

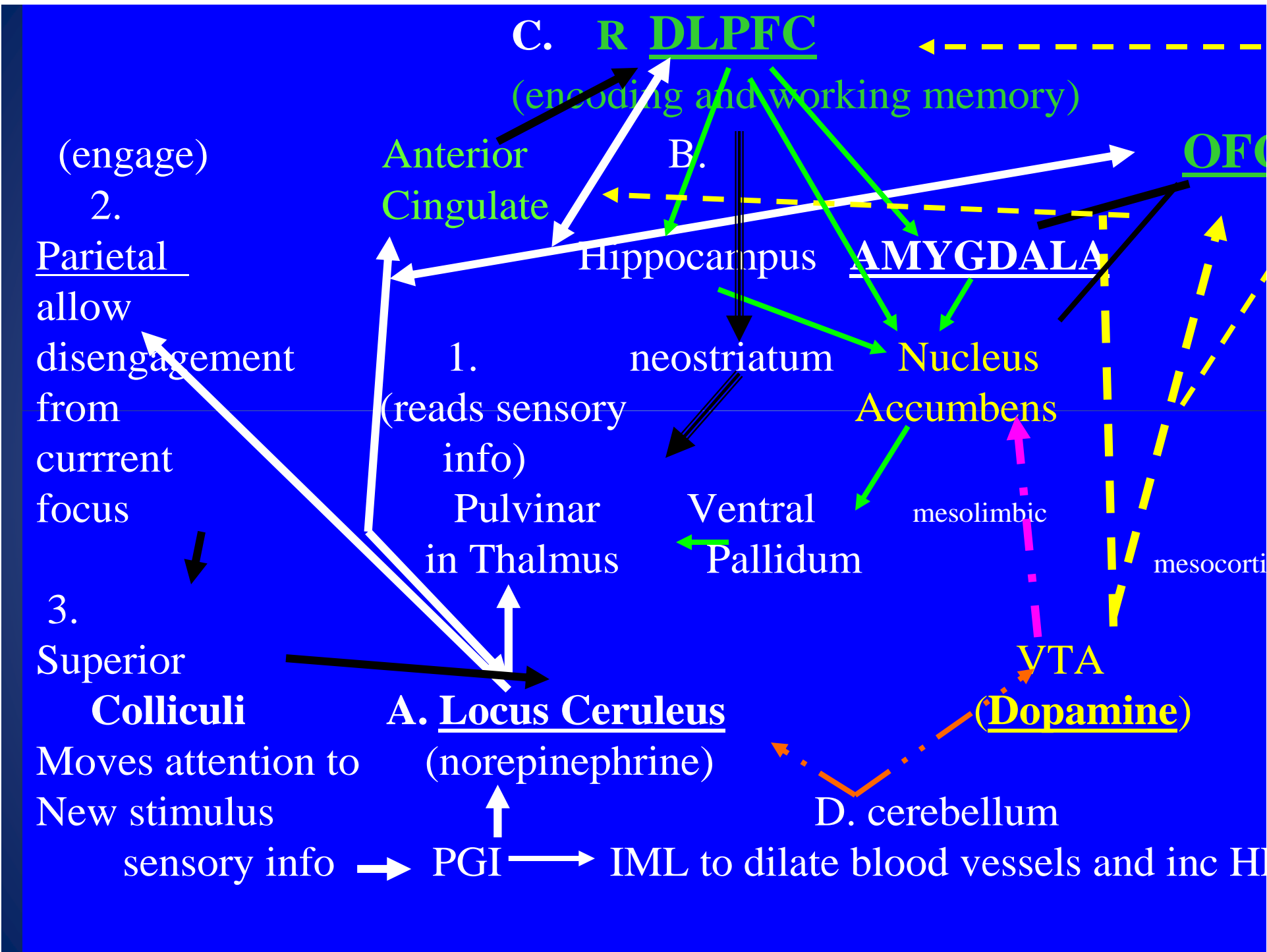
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- Neurobiology of ADHD
- Role of Working Memory
- Overlap with Reading Disorders
- Timing of Intervention for Reading Disorders and Working Memory
- Development of the Adolescent Brain and Reasons for Experimentation
- Susceptibility to Risk for Substance Abuse in Untreated ADHD
- Reasons for Decreased Risk for Substance Abuse in treated ADHD

Similarities between Adult and Child ADHD

- Cerebello-thalamo-striatal-cortical network deficits are the same in adults as they are in children and adolescents.
- Neuroimaging similar to childhood ADHD has been found in adults in the dorsal caudate, the basal ganglia (frontal striatal) and the cerebellum.
- Schneider, et al 2006



R DLPFC

(encoding and working memory)

OFC

**Anterior
Cingulate**

1.
(reads sensory
info)

Pulvinar
in Thalamus

A. Locus Ceruleus

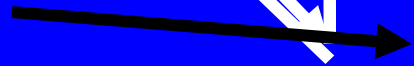
(norepinephrine)

