# How Our Understanding of ADHD is Changing

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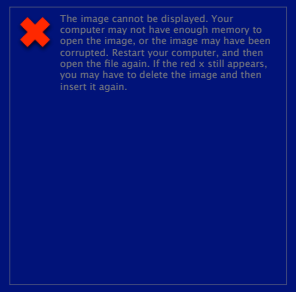

# Thomas E. Brown, Ph.D.
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Eli Lilly, Shire

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# Overview

1. What is the essential problem in ADHD?
2. Brain differences that underlie ADHD
3. How it's most effectively assessed
4. How it's most effectively treated
5. How it's related to other disorders

# What is essential problem in ADHD?

- Old: behavior problems & not listening
- New: developmental impairment of the brain's management system: EF

- Aspects of brain's EF don't come online in usual time frame.
- And don't work consistently

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# Executive Functions

- Wide range of central control processes of the brain
- Connect, prioritize, and integrate cognitive functions–moment by moment
- Like conductor of a symphony orchestra

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# "Will you do it and, if so, how and when?"
(Lezak, 2004)

| | |
|---|---|
| Will you do it? | Motivation/Activation |
| How will you do it? | Planning/Organizing |
| When? | Timing/Remembering |

# Brown's Model of Executive Functions Impaired in ADHD

## Symptom Characteristics

- Dimensional, not "all-or-nothing"
  - Everyone sometimes has some impairments in these functions; in ADHD, it is a chronic, severe impairment
- Situational variability: "If I'm interested"
  - Most persons with ADHD have a few activities where ADHD impairments are absent

**ADHD looks like a willpower problem, but it isn't!**

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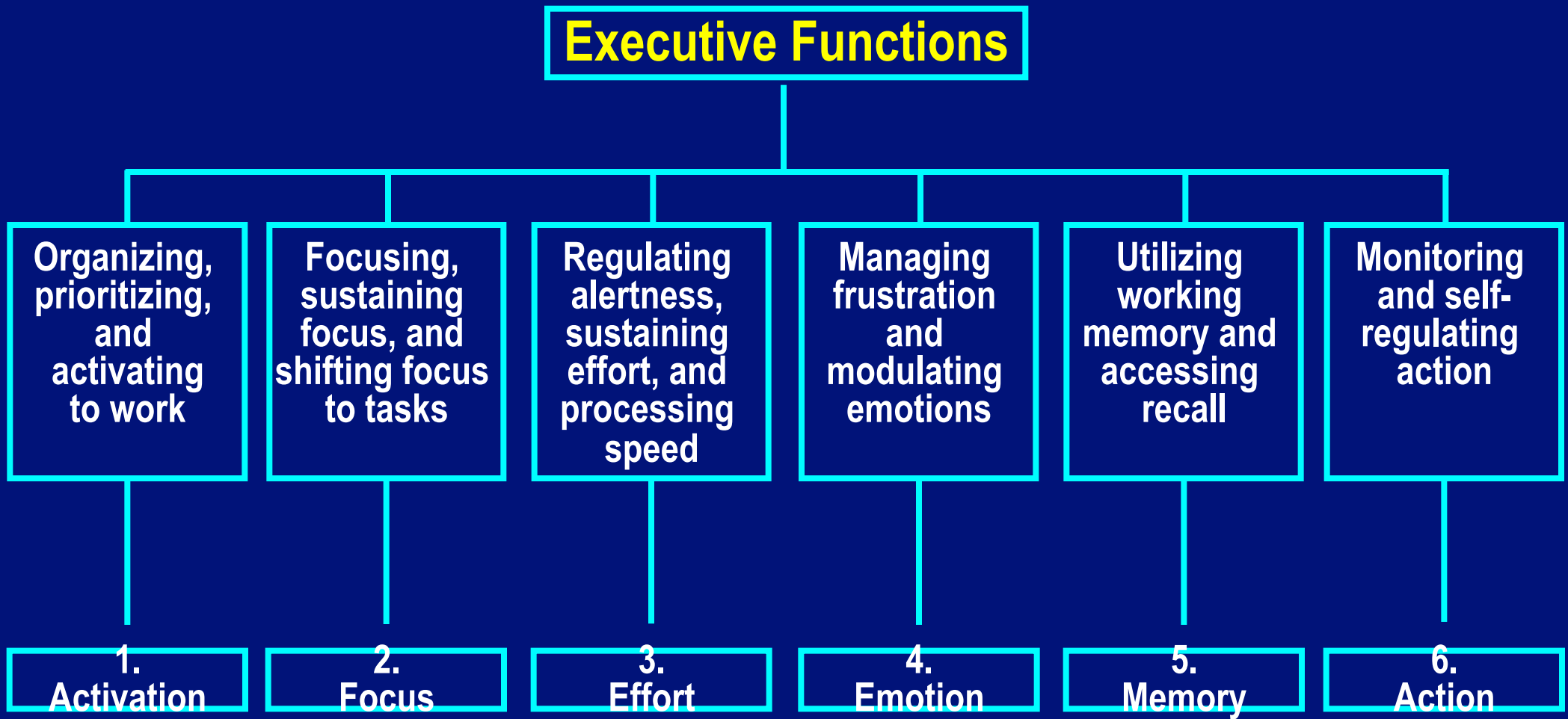
# Brown's Model of Executive Functions Impaired in ADHD




Brown TE. *Manual for Attention Deficit Disorder Scales for Children and Adolescents;* 2001.

# Executive Functions are complex and operate in dynamic, integrated ways

For example, EF of "focus"

- Does not mean
  - as in holding the camera still to take a photo of an unmoving object
- Does mean
  - as in focusing on the task of driving a car

# A Working Definition of ADHD
(TEBrown, 2013)

- a complex syndrome of
- developmental impairments of executive functions,
- the self-management system of the brain,
- a system of mostly unconscious operations.
- These impairments are situationally-specific,
- chronic, and significantly interfere with functioning in many aspects of the person's daily life.

