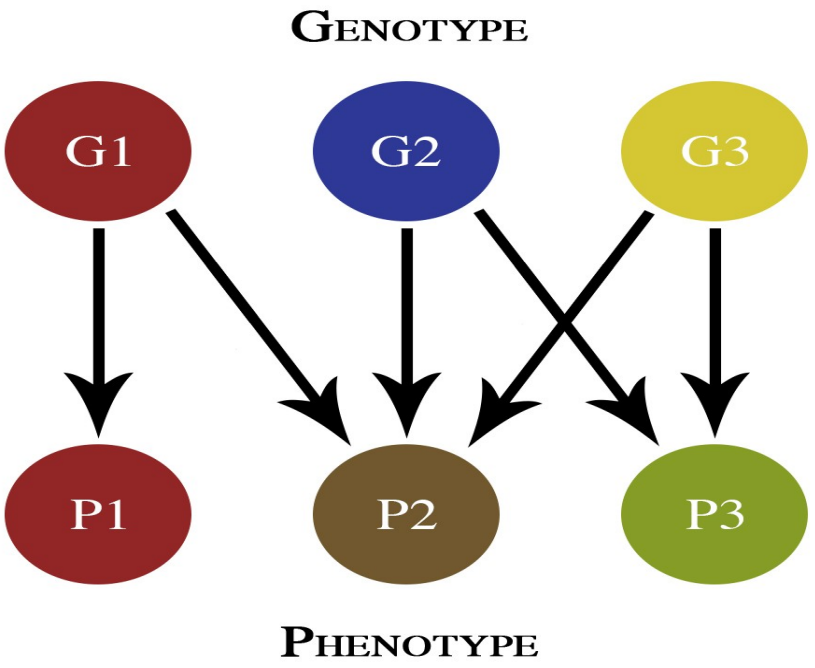
# Neuropsychiatric patologi

- Working memory
  - Executive disabilities
- Inhibition
  - Impulsivity
- Response variability
  - Unstabile arousel/sustanied attention
- Delay aversion
  - Motivation

# Attention

# Pleiotropy



# specificitet

- DNA  Pathology
- Protein
- Neurobiology
- Neurophysiology
- Neuropsychology
- Behaviour  Symptomatology

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# The World Federation of ADHD International Consensus Statement: 208 Evidence-based conclusions about the disorder

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| Findings | Items |
|---|---|
| The syndrome we now call ADHD has been described in the medical literature since 1775. | 1–13 |
| When made by a licensed clinician, the diagnosis of ADHD is well-defined and valid at all ages, even in the presence of other psychiatric disorders, which is common. | 14–19 |
| ADHD is more common in males and occurs in 5.9 % of youth and 2.5 % of adults. It has been found in studies from Europe, Scandinavia, Australia, Asia, the Middle East, South America, and North America. | 20–25 |
| ADHD is rarely caused by a single genetic or environmental risk factor but most cases of ADHD are caused by the combined effects of many genetic and environmental risks each having a very small effect. | 26–62 |
| People with ADHD often show impaired performance on psychological tests of brain functioning, but these tests cannot be used to diagnose ADHD. | 63–70 |
| Neuroimaging studies find small differences in the structure and functioning of the brain between people with and without ADHD. These differences cannot be used to diagnose ADHD. | 71–77 |
| People with ADHD are at increased risk for obesity, asthma, allergies, diabetes mellitus, hypertension, sleep problems, psoriasis, epilepsy, sexually transmitted infections, abnormalities of the eye, immune disorders, and metabolic disorders. | 78–100 |
| People with ADHD are at increased risk for low quality of life, substance use disorders, accidental injuries, educational underachievement, unemployment, gambling, teenage pregnancy, difficulties socializing, delinquency, suicide, and premature death. | 101–136 |
| Studies of economic burden show that ADHD costs society hundreds of billions of dollars each year, worldwide. | 137–147 |
| Regulatory agencies around the world have determined that several medications are safe and effective for reducing the symptoms of ADHD as shown by randomized controlled clinical trials. | 148–157 |
| Treatment with ADHD medications reduces accidental injuries, traumatic brain injury, substance abuse, cigarette smoking, educational underachievement, bone fractures, sexually transmitted infections, depression, suicide, criminal activity and teenage | 158–177 |

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Original article

# Updated European Consensus Statement on diagnosis and treatment of adult ADHD

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health conditions.

