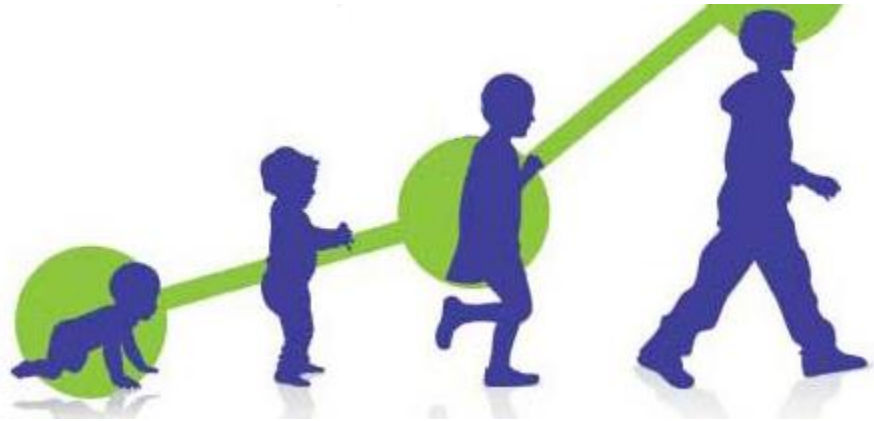
Pharmacotherapies for Anxiety and Depression



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DISCLAIMER

I receive my financial support exclusively from my clinical work and legal consultation service. Neither I, nor my immediate family, receive funding from commercial sponsors or research organizations. I hold stock in Johnson & Johnson as a result of my previous employment with J&JPRD, amounting to less than $50,000. I am receiving a stipend for this presentation.

Objectives

1. Review the range of neuropsychological outcomes as well as mental health problems that are associated with prenatal alcohol exposure throughout the lifespan.

2. Describe the most commonly utilized medications used to address these difficulties as well as their dosages, adverse effects, therapeutic endpoints and parameters for maintenance treatment.

3. Recognize the necessity for an individualized approach to medication therapy for each patient/client living with FASD. The presenter will discuss strategies for individualizing medication interventions and how to identify their benefits and costs as well as potential nutritional supplements.

Agenda

- Brief overview of the epidemiology of FASD and the impact of gestational alcohol exposure upon the developing brain.
- Impediments to informed treatment and the liabilities of psychotropic intervention.
- Pragmatic approaches to assessment and intervention: an algorithmic approach.
- Specific medications available for use.
- Other complementary dietary treatments.

Clinical Features of Fetal Alcohol Syndrome (FAS)

- Structural:
  - Smaller-than-normal head size for the person's overall height and weight (at or below the 10th percentile).
  - Significant changes in the structure of the brain as seen on brain scans such as MRIs or CT scans.

FAS-cont'd

- Neurologic problems with the nervous system that cannot be linked to another cause.
  - Poor coordination.
  - Poor muscle control.
  - Problems with sucking during infancy.

FAS-cont'd

- Functional impairment well below what's expected for age, schooling, or circumstances.
  - FAS: Cognitive deficits (e.g., low IQ), or significant developmental delay in children who are too young for an IQ assessment.

Clinical Features of Fetal Alcohol Spectrum Disorder (FASD)

- Three of any of the following:
  - Cognitive deficits (e.g., low IQ) or developmental delays
  - Executive functioning deficits
  - Motor functioning delays
  - Attention problems or hyperactivity
  - Problems with social skills
  - Other problems such as sensitivity to taste or touch, difficulty reading facial expression, and difficulty responding appropriately to common parenting practices (e.g., not understanding cause-and-effect discipline)

Psychiatric Disorders in FASD

- Attention-deficit/hyperactivity disorder (ADHD)
  - disrupted school experience was reported for 14% of school children and 61% of adolescents and adults with FASDs.
  - 25% had dropped out.

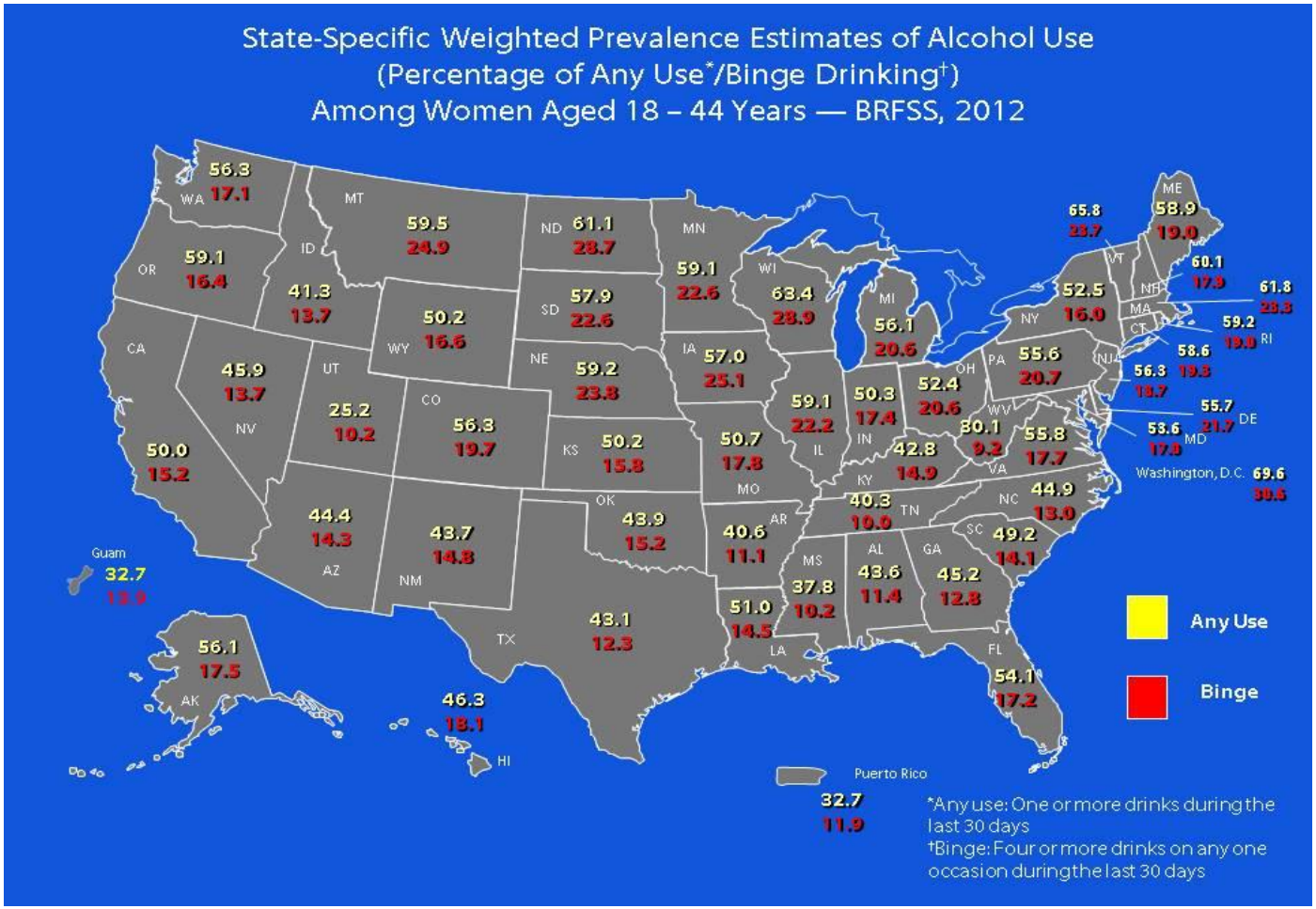
- Conduct disorder (aggression toward others and serious violations of rules, laws, and social norms).
  - Trouble with the law is reported overall for 14% of children and 60% of adolescents and adults with FASDs.

