Executive Functions: What they are, Genetic and Environmental Influences and Clinical Implications



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



- Flexibility -- take advantage of serendipity (unexpected opportunities) - circumvent unexpected obstacles adapt to changed demands or priorities - when see new evidence being able to change your opinion or admit you were wrong
- Self-control -- to not react impulsively & do something you'd regret (e.g., email; social faux pas) instead pause & think before acting -- resist temptations - not get in cycle of 'tit for tat' - not jump to an interpretation of intent or meaning
- Discipline / Perseverance -- to see a task through to completion despite setbacks, frustrations, boredom, & all the temptations to do something more fun

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ALL of the above are

"Executive Functions"

or rely on them



The 3 core Executive Functions are:

- Cognitive Flexibility (including creative problem-solving & flexibility)
- Inhibitory Control

(which includes self-control & discipline, also selective attention)

• Working Memory (holding info in mind & MANIPULATING it; essential for reasoning)

Higher-order Executive Functions are:

Problem-solving

Reasoning
Planning

Inhibitory control predicts academic performance in the earliest elementary grades through university better than does IQ.

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 beneficial direction and yield large improvements in health, wealth, and crime rate for a nation."

(b) Working Memory:

Holding information in mind and mentally working with it



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.



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

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.

Inhibitory control is a HUGE challenge for children.

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

Children with immature prefrontal cortices, and adults with prefrontal damage, sometimes err even though they know what they should do and want to behave correctly.

They may get **erroneously** labeled as "bad," "intentionally difficult," or "willful."

It is NOT that they don't know, or have forgotten, what correct performance entails.

It is NOT that they are trying to be 'bad.'

It's immature inhibitory control (like the child who hits another in the heat of the moment though he knows perfectly well he shouldn't hit).

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



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



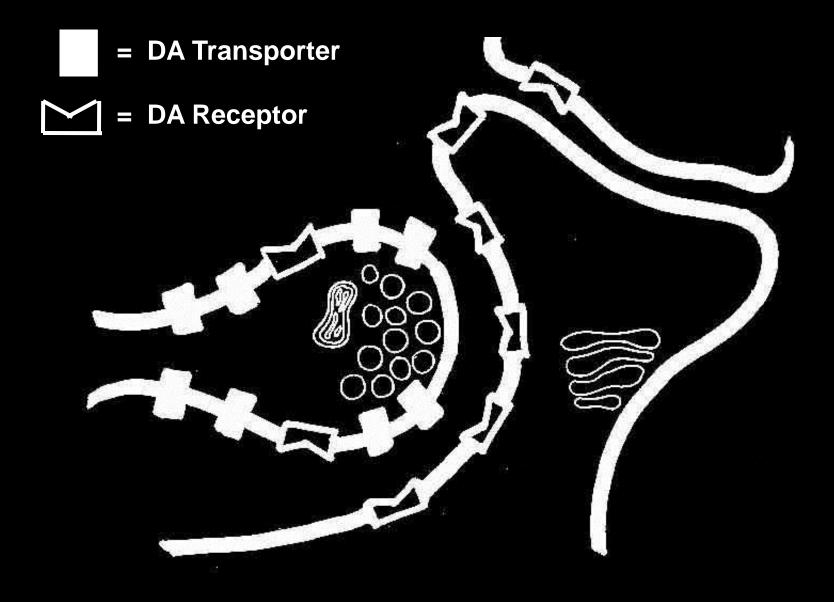
Much of the presynaptically released dopamine doesn't reach the postsynaptic neuron, and needs to be cleared from the space between and around the neurons.



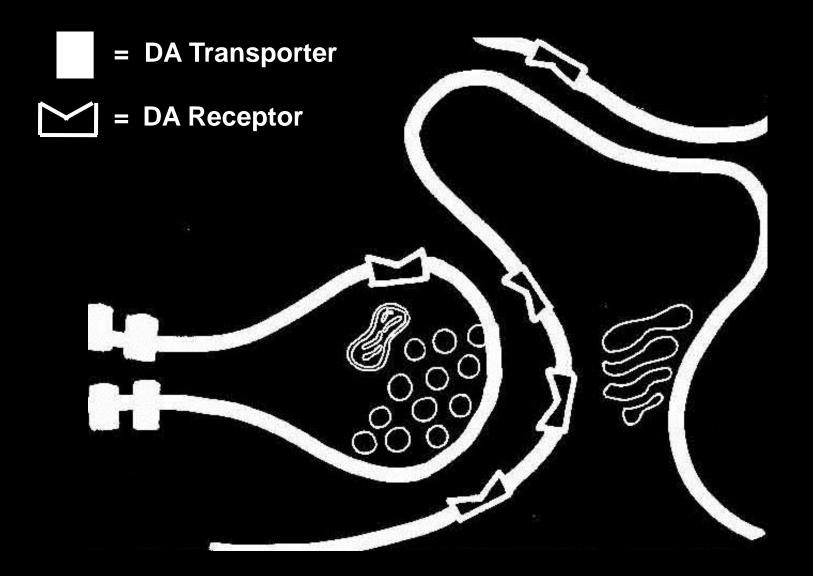
The best mechanism from clearing away released dopamine is by dopamine transporter (DAT) protein.

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





Prefrontal Cortex



In ADHD there is a primary problem in the striatum (PFC-striatal circuit) I hypothesize that in ADD there is a primary problem in PFC (in the PFC-parietal network)

Polymorphisms of the <u>dopamine</u> 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 hyperactiveimpulsive 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)

The dopamine receptor subtype, DRD4, is present in prefrontal cortex in humans, but not in the striatum.

(Meador-Woodruff et al., 1996)

Polymorphisms of the <u>DRD4</u> gene should affect prefrontal cortex and therefore should be linked to ADD (inattentive type of ADHD) DAT1 gene expression preferentially affects caudate volume,



while DRD4 gene expression preferentially affects prefrontal gray matter volume (Durston *et al.*, 2005) The Role of Parenting and Dopamine D4 Receptor Gene Polymorphisms in Children's Inhibitory Control Smith et al. 2013 Developmental Science, *16*, 515-30.

In the face of less positive parenting, children with \geq 7-repeat allele displayed lower Inhibitory Control than children without a 7-repeat allele

A link between the DRD4 gene and ADD is consistent with the finding of Auerbach et al. (2001) Significant relation between individual differences in sustained attention & working memory and polymorphism of the DRD4 gene in normal infants (those with a 7repeat-allele performed worse)

ADD is a different disorder from ADHD.

They have....

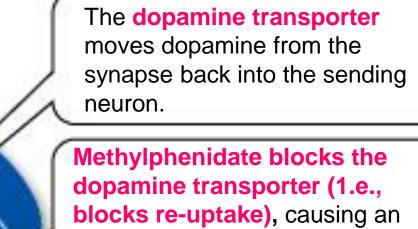
- different cognitive & behavioral profiles,
- different patterns of comorbidities,
- different responses to medication, and
- different underlying neurobiologies.

ADD (ADHD without hyperactivity), a neurobiologically and behaviorally distinct disorder from ADHD (with hyperactivity)

Adele Diamond (2005)

Development and Psychopathology, 17, 807-825

Methylphenidate's Mechanism of Action at High Doses



increase in dopamine concentration at the synapse.

