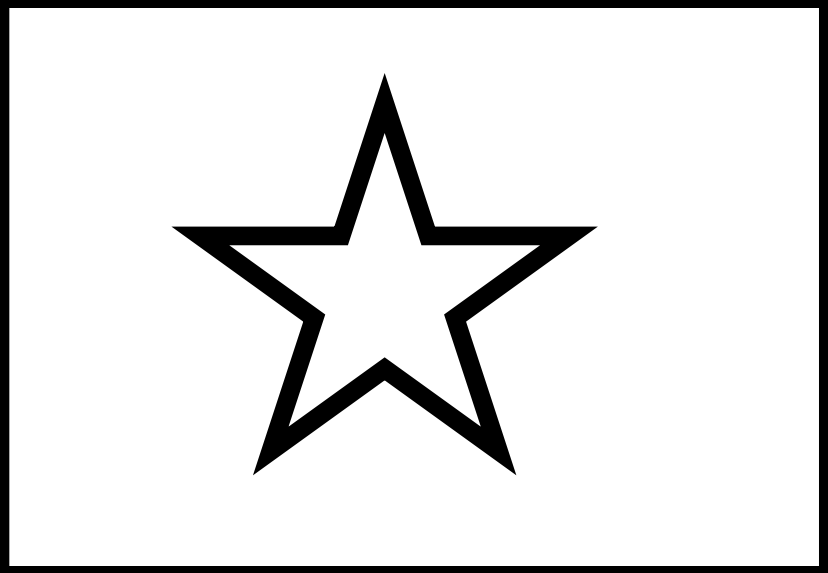

Roughly twice as many pass separated as pass integrated (3x at 3 years)
Percentage of Children Successfully Switching Dimensions
70
60
50
40
30
20
10
0
10.5%
15.8%
12.5%
37.5%
35.7%
64.3%
2½ -year-olds
3 -year-olds
3½ -year-olds
Age Groups
Integrated Dimensions
Separated Dimensions

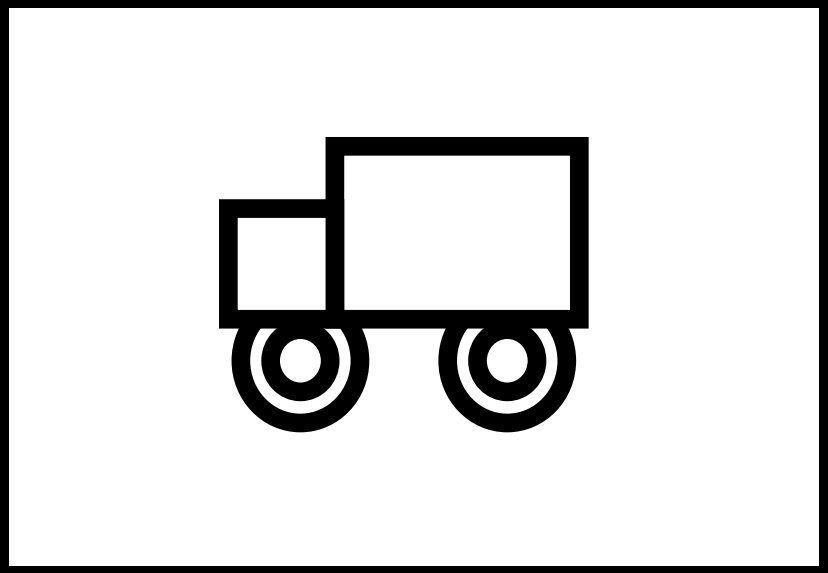

Roughly 6 months ahead
on Separated vs. Integrated Dimensions
Postswitch Percent Correct
70
60
50
40
30
20
10
0
10%
17%
18%
44%
41%
63%
29.3 – 34.4
mean = 32.1
N = 19
35.8 – 40.4
mean = 37.6
N = 24
41.2 – 45.7
mean = 43.1
N = 14
Integrated Dimensions
Age in Months
Separated Dimensions

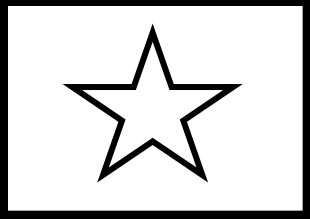
Children's performance on the dimensional change card sort task: Separation aids ability to switch dimensions

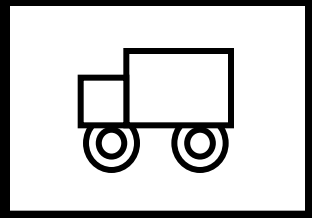
Adele Diamond,
Stephanie Carlson, & Danielle Beck

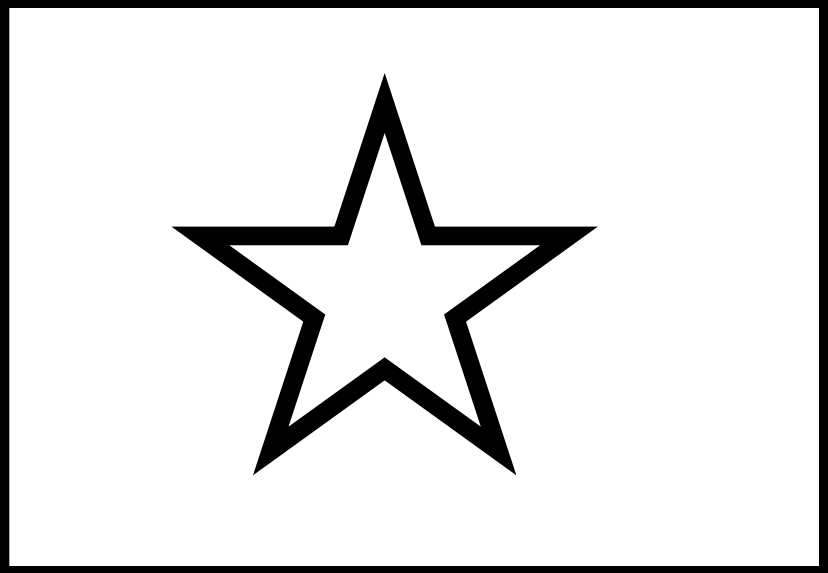
(2005)
Developmental Neuropsychology
vol 28, p.689-729

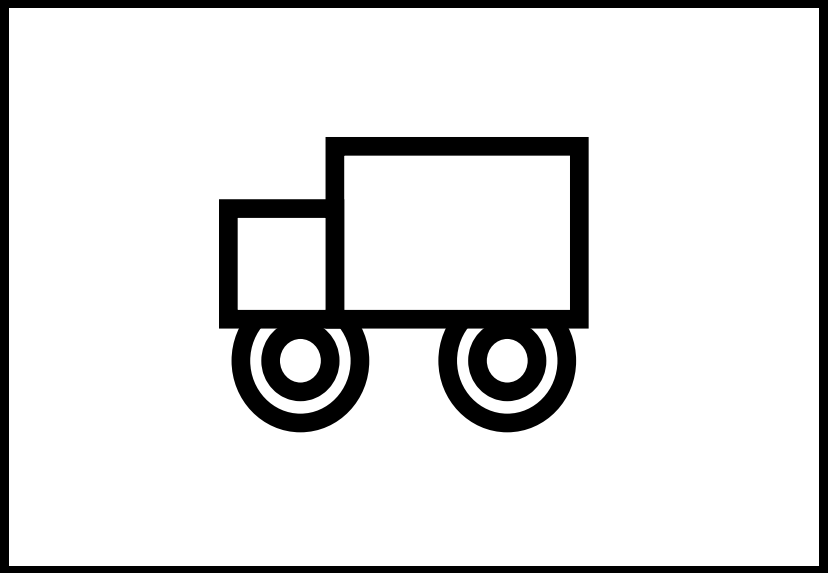


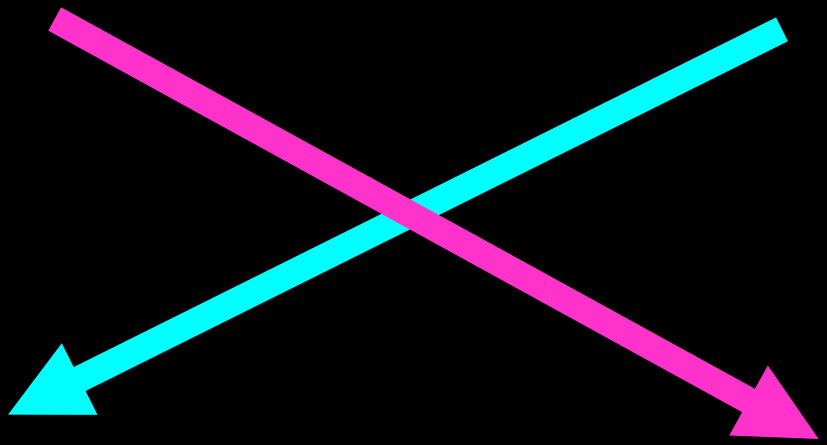


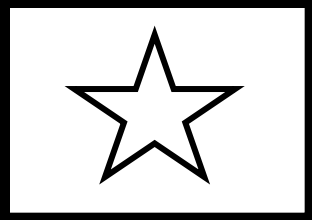


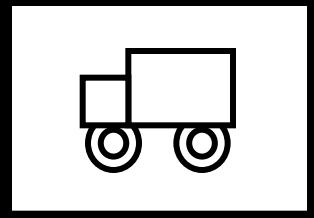












- Patricia Brooks, Julie B. Hanauer, Barbara Padowska, & Heidy Rosman
(2003)
The role of selective attention in preschoolers' rule use in a novel dimensional card sort.
Cognitive Development
vol 117, p 1-21

- Josef Perner & Birgit Lang
(2002)
What causes 3-year olds' difficulty on the dimensional change card sorting task?
Infant & Child Development
vol 11, p. 93-105

Developmental Progression

Succeed at….	at Age
Reversals (intra-dimensional shift)	2½
- extra-dimensional switches (1 dimen. to another) -	
DCCS - Separated Dimensions	3½
DCCS (Standard) - Integ. Dimen.	4½
DCCS - Mixed Block…… (switching dimensions randomly across trials)	7½

Remember

Working Memory & just holding information in mind (Short-Term Memory) are distinct.

Congruent Trials

Push Left

Incongruent Trials

Push Right

Push Right

Push Left

A Classic Simon Task

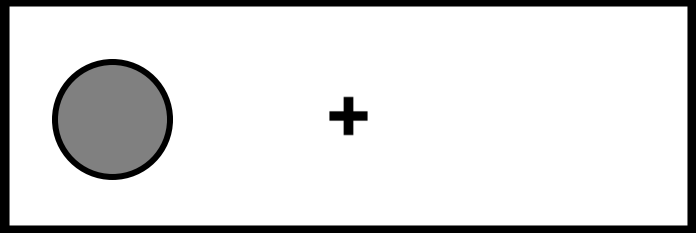
A Simon Task

The Rules are:

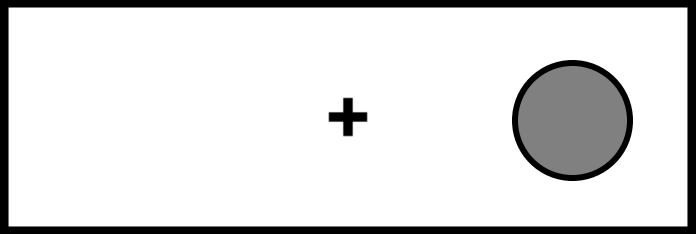
Whenever you see a BUTTERFLY, press LEFT.

Whenever you see a FROG, press RIGHT.

Dots - Congruent

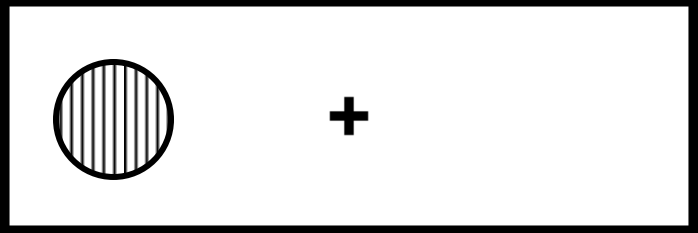


Push Left

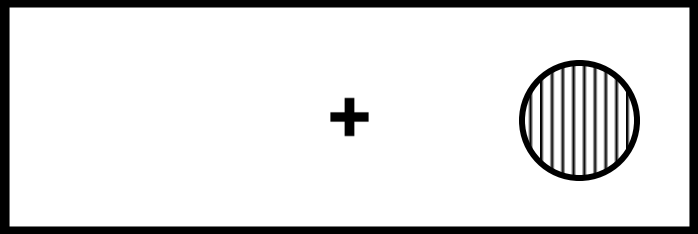


Push Right

Dots - Incongruent



Push Right



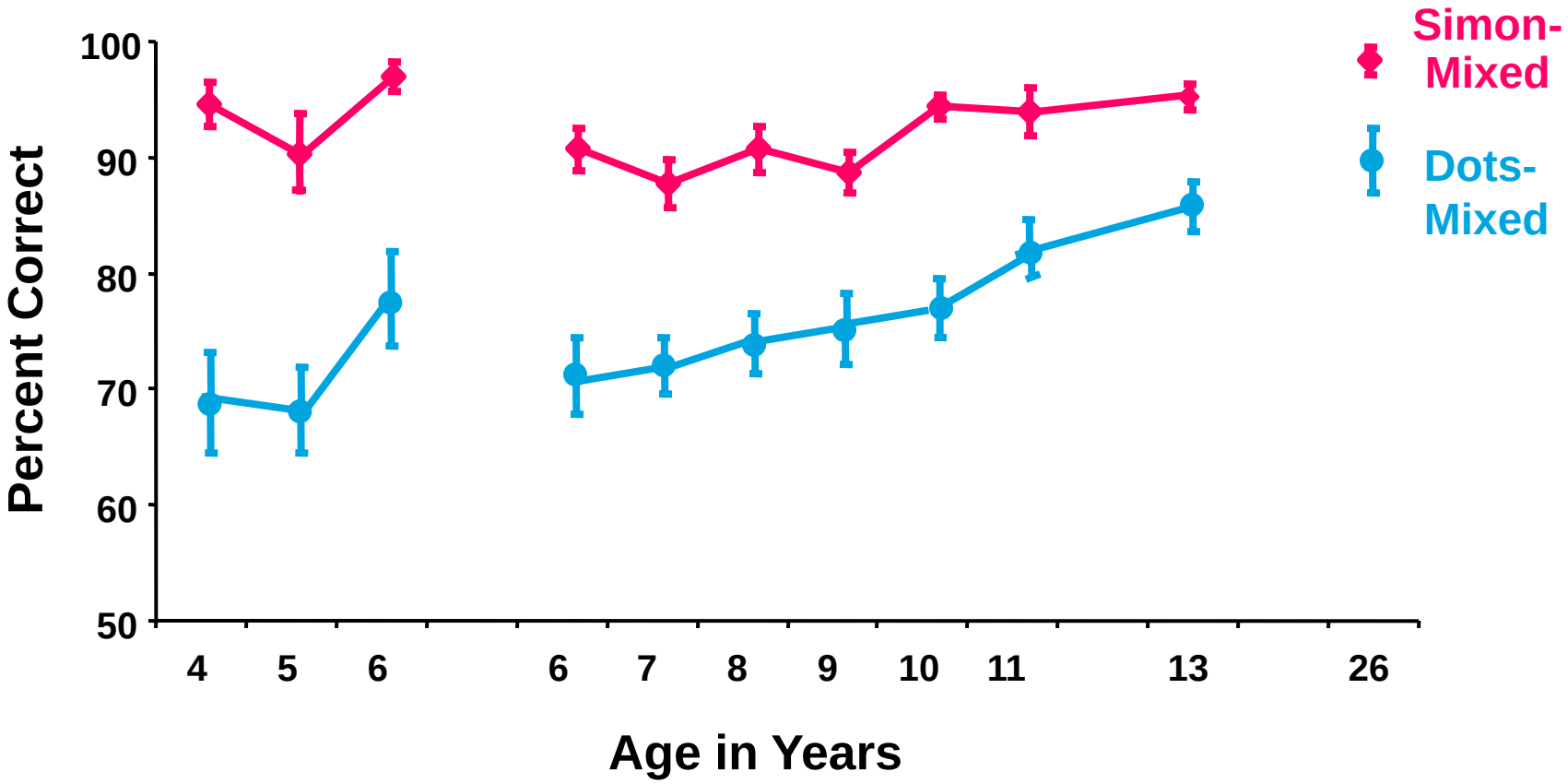
Push Left

Whenever you see a Gray Disc, press on the SAME side as the stimulus.

Whenever you see a B&W Striped Disc, press on the side OPPOSITE the stimulus.

Requires the extra step of mentally translating same/opposite into Left or Right.

Comparison of Mixed Conditions of Hearts-Flowers and Simon in Percentage of Correct Responses



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& Adele Diamond

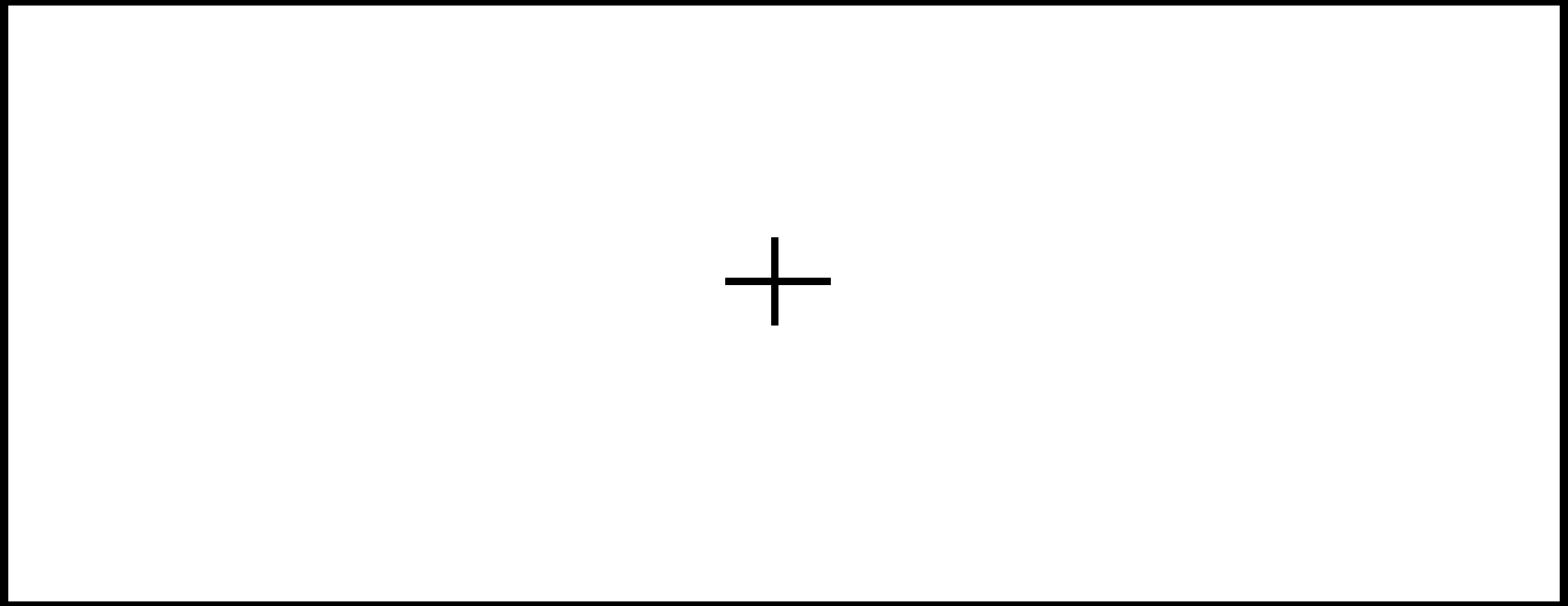
published in Neuropsychologia

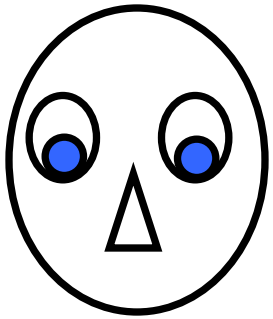
vol 44, pages *2037 - 2078*

EYES - CONGRUENT

When the eyes are looking straight down, press on the same side as the eyes.

