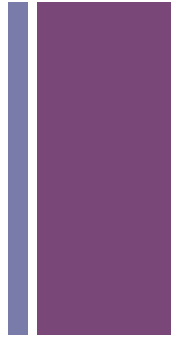


Altering the course of neurodevelopment: a framework for understanding the enduring effects of psychotropic drugs

Susan L. Andersen and Carryl P. Navalta

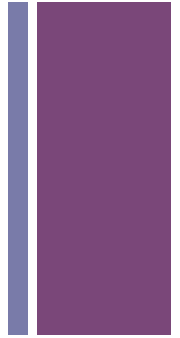
Jessica Santerre and Michelle Spina

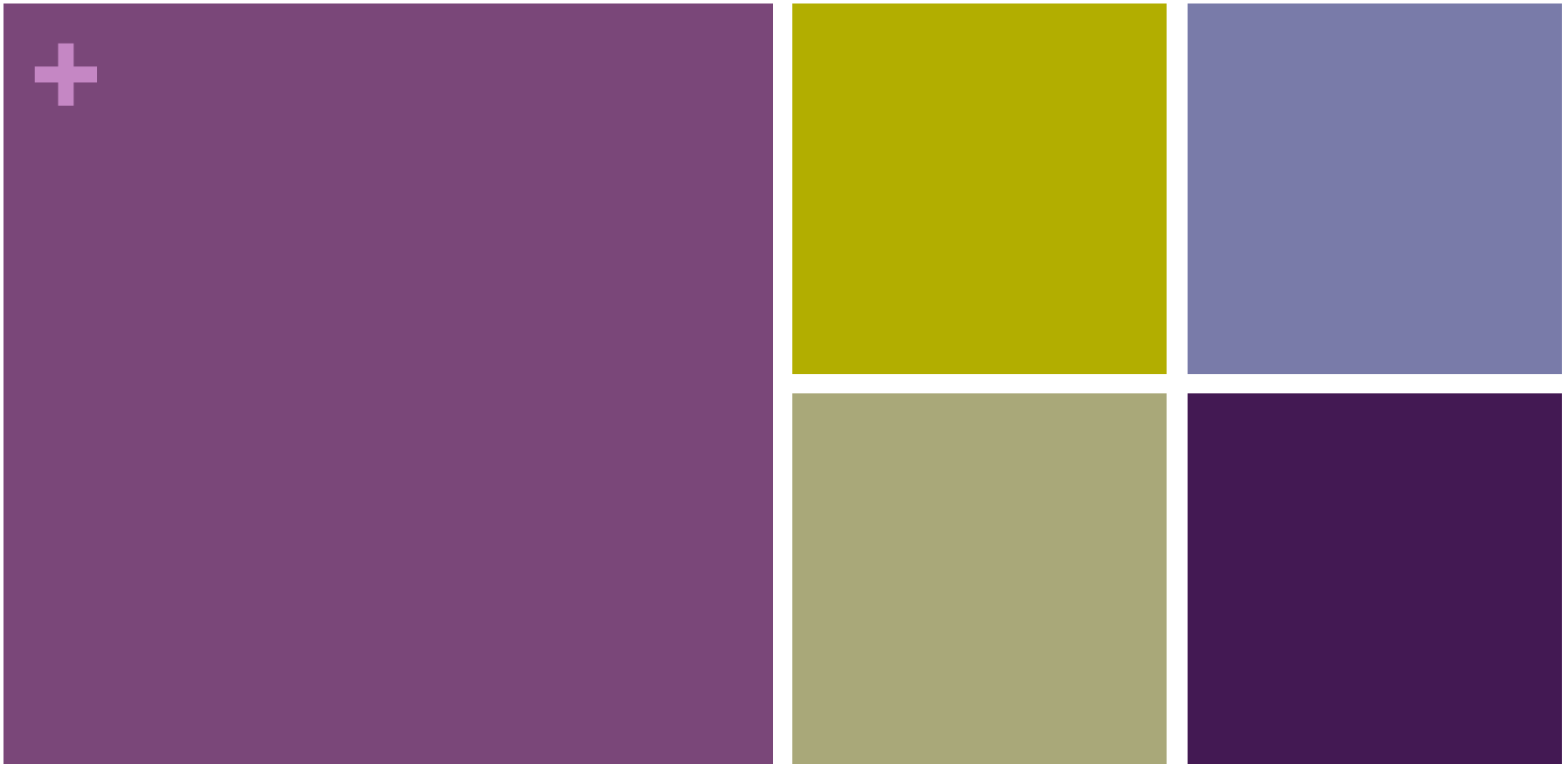


- Drug exposure during childhood and adolescence alters the development of the brain