DSM-IV required that symptoms and impairment were present before age 7, but as research demonstrated no differences between children with an age of onset before and after age 7 [106] this criterion was changed to several symptoms by age 12. Similar findings have also been reported regarding adults reporting later-onset of symptoms [107,108], and there is disagreement both within and across sources concerning recall of symptom onset [109]. The fact that adults with ADHD frequently fail to recall childhood behavior led to the suggestion that clinicians take note that the onset of the disorder was during the developmental period, or they should use age 16 years as the upper age limit. Using this criteria captured all cases of childhood ADHD and 99% of adults with the disorder [110]. The decision of DSM-5 to extend the age of onset to 12 instead of 16 may have a negative impact on adults with ADHD who have difficulties with retrospective recall of childhood behaviors, and may not receive the diagnosis for this reason. This may be particularly true for those who had some compensation due to high intelligence, or lived in a highly structured or supported environment, or presented predominantly with inattentive symptoms. In such cases, the presence of a collateral informant (generally a parent or spouse) is of great value. Many adults with ADHD that are used to their lifelong symptoms, have limited awareness of how ADHD symptoms adversely impact their interpersonal relationships and affect their life; some reporting higher symptoms but lower impairments or vice versa.

Such inconsistency has been attributed to a lack of introspection and an incoherent self-view [111,112], and supports the utility of a collateral informant. If a significant other is not available, school reports or social care reports may be helpful.

the disorder.

Clinicians should also be aware that high functioning adults with ADHD may not present with a typical pattern of functional impairments in their daily life. Adaptive or compensatory skills can develop that mask the more overt behavioral problems related to ADHD [150]. Some may find work that is well suited to their symptom profile. Furthermore, in ADHD neurocognitive performance and inattentive symptoms are sensitive to the salience of task activities [151,152]. Such people with ADHD may excel in certain aspects of their lives, but still be impaired in others, such as more routine and mundane tasks such as paying bills, looking after the house, or developing stable social relationships. Problems can include subjective distress from symptoms such as mental and physical restlessness, sleep problems, and emotional instability; and the use of drugs such as cannabis or alcohol to reduce these symptoms.

Adult diagnoses may be missed in clinical practice due to lack of knowledge about ADHD in adulthood among practitioners and due to the high frequency of comorbid psychiatric conditions [201]. The lifetime co-morbidity rate is 60–80%. Having three or more disorders was associated with a ten-fold increase of the chance of having ADHD in a population study in 20 countries [3]. Before treatment start, all comorbidities must be established so that the best order of treatment can be determined together with the patient. In the study by Fayyad et al, data on ADHD and comorbidities was collected on 26,744 respondents [202]. In adults with ADHD having one comorbidity was found in 23% of cases, two in 14% of cases and three in 14% of cases. Rates were particulary high for any mood disorder (22%), any anxiety disorder (34%), substance use disorders (11%) and any behavioural disorder (15%).

Psychiatric comorbidity is thus a clinically important dimension of ADHD heterogeneity and a factor that contributes to the persistence of ADHD in adulthood [203,204]. It is important for the diagnosis of ADHD, as well as the correct targeting of treatments, to identify mood, anxiety, eating, sleep, somatic and substance use disorders, in addition to personality, tic and autistic spectrum disorders [205]. Because adults with ADHD often exhibit low self-esteem, low mood, mood lability and irritability, these symptoms may sometimes be confused with dysthymia, cyclothymia, bipolar disorder or borderline personality disorder. Furthermore, daily mood changes in ADHD are very common, and represent a poorly regulated but essentially normal range of moods, rather than the more severe extremes of depression and elation as seen in bipolar disorder. It has been argued that chronic mood instability should be considered part of the core syndrome of ADHD [206,207]. ADHD and borderline personality disorder share symptoms of impulsivi-