PRESS WHERE THE EYES ARE LOOKING





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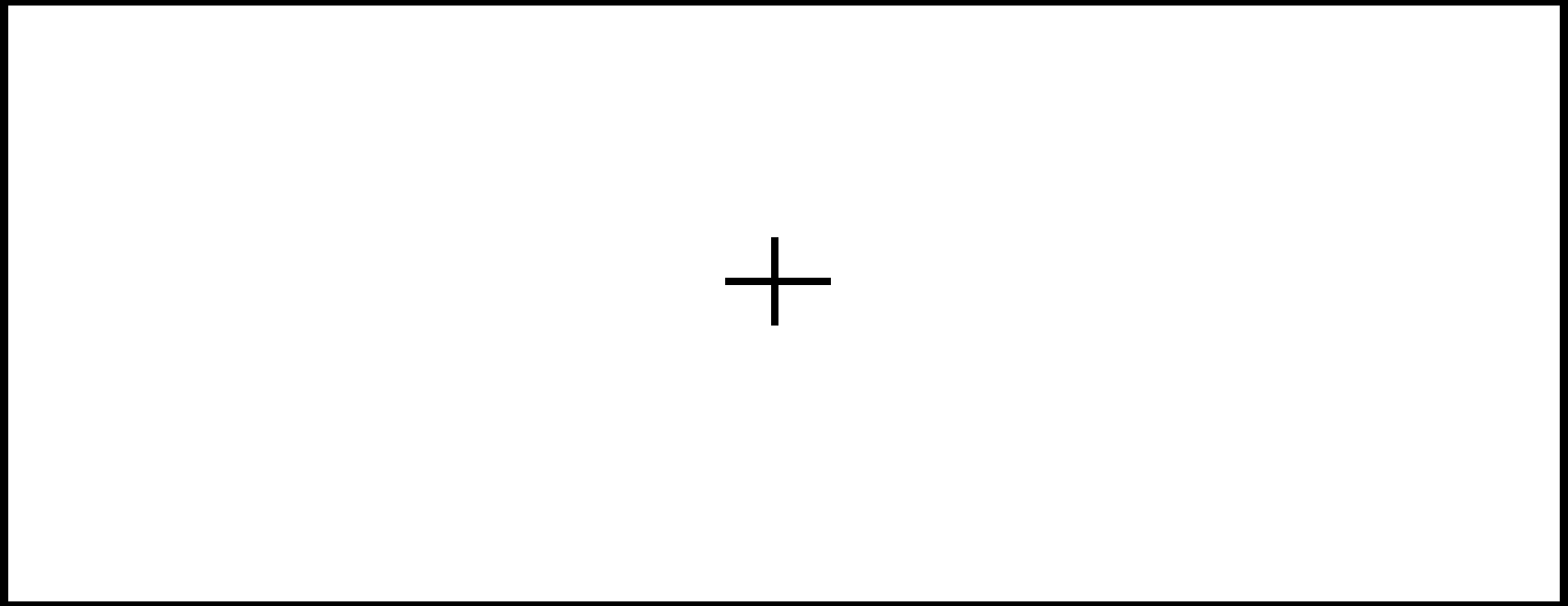
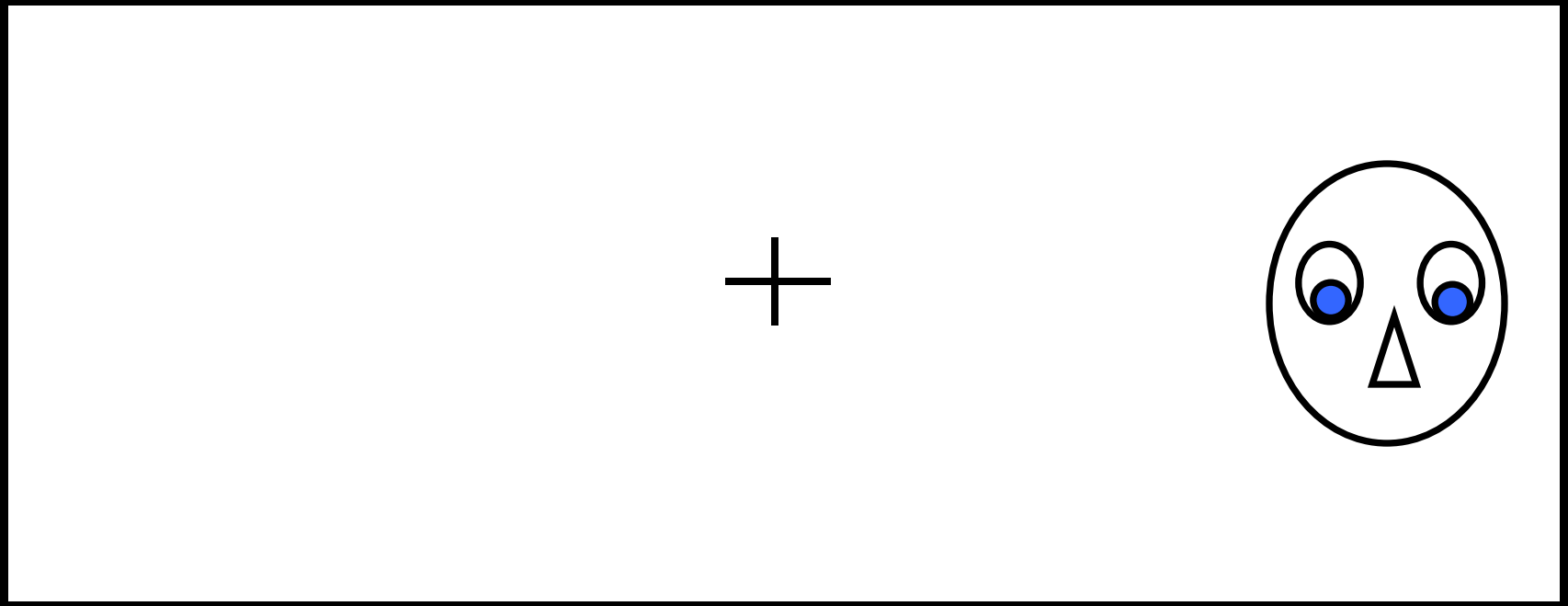
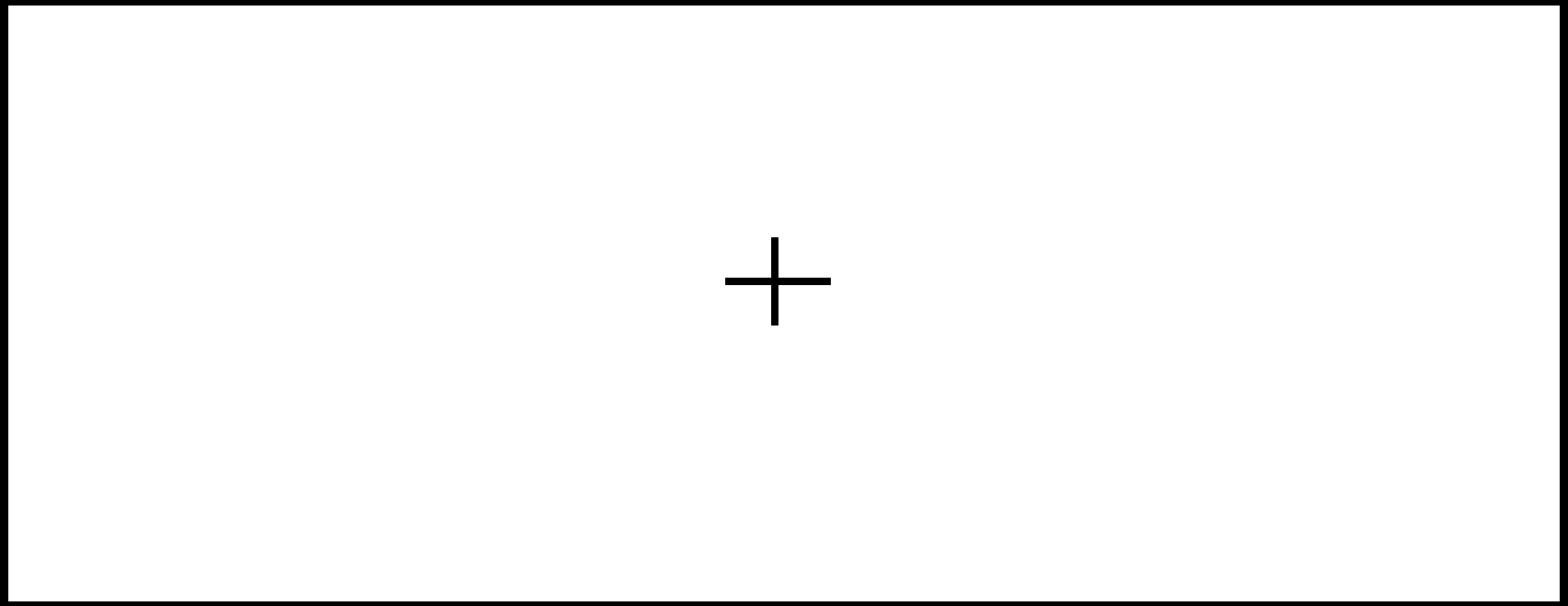


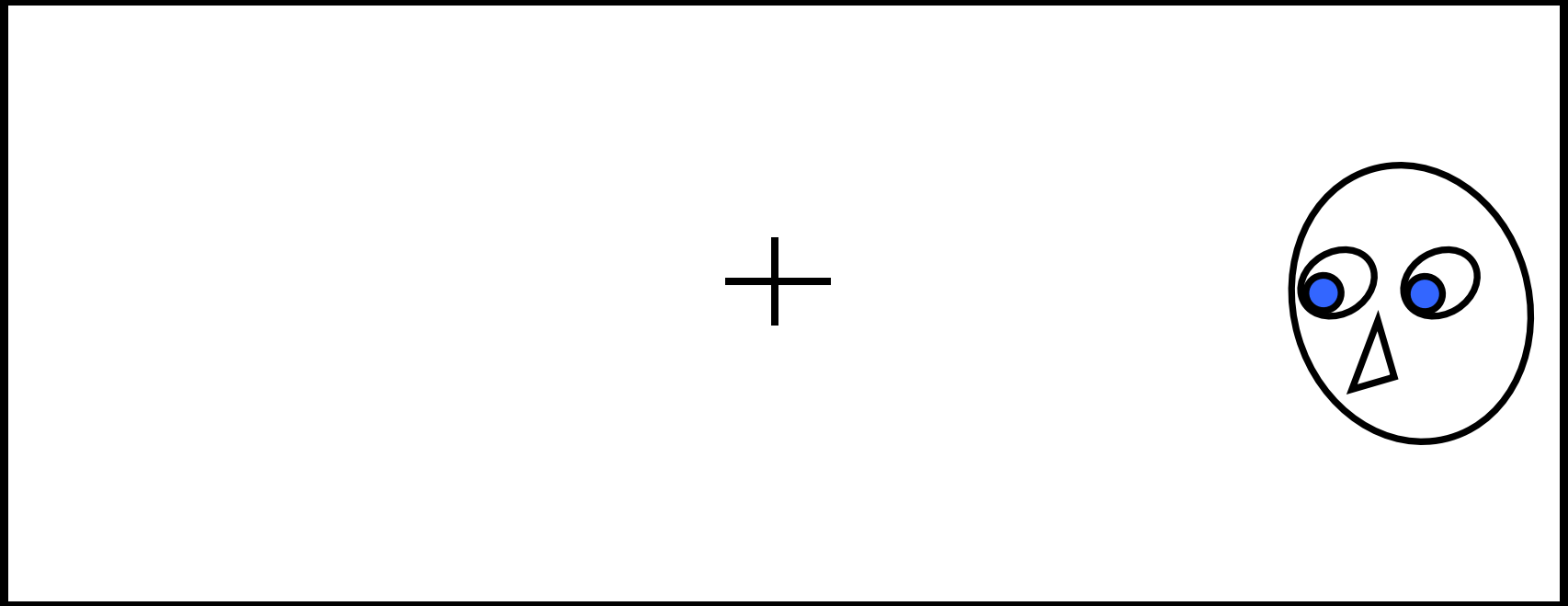


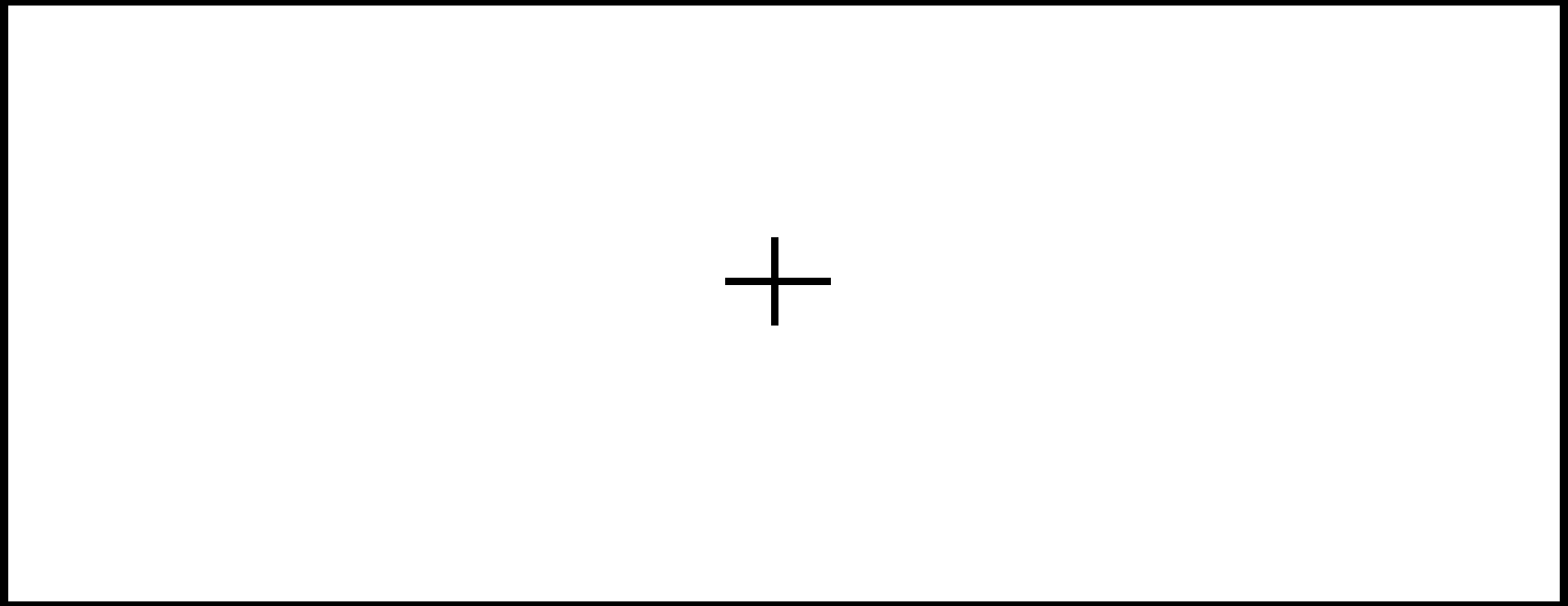
EYES - INCONGRUENT

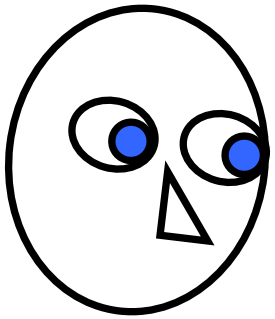
When the eyes are looking diagonally to the other side, press on the side opposite to where the eyes are.

PRESS WHERE THE EYES ARE LOOKING







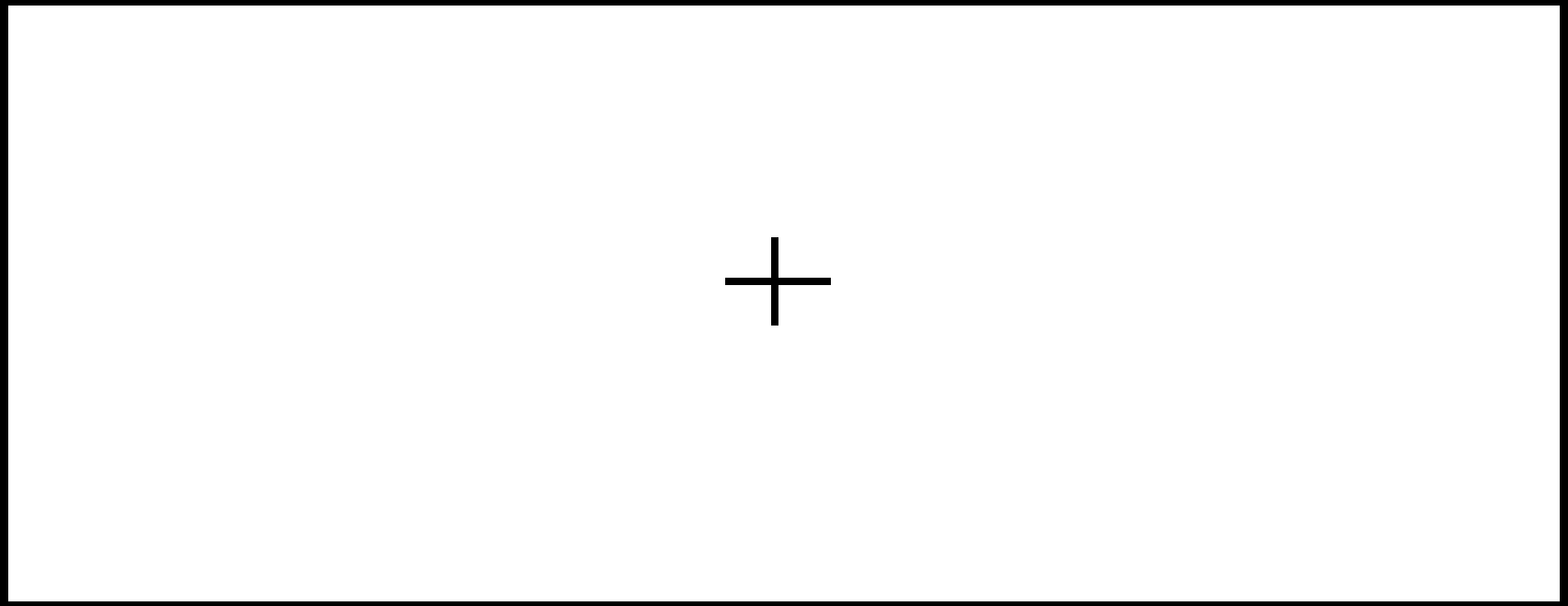


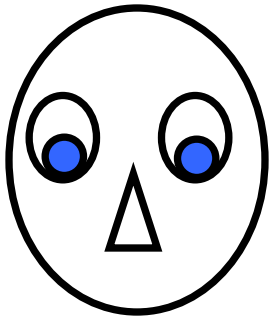
EYES - MIXED

Now sometimes the eyes will be looking straight down and sometimes they will be looking diagonally to the opposite side.

Remember:

PRESS WHERE THE EYES ARE LOOKING





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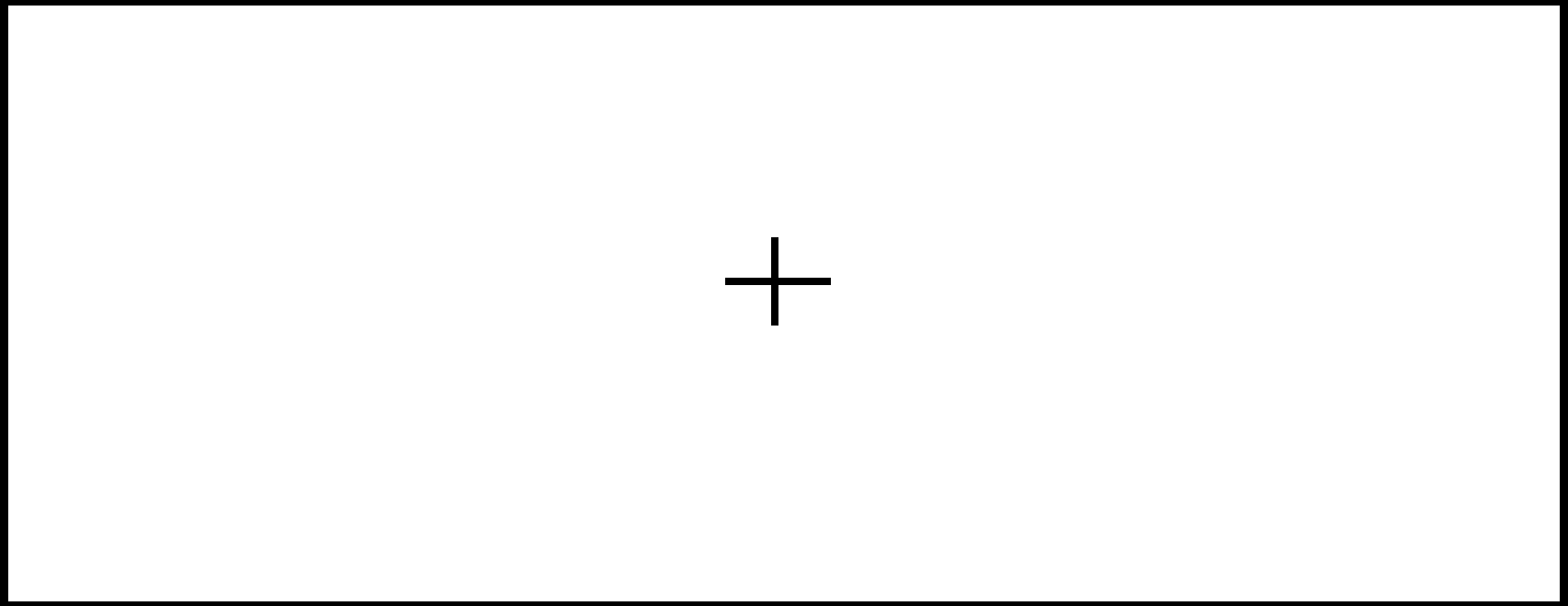