- Oppositional Defiant Disorder and Disruptive Mood Dysregulation Disorder.
  - Difficulty controlling anger and frustration.
  - About 53% of the adolescents with FASDs had been suspended from school, 29% had been expelled.

- Alcohol or drug dependence

- FASD appears to be a risk factor for other psychiatric problems, such as depression, anxiety disorders, eating disorders, and post-traumatic stress disorder.

Risk Pool


State-Specific Weighted Prevalence Estimates of Alcohol Use
(Percentage of Any Use*/Binge Drinking†)
Among Women Aged 18 – 44 Years — BRFSS, 2012
WA 56.3 17.1
OR 59.1 16.4
CA 50.0 15.2
ID 41.3 13.7
NV 45.9 13.7
MT 59.5 24.9
WY 50.2 16.6
UT 25.2 10.2
AZ 44.4 14.3
CO 56.3 19.7
NM 43.7 14.8
ND 61.1 28.7
SD 57.9 22.6
NE 59.2 23.8
KS 50.2 15.8
OK 43.9 15.2
TX 43.1 12.3
MN 59.1 22.6
IA 57.0 25.1
MO 50.7 17.8
AR 40.6 11.1
LA 51.0 14.5
WI 63.4 28.9
IL 59.1 22.2
MI 56.1 20.6
IN 50.3 17.4
OH 52.4 20.6
KY 42.8 14.9
TN 40.3 10.0
MS 37.8 10.2
AL 43.6 11.4
GA 45.2 12.8
FL 54.1 17.2
SC 49.2 14.1
NC 44.9 13.0
VA 55.8 17.7
WV 30.1 9.2
PA 55.6 20.7
NY 52.5 16.0
VT 65.8 23.7
NH 60.1 17.9
ME 58.9 19.0
MA 61.8 28.3
CT 59.2 19.0
RI 58.6 19.3
NJ 56.3 18.7
DE 55.7 21.7
MD 53.6 17.8
Washington, D.C. 69.6 30.6
Guam 32.7 13.9
AK 56.1 17.5
HI 46.3 18.1
Puerto Rico 32.7 11.9
Any Use
Binge
*Any use: One or more drinks during the last 30 days
†Binge: Four or more drinks on any one occasion during the last 30 days

Estimates of Incidence

- CDC-sponsored medical records reviews have identified 0.2 to 1.5 infants with FAS for every 1,000 live births in certain areas of the United States. The most recent found FAS in 0.3 out of 1,000 children from 7 to 9 years of age.

- Direct assessment of school-aged children in several U.S. communities estimate FAS incidence, ranging between 6 to 9 out of 1,000 children.

- Community studies using physical examinations estimate that the full range of FASD's in the United States and some Western European countries might range as high as 20 to 50 out of 1,000 school children (or 2% to 5% of the population).

Prevalence

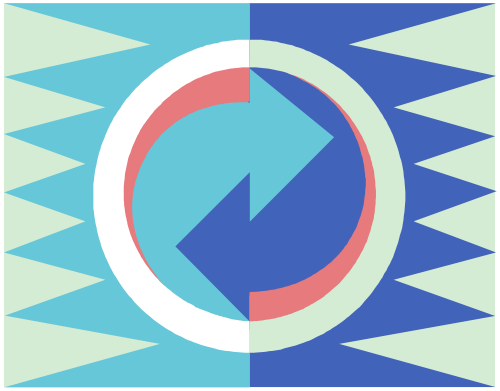
- A total of 13%–20% of children living in the US between 1994-2011 experienced a mental disorder in a given year.

- This suggests that FASD accounts for up to 25% of the mentally ill children in the US.

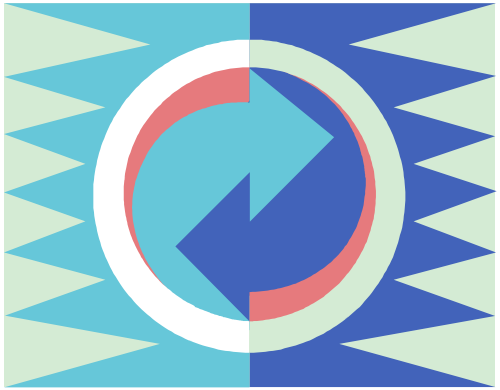
Constraints to Evidence-Based Psychotropic Treatment: It's Complicated!

- Genetic and epigenetic vulnerabilities.
- Alcohol as a behavioral teratogen, a proxy for other behavioral teratogens.
- Complexities of gestational brain development.
- Postnatal brain development and the potential for recovery (resilience).

Rutter (1978): Cycles of Disadvantage



Generation 1:
- Poverty
- Malnutrition
- Educational Disadvantage
- Psychosocial Adversity
- Genetic or other heritable factors



Generation 2:
- Epigenetic effects.
- Unrecognized brain injury from malnutrition, physical abuse, toxic exposures, infectious disease
- Unrecognized brain maldevelopment from environmental and psychosocial deprivation
- Amplification of psychosocial disadvantage

Genetic and Epigenetic Factors

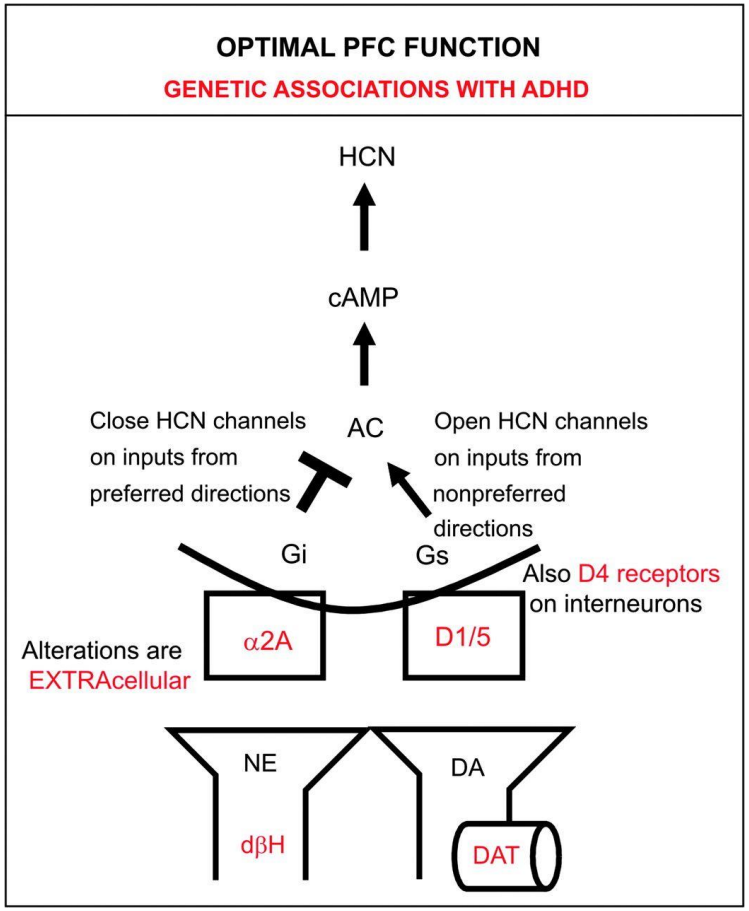
- Family, twin and adoption studies have shown that, for schizophrenia, autism, manic depressive illness, major depression, attention deficit hyperactivity disorder, panic disorder, alcohol abuse disorder and other mental illnesses, the transmission of ***risk*** is due to heredity.

- Multiple genes act in concert with non-genetic factors to produce a risk of mental disorder.

Impaired Executive Function:
A Core Deficit in Many Psychiatric Disorders

- ADHD
- Schizophrenia
- ODD and other behavioral disorders
- Developmental learning disorders
- PTSD

The intracellular signaling mechanisms modulating spatial working memory networks in PFC under optimal conditions.