# 2. Brain differences underlying ADHD
## (temporary and/or longer term)

- Delay in unfolding of brain development that supports executive functions
- Impaired white matter connections between brain regions
- Impaired control of oscillations that coordinate brain region communications
- Inadequate release/reloading of transmitter chemicals at synapses

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# ADHD sx may be temporary or longer-term

## 4 Trajectories for Inattention Sx

2000 Canadian kids followed age 6 to 12 yrs

Annual tchr ratings of inattn & hyper separately

1. inattn probs-minimal/stable 46%
2. Inattn probs-significant 17%
3. Inattn increasing w/age 18%
4. Inattn decreasing w/age 19%

(Pingault, et al, 2011)

# Results of Different Trajectories

- Kids w/ highest levels of tchr-reported inattention in grades K-12
- Had higher rate of no diploma
- 71% hadn't earned diploma by 23 yo
- Only 12% of kids w/ lower tchr-reported inattention had no diploma by 23 yo

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# Development of Brain Structures that Support Executive Functions

- Structures and functions that support EF not fully developed in early childhood for anyone
- Neural networks underlying EF begin development at 2-4 years old, but don't fully develop until one's 20s

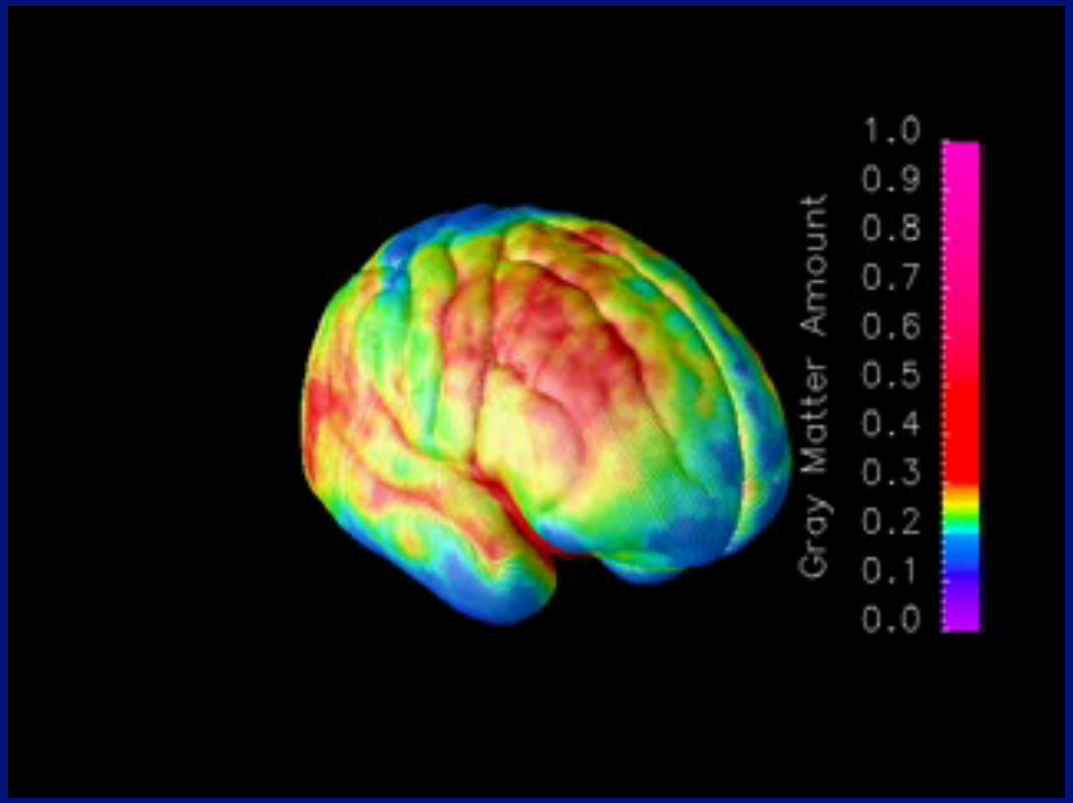
Rothbart MK, Posner MI. Mechanism and variation in the development of attentional networks. In: Nelson CA, Luciana M, eds. *Handbook of Developmental Cognitive Neuroscience*; 2001.

# Continuing Brain Development in Late Childhood and Adolescence

- Between 6-15 years, extreme growth (to 80%) occurs at the collosal isthmus that supports associative relay, while considerable synaptic pruning occurs
- Brain myelination increases 100% during the teenage years
- Dopamine (DA), norepinephrine (NE), and serotonin (5-HT) transmitter systems in the brain continue to develop into one's 20s

Thompson PM, et al. *Nature.* 2000;404(6774):190-193.
Benes FM, et al. *Arch Gen Psychiatry.* 1994;51(6):477-484.

# Prepubescent Growth Spurt in Cortex (thickens just before puberty, then thins)




Aggregate of 52 MRI scans of normal kids scanned X4 @ 2 yr intervals

Cortex thickness peaks at:

11 yo in females

12.5 in males

Then prunes for More efficient circuits

Pruning is gradual, over years

mostly caudal to rostral

[View of right orbital lateral cortex; blue is thinner]