Synapse

Dopamine

Dopamine receptor

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

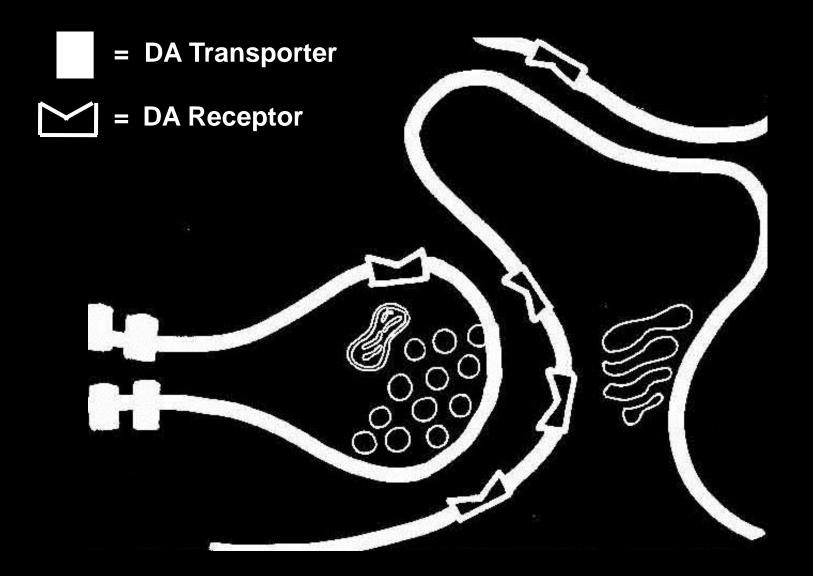
Barkley et al., 1991; Barkley, 2001; Milich et al., 2001; Weiss et al., 2003

On the other hand, a significant percentage of children with **ADD** 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)

Recent research shows that low doses of MHP (dosages that are usually more effective in treating **ADD**) 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

Prefrontal 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.

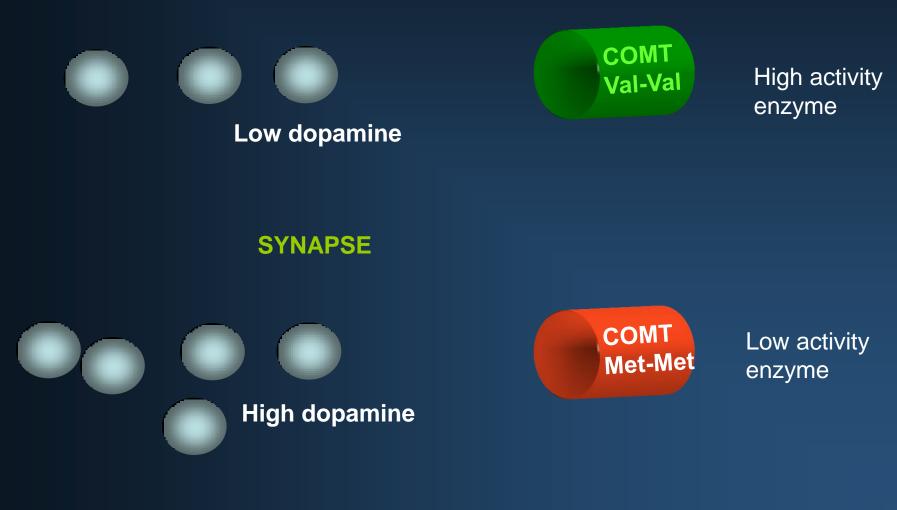
It's located on chromosome 22.

A single base pair substitution CGTG to CATG

translates into a substitution of

Methionine for Valine at codon 158

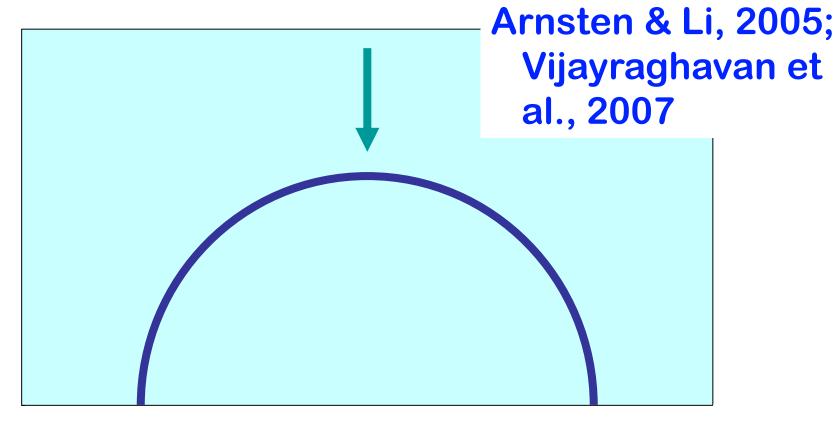
Catechol-O-methyltransferase (COMT) Val158 Met



Zalsman et al.

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

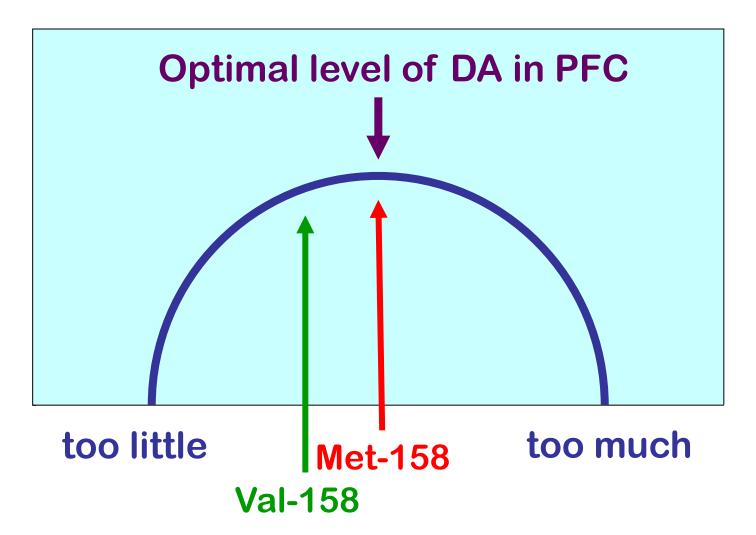
The Optimum Level of Dopamine in PFC is an Intermediate Level