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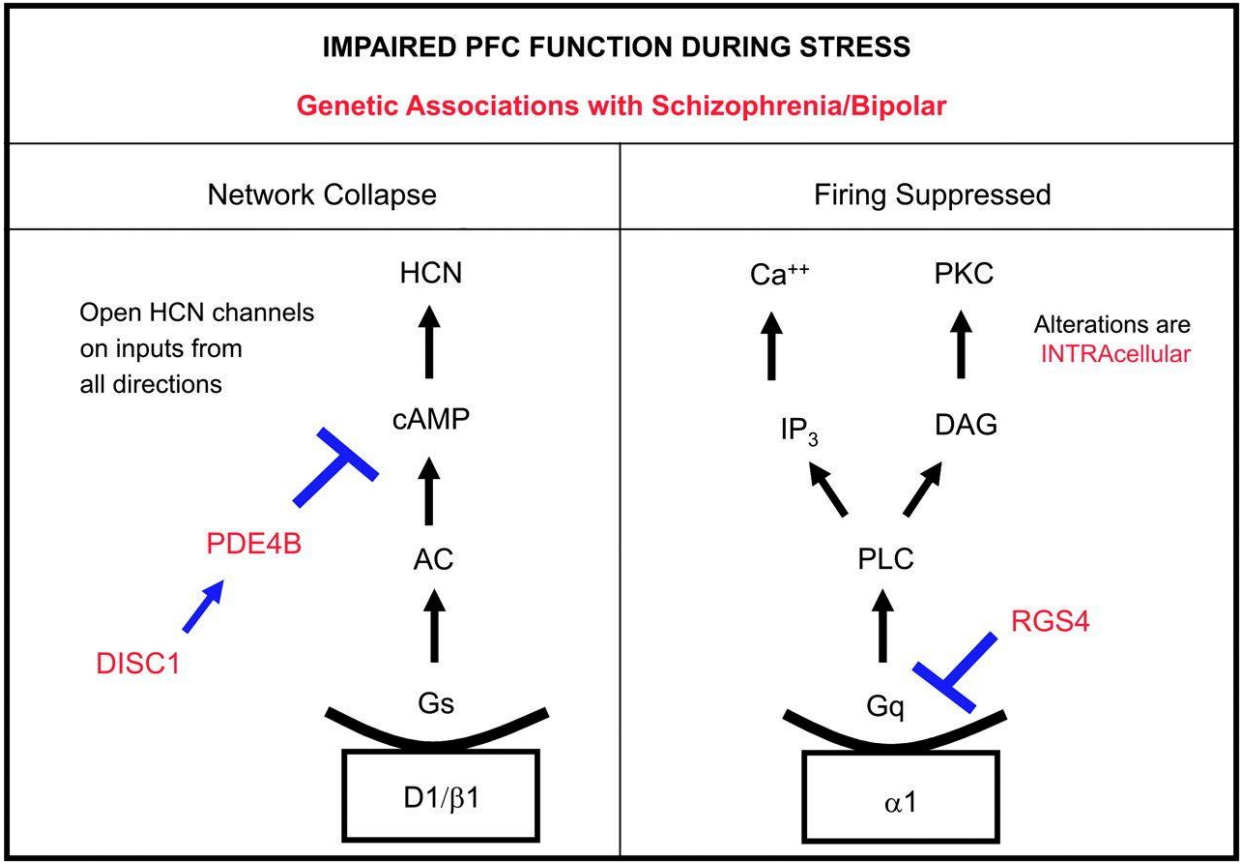
Cerebral CORTEX

The intracellular signaling mechanisms that impair PFC function under conditions of stress and their relationship to genetic linkages with schizophrenia and bipolar disorder.



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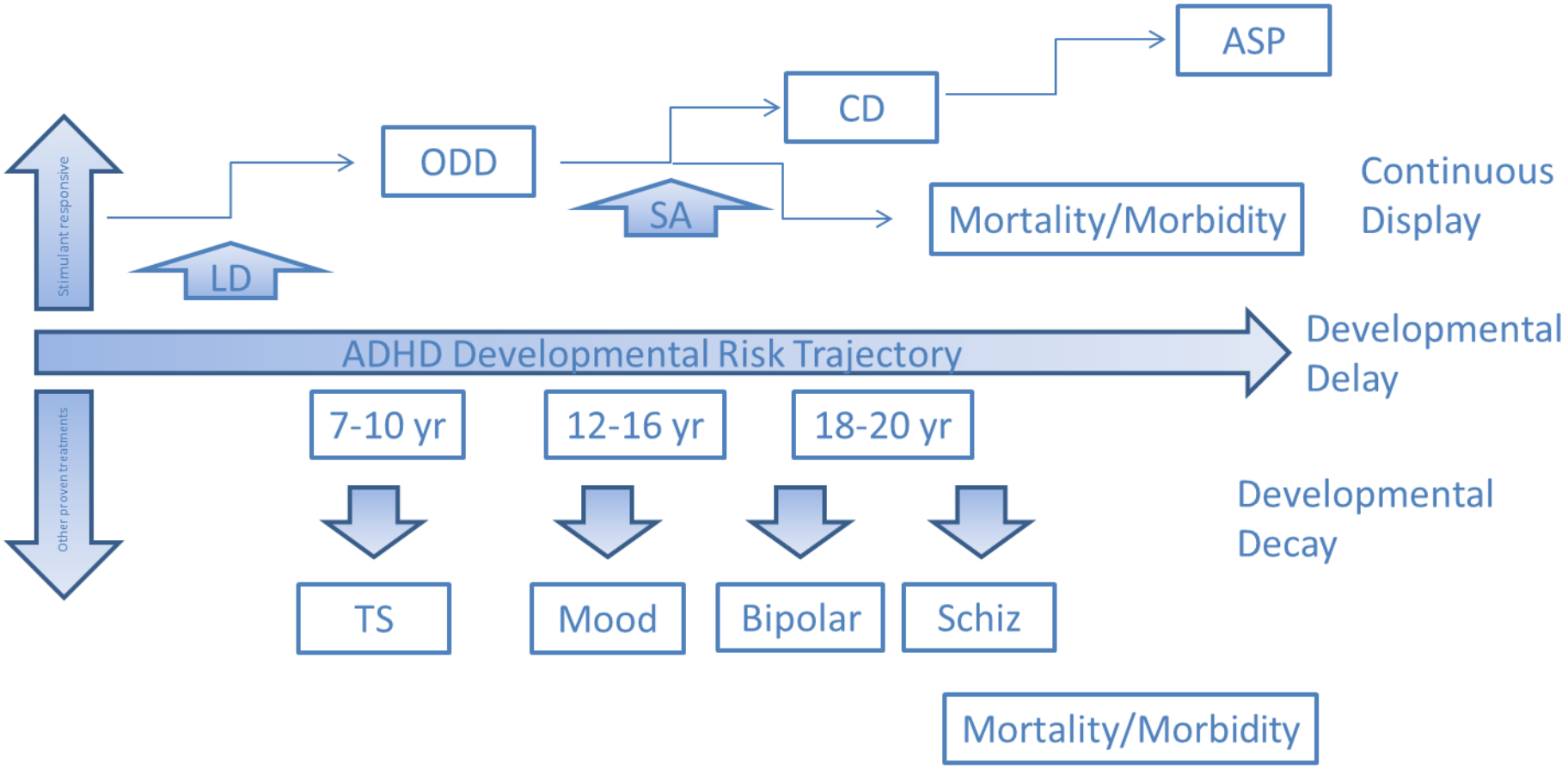
Cerebral CORTEX

ADHD Developmental Trajectories



Alcohol: Toxin, Proxy & Psychotropic

- Alcohol exerts clear toxic effects on the developing organism and especially the brain.
  - Impaired growth and protein synthesis.
  - Inhibited neuroblast migration.
  - Arrested neuronal differentiation (impacting synapses and dendritic arbors).
  - Suppression of oligodendrocyte protective factors (white matter growth and regeneration).
  - Cell death.