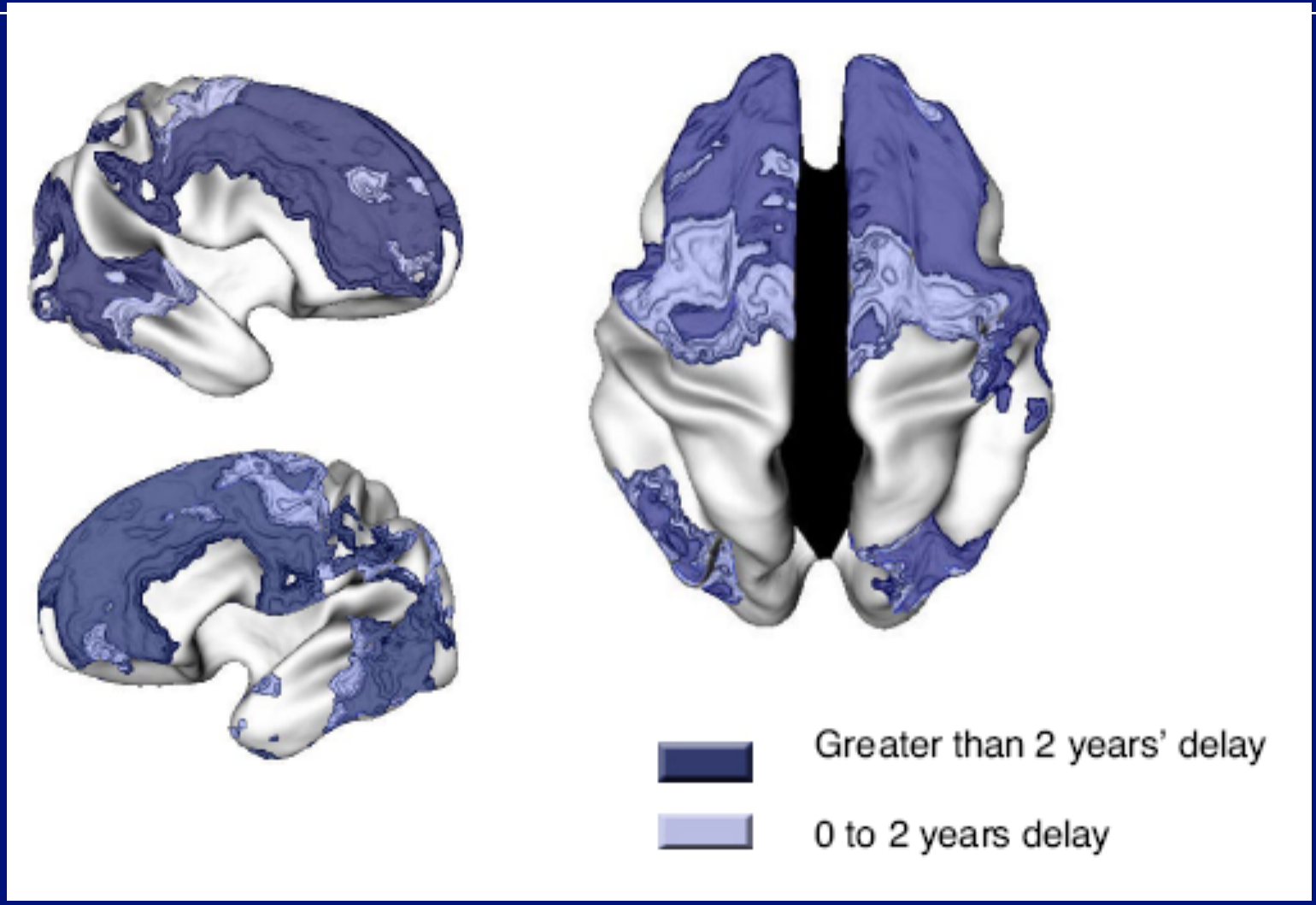
J. Giedd (2003) NIMH

# Cortex Maturation in ADHD vs NC

- MRI studies of 40K cortex sites in 223 youths with ADHD vs matched controls
- Brain maturation was delayed ~3yrs in specific regions in ADHD youths vs NC
- Frontal areas of cortex slower in ADHD
- Medial PFC developed lagged 5 yrs

(Shaw, et al, PNAS, Nov, 2007)

# The Brain Matures Later in ADHD




*Shaw et al. (2007) PNAS*

# Is ADHD Brain Wired Differently?

- New model shifts focus from regional brain abnormalities to dysfunction in distributed network organization.
- DTI shows converging evidence for white matter pathology & disrupted anatomical connectivity in ADHD

(Konrad & Eichoff, Human Brain Mapping, 2010)

# Structural & Functional Connectivity in ADHD

- fMRI and DTI (diffusion tensor imaging) show connectivity between brain regions is impaired in ADHD
- Shown in default mode network at rest and in failure to attenuate DMN during active task performance
- Overall white matter volume is reduced in children & adolescents with ADHD

Konrad & Eickhoff (2010); Nagel, Bathula, Herting, et al, (2011)

# Meta-Analysis of 55 fMRI studies
## of ADHD Children & Adults vs Controls
## (Cortese, Castellanos, et al, 2012)

- ADHD involves dysfunctions in multiple large scale brain networks
- Mostly hypoactivation in control networks
- Also hyperactivation in default & visual circuits
- Inconsistency in ADHD results from faulty inter-regulation between networks

# Chemical Dynamics of Brain also contribute to impairments of ADHD

- Not due to overall "imbalance of chemicals" (not too much/too little salt in soup)
- But to inadequate release and/or reloading of transmitter chemicals in countless infinitesimal network junctions
- Except for "messages" re priority interests or fear of imminent unpleasantness

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# In the Human Brain

- 100 billion neurons
- each one linked to >1000 others
- in complex sub-systems
- that have to “talk to each other”
- using low voltage electrical impulses
- that have to jump across gaps
- so fast that 12 can cross in 1/1000 sec.

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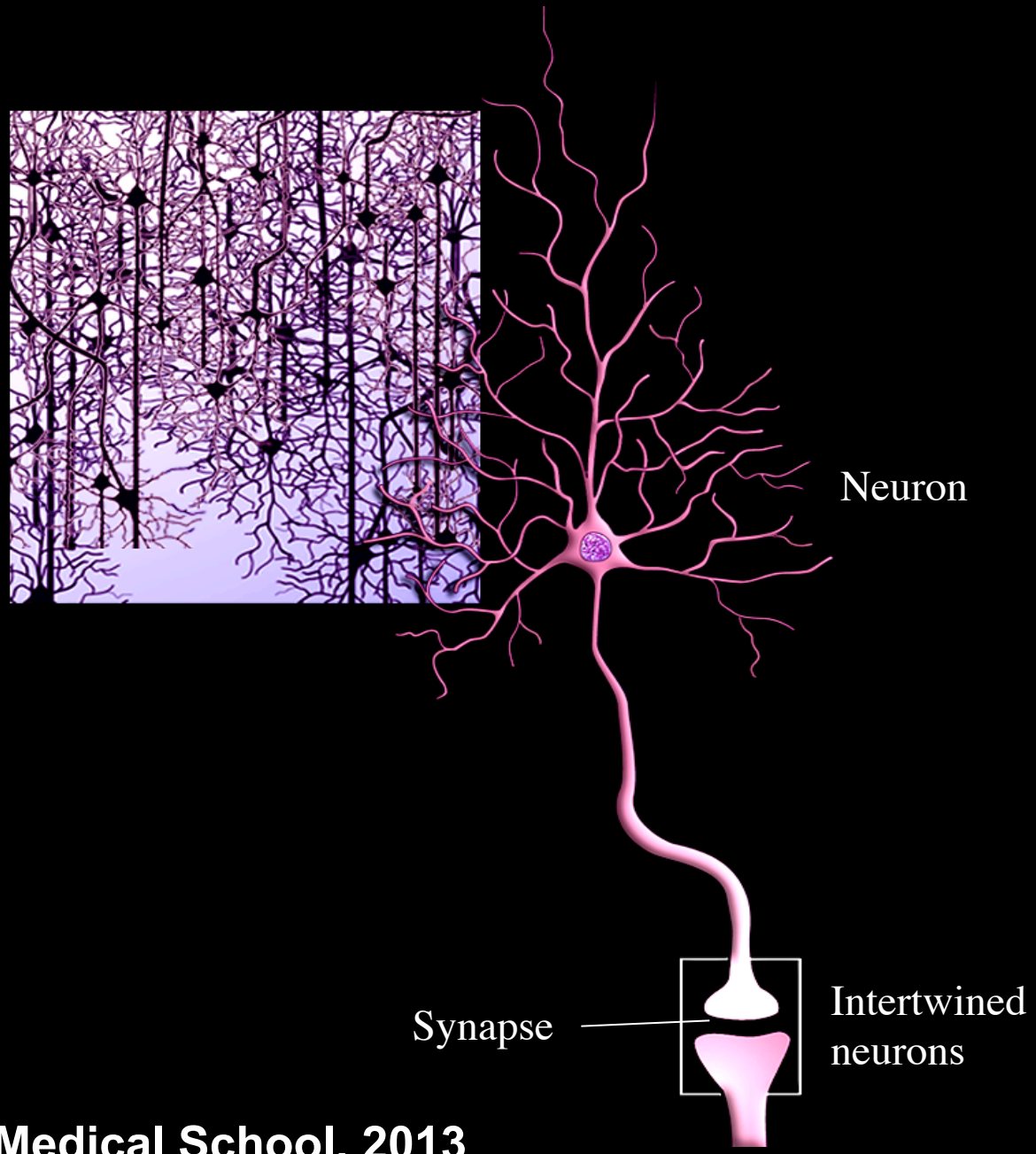


