Chapter

Traditional Scales Diagnosis and Endophenotypes in Attentional Deficits Disorders: Are We on the Right Track?

Annabel Jiménez-Soto, Juan Pedro Vargas, Estrella Díaz and Juan Carlos López

Abstract

The concept of ADHD has changed widely through the history of mental health classification manuals. In the past three decades, the number of ADHD diagnoses has hugely increased worldwide. One of the reasons to explain this fact could be the lack of precision, differentiation and adjust of the criteria and indicators of this disease. Research has detected as well, some subjectivity bias in the traditional assessment (based in questionnaires and behavioral scales), which is affecting to the precision in the diagnose and to the further adjustment to the treatment. In this regard, these diagnoses are based in symptoms but not in etiology of the disorder. Therefore, different disorders will share the same treatment, regardless etiology. A different approach is based on the study of vulnerable traits associated with impulsivity and attentional deficit. In a quantitative fashion; these traits could be used to define a specific endophenotype. This view would allow us a more precise medical/psychological assessment focus on patient along the life spam, avoiding a diagnostic based on the number of symptoms. Here, we discuss about the differences between traditional diagnosis scales and the possibilities to find endophenotypes in order to address a specific treatment.

Keywords: ADHD, assessment, diagnosis, impulsivity, endophenotypes

1. Introduction

Attention Deficit Hyperactivity Disorder, better known as ADHD, is one of the most common diagnoses among children nowadays and its prevalence worldwide is estimated at 5% for children, and 2.5% for adults [1]. However, the prevalence showed in different studies and countries varies quite a lot and does so in wide ranges, which is commonly associated with theoretical and methodological approaches to understand and assess the disorder. Understood as a brain disorder, ADHD has been defined on multiple occasions trying to account for the symptom variability and heterogeneity present in people with ADHD [2–5]. Due to the great symptomatic variability showed by these patients, the lack of biological or genetic markers of the disorder recognized by the APA itself and the heterogeneity

expressed in the cognitive functioning of these individuals [1], explanatory models of the disease are increasingly abundant and diverse, making the diagnose a complicated, questioned and commonly criticized process.

There are different times in the history of medicine, psychology and psychiatry in which several authors identified ADHD as a syndrome for the first time [6–8], even though it is not until 1968 when the disorder was full described in one of the main manuals of mental health [9]. In its second edition, the diagnostic category for childhood and adolescence included a new syndrome that was termed as "hyperkinetic reaction". The manual described this syndrome as a disorder characterized by overactivity behavior, restlessness, easy distraction and short attention span. It was more common in children and generally improved during adolescence [9]. Afterwards, the DSM III published for the first time a reference to the disorder as we know it currently. Named as "attention deficit disorder" and included into the behavioral category of diseases that occurs in the infancy or childhood, the diagnosis was subdivided into two subtypes: attention deficit hyperactivity disorder and attention deficit non-hyperactivity disorder. On the one hand, it is mentioned among the clarifications that the symptoms may not be directly observable by the clinician [10]. In addition, it included indicators among the criteria of the disorder such as "often does not seem to listen" or "often acts before thinking", constructs that are hardly observable in an objective way.

