

بیش فحالی

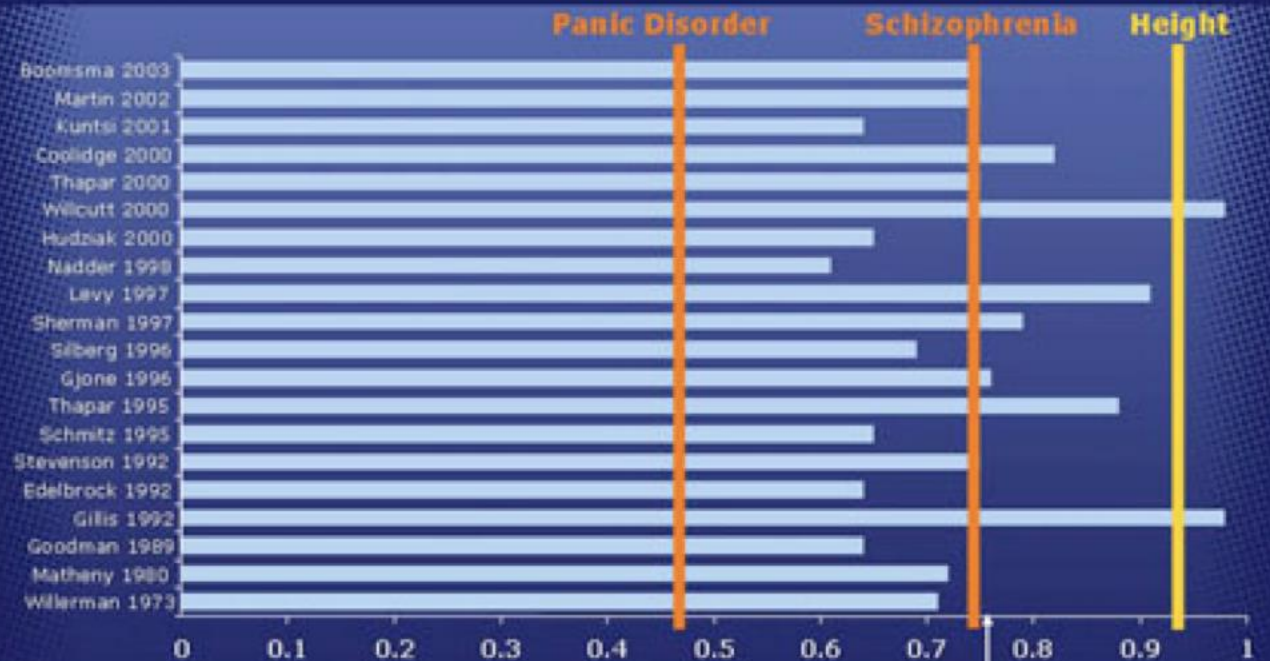
دکتر جواد علاء‌قندزاد

استاد دانشگاه علوم پزشکی تهران

High genetic loading of ADHD

ADHD Educational CME Initiative

ADHD Has a Substantial Genetic Component



Mean heritability of ADHD = 0.76

Faraone SV et al. *Biol Psychiatry*. 2005; 57: 1313-1323.

prevalence

10-12 percent of children worldwide

Increasing recognition of adult ADHD:

Could be due to undiagnosed ADHD in children cropping up in adulthood ➤

The way we interact with the world (smart phone use, the combination email, text, real world interactions, multiple apps and streams of media and social media all coming at once trying to manage life) creates clouds of pulls on our attention ➤

Myths about ADHD

ADHD has to do with intelligence

ADHD isn't a real medical condition

People with ADHD just need to try harder

People with ADHD can't ever focus

All kids with ADHD are hyperactive

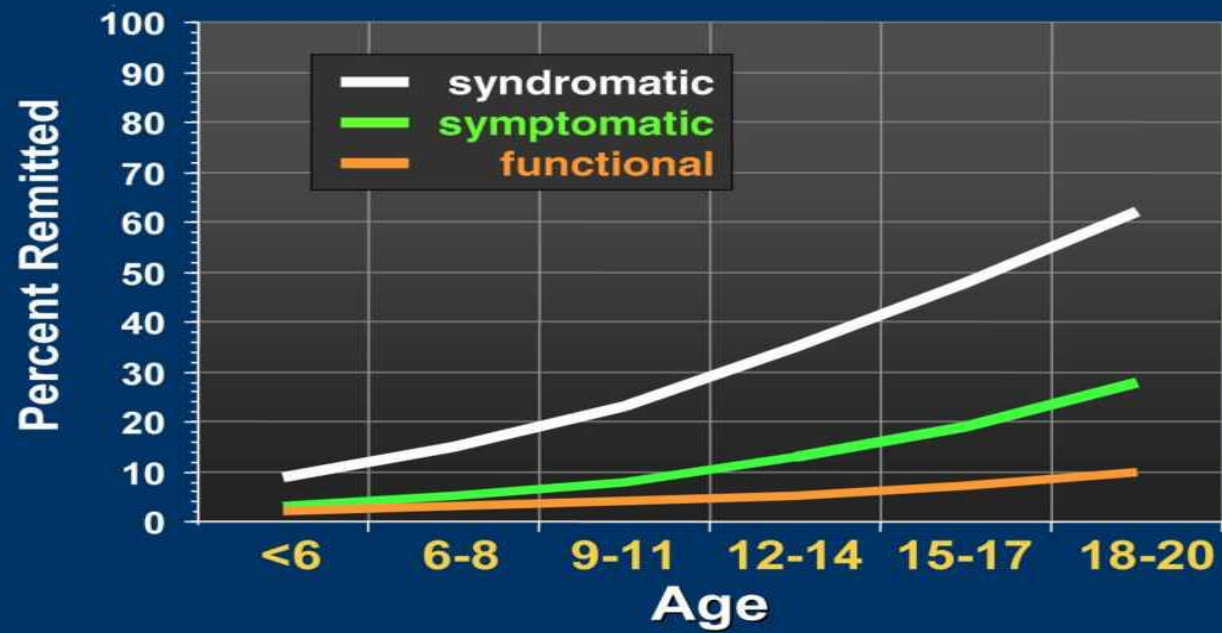
Only boys have ADHD

ADHD is a learning disability

ADHD is a result of bad parenting

ADHD is a childhood condition

Age-Specific Prevalence of ADHD Remission: DSM-III-R ADHD



Biederman et al. *Am J Psychiatry* 2000;157:816.

Interesting phenomena observed in ADHD

Hyperfocusing for subjects that they enjoy

Time blindness

They procrastinate ✓

They do well, however, if given deadline or consequences ✓

It has to do with working memory ✓

It has to do with dopamine ✓

The Pile System

Spacial organization skill are subpar ✓

They pile things up ✓

What is wrong in ADHD?

Evolving cognitive models of ADHD

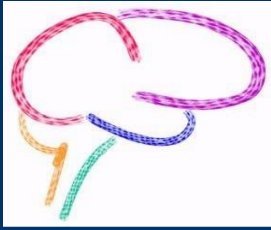
WHY ADHD

ADHD=EFDD???

Executive Function Deficit Disorder

Definition of Executive Functioning

- Executive control functions, called into action in nonroutine or novel situations, to provide conscious direction to the functional systems for efficient processing of information (*Stuss & Benson, 1986*)
- Those mental processes we use for sustaining problem-solving toward a goal (*Luria, 1966; Behkterev, 1902; Welsh & Pennington, 1988*)
- Those capacities that enable a person to engage successfully in independent, purposive, self-serving behavior: (1) volition; (2) planning; (3) purposive action; and (4) effective performance. All are necessary for appropriate, socially responsible, and effectively self-serving adult conduct (*Lezak, 1995*)
- Human social intelligence (*Dimond, 1980*)