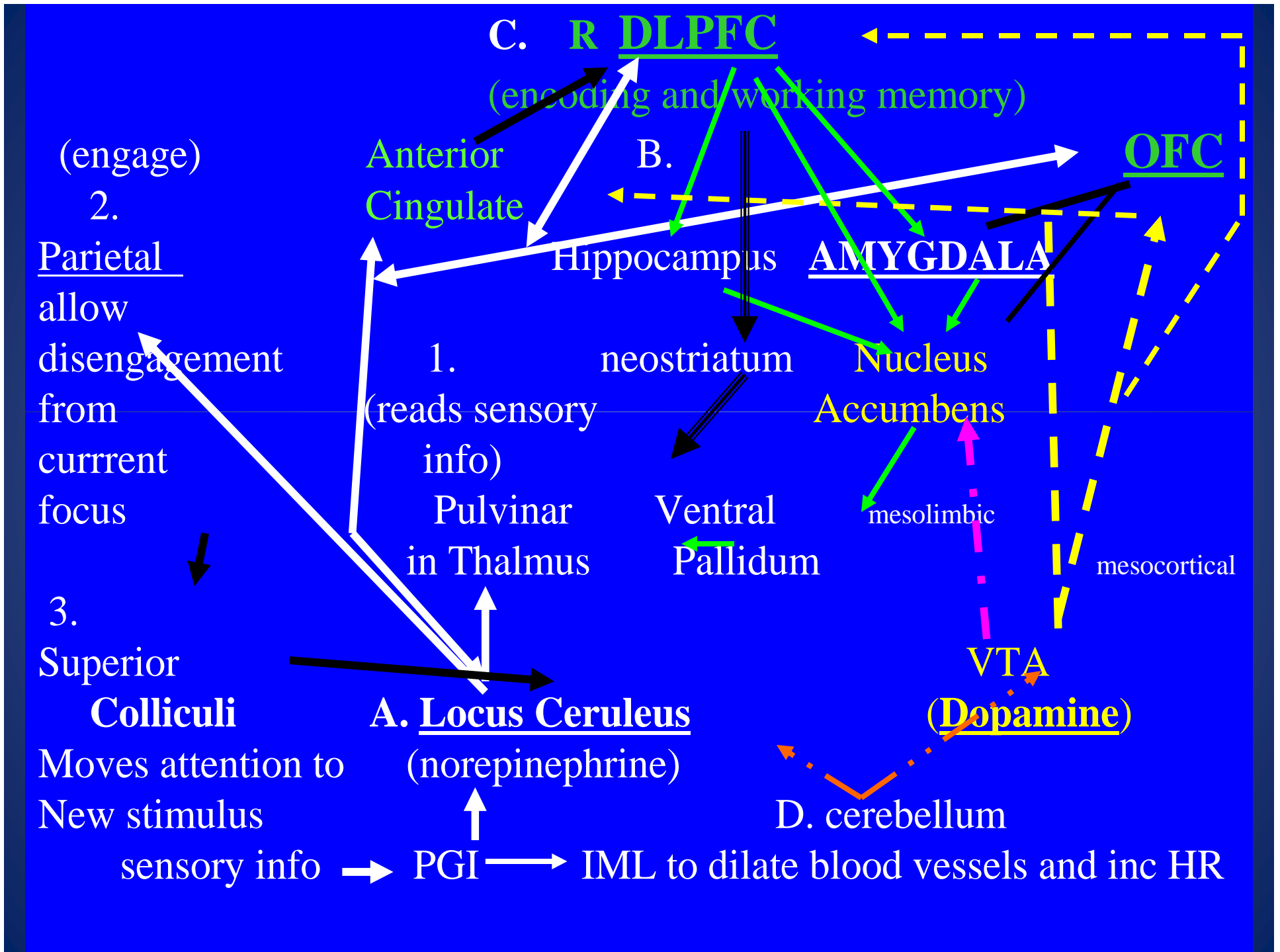
PGI → IML to dilate blood vessels and inc H