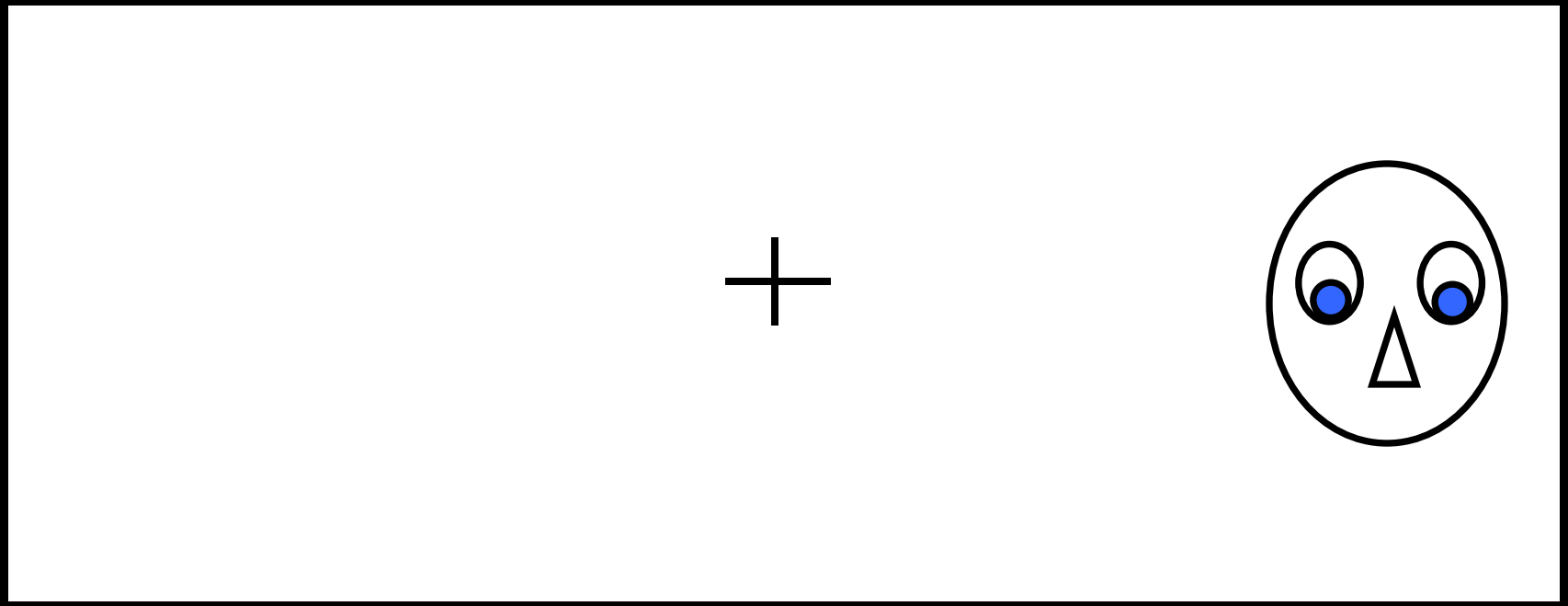

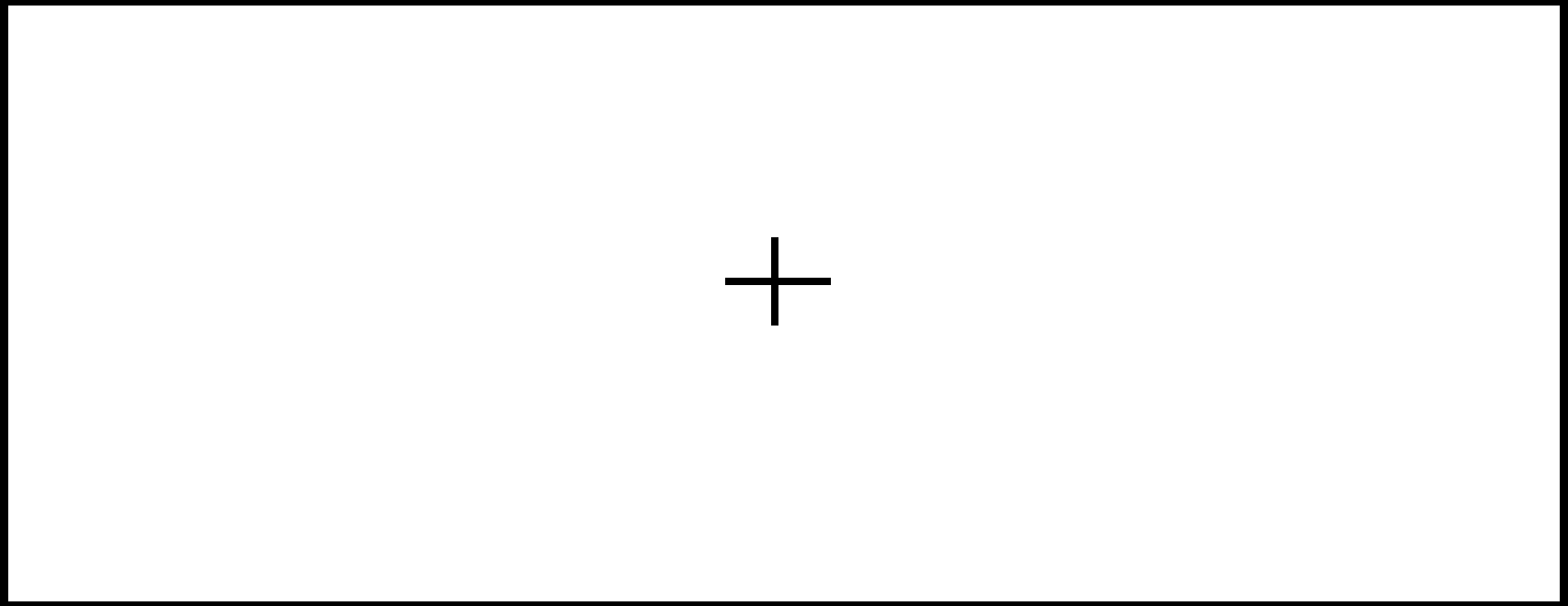

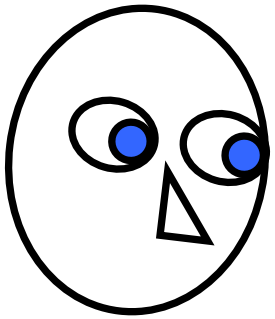

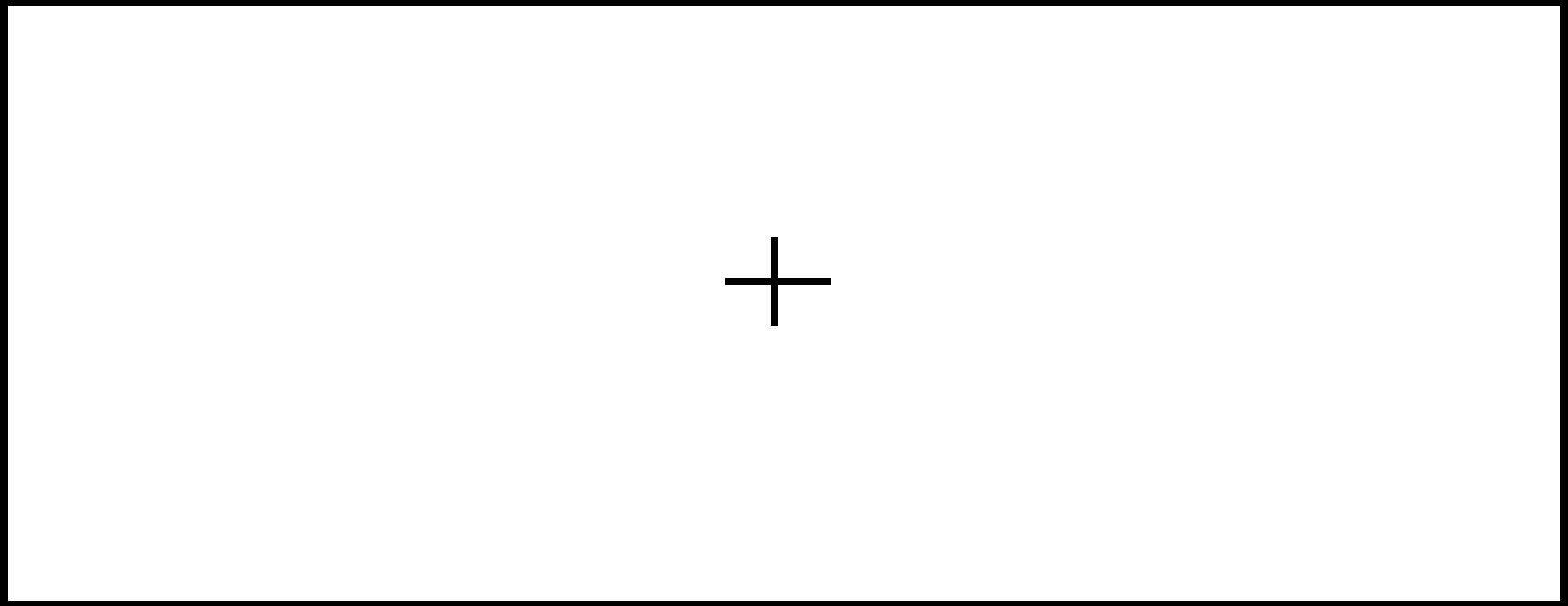

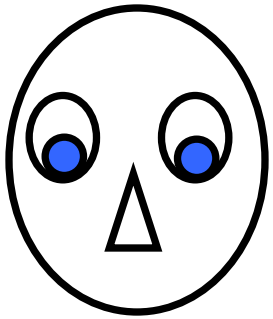

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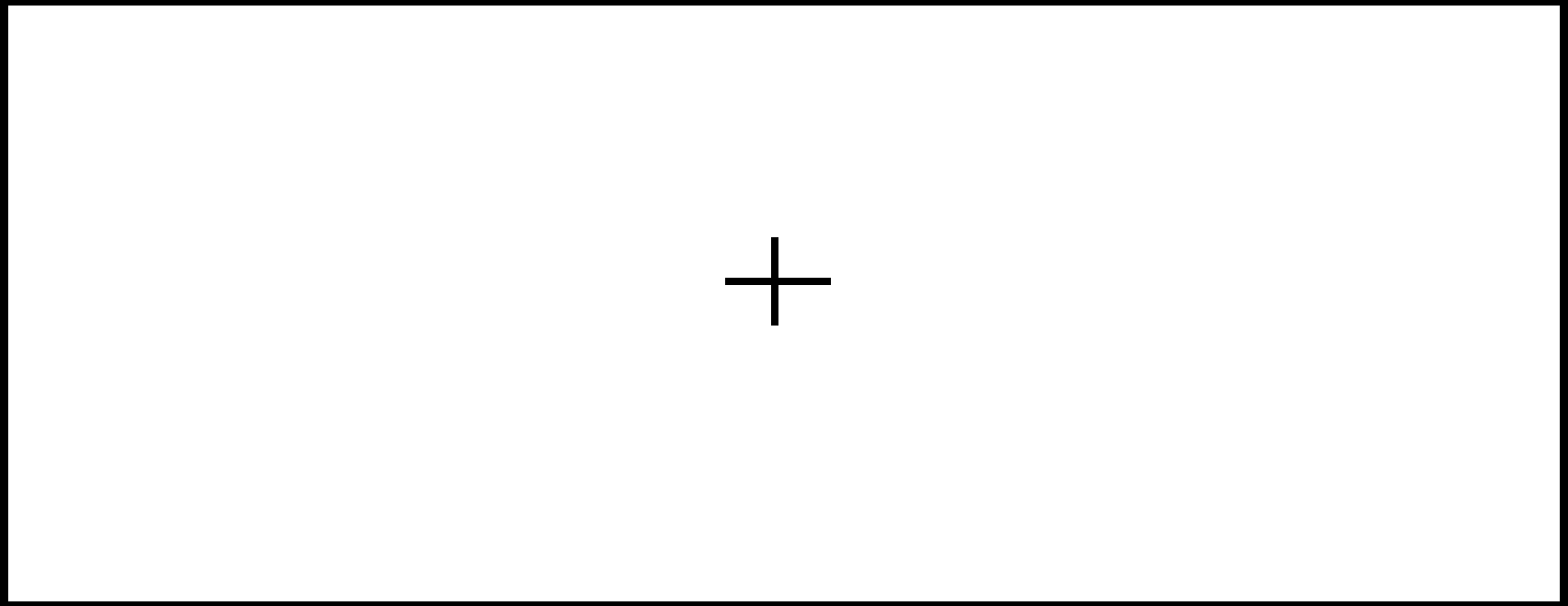
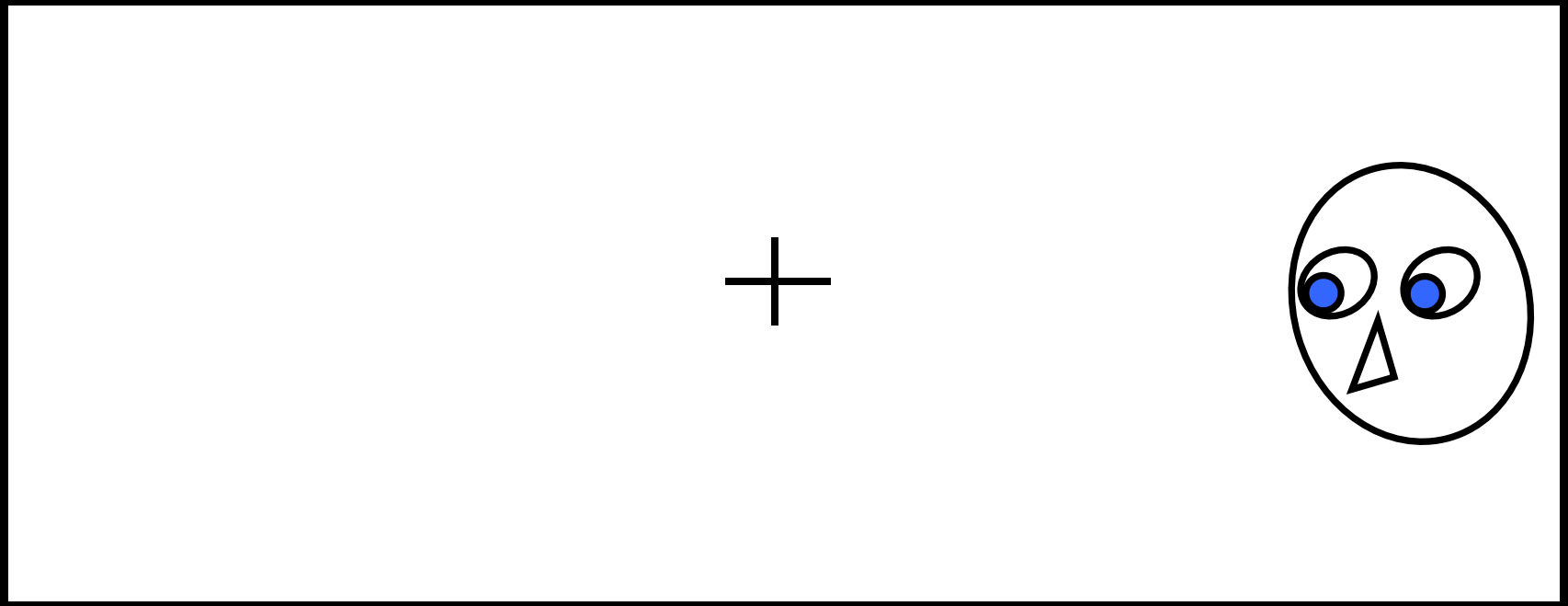
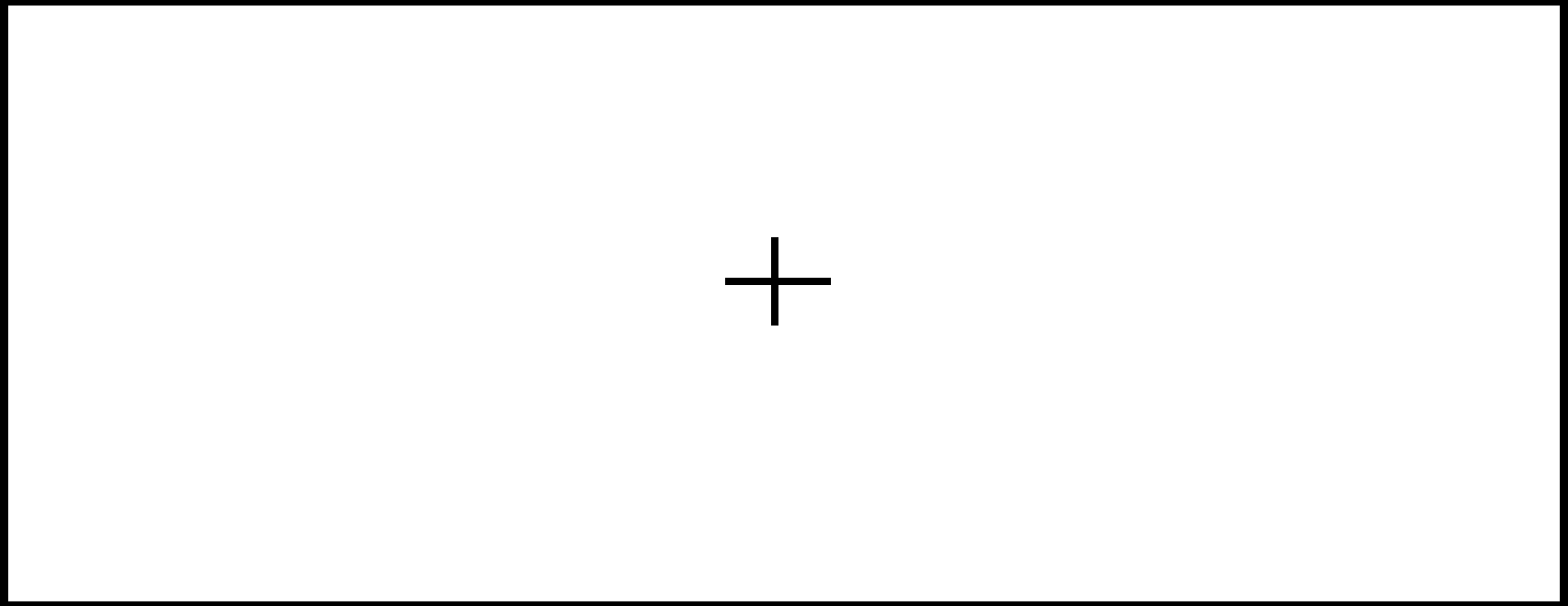
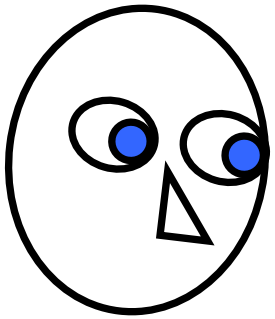
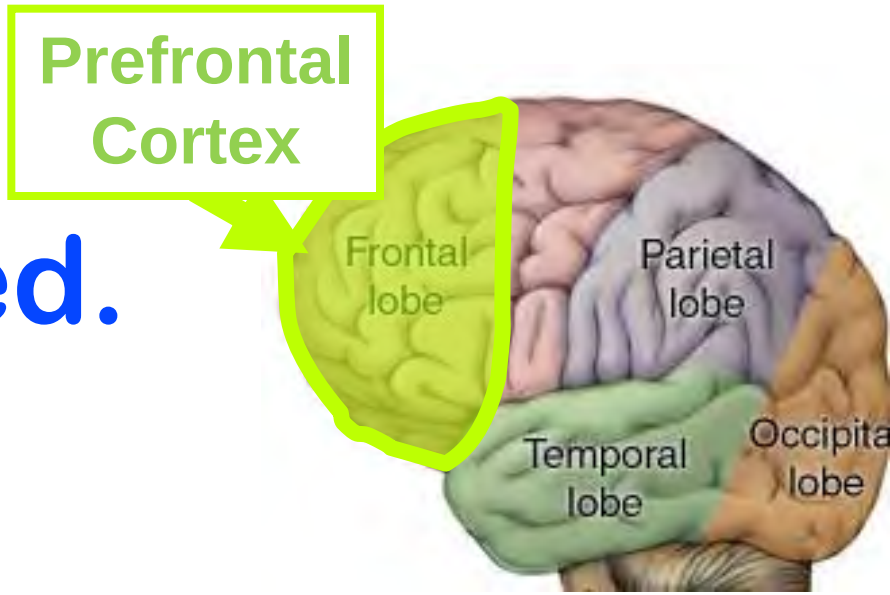