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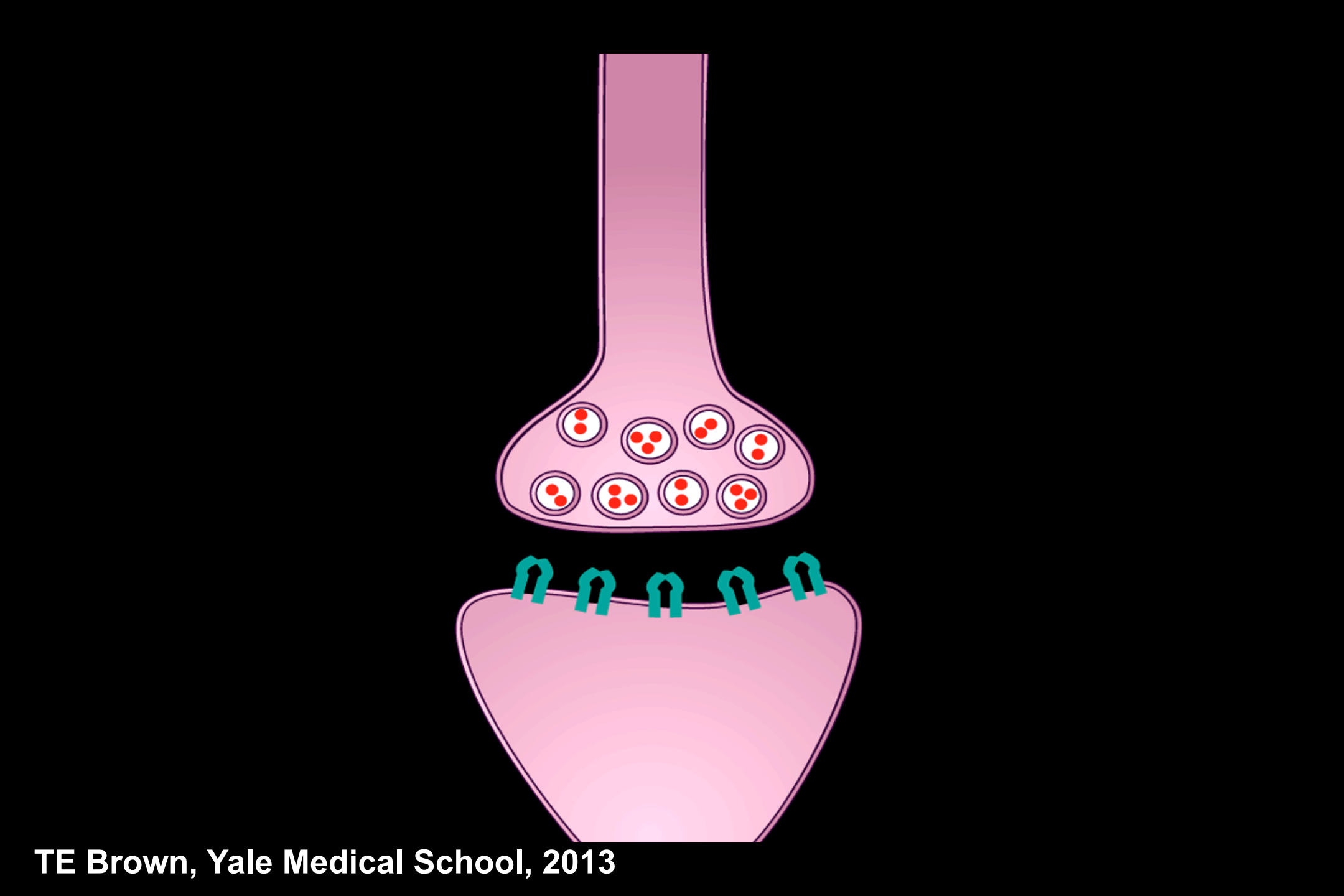
# Chemicals Jump the Gaps

- Inside brain >50 different chemicals are continuously made
- every neuron system uses 1 of them
- stored in little vesicles near tip of neuron
- when electrical impulse comes, mini-dots of that chemical are released,
- cross the gap, fire next neuron, then reload in fractions of a second



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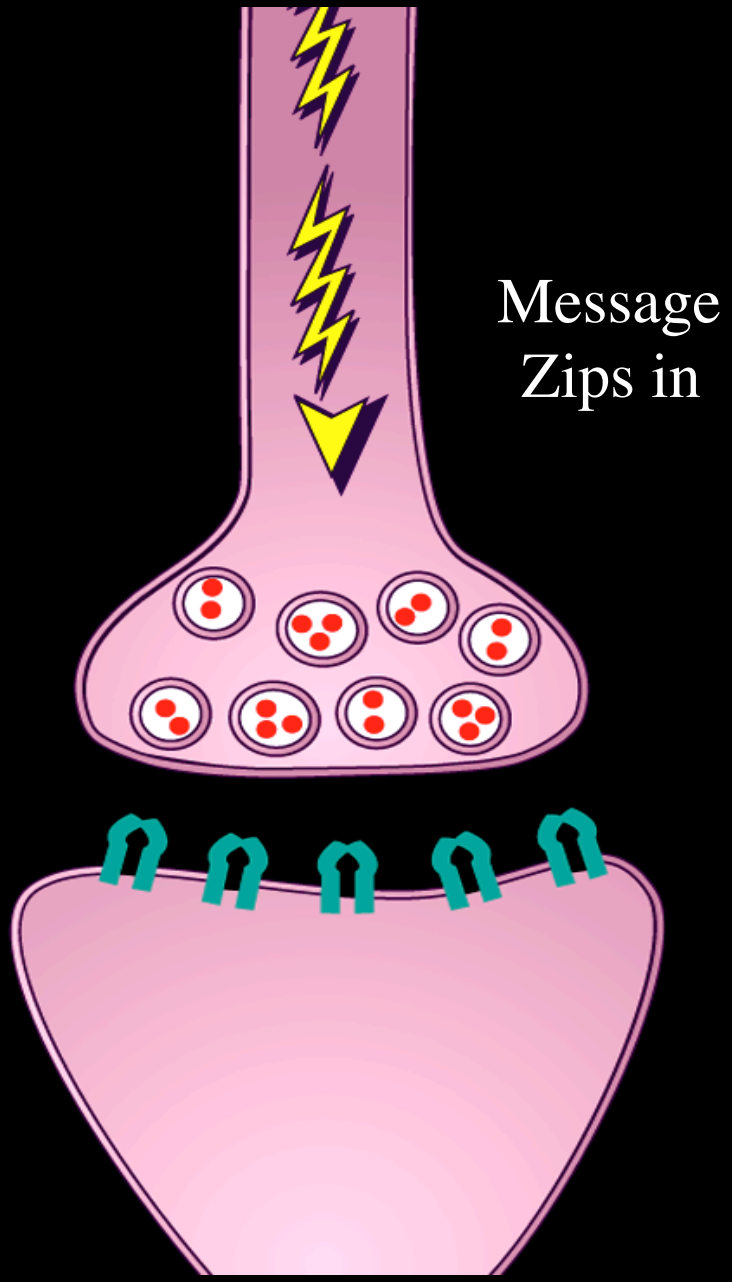