Executive Function in ADHD

Linking Goals → Strategies → Actions



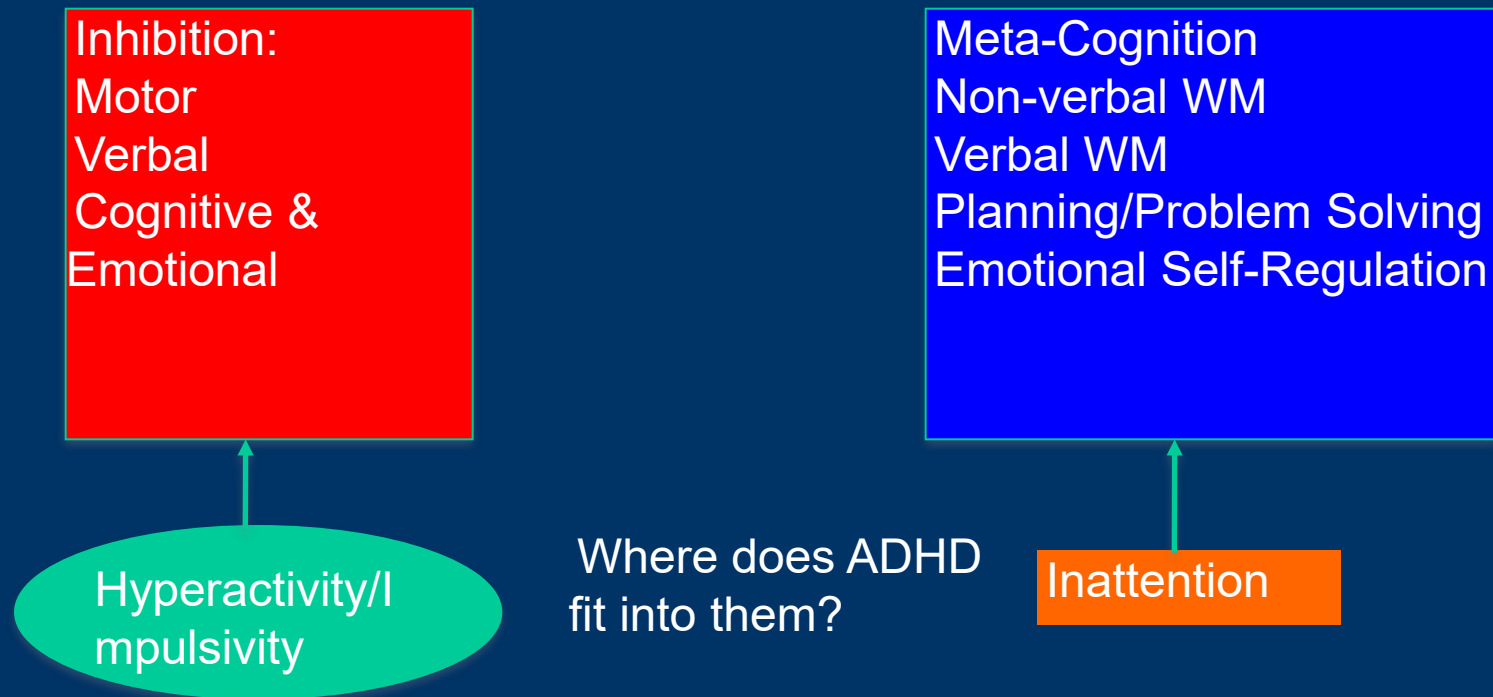
Creativity
Productivity
Identity

Common EF Constructs

- Inhibition and interference control
- Self-awareness and self-monitoring
- Nonverbal working memory
- Verbal working memory
- Planning and problem-solving
- Anticipation and preparation to act
- Self-regulation across time
- Emotional self-control

How Does ADHD Fit into EF?

- EF comprises 2 Broadband Domains



EFs do not fully explain what we observe in ADHD

The strongest association is with working memory and it is mostly spatial working memory

On any individual measure of EF, between 16% and 51% of children with ADHD were classified as impaired.

When multiple deficits were compared, only 31% of children with ADHD, versus 9% of controls, displayed pervasive impairment (deficits on 3 or more measures)

Only 10% of ADHD children showed deficits across all five domains.

By contrast, 21% of children with ADHD (and 53% of controls) were unimpaired on all five measures.

This combined analysis recapitulates the conclusion that 'EF weaknesses are neither necessary nor sufficient to cause all cases of ADHD'

Explaining why ADHD?

1. Executive dysfunctions

Task related networks

2. Default Mode Network.....

Executive function networks

Goal directed

Taks oriented

Dorsolateral prefrontal cortex and other areas responsible for impulse control like striatum

Default Mode Network

It is anatomically distributed among the medial prefrontal cortex (MPFC), PCC/precuneus, left lateral parietal cortex (LLP), and right lateral parietal cortex (RLP)

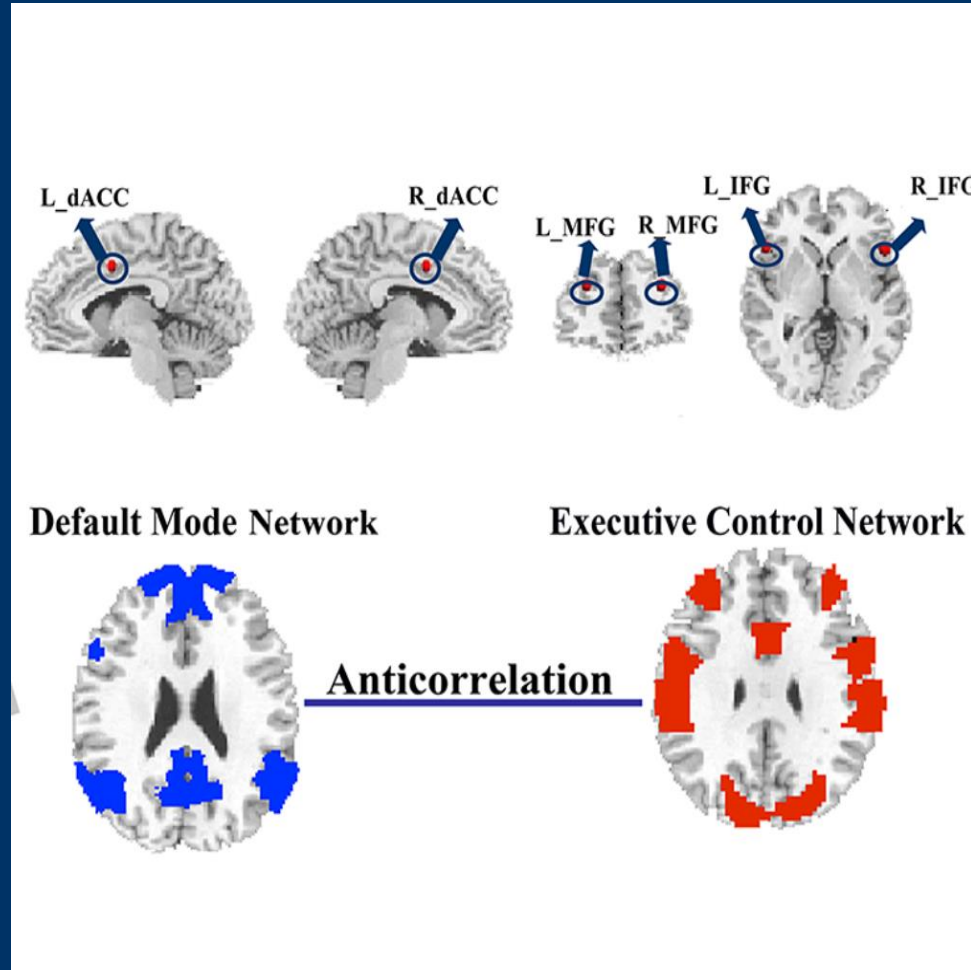
They act in a seesaw mode

They are anti-correlated

Dopamine is the conductor directing when each should be active

To successfully perform a task, the DMN must be actively suppressed

Default Mode Network and Executive Control Network are correlated



The human connectome project

USC Mark and Mary Stevens Neuroimaging and Informatics Institute

The NIH Human Connectome Project



Human Connectome Project

Enter search keyword

Home

About

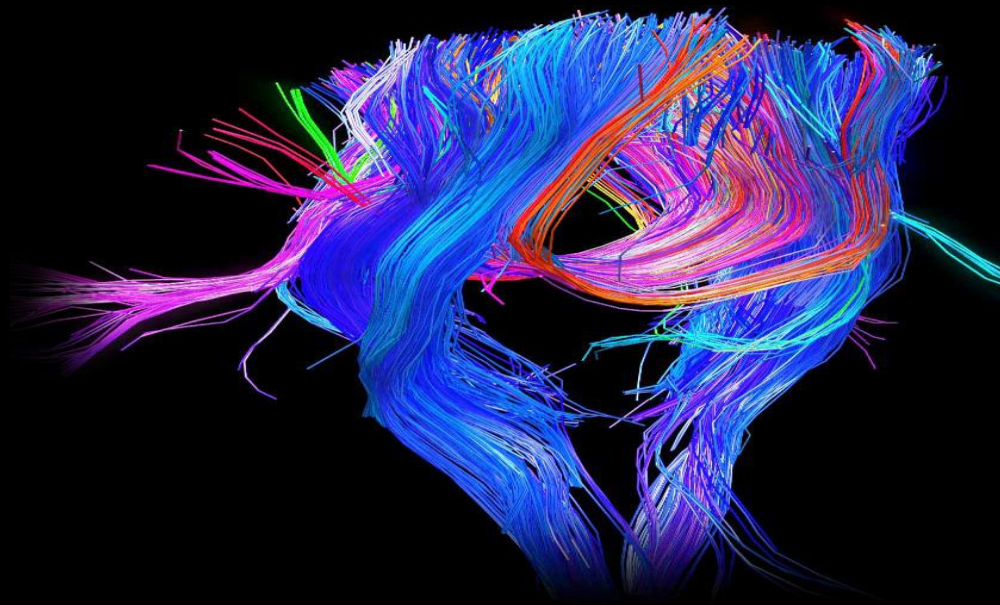
Data

Informatics

Gallery

Publications

News



The Human Connectome Project

Navigate the brain in a way that was never before possible; fly through major brain pathways, compare essential circuits, zoom into a region to explore the cells that comprise it, and the functions that depend on it.

The Human Connectome Project aims to provide an unparalleled compilation of neural data, an interface to graphically navigate this data and the opportunity to achieve never before realized conclusions about the living human brain.

Laboratory of Neuro-Imaging

News

RSS News

National Geographic features the Human Connectome Project

New research from members of our HCP team suggests that brain circuitry is organized more like Manhattan's street grid than London's chaotic tangle of random roadways. Read the full article in the February 2014 issue of National Geographic.

