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The Role of Neuropsychological Assessment in Adults with Attention Deficit/ Hyperactivity Disorders

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ABSTRACT

Attention-Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, hyperactivity and/or impulsivity. While ADHD was initially recognized as a childhood syndrome, scientific evidence accumulated to indicate that a significant proportion of ADHD children continue to experience symptoms of ADHD in adulthood. Moreover, the question of ADHD diagnosis can arise in adult patients who were not diagnosed in childhood. Currently, the diagnosis of ADHD in adulthood is based on the revised criteria described for children. However, their application for adults may be difficult for many reasons including compensation and comorbid disorders. To date, no clinical, neuropsychological, biological or imaging marker is available for the diagnosis of ADHD. Considering that ADHD is based on a neuropsychological model, in this article we will examine the usefulness of neuropsychological testing in the diagnosis of ADHD in adults. We will first present diagnostic criteria of ADHD and the limits of their application in adults. We will then detail the neuropsychological data available in adult ADHD and the French and international clinical recommendations for neuropsychological assessment in adults. Finally, we will explore the predictive value of neuropsychological scores in the diagnosis of ADHD and discuss key methodological points and perspectives for clinical research.

Keywords: Attention-Deficit Hyperactivity Disorder; neuropsychological assessment; cognitive tests

1. Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) was initially described in children and adolescents. The prevalence of ADHD for subjects 18 years old or younger is estimated to be 5.3% in the general population [1]. The diagnosis involves clinical examination but also information from schools, caregivers, and parents. Moreover, specific questionnaires have been developed for objective measurement for this diagnosis. ADHD is diagnosed in children and adolescents using standard guidelines from the American Academy of Pediatrics [2] or the National Institute of Mental Health[3]. The Diagnostic and Statistical Manual of Mental Disorders, version 5 (DSM-5, American Psychiatric Association, 2012) formalized a set of criteria that represent the gold standard with additional examples of behavior (for details see appendix 1). The 3 clinical subtypes of ADHD (predominant inattentive, predominant hyperactive/impulsive and mixed subtypes) are now referred to as '*current presentation*'.

It is now well established that symptoms of ADHD could persist in adulthood. A meta-analysis of ADHD follow-up found that in 15% of the cases the diagnosis was maintained until adulthood [4]. According to the World Health Organization World Mental Health Survey Initiative, the average prevalence of ADHD in adults is 3.4% (range 1.2-7.3%) [5]. Symptoms reported in children with ADHD evolve in adulthood [6]. Attention, executive functions and motivational impairments are the core of cognitive difficulties [7]. More precisely, there is high level of distractibility and a low level of concentration in adults for tasks that involve goal-directed behavior, as well as a reduced ability to maintain an activity, especially for low-rewarding tasks. Inhibition, organization and planning functions are also often impaired. Over time, motor hyperactivity which is easily diagnosed in children, decreases. The need to move is often channeled in adults through sports, active work and stimulating projects [4, 8]. Physical hyperactivity can give way to psychic hyperactivity. Adult ADHD is marked by impulsive behavior and speech [9]. This multidimensional syndrome leads to academic difficulties and limitations in professional achievements. It also causes difficulties in social and family relationships and self-esteem [10].

The most widely accepted model to account for symptoms of ADHD is Barkley's model of executive deficits [11]. Barkley considers the disorder of inhibition as a central deficit, implicated in the suppression of the predominant response, the stopping of a current response, and the control of interferences and emotions. Although inhibition deficit is frequently reported, it seems that in fact other cognitive deficits in ADHD are closely related to poor functional outcome, which challenges Barkley's model. Therefore, a focus on neuropsychological functioning seems crucial [12].

To discuss the relevance of cognitive markers for the diagnosis of ADHD in adults, we will first specify the diagnostic criteria and neuropsychological results of meta-analyses. We will then put forward clinical recommendations from experts in adult ADHD and consider the predictive value of neuropsychological assessment in the individual diagnosis of ADHD. Finally, we will discuss key methodological points of neuropsychological assessment in clinical research.

2. Diagnosis of ADHD in adulthood

Neither clinical, neuropsychological, biological or imaging markers are currently available for diagnosing ADHD [13]. Many experts highlight that diagnosis can be difficult in the adult population [14]. The obstacles consist of: 1/ a less discriminant professional environment for adults to detect disorders than in schools; 2/ the difficulty of retrospective diagnosis and the question of the reliability of the patient's and/or family's memories [10, 12, 15]; 3/ the modification of the expression of ADHD symptoms in adulthood which are less typical than in children and influenced by adaptive behaviors; 4/ the presence of compensatory mechanisms that could mask cognitive deficits; 5/ and the presence of comorbid psychiatric and substance use disorders that may overlap, mimic, or mask the symptoms of ADHD (for an overview of common comorbidities see Kessler et al., 2006 [16] and Wilens et al., 2009 [17]). These obstacles may result in an underestimation of ADHD in adulthood [18].