In 1987, the American Psychiatric Association revised the text of the third manual that resulted in the DSM III-R. This review included ADHD as a discrete disorder, for which it was necessary to display both related symptoms, inattention and hyperactivity. If just inattention symptoms were present, but not the hyperactivity, the diagnosis was "undifferentiated attention deficit disorder" [11]. Despite the increased requirements for the diagnosis, the number of people being diagnosed kept growing. A few years after the fourth version of the diagnostic manual of mental disorders, published in 1994, described the basis of what we currently understand by ADHD. The disorder described affected three main axes: attention, hyperactivity and impulsivity. And it gave rise to different subtypes of the disorder that were classified into inattentive, hyperactive–impulsive, or combined [12]. Although it has been more than twenty years since this description, it is remarkable that an exhaustive differentiation between hyperactivity and impulsivity as constructs has not been made yet when ADHD is defined or assessed. Since then and until the last release of the Diagnostic Manual of Mental Disorders, there were no remarkable changes in the way of defining the disorder [13]. In contrast, the latest version of the manual, DSM 5 [1], makes some important changes in the disorder definition, its causes and specific characteristics. In this edition of the manual, ADHD is defined as a neurodevelopmental disorder, and in an inconsistent way, the age of symptoms onset was increased from seven to twelve years old. This change in the age of symptoms onset also applies to the ICD-11 versus ICD-10 versions [14, 15]. Furthermore, one of the most significant changes in DSM 5 for ADHD comes from the introduction of a paragraph that states: "The signs of the disorder may be minimal or absent when the individual receives frequent rewards for appropriate behavior, is under close supervision, in a new situation, participating in especially interesting activities, has constant external stimulation (e.g., with electronic displays), or is in situations where he or she interacts face-to-face with another person (e.g., in the clinician's office)" [1]. What could that possibly mean? We do not know what is the meaning of this statement, but the result of DSM 5 changes is a sharply increased prevalence of the disorder. This has gone hand in hand with modifications in the DSM, since diagnostic criteria in the recent version remain vague. That is the reason why nowadays is easier to receive a diagnosis based on these criteria than twenty years ago. DMS 5 relativizes the importance of symptoms, which goes from assuming

"clear evidence of clinically significant dysfunction in the social, academic or occupational sphere" [13] to "interfering with or reducing the quality of life of any of them" [1]. In addition, the number of symptoms needed to meet the criteria for inattention or hyperactivity-impulsivity was reduced from six to five for adolescents and adults over 17 years old.

2. ADHD traditional assessment: what could be wrong?

Nowadays, the most used instruments to assess ADHD are tests and scales of behavior, which are usually completed by parents and teachers. These tools are generally based on the diagnostic indicators of ADHD, describing some symptoms or behavior included in the disorder. Although behavior scales and tests currently remain the most widely used assessment method, the validity and reliability of these tools are not consistent in the literature [16]. Even when clinical practice guidelines on ADHD have recommended a neuropsychological assessment of symptoms, beyond the subjective reports provided by scales and tests, at present, this assessment is still considered dispensable to establish the diagnosis of ADHD [16–19]. Fortunately, the use of neuropsychological tests to assess the effects of these patients is becoming increasingly common.

Perhaps one of the most important problems when assessing ADHD is the bias produced by the use of tests and behavioral scales. The subjective experience of responding to a survey can record biases such as social desirability, the anticipation of the hypothesis, and even false and premeditated responses. In addition, when relatives are the ones who report on the behavior of a third party, the problems of subjectivity are even greater [20]. This fact has been repeated for more than thirty years. Parents and teachers tend to rate up to 50% of healthy children as inattentive, distracted, restless or hyperactive [21]. This subjectivity is also sensitive to the halo effect, which has shown a bilateral effect between inattention and hyperactivity-impulsivity symptoms. That is, the greater the number of symptoms in one of the criteria, the higher the score in the other [22]. Moreover, depending on whether it is the mother, father or teacher who fill in the questionnaires, patients can be diagnosed with one or another subtype of the disorder [23], with parents reporting the most symptoms [24]. Besides, the correlation between parents and teachers' reports is generally low [25].

Another assessment problem about ADHD is related to development. That is, evaluation and diagnosis do not take into account that the symptoms of the disorder are not stable during the life span [26]. Additionally, according to the scientific literature, the persistence of the disorder in adulthood varies between 4 and 66% [27]. These diagnostic differences between youths and adults are usually explained by the existence of undiagnosable subthreshold ADHD in adults [28], or the existence of two syndromes with different trajectories [29]. In this regard, a recent study that followed a sample of people diagnosed with ADHD for nine years found that when the participants were 18 years old on average, only 16.7% still met the criteria for the diagnosis of ADHD, and 11% were classified as having sub-threshold ADHD [30]. This means that 72.3% of the whole sample did not show any disturbance after nine years of follow-up.