Alcohol: Toxin, Proxy & Psychotropic-cont'd

- There is no evidence of a threshold for safe alcohol use.
- There are a number of studies establishing dose-response effects on neuroanatomic as well as psychological parameters.
- Moreover, alcohol use frequently indicates a greater risk for co-exposure to other behavioral teratogens (cigarettes).

Alcohol: Toxin, Proxy & Psychotropic-cont'd

- Alcohol may amplify its teratogenic risk by its impact upon nutritional reserves (folic acid).

- Alcohol is itself psychotropic and its effects on GABA-ergic neuronal systems (which can be detected in the first trimester of gestation) may moderate connectivity, firing thresholds and topographical synchronization.

Choreography of the Gestational Brain

- Neurons progress uniformly through predictable stages of neuroblast formation, proliferation, migration, differentiation, afferentation/efferentation, and myelination.

- But each cortical area undergoes these stages at different gestational ages:
  - caudal to rostral gradient in the brain stem and diencephalon.
  - posterior to anterior gradient of maturation in the cortex (occipital lobes to frontal and prefrontal lobes.

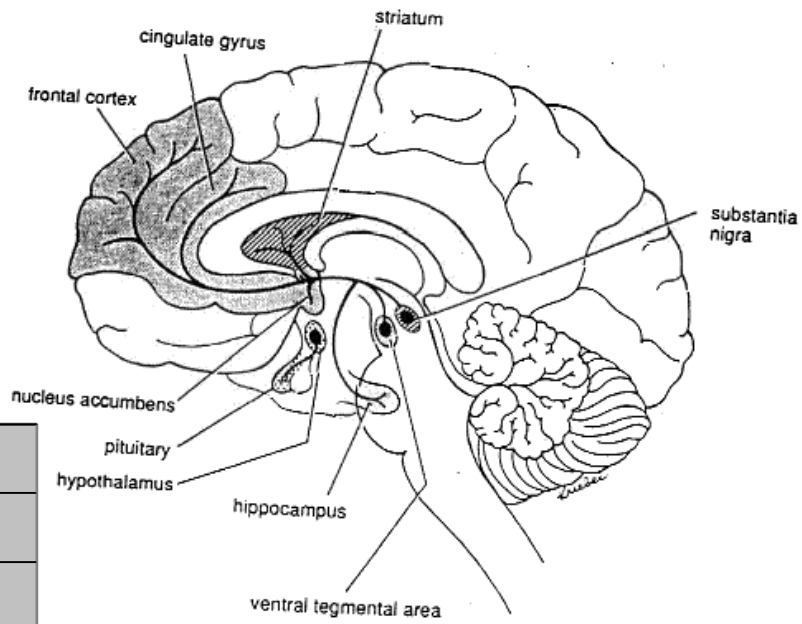
- Each stage is impacted by alcohol exposure.

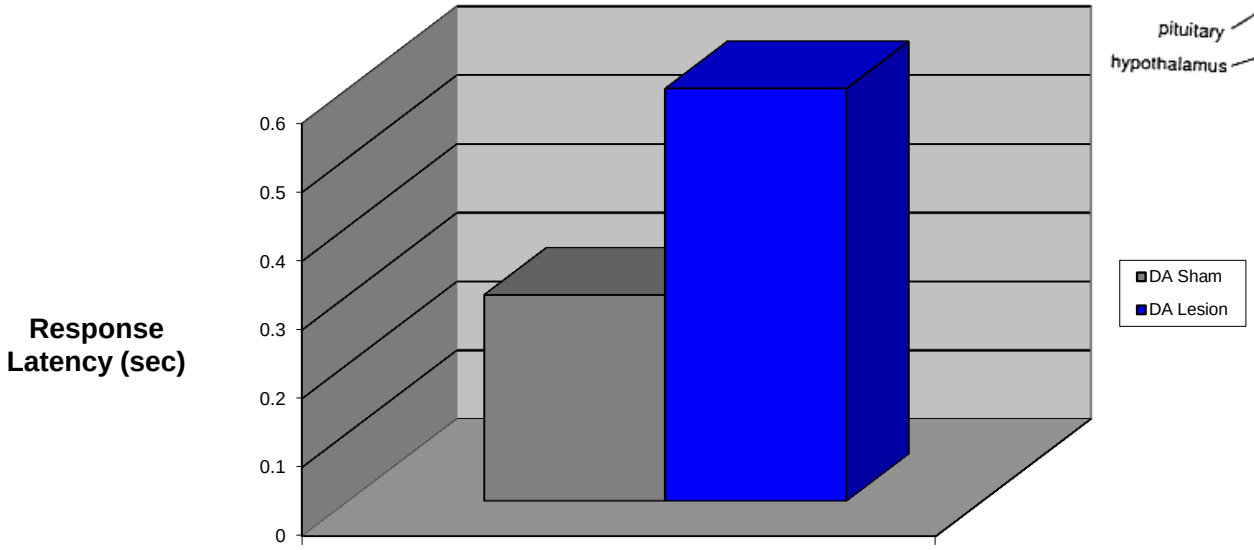
Choreography of the Gestational Brain-cont'd

- Caudal structures may be more vulnerable to early exposures.
- "Pivotal" neuronal groups (small numbered cell populations that control or modulate large neuronal networks) have less redundancy.
  - Mid-brain ARAS
  - Hippocampus

Effects of 6 OH-DA after Pretreatment with DMI: Deficits in Response Latency & Speed

Depletion of mesencephalic dopaminergic projections results in increased response latency and slower response times without affecting accuracy.