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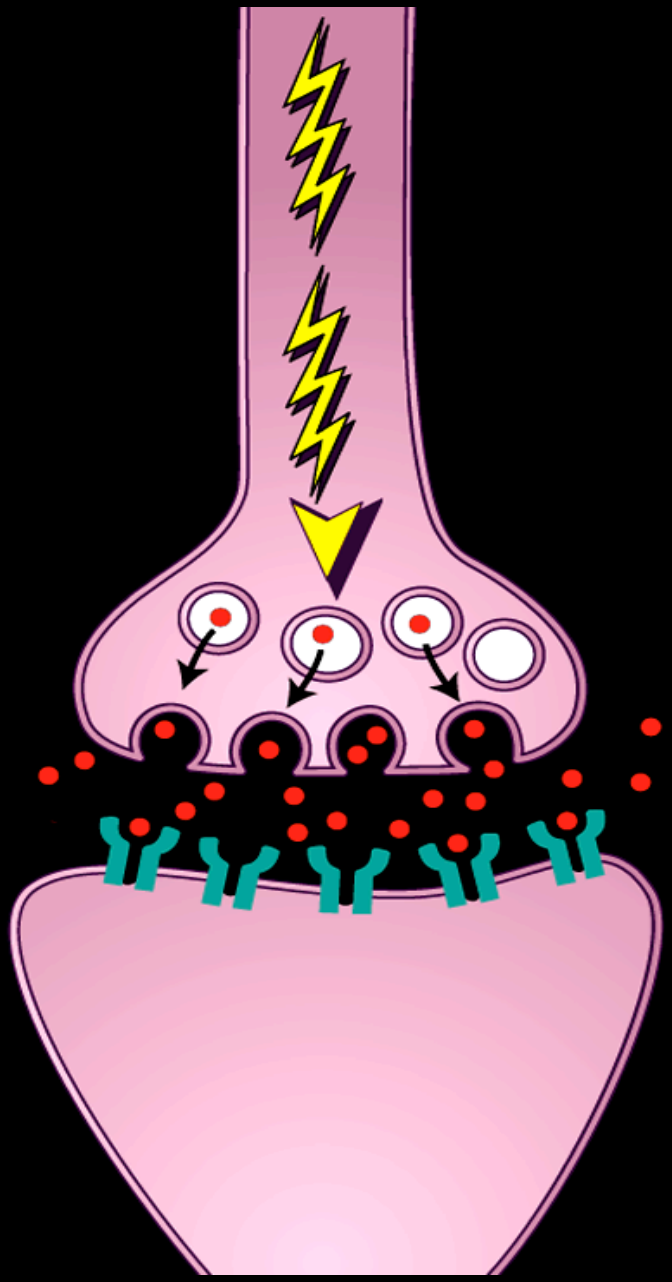

Releasing
transmitter

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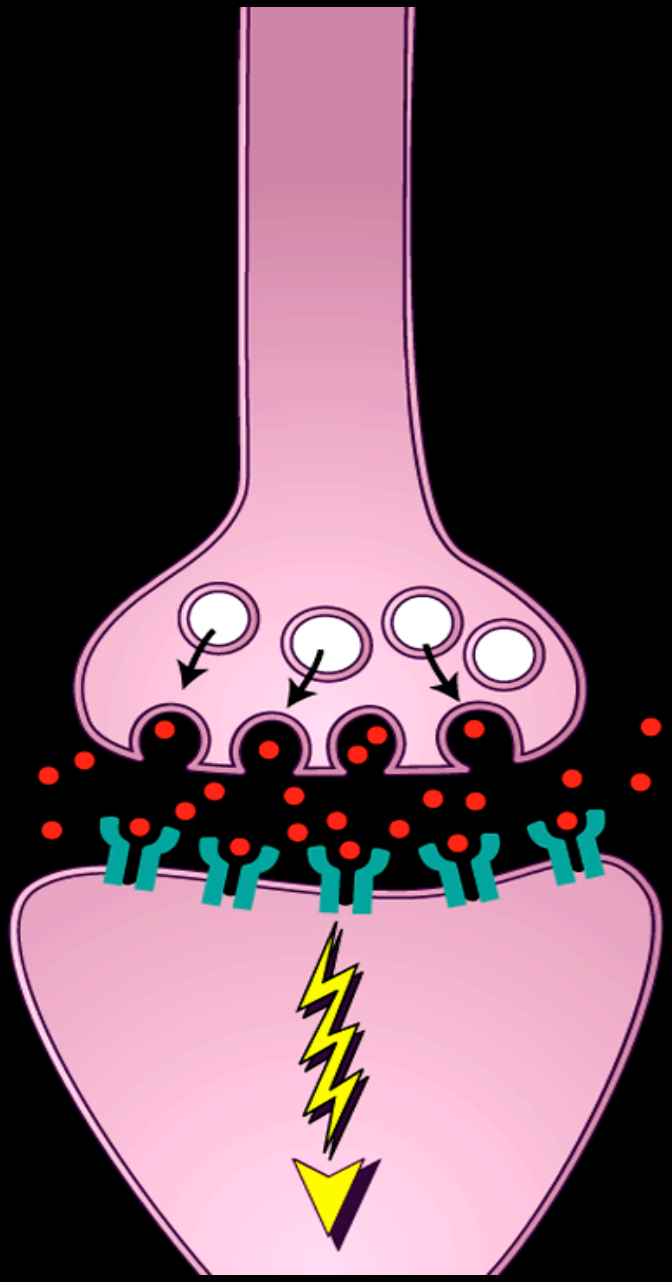