Attention-deficit hyperactivity disorder 2

# Adult attention-deficit hyperactivity disorder: key conceptual issues

*Philip Asherson, Jan Buitelaar, Stephen V Faraone, Luis A Rohde*

**For many years, attention-deficit hyperactivity disorder (ADHD) was thought to be a childhood-onset disorder that has a limited effect on adult psychopathology. However, the symptoms and impairments that define ADHD often affect the adult population, with similar responses to drugs such as methylphenidate, dexamphetamine, and atomoxetine, and psychosocial interventions, to those seen in children and adolescents. As a result, awareness of ADHD in adults has rapidly increased and new clinical practice has emerged across the world. Despite this progress, treatment of adult ADHD in Europe and many other regions of the world is not yet common practice, and diagnostic services are often unavailable or restricted to a few specialist centres. This situation is remarkable given the strong evidence base for safe and effective treatments. Here we address some of the key conceptual issues surrounding the diagnosis of ADHD relevant to practising health-care professionals working with adult populations. We conclude that ADHD should be recognised in the same way as other common adult mental health disorders, and that failure to recognise and treat ADHD is detrimental to the wellbeing of many patients seeking help for common mental health problems.**

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This is the second in a Series of two papers about attention-deficit hyperactivity disorder

**MRC Social Genetic and Developmental Psychiatry, Institute of Psychiatry**

## *Panel 3*: Key points and conclusions

**Main findings**

- Adult ADHD is a common mental health problem affecting 2·5–3·4% of the adult population
- Undiagnosed ADHD is found in 10% or more of non-psychotic patients attending general adult, addiction, and prison mental health services
- Beyond the core symptoms of inattention and hyperactivity-impulsivity, ADHD is characterised by a wide range of mental health symptoms and impairments including initial sleep insomnia, excessive mind-wandering, restlessness, emotional instability, and behaviour showing difficulty with executive functions
- ADHD symptoms and impairments can mimic other common mental health disorders, leading to incorrect diagnoses and targeting of treatments
- The treatment response of adult ADHD symptoms and impairments to stimulants and atomoxetine shows these drugs to be among the most effective pharmacological treatments for any mental health disorder
- Pharmacoepidemiological studies show reductions in criminal convictions, accidental injuries, substance misuse, and suicides after treatment of ADHD