(engage)
2.
Parietal
allow
disengagement
from
current
focus

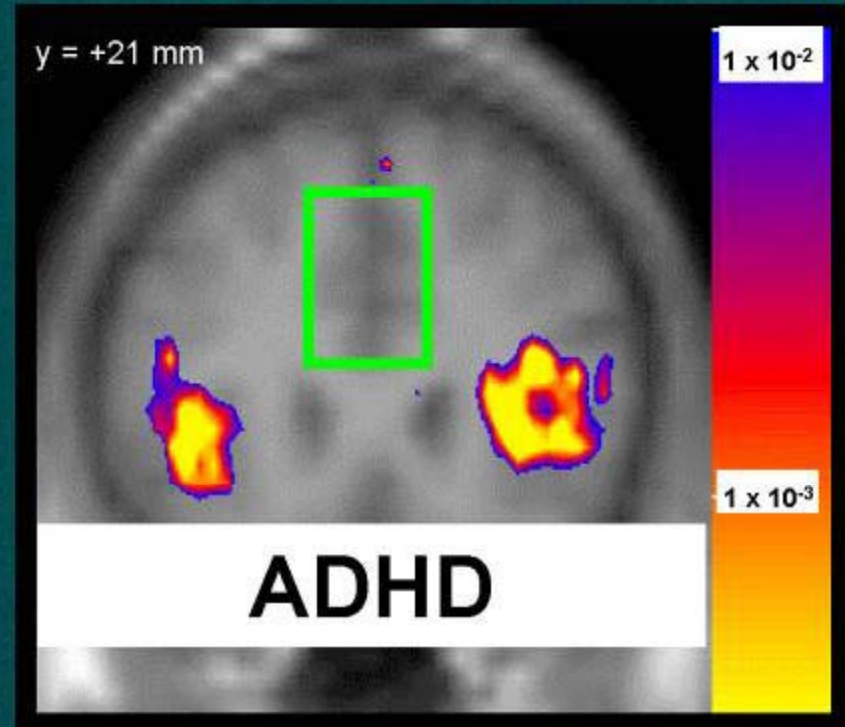
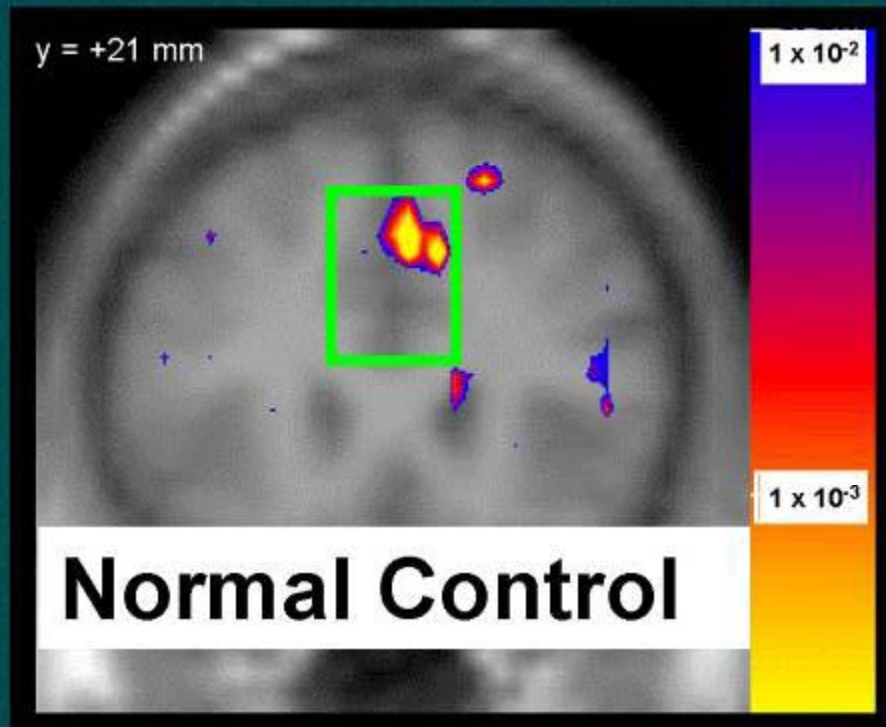
3.
Superior
Colliculi
Moves attention to
New stimulus

sensory info →





Dorsal Anterior Cingulate Cortex Fails to Activate in ADHD



Castellanos, Biol Psychiatry, 2008

Decrease in dorsal anterior
cingulate

Circuitry deficit in ADHD (Fan, 2005)

- Alerting system which primarily involves the thalamus as well as the right frontal and superior parietal areas and is influenced by norepinephrine,
- Orienting system which primarily involves the frontal eye fields as well as the temporal-parietal junction, parietal lobe, superior coliculi and the pulvinar and is influenced by cholinergic systems
- Executive system which primarily involves the anterior cingulate as well as the lateral prefrontal area and the ventral tegmentum and is influenced by dopamine.

- Alerting involves achieving and maintaining an alert state,
- orienting involves selection of information from sensory input
- and executive control involves resolving conflict among responses.
- Attention in ADHD/ADD may involve mostly the alerting system although in treatment naïve patients, ADHD may be more likely a deficit in the executive system, namely in the fronto-striatal circuitry.

- Konrad (2006) have found that the orienting system and the putamen may try to compensate for the deficits in the alerting and executive systems and thus, ADHD may then involve all three systems.
- It is important to note that medications, like stimulants, seem to attempt to normalize the alerting and executive systems. Cholinergic neurotransmitters control the orienting system.