+ Outline

- Developmental Framework
- ADHD
- Childhood Depression
- Conclusions

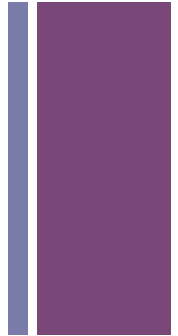




Developmental Framework

+ Introduction

- Past research: prenatal exposure to drugs
 - Prenatally-exposed animals do not appear to be affected immediately by treatment
- Examination later in life
 - Expression of effects is delayed
 - Neuronal imprinting



+ The scope of the problem: the clinical picture

- Treatment of symptoms must be weighed against the potential for unknown long-term side effects resulting from the medication
- Children are initiated into stimulants and antidepressant pharmacotherapy at progressively younger ages

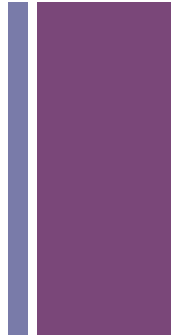




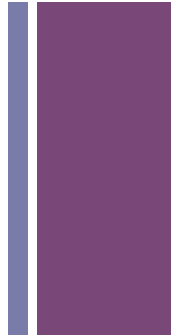
Table 1
Drug prevalence rates for children and adolescents

Study ^a	Drug type ^b	Age range (years)	Prevalence (per 1000)
Olsson et al. (2002) 1996 national survey (MEPS)	All psychotropics	0-5	8.2
		6-14	54.1
		15-18	51.5
	Stimulants	0-5	3.1
		6-14	41.4
		15-18	15.6
	Antidepressants	0-5	1.2
		6-14	10.6
		15-18	21.2
	Goodwin et al. (2001) 1992-1996 national survey (NAMCS)	Stimulants	0-3
4-8			18.4
9-12			31.6
13-16			19.3
17-19			5.8
Antidepressants		0-3	1.7
		4-8	2.1
		9-12	10.5
		13-16	16.1
		17-19	17.0
Neuroleptics		0-3	0.7
		4-8	1.3
		9-12	2.5
		13-16	1.9
		17-19	4.0
Zito et al. (2003) 1996 survey of two state Medicaid programs and one health maintenance organization	All Psychotropics	0-4	9.8-17.7
		5-9	58.5-95.4
		10-14	72.0-129.4
		15-19	54.5-82.8
	Stimulants	0-4	3.7-6.8
		5-9	40.3-78.4
		10-14	42.6-81.8
		15-19	12.1-13.1
	Antidepressants	0-4	0.5-2.0
		5-9	7.6-12.6
Rushton and Whitmire (2001) 1998 survey of one state Medicaid program	Stimulants	1-5	13.0
		6-14	1.0
	SSRI's	1-5	95.0
		6-14	15.0
Zito et al. (2000) 1995 survey of two state Medicaid programs and one health maintenance organization	Stimulants	2-4	5.1-12.3
	MPH		4.0-11.1
	Antidepressants		0.7-3.2
	TCA's		0.5-2.4
	Clonidine		1.4-2.3
	Neuroleptics		0.2-0.9

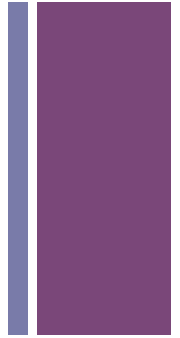
^a MEPS = Medical Expenditure Panel Survey; NAMCS = National Ambulatory Medical Care Survey.

^b SSRI = Selective Serotonin Reuptake Inhibitor; MPH = Methylphenidate; TCA = tricyclic antidepressant.

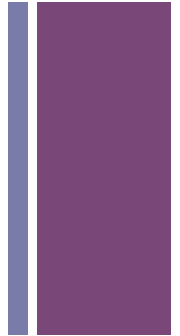
■ Table 1 provides an index of frequency of prescription rates occurring for various stimulants



+ Why the need for long-term studies of medication exposure?