Message
Zips on

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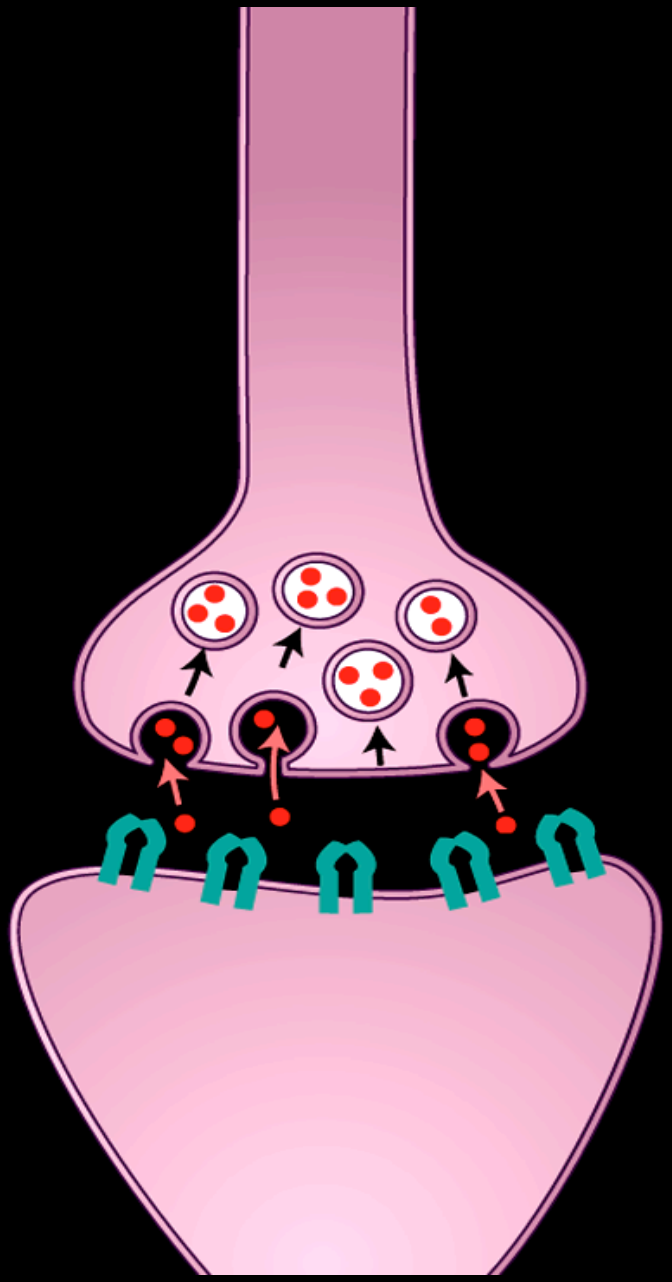

Reloading
transmitter

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# 3. How Can Executive Function Impairments of ADHD Be Assessed?

- When ADHD was seen as just a disruptive behavior disorder in childhood, diagnosis was based on observing overt behavior
- EF impairments of ADHD are largely cognitive, covert, and not easily observed
- Performance of complex, everyday tasks is a more sensitive diagnostic indicator of EF impairments

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# Assessment of ADHD
## requires data on daily functioning in various tasks & settings over time

- clinical interviews (semi-structured) including ADHD rating scales (developmentally sensitive)
- chronic impairment in most, but not all, situations
- Neuropsychological tests, computerized tests, imaging studies, EEG studies are not useful

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# Executive Functions: Development and Demands

- EF capacity develops through childhood, into adolescence, and beyond; it is not fully present in early childhood
- Environmental demands for EF increase with age, from preschool through adulthood
- EF impairments often are not noticeable by age 12 yrs!

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# When Are ADHD Impairments Noticeable?

- Some are obvious very early and are noticeable in preschool years
- Some are not noticeable until middle elementary or junior high
- Some are not apparent until child leaves home to go to college or later

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# Problems with Emotions in ADHD

- not only with brakes: controlling negative emotions, e.g. anger, frustration
- also with ignition: activating positive emotions, e.g. interest, motivation

# Brown ADD Scale-Cluster 4
# **Managing Frustration and Modulating Emotions**

Emotion takes over too much of thinking or feeling…Like a computer virus in the mind. Can't push emotion to "back of mind" and get on with what needs to be done.

-frustration -anger -hurt feelings -worry

-wanting -discouragement -sadness

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# Emotion is mechanism by which brain allocates attention

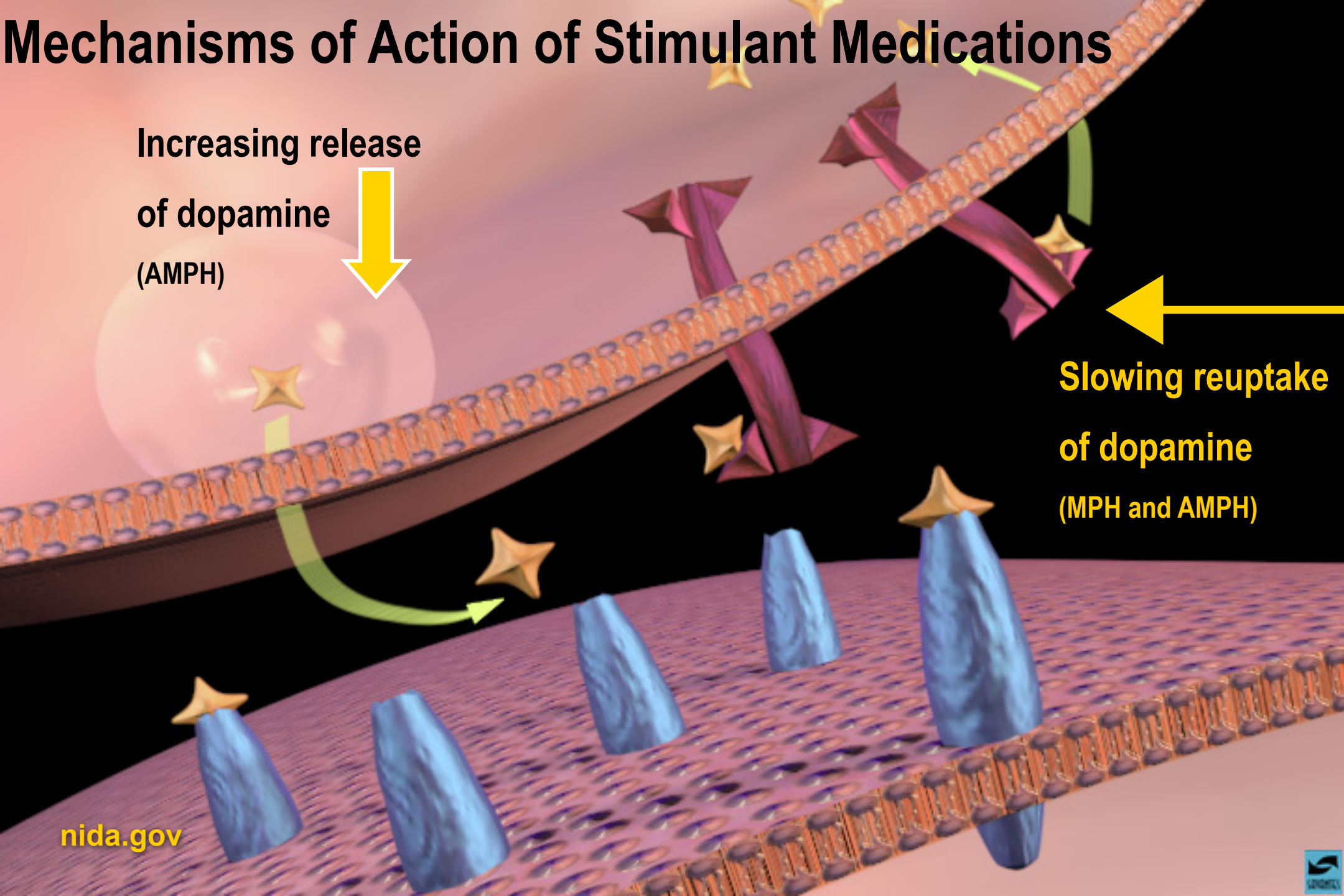
- "All information processing is emotional … emotion is the energy level that drives, organizes, amplifies & attenuates cognitive activity." (K. Dodge, 1991)
- Emotional value is automatically, uncsly assigned to stimuli (amygdala, medial PFC)

