ADHD and Dopamine

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ADHD

- Currently a “cognitive disorder” with symptoms including:
  - Inattentiveness
  - Hyperactivity
  - Impulsiveness

From a cognitive viewpoint

- Internal events (thoughts and plans) are addressed for short sequences of time and rapidly shift.
  - problems with generating and following plans
  - lack of organizational skills
  - forgetfulness

Prevalence

- Estimates range from
  - 1-3% to 3-5% of the US population
- No clear biological marker for ADHD
- Even children/people without ADHD benefit from stimulant medication

- (Carey, 2000; NIH-sponsored ADHD Consensus Development panel; Barkley, 1999)

A Cultural Fad?

- Parent/Teacher mentality:
  - “My child is misbehaving; it must be ADHD”
  - “Your child is not paying attention in class; perhaps he has ADHD”
- “We gave him ADHD medication and now he pays better attention!”

Physiological ties

- Barkley's (1997)
  "Response disinhibition theory"
- The problem: "Executive Dysfunction"
- Executive functions consist of higher-order cognitive functions
  - planning ahead
  - delaying gratification for future reward
  - impulse control

Response disinhibition theory, cont.

- Pathways originating in the pre-frontal cortex lead to dopaminergic activity that
  - inhibits unwanted attention-switching
  - controls impulsive behavior
- failure to evoke sufficient dopaminergic response results in an inability to inhibit certain thoughts and/or behaviors.

Critique of Barkley's Theory...

- Barkley's (1997) theory may be an oversimplification.
- Barkley's theory appears to describe two underlying factors of a larger framework:
  1. slower acquisition of long sequences of behavior
  2. deficient extinction of previously reinforced behavior

Dynamic developmental behavioral theory (2004)

- Altered dopaminergic function fails to appropriately modulate glutamatergic and GABAergic signal transmission (Sagvolden, Johansen, Aase, & Russell, 2004).