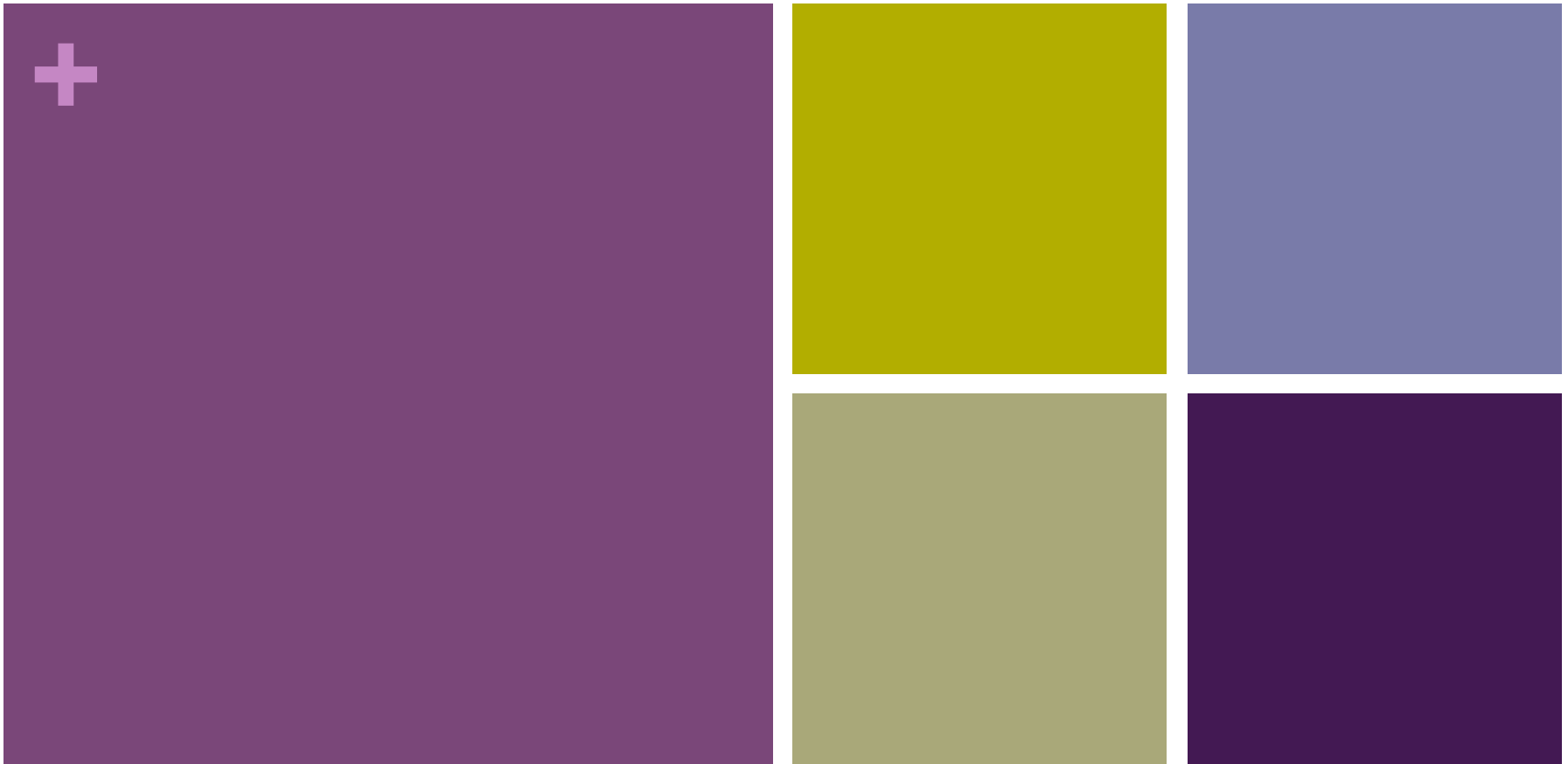


- The developing brain is different
- The same medications are utilized in both the immature and mature brain
 - Are the long-term effects in children comparable to those in adults?