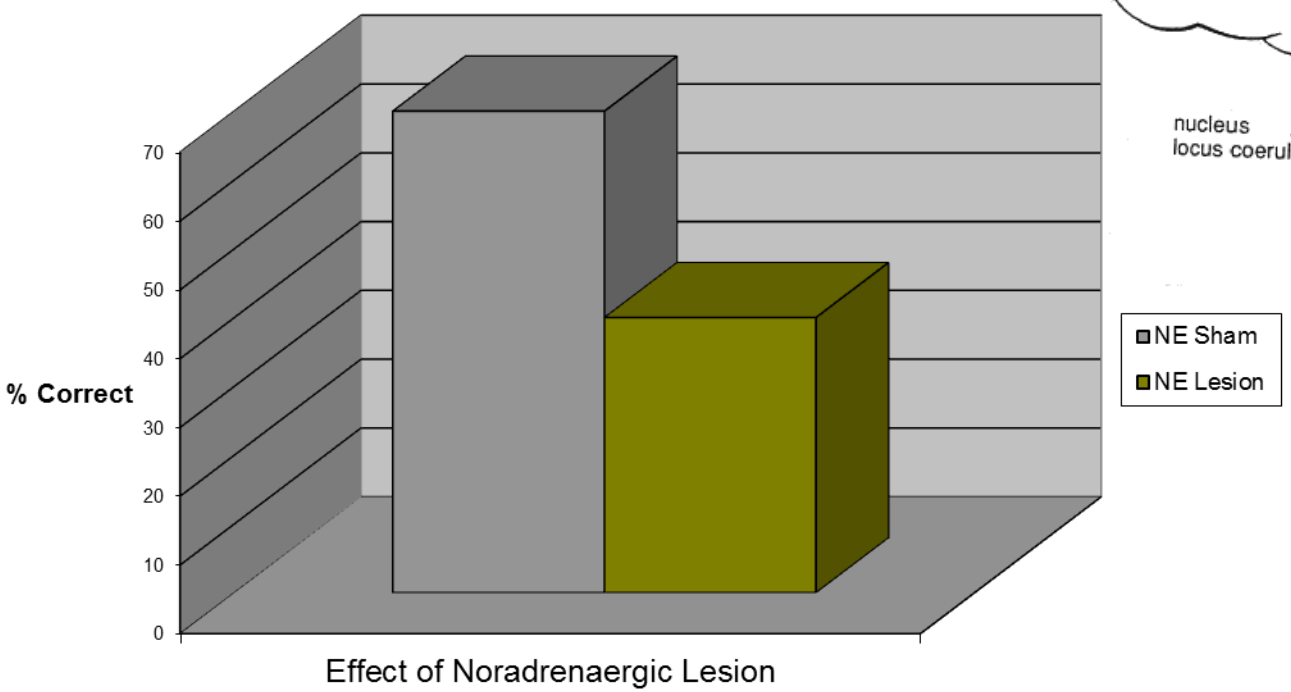


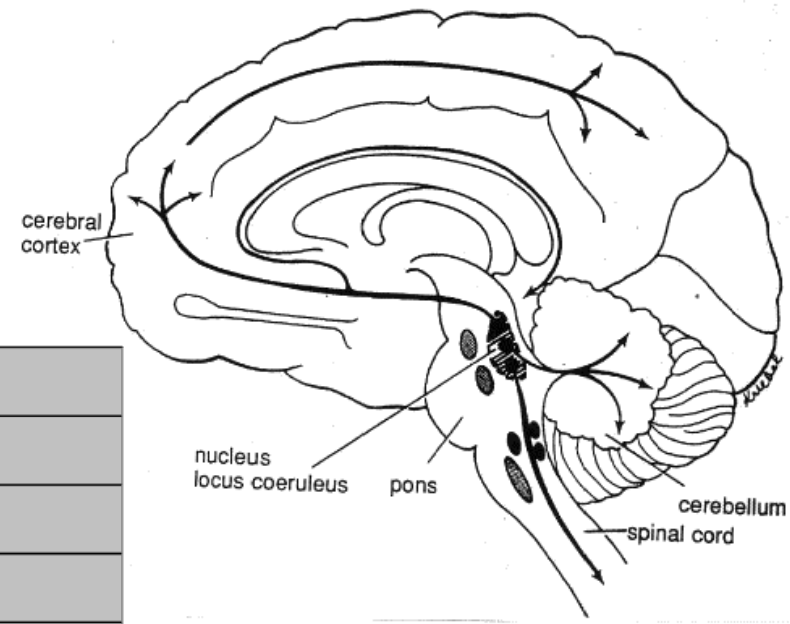


Effects of Dopaminergic Lesions

Effect of 6 OH-DA after Pretreatment with Mazindol: Increased Distractibility

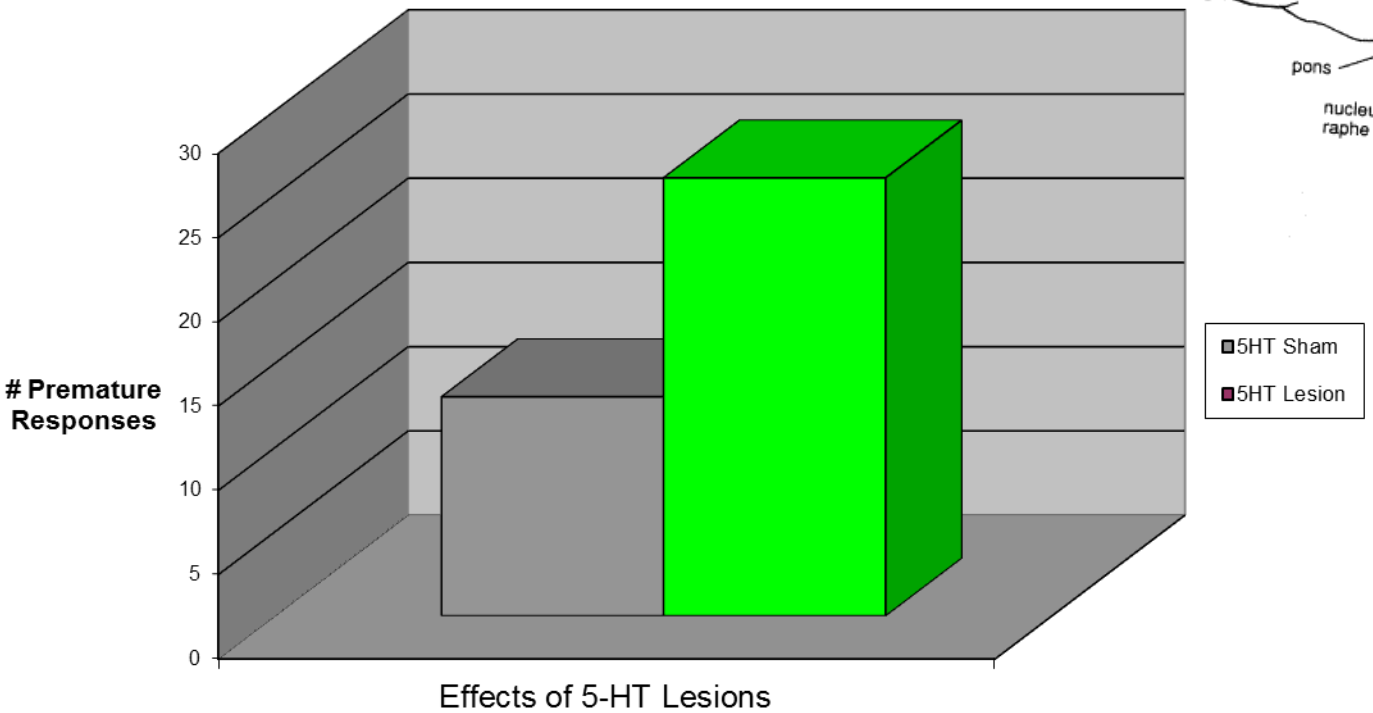
Ceruleo-cortical NA depletion had no effects on accuracy or response latency at baseline. The animals' accuracy after the introduction of white noise significantly decreases.

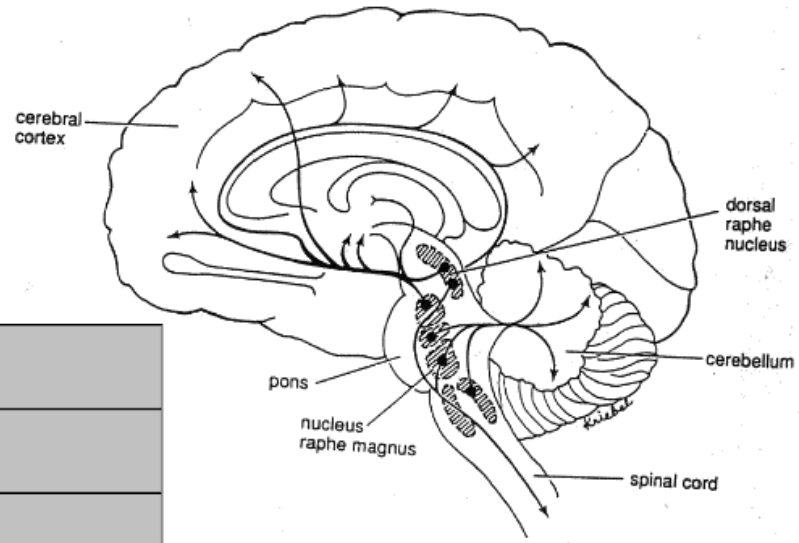




Treatment with Intraventricular 5,7 DHT: More Impulsive Responding & Less Response Inhibition