Director of NIH Praises the Human Connectome Project

The Symphony Inside Your Brain By Dr. Francis Collins Ever wonder what is it that makes you, you? Depending on whom you ask, there are a lot of different answers, but these days some of the world's top neuroscientists might say: "You are your connectome." Read the full article at: <http://directorsblog.nih.gov/the-symphony-inside-your-brain/>

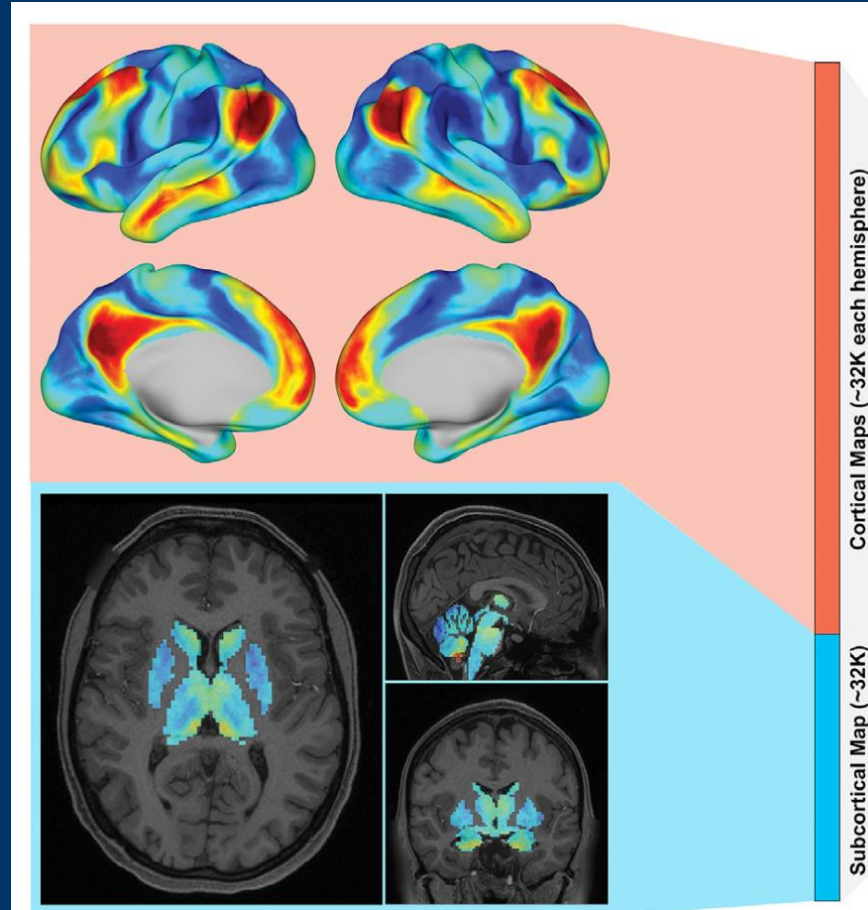
Muse's latest album uses a Human Connectome Project rendering of white matter tracks.

The Human Connectome Project (HCP) Consortium is pleased to have had its graphical renderings of brain connectivity chosen by Grammy Award winning international recording artists Muse (www.muse.mu) for the cover of their latest album 'The 2nd Law'. The images selected illustrate the complexity of the neural wiring of the human brain as computed using sophisticated [...] [>> more news articles](#)

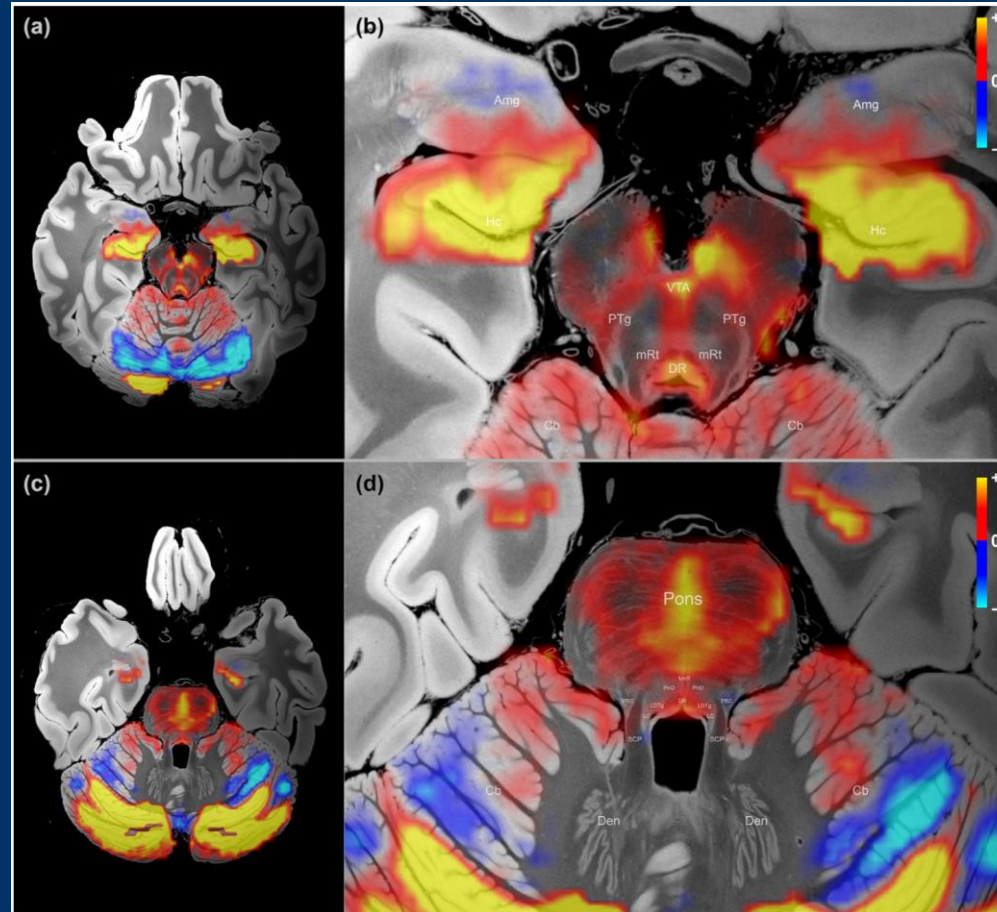
Powered by [LONI](#) & Martinos Center for Biomedical Imaging

Human Connectome Project funded by National Institute of Health

Default Mode Network



The warm color (yellow/orange) indicates positive association or correlation with the DMN, and the cold color (blue) indicates negative association or anti-correlation with the DMN



ADHD symptomatology has been hypothesized to be due to the intrusion of Default Mode Network (DMN) activity over task-related networks (also called “task-positive” networks; Sonuga-Barke & Castellanos, 2007)

DMN has been linked to mind-wandering, remembering past events, planning the future, considering the perspectives of others (Buckner, Andrews-Hanna, & Schacter, 2008), and its function is attenuated during externally oriented cognition (Andrews-Hanna, Reidler, Huang, & Buckner, 2010).

Brain networks that are active when we are not doing anything; not engaged in any kind of tasks

Communicating with DMN networks

Medial prefrontal cortex, posterior cingulate cortex, lateral parietal lobe

These areas are not working in synchrony in ADHD, lack of sleep

Medications in treating patients with ADHD

تازه های درمان دارویی در درمان اختلال نقص تمرکز بیش فعالی

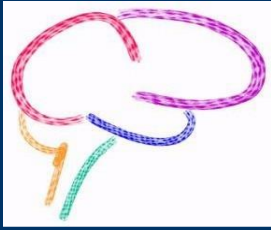
prevalence

10-12 percent of children worldwide

Increasing recognition of adult ADHD:

Could be due to undiagnosed ADHD in children cropping up in adulthood ➤

The way we interact with the world (smart phone use, the combination email, text, real world interactions, multiple apps and streams of media and social media all coming at once trying to manage life) creates clouds of pulls on our attention ➤