The fact that the symptoms are not stable over time is something we have known for over two decades now [26]. Nevertheless, the diagnostic criteria and indicators are the same for all age groups. The only difference we can find is related to the number of indicators needed to meet the criteria, where adults need five instead of six indicators to meet the criteria of inattention or hyperactivity-impulsivity. Something similar happens concerning symptoms shown in people with ADHD.

Despite the efforts to find functional subtypes within the disorder, findings have displayed a high diversity/heterogeneity in the symptoms and disturbances of the disorder [31, 32], that resembles the behavioral repertoire of these individuals [33]. This fact makes extremely difficult to accept the definition of the disorder as it is currently understood.

2.1 Comorbidity gets worse the current ADHD definition

Another great problem reported is the wide and diverse comorbidity commonly found in the disorder, such as the concurrent presence of a dissocial disorder or oppositional defiant disorder [34]. The problem is even greater if we consider that the three main axes of the disorder (hyperactivity, impulsivity and inattention) are affected in a wide variety of psychopathological conditions [35]. According to the DSM 5, there are up to 16 comorbidities frequently associated with the disorder, such as oppositional defiant disorder, autism spectrum disorders, anxiety, depression, intellectual disability, or other neurodevelopmental disorders [1]. They have also been assessed for their concurrent occurrence with ADHD, coordination disorders, substance abuse disorders and even Tourette's syndrome [35].

Several authors have suggested that comorbidities are variable because they are specifically related to each subtype of the disorder. Thus, externalizing problems seem to be more comorbid in patients with hyperactive–impulsive or combined subtype, while internalizing is more common in people with inattentive subtype [36]. According to APA, ADHD combined subtype is associated with the oppositional defiant disorder in approximately 50% of the diagnosed cases and up to 25% of the inattentive subtype, whereas behavioral disorders among all the diagnoses are present in a quarter of them [1].

In this regard, people with ADHD generally display more symptoms associated with anxiety disorders or depression than general population, and these comorbid symptoms are also stable over time [37]. Concerning depression, a meta-analysis with more than 300,000 participants reported that ADHD was also comorbidly related to the occurrence of suicidal behavior [38]. These facts make that pure diagnosis of ADHD cases are very rare and complicated to find [35]. For instance, a study analyzed 1919 cases of diagnosed ADHD, finding that 66% of participants had at least one comorbidity with learning, sleep, anxiety or opposition disorders [39]. The overlap of symptoms in ADHD and other disorders is a quite important problem in the assessment, and it represents a challenge for its correct diagnosis [40]. This could be the reason why diagnostic criteria and indicators of the DSM 5 show a lack of validity. It is difficult to think of a child who is not "hard to keep up with" or "runs or talks too much." That is, many times the symptoms described for ADHD define the usual and normal behavior of children [33].

We tried to assess how people interpret the measure of ADHD symptoms in a survey made by our laboratory. Using the diagnostic criteria to explore the symptoms of ADHD among the general population, participants indicate as present in their behavioral repertoire on average at least five symptoms of the disorder, being more frequent the symptoms of inattention than those of hyperactivity/impulsivity [41]. With these indicators, many children who do not suffer from this disorder, but show some behavior outside of what is considered "normal", could easily be diagnosed with ADHD if just the DSM's criteria were used to assess the disorder. Thus, the current overdiagnosis might be due, among other problems, to the lack of consensus in the evaluation criteria [42]. For some authors, this fact makes DSM not to be reliable enough for ADHD diagnosis [33], and therefore other criteria should be considered for an accurate ADHD diagnostic [43].

It might appear that symptoms described in the indicators of ADHD usually define the normal behavior of children [33]. This explains why the criteria for maintenance of the symptoms in time and the contexts in which they appear are so important to evaluate when assessing this disorder. Currently if a child presents some behavior related to the description of ADHD, it is more than likely that he or she will receive the diagnosis. Although DSM 5 and ICD 11 focus on specific situations and how long a symptom lasts, the environmental triggers are not usually assessed, addressing the assessing to behavior patient. What is most disturbing is the fact that diagnosis is also defined in light of these described behavior, which would lead to a problem of reification pointed out by several authors [44–46].