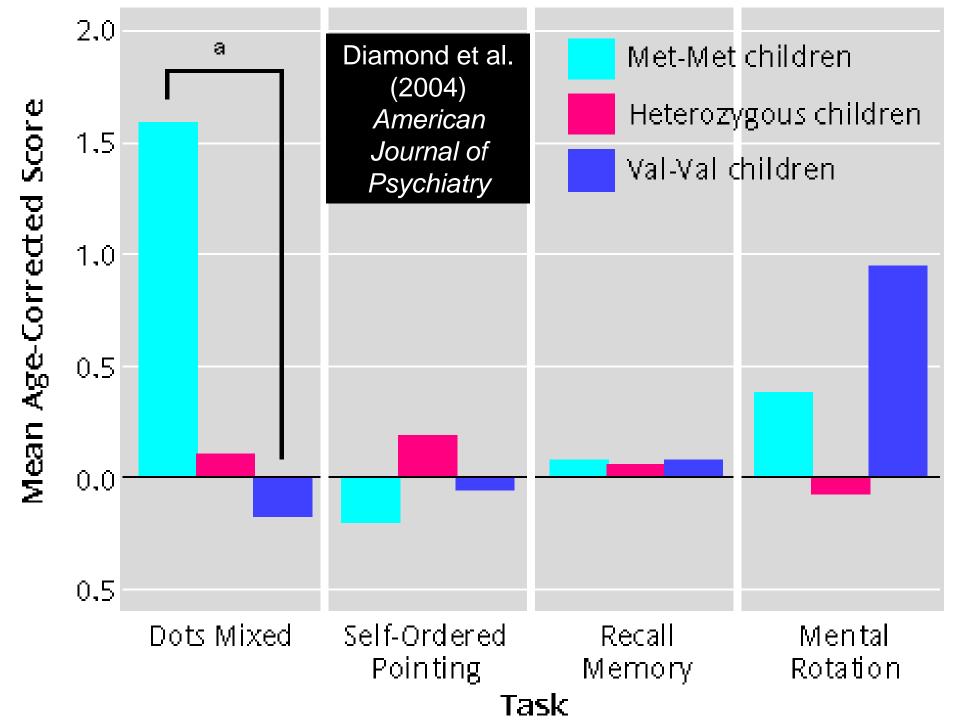
too much



Differences in COMT Genotypic lead to Differences in PFC DA Levels



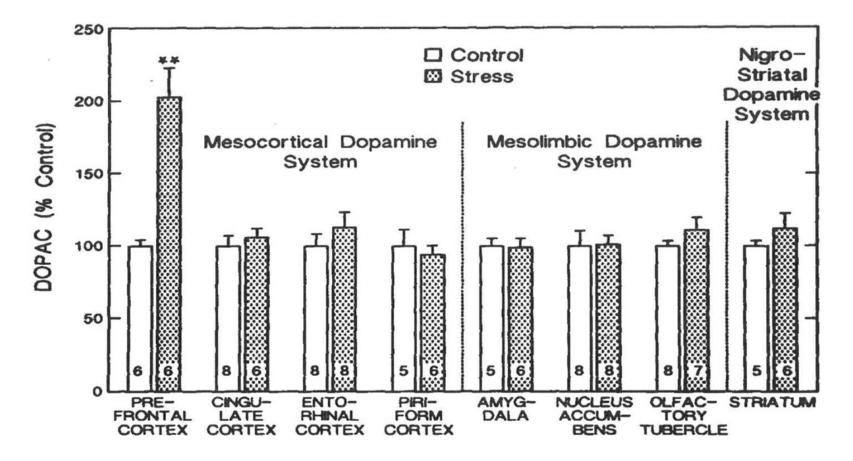
This is specific to EFs: There is no relation between COMT genotype and IQ or other non-PFC functions.



What's the downside of Met variant of COMT?

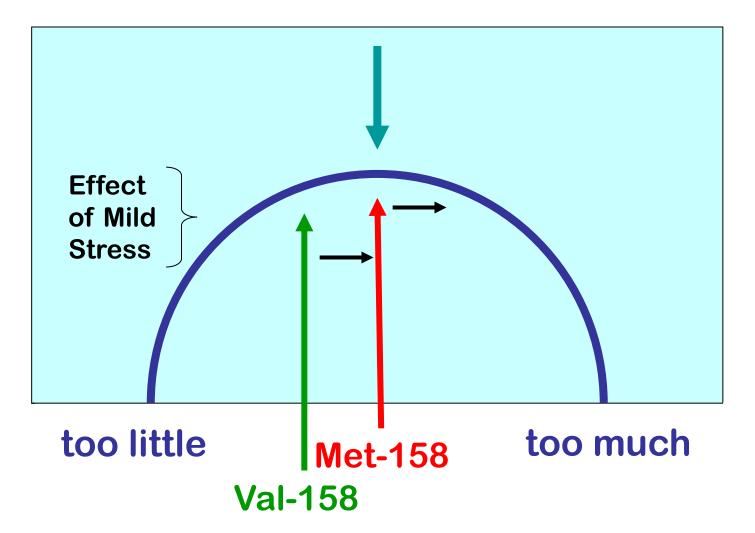


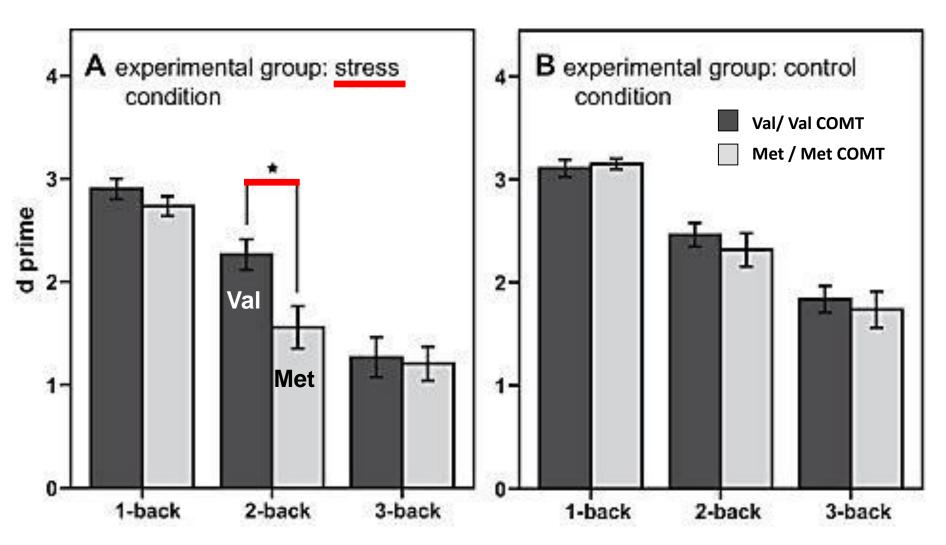
Stress and Prefrontal Cortex Even mild stress increases DA release in PFC but not elsewhere in the brain



(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-Val¹⁵⁸ showed *better* EF performance than young adults homozygous for COMT-Met¹⁵⁸ Persons homozygous for COMT-Met¹⁵⁸ 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-Val¹⁵⁸ 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-Met¹⁵⁸ 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.

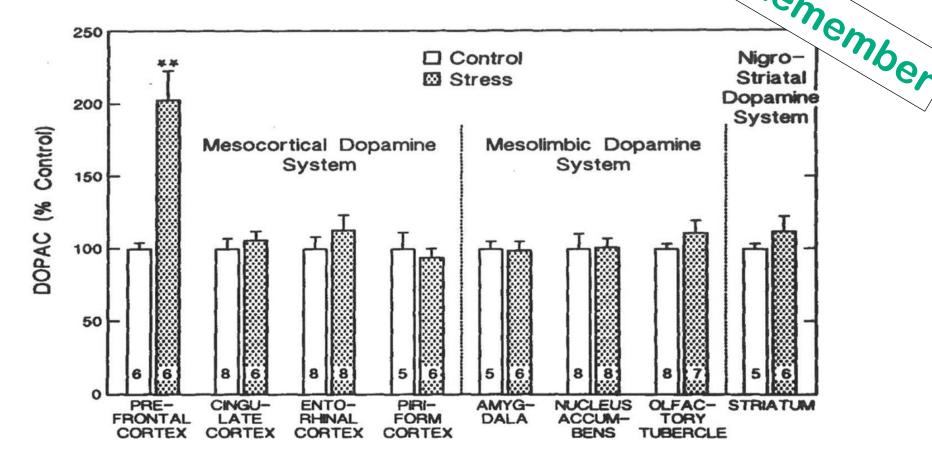
Perhaps some children homozygous for COMT-Met¹⁵⁸ are among the orchids -- they might look like a disaster when in a stressful environment, yet might blossom brilliantly in the right environment. The COMT Met-158 genotype, which confers risk on individuals when they are in adverse, stressful circumstances, 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.