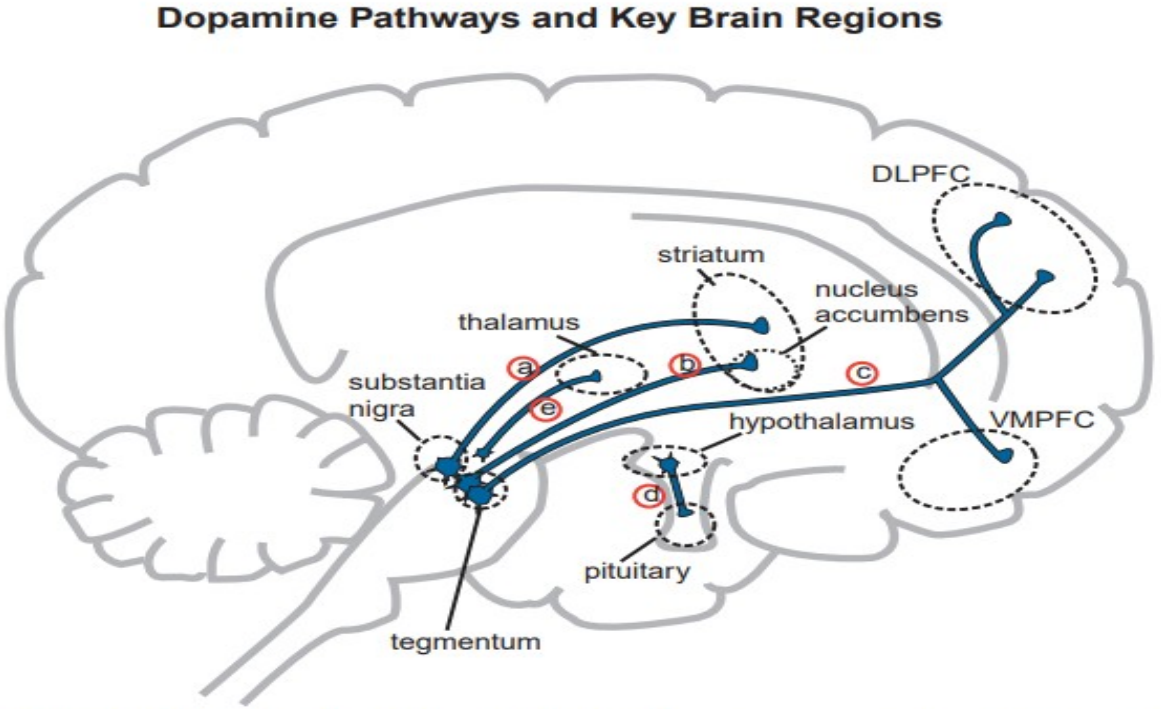



**Figure 4-11. Five dopamine pathways in the brain.** The neuroanatomy of dopamine neuronal pathways in the brain can explain the symptoms of schizophrenia as well as the therapeutic effects and side effects of antipsychotic drugs. (a) The **nigrostriatal dopamine pathway**, which projects from the substantia nigra to the basal ganglia or striatum, is part of the extrapyramidal nervous system and controls motor function and movement. (b) The **mesolimbic dopamine pathway** projects from the midbrain ventral tegmental area to the nucleus accumbens, a part of the limbic system of the brain thought to be involved in many behaviors such as pleasurable sensations, the powerful euphoria of drugs of abuse, as well as delusions and hallucinations of psychosis. (c) A pathway related to the mesolimbic dopamine pathway is the **mesocortical dopamine pathway**. It also projects from the midbrain ventral tegmental area but sends its axons to areas of the prefrontal cortex, where they may have a role in mediating cognitive symptoms (dorsolateral prefrontal cortex, DLPFC) and affective symptoms (ventromedial prefrontal cortex, VMPFC) of schizophrenia. (d) The fourth dopamine pathway of interest, the **tuberoinfundibular dopamine pathway**, projects from the hypothalamus to the anterior pituitary gland and controls prolactin secretion. (e) The fifth dopamine pathway arises from multiple sites, including the periaqueductal gray, ventral mesencephalon, hypothalamic nuclei, and lateral parabrachial nucleus, and it projects to the thalamus. Its function is not currently well known.