2.2 Hyperactivity and impulsivity: different concepts, same diagnose

Another problem of criteria and indicators is related to hyperactivity and impulsivity concepts. Although both are defined in the DSM with different indicators for the disorder (6 for hyperactivity and 3 for impulsivity), they share the diagnostic category of hyperactive–impulsive [1], giving rise to a single subtype of the disorder. However, we currently know that hyperactivity and impulsivity belong to different constructs and domains and they are not understood as parts of a continuum.

Impulsivity is defined as a multidimensional concept, and it includes problems in decision making processes regarding long/short term reinforcement, a lack of behavioral inhibition related to future consequences, and an inappropriate behavior [2, 47, 48]. In addition, impulsive behavior displays a lack of sensitivity to negative consequences, and fast and unplanned responses [49]. Thus, impulsive behavior is a kind of no reflective behavior defined as a failure in inhibitory processes. This might be due to lower development of executive functions, getting worse in specific context as familiar or academic situations [50, 51]. It is commonly agreed that an impulsive person is one who "usually speaks or acts without reflection or caution, allowing himself or herself to be carried away by the impression of the moment". In contrast, we define hyperactivity as a "behavior characterized by excess activity".

Although both are expressed through lack of control, impulsivity could be better understood as a lack of cognitive inhibition and hyperactivity as a lack of motor inhibition. To verify this, some authors have evaluated the levels of hyperactivity and impulsivity in a sample of more than 10,000 healthy children, concluding emphatically that the measures of hyperactivity and impulsivity address different constructs [52]. In this regard, it is not complicated to imagine a person of any age who can be very energetic, in terms of activity, and yet be extremely reflective in terms of decision making. In the same way, we can also imagine someone who is not very energetic in his or her daily activities and notwithstanding is very impulsive when it comes to decision making. In light of all these results, we can see that the assessment of ADHD is a rather complicated process. There are no specific diagnostic tests to assess the disorder objectively, and the current assessment process is not free of problems and biases, which makes diagnosis even more difficult. The assessment of ADHD cannot and should not be carried out exclusively using questionnaire reports and behavior scales [53]. Only the combined use of reports and neuropsychological tests would produce an adequate assessment of the disorder [54], since the scales and tests do not measure the same as the experimental tasks [55].

2.3 ADHD treatment: do all roads lead to Rome?

According to DSM 5, a diagnosis of ADHD can lead to three different subtypes of the disorder: predominantly inattentive, the criteria of inattention is met, but

not those of hyperactivity-impulsivity; predominantly hyperactive–impulsive, the criteria of hyperactivity-impulsivity are met, but not those of inattention; and the third subtype would be a combined presentation of the disorder, where both traits of inattention and hyperactivity-impulsivity would be affected [1]. In addition, the manual also includes two diagnostic categories when the criteria for the main subtypes are not met: other specified attention-deficit/hyperactivity disorder and unspecified attention-deficit/hyperactivity disorder. Nevertheless, there are no main differences in the therapeutical interventions and psychopharmacological treatments for these ADHD subtypes, and all of them will probably receive the same health/medical cares.

ADHD is usually treated as a problem of neurochemical dysfunction, accordingly the treatment commonly used is the administration of psychostimulants, which in a high number of cases reduces the frequency and duration of symptoms [17]. That is, regardless of the subtype diagnosed, patients are usually treated, at least in the initial phase, with the same drug. However, we now know that, although the systemic administration of stimulants such as methylphenidate, a psychostimulant that acts by inhibiting the reuptake of dopamine and noradrenaline, improves the symptoms for a while in most cases, but not in the long term [56]. This situation causes the beginning of continuous changes in treatments. This fact clearly indicates that the problems associated with this disorder depend on several pathways. One of them seems to be dependent on prefrontal dopaminergic pathways, and at the other extreme, we can find the opposite profile, triggering a pattern probably independent on these prefrontal pathways. In any case, at present we do not have diagnostic tools that allow us to identify these different populations within the same diagnosis [41].