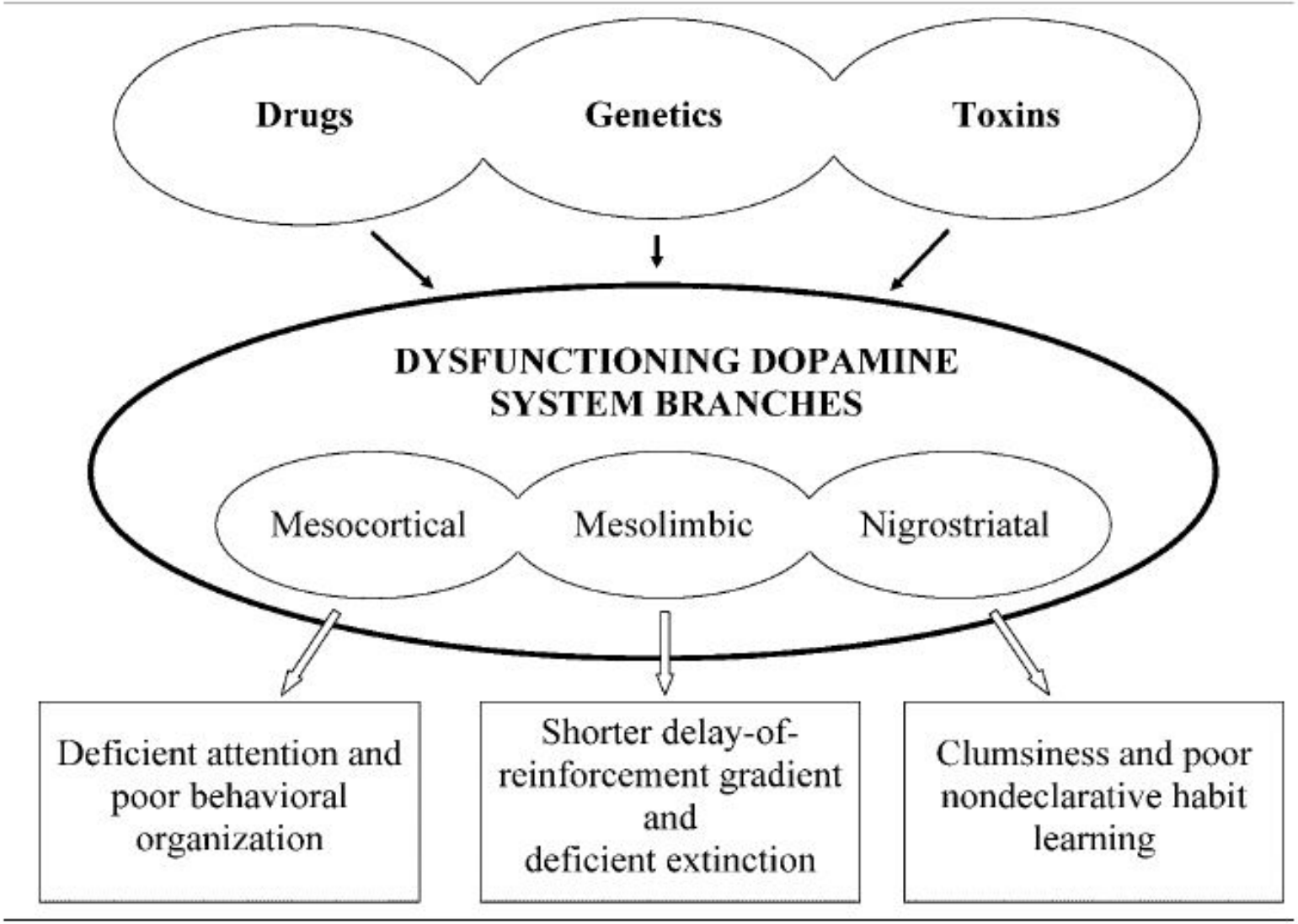


Figure 1. Dysfunction of dopaminergic systems resulting from drug abuse, genetic transmission, or environmental pollutants may cause ADHD symptoms by interacting with fronto-striatal circuits (not shown).

Pathways/Branches

- A hypofunctioning mesocortical dopamine path may cause:
  - Attention response deficiencies, including a deficient orienting response
  - impaired saccadic eye movements (poor attention responses towards a target)
  - poor behavioral planning (poor “executive” functions)

Pathways/Branches

- A hypofunctioning nigrostriatal dopamine path may cause
  - impaired modulation of motor functions
  - deficient nondeclarative habit learning and memory

Pathways/Branches

- A hypofunctioning mesolimbic dopamine path may cause:
  - shorter delay-of-reinforcement gradient and deficient extinction.
  - (Examples to follow)

Are we sure it's dopamine?