[how threatening, important, interesting is this?]

(Damasio, 1994, 1999; Ledoux, 1996, 2002,)

# 4. Treatment of ADHD

- Education of patient and family about the scientific understanding of ADHD and its treatment
- Medications to improve EF functioning; like eyeglasses, they relieve sx, but do not cure; effective for about 80% of those affected; need "fine-tuning"
- Non-phamacological treatments-???


Mechanisms of Action of Stimulant Medications
Increasing release
of dopamine
(AMPH)
Slowing reuptake
of dopamine
(MPH and AMPH)
nida.gov

# Dual Action of Stimulant Meds

PET studies suggest stimulant meds:

1. Engage dorsal attention network, i.e. enhance the signal
2. Deactivate ventral resting state network (default mode network). i.e. reduce the background "noise"

**(Volkow, et al 2008; Swanson, et al, 2011)**

# Motivation & Reward Impairments in ADHD
## (Volkow, Wang, et al, 2004, 2009)

- PET scans indicated decreased DA release in reward circuits of adults with ADHD vs controls
- Also decreased receptors for DA in the accumbens which correlated with attention measures
- MPH increased motivation for task, PBO did not.

# 4. Efficacy of Non-Pharmacological Txs
## shown in reviews & meta-analyses
(Nigg, 2012; Bloch, 2011; Markomichali, 2009; Arns, 2009; Fabiano, 2009)

- Restricted elimination diet
- Artificial food color exclusion
- Free fatty acid supplementation
- Cognitive training
- Neurofeedback
- Behavioral interventions

# Meta-analysis Findings

Limitations of previous meta-analyses:

- Non-randomized designs
- Non-ADHD samples or outcome measures
- Estimates of efficacy are based on unblinded assessments, often by persons invested in that treatment

# Meta-analysis Findings
## (Sonuga-Barke, et al, 2013)

- "Free fatty acid had small beneficial effects on ADHD sx while elimination of food coloring helped only pts w/food sensitivities"
- "Evidence for value of neurofeedback, cognitive training, and behavioral interventions is limited to unblinded ratings by individuals likely to have investment in tx success"

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# Reviews of CogMed Efficacy Claims
## Melby-Lervag, 2013; Hulme, 2012; Shipstead 2012)

- "Working memory training has positive benefits on tasks similar to those trained…but there is no evidence of transfer to other less directly related tasks."
- "There is no good evidence that the CogMed working memory training program is effective…as an effective treatment for ADHD"

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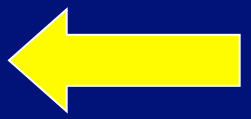
# 5. ADHD Is a Complex Disorder Often Complicated by Comorbidity

- In 50-70% of cases, ADHD is further complicated by one or more additional psychiatric or learning disorders
- Not only is it possible to have another disorder with ADHD, it is 6 times more likely in lifetime than for those without ADHD

Pliszka SR, et al. *ADHD with Comorbid Disorders*; 1999. Brown TE. ADHD Comorbidities: Handbook for ADHD *Comorbidities in Children and Adults*; 2009.

# Psychiatric Comorbidities in adults with ADHD

| | 12 mo. | | Lifetime | |
|---|---|---|---|---|
| | % | OR | % | OR |
| Any mood | 25.5 | 3.5 | 45.4 | 3.0 |
| Any anxiety | 47.0 | 3.4 | 59.0 | 3.2 |
| Any substance | 14.7 | 2.8 | 35.8 | 2.8 |
| Any impulse[1] | 35.0 | 5.6 | 69.8 | 5.9 |
| Any psychiatric | 66.9 | 4.2 | 88.6 | 6.3 |



([1]impulse = antisocial pd, ODD, CD, Intermittent explosive disorder, bulimia, gambling

(from Ntnl Comobidity Survey-Replication data presented by R.Kessler at APA, 5/1/04)

i

# A Conceptual Growing Edge…

Understanding of ADHD as developmentally impaired Executive Functions has broad implications

- Exec functions cross boundaries of disorders, brain structures and the boundary between pathology and normality

- ADHD is not just one disorder among many----it cross-cuts other disorders

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# Impairments of EF can have wide impact upon mind

- "without basic attention and working memory there is no prospect of coherent mental activity…" (1)
- "…attention serves all the other functions." (2)

[1]Damasio (1994); [2]Fuster (2003)

- Exec Functions are the "operating system" of the mind

# Key Points -A

1. Essential problem in ADHD is developmental impairment of EF
2. Brain differences that underlie ADHD include delay in maturation of some EF areas, disrupted regional communications and inconsistent neuronal communication.
3. It's most effectively assessed with clinical interviews & rating scales for impairment, not with neuoropsychological tests