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



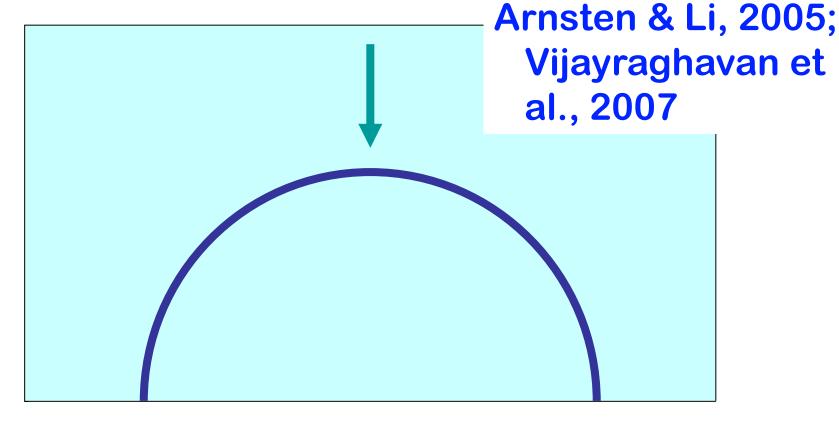
Shors & Leuner, 2003

Stress and Prefrontal Cortex Even mild stress increases DA release in PFC but not elsewhere in the brain Remember Nigro-Chriatal



(Roth et al., 1988)

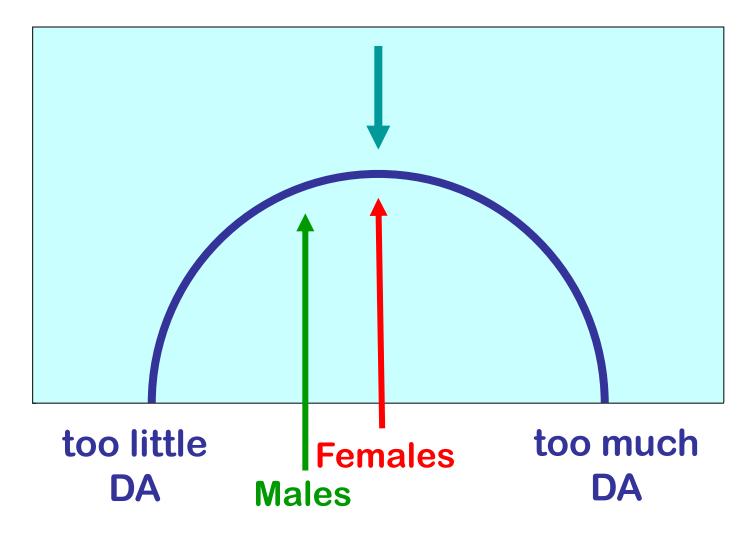
The Optimum Level of Remember Dopamine in PFC is an Intermediate Level



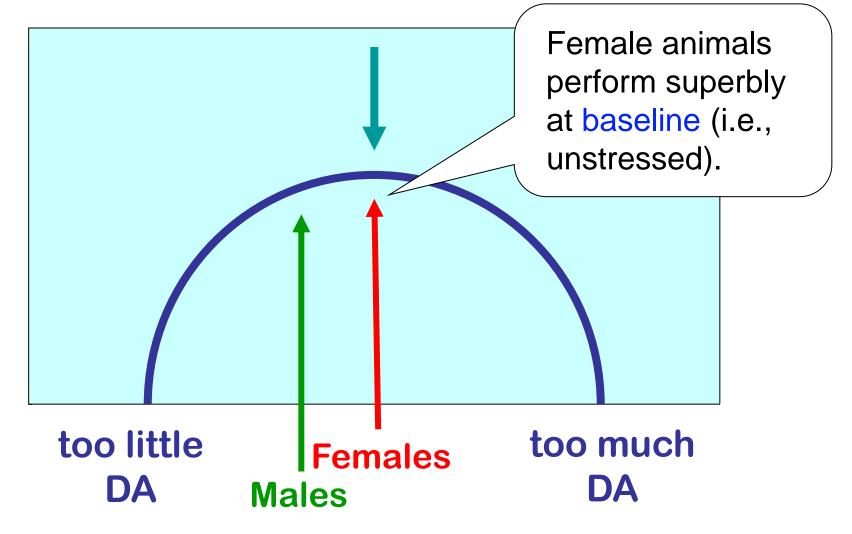
too much



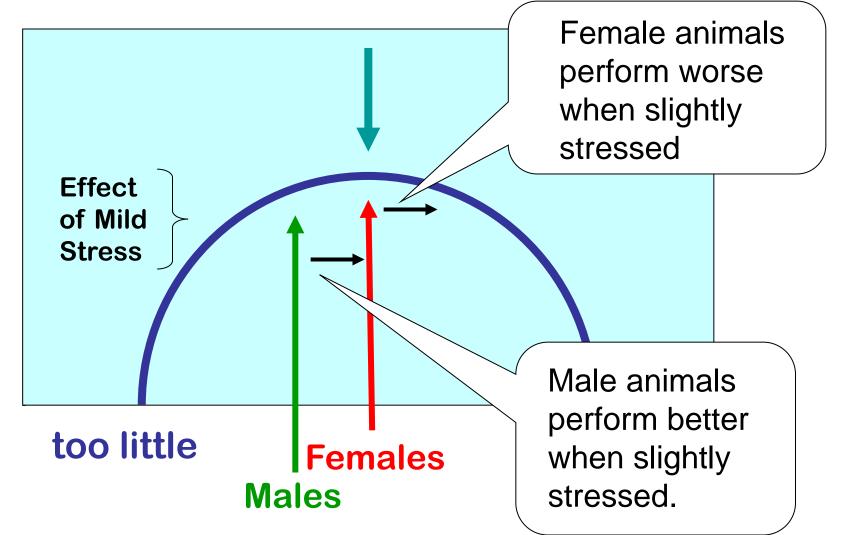
Hypothesis: Gender Difference in Baseline Level of Dopamine in PFC



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?

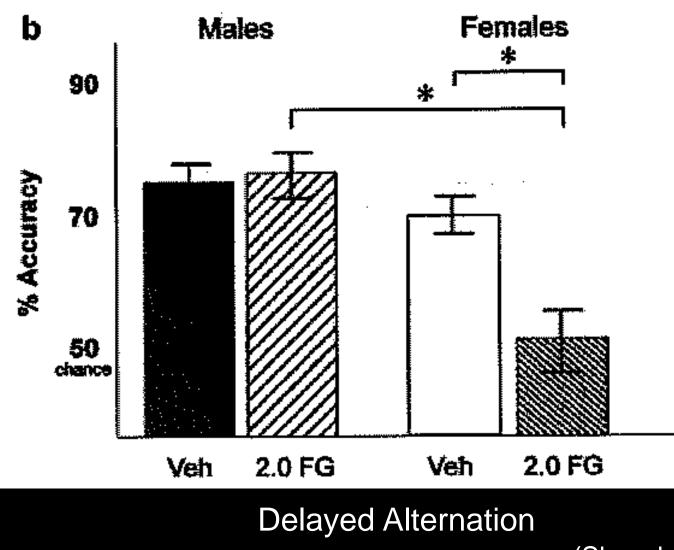
Why might Females have higher baseline levels of DA in PFC than Males?

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

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

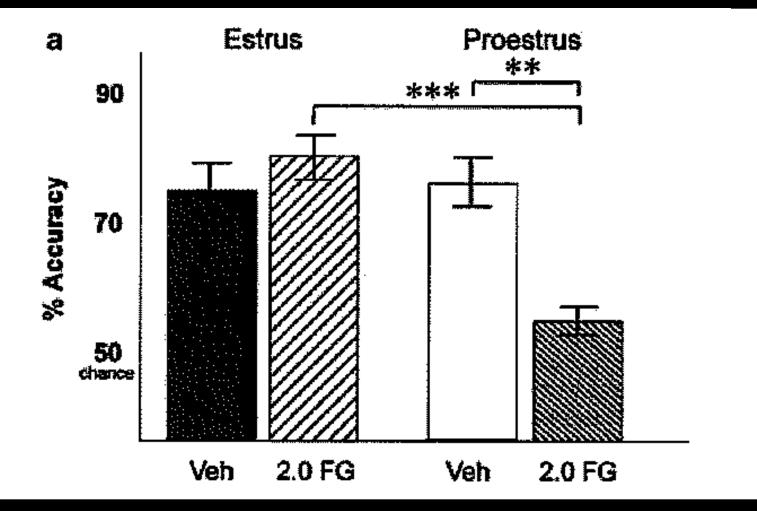
Varies with estrus cycle in rats; inverse relation between COMT activity and estrogen levels.