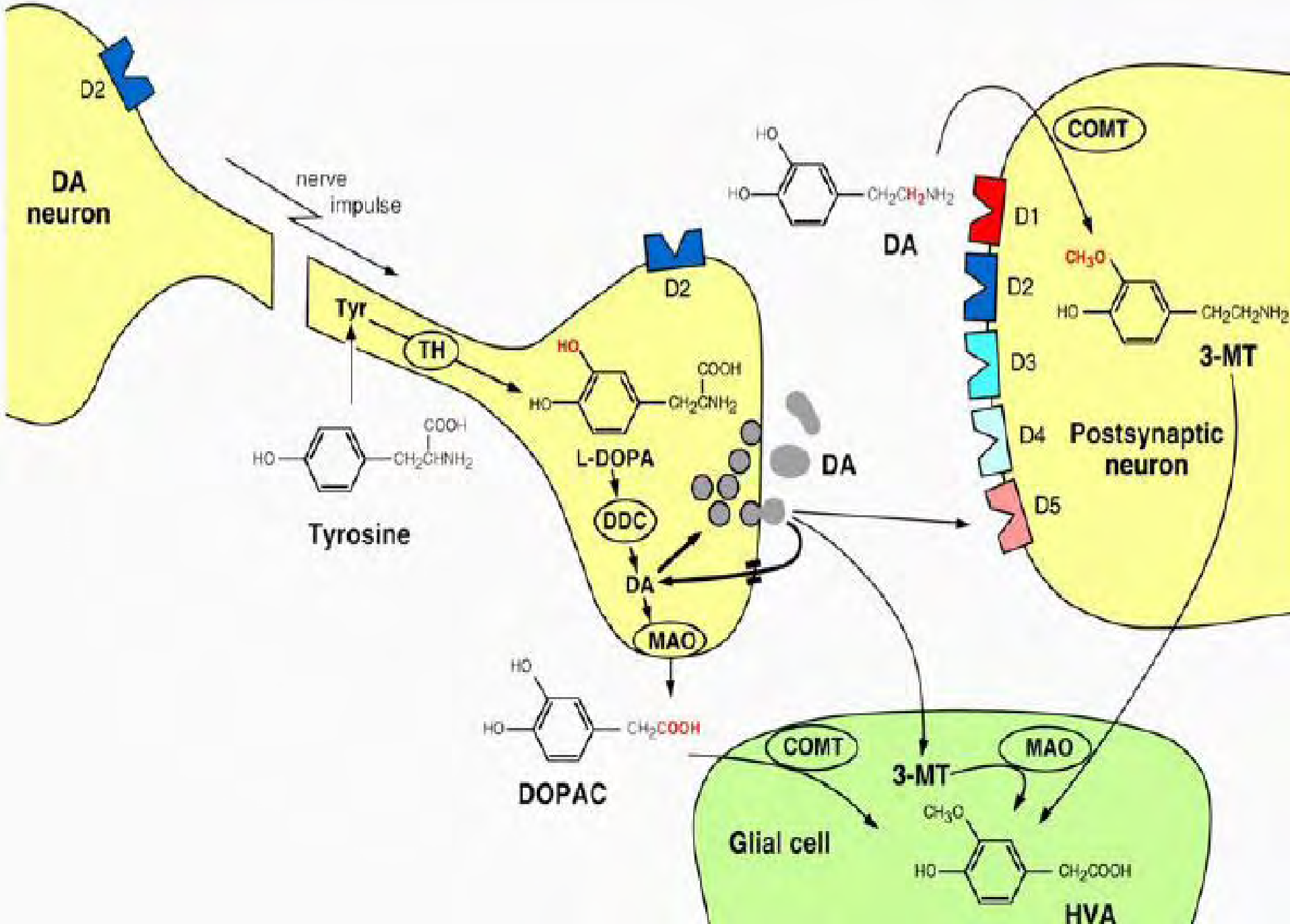
- Children with ADHD do not appear to be as hyperactive in novel situations.
  - Consistent with dopamine release for novel stimuli, as discussed in a prior presentation ☺

Increasing Dopaminergic Activity

- The current treatments increase DA activity:
- Methylphenidate blocks the reuptake of NE and DA and increases their release (Ritalin)
- Dextroamphetamine and Amphetamine (Adderall) works the same way
- Wellbutrin (Buproprion) is not approved for use with ADHD, but because it mildly inhibits DA reuptake, doctors use it “off-label” to help with ADHD symptoms.

Increasing NE activity may help, too?