Executive Function in ADHD

Linking Goals → Strategies → Actions

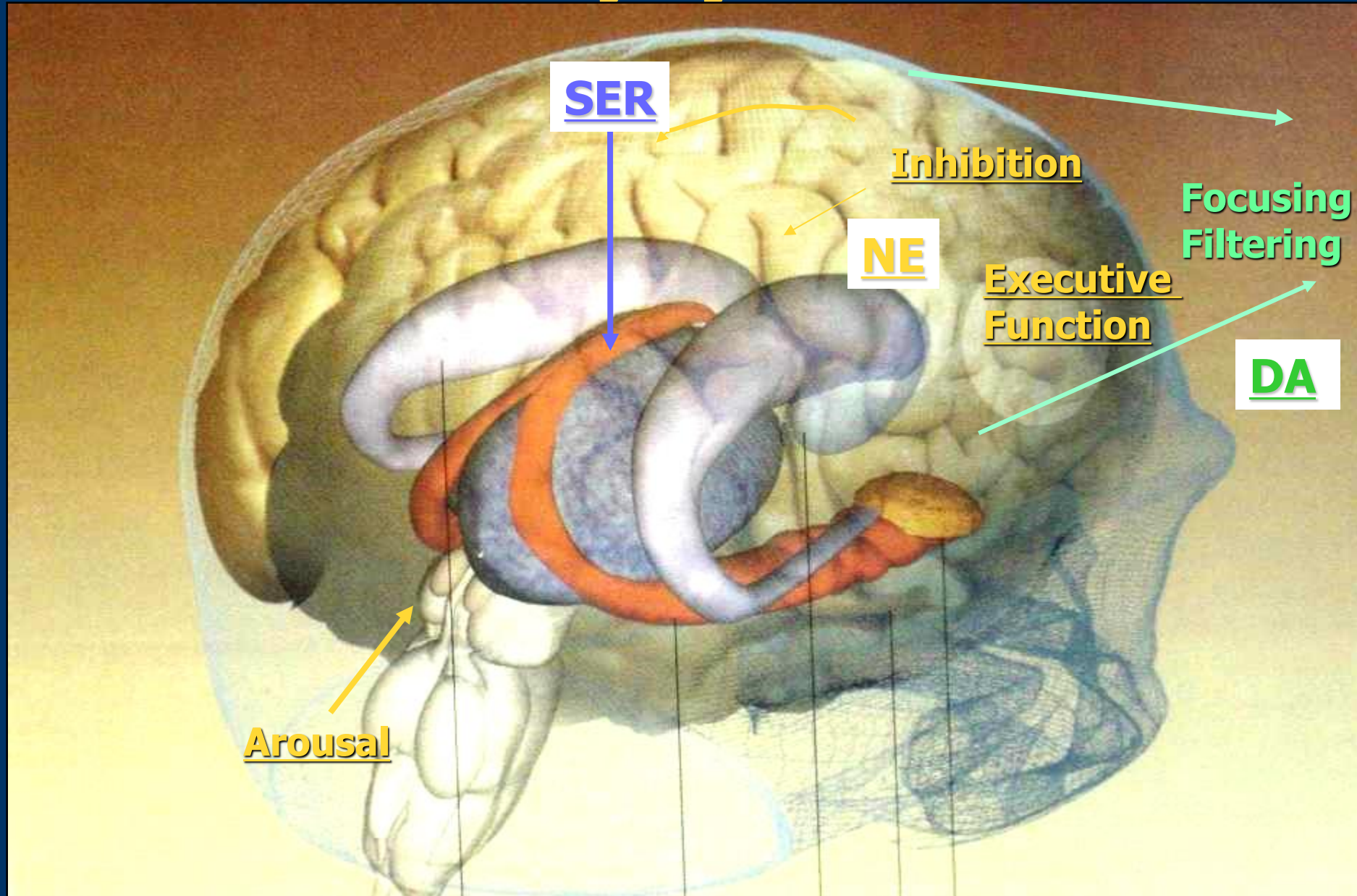


Creativity
Productivity
Identity

Role of DA and NE in ADHD

**Neurotransmitters in psychopathology
and treatment**

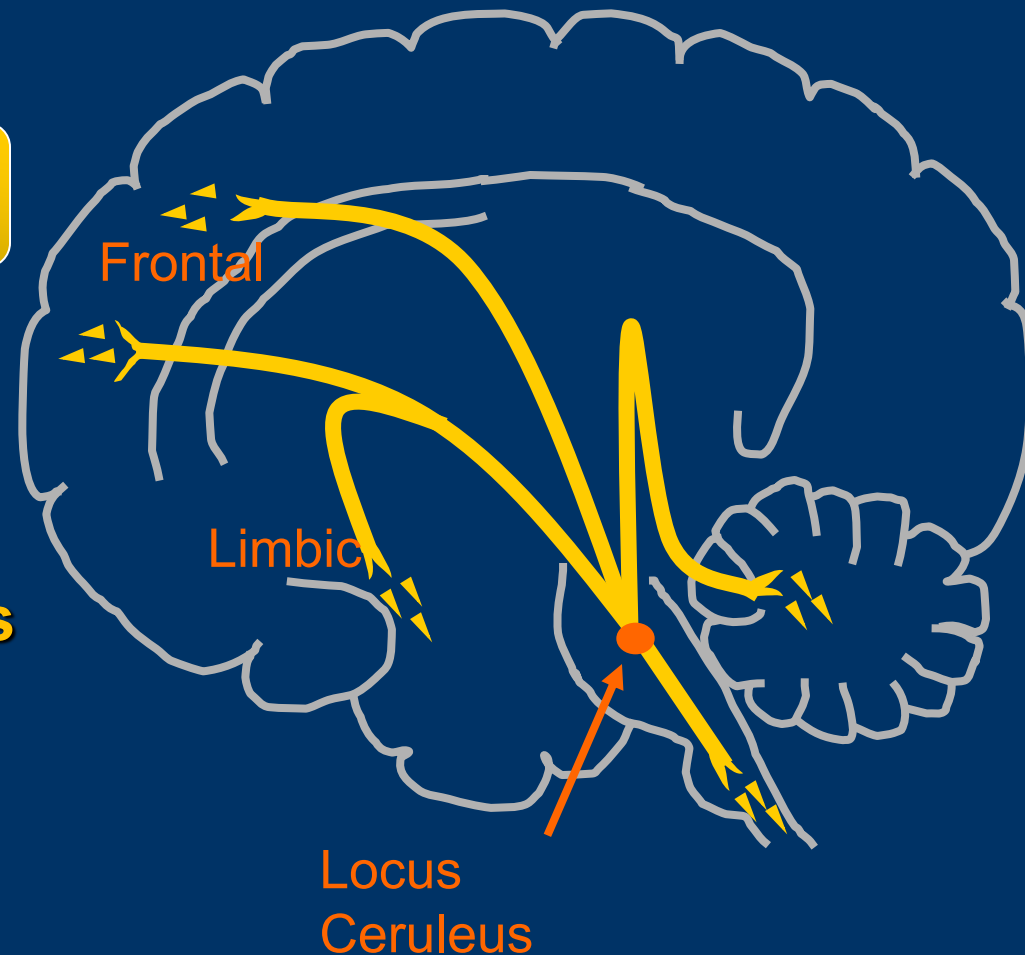
Core Modulatory Systems

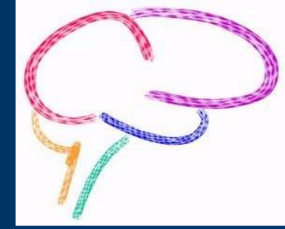


Neurotransmission Relative to ADHD

Norepinephrine

- Dampens noise
- Executive operations
- Increases inhibition





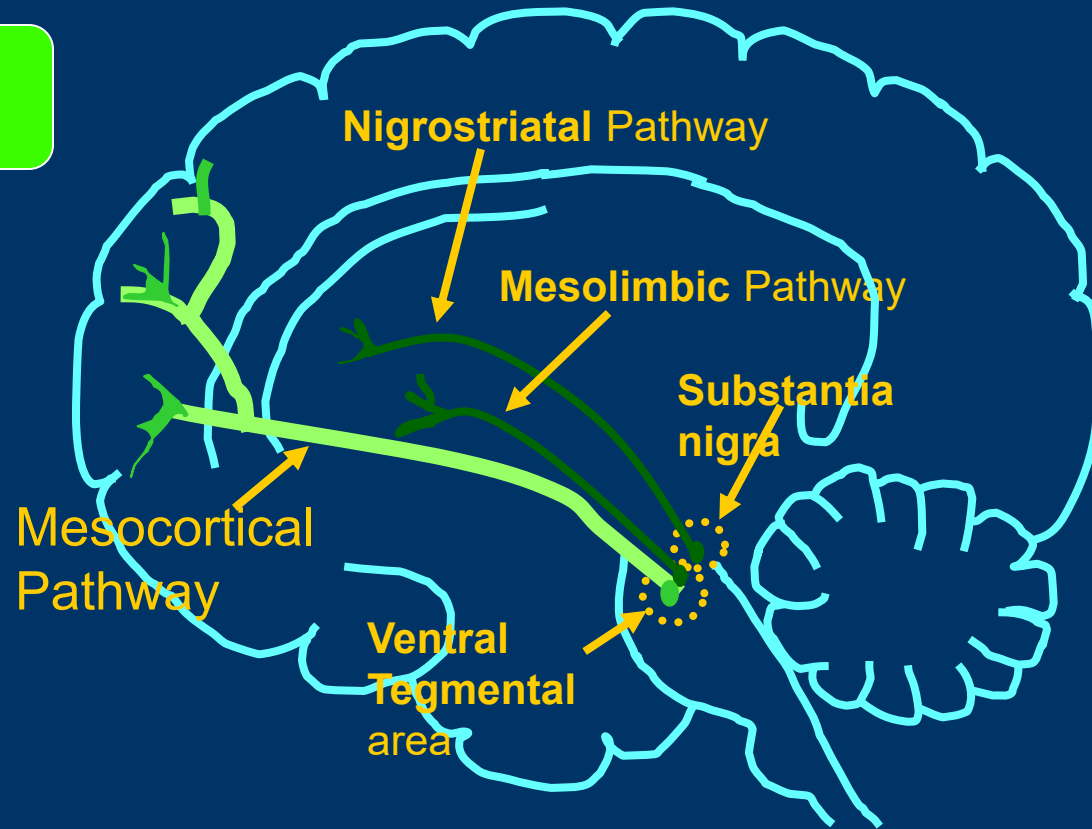
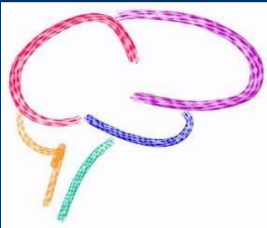
Essential Roles of NE

- Arousal
 - Alerting & Energy
 - Acute Response
- Executive Function
 - Prioritization & Sequencing
 - Memory storage and retrieval
 - Meaning & Significance
- Inhibition
 - Cortical Sensory Down-regulation
 - Decreases Distractibility
when paying attention to something else.

Dopamine Neurotransmission Relative to ADHD

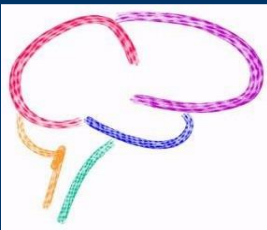
Dopamine

- Enhances signal
- Improves attention
 - Focus
 - On-task behavior
 - On-task cognition