- Positive benefits for children
 - ADHD: improved social skills, academic progress, and reduced drug abuse liability
 - Depression: Prevention of future depressive episodes

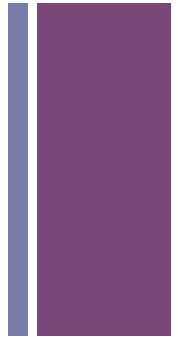
- Recent findings implicate the use of SSRI's in childhood as a risk factor for subsequent suicidal behavior.



What are the drugs that are prescribed?

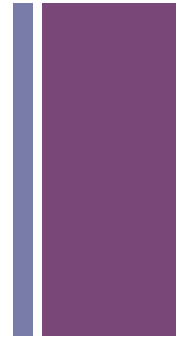
+ Drug prevalence and utilization

- Main classes of psychotropic drugs prescribed:
 - Stimulants- 4 million children take stimulants annually in the US (Zito et al., 2000; Connor, 2002)
 - Antidepressants- one of the fastest growing treatments in the psychiatric community (Zito and Safer, 2001; Zito et al., 2002)
- The amount of children using psychotropic drugs is increasing
 - 1993-1997: 10-fold increase in the use of SSRI's in children 5 years of age and younger in Canada
 - Preschoolers (0-5) represent the fastest rising group



+ Theoretical framework of enduring drug action

- Delayed effects on anatomy and function
- The effects are more extensive and permanent when compared with adults exposure to the same drug (Andersen, 2003)
- Little is known about the processes underlying these changes
- “Equal, but opposite” (Andersen, 2003)
 - Chronic drug exposure in adult animals results in an accommodation to the effects that occur by a series of compensatory reactions
 - Chronic drug effects are assimilated in juvenile animals by incorporating drug-induced changes in the form of permanent developmental alterations of the system



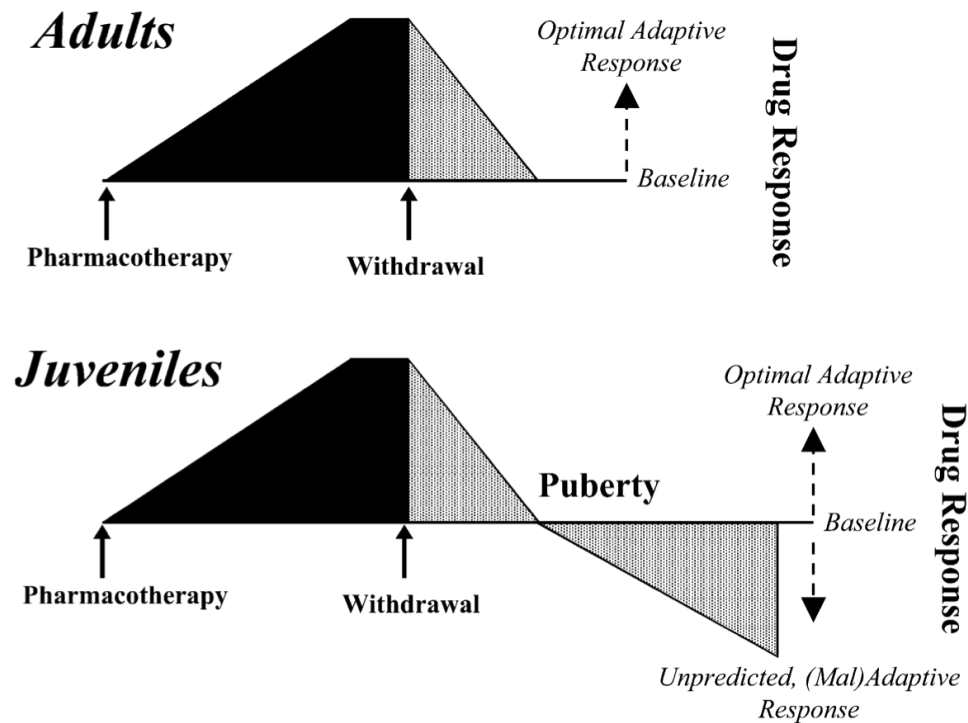
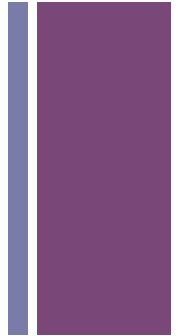