- Atomoxetine is an NE reuptake inhibitor (NRI): “Straterra”
- Reboxetine is a NRI as well, not marketed for use in the U.S. (yet)
- To keep in mind: DA and NE are both modulatory neurotransmitters, whose pathways frequently overlap

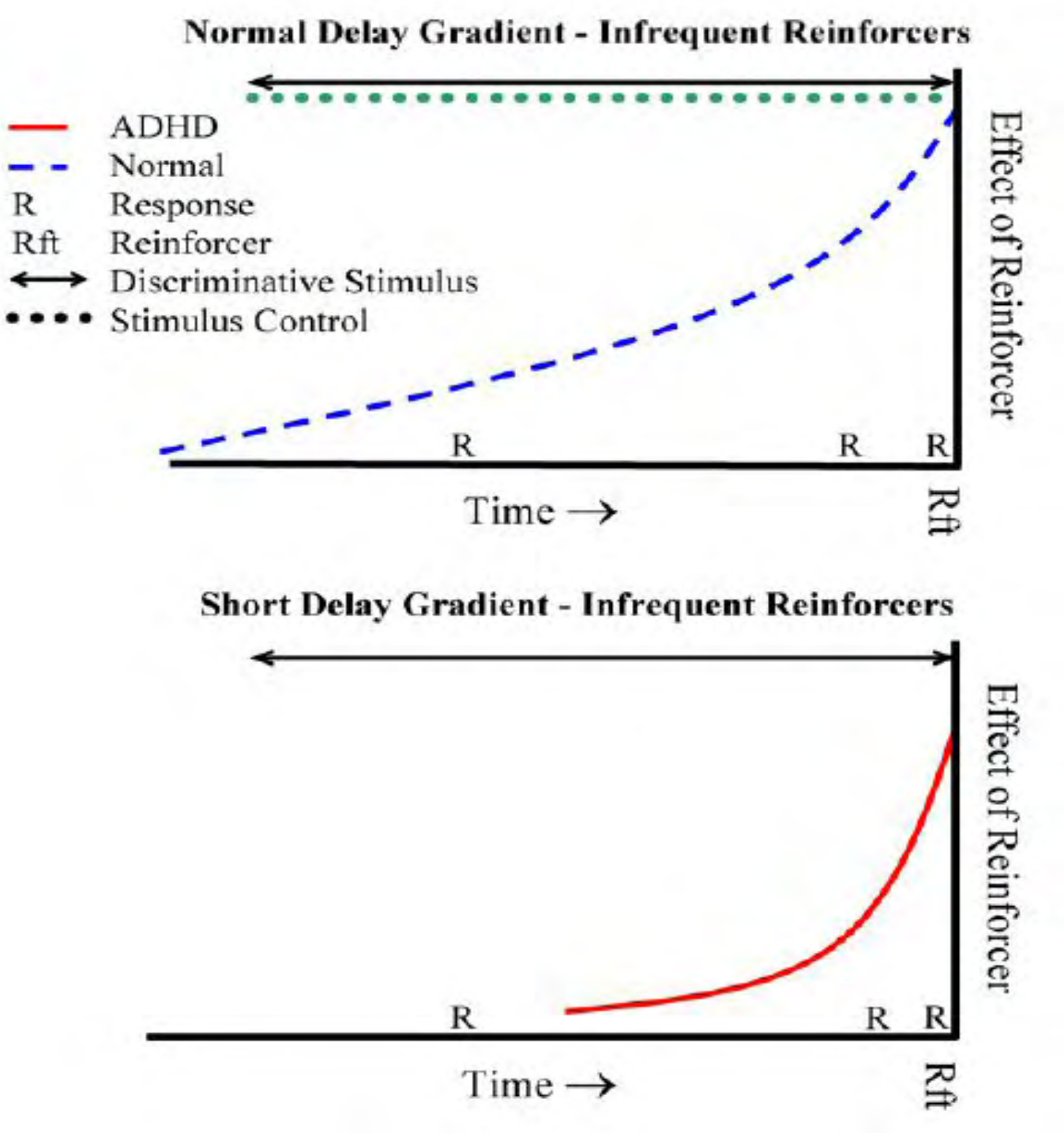

D2
DA neuron
nerve impulse
Tyr
TH
Tyrosine
D2
L-DOPA
DDC
DA
MAO
DOPAC
DA
COMT
D1
D2
D3
D4
D5
3-MT
Postsynaptic neuron
Glial cell
COMT
3-MT
MAO
HVA