In fact, the diagnosis of ADHD in adulthood is based on the revised criteria described for children. The clinical differences observed between children and adults with ADHD have led to the modification of the number of criteria required to make the diagnosis in adulthood. Only five criteria

are required in each of the two lists for adults (> 17 years old) while six are needed for children (see appendix 1).

Another limit to make the diagnosis of ADHD in adulthood was suggested by Moffitt et al. [19] who challenged the idea that ADHD always starts in childhood. In a longitudinal birth cohort study of 1,037 individuals, the authors identified ADHD syndrome in adults who did not completely meet the ADHD criteria during childhood. In this study, subjects were followed up to the age of 38 with a 6% prevalence of ADHD syndrome in childhood and 3.1% in adulthood. Eighty-seven percent of the subjects fulfilled the DMS-5 ADHD diagnostic criteria in adulthood when the criterion of age of onset at 12 years was not applied. Subjects with late-onset ADHD showed different clinical presentations, cognitive disorders and genetic influences from those with childhood onset [20]. These findings on a new phenotype of late-onset ADHD call for replication studies.

Cognitive markers of persistence and remission of ADHD syndrome from childhood to adulthood are being investigated. Given the impact of cognitive impairment in adults with ADHD, there is a need for neuropsychological assessment and to study the use of cognitive markers for the diagnosis of ADHD.

3. Neuropsychological data in adults with ADHD across meta-analyses

In this section we will focus on meta-analyses because there is significant literature in this field. Descriptive information and cognitive effect sizes in the meta-analyses included are provided in table 1.

Attention and executive functioning, especially inhibition, decision-making, reaction time, reaction time variability and time estimation processes were frequently investigated. Studies on intelligence and memory remain scarce and no meta-dataset was published on language, praxis or metacognitive abilities in adults with ADHD.

Most of the meta-analyses demonstrated executive, attention and memory difference in adults with ADHD compared to controls, highlighting an absence of domain-specific neuropsychological impairment. Greater and most frequent differences were observed in executive and attention domains

with moderated to large effect sizes especially in inhibition and flexibility processes. The highest discriminant values between ADHD and healthy controls for inhibition processes were reaction time on the Stop Signal Task (d=0.85) [7] and errors of commission on the Continuous Performances Test (d=0.64) [21]. In flexibility processes, the highest *d* values were found for the Trail Making Test part B (d=0.72 and d=0.65) [21, 22]. In the attention domain, the highest *d* values were reported on the standard deviation errors on the SAdots task (d=0.71) [23] and on the errors of omission (d=0.76) and the discrimination index (d') (d=0.65) on the Continuous Performance Test for sustained attention [7]. One study reported that ADHD patients appear to be more impaired on attention measures when cognitive complexity is increased [23]. Regarding the memory domain, Hervey and colleagues reported the largest effect size of their meta-dataset on a recognition measure of the California Verbal Learning Test (d=0.90). This was consistent with higher *d* memory values in Schoechlin's meta-analysis. Studies on memory functions in adults with ADHD remain rare and the nature of impairment is unclear. Only one meta-analysis by Skodzik et al. in 2017 [24] focused on memory functioning in adults with ADHD. Authors included nineteen studies encompassing data on verbal and non-verbal memory tasks containing both delayed recall scores and measures of memory acquisition [24]. They reported greater differences between ADHD patients and controls on delayed free recall measures, suggestive of lower performance of stored information access for ADHD patients. Results were highly related to lower performances on memory acquisition subtests (i.e. learning deficits) in the regression analysis. However, authors were unable to establish a causal link between these encoding and long-term memory deficits due to variations in study designs in this meta-analytic context.

Most of the weighted mean effect sizes were considered as small among all nine meta-analyses and some studies indicated normal cognitive scores in ADHD [23] or better performance for ADHD subjects in these same cognitive domains [7, 21, 23, 25]. In fact, 4 out of the 9 meta-analyses [7, 21, 23, 25] showed better performances for ADHD patients than controls in working memory, inhibition, time estimation, decision-making and reaction time measures with effect sizes ranging up to 0.40.

The validity of these meta-analyses is biased by limitations including insufficient information on patients' characteristics (controls for drug treatment, comorbidities and ADHD presentation),

methodological variability and the uncertain discriminant validity of cognitive tools. Future research on neuropsychological patterns in adults with ADHD is needed and should be associated with methodological improvements. In fact, we know that cognitive differences may disappear when ADHD patients are compared to non-ADHD patients with psychiatric disorders. For example, Walker et al. found no difference between 30 adults with ADHD and 30 psychiatric controls on the 18 neuropsychological variables of executive, attention, and working memory tests, whereas ADHD patients were significantly different from 30 healthy controls on 11 of the 18 cognitive measures [26]. These findings were consistent with those of Holst et al. [27] Cognitive heterogeneity highlighted by multi-domain cognitive impairment and sometimes by inconsistent cognitive deficits on the same cognitive function make the contribution of individual cognitive markers in the diagnosis of ADHD questionable.