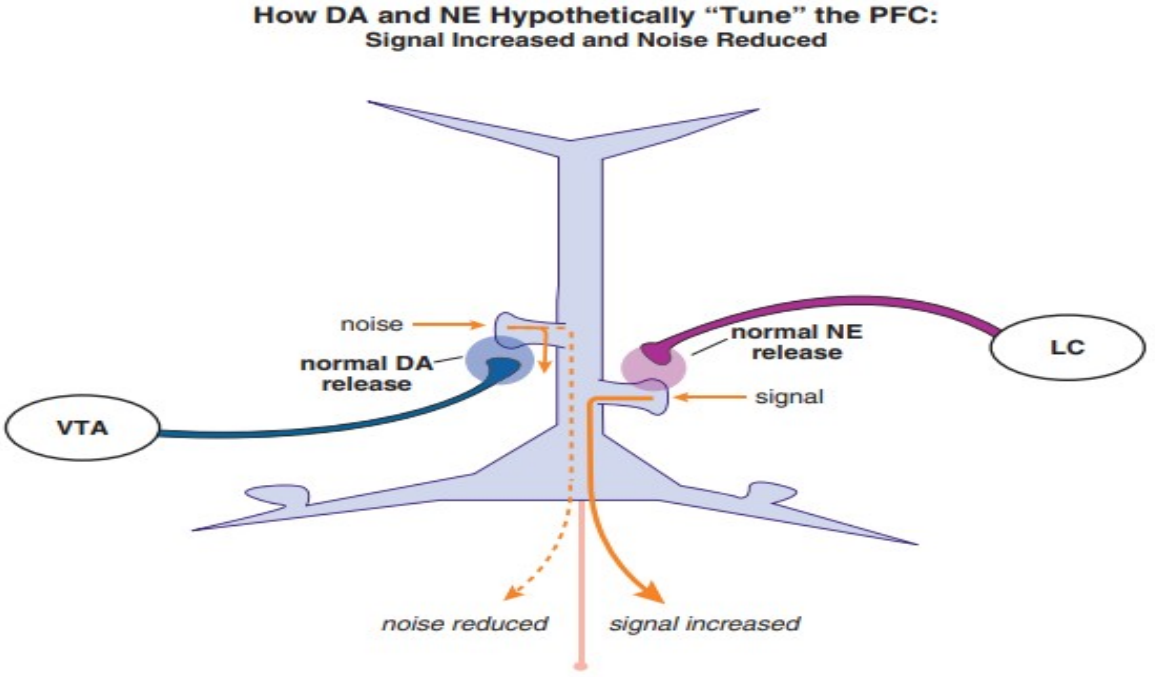



**Figure 12-17. Dopamine and norepinephrine "tune" the PFC.** The same pyramidal neuron may receive NE input from the locus coeruleus (LC) on one spine and DA input from the ventral tegmental area (VTA) on another spine. When properly "tuned," $D_1$ receptor stimulation will reduce the noise while $\alpha_{2A}$ receptor stimulation will increase the signal, resulting in appropriate prefrontal cortex functioning, guided attention, focus on a specific task, and control of emotions and impulses.

**FIGURE 3** Working model of catecholamine actions on prefrontal cortex (PFC) circuits at the molecular level. Note: The top–down regulatory abilities of the PFC depend on networks of pyramidal cells that excite each other through *N*-methyl-D-aspartate (NMDA) glutamate synaptic connections on dendritic spines, schematically shown in this figure. The catecholamines norepinephrine (NE) and dopamine (DA) have powerful and dynamic influences on the functional strength of network synapses. By increasing or decreasing cyclic adenosine monophosphate (cAMP) signaling, they alter the open state of ion channels on the spine and determine whether a network input is able to get through to reach the cell body. NE engagement of $\alpha_{2A}$ receptors on spines inhibits cAMP production, closes nearby potassium channels, and increases the strength of network connections. Conversely, moderate levels of DA engaging $D_1$ receptors on a different set of spines can gate out inappropriate network inputs via increased production of cAMP. However, high levels of cAMP production during stress disconnect all network inputs and shut off cell firing. These stress effects may arise from excessive DA $D_1$, and possibly NE $\beta_1$, receptor stimulation. Attention-deficit/hyperactivity disorder (ADHD) medications likely have some of their therapeutic effects by enhancing catecholamine actions in PFC. Stimulant medications such as methylphenidate (MPH) and the nonstimulant medication, atomoxetine (ATM) all block the NE transporter (NET); stimulants also block the DA transporter (DAT). Animal studies show that these agents can improve PFC function by indirectly increasing NE and DA stimulation of the $\alpha_{2A}$ and $D_1$ receptors, respectively. However, excessive doses of these medications impair PFC function. In contrast, the $\alpha_{2A}$ agonist guanfacine (GFC) appears to have therapeutic effects by mimicking NE at postsynaptic $\alpha_{2A}$ receptors on spines, thereby strengthening PFC network connections.