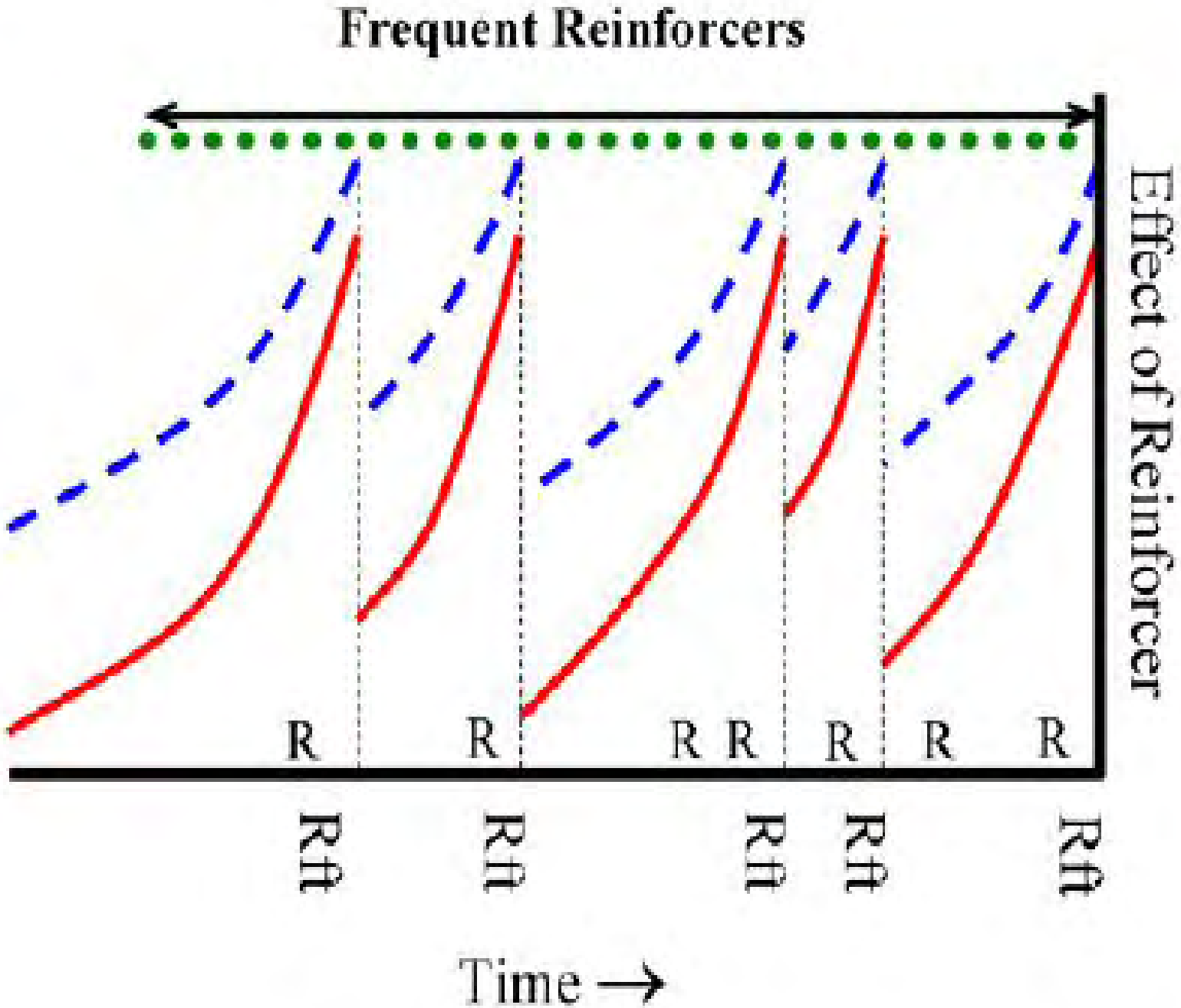
Reinforcement and Learning

- Frequent reinforcement leads to better learning and attention, which is why small, frequent rewards are used in classrooms that specifically work with ADHD children.
- Why?