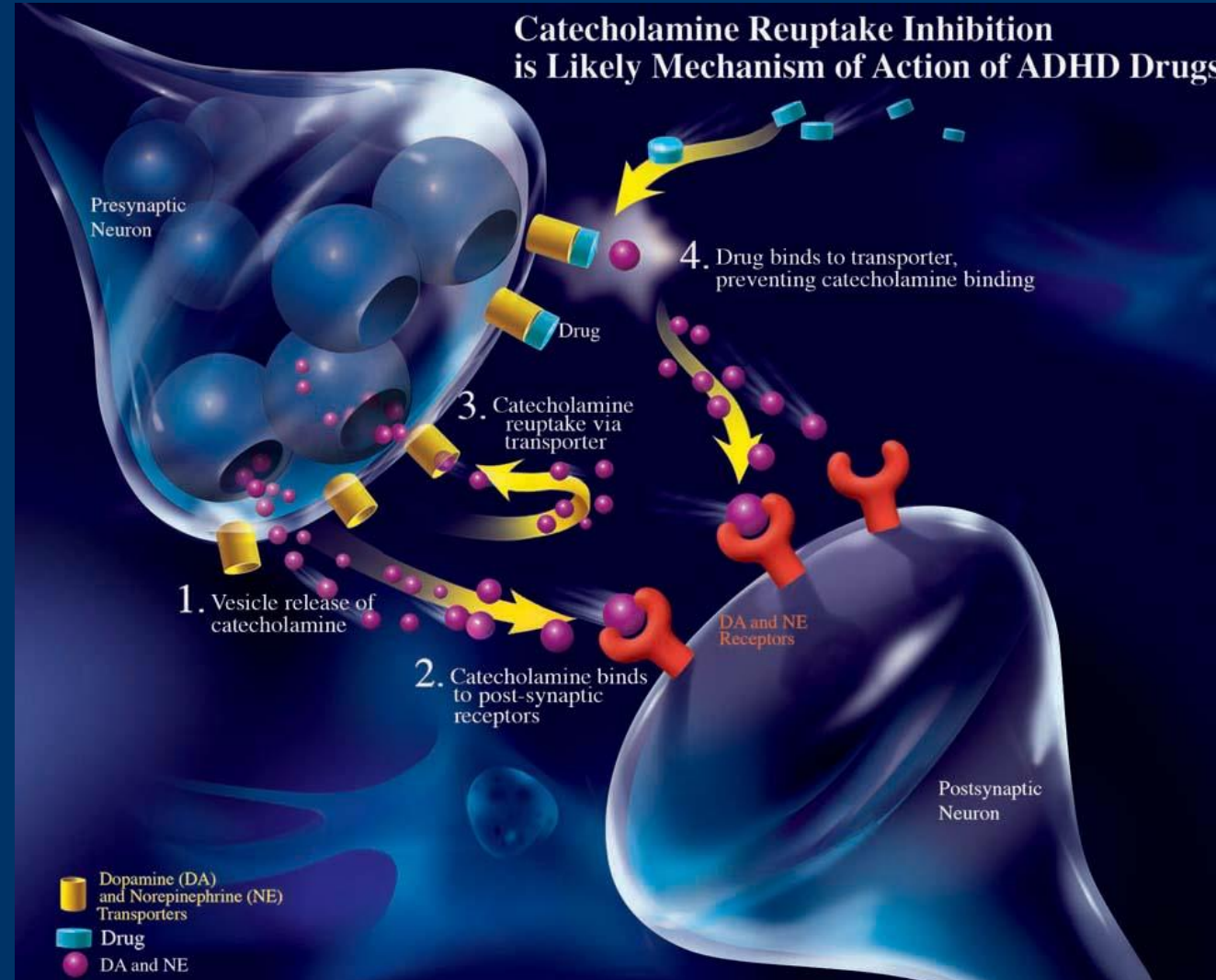


Dopamine

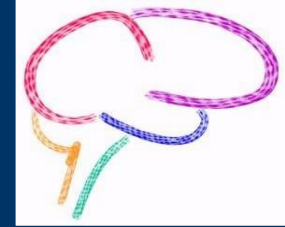
- Role in ADHD
 - *Focusing of Attention*
 - *Activation of Executive Function*
 - *Decrease Distractibility*
 - Dopamine typically *inhibitory* tonically (PFC)
 - *Reward & Pleasure → Meaning & Purpose*



Catecholamine Reuptake Inhibition is Likely Mechanism of Action of ADHD Drugs



Contrasting Effects on Attention



RITALIN

Narrower

Both

- Attention
- Organization
- Behavior

ADDERALL

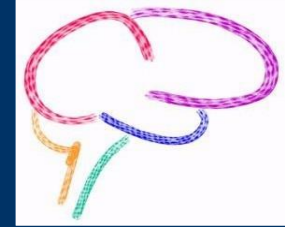
Wider

- More Inhibiting
- Less Affect, Fixed
- Less (-) Social

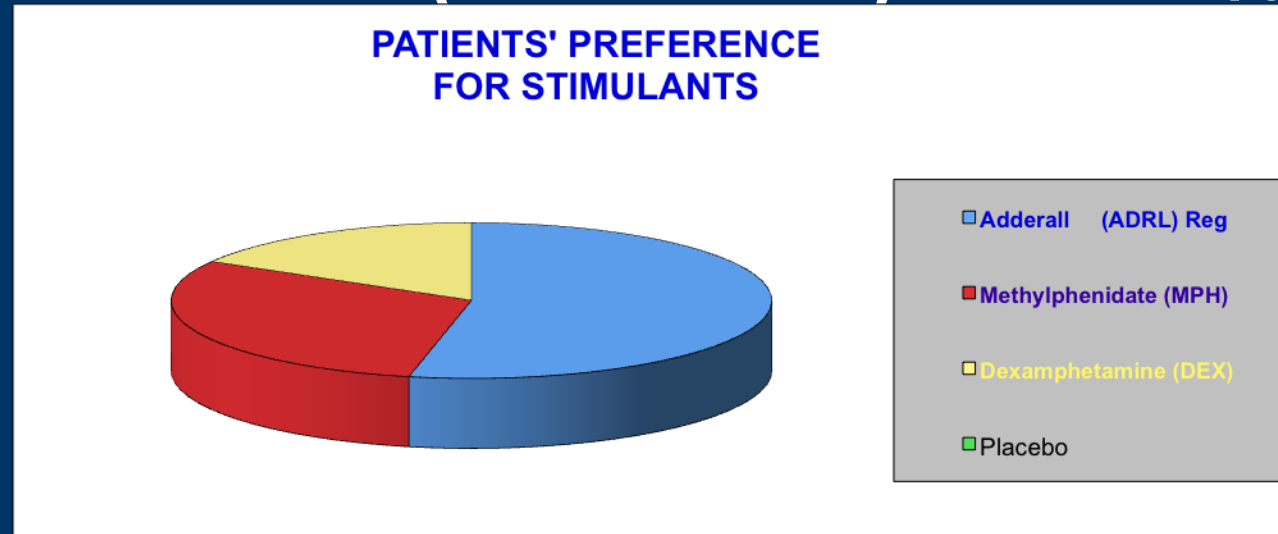
- More Activating
- More Affect; Flexible
- More + Social

RESULTS:

PREFERENCE for STIMULANTS



- Overall patient preference favored
 - AMPH (Adderall) = 55 %
- About equivalent number preferred
 - MPH (Ritalin) = 22%
 - DEXAMPH (Dexedrine) = 19%



Clinical Differences MPH vs AMPH

Methylphenidate

- Activation – Energy
 - Less
- Task Flexibility
 - Less → one thing
- Neurotransmitters
 - DA >> NE

Amphetamine

- Activation – Energy
 - Greater
- Task Flexibility
 - Greater → multitask
- Neurotransmitters
 - DA > NE >> Ser.

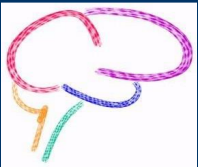


Task Differentiation

Single Tasking – *MPH*
Ritalin



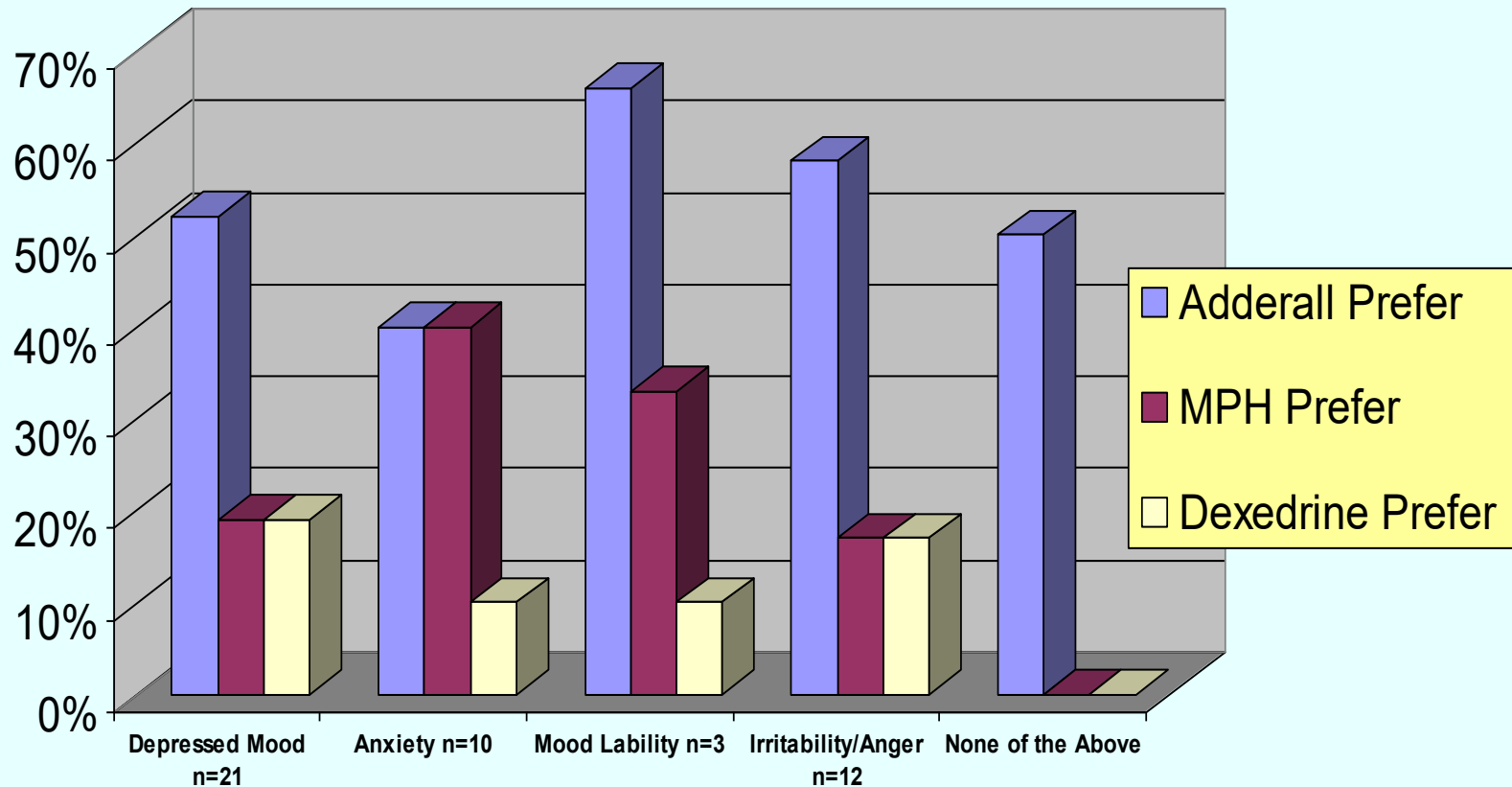
Multitasking – AMPH
Adderall



Personality Characteristics

PERSONALITY CHARACTERISTICS & STIMULANT MEDICATION PREFERENCES

in 30 Adults with ADD



Clinical Preference for MAS (Adderall XR) vs MPH (Concerta)