Stress & PFC



(Shansky et al., 2004)

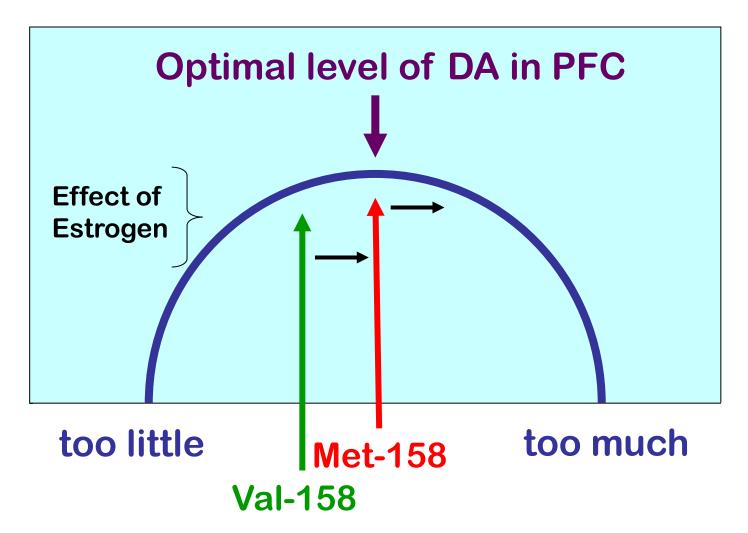
Stress & PFC (Females only)



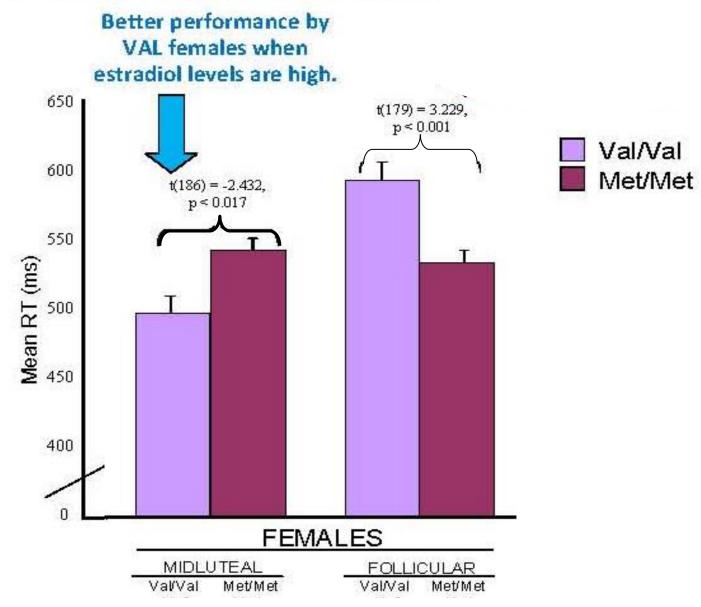
Delayed Alternation

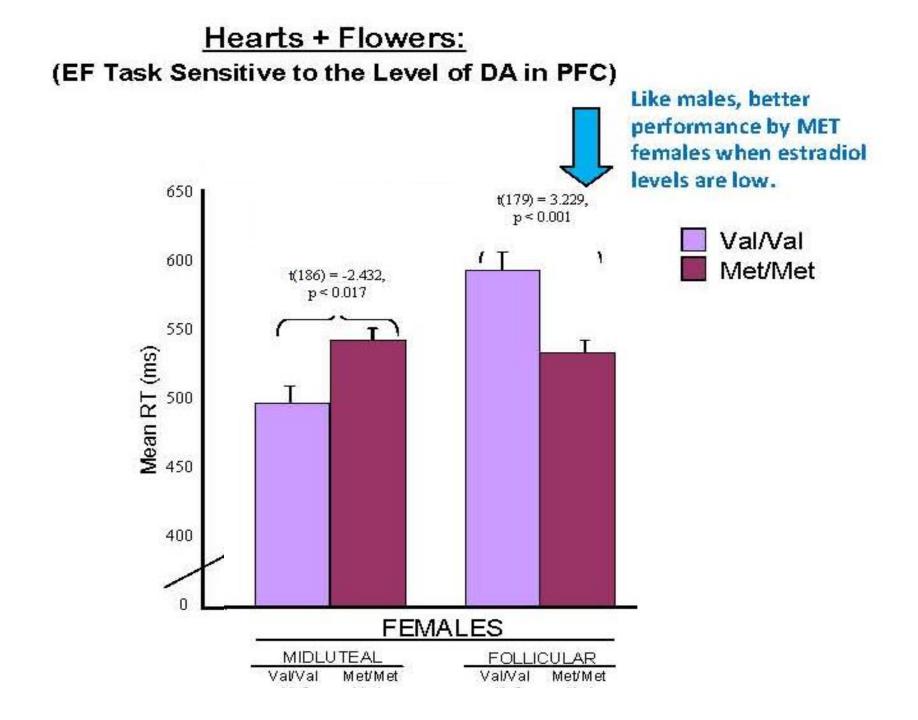
(Shansky et al., 2004)

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



<u>Hearts + Flowers:</u> (EF Task Sensitive to the Level of DA in PFC)







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

If women have higher baseline levels of DA in PFC that would have implications for gender and menstrual-phase differences in the optimal dosage levels of medications that affect PFC DA levels.

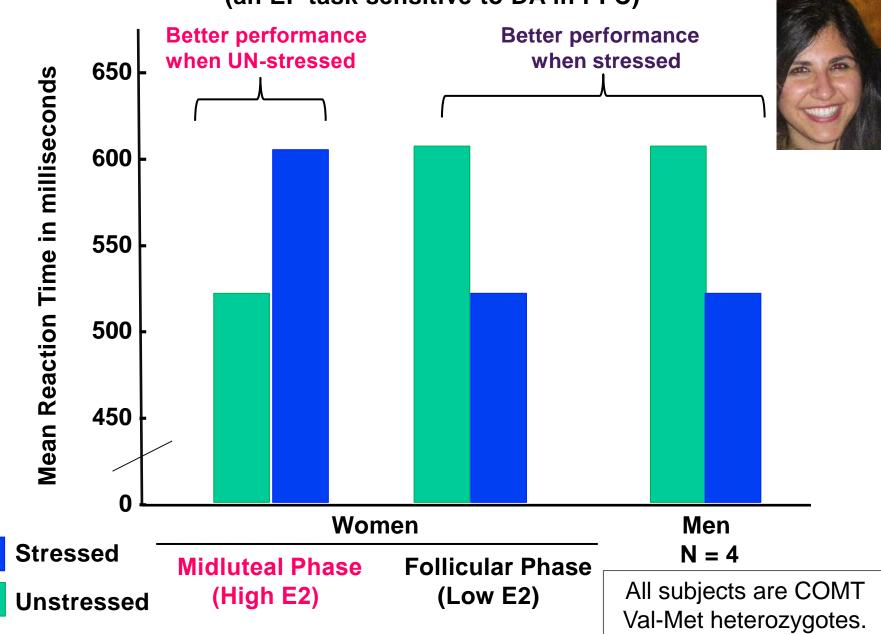
Effect of Stress on Trace Eyeblink Conditioning in Male and Female Rats