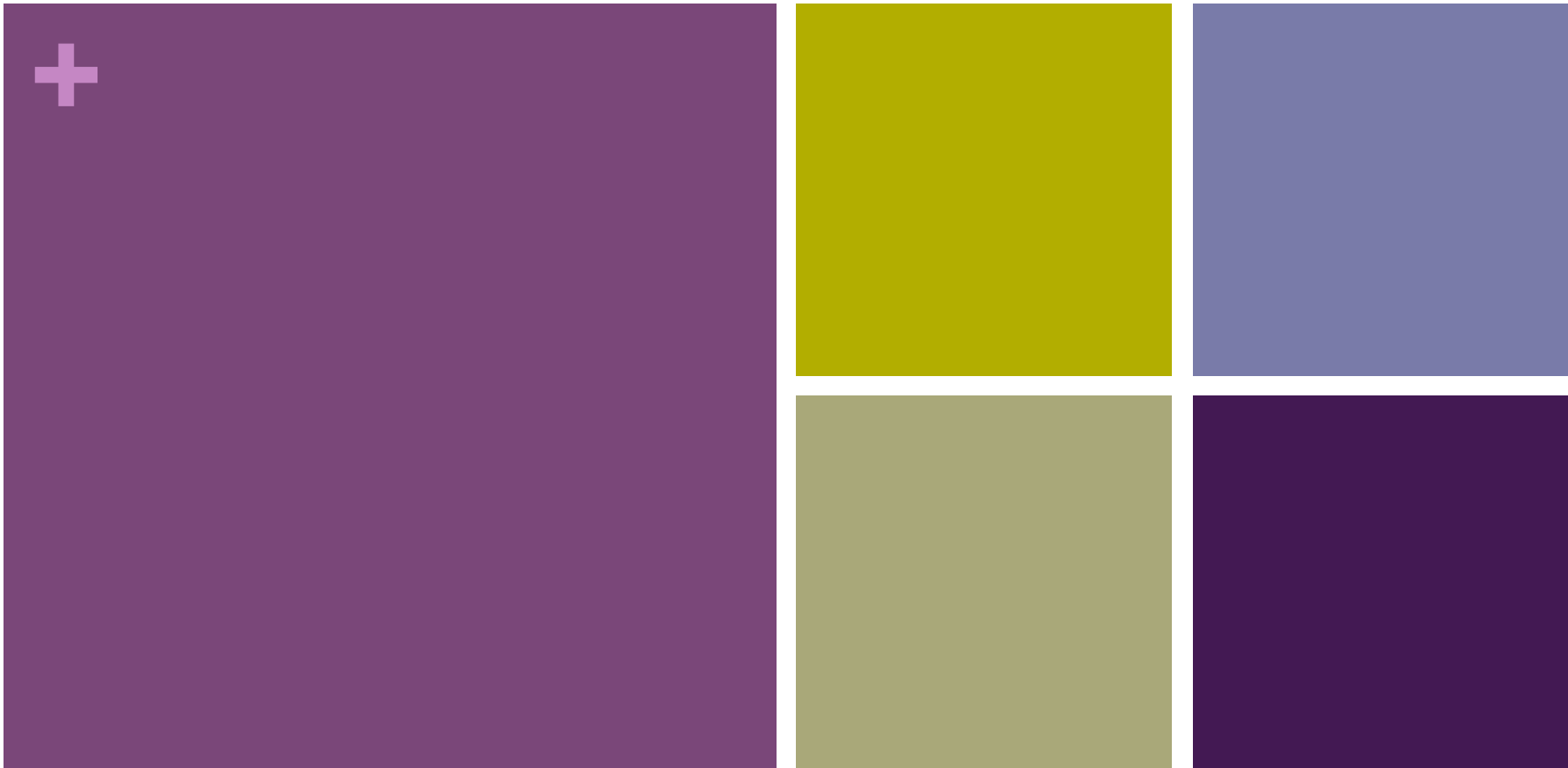
Fig. 1. Diagram illustrating the different trajectories of drug response that depend on maturational stage of exposure. Top: adult (post-pubertal) drug exposure (left) produces an improvement in symptoms that increases with time. Upon withdrawal (right), response to drug challenge returns to original baseline levels. Bottom: Juvenile (pre-pubertal) drug exposure (left) may (or may not) also produce symptom improvement or sensitized response. Once the drug is withdrawn, response to drug challenge wanes with time in a manner similar to adults, but then continues to transform after puberty and manifests as the opposite of the original target of pharmacotherapy. This transformation may include the appearance of adaptive (e.g., tolerance to stimulant effects; (Andersen et al., 2002)) or maladaptive characteristics (e.g., anhedonia following pre-pubertal stimulant exposure; (Bolanos et al., 2003; Carlezon et al., 2003)), or possibly depression in response to antidepressants (Mirmiran et al., 1985).