Coincidence Detection

- Dopamine stimulation (caused by a reward) may increase NMDA receptor opening times.
  - NMDA receptors are involved in learning
  - Therefore, DA release increases the “time window” available for coincidence detection.
- With ADHD, the “time window” is shorter.


Normal Delay Gradient - Infrequent Reinforcers
ADHD
Normal
R Response
Rft Reinforcer
Discriminative Stimulus
Stimulus Control
Effect of Reinforcer
R
R
R
Time →
Rft
Short Delay Gradient - Infrequent Reinforcers
Effect of Reinforcer
R
R
R
Time →
Rft


Frequent Reinforcers
Effect of Reinforcer
R
R
R R
R
R
R
R
R
R
R
Time →

Acqusition and Extinction

- Two main behavioral observations:
  1. Altered reinforcement of novel behavior
  2. Deficient extinction of previously reinforced behavior
- Typical mesolimbic dopamine-mediated acquisition and response extinction, anyone?

Acquisition/Extinction → Behavior

- A lack of potentiating neuronal connections associated with reinforced (adaptive) behavior
- A lack of weakening (extinguishing) neuronal connections associated with non-reinforced (maladaptive) behavior.

Potential causes for hypofunction

- Reduced dopaminergic response might be due to a combination of:
  - insufficient glutamate input from the prefrontal cortex to dopamine neurons
  - a faulty regulation of dopamine release
- So, what might cause this? Where do we look?

Genetics (Brown, 2004)

- Genetic involvement supported by family, adoption, and twin studies.
- Identified possibilities:
  - D4 receptor (DRD4 gene)
  - DAT1 gene (dopamine transporter)
  - Synaptosomal-associated protein 25 (SNAP-25)

Genetics (Brown, 2004) cont.