2.4 ADHD as a neurodevelopmental problem: is it possible to find an anatomical profile?

Although the ADHD is considered as a neurodevelopmental disorder, in the last years there is an increasing number of studies that point to the possibility that ADHD can emerge in adults without previous history of the disorder [57]. These studies may indicate that at least some of the ADHD cases are not related to neurodevelopmental issues. In any case, there are an overwhelming number of studies that suggest a link between the development of the central system and the ADHD. The disturbances related to ADHD are extremely complex, especially given the large number of brain structures involved in the affected processes. Brain imaging techniques have made a critical contribution to deepening our understanding of the neuroanatomical etiology of ADHD. Studies using magnetic resonance have provided us with precise information about the volume of gray matter, density, cortical thickness or integrity of white matter, as well as its connectivity [58–60]. Neuroanatomical development varies throughout childhood until reaching the adult stage, in some cases in a linear fashion, such as the increase in cortical white matter, and in others in an inverted U-shape from the pre-pubertal phase until entering the adult phase, as in the case of cortical gray matter thickness [58]. In addition, this maturation is also carried out unevenly between areas, generally beginning development earlier in the older phylogenetic zones than in the more recent ones, as occurs in the prefrontal cortex. This is also the case in the motor and sensory areas, where development begins earlier than in areas associated with more complex functions, such as those involving cognitive control or attention [58, 59]. These findings are important because an altered maturation process of these latter cortical areas has been identified in patients with ADHD [61], mainly in the frontal cortex [62]. In fact, it has been described that the symptomatology of ADHD in the

general population is negatively correlated with total brain size [63], probably due to the decrease in the volume of gray matter in various subcortical structures such as accumbens, amygdala, caudate, hippocampus and putamen; and cortical structures such as the prefrontal cortex and parietal–temporal [63–65]. This decrease is also accompanied by a delay in maturation [66], and is usually more pronounced in childhood, with some persistent reductions in frontal areas in a subgroup of ADHD patients with symptoms lasting into adulthood.

At the functional level, it is observed some correlates that indicate variations in patients with ADHD in relation to patients without a diagnosis of this disorder. For instance, the cortical and subcortical areas described above fluctuate spontaneously when passing from a resting phase to an explicit task phase. The active networks in the resting state reduce their activity when they increase the focused attention processes, with both networks showing a process of negative feedback depending on attentional demands [67–69]. This inverse correlation between the networks of cognitive control and those of rest are diminished or absent in children and adults with ADHD, which is why they show the continuous problems of sustained attention [68, 70, 71]. Furthermore, it is possible, that the connectivity patterns of cortico-limbic, cortico-striatal, and thalamocortical loops are altered in children with ADHD [68, 72]. Specifically, a decrease in the activation of the network connecting the frontal and neostriatal areas next to the thalamus-parietal is observed in ADHD children in goal-directed tasks; although the most common alterations show patterns of hypoactivation of the frontoparietal network, a network related to executive functions [73]. Similarly, the motor inhibition tasks also produce consistent decreases in children diagnosed with ADHD in the associative and sensorimotor network, networks that include the supplementary motor area, anterior cingulate gyrus, and the putamen and caudate nuclei [73, 74].

2.5 Genetic profile in ADHD

The heritability for ADHD has been estimated between 70 to 90% from studies using families and twins with ADHD [75, 76]. By DSM 5, the heritability of ADHD is considerable, being more frequent among first-degree biological relatives of individuals with the disorder. Although ADHD is not associated with specific physical traits, the manual indicates that the presence of minor physical abnormalities such as hypertelorism, bowed palate and low ears, are common among these individuals [1].

Clinical research in ADHD has also identified several genes associated with the disorder which are related to the metabolism, transport and reception of certain neurotransmitters, especially dopamine, noradrenaline and serotonin. Among the genes that have been most frequently correlated with ADHD are the serotonin transport gene 5-HTT and the serotonin receptor gene HTR1B. Regarding dopamine: the DAT1 transporter gene and the DRD2, DRD4 and DRD5 receptor genes; and the gene responsible for the conversion of dopamine into noradrenaline DBH, among others [77–80]. This genetic involvement at the neurotransmitter level would be at the basis of hypofrontality, or reduced activity in the frontal lobes in these patients [81–83]. The frontoparietal network is usually more affected in subjects with an inattentive subtype while in the hyperactive–impulsive type it is usually the frontostriatal network [84]. These dysfunctions have also been found in frontoparietotemporal, frontocerebellar and even frontolimbic circuits [85].