Shors & Leuner, 2003

Predicted Results Hearts and Flowers Task - Golnoush

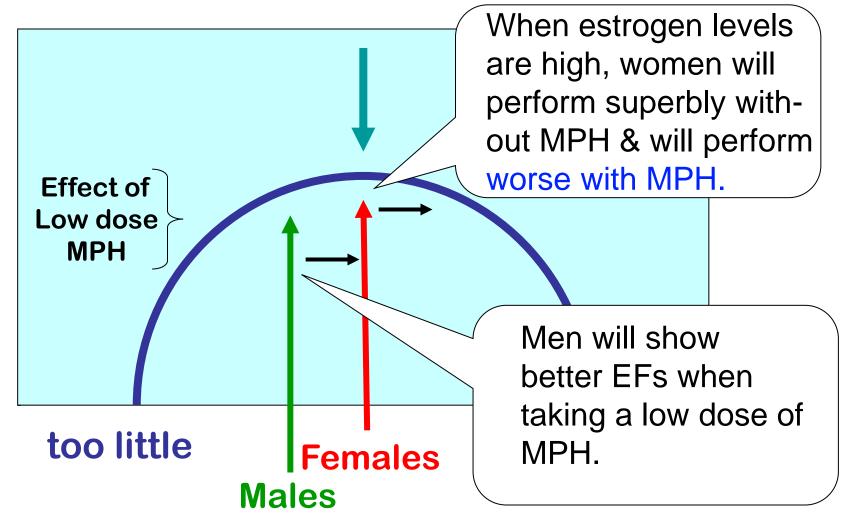
(an EF task sensitive to DA in PFC)



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. **Debra Yew & Michael Bichin**

At low doses the mode of action of MPH is different -it preferentially increases Remember DA in PFC. Berridge et al. 2006; **Devilbiss & Berridge 2008;** Schmeichel & Berridge 2013; Spencer, Klein, & Berridge 2012

Hypothesized Gender Difference in the Cognitive Effect of Low Dose MPH



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 <u>behavior</u> 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 hope to put that to the test soon.

Nowhere is the importance of social, emotional, and physical health for cognitive health more evident than with PFC & EFs.



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PFC & EFs are the first to suffer, & suffer disproportionately, if we are

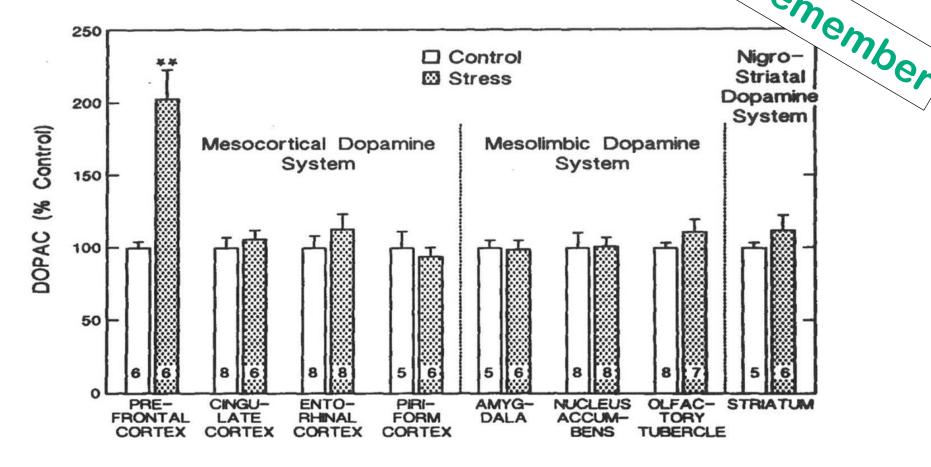
- sad or stressed
- Ionely
- or not physically fit

Conversely, we show better EFs when we're happy, feel socially supported, & we're physically fit. **Our brains work better** when we are not in a stressed emotional state. Amy Arnsten, 1998 The biology of being frazzled

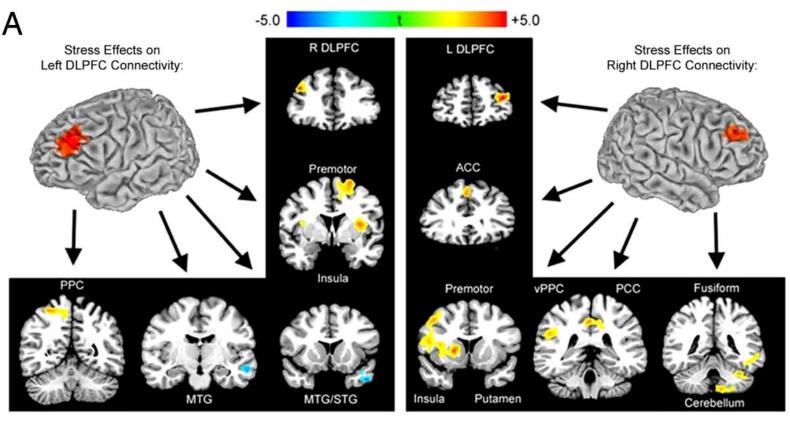


This is *particularly* true for PFC & EFs.

Stress and Prefrontal Cortex Even mild stress increases DA release in PFC but not elsewhere in the brain Remember Nigro-Striatal



(Roth et al., 1988)



In college students, one month of stress in preparation for a major exam disrupts prefrontal cortex functional connectivity. Stress decreases coupling between left DL-PFC and right DL-PFC, and between DL-PFC and premotor cortex, the ACC, the insula, posterior parietal cortex (PPC), and the cerebellum. Liston et al. (2009) *PNAS*

Stress impairs EFs and can cause anyone to look as if he or she has an EF impairment (like ADHD) when that's not the case at all. (You may have noticed that when stressed you can't think as clearly or exercise as good self-control.)

Our brains work better when we are not feeling lonely or socially isolated.

Loneliness: Human Nature and the Need for Social Connection 2008 a book by John Cacioppo & William Patrick

This is *particularly* true for PFC & EFs.



Roy Baumeister et al. (2002, *Journal of Personality and Social Psychology*)

- One group of subjects were told beforehand they'd have close relationships throughout their lives;
- another group was told the opposite;
- a third group was told unrelated bad news.
- On simple memorization questions, the groups were comparable.
- On sections involving logical reasoning (EF), subjects told they'd be lonely performed much worse.

Campbell et al. (2006) found that during math tests there was Prefrontal Cortex worked less efficiently among participants who felt isolated. We are fundamentally social. We need to belong. We need to fit in & be liked. **Children who are lonely or** ostracized will have more difficulty learning.

We are not just intellects, we have emotions we have social needs & we have bodies



You need your sleep.





Lack of sleep will produce deficits in EF skills, and cause someone to look as if he or she

has an EF impairment, like ADHD.



Our brains work better when our bodies are physically fit.

Nature Reviews Neuroscience (January 2008) "Be Smart, Exercise Your Heart: Exercise Effects on Brain and Cognition" Charles Hillman, Kirk Erickson & Art Kramer

"There is little doubt that leading a sedentary life is bad for our cognitive health."

This is *particularly* true for PFC & EFs.



Nature Reviews Neuroscience (January 2008) "Be Smart, Exercise Your Heart: Exercise Effects on Brain and Cognition" Charles Hillman, Kirk Erickson & Art Kramer

Evidence shows that physical activity (especially aerobic exercise) robustly improves cognition and brain function. In particular, the frontal lobe and the executive functions that depend on it show the largest benefit from improved fitness.

The positive effects of aerobic physical activity on cognition and brain function are evident at the molecular, cellular, systems, and behavioral level.

and there have been many more review papers since 2008 including:

Streiner, D. L. (2009). The effects of exercise programs on cognition in older adults: A review. *Clinical Journal of Sport Medicine, 19*(5), 438.