# Key Points - B

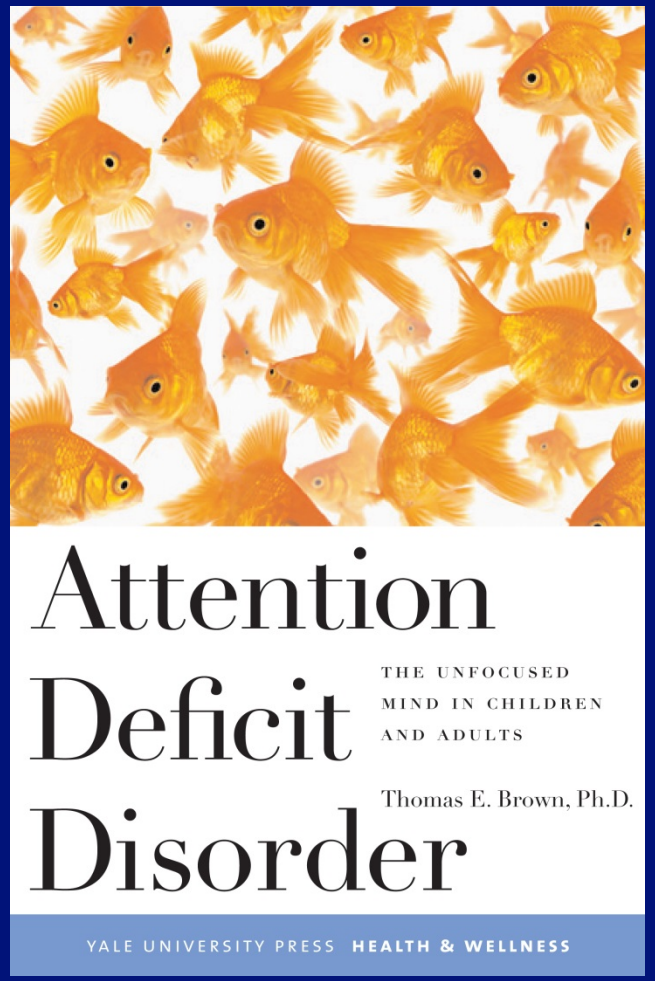
4. It's most effectively treated with medications. Behavioral treatments may be somewhat helpful for some symptoms, but evidence is limited and often biased.

5. It's related to other disorders as operating system of computer is related to software.

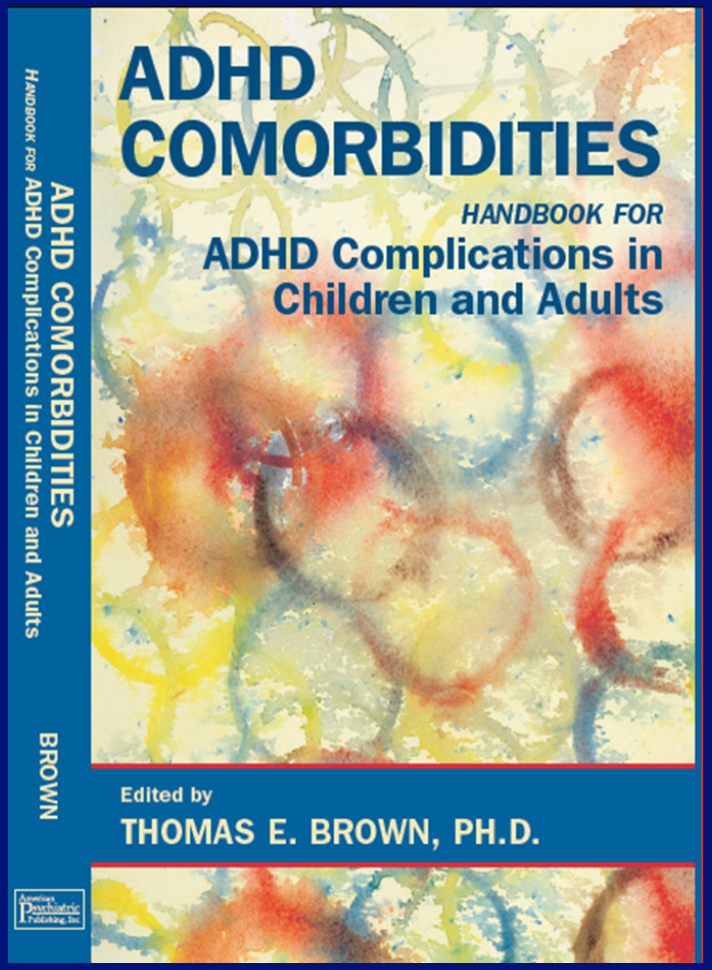
# Books by Thomas E. Brown, Ph.D.

## www.DrThomasEBrown.com

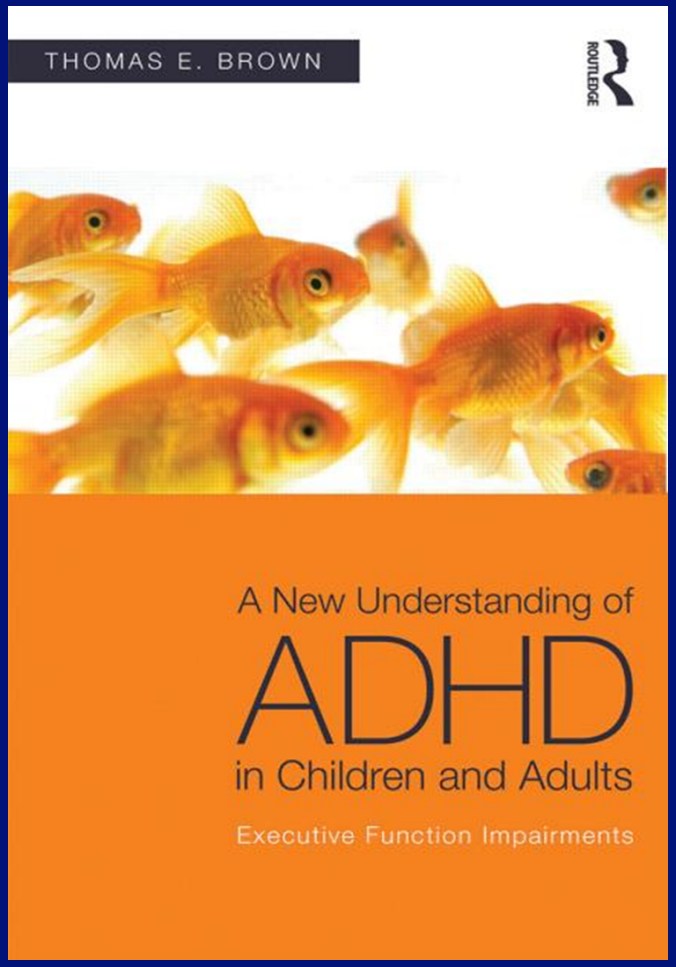
2005




2009




2013



# Smart but Stuck:
## Emotions in Teens & Adults with ADHD
## by Thomas E. Brown

New book
to be
released
March,2014
Jossey-Bass/Wiley