Working Memory and ADHD-another twist on ADHD

- Working memory-Working memory refers to the cognitive ability to temporarily store and mentally manipulate limited amounts of information for use in guiding behavior.
- controversial-
- Tannock, (2008) believes 40 % of ADHD/ADD patients. She believes that the inability to inhibit behavior is a separate entity
- Baddeley believes that there are 3 components of working memory:
 - A. Phonological loop-left hemisphere, left VLPFC and Left parietal
 - B. Visual Spatial-Right parietal and frontal fields
 - C. Central executive-DLPFC=attention
- Baddeley believes that it is the inability to hold onto information in order to guide behavior (deficit in working memory) that causes the behavior problems associated with inhibition.

Is working memory more a function of inattention associated with ADHD?

- Martussen and Tannock, 2006
- Symptoms of inattention, but not symptoms of hyperactivity/impulsivity, predicted performance on verbal and visual-spatial central executive functions of working memory measures independent of age, verbal cognitive ability, and reading and language performance.
- The results are also consistent with prior research demonstrating the neuropsychological impairments are more strongly associated with the inattention symptom dimension than with the hyperactive-impulsive dimension.

- But-ADHD-related working memory deficits were apparent across all three cognitive systems of WM-- with the largest magnitude of deficits apparent in the CE (Rapport, 2008)
- Supports Baddeley's interpretation
- Who is right? Most researchers are leaning towards Baddeley
- 4 types working memory:
 1. Auditory-visual-2 components
 - a. Storage
 - b. Manipulation
 2. Visual Spatial-2 components
 - a,. Storage
 - b. Manipulation

Role of stimulants on working memory

1. Dose effect on stimulants (Bedard, 2004)

- Low dose influences stop inhibition response more than high dose
- High dose effects visual spatial working memory better than low dose.

2. MPH effect on WM in ADHD/ ADHD and anxiety DO (Bedard and Tannock, J Atten Disord, 2008)

- MPH improved auditory-verbal manipulation but only in the non-ANX children with ADHD. It had no effect on auditory-verbal (AV) storage of information.
- Also, MPH improved the ability to manipulate and store visual-spatial information in ADHD groups, but beneficial effects on visual-spatial storage were evident only in children without comorbid **Anxiety**

3. AV storage is associated predominantly with reading disorder and language impairment ([Martinussen et al., 2005](#)).

4. Visual spatial memory influences orthographic component of Reading not phonological deficits (Willcutt)

Summary

- MPH does not affect auditory verbal storage of working memory=phonological reading disorder, so reading interventions for phonological disorders may work best unless there is an intervention for working memory-see later
- MPH will improve the visual spatial components of working memory including storage and manipulation=orthographic reading disorder or reading fluency

Why did we get interested in this?

Prior to WISC IV : Assessment

1. WISC III-PIQ, VIQ and FSIQ
2. Woodcock Johnson III-picked up Reading, Spelling, Math and a Disorder of Written Expression.
3. Cognitive Battery of Woodcock Johnson III
Measured how we learn or process information
 - a. Auditory processing
 - b. Visual processing
 - c. Processing speed
 - d. Comprehension
 - e. Long and short term memory

(WISC III was often the only assessment used to predict performance)

ADD/ADHD and processing

Tested 77 students who did well on stimulants in elementary school but who began to struggle in Middle school.

Average IQ was 122 and no one had an IQ < 100

Test used is Cognitive Battery of a Woodcock Johnson III

- There are 5 ways we process:
- 1. Auditory
- 2. Visual
- 3. Processing Speed
- 4. Long and Short term memory
- 5. Comprehension

88% had an auditory processing problem

92% had a DO Written Expression

70% had processing speed problem

Types of Auditory Processing Problems

Input

- Phonemic awareness-each letter has a sound
- Phonologic awareness-Each syllable has a specific sound.
- Auditory figure ground discrimination-a child can't distinguish a voice (figure) from background noise (ground).
- Auditory lag-Here a child must concentrate on what is being heard for a fraction of a second before it is understood. The child may miss words or phrases that immediately follow. Speech pathologists refer to this as an auditory processing problem or receptive language problem.

Are Reading Disorders Universal?