1. Increased Cognitive Flexibility

- Less perseveration
- Greater Creativity – Flexible Problem-Solving

2. Enhanced Energy

- More alert, Engaged
- Greater Perseverance

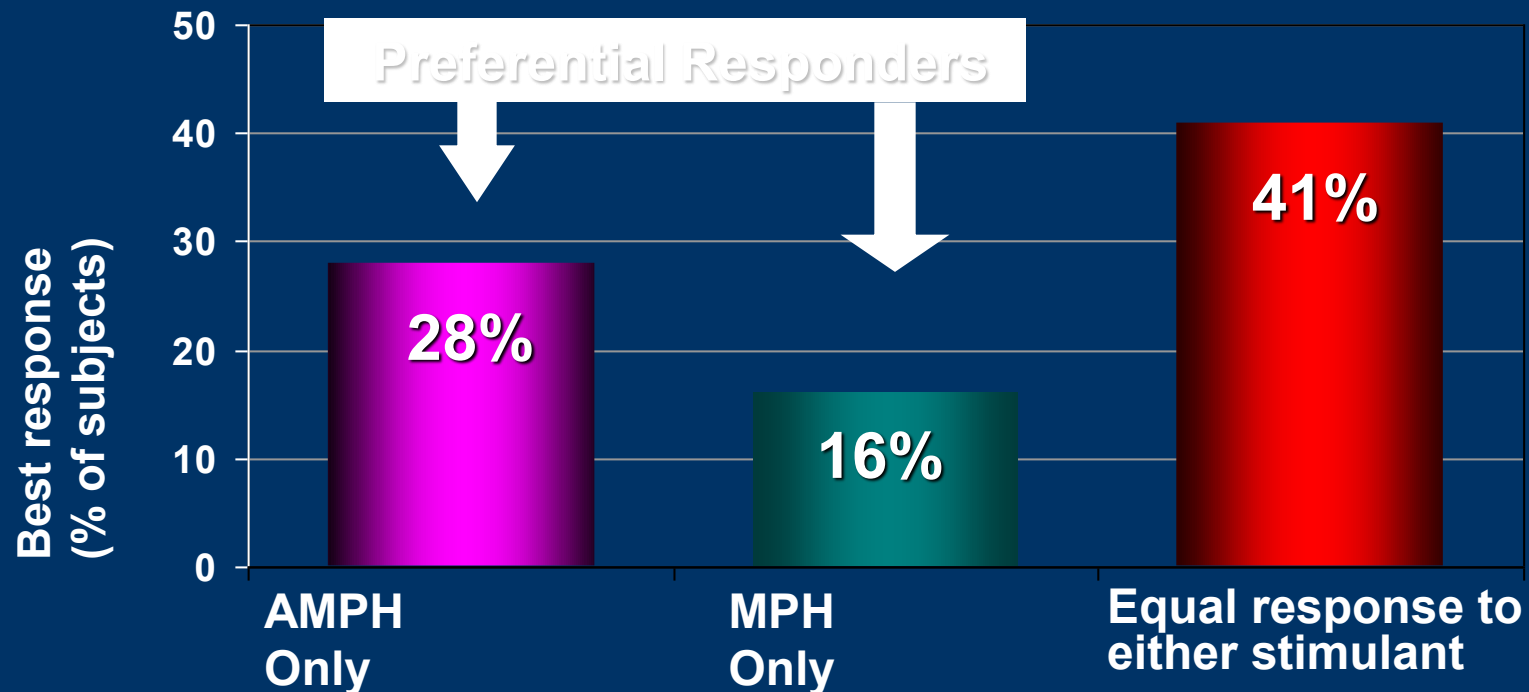
3. Social Interaction

- Enhanced Involvement
- Better Social Processing
- More interactive / Engaged



No Single Stimulant is Best

Meta-Analysis of Within-subject Comparative Trials Evaluating Response to Stimulant Medications



Arnold et al. *J Attention Dis.* 2000;3:200.

AMPH=amphetamine.
MPH=methylphenidate.



Medication Management

Do Your Own Clinical Trial

Optimize Treatment Response

— Find the Best *Medication*

- Preferential Responder - AMPH / MPH
- *Personality* Factors
- *Developmental* Factors

— Find the Best *Dose*

- *Duration* of Action
- *Task* Performance

— Find the Best *Response*

- *Behavioral* Control
- *Social* Functioning
- *Creativity & Organization*

**What are the mode of action
of pharmacological
treatments for ADHD**

Hypothesized mode of action of pharmacological treatments for ADHD

Stimulants



Methylphenidate

Targets the DAT and the NET, inhibiting DA and NA reuptake, thereby increasing DA and NA levels in the synaptic cleft²⁴⁻³¹



Amphetamine

Targets the DAT and the NET, inhibiting DA and NA reuptake, thereby increasing DA and NA levels in the synaptic cleft^{24,25,32-34}
Also binds VMAT2, promoting the release of DA into the synapse³⁵⁻³⁷

Non-stimulants



Atomoxetine

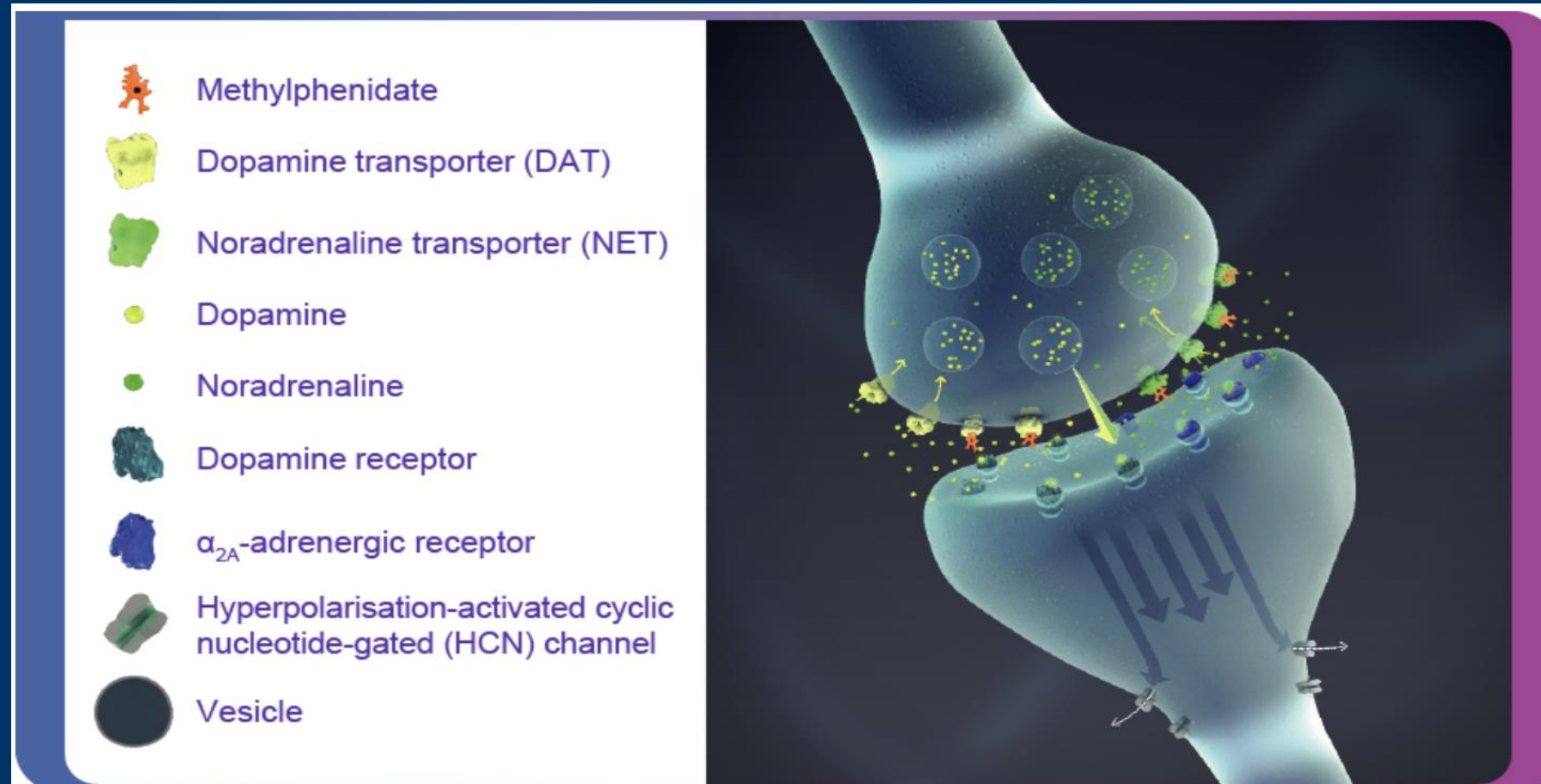
Targets the NET, inhibiting the reuptake of NA, therefore increasing NA levels in the synaptic cleft^{38,39}