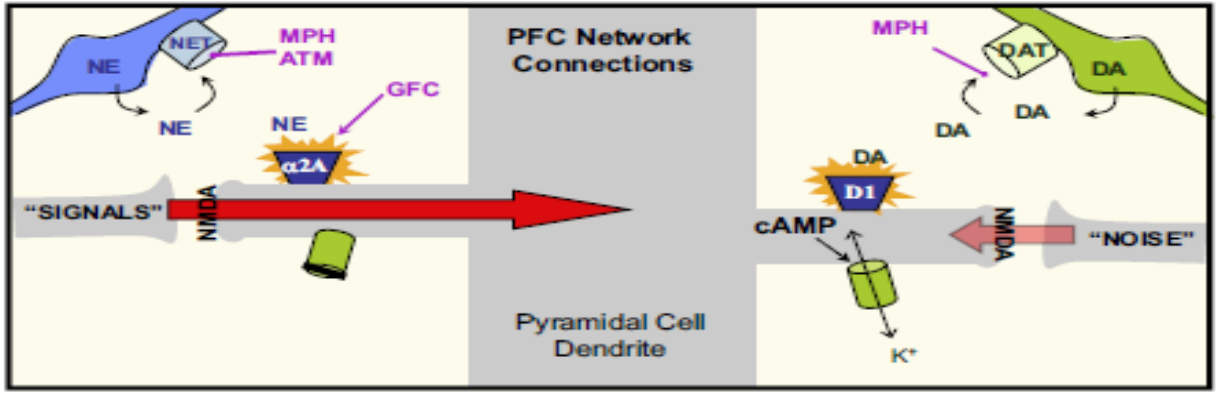



**Fig. 2.** The PFC is very sensitive to its neurochemical environment; both insufficient and excessive catecholamine release impair PFC function. The catecholamines norepinephrine (NE) and dopamine (DA) are released in the PFC according to arousal state: very little during fatigue (and boredom?), a moderate amount of phasic release to relevant stimuli during alert, nonstressed waking, and high tonic release under stressful conditions. Moderate levels of NE engage postsynaptic $\alpha_{2A}$-receptors to improve PFC function, while higher levels engage $\alpha_1$- and β-receptors, which impair PFC function. Thus, optimal regulation of PFC function depends on postsynaptic $\alpha_{2A}$- and moderate D1-receptor stimulation. Animal studies suggest that therapeutic doses of stimulants improve PFC function by increasing endogenous noradrenergic and dopaminergic stimulation of $\alpha_{2A}$- and D1-receptors, respectively. ADHD = attention deficit/hyperactivity disorder.

**Panel 1: Age-appropriate attention-deficit hyperactivity disorder symptoms (DSM-5)**

- Mind seems elsewhere, even in the absence of any obvious distraction
- Starts tasks, but quickly loses focus and is easily side-tracked
- Fails to finish tasks in the workplace
- Reporting unrelated thoughts
- Problems returning calls, paying bills, keeping appointments
- Difficulty in managing sequential tasks; difficulty in keeping materials and belongings in order; messy, disorganised work
- Poor time management
- Tends to fail to meet deadlines
- Feeling restless
- Unable or uncomfortable being still for an extended time, such as in restaurants or meetings
- Might be perceived by others as being restless and difficult to keep up with
- Butts into conversations or activities, might start using other people's belongings without permission, might intrude into or take over what others are doing