The approaches to the genetics of ADHD have been many and varied. Some studies have found an altered maturation of the cortex, characterized by a delay in cortical maturation in people with ADHD [61, 86]. A study with 366 subjects with a diagnosis of ADHD and a large control group (n = 1047), analyzed the genetics

of the disorder by calculating the variation in the copy number of certain genes. The authors found a difference that they called rare in 50 of the 366 subjects with the disorder, 13.66% of the participants with ADHD. In the control group, the abnormality was present in 75 of 1047 cases (7.16%) [87]. It is curious to argue that these differences could be good predictors of the possible genetic origin of the disorder; however, they also found similar results with other diseases, as autism or schizophrenia. And recently, it has been published what is considered to be the largest genetic study of ADHD. Researchers from around the world have participated in the project and it has been proposed as the first gene map around ADHD that identifies variants surpassing genome-wide significance in 12 independent loci. These findings, described by the authors, "are compelling, but only capture a tiny fraction of common variant risk for ADHD" [88]. Furthermore, the contribution of these genes to ADHD heritability is very low [89] and recent studies suggest that we have to look at how the different genes interact each other and with environmental etiological factors [90].

Although technological progress in recent decades has enabled great and important advances in understanding the genetic disposition and physiological and behavioral functioning of many disorders, biological markers for the disorder are still lacking. According to APA "Although specific genes have been correlated with ADHD, these are neither necessary nor sufficient causal factors" [1].

3. Searching a specific phenotype across measurable traits

Above we have discussed about ADHD definition and the difficulties when we try to carry out an accurate diagnosis. In addition, we have indicated that, regardless the diagnosis, the medical care is usually the same. That is, we should not need to differentiate between diagnoses in order to choose a treatment. An alternative to this traditional view of current diagnostic scales could be the objective quantification of specific features that reflect a mental disorder. In this regard, we should give up the idea of how many symptoms are met per patient to be diagnosed of ADHD, and keen on objective scales of how deep is a symptom. In addition, data from genetic studies and brain activity could help us to define the profile of different disorders. This is important because it would allow us to link these measures with quantifiable cognitive/behavioral features in order to develop a possible endophenotype.

One important line of research has identified EEG-based markers as event-related potential and frequency analysis. The use of these markers may improve the diagnosis by offering an alternative to the present symptom-based system. At present, the benefit of using neurofeedback EGG on ADHD is controversial [91, 92]. Although studies on the use of EEG to identify biomarkers related to ADHD is promising, at the moment there are several difficulties. One of the main challenges is defining the ADHD population and the different sub-groups [93]. An alternative to EEG-based markers comes from studies from experimental psychology. For more than a century, the experimental psychology has described the basis of the psychological processes in multiple paradigms. As the ADHD is not a unified disorder, we propose to disentangle some traits related to the ADHD and apply the models from experimental psychology.

4. ADHD focused on impulsivity

Attention is a basic psychological process that facilitates the control of cognitive processes. Traditionally, the distinction made between different dimensions of attention

in current models has been associated with different neural networks. Therefore, when we talk about attention we do not talk about a unitary concept [94, 95]. One of the most complete models about attention processes is the one proposed by Posner and Petersen [96]. In its different formulations, it has conceptually modified the basic principles of its original proposal and currently allows to distinguish between several attentional functions. Specifically, it proposes the existence of three networks: the orientation network, the alert network and finally the executive control network. Each one of them would have its own function, supported by an associated brain circuit and mediated by a different neuromodulator. This model has been extended and reformulated in several occasions, highlighting the value of studies that emphasize individual differences between groups of subjects [97].