- **Chronic, early childhood exposure to stimulants and antidepressants may exacerbate symptoms later in life rather than reduce them, or even result in a new constellation of psychiatric symptoms**

+ Overproduction and pruning of synapses during development

- Drug exposure will have its greatest impact on areas undergoing more active development
- Exposure to psychotropic agents during development will act to either instruct the wiring of the brain or select existing synapses
- Altering neurotransmitter levels will have its greatest impact during childhood to adolescence, when the synaptic selection process reaches its peak





ADHD

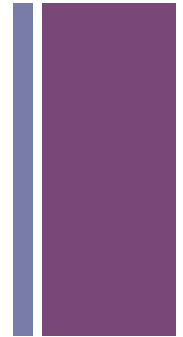
The clinical disorder

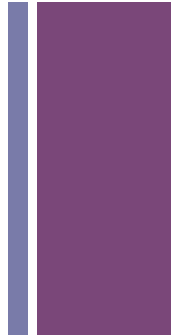


- Most prevalent childhood psychoatric disorder
- MRI studies report reductions in the corpus callosum, prefrontal cortex, caudate nucleus, and the globus pallidus, in some but not all the studies.
 - The reductions tend to be lateralized to the right hemisphere.
 - Children with ADHD overall have a 3-4% smaller total cerebral volume.
- Hypofunctioning of the cortex
 - Could explain reduced attention and impulsiveness
- Hyperfunctioning of the striatum
- Increased motor activity
- 60% of children and adolescents with ADHD grow out of their symptoms and the disorder wanes by adulthood
 - This different developmental trajectories for ADHD may possibly be the byproduct of medication exposure

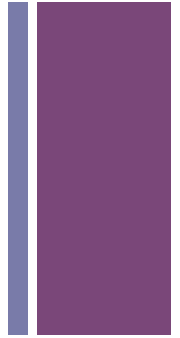
+ Stimulant effectiveness in ADHD

- MTA found that MPH (Ritalin) was superior to behavioral treatment
- Combined treatment (MPH + behavior therapy) provided some advantages
- Stimulants exert euphorigenic effects in adults however, they produces dysphoria in children, precluding its abuse liability