## *Panel 2:* Symptoms and impairments of ADHD that can mimic other mental health disorders

**Anxiety**

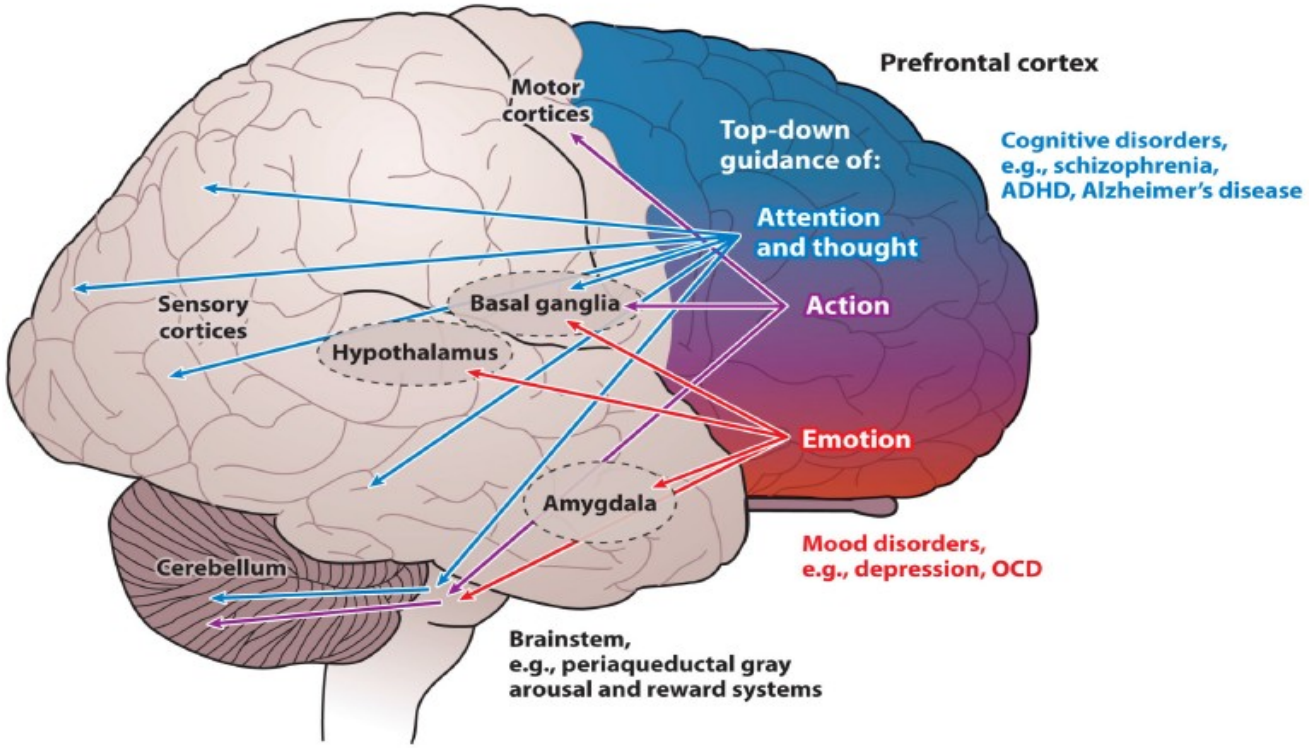
- Worrying about performance deficits, excessive mind-wandering, feeling overwhelmed, feeling restless, avoidance of situations due to ADHD symptoms, such as difficulty waiting in queues or social situations requiring focused attention, and sleep problems linked to mental restlessness

**Depression**

- Unstable moods, impatience, irritability, poor concentration, sleep disturbance, low self-esteem
- Personality disorder (eg, borderline and antisocial)
- Chronic trait-like psychopathology linked to behavioural problems, emotional instability, impulsive behaviour, and poor social relationships

**Bipolar disorder**

- Restlessness, sleep disturbance, mood instability, ceaseless unfocused mental activity, and distractibility


Prefrontal cortex
Motor cortices
Top-down guidance of:
Cognitive disorders, e.g., schizophrenia, ADHD, Alzheimer's disease
Attention and thought
Action
Sensory cortices
Basal ganglia
Hypothalamus
Emotion
Amygdala
Mood disorders, e.g., depression, OCD
Cerebellum
Brainstem, e.g., periaqueductal gray arousal and reward systems

# Neuropsychiatric patologi

- Working memory
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- Inhibition
  - Impulsivity
- Response variability
  - Unstabile arousel/sustanied attention
- Delay aversion
  - Motivation

# Clinical diagnosis

- ADHD is diagnosed clinically, and no scale nor test are cable of capturing the complexity of the symptomatology
- Diagnostic scales are of value
- But in the end the diagnostic assessment is done by the psychiatrist clinically and not formally