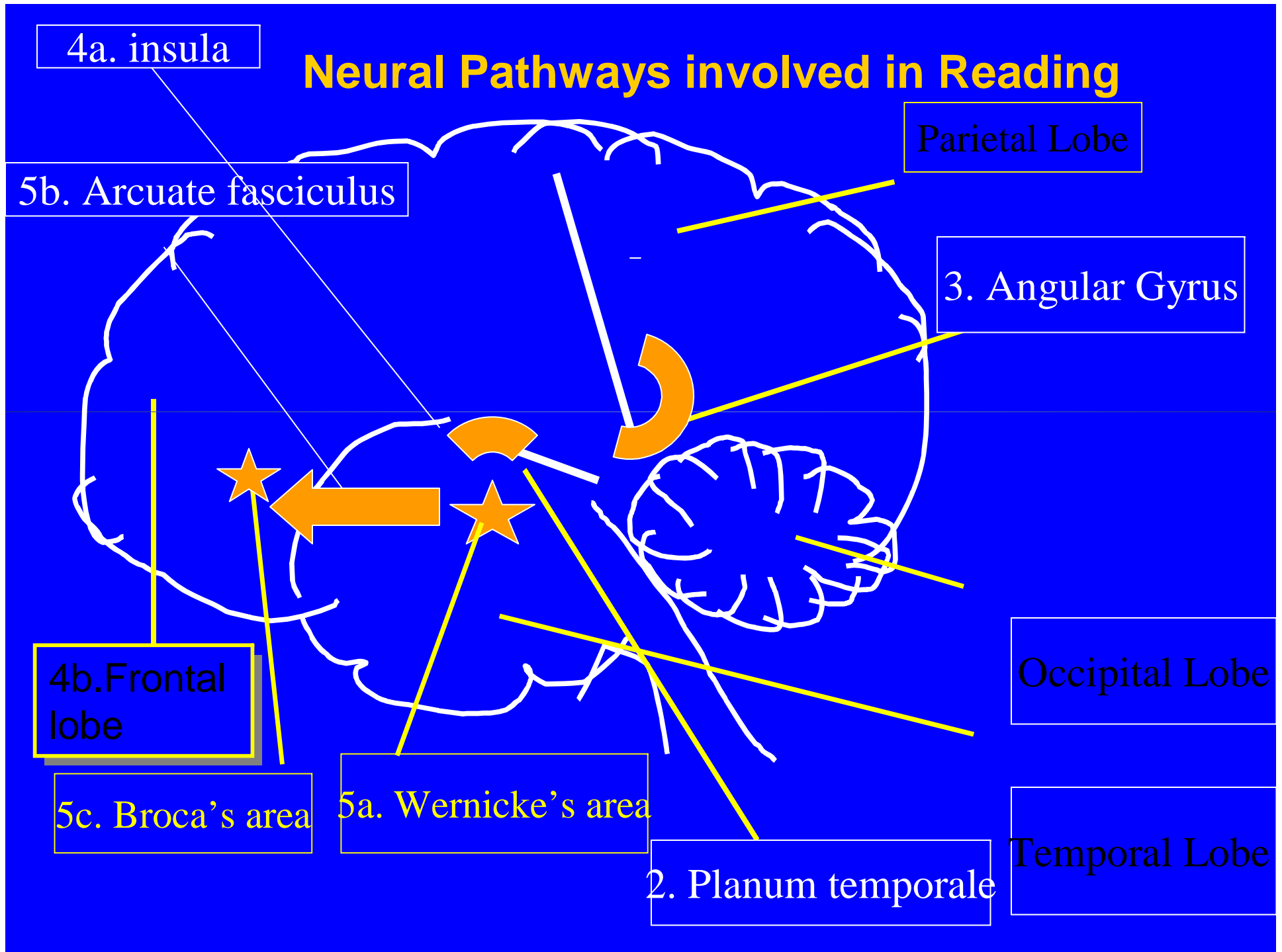
- Yes
- The English language is not as phonetically accurate as the German Language-more difficult to learn if you have a phonological dyslexia.
- What about languages that use more symbols-like Chinese-naming speed is used to pick up surface dyslexia and this is found in people who speak that language

3 types of dyslexia that we might be able to intervene upon:

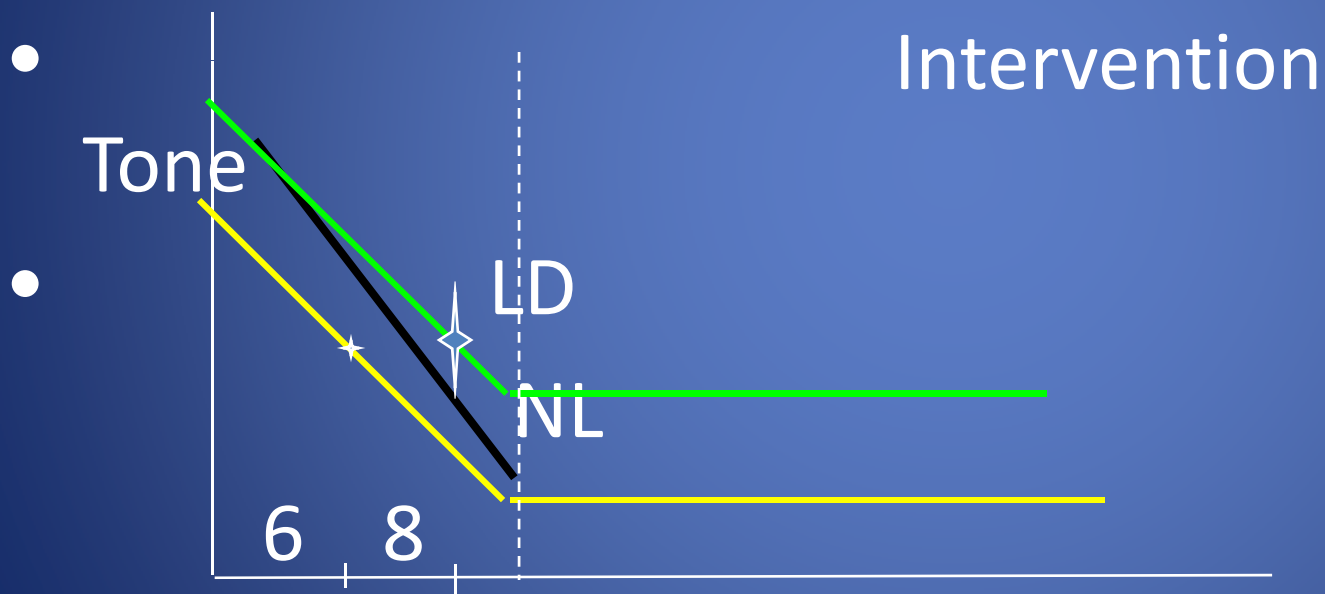
1. Phonological
2. Surface
3. Both

Neurobiology of Learning Disorders

Neural Pathways involved in Reading



- Is timing important to reading interventions?
- Wright, B. (2004)-suggests that processing problems associated with language impairment, dyslexia and auditory processing problems is a developmental delay that if not corrected before age 10 will become permanent during adolescence:



An LD child at age 8 will have the processing of a NL child at age 6

A technique called Fast Forward has been shown to correct the problem associated with dysphonetic dyslexia on fMRI in young children (Temple, 2000, 2003).

However, these corrections are only seen when intense reading interventions are used at the same time the Fast Forward program is being used.

- Are ADHD/ADD children able to respond to interventions for dyslexia if they are not on stimulants?
- Tannock and PHAST
- NO

Visual spatial memory influences

**orthographic component of Reading not
phonological deficits (Willcutt)**

**ADHD has a visual spatial memory component
that is influenced by higher doses of
stimulants**

**Therefore, children with ADHD and Reading
Disorders associated with fluency may not
only need stimulants but may need higher
doses of stimulants to have the best effect
when doing reading interventions.**

Are there any other ways to improve
working memory besides
medication?

Cognitive training of working memory

Klingberg (2005, 2002, 2008)

Cognitive training improved auditory verbal working memory and visual spatial working memory

The training reduced parent ratings in symptoms of inattention, response inhibition and hyperactivity/impulsivity (adding more credibility to Baddeley's theory of WM) without the use of stimulants

However, when stimulants were used, visual spatial working memory was significantly enhanced using the cognitive training

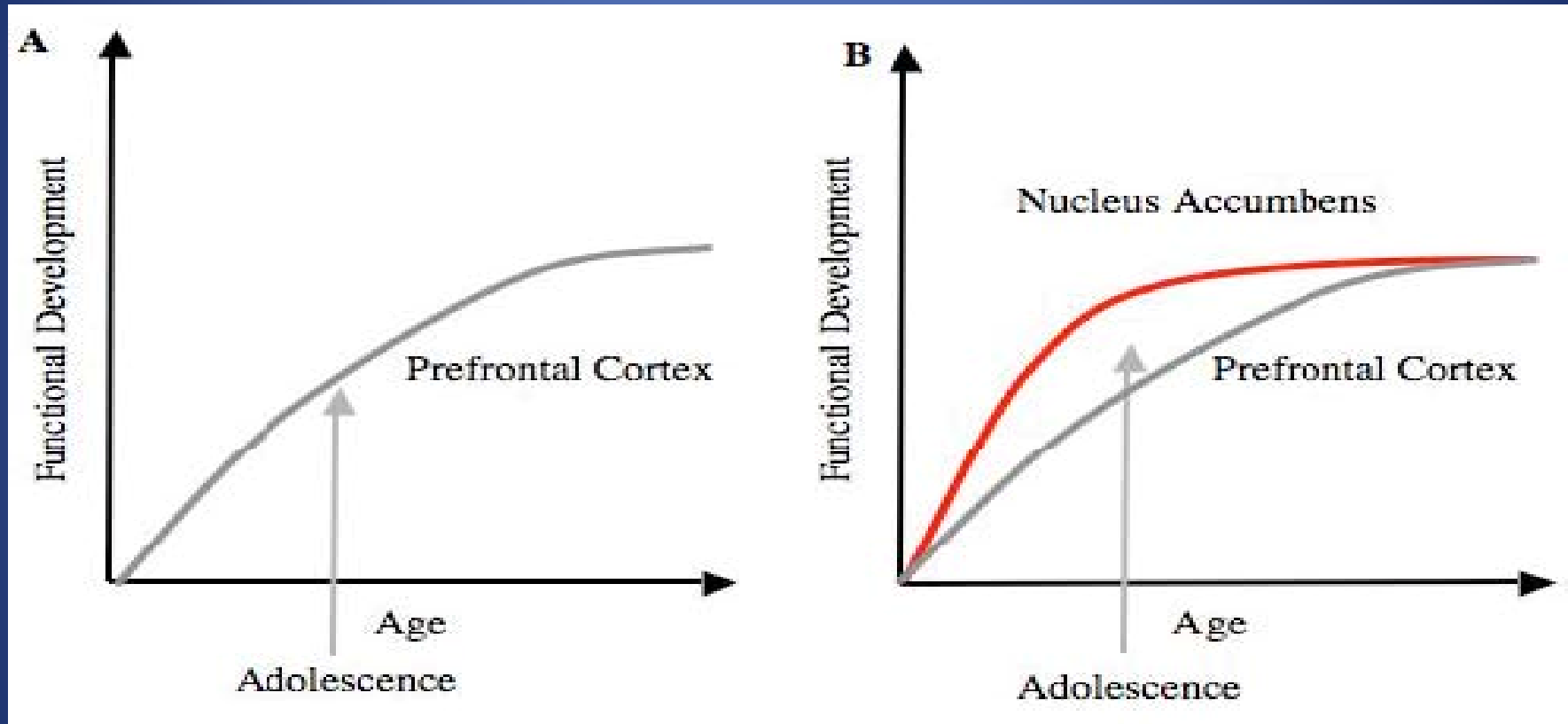
- Perhaps phonological dyslexia may be enhanced if cognitive training for auditory storage WM is used with a reading intervention-more research is needed.