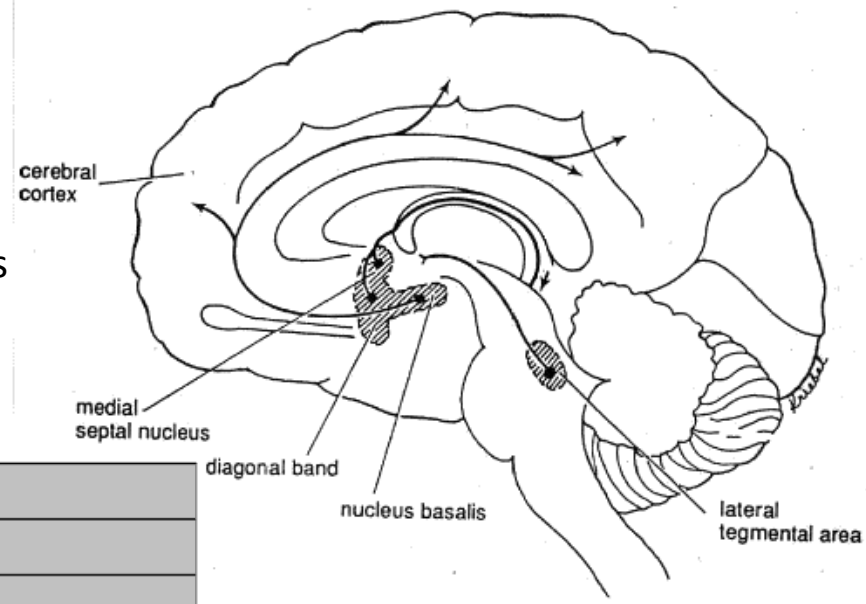
Serotonin depletion results in increased premature responses. Also, not shown, a significant improvement in accuracy is observed.

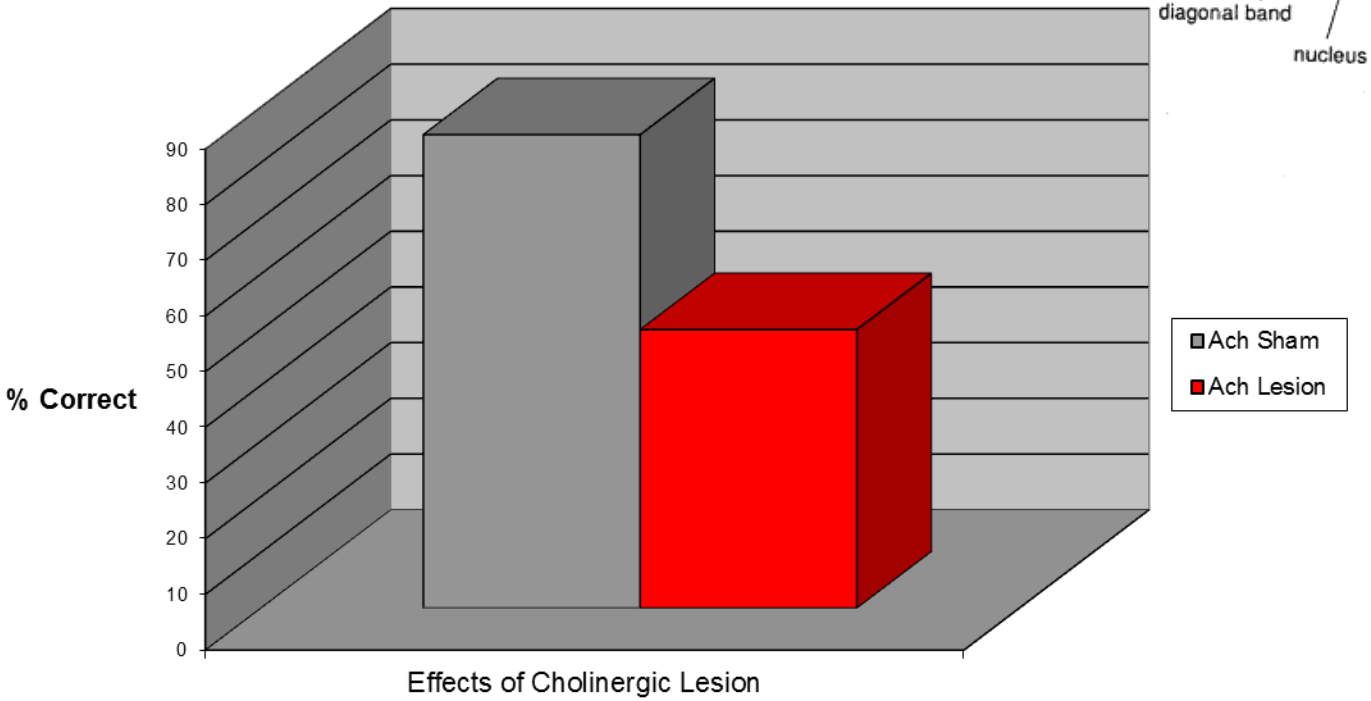




Cholinergic Depletion by Excitotoxic Lesion to Nucleus Basalis of Meynert

Loss of cholinergic neurons projecting to the neocortex, amygdala and hippocampus results in significantly decreased accuracy in discriminating visual targets by enhancing signal-to-noise perception.

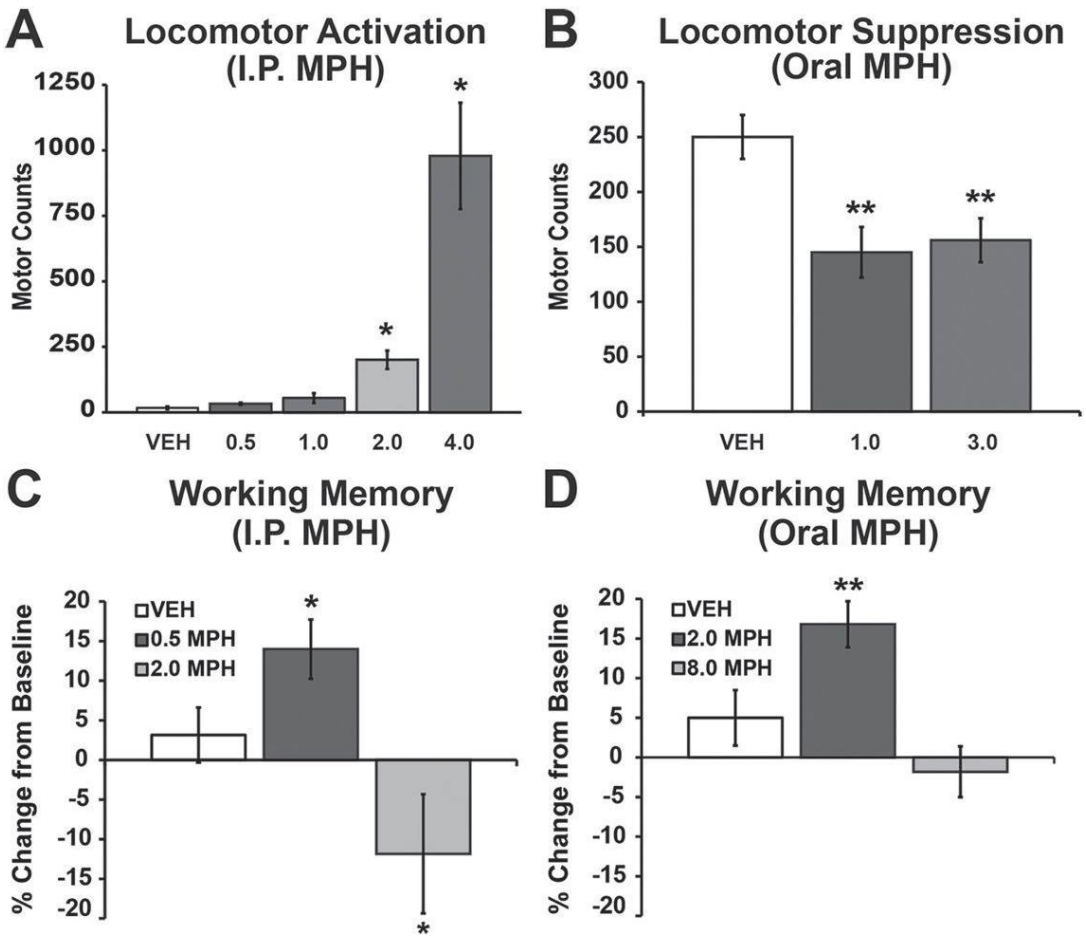




Liabilities of Psychotropic Treatment in FASD

- Altered target organ (brain) compromises therapeutic effect size.
  - Fewer neurons
  - Less responsivity
  - Less communication
- And amplifies the frequency and severity of adverse effects.