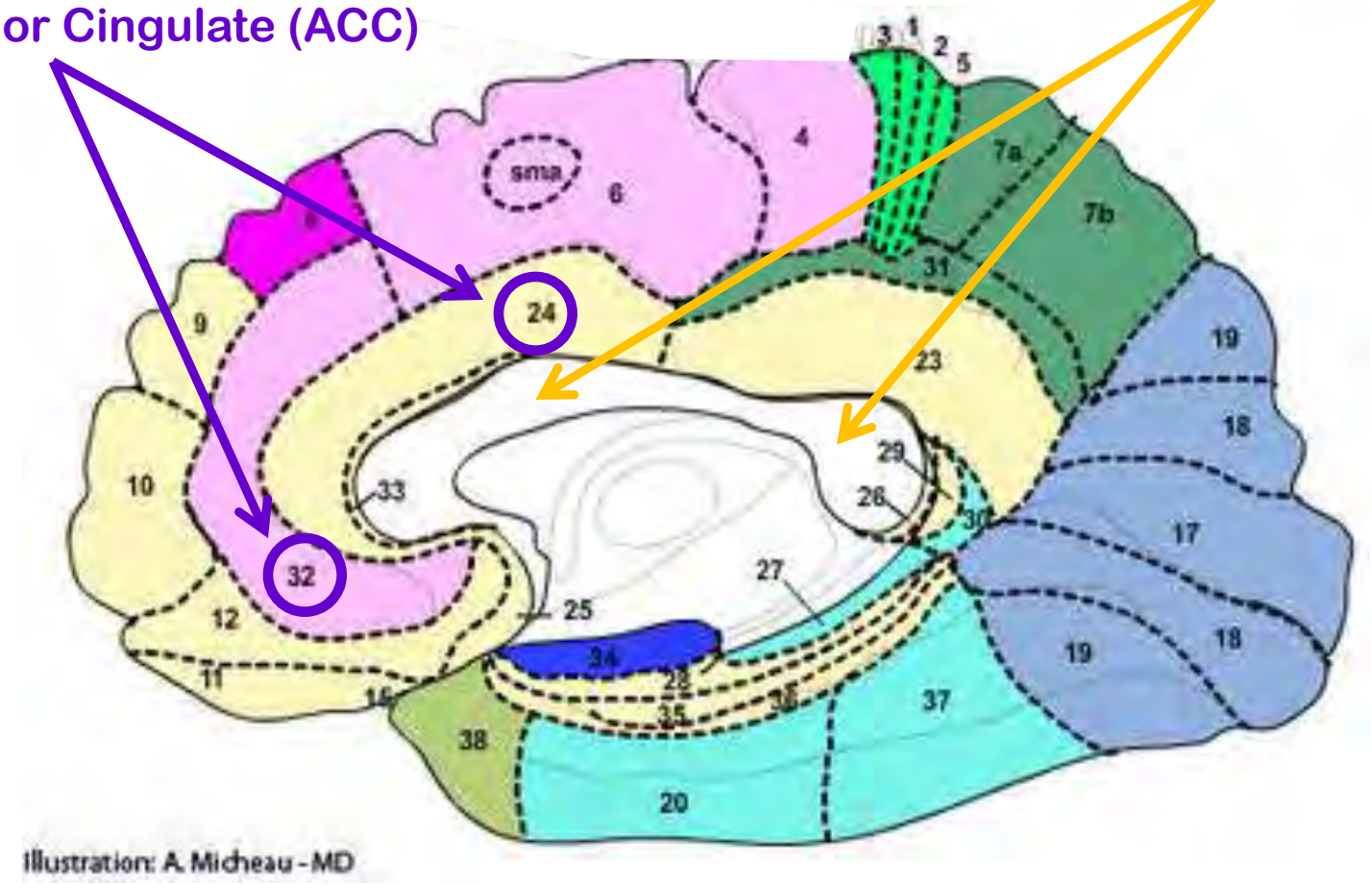


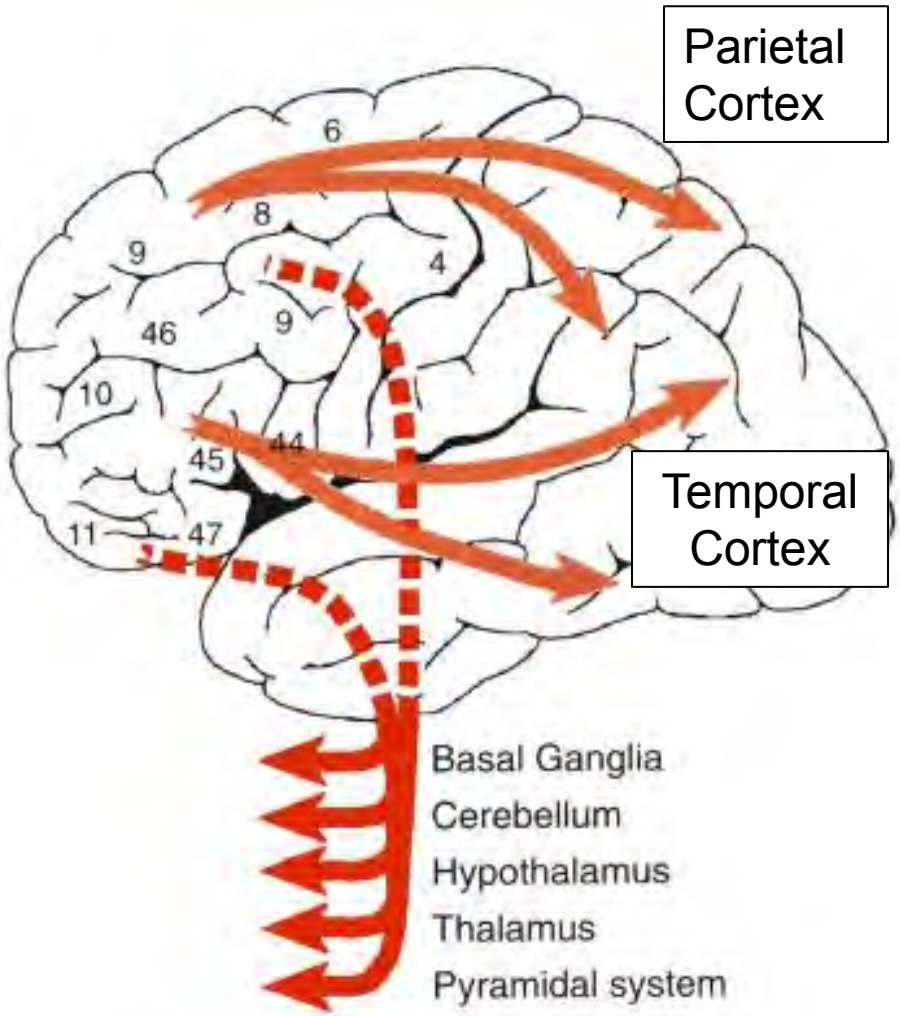
Executive Functions depend on Prefrontal Cortex and the other neural regions with which it is interconnected.

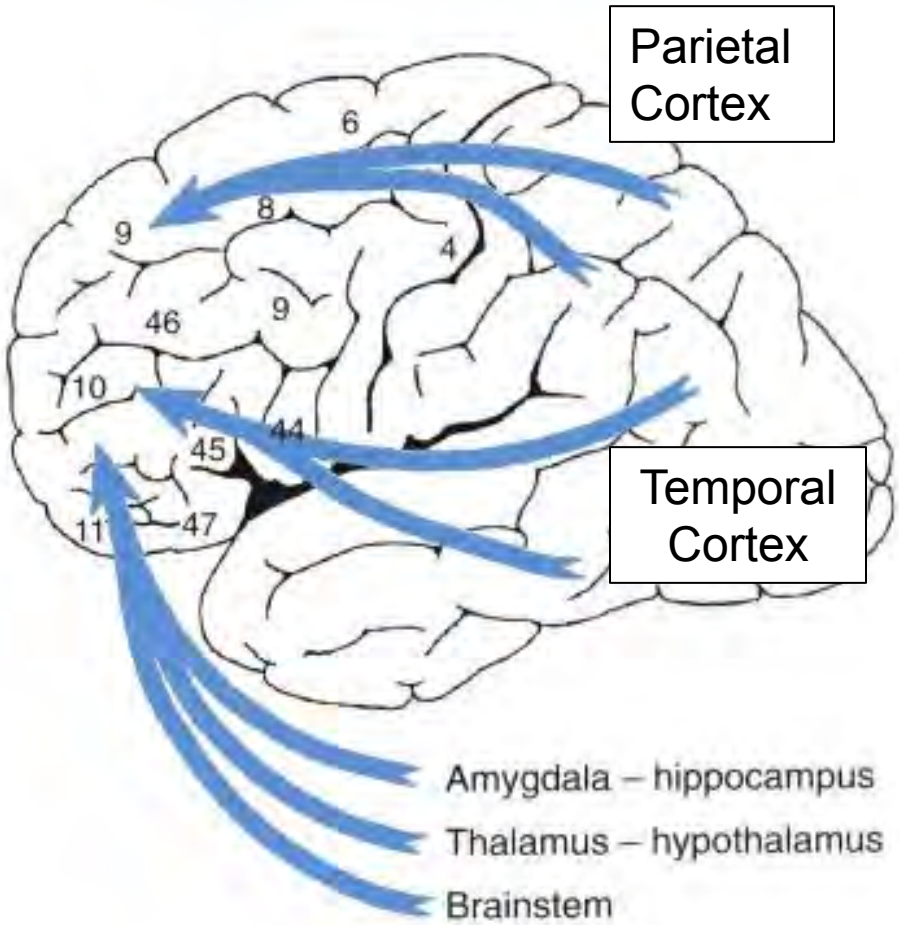


Corpus Callosum

Anterior Cingulate (ACC)




Parietal Cortex
Temporal Cortex
6
8
9
4
46
9
10
44
45
11
47
Basal Ganglia
Cerebellum
Hypothalamus
Thalamus
Pyramidal system


Parietal Cortex
Temporal Cortex
6
8
9
4
46
9
10
44
45
11
47
Amygdala – hippocampus
Thalamus – hypothalamus
Brainstem

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

Much of presynaptically released dopamine doesn't reach the postsynaptic neuron, and needs to be cleared from the space between and around the neurons.

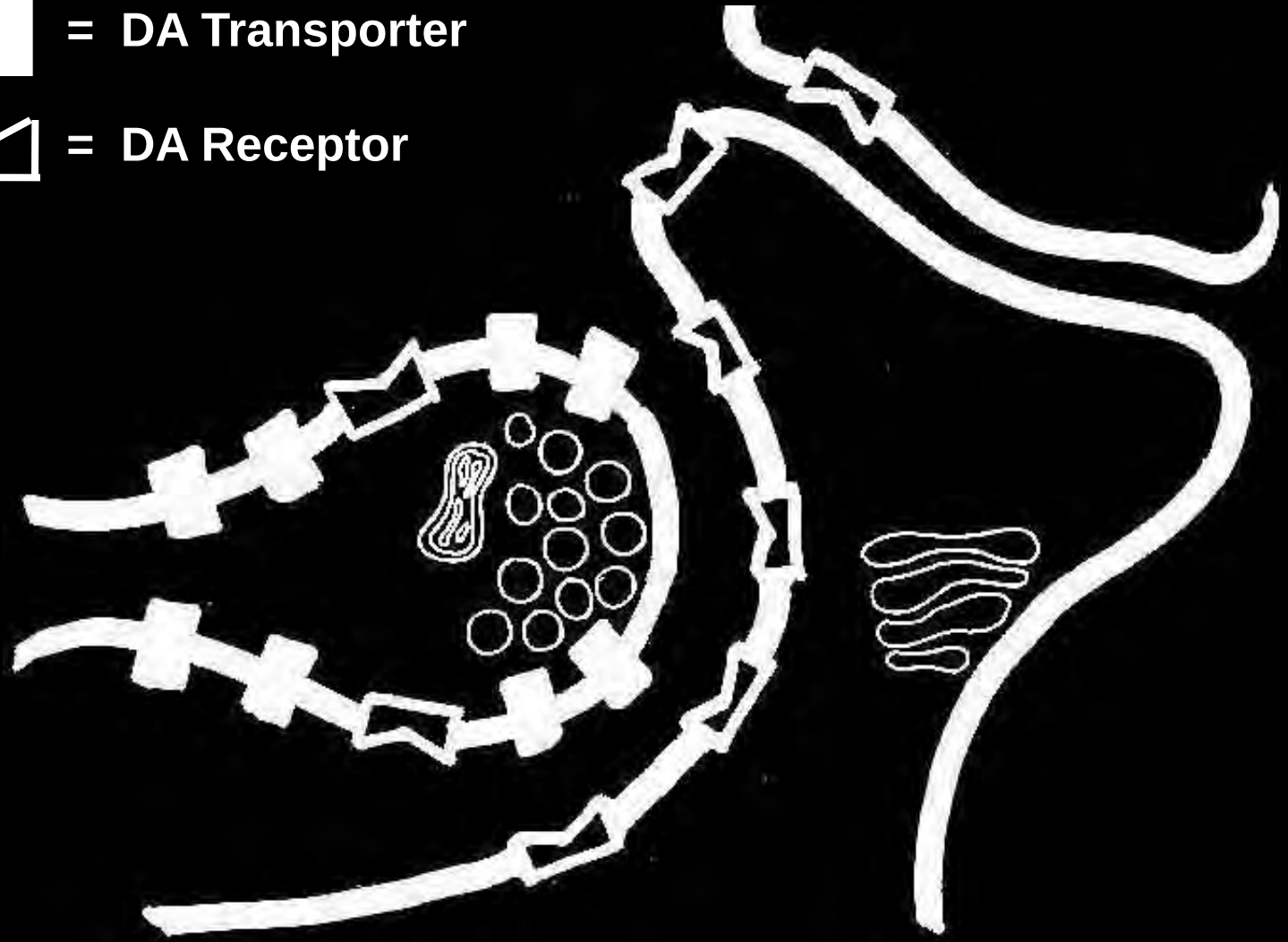
The best mechanism from clearing away released dopamine is by dopamine transporter (DAT) protein.

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

Striatum

= DA Transporter

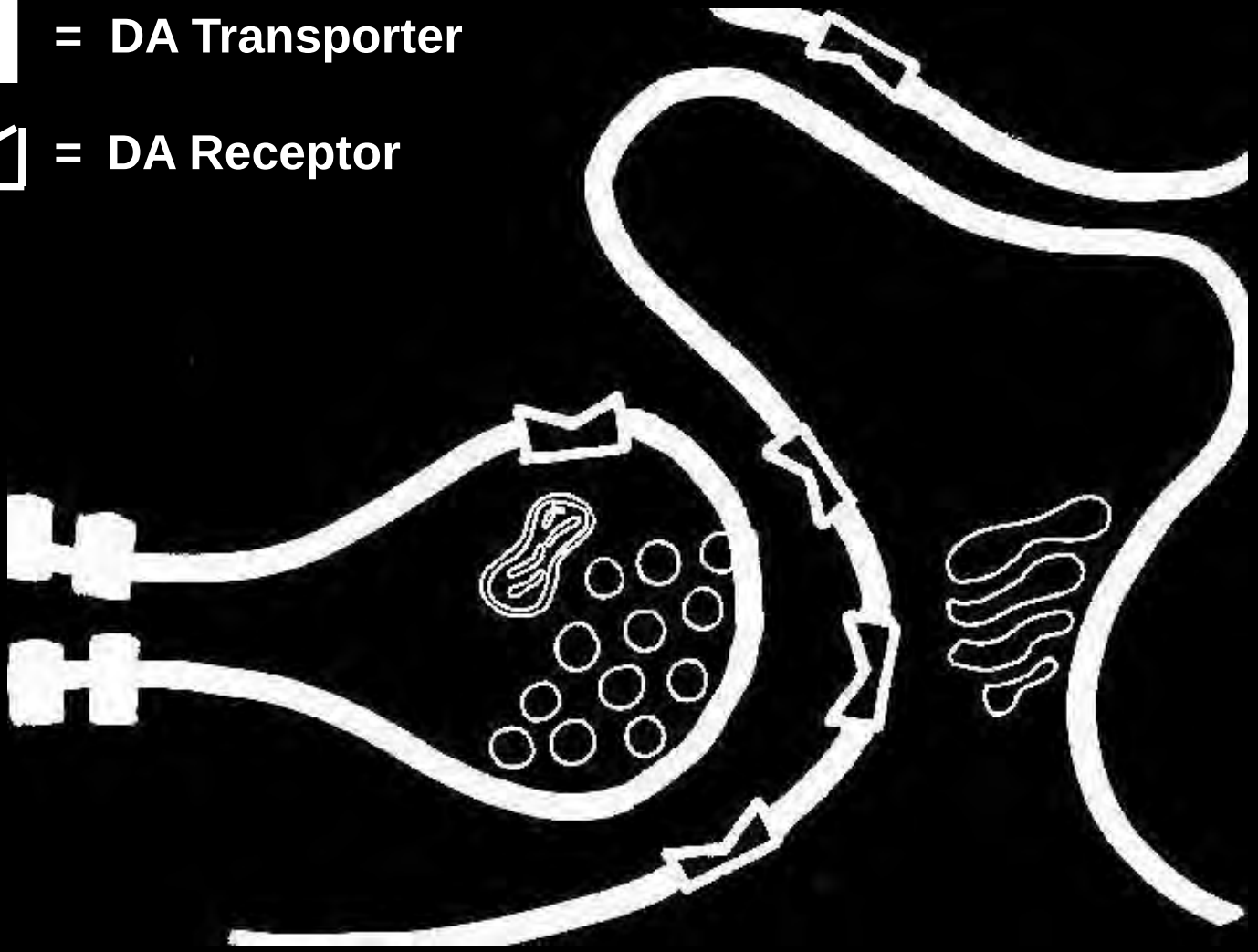
= DA Receptor



Prefrontal Cortex

= DA Transporter

= DA Receptor



Polymorphisms of the dopamine transporter (DAT1) gene should be important for the striatum.

The striatum is implicated most in the impulsive & hyperactive aspects of ADHD;
whereas PFC is implicated most in the cognitive deficits.

Polymorphisms of the dopamine transporter (DAT1) gene should be important for the striatum and for the forms of ADHD linked to the striatum (ADHD that includes hyperactivity)

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)

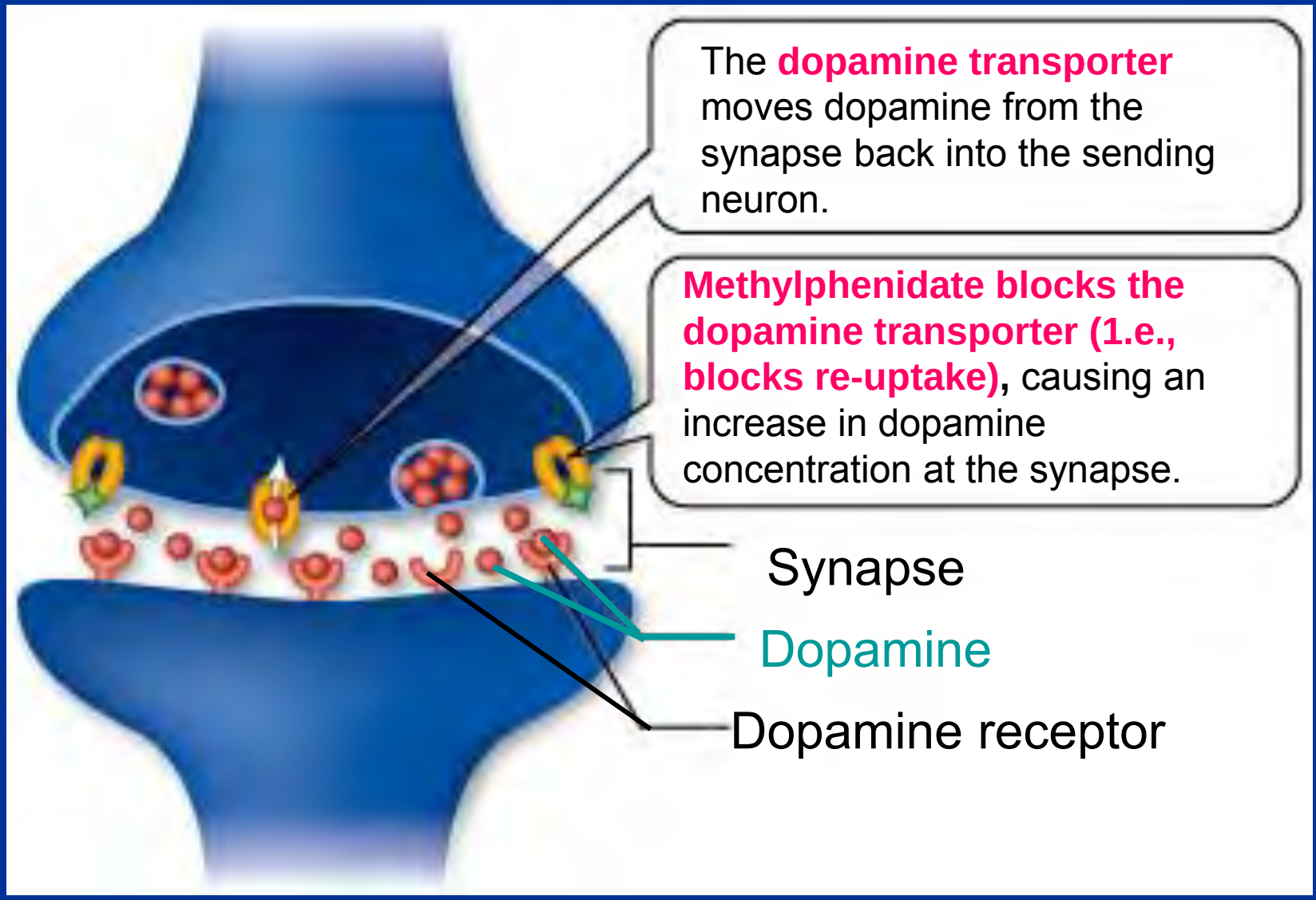
DAT binding specifically in the striatum has been found to be related to motor hyperactivity but *not* to inattentive symptoms.

(Jucaite *et al.*, 2005)

Most children with ADHD-H or ADHD-C respond positively to methylphenidate (Ritalin) in moderate to high doses.

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

Methylphenidate's Mechanism of Action at High Doses



On the other hand, a significant percentage of children with ADHD-IA are not helped by methyl-phenidate 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)

Recent research shows that low doses of MHP (dosages that are usually more effective in treating ADHD-IA) preferentially increase dopamine release in the PFC & preferentially enhance signal processing in PFC.

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

The doses of MPH that are optimal for controlling behavioral problems

are probably too high for aiding cognitive problems

indeed they can have the effect of an ADHD patient being *less* able to concentrate & attend (more in a daze)

How do you determine whether a particular dose of MPH is optimal for a child?

Usually you ask a parent.

Usually parents base their answers on whether the child's behavior is better.

No one uses cognitive measures to see if the children's attention, working memory, or any other EFs are better.