Reasons for experimentation in adolescents

Adolescent Developmental Brain Vulnerabilities

- Human imaging studies that will be reviewed, suggest an increase in subcortical activation (e.g., accumbens) when making risky choices (Montague & Berns, 2002; Matthews, Simmons, Lane, & Paulus, 2004; Kuhnen & Knutson, 2005) that is exaggerated in adolescents, relative to children and adults (Ernst et al., 2005; Galvan et al., 2006).

What causes Adolescents to experiment-role of early development of the amygdala



- Casey, et al 2008

Nucleus Accumbens vs PFC

- Given evidence of prefrontal regions in guiding appropriate actions in different contexts (Miller & Cohen, 2001) immature prefrontal activity might hinder appropriate estimation of future outcomes and appraisal of risky choices, and might thus be less influential on reward valuation than the accumbens.
- During adolescence, relative to childhood or adulthood, immature ventral prefrontal cortex may not provide sufficient top-down control of robustly activated reward processing regions (e.g., accumbens), resulting in less influence of prefrontal systems (orbitofrontal cortex) relative to the accumbens in reward valuation.

These findings suggest different trajectories for reward- or incentive-based behavior, with earlier development of these systems relative to control systems (PFC) that show a protracted and linear developmental course, in terms of overriding inappropriate choices and actions in favor of goal-directed ones.

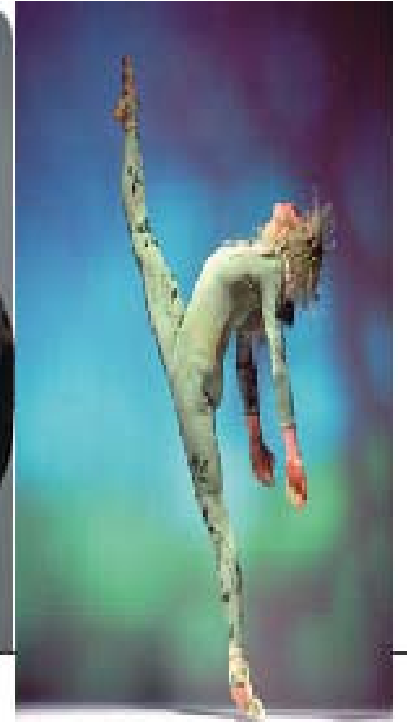
Why is the brain programmed this way

- Seeking out same-age peers and fighting with parents, which all help get the adolescent away from the home territory for mating is seen in other species including rodents, nonhuman primates and some birds (Spear, 2000).
- Humans had to engage in high-risk behavior to leave their family and village to find a mate and risk taking at just the same time as hormones drive adolescents to seek out sexual partners.

- In fact, Luna, et al. (2004) has suggested that these risk taking behaviors may be necessary to sculpt the brain in order to reach the adult pattern necessary for efficient processing.
- Hence, adolescence is a crucial period of plasticity when brain circuitry and behavior are beginning to be established.
- Risk taking and novelty seeking may provide a mechanism for increasing exposure to the environment necessary for successful sculpting of the brain.

However, in today's society when adolescence may extend indefinitely, with children living with parents and having financial dependence and choosing mates later in life, this evolution may be deemed inappropriate

Secondary to the extended adolescence, many of high risk behaviors may be engaged in that may increase chances for harmful circumstances (e.g., injury, depression, anxiety, drug use and addiction (Kelley, Schochet, Landry, 2004)).



Do sex hormones play a role in out risky behaviors?