Tseng, C. N., Gau, B. S., & Lou, M. F. (2011). The effectiveness of exercise on improving cognitive function in older people: A systematic review. *The Journal of Nursing Research, 19*(2), 119-130.

Voss, M. W., Nagamatsu, L. S., Liu-Ambrose, T., & Kramer, A. F. (2011). Exercise, brain, and cognition across the lifespan. *Journal of Applied Physiology, 111*(5), 1505-1513. For example, the pre-Supplementary Motor Area (SMA) is important for sequential tasks,

whether they are sequential motor tasks or

sequential numerical, verbal, or spatial cognitive tasks.

Hanakawa et al., 2002

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

When cognitive development is perturbed,

as in a neurodevelopmental disorder,

motor development is often adversely affected as well.



For example.....

At least half of all children with ADHD, dyslexia, or autism have poor motor coordination & fit the diagnosis for developmental coordination disorder.

At least half of all children with developmental coordination disorder would also fir the diagnosis for ADHD, dyslexia, or autism.



Science asked me to write a review of all interventions shown to improve EFs in young children Diamond, A. & Lee, K. (2011)**Interventions shown to Aid Executive Function Development** in Children 4-12 Years Old Science, vol. 333 accompanying online tables

Diverse activities including computerized training, aerobics, martial arts, yoga, mindfulness, & certain school curricula have all been shown to improve executive functions.

I predict that almost any activity can be the way in, can be the means for disciplining the mind and enhancing resilience. **MANY** activities not yet studied might well improve EFs.



It all depends on the spirit in which an activity is presented, the way one does the activity, and the amount of time spent doing it, pushing oneself to do **better.** The most important element is probably that the child really want to do it, so s/he will spend a lot of time at it. It's the discipline, the practice, that produces the benefits.

Might as well have children do something they can put their heart and soul into.























could be caring for an animal....







Could be a SERVICE ACTIVITY such as Free the Children

Children Changing the World More than 1.7 million youth involved in innovative education and development programs in 45 countries.

Educates, engages, and empowers young people to be confident young change-makers and lifelong active citizens.



Educators whose students are engaged in Free the Children report:

97% of their students now believe they can make a difference in the world.	confirm that their students are89% more confident in their goal-setting and completion.
85% find a greater atmosphere of caring and compassion in the school.	of their students have 90% demonstrated increased leadership among their peers.

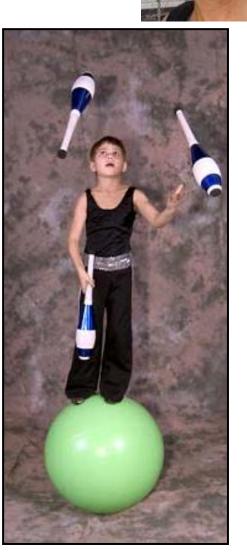
Circus Arts







Jackie Davis



For 10's of 1,000's of years, across *all* cultures, storytelling, dance, art, & play have been part of the human condition. People in *all* cultures made music, sang, danced, and played games. There are good reasons why those activities have lasted so long and been found so ubiquitously.

Music-making, singing, or dancing together address our physical, cognitive, emotional, & social needs.



They

...challenge our executive functions, ...make us happy & proud, ...address our social needs, and ...help our bodies develop The different parts of the human being are fundamentally interrelated.

Each part (cognitive, spiritual, social, emotional, & physical) probably develops best when no part is neglected.

Diamond, 2000

What nourishes the human spirit may also be best for Executive Functions.

Perhaps we can learn something from the traditional practices of people across many cultures & 1,000's of years.

thanks so much for your attention

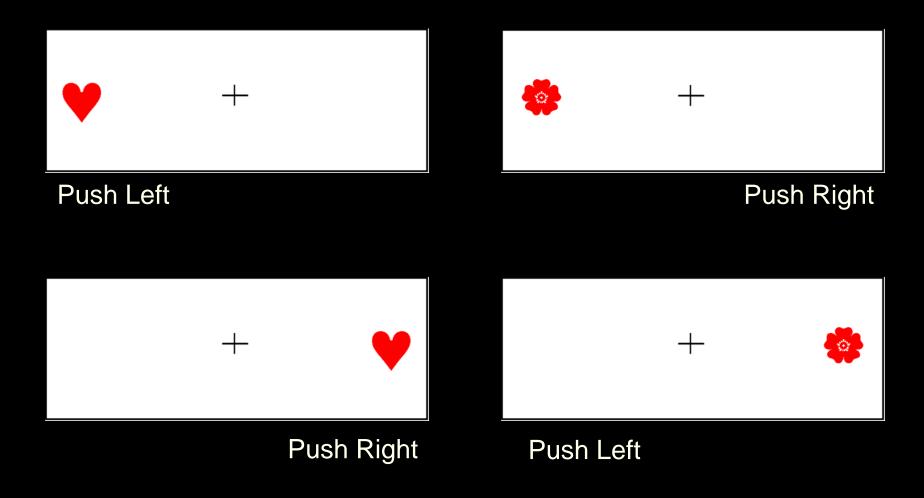


My thanks to the NIH (NIMH, NICHD, & NIDA), which has continuously funded our work since 1986, & to the Spencer Fdn, CFI, NSERC, & IES for recent support our work and especially to all the members of my lab.

HEARTS & FLOWERS

Congruent

Incongruent



HEARTS - CONGRUENT

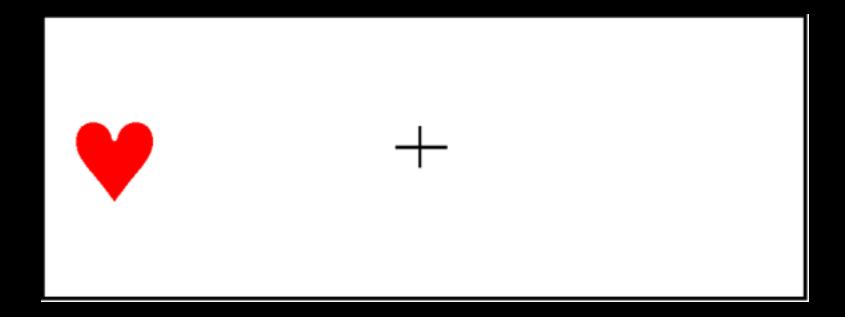
Each time you see a HEART, press with the thumb or forefinger on the SAME side as the stimulus.

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.

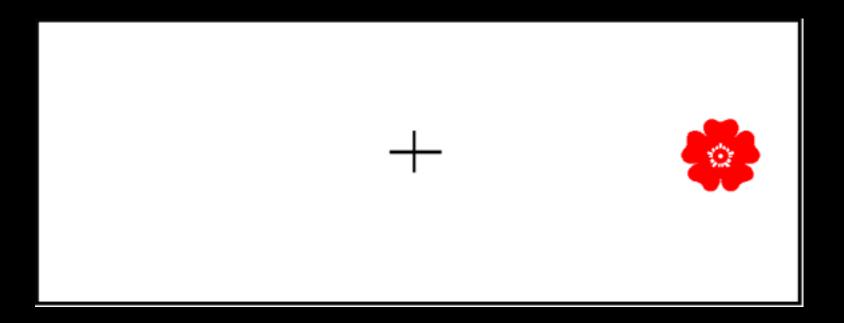
For example, if a flower appears on the left, press with your right hand.

(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 OPPOSITE 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.