I hypothesize that many children with ADHD are being prescribed a level of MPH that is too high for optimal performance in school

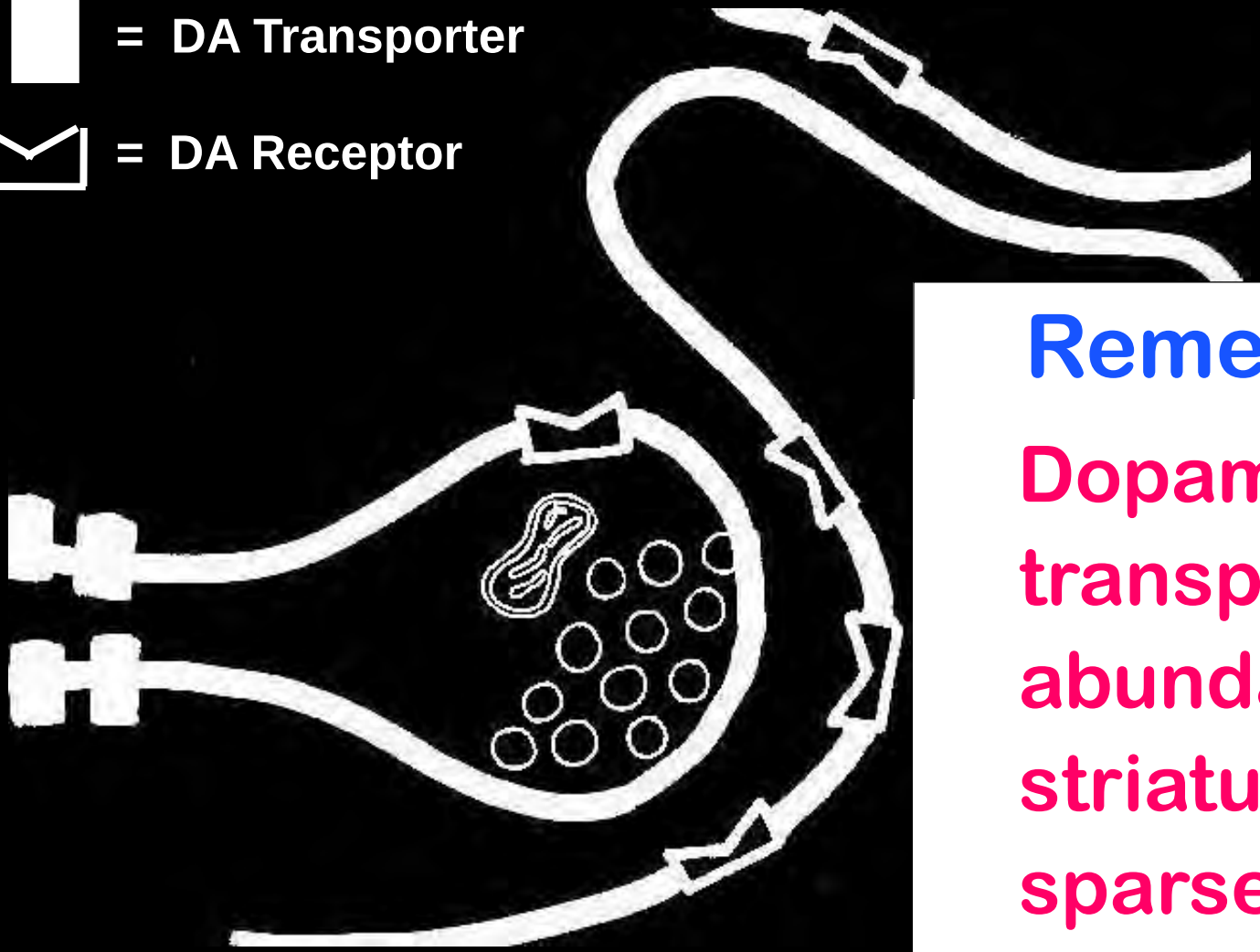
and that the high level of MPH is actually *impairing* their ability to get as much out of class as they could without medication.

We are currently putting that to the test.

Prefrontal Cortex

= DA Transporter

= DA Receptor



Remember:

Dopamine transporter is abundant in the striatum but sparse in pre-frontal cortex.

This makes prefrontal cortex more dependent on secondary mechanisms (such as the COMT [catechol-O-methyltransferase] enzyme) for clearing dopamine from extracellular space than are other brain regions, such as the striatum.

COMT Gene

catechol-O-methyltransferase gene

codes for the COMT enzyme, which methylates released dopamine.

It's located on chromosome 22.

A single base pair substitution

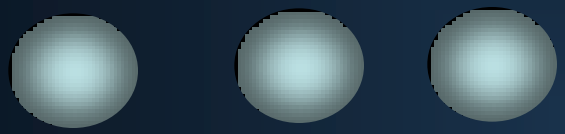
C**G**TG to C**A**TG

translates into a substitution of

Methionine for Valine at codon 158

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

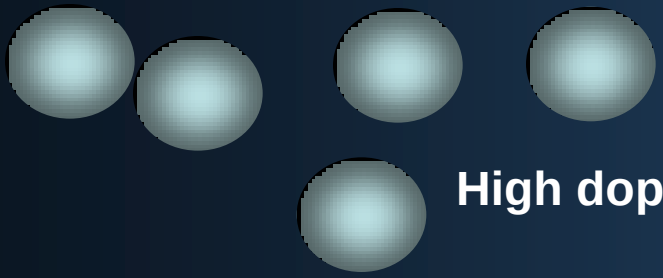
Catechol-O-methyltransferase (COMT) Val158 Met



Low dopamine

High activity enzyme

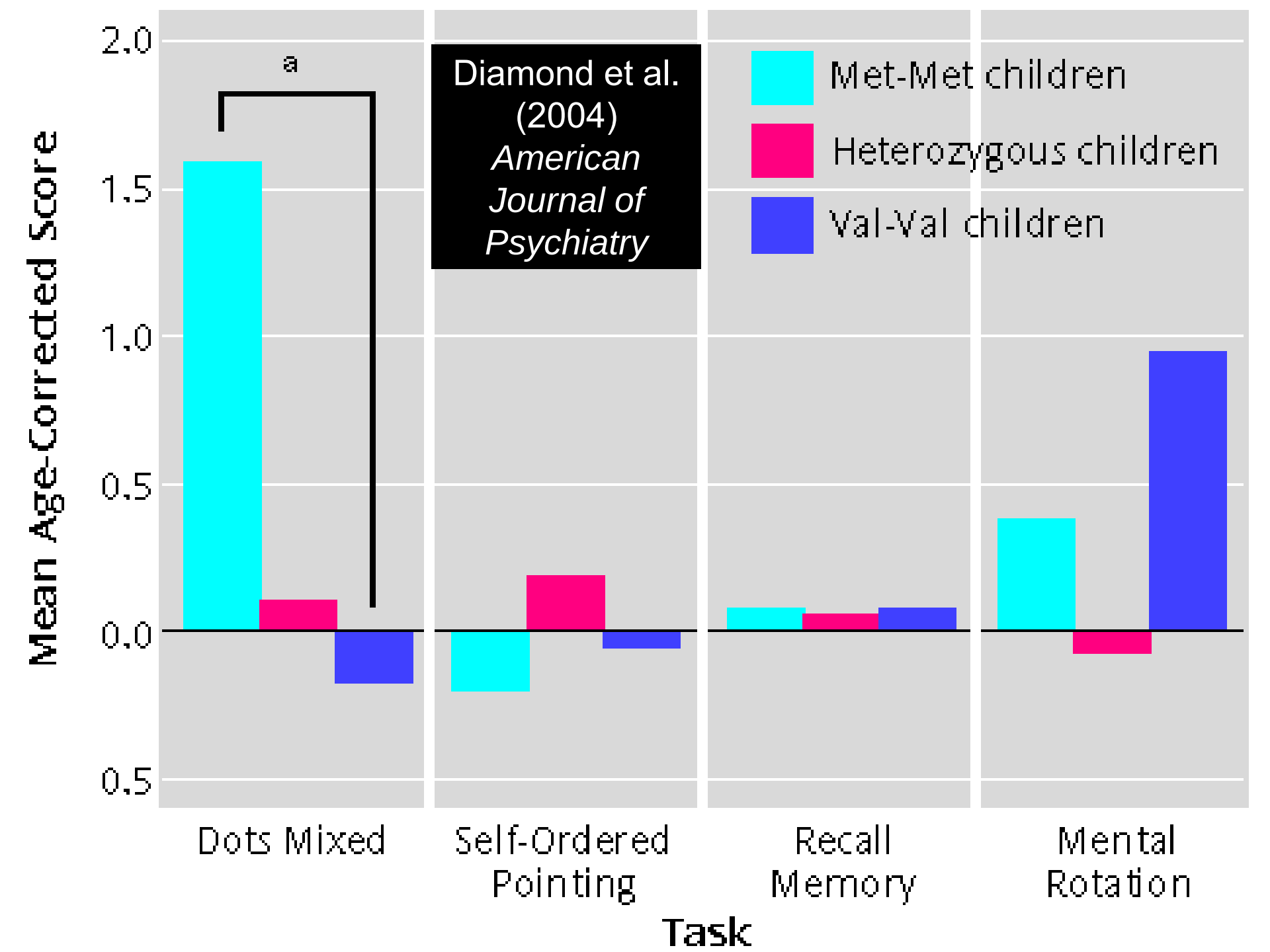
SYNAPSE



High dopamine

Low activity enzyme

The Methionine variant of the COMT gene is generally associated with better PFC function and better executive functions.

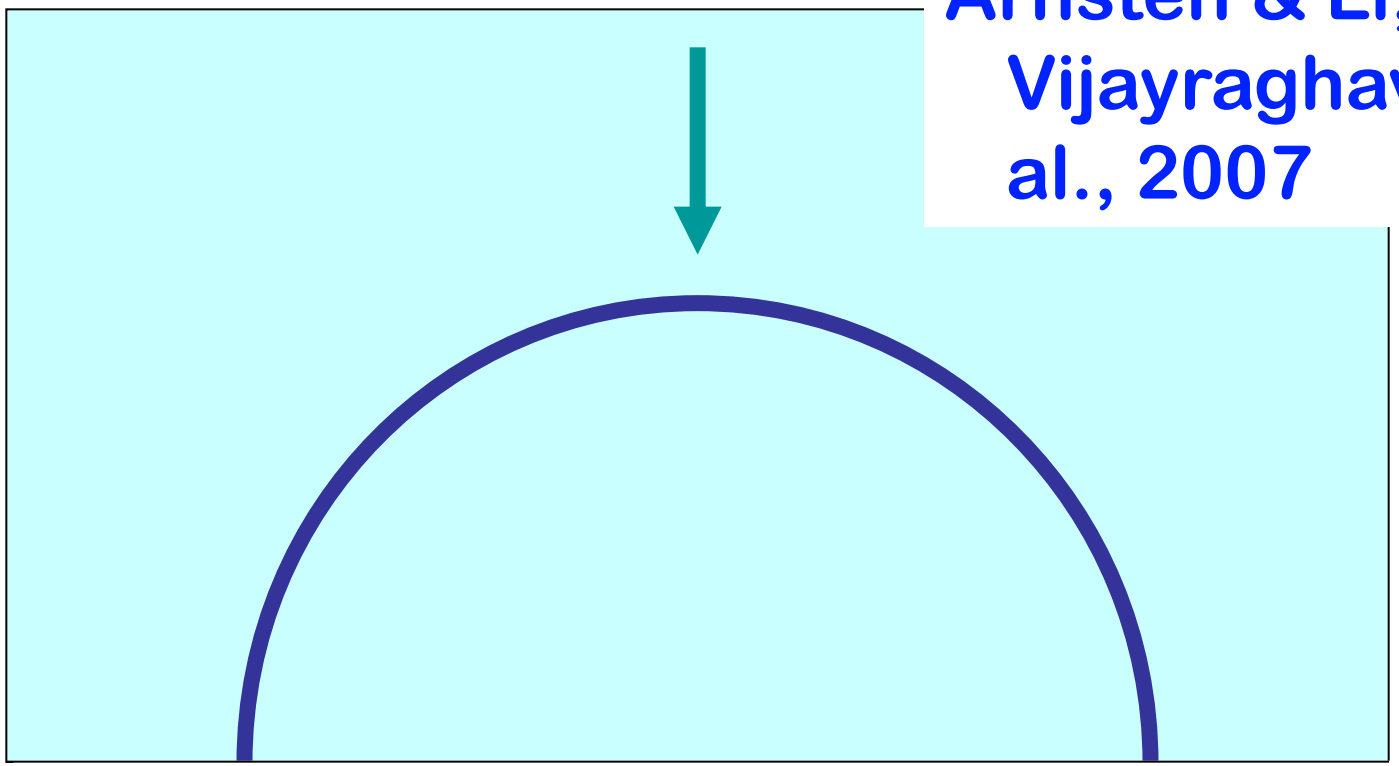

Diamond et al.
(2004)
American
Journal of
Psychiatry
Met-Met children
Heterozygous children
Val-Val children
a
2.0
1.5
1.0
0.5
0.0
0.5
Mean Age-Corrected Score
Dots Mixed
Self-Ordered
Pointing
Recall
Memory
Mental
Rotation
Task

This is specific to EFs:

There is no relation between COMT genotype and IQ or other non-PFC functions.

The Optimum Level of Dopamine in PFC is an Intermediate Level

Arnsten & Li, 2005; Vijayraghavan et al., 2007



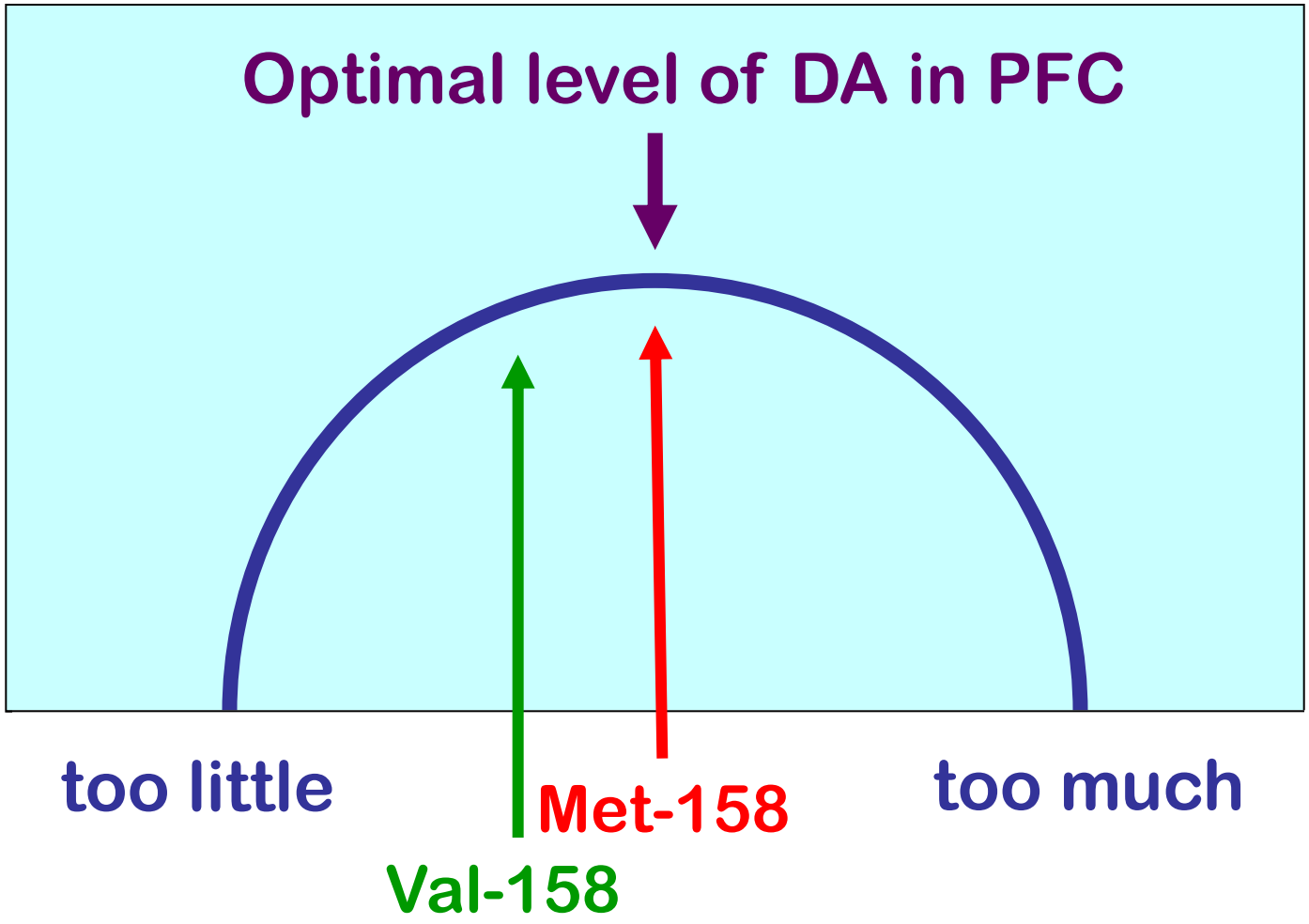
too little

too much

Remember

The Methionine variant of the COMT gene is generally associated with better PFC function and better executive functions.

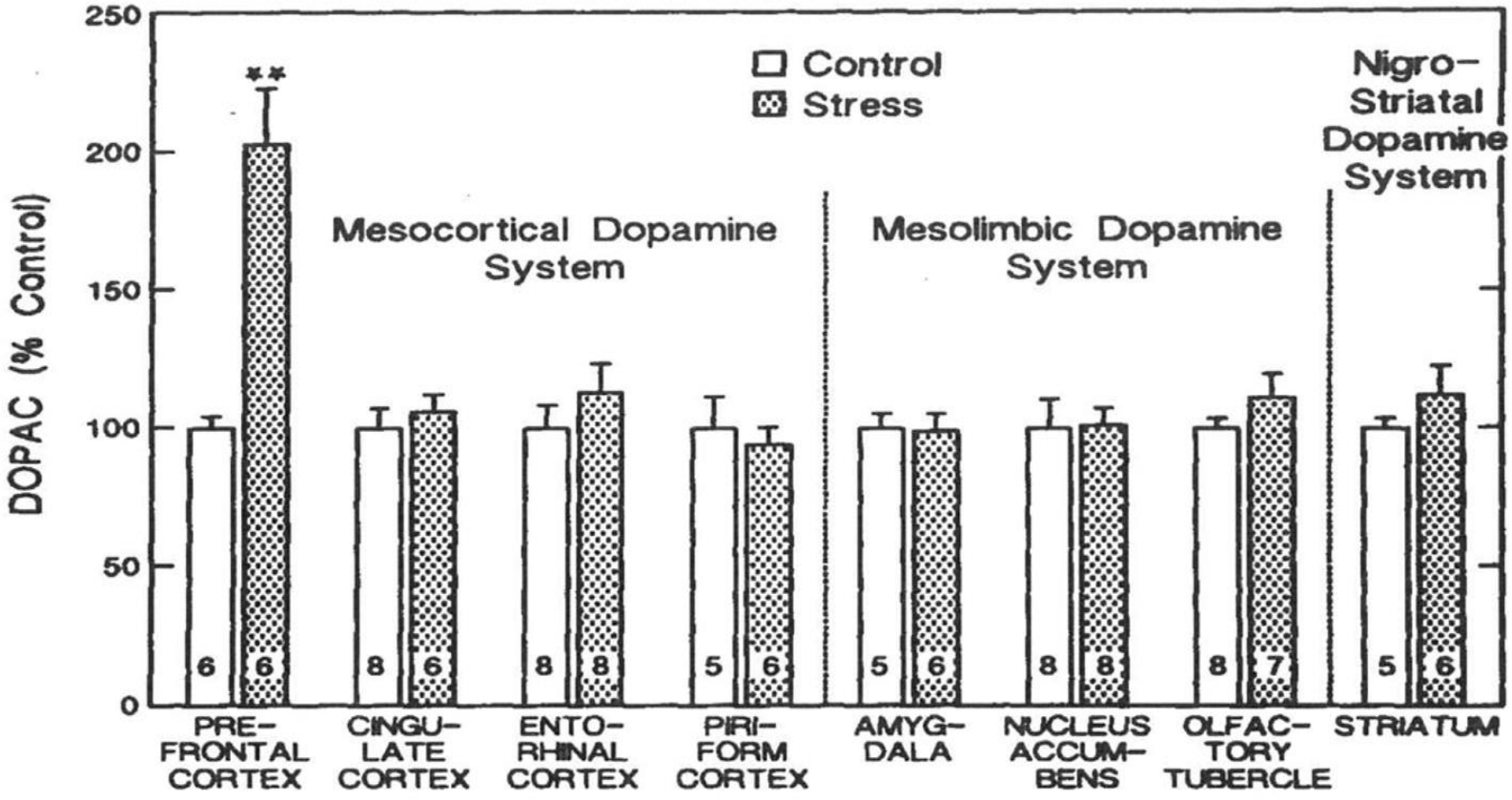
Differences in COMT Genotypic lead to Differences in PFC DA Levels



What's the downside of Met variant of COMT?