The executive network has been directly related to goal-directed processes, frontality and action control. Not surprisingly, attention disorders and hyperactivity/impulsivity have gone hand in hand. Thus, when hyperactivity or impulsivity is suspected, its effect on attention is habitually analyzed. However, we do not currently know if the attentional disorders are cause, effect or simply part of shared circuits in ADHD.

The explanatory models range go from those that propose ADHD as the affectation of a single aspect related to the inhibition of response, to models that propose that the disorder is the sum of multiple deficits [98]. Single deficit proposals are related to low capacity in inhibitory control, state regulation and delay avoidance. Specifically, it is related to the lack of capacity to inhibit a response to an attractive and irresistible stimulus associated with immediate reinforcement [2]. In addition, this trait is associated with behavioral impairment of non-verbal working memory, language internalization, and self-regulation on which such inhibition is partially dependent. In other words, ADHD is probably not due to deficits in the processes, but rather to the regulation and control done over those processes.

Impulsive processes have usually been described in at least two different ways. One of them refers to a slow way that involves deliberation and action even considering its negative consequences. The other is the fast way; that is, without thinking of short- or long-term outcomes [99]. This has been translated into two models generally known as cool vs. hot, top-down vs. bottom-up, stopping vs. waiting, action restraint vs. action cancelation or motor vs. choice [100, 101]. Thus, the motor component reflects spontaneity or action without thinking, while unplanned impulsivity reflects a lack of reflection on future consequences. This activity is easily measurable in both human and animal models. In fact, it has been used to analyze patients with ADHD [102]. This view transforms the analysis of impulsive behavior in a quantitative dimension [103], which allows a quantification of the level of impulsivity of individuals, both in human and non-human models, depending on both internal and external variables. This is important because it allows us the study of models of impulsivity from the current theories of learning.

4.1 Impulse control and cognitive correlates in ADHD diagnose

Impulse control is one of the main and consistently affected function in the scientific literature on ADHD [82, 104–107], and it is also one of the difficulties more often reported by parents of boys and girls with ADHD [25]. Accounted as one of the key affectations in ADHD [108, 109], good abilities in impulse control are considered decisive in the future development of individuals [110, 111]. Despite being a common problem among ADHD diagnosed patients, it is more frequently found in people with diagnosed of combined subtype [55].

In addition, these patients show general deficits on working memory [112], and is considered as one of the main alterations and possible axes of the disorder [2, 82].

The central executive appears to be one of the more affected dimensions [113], as well as visuospatial skills [81, 84, 114]. Some authors have found that the greatest deficits in working memory in ADHD were related to tasks involving the central executive [115], while others have proposed that lower performance level in tasks related to executive functions could be explained by deficits in discrimination of interferences in working memory [116]. Interference control is more compromised in subjects with ADHD than in typically developing individuals [117, 118] and visual perception is highly related to higher cognitive processes such as reading comprehension and arithmetic skills [119]. In addition, people with ADHD usually show deficits in tasks that assess visual working memory [120, 121], alterations in visuospatial skills related to working memory [122], and in the ability to process spatial information adequately [123]. However, we do not have standardized tests focused on quantification of the deficit, only a qualitative view of the deficit itself. This might be the reason why it has not found any differences between subtypes of the disorder for this domain yet [124].

Deficits in attention, impulse control, or working memory are just some of the neuropsychological findings in patients with ADHD. Planning and problem solving have also been pointed above as a common deficit in the disorder [82, 125–127], as well as timing skills [128–130], which have also been linked to problems with attention, language, reading and executive functions [131].

Despite the numerous findings identified in the neuropsychology of ADHD, on the one hand, the disturbances expected for the diagnosis not always are found in the assessment process [41]. In addition, they are not only present in this disorder but also in other conditions. Furthermore, the neuropsychological deficits profiles identified are also present in the general population, but in children with ADHD the values are utmost [132].