Guanfacine

Binds to postsynaptic α_2A -adrenergic receptors, mimicking NA⁴⁰

Hypothesized mode of action of methylphenidate



Hypothesized mode of action of pharmacological treatments for ADHD

Stimulants



Methylphenidate

Targets the DAT and the NET, inhibiting DA and NA reuptake, thereby increasing DA and NA levels in the synaptic cleft²⁴⁻³¹



Amphetamine

Targets the DAT and the NET, inhibiting DA and NA reuptake, thereby increasing DA and NA levels in the synaptic cleft^{24,25,32-34}
Also binds VMAT2, promoting the release of DA into the synapse³⁵⁻³⁷

Non-stimulants



Atomoxetine

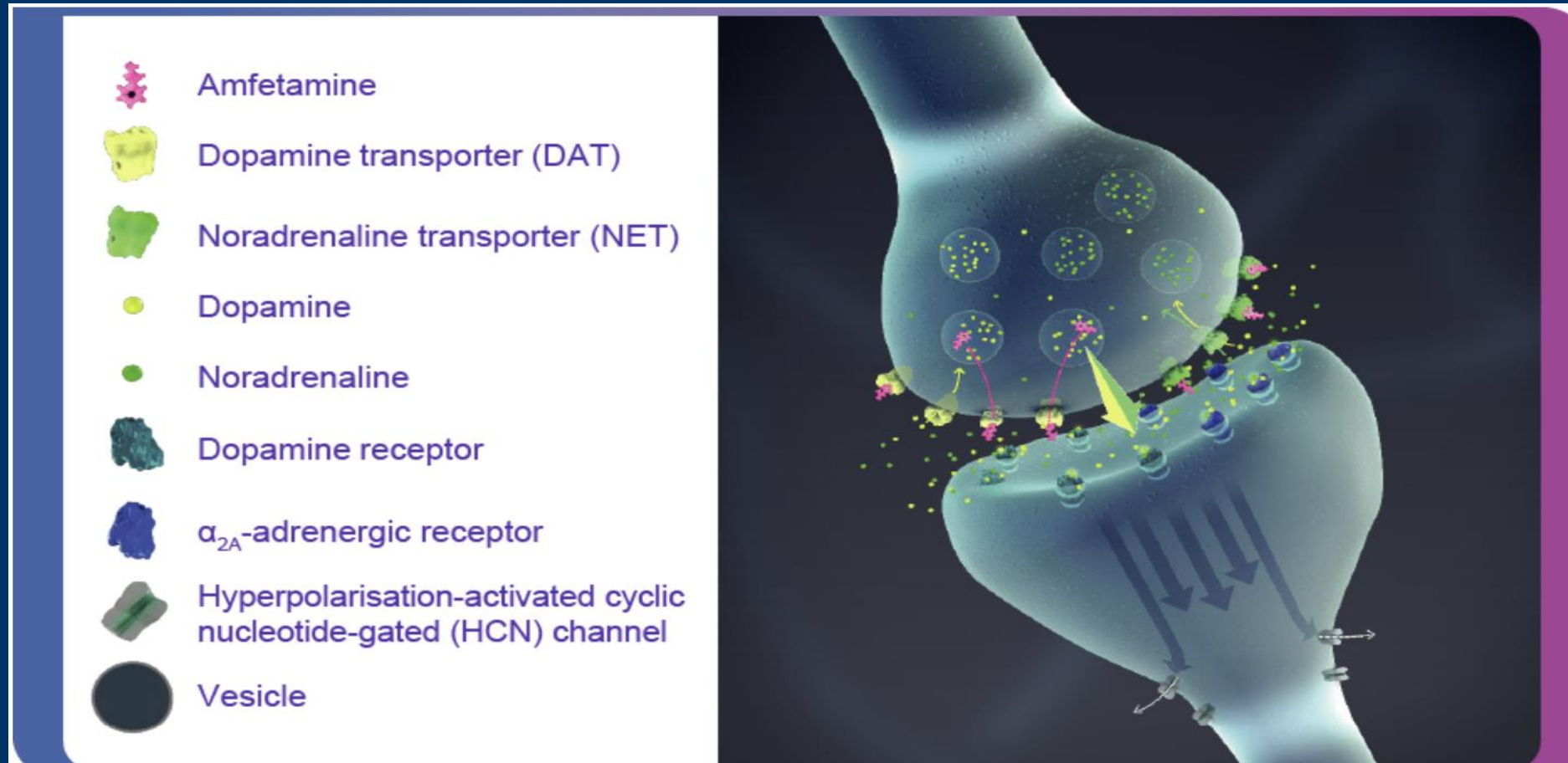
Targets the NET, inhibiting the reuptake of NA, therefore increasing NA levels in the synaptic cleft^{38,39}



Guanfacine

Binds to postsynaptic α_2A -adrenergic receptors, mimicking NA⁴⁰

Hypothesized mode of action of amphetamine



Hypothesized mode of action of pharmacological treatments for ADHD

Stimulants



Methylphenidate

Targets the DAT and the NET, inhibiting DA and NA reuptake, thereby increasing DA and NA levels in the synaptic cleft²⁴⁻³¹



Amphetamine

Targets the DAT and the NET, inhibiting DA and NA reuptake, thereby increasing DA and NA levels in the synaptic cleft^{24,25,32-34}
Also binds VMAT2, promoting the release of DA into the synapse³⁵⁻³⁷

Non-stimulants



Atomoxetine

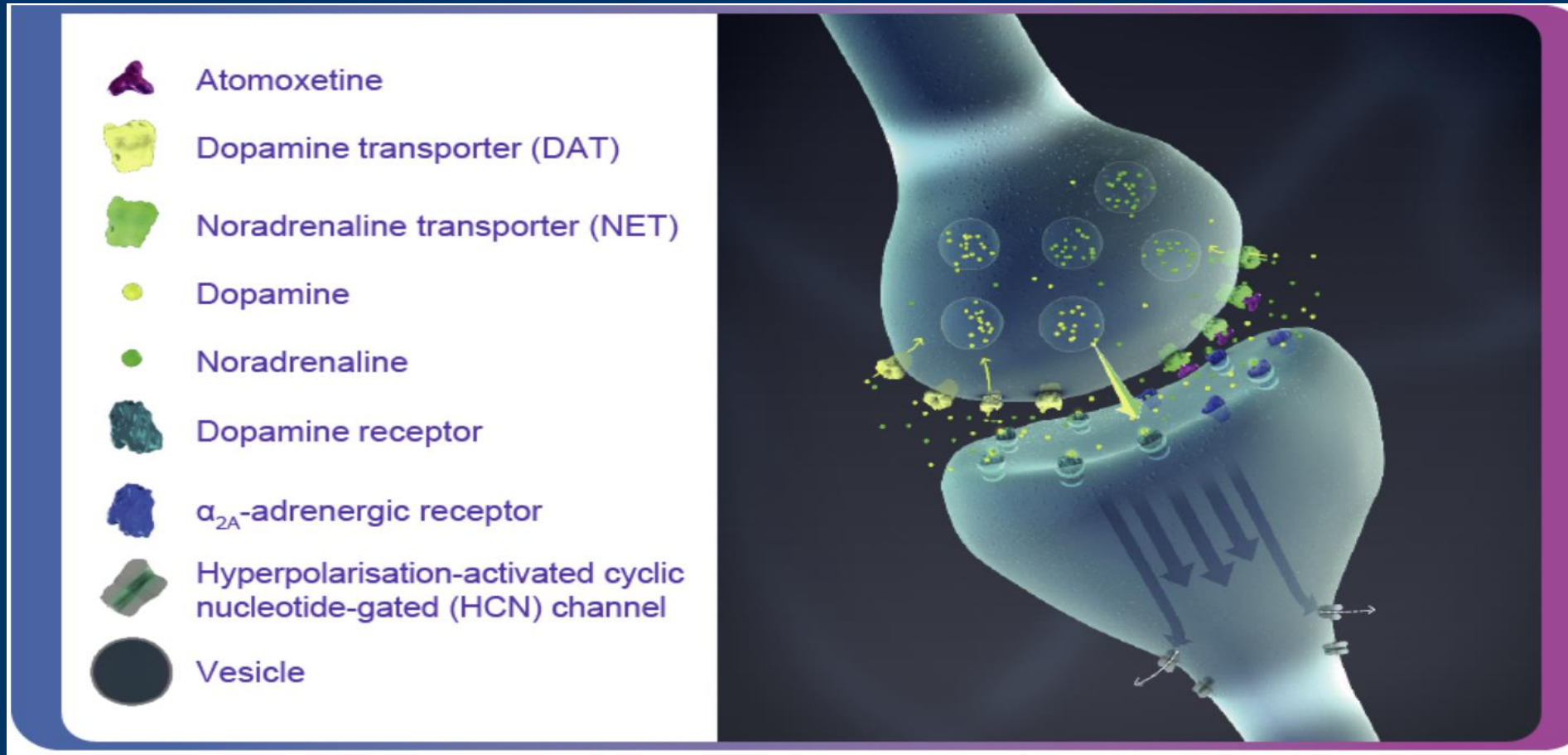
Targets the NET, inhibiting the reuptake of NA, therefore increasing NA levels in the synaptic cleft^{38,39}