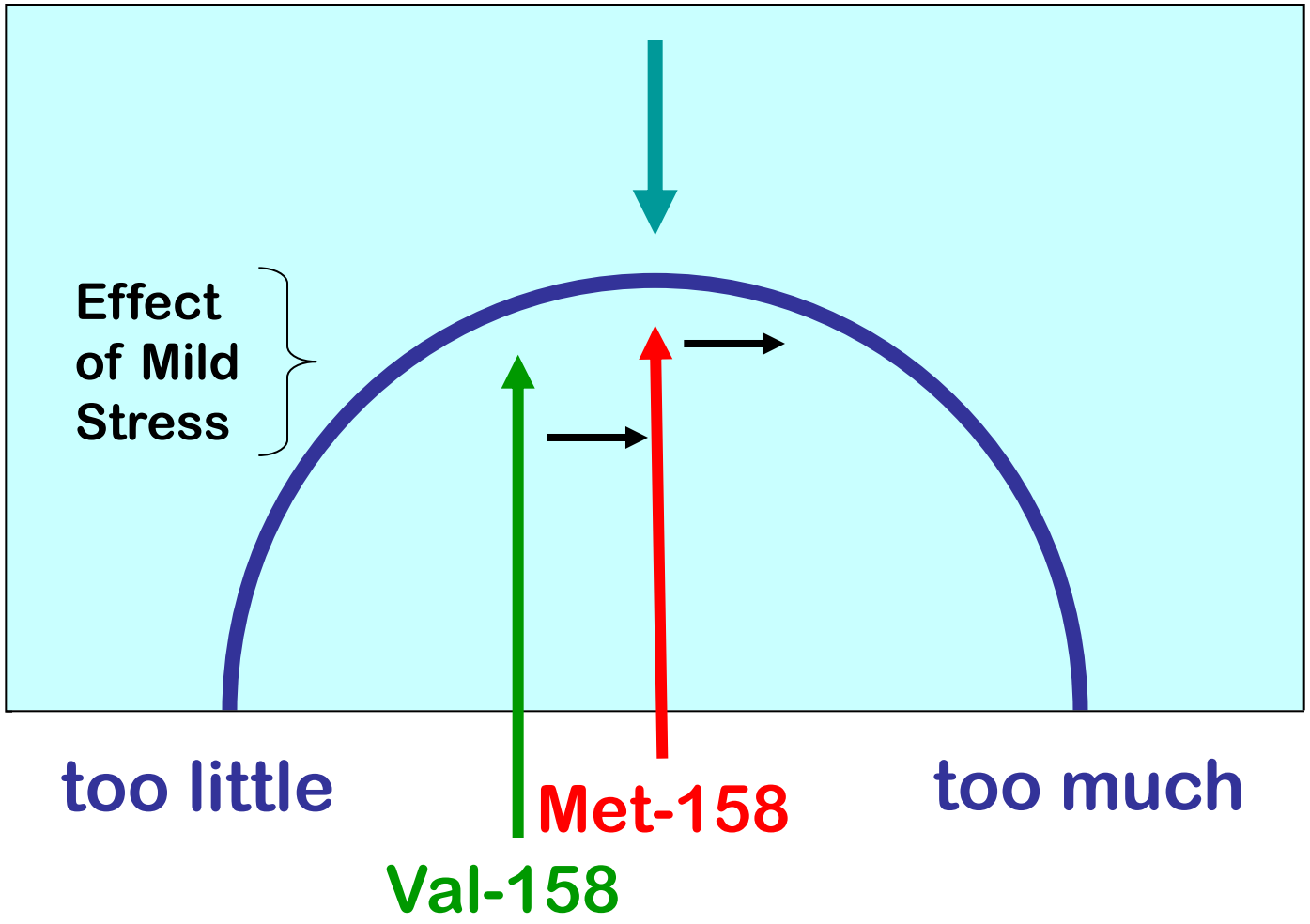
Stress and Prefrontal Cortex

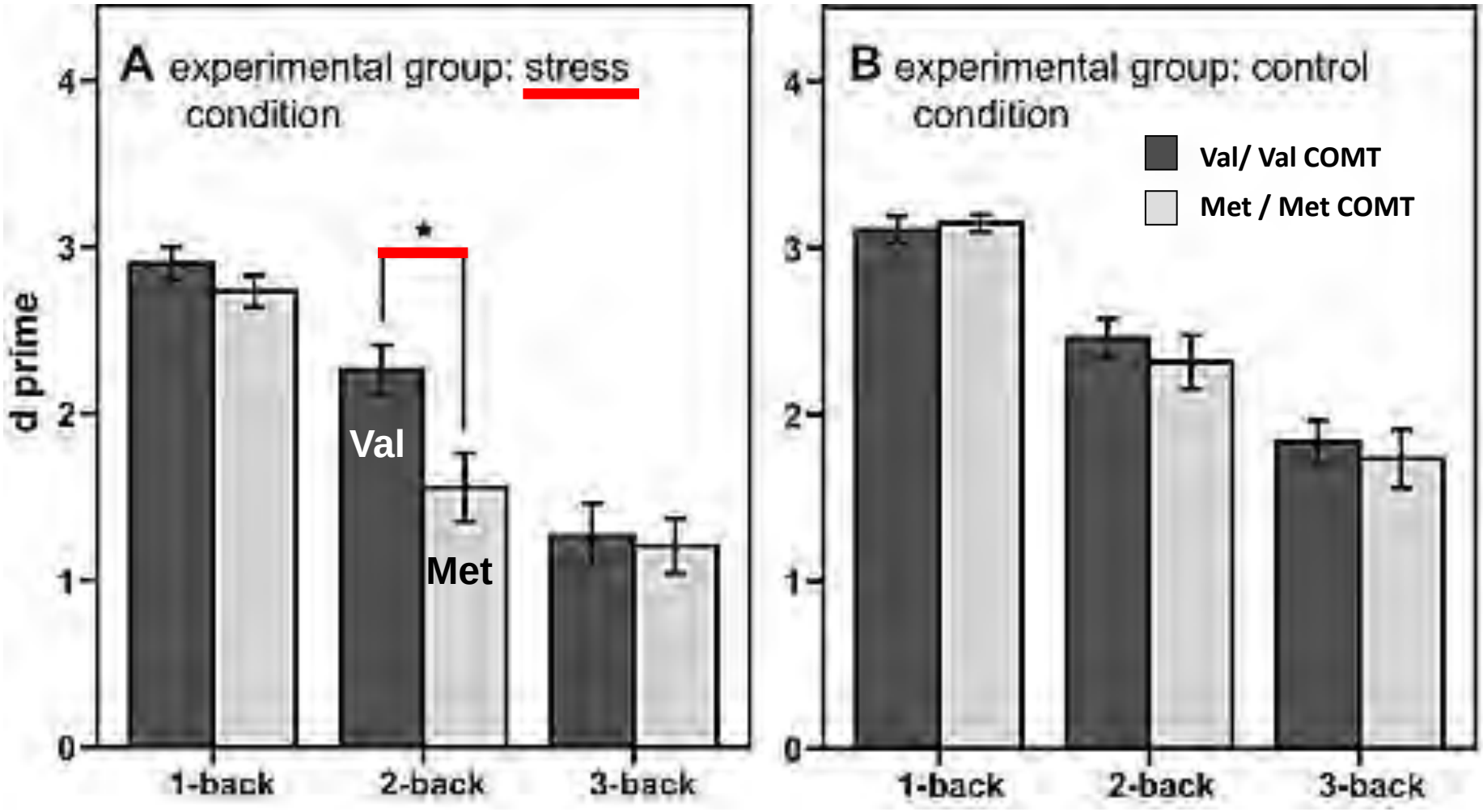
Even mild stress increases DA release in PFC but not elsewhere in the brain



(Roth et al., 1988)

Genotypic Difference in PFC DA Levels leads to Genotypic Differences in Stress Reactivity





Buckert et al. (2012): Under stress, young adults homozygous for COMT-Val^{158} showed ***better*** EF performance than young adults homozygous for COMT-Met^{158}

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

- be more sensitive to stress

  Buckert et al. 2012; 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’ll do okay even in a stressful environment, but might lack the exquisite fine-tuning of prefrontal cortex needed to achieve the brilliance of which a COMT-Met^{158} child might be capable.

Research shows that some of the children who look the worst when they are in an unsupportive, stressful environment are exactly those who blossom the most when in a good environment.

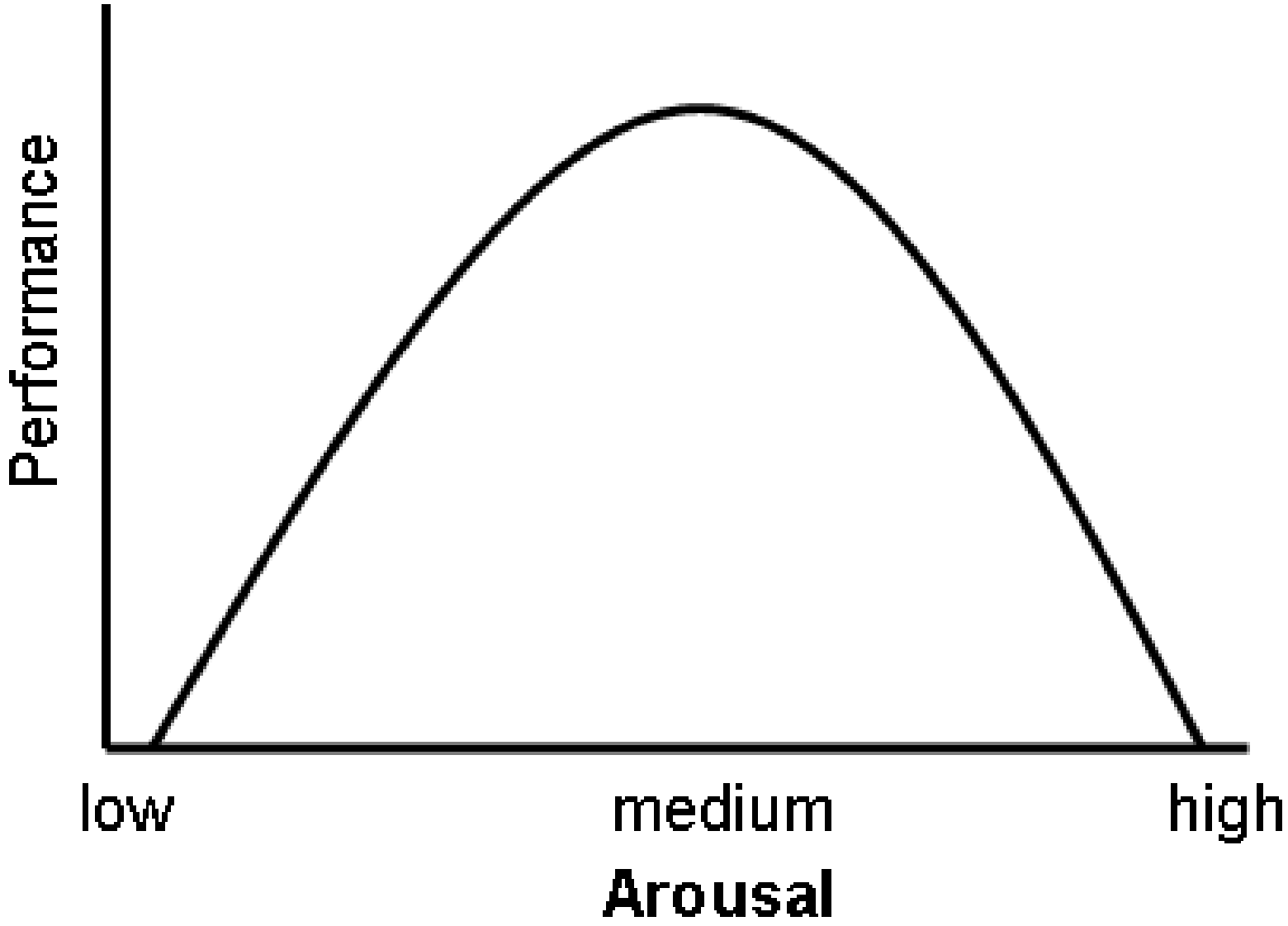
Perhaps some children homozygous for COMT-Met^{158} are among the orchids -- they might look like a disaster when in a stressful environment, yet might blossom brilliantly in the right environment.

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

A child 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.

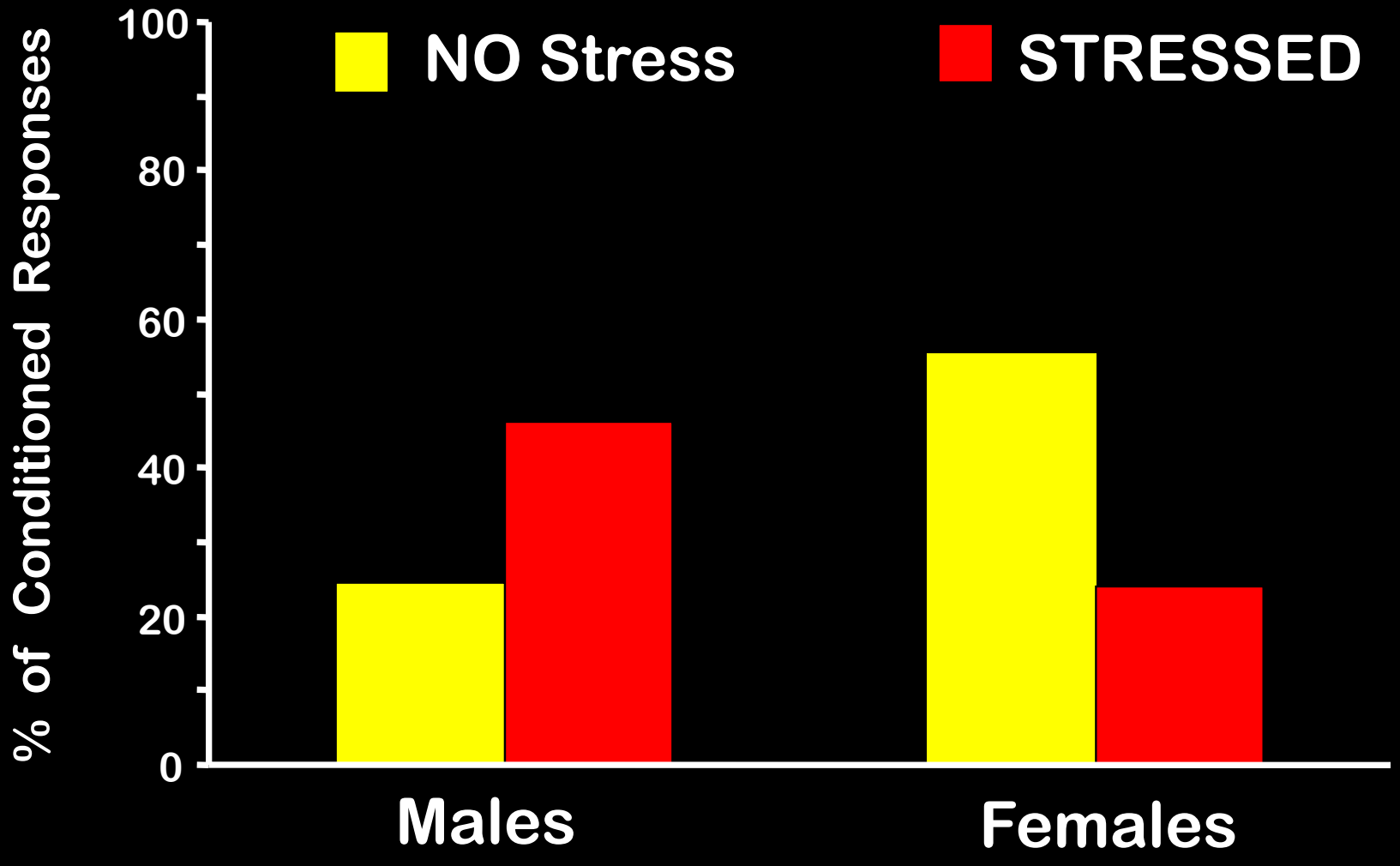
Many of us were taught that people perform better on challenging cognitive tasks when they are slightly stressed / a bit on edge, rather than when calm.

Yerkes – Dodson Curve



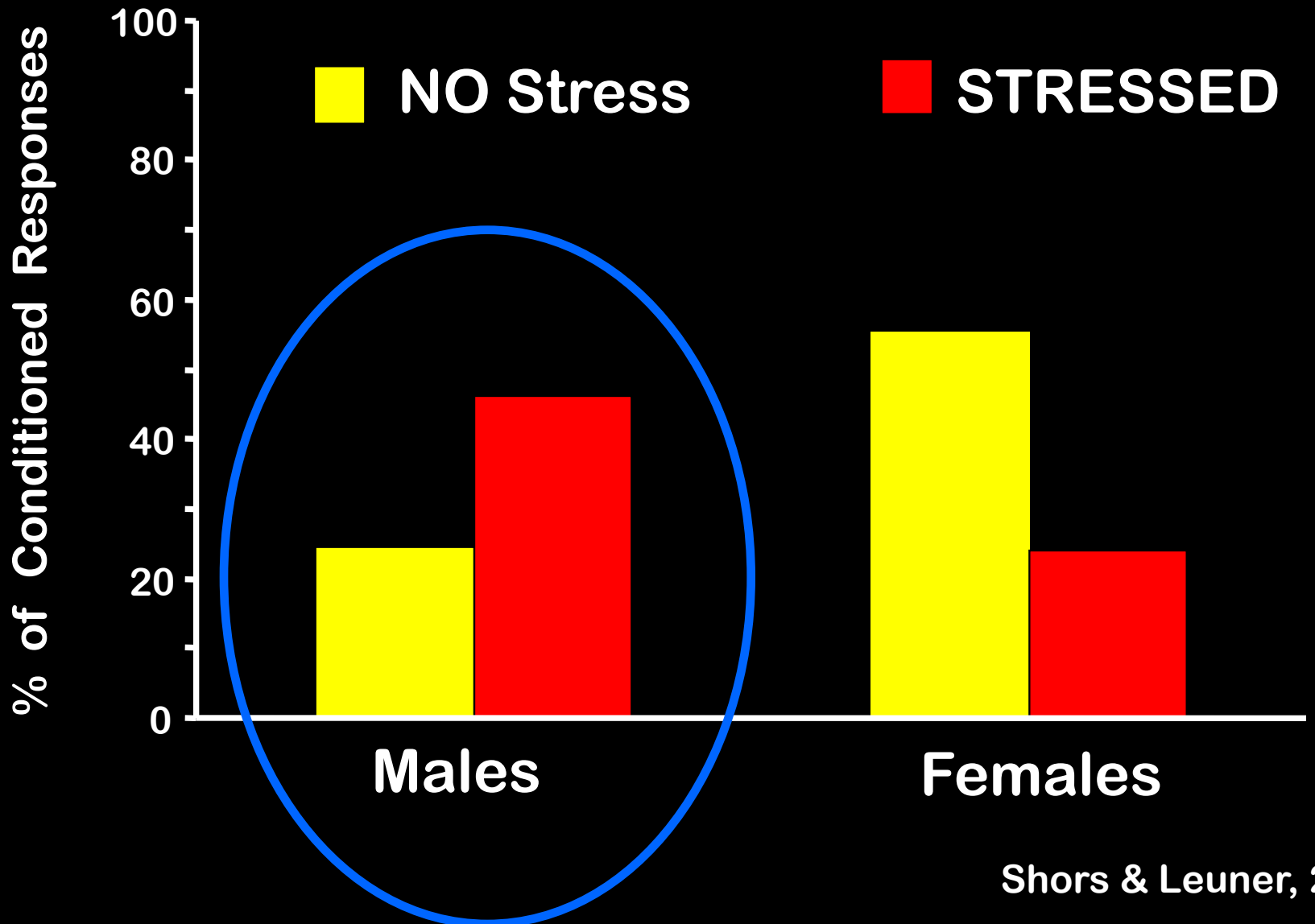
That people perform better on challenging cognitive tasks when slightly stressed is probably NOT true for females.