Differential Effects of Oral to IP MPH



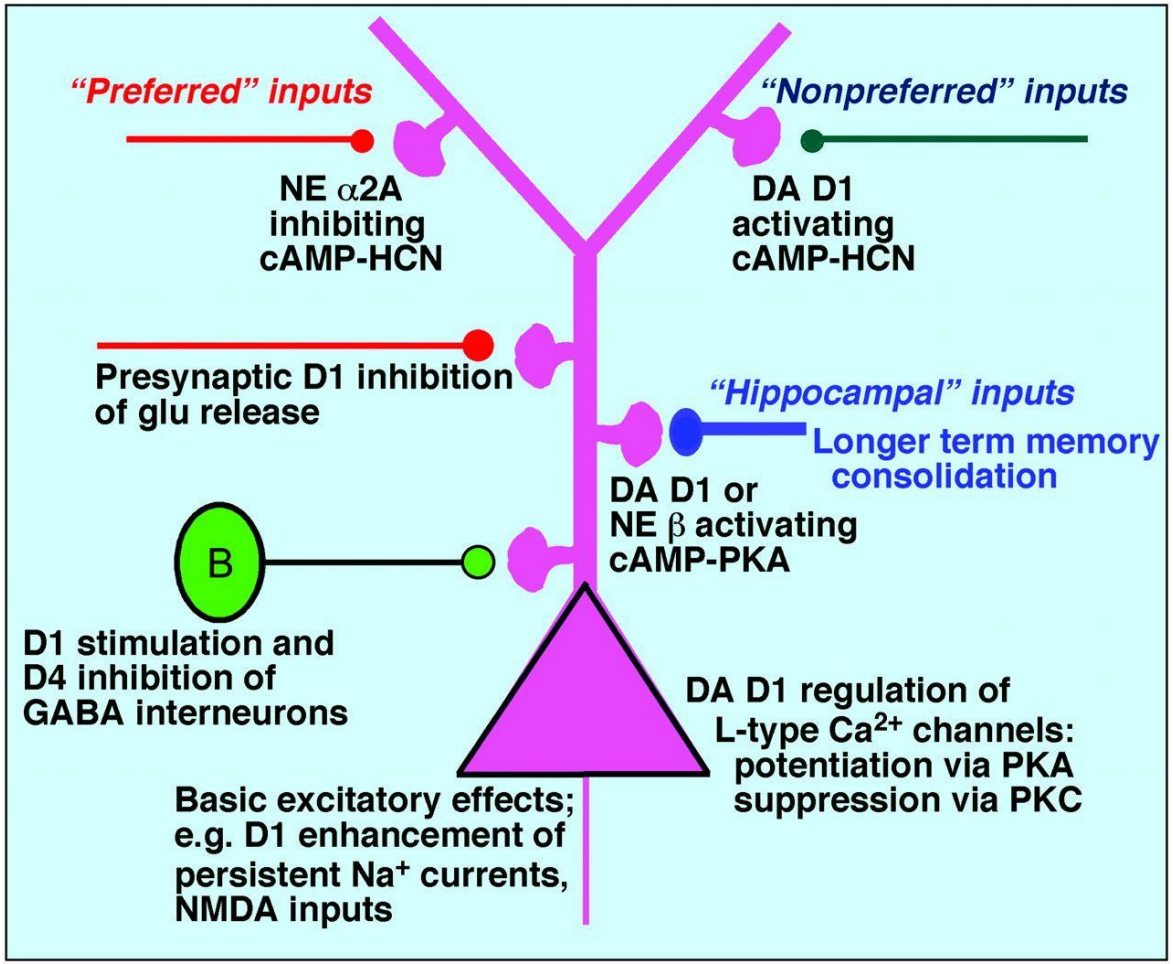
Pragmatic Considerations

- Consider every agent you use as “off label”.
- Be systematic:
  - Assessment
  - Baseline measures
  - Consent/Inform
  - Dosing strategies (start low/go slow)
  - Effects (Therapeutic and Adverse)
  - Follow up (increased frequency during titration)
  - Give up if its not working (Risk-Benefit considerations)
  - Heterogeneous interventions (avoid medication-only)

Algorithmic Approach

- Choose an agent that would be most effective based upon your clinical assessment of the most troublesome symptoms or behaviors.
- Learn from outcome. An adverse drug response frequently tells you what drug to try next.
- Have a hierarchy of agents based upon:
  - Approved and safe in children for other indications.
  - Research and case reports of potential effectiveness.

Examples of catecholamine modulation of PFC neuronal physiology.



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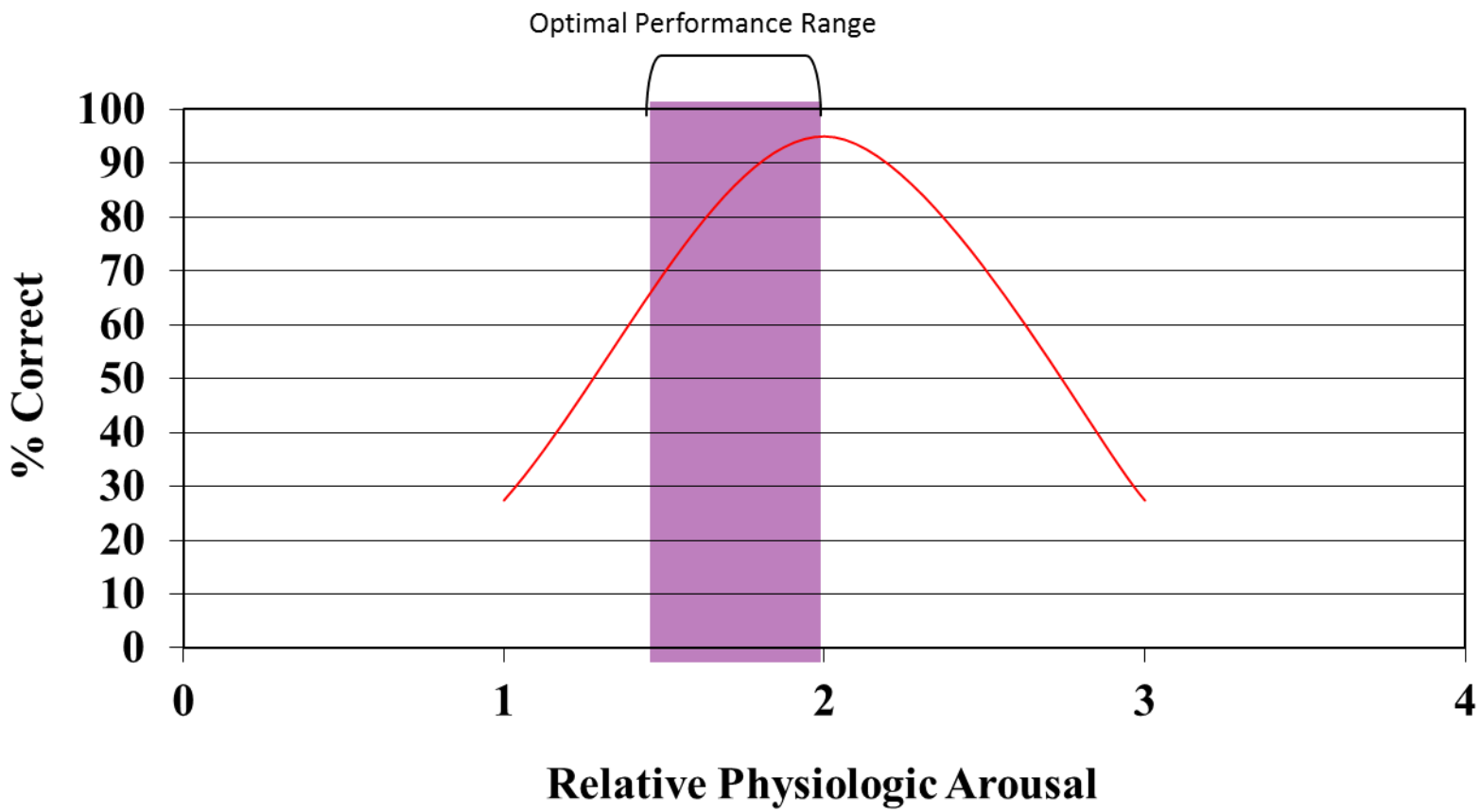
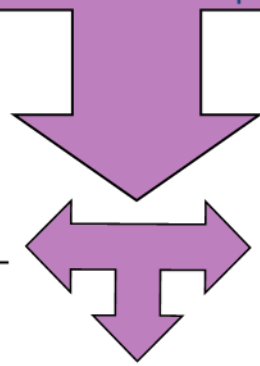
Cerebral CORTEX