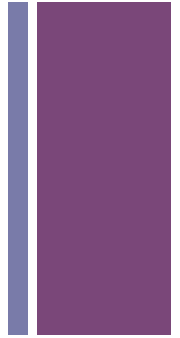




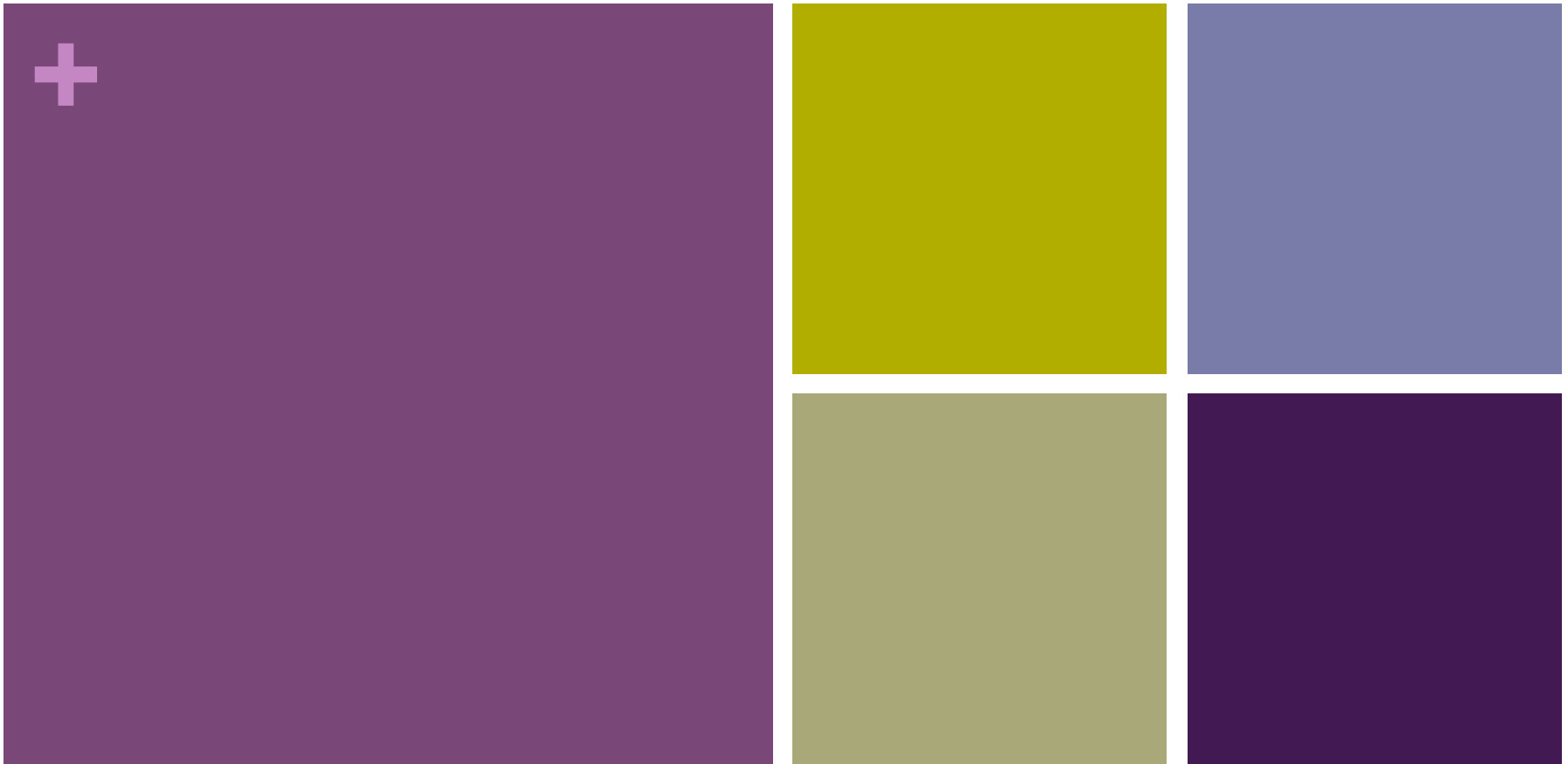
- Little is known about the enduring effects
- MPH use during childhood produces temporary decrease in weight gain that is not apparent by adulthood
- Reports of growth retardation following exposure in preschoolers are emerging



- Functional brain activity in children with ADHD is difficult
 - PET controversial in children
- New approaches to studying children are becoming more widespread



- Finding of alterations in brain structure as a function of medication exposure
 - Krause et al., 2000: using a previously unmedicated ADHD adult population, showed a reduction in DAT after four weeks of MPH treatment
 - Castellanos et al., 2002: white matter is decreased in nonmedicated children with ADHD vs. medicated children with ADHD suggests slower processing within and between regions.
- No long-term, chronic exposure studies have been conducted on brain function to determine the effects of drug imprinting on the immature brain



Childhood Depression

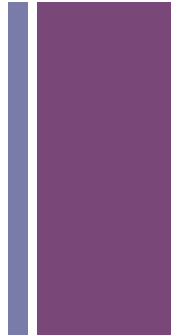
+ The clinical disorder

- Rare among children (1-2%)
- More common among youth (25%)
- Teenagers (1-3%)

- Symptoms:
 - Feeling blue
 - Depressed mood
 - Feel too tired
 - Feel life is not worth living
 - Poor appetite