Effect of Stress on Trace Eyeblink Conditioning in Male and Female Rats



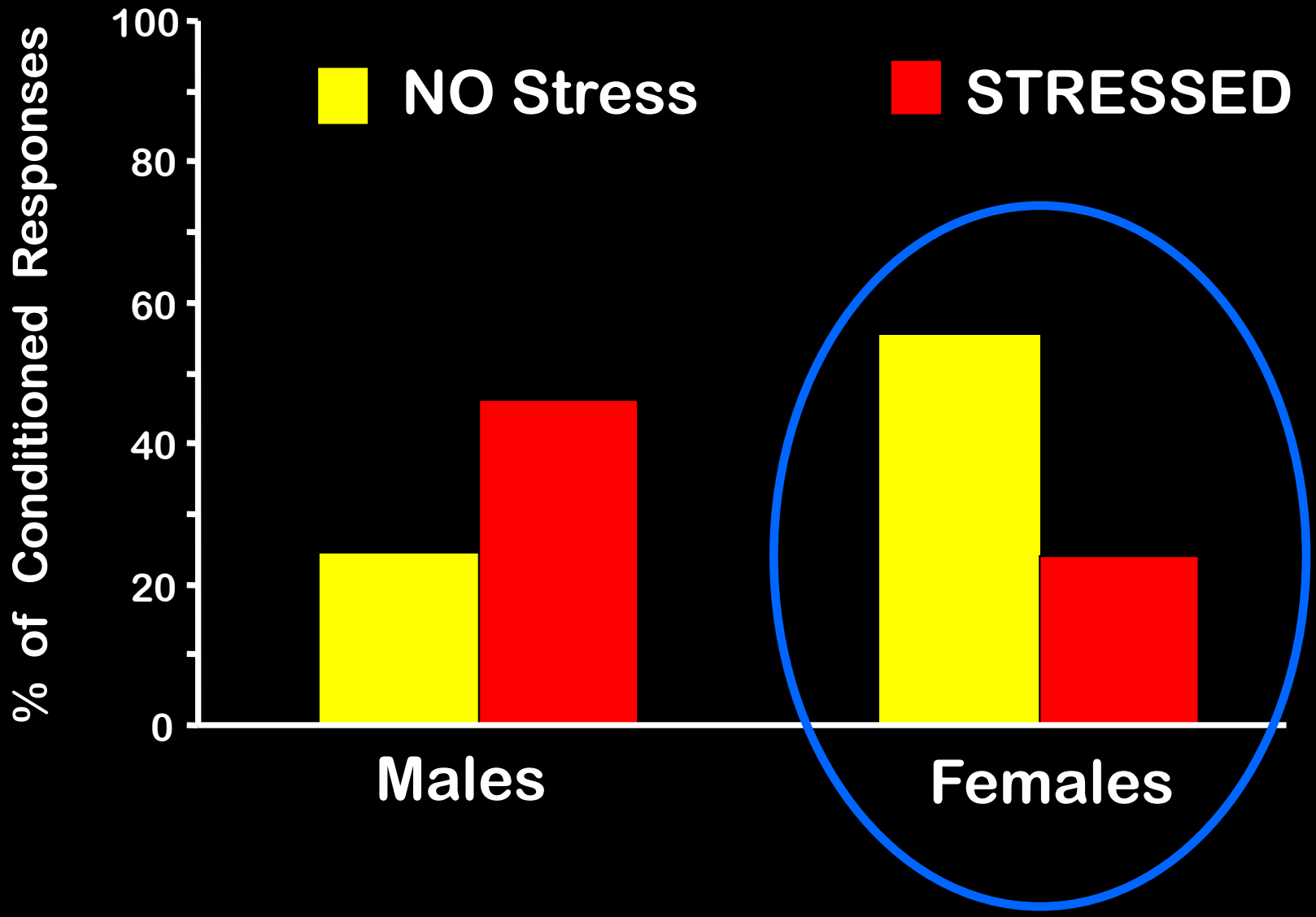
Shors & Leuner, 2003

Effect of Stress on Task Performance in Male and Female Animals



Shors & Leuner, 2003

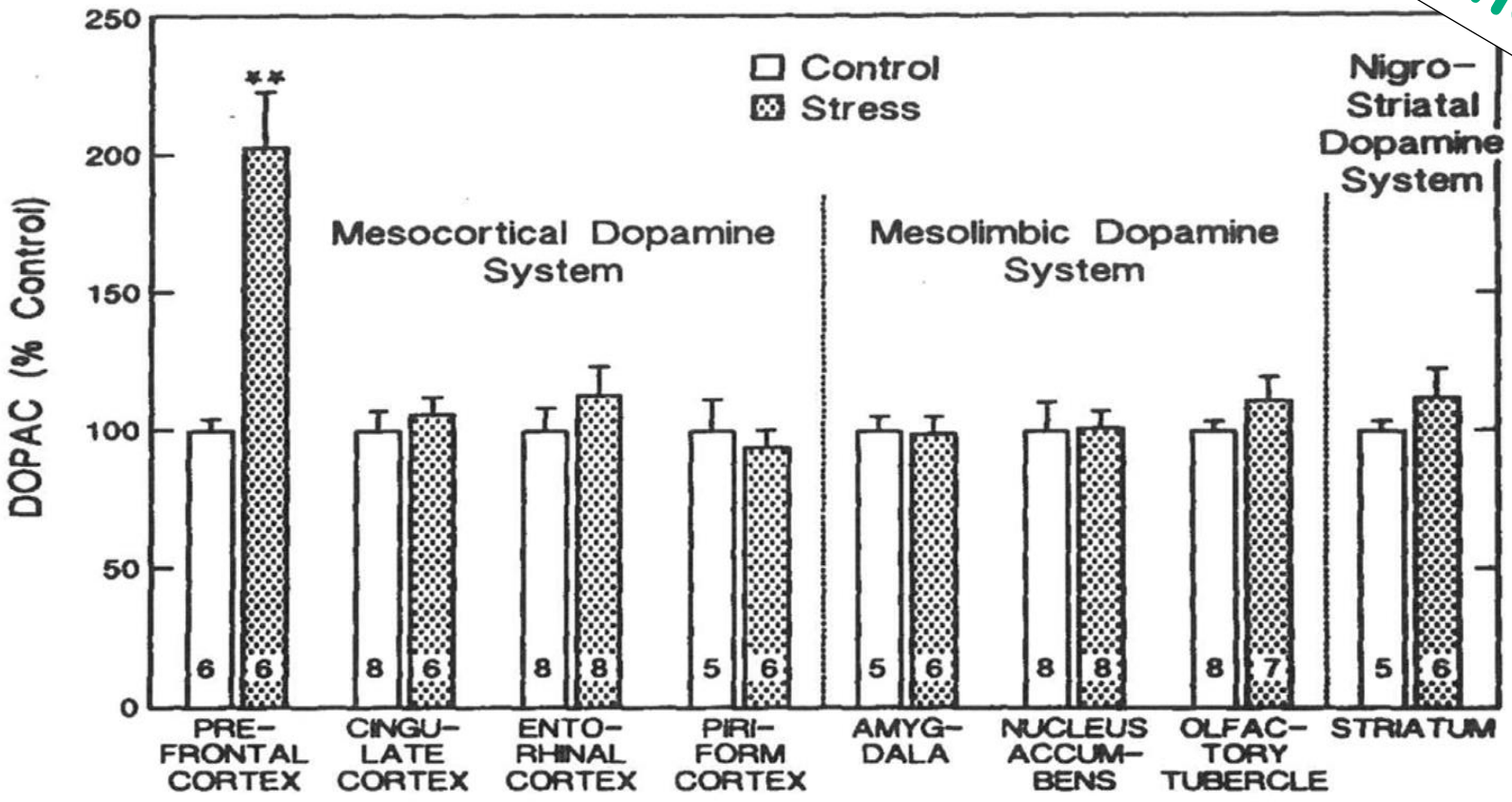
Effect of Stress on Task Performance in Male and Female Animals



Stress and Prefrontal Cortex

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

Remember

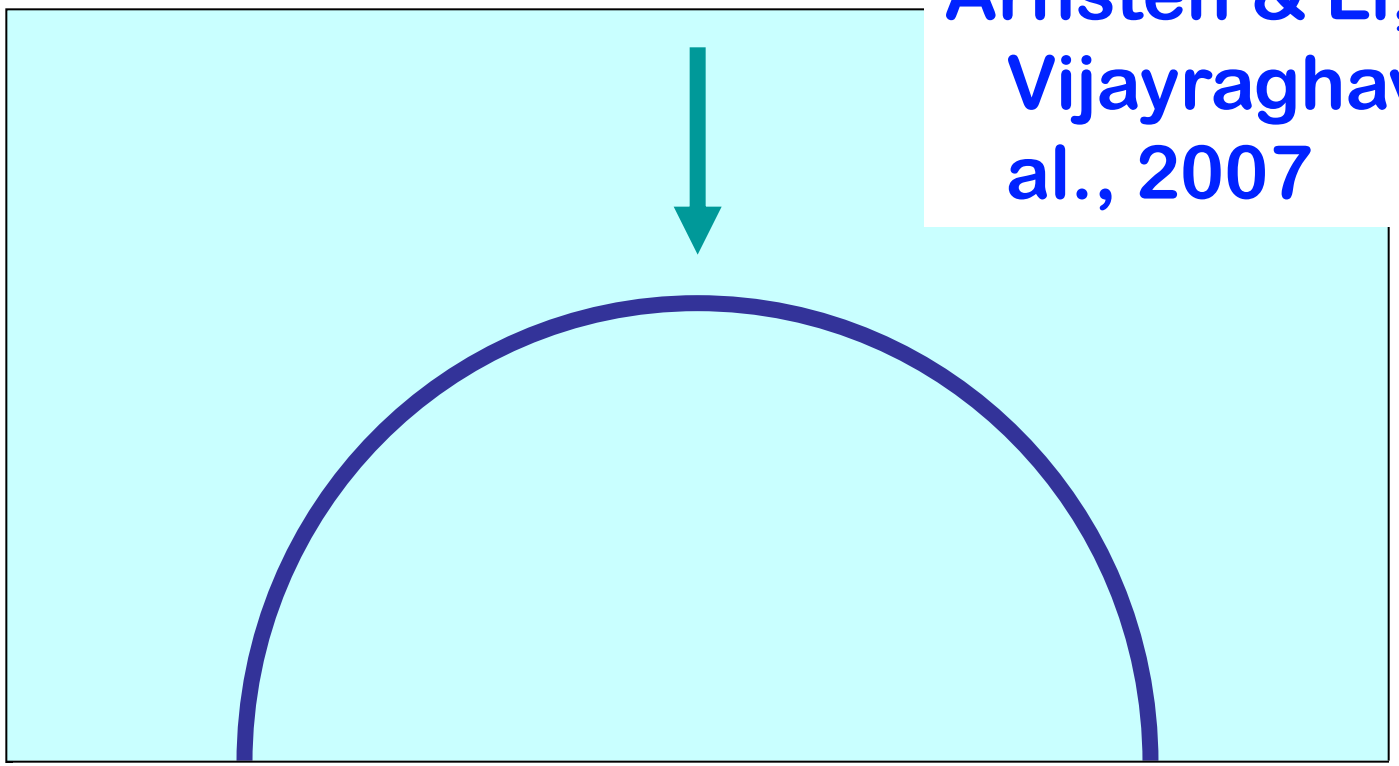


(Roth et al., 1988)

The Optimum Level of Dopamine in PFC is an Intermediate Level

Remember

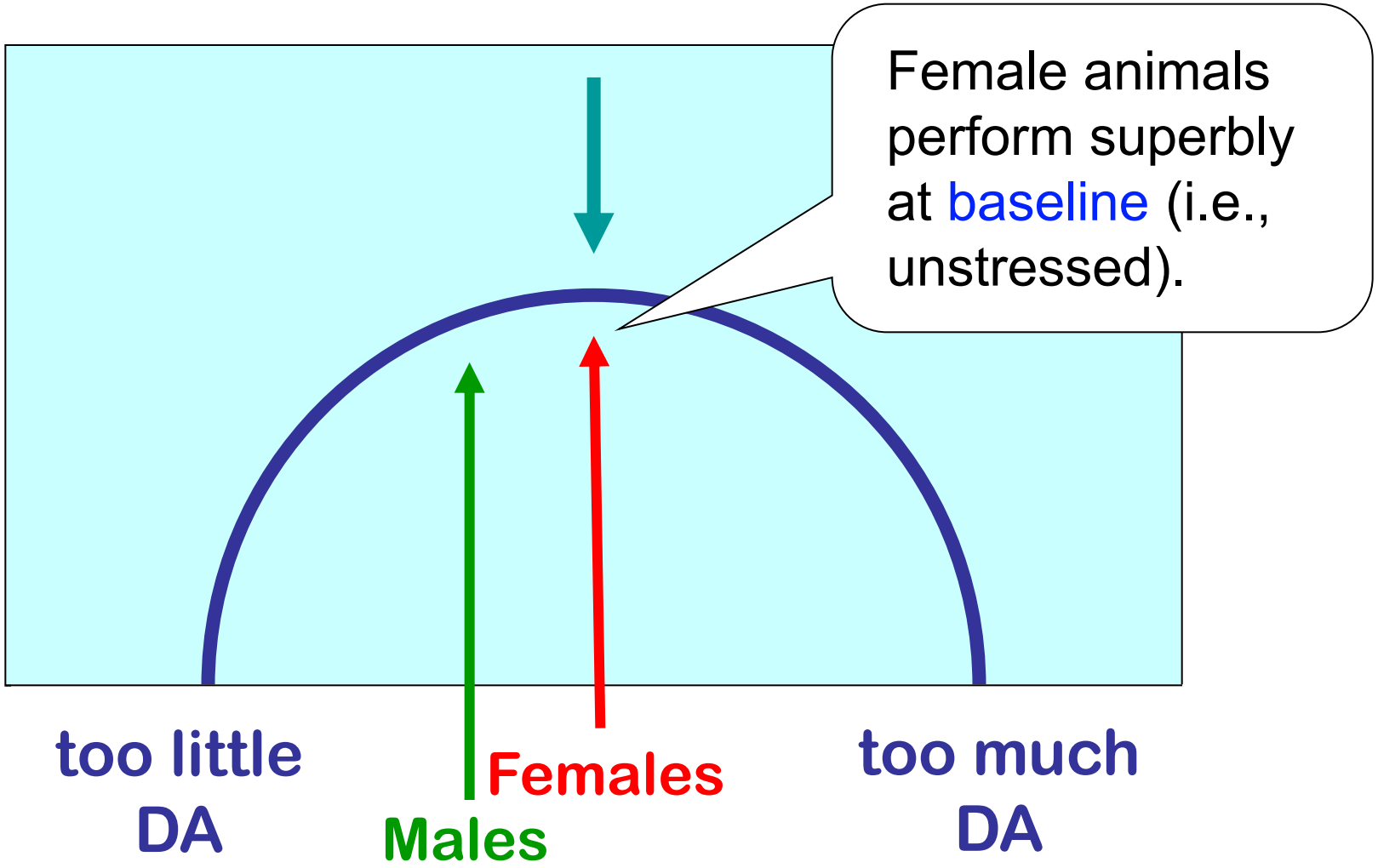
Arnsten & Li, 2005; Vijayraghavan et al., 2007



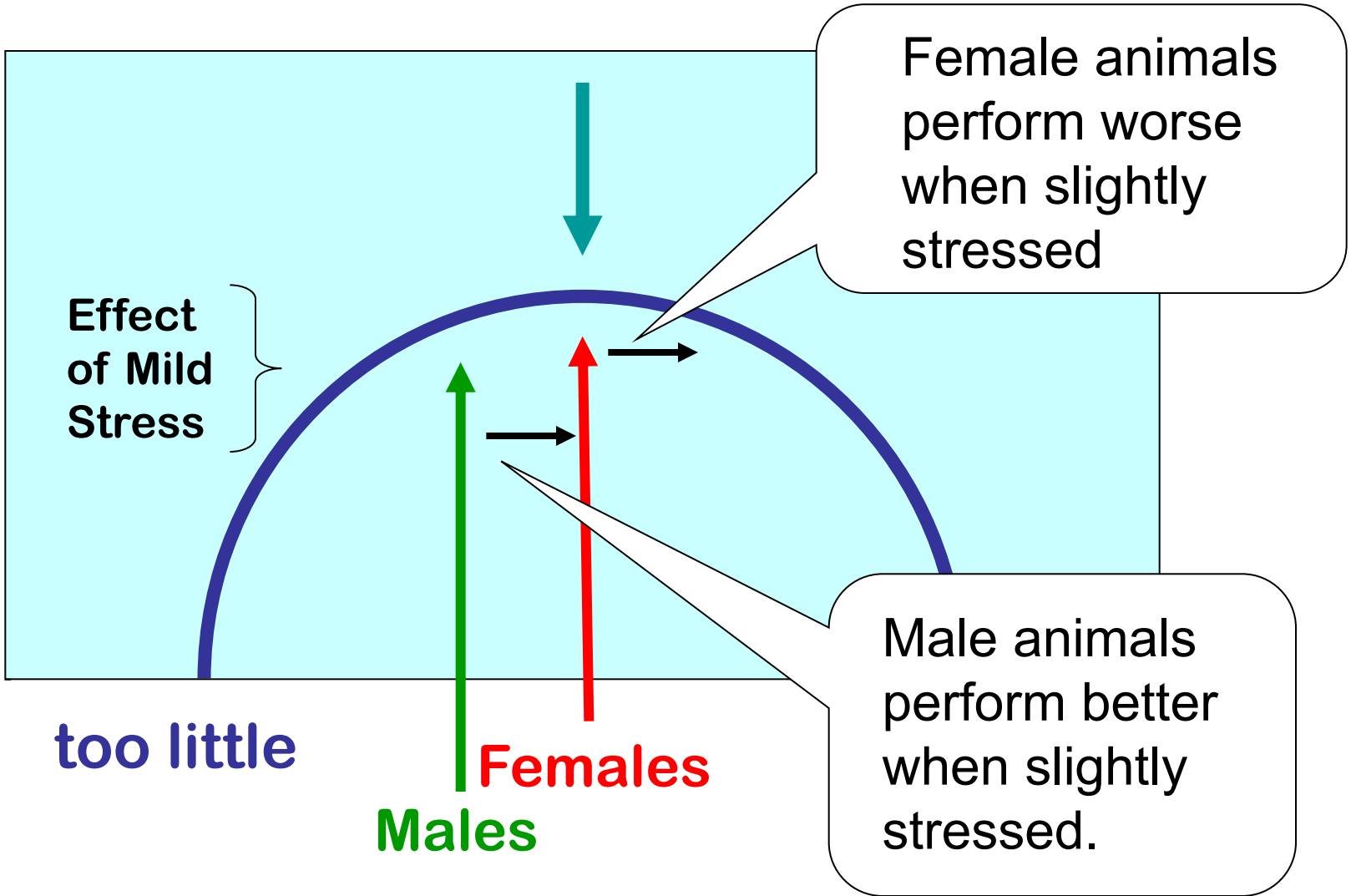
too little

too much

Hypothesis:
Gender Difference in Baseline Level of Dopamine in PFC



It follows from the Hypothesis of a Gender Difference in Baseline Level of Dopamine in PFC…



WHY?

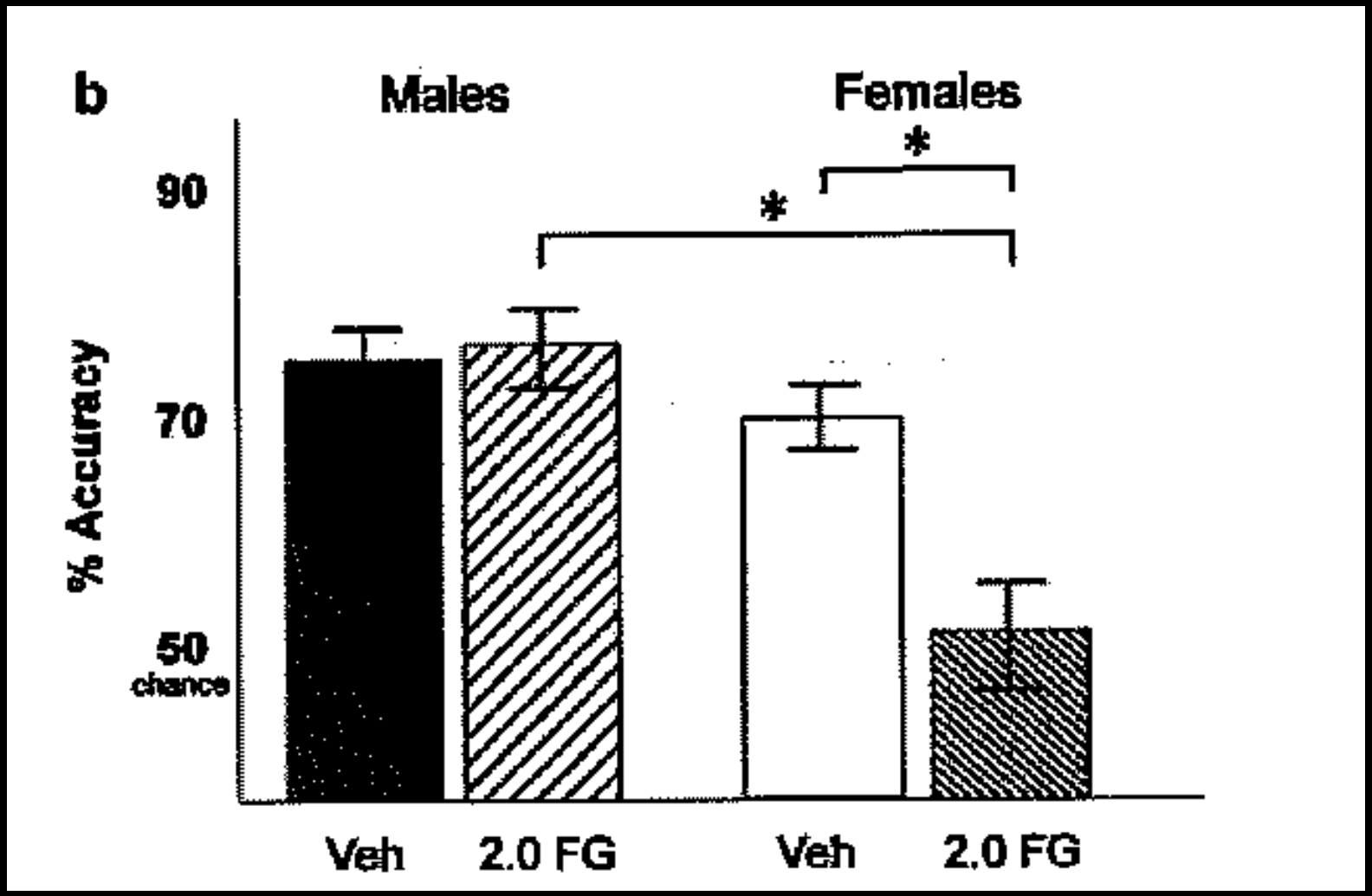
Why might Females have higher baseline levels of DA in PFC than Males?

Estrogen down-regulates COMT transcription (Ho, 2006).

COMT enzymatic activity is 30% lower in women than men.

Varies with estrus cycle in rats; inverse relation between COMT activity and estrogen levels.