- Sex hormones do not influence the amygdala directly, but oxytocin does play a role in regulating social bonding and recognition and memory of social stimuli.
- Sex hormones do influence oxytocin.
- Peers have a greater influence than families on adolescence and may be the reason for initial experimentation and relapse (Brook, 1980, Brown, 1993)

Sex hormones and oxytocin

- Adolescents are more likely to seek out risky behaviors in driving games when peers are present.
- Areas of the brain were activated on fMRI when peers were present and risky behaviors occurred than when the adolescents were alone.
- These areas included the medial frontal cortex, L. ventral striatum (accumbens). L superior temporal sulcus and L medial temporal structures.
(Steinberg, et al, 2008)

Therefore oxytocin's influence on social bonding and recognition and memory for social stimuli coupled with the increased risk for experimentation found during adolescence can explain why adolescents increase risk taking behaviors, especially in the presence of peers



May 2006

S	M	T	W	T	F	S
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

Untreated ADHD and risk for substance Abuse

- Wilens-Children treated for ADHD have a 2 times lower risk for substance abuse

ADHD and continued treatment

- Castellanos (2002) reviewed total cerebral volume of treated and untreated adolescents with ADHD.
- Total white matter in the unmedicated ADHD adolescents was lower than medicated and normals.
- It is hypothesized that perhaps the trophic effect on myelination, dendritic branching, and length of spines in the treated ADHD youth was somehow protective.

*ADHD and early treatment

- Decreased D2 receptors increases the risk for substance abuse
- *Research by Thanos et al (2007)-Over-expression of D2 receptors reduces alcohol and cocaine self administration in mice (Thanos, et al, 2001, 2004, 2005,) and decreases drug liking and may be protective against substance abuse in humans (Volkow, et al, 2002, 2006).
- * Thanos found significantly reduced rates of cocaine self stimulation during adulthood in periadolescent rats treated with 2mg/kg oral methylphenidate for eight months as compared to periadolescent rats treated with 1mg/kg or rats receiving water.

ADHD and early treatment

The availability of D2 receptors was significantly lower after two months of treatment in rats given 1 or 2 mg/kg of methylphenidate compared with control rats, but after 8 months of treatment it was significantly higher.

- *The rats given 2mg/kg of methylphenidate at eight months had greater D2 receptor binding availability than rats given 1mg/kg.
- *Therefore, chronic methylphenidate treatment (started in adolescence) attenuated cocaine self-administration during adulthood.

There are three processes which are still maturing during adolescence, processing speed, response inhibition and working memory.

Research suggests, that the problem with processing speed or working memory is a developmental delay associated with poor or delayed myelination (Niorgi, 2006, Luna 2004)

Therefore, children who are untreated for their ADHD during adolescence may not follow normal developmental trajectories for WM and PS

These processes in normal adolescents do not mature until about age 22 (Luna, 2004).

Could the effect on WM and PS decrease academic achievement and increase the risk of substance abuse

Hops (1999) has shown that substance abuse in adolescents at age 14-15 can be predicted by social and academic failure by age 7-9.

Tapert (2002) has shown that adolescents with attention difficulties predicted substance abuse and dependence eight years later.

These students had not been identified by school systems as having a learning disorder.

- There is also research that shows that decreases in white matter myelination is also seen in the left temporal parietal area in children who are poor readers (Beaulieu, 2005)

Therefore dyslexia may also be associated with delayed white matter maturation and although reading interventions do not have the robust effect it would before age 9, perhaps interventions for reading disorders during adolescence involve stimulating this white matter maturation process.

Summary

1. Childhood and adult ADHD have similar involvement of the Cerebello-thalamo-striatal-cortical loop deficits on neuroimaging.
2. Processing deficits may be the reason children who responded well to stimulants in elementary school may not seem to be responding to the stimulants as cognitive demands become greater-
3. It is wrong to assume that every child with ADHD/ADD who reads poorly does so because of the ADHD/ADD
4. There may be other factors associated with ADHD/ADD that may relate to reading disorders-working memory
5. Working memory may be related not only to inattention but may also be related to hyperactivity and/or impulsivity

Summary

5. Early intervention for reading disorders before age nine may not work as robustly after age nine secondary to neurobiological changes that occur during adolescence.
6. Any intervention for reading disorders in children with ADHD/ADD may not respond if they are not on their stimulant medication-but more likely surface dyslexia.
7. Some components of working memory can be improved with stimulants, especially visual spatial working memory but not auditory storage, associated with phonological reading disorders. Reading interventions for this may be the only really effective intervention along with cognitive training for auditory verbal working memory storage.
8. Not treating children with ADHD may prevent normal white matter development during adolescence-this may influence WM, PS and Reading disorders. These youth may have poor academic success and may engage in experimentation with drug use
9. Adolescents may respond to other interventions (for processing speed deficits and reading disorders) that involve white matter myelination because this process does not finish maturing until around age 22.
10. Early treatment with stimulants may decrease the risk of developing a substance abuse problem by 2 X
11. Experimentation may be necessary for sculpting the brain but one would hope the experimentation is positive.
12. The adolescent brain needs monitoring during adolescents because peers will have more influence than parents.