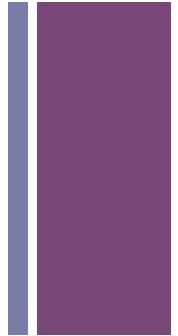
- Comorbid with childhood anxiety

- Responds well to antidepressant agents



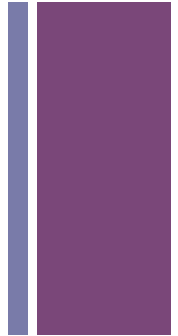
+ Brain Regions

- Smaller whole brain volume.
 - Mostly restricted to frontal lobe.
- Reduced frontal white matter volumes
 - Increased prevalence and severity of white matter signal hyperintensities
 - Increased frontal gray matter volumes.
- Larger left side, but not right sided prefrontal cortical volumes.
- Elevated choline levels in left, but not right dorsolateral prefrontal cortex.
- Larger left bilateral amygdala: hippocampal volume ratios.
 - Lower left amygdala choline: creatine-phosphocreatine ratios.
 - Blunted amygdalar response to fearful faces.
- Higher 5-HT transporter availability in the hypothalamic/ midbrain region.



+ Antidepressant effectiveness

- Only 56% of children responded favorably to an SSRI versus 33% placebo response.
 - Compared to 78% successful treatment in adults.
- **Could SSRI's actually worsen the course of this disorder by altering the developmental trajectory of the serotonin system????**

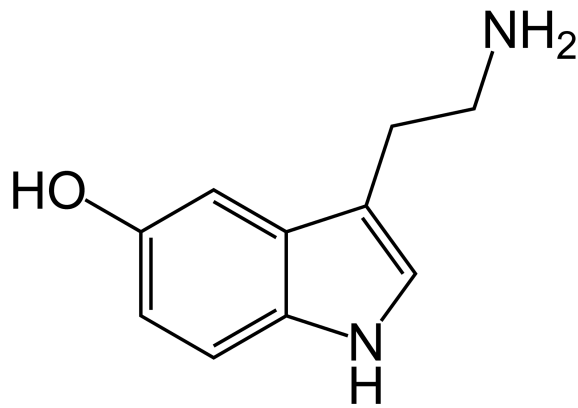


+ SSRI's and Suicide

- Recently, a possible role for SSRI's as an increased risk factor for suicide in children and adolescence with depression was articulated.
 - Paxil: Risk of self harm and potentially suicidal behavior increased 1.5-3.2 fold compared to placebo.
- Preliminary clinical findings suggest that cortisol and growth hormone levels during adolescence are associated with suicidal behavior during early adulthood.
 - Adolescents with depression, who later attempted suicide showed increased levels of cortisol prior to sleep onset.
 - Prior to sleep the hypothalamic-pituitary-adrenal axis is most quiet.
 - Also, young adults who attempted suicide showed significantly greater amounts of growth hormone during the first few hours of sleep.

+ 5-HT Development

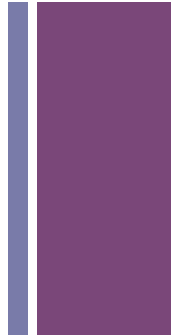
- Within the basal forebrain, 5-HT forms synapses between birth and 14 days of age.
 - The number of 5-HT labeled varicosities (or spines) rises from 21.3% to 42% of values at birth.
 - These varicosities then decrease to 17.1% during the third week before rising again to 46% in adulthood.
 - This second rise is hypothesized to influence the functional state of their targets.



- Pattern of innervation is region specific
 - Differences in amygdala, frontal cortex, striatum and nucleus accumbens.

+ Antidepressant action

- Antidepressants are believed to exert their therapeutic actions by increasing the availability of serotonin and norepinephrine.
 - Also, dopamine which this article fails to mention. (Wellbutrin)
- This increase, in turn, results in postsynaptic receptor sensitization and elevated extracellular levels of serotonin.
 - Most likely mediated by the 5-HT autoreceptor system.
 - Autoreceptors are **desensitized** by SSRI administration thus producing increases in 5-HT release.



+ Exposure to antidepressants during development

- The effects of juvenile exposure to tricyclic antidepressants endure into adulthood.
- Juvenile exposure causes the following in ADULT rats:
 - Increased REM
 - Additional depressive behavioral symptoms
 - Diminished pleasure-seeking
 - Decreased aggressiveness
 - Impaired sexual activity
 - Anxiety like behavior
 - Increased immobility in the force swim test
- **Tricyclic antidepressants are not commonly used anymore anyway...**
- **NO DATA YET ON SSRI's... ☹**

+ Conclusions

- The prevalence of psychotropic drugs to treat childhood psychiatric disorders is increasing.
- **But what impact do these drugs have on the developing brain?**
- There is much to be learned....