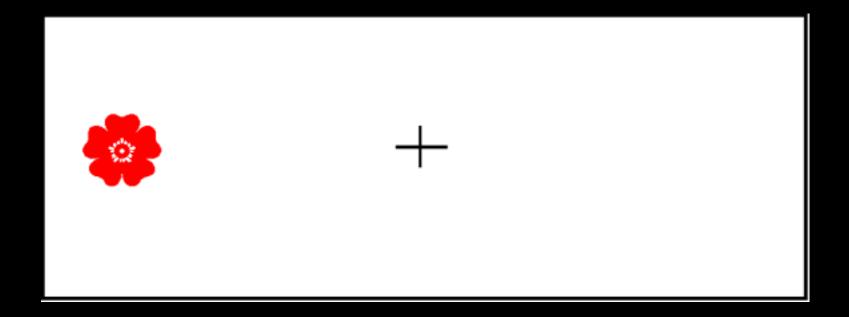
The rules stay the same:

For HEARTS, press on the SAME side.

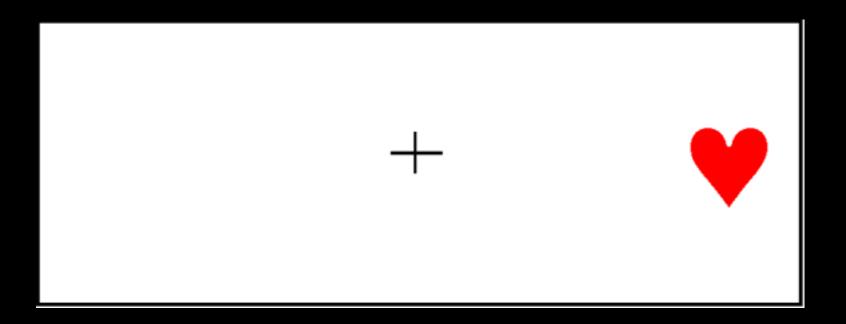
For FLOWERS, press on the OPPOSITE side.

HEARTS - SAME SIDE FLOWERS - OPPOSITE SIDE









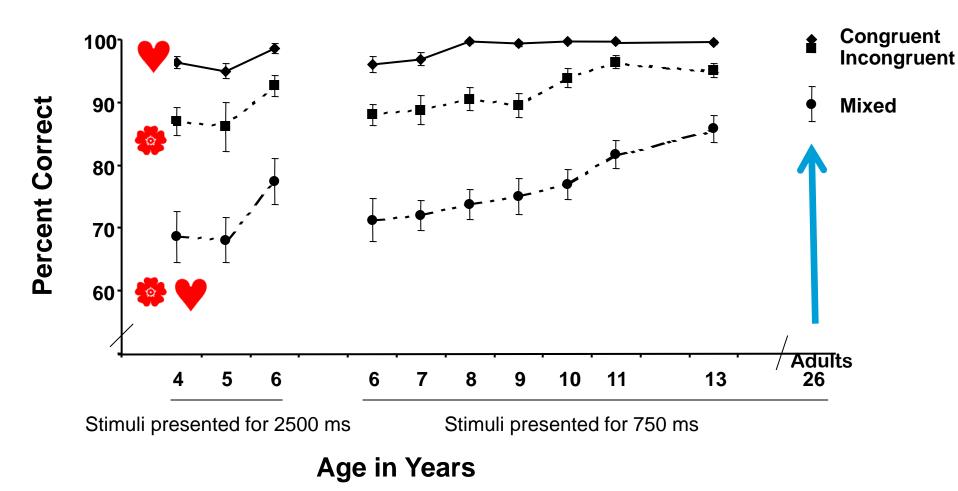


It is *not* that children forget the rules.

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.

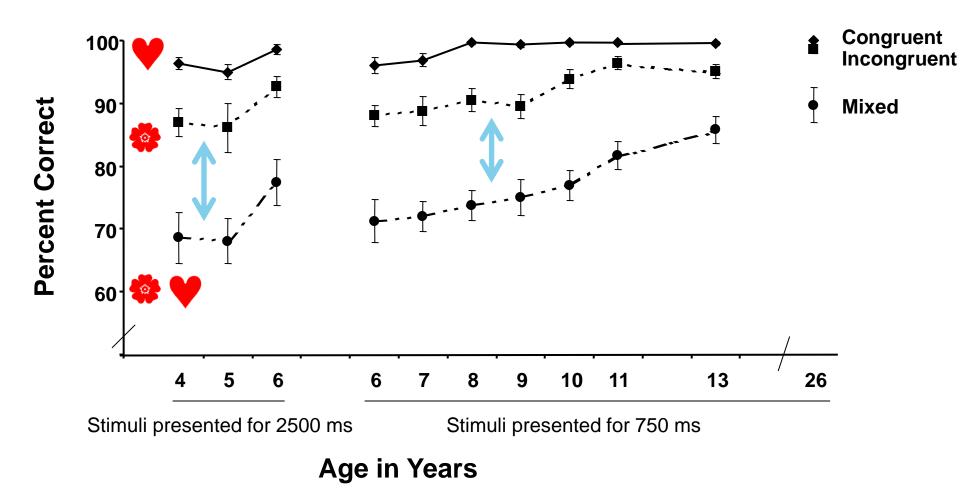
The problem seems to be in quickly translating the rule into the correct response.

Hearts and Flowers Task: Accuracy



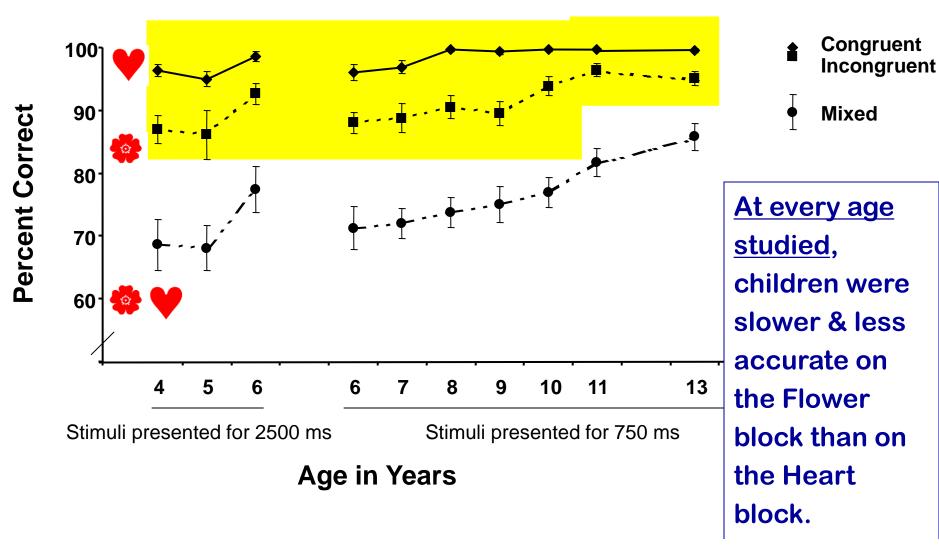
Davidson et al. (2006). Neuropsychologia, 44, 2037 - 2078

Dots Conditions: Accuracy



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

Hearts and Flowers Task: Accuracy

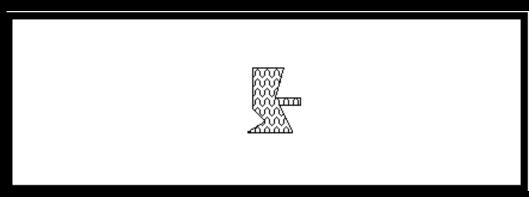


That effect is *completely* absent in adults.

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



Abstract Figures - Center Presentation







Push Right

ABSTRACT SHAPES TEST: A MEMORY LOAD TASK	
Press Left	
Sur?	
Press Right	
ŝ	
Press Right	
k	
Press Right	
Press Left	
Press Left	

Increasing demands on INHIBITION (the Flower block vs. the Heart block) is more difficult for 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 <u>far</u> 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.