Guanfacine

Binds to postsynaptic α_2A -adrenergic receptors, mimicking NA⁴⁰

Hypothesized mode of action of atomoxetine



Hypothesized mode of action of pharmacological treatments for ADHD

Stimulants



Methylphenidate

Targets the DAT and the NET, inhibiting DA and NA reuptake, thereby increasing DA and NA levels in the synaptic cleft²⁴⁻³¹



Amphetamine

Targets the DAT and the NET, inhibiting DA and NA reuptake, thereby increasing DA and NA levels in the synaptic cleft^{24,25,32-34}
Also binds VMAT2, promoting the release of DA into the synapse³⁵⁻³⁷

Non-stimulants



Atomoxetine

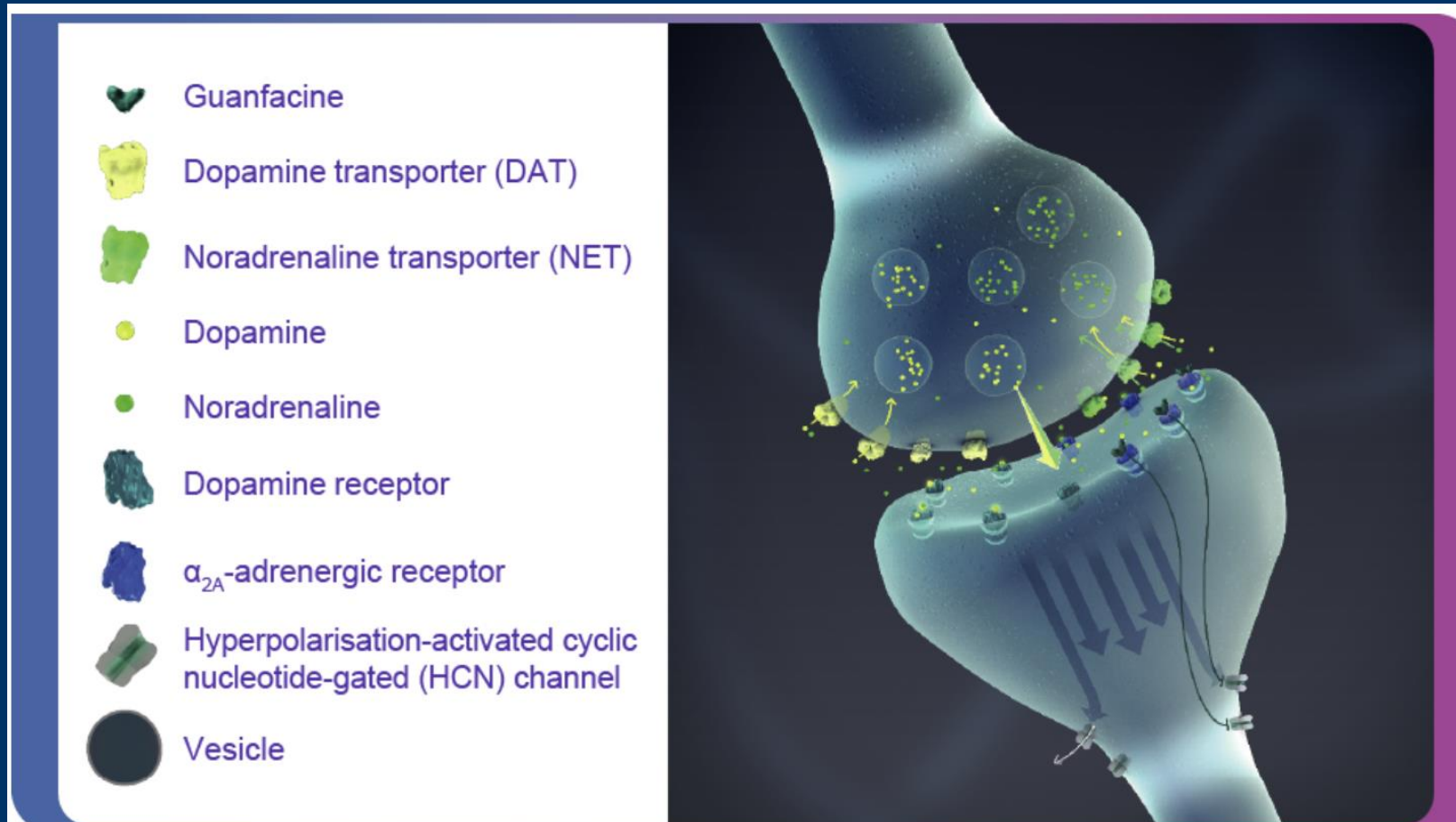
Targets the NET, inhibiting the reuptake of NA, therefore increasing NA levels in the synaptic cleft^{38,39}



Guanfacine

Binds to postsynaptic α_2A -adrenergic receptors, mimicking NA⁴⁰

Hypothesized mode of action of guanfacine



**How does the mechanism of
delivery differ between
pharmacological therapies for
ADHD?**

Immediate-release tablets or capsules are the most widely used drug-delivery systems.

They are designed to undergo disintegration in the stomach into smaller granules and subsequent dissolution in the fluids of the gastrointestinal tract.

Extended-release formulations are designed to produce slow, uniform absorption of the drug.

Multiple bead system consists of a water-soluble gelatin capsule that dissolves quickly once swallowed, releasing drug-containing beads of two different dissolution rates.

Multiple bead formulations release a steady level of drug into the bloodstream, allowing for once-daily dosing.

Once-daily dosing has practical advantages, particularly in young individuals, and the potential for stimulant abuse may be lower for extended-release formulations compared with immediate-release formulations.

Osmotic-controlled release oral delivery system is designed to provide a longer duration of effect than the multiple bead system.

For example, methylphenidate is available in this formulation.

The outer layer of the capsule is coated with methylphenidate, which quickly releases once the pill is ingested.

The inner layers are set up along an osmotic gradient; the first compartment, with a small amount of the drug, releases via simple diffusion, but the second compartment, with a higher amount of the drug, releases as a result of the osmotic pressure created when water reacts with the third compartment.

Prodrugs are pharmacologically inactive molecules that are converted into one or more active metabolites through a natural metabolic process.

Prodrugs are designed to enhance the attributes of the active drug, such as enhanced solubility, increased or enhanced absorption and distribution and prolonged systemic availability.

Lisdexamfetamine dimesylate is a prodrug where lysine is covalently linked to amphetamine and the drug only becomes active after lysine is cleaved by enzymes in the bloodstream.

The lisdexamfetamine prodrug becomes active only after it has been absorbed by the intestinal tract and has been converted to dextroamphetamine and *l*-lysine.

New medications

Azstarys

Serdexmethylphenidate/dexmethylphenidate

Dexmethylphenidate: Catecholamine reuptake inhibitor

Serdexmethylphenidate: Prodrug of dexmethylphenidate

Significant ADHD Symptom Improvement with 30-Minute Onset and 13-Hour Duration of Efficacy Delivered by Once-Daily Corium Product

Qelbree

viloxazine extended-release capsules

noradrenergic medication

Comes in capsule form; parents can break open the capsules and sprinkle the contents of a Qelbree capsule into a teaspoonful of applesauce.

Quick onset

Extended-release formulation

New horizon in treatment

EndeavorRx

New trends in ADHD treatment

EndeavorRx is an ADHD treatment for kids aged 8-12.

It's delivered through an immersive video game experience on mobile devices

However, It is not intended as a stand-alone therapeutic, nor is it a substitute for medication.

How can clinicians improve adherence to pharmacological therapies for ADHD?

Psychoeducation and an individual's acceptance of their ADHD may help adherence to pharmacotherapy, particularly in adolescents

The decision regarding which medication is used to treat ADHD may depend on a range of factors, including:

presence of psychiatric comorbidities;

undesirable effects of the medication;

individual compliance needs; potential for drug diversion;

and the personal preference of the individual and their family or carers.

Adherence to pharmacological therapy for ADHD can be suboptimal, which may negatively affect treatment outcomes.

For example, individuals with ADHD and their families may think that a pharmacotherapy has less than optimal effectiveness and is associated with intolerable adverse effects, which may contribute to poor adherence.

Psychoeducation and an individual's acceptance of their ADHD may help adherence to pharmacotherapy, particularly in adolescents.

In support of this, adolescents' perceptions of the degree of stigma associated with ADHD have been reported to affect receptiveness to treatment.

Multiple daily doses of medication, including dosing during school hours, could also be considered a source of embarrassment for some students with ADHD.

Moreover, ADHD-related forgetfulness may cause difficulty in adhering to a treatment plan that requires multiple daily doses; therefore, for some individuals once-daily dosing may be more helpful.

It is recommended that clinicians ensure that individuals with ADHD are fully informed of the balance of risks and benefits of any treatment for ADHD, and check that problems with adherence are not due to misconceptions.

Encourage people with ADHD to be responsible for their own health, including taking their medication as needed.

Provide the individual with clear instructions about how to take their medication in picture or written format. This information may include dose, duration, adverse effects and dosage schedule.

Advise the individual to use visual reminders to take their medication regularly (e.g. alarms, apps, clocks, pill dispensers or notes on calendars or fridges).

Suggest that the individual takes their medication as part of their daily routine (e.g. before meals or after brushing their teeth).

Encourage the individual with ADHD and their family or carers to attend peer support groups and encourage parents or carers to oversee ADHD medication for children and adolescents.

دارو را چه زمانی قطع کنیم؟

برای قطع یا کاهش دوز دارو توجه به موارد زیر می توانست کمک کننده باشند

- کودک بیش از یک سال است که دارو مصرف می کند و علایمی ندارد.
- علائم کودک مبتلا بهتر و بهتری شود، اما دوز دارو ثابت مانده باشد،
- رفتار کودک مبتلا با وجود فراموش کردن یک یا دو دوز دارو، مناسب باشد،
- کودک مبتلا توانایی جدیدی برای تمرکز پیدا کرده باشد.