Dodsen-Yerkes Law



ADHD without co-morbid symptoms of anxiety.

Begin with low-dose amphetamine (2.5-5.0 mg bid). Increase dose in 2.5 mg steps every two weeks. Dose ceiling at 30 mg/day. Alternatively, MPD derivatives at 5mg with 5 mg increments to optimize.



If child becomes activated with aggressive behavior, increased activity, sustained sleeplessness and/or anorexia, try an alpha-2 adrenergic agonist (guanfacine 0.5 mg bid) or atomoxetine.

If child becomes self-injurious or develops stereotypies, try an SSRI (fluoxetine 4-5mg qAM).

Target behaviors decrease without disturbing sleep or appetite. Titrate dose to optimize clinical response.

ADHD with symptoms of anxiety

Prominent clinical feature manifested by tactile defensiveness, hyperacusis, autonomic overactivity. Begin Guanfacine, 0.5 mg bid or tid. Step up dose as clinically indicated by 0.5-1 mg steps at two week intervals. Ceiling at 9 mg/day.

If child develops predatory behavior or calculated aggression, try atomoxetine.

If child becomes depressed, over-sedated, self-injurious or develops stereotypies, try an SSRI (fluoxetine 4-5mg qAM).

Target behaviors decrease without disturbing sleep or appetite. Titrate dose to optimize clinical response.

Prominent symptoms of anxiety with sensory over-reactivity, behavioral stereotypy or resistance to change

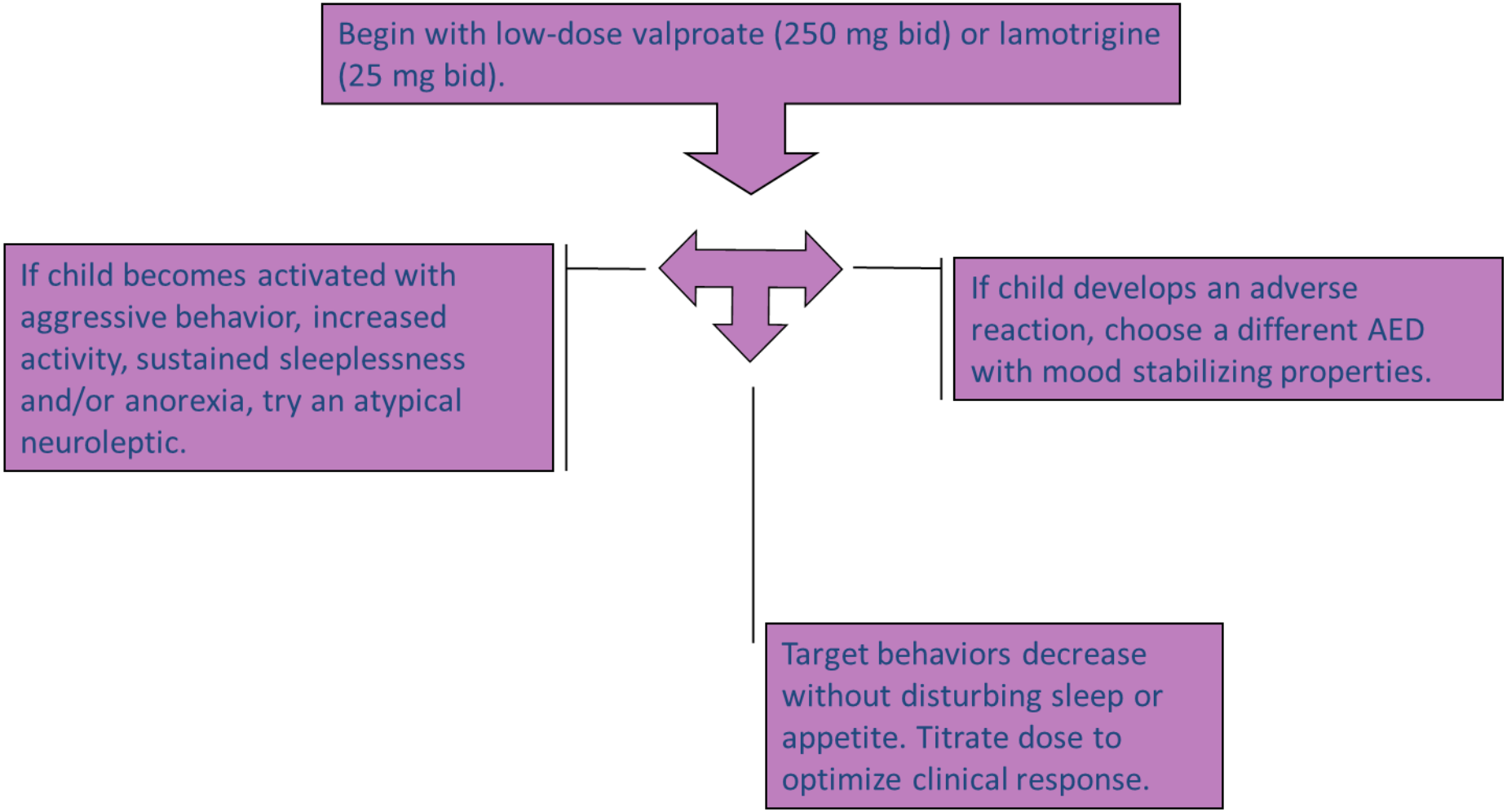
Begin with low-dose fluoxetine (4-5 mg qAM). Re-assess every two-to four weeks and step up dose in 4-5 mg steps. Ceiling dose at 40 mg.

If child becomes activated with aggressive behavior, increased activity, sustained sleeplessness and/or anorexia, try an alpha-2 adrenergic agonist (guanfacine 0.5 mg bid).

If child develops increased self-injurious behaviors or develops more intense stereotypies or sleep disturbance, stop fluoxetine and consider an atypical neuroleptic or antiepileptic.

Target behaviors decrease without disturbing sleep or appetite. Titrate dose to optimize clinical response.

Prominent symptoms of mood instability



Complementary Medicines

- Nutritional supplements:
  - Fish oil
  - Vitamin D3
  - L-methyl folate
  - Zinc
- Antioxidants:
  - N-acetyl cysteine

Summary

- FASD is a complicated congenital brain condition with notable clinical heterogeneity, which confers significant risk for early onset psychiatric disorders.
- Psychotropic treatment may offer some benefit but altered brain structure and function may limit overall effectiveness.
- A systematic approach offers the best practical solution to such intervention.
- Psychotropic treatment should be used to amplify the benefits of other psychosocial and psychoeducational interventions rather than be the only intervention.

Thank You!

Q&A