4.2 Starting the route from animal models

Research in animal models offers an in-depth approach to the possible etiology and development of some diseases, being considered invaluable for the preclinical evaluation of treatments and interventions [133]. In this way, it is generally agreed that those disorders that have previously been studied from the perspective of animal models are currently better understood than others [134]. In this regard, animal models of ADHD, as other brain disorders, need to meet certain characteristics of validity, essential to be considered as an adequate animal model. Similar behavioral characteristics of the disorder are usually known as "face validity". When models show a theoretical consistency with the disorder or disease, we speak of "construct validity". Finally, for being an adequate model, neuroscientific findings, for instance genetic and neurobiology data, should be similar to those displayed in clinical population of the disease in order to ensure "predictive validity" [135, 136].

One of the most analyzed traits studied in animal models has been impulsivity. This is an easy trait to measure at cognitive or behavioral level, besides being closely linked to attention. Recent studies have been able to link different behavioral procedures in order to define possible attentional deficit profile. And these procedures can be used in both, human and non-human animal models, allowing us a quantifiable view of symptoms, making access a deeper view of the disorder.

Autoshaping is currently considered as a valid animal model of impulsivity [137]. This model is based on the study of the motivational aspects of the relationships between the presentation of a conditioned stimulus (CS), the responses to the presence of this stimulus and, finally, the presentation of the unconditioned stimulus (US). The autoshaping, also denominated as sign-tracking, describes the

progression of direct movements of orientation-approach to the key or CS that precedes the US [138, 139]. This model allows differentiating how each experimental subject attributes the motivational salience of the signal and the reward, and it is beginning to be used with the aim of assessing individual differences. López et at. [140], studied the behavioral profile in animals classified as sign (ST) and goal (GT) trackers in order to analyze the relationship between impulsivity and attentional processes. Results in prepulse inhibition (PPI), a procedure used to analyze early attentional gating mechanisms, showed a consistent decrease in PPI response in ST animals. That is, animals with a trend to show an impulsive behavior displayed a deficit in a preattentional phase, indicating the more impulsive behavior the higher deficits probability in early phases of attentional process.

Using the same paradigm, Serrano et al. [141] found processing differences of a CS in latent inhibition (LI), other easily quantifiable procedure. LI is a learning process associated to selective attention assessment. This procedure consists in a repeated display of a stimulus without consequences, and after a habituation period, the stimulus is associated to a reward/punishment. The CS-US association tends to be slower in this situation in general population. Yet, animals classified as impulsive (that is, ST) showed a low LI. That is, impulsive animals displayed a slower habituation rate to a neutral stimulus, indicating impulsive animals had paid attention to a higher number of irrelevant stimuli than the rest of population.

The procedures describe above are focused on the named hot model of impulsivity [139]. This kind of impulsivity is usually shown by ST animals, and it is closely related to dopamine neurotransmitter. In fact, nucleus accumbens shows higher levels of dopamine release in the presence of a CS [142]. Besides, D2 dopamine receptors stimulation reduces ST behavior selectively, in a similar way to medial prefrontal cortex lesion [140, 141]. Thus, this model integrates information at different level from this animal model that cover biochemical, anatomical and behavioral level. In this regard, all these data might indicate a higher vulnerability to attentional problems as described in ADHD in impulsive animals.

5. Conclusions

One of the major challenges in the treatment of psychological and psychiatric disorders is to understand the influence of individual differences or traits variability on the potential outcome of treatment. A future goal could be to tailor the treatment to fit the patient profile, rather than assuming a generic approach based on a broad diagnosis. Moreover, many ADHD patients change to more severe clinical diagnosis when they reached adolescence or late adolescence. In this regard the detection of risk factor is essential to focus on detecting what symptom could be a risk factor of possible mental illness in the future. The search of a specific drug for the treatment of different types of ADHD makes increasingly evident the necessity to measure multiple domains of brain and behavior. Here we highlight an alternative to traditional diagnosis scales that would allow a better accurate treatment, regardless of the general symptoms shown.

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Author details

Annabel Jiménez-Soto, Juan Pedro Vargas, Estrella Díaz and Juan Carlos López*
Animal Behavior and Neuroscience Lab, Universidad de Sevilla, C/Camilo José Cela s/n 41018, Seville, Spain

*Address all correspondence to: jclopez@us.es

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