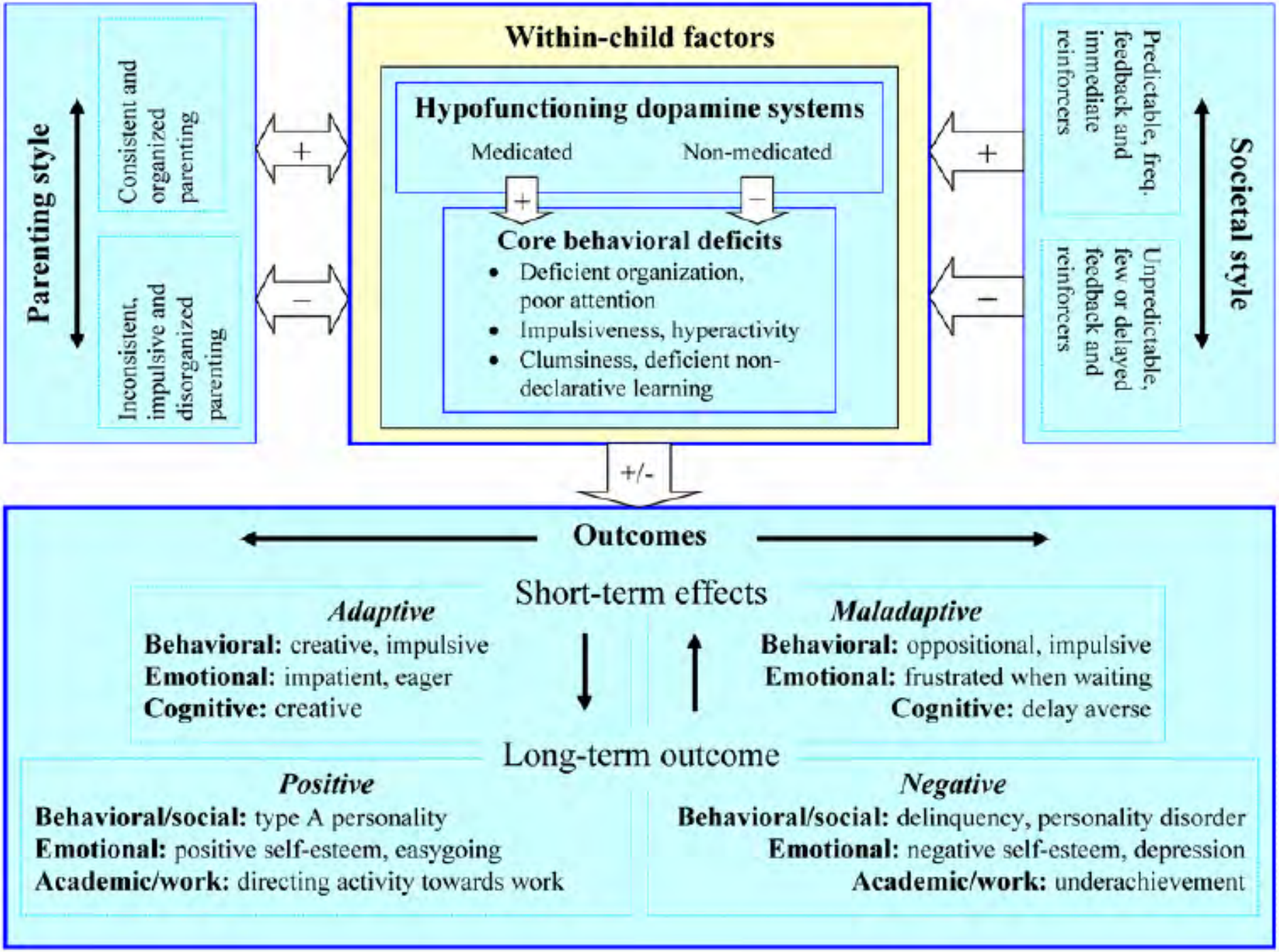
- “Each gene confers a very low added risk- roughly 1% to 3%- of developing ADHD”
- The pathophysiology of ADHD remains unknown. Researchers are now exploring:
  - Genes that regulate norepinephrine and nicotine levels in the brain.
  - Twins with ADHD often share a form of nicotinic acetylcholine receptor alpha 4.

Genetics (Brown, 2004) cont.

- Back to Dynamic developmental behavioral theory (Sagvolden, 2004)
  - Both Genetics and Environmental factors
- "How do genes work in different environments?" "How do genes lead to impairment? That's the next step." (Smalley, as cited in Brown, 2004)

End of Presentation

- For those curious, a diagram of Dynamic Developmental Behavioral Theory (Sagvolden et al, 2004) is shown on the next slide.


Parenting style
Consistent and organized parenting
Inconsistent, impulsive and disorganized parenting
+
−
Within-child factors
Hypofunctioning dopamine systems
Medicated
Non-medicated
+
−
Core behavioral deficits
• Deficient organization, poor attention
• Impulsiveness, hyperactivity
• Clumsiness, deficient non-declarative learning
+
−
Predictable, freq. feedback and immediate reinforcers
Unpredictable, few or delayed feedback and reinforcers
Societal style
+/-
Outcomes
Short-term effects
Adaptive
Behavioral: creative, impulsive
Emotional: impatient, eager
Cognitive: creative
Maladaptive
Behavioral: oppositional, impulsive
Emotional: frustrated when waiting
Cognitive: delay averse
Long-term outcome
Positive
Behavioral/social: type A personality
Emotional: positive self-esteem, easygoing
Academic/work: directing activity towards work
Negative
Behavioral/social: delinquency, personality disorder
Emotional: negative self-esteem, depression
Academic/work: underachievement