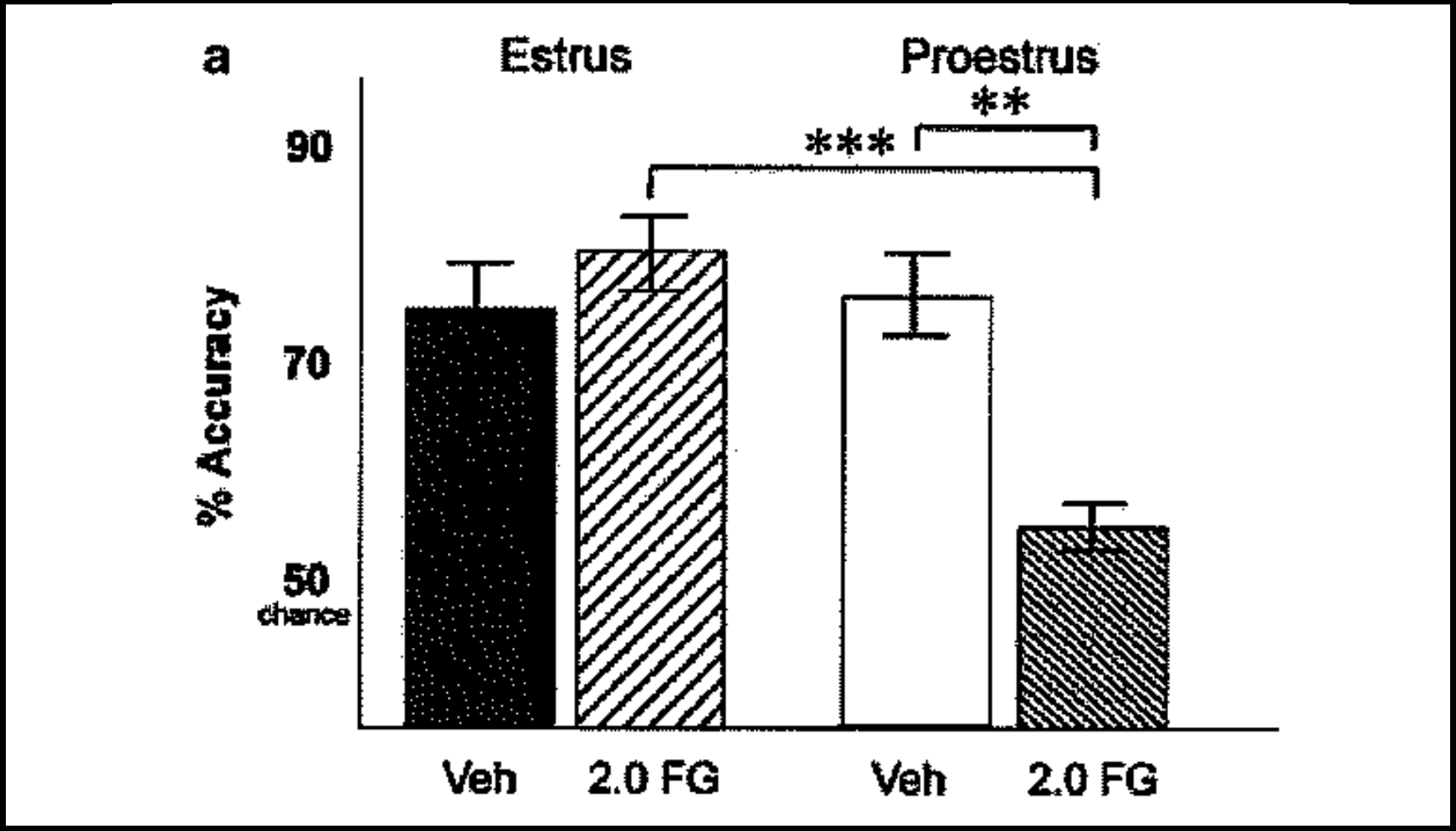
Stress & PFC



Delayed Alternation

(Shansky et al., 2004)

Stress & PFC (Females only)

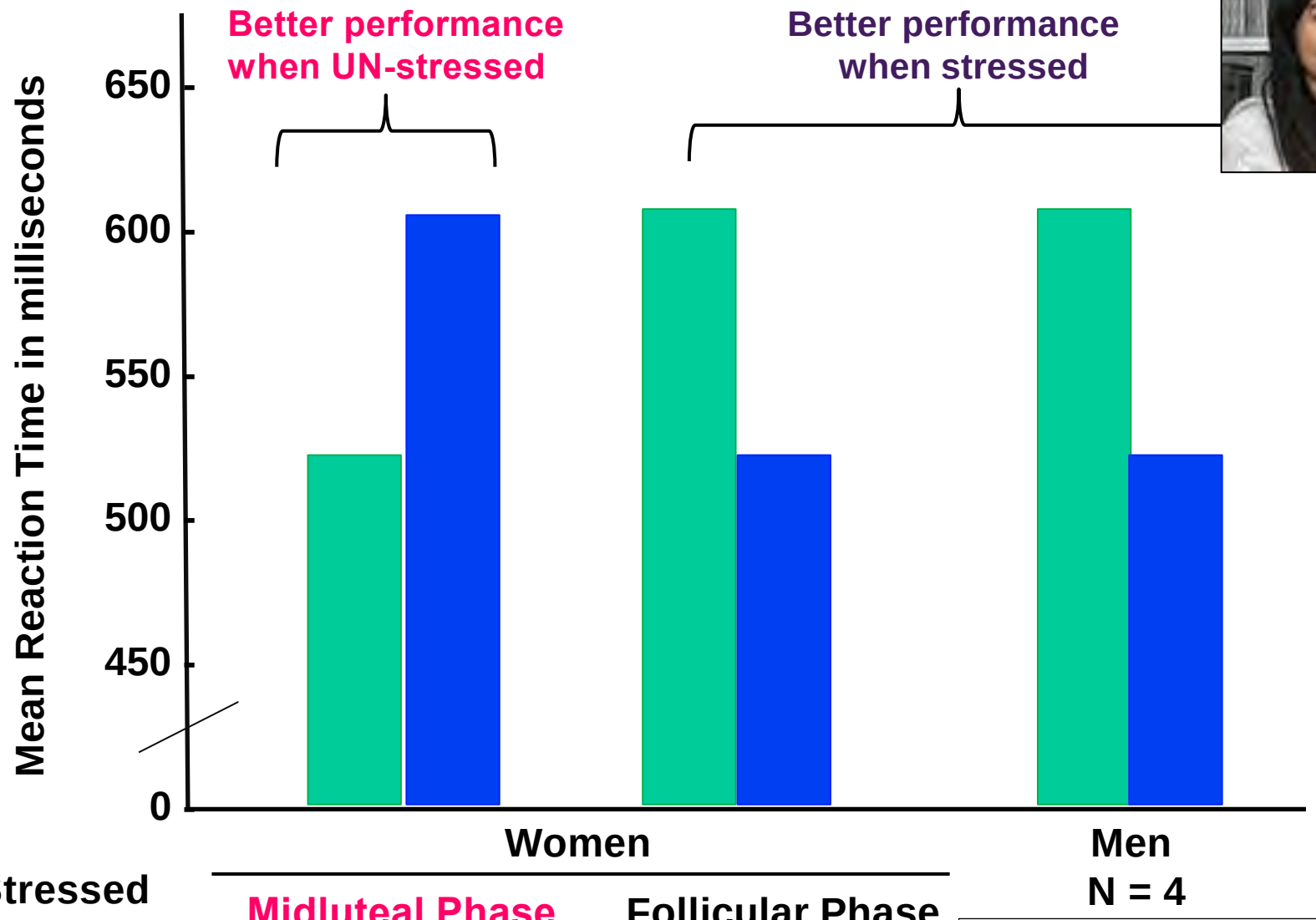


Delayed Alternation

(Shansky et al., 2004)

Predicted Results Hearts and Flowers Task - Haolu

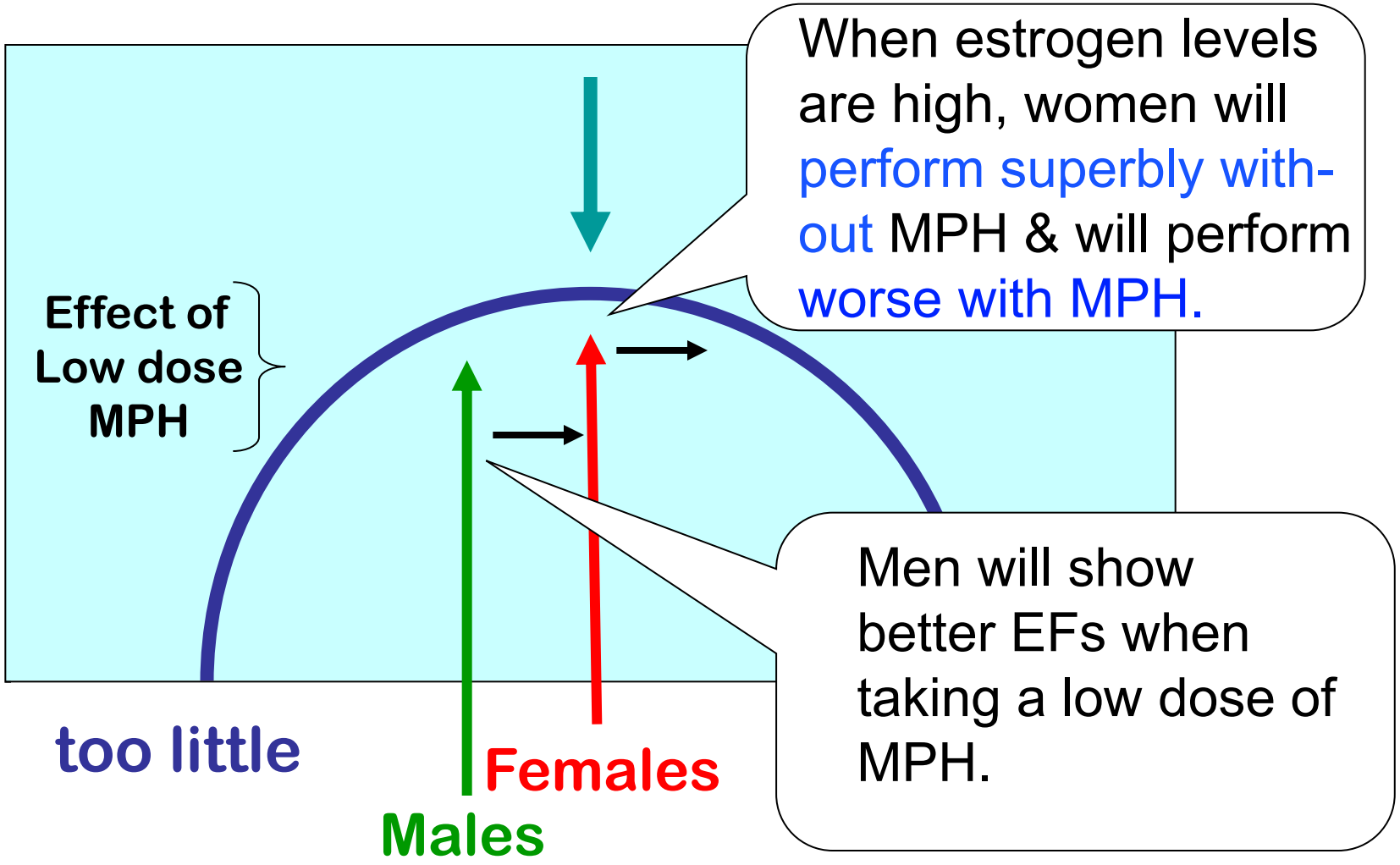
(an EF task sensitive to DA in PFC)



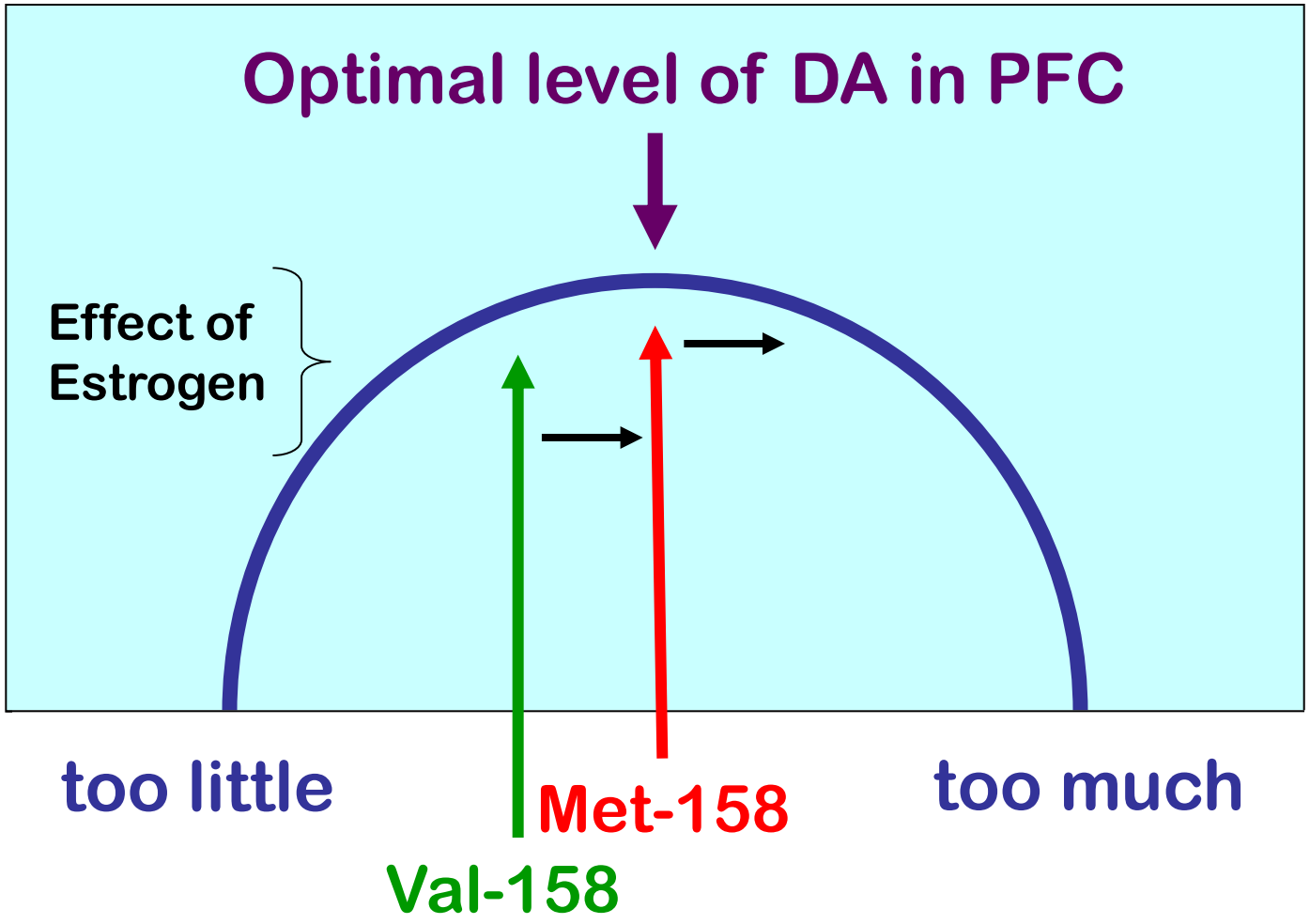
All subjects are COMT Val-Met heterozygotes.

To test our hypothesis concerning the mechanism by which stress affects cognition differently in men & women, we are attempting to model the effects of mild stress on EFs pharmacologically (using MPH).

Hypothesized Gender Difference in the Cognitive Effect of Low Dose MPH

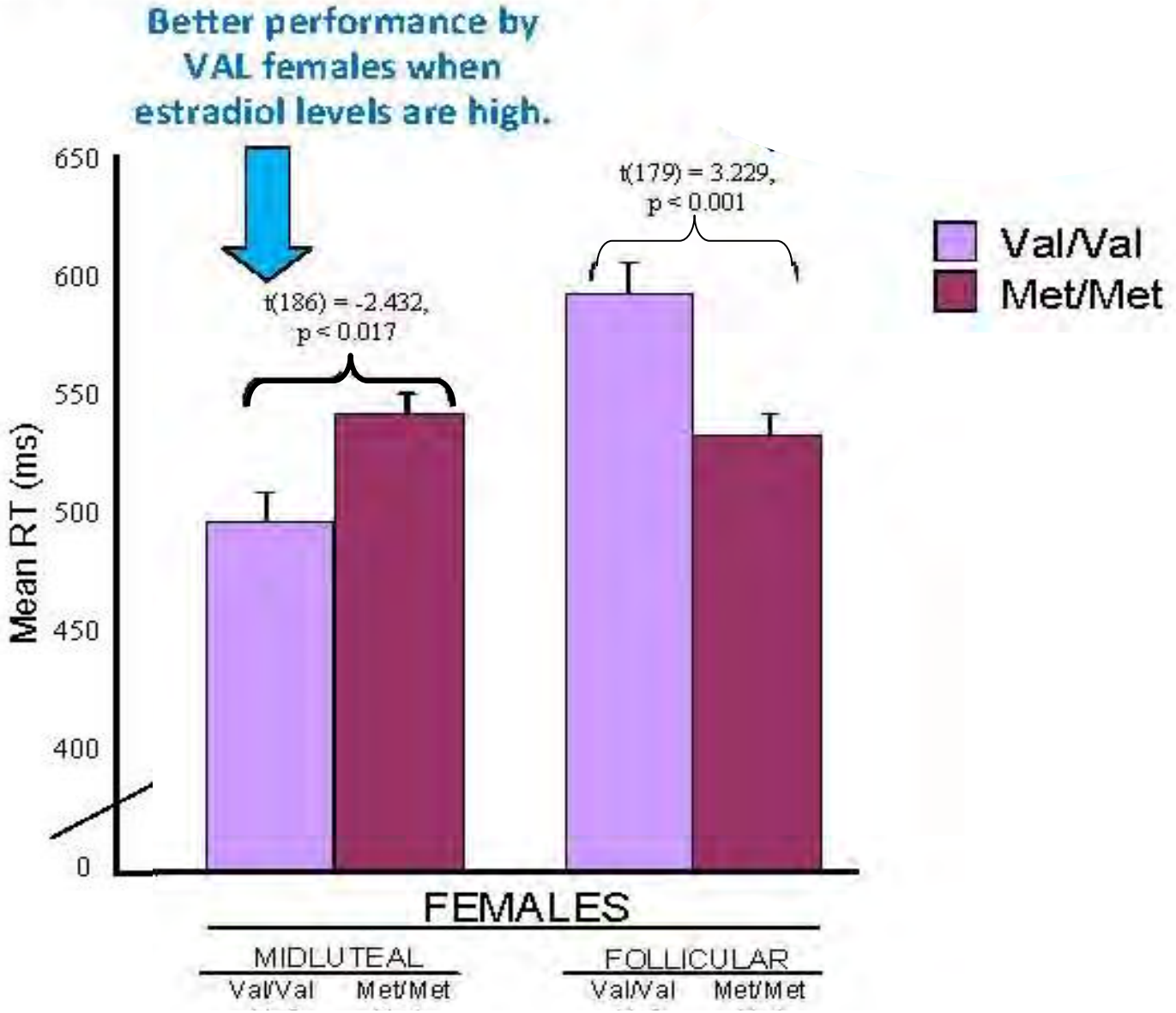


Hypothesized that which Version of the COMT Gene would be most Beneficial for EFs would vary by Estrogen levels



Hearts + Flowers:

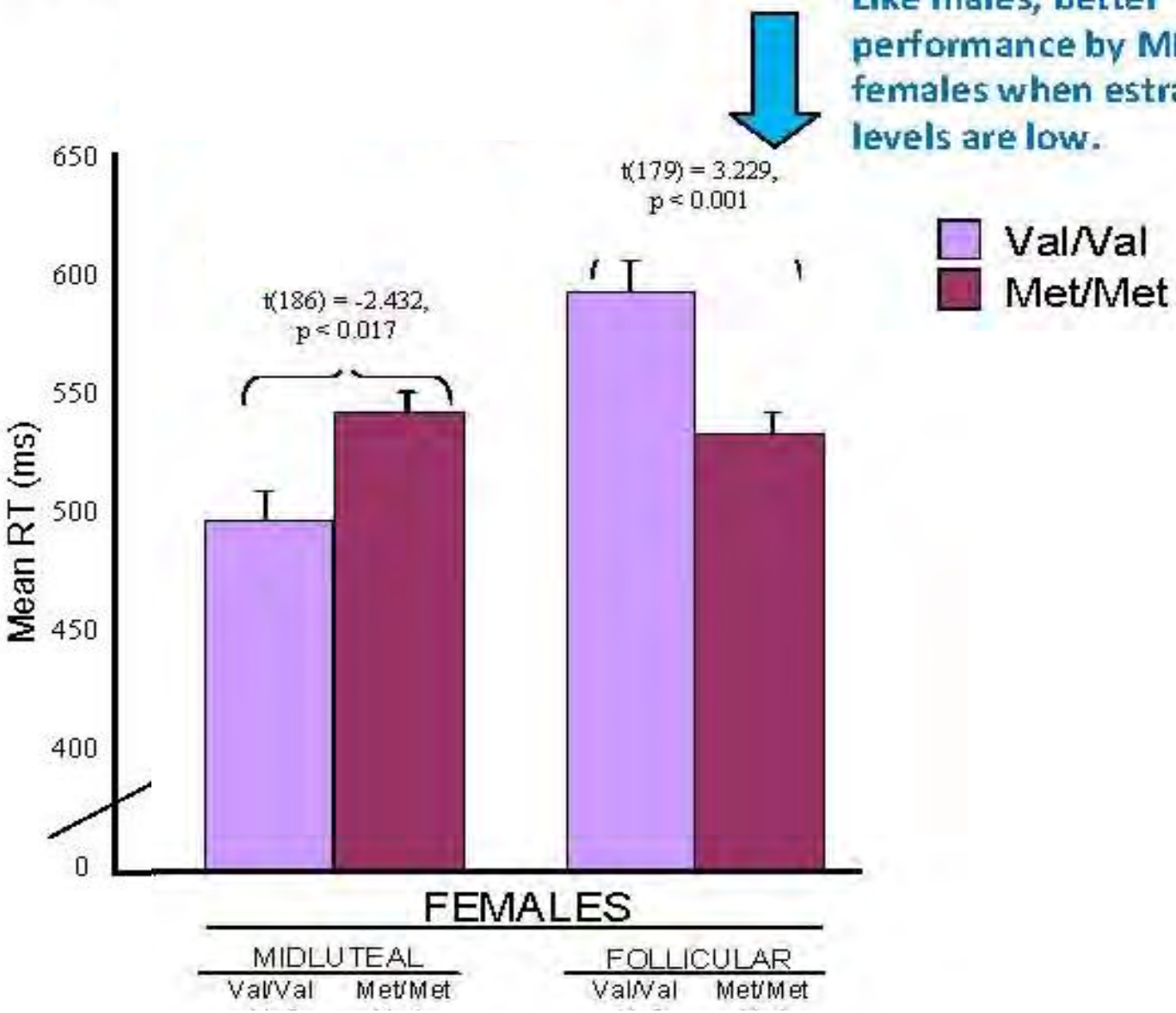
(EF Task Sensitive to the Level of DA in PFC)



Hearts + Flowers:

(EF Task Sensitive to the Level of DA in PFC)

Like males, better performance by MET females when estradiol levels are low.



Jeanette Evans

John Fossella, Elizabeth Hampson, Clemens Kirschbaum, C., & Adele Diamond

Jan. 15, 2009

Gender Differences in the Cognitive Functions Sensitive to the Level of Dopamine in Prefrontal Cortex.

Presented at inaugural conference of a series on "Executive Function & Dysfunction," University of Boulder, CO

Adele Diamond

2011

Biological and social influences on cognitive control processes dependent on prefrontal cortex

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thanks so much for your attention

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