4. Clinical recommendations and procedure for neuropsychological assessment in adults with ADHD

4.1. ADHD diagnostic procedure in memory clinics

Two French ADHD experts have proposed an algorithm procedure to identify ADHD in adults referred to memory clinics [6]. Keys steps and specific questionnaires are detailed to investigate cognitive and/or behavioral complaints. More specifically, risk factors for neurodevelopmental disorders and developmental steps are recommended for investigation and completion by screening questionnaires when appropriate. In highly suspected ADHD syndrome, patients should be referred for multidisciplinary assessment in neurology, psychiatry, neuropsychology and speech therapy. In other words, with atypical scores on routine neuropsychological assessment in memory clinics in the absence of neurodevelopmental disorders, patients should be referred for multidisciplinary assessment. Use of structured DIVA2.0 interviews is recommended by the authors.

4.2. International consensus on cognitive functions to assess adults with ADHD: Delphi consensus

International experts in adult ADHD recently supported the place of neuropsychological tests in ADHD. In 2019, this group used the Delphi method to list and hierarchize underpinning cognitive functions of neuropsychological assessment in adult patients already diagnosed with ADHD [28]. Except for the divided attention function, all cognitive domains, including executive, attention, speed and memory presented by the expert panel had to be included in the neuropsychological assessment,. The first five of the 16 consensus cognitive functions for inclusion in the neuropsychological assessment according to the Delphi method and their respective measures were: sustained attention [assessed with the Continuous Performance Test (CPT)]; distractibility [CPT]; inhibitory control/interference control [Go/No Go test]; task planning/organization [Behavior Rating Inventory of Executive Function]; and working memory [Digit Span test]. The authors do not require assessment of the 16 neuropsychological functions identified as important for neuropsychological assessment of adult ADHD.

5. The predictive value of neuropsychological tests in the diagnosis of ADHD

The predictive value of cognitive tests in the individual diagnosis of ADHD is of great importance. In 1999, Lovejoy et al. reported significant cognitive differences between 26 adults with ADHD and 26 controls on 5 of the 6 cognitive tests (COWA, Stroop, Trail Making Test A, TMTB and the WAIS-R distractibility tests). However, they concluded that cognitive tests had a low predictive power for group membership on an individual scale [29]. In fact, classification probability analyses found a negative predictive value (NPV) and false negative rates, respectively from 55-69% and 31-45%, which could not determine the absence of ADHD syndrome with normal cognitive scores. In 2010, Walker et al. evaluated the predictive power of the CPT task and found a significant difference between ADHD patients and healthy controls but also between ADHD patients and psychiatric controls [26]. This test is widely used in clinical practice to assess and manage ADHD population. Therefore, the number of omissions on that test, indicative of the sustained attention process, was included in the diagnostic efficiency procedure. Positive and negative predictive values were 86 and 71% respectively when diagnostic efficiency was calculated for ADHD patients and healthy controls.

However, these rates decreased when the scores for ADHD patients and psychiatric controls were introduced in the statistical model (61 and 67 % respectively). These results were previously reported by Katz et al. on discriminant analyses with 60% misclassification of depressed patients in the ADHD group [30]. Recent studies have found an even lower rate of discriminative with this test between adults with ADHD and healthy controls. Baggio et al., showed a misclassification of 80,3% with the CPT test for the inattentive ADHD presentation and 22,5% for the hyperactive presentation [31]. Brunkhorst-Kanaan et al., reported a sensitivity of 76% and a specificity of 40% (QB tests, cardinal variable Activity measure: AUC of 0.65) [32]. Petterson et al., reported a NPV of 52,4 % but detailed that the use of the CPT in combination with the DIVA interview increase the specificity by 10% [33]. In keeping with previous results, Walker and colleagues highlighted the high probability of missing the ADHD in patients with normal cognitive scores. These disappointing results are also found in the meta-analysis by Mostert et al. These authors performed a stepwise backwards logistic regression of 6 neuropsychological variables to predict ADHD in adults [23]. Variables used were digit span forward, total standard deviation of reaction time in the Flanker task, standard errors and response bias in the Sadots task, impulsivity high reward (k100) on the delay discounting task and absolute median deviation on the time estimation task. Detailed sensitivity rates of 64.9% and specificity of 82.1% were reported, suggesting that ADHD is neuropsychologically heterogeneous in terms of several cognitive impairment scores. Finally, ROC analyses by Holst and colleagues showed low sensitivity (64%) and specificity (67%) according to ten significant cognitive variables for which significant group differences were found in the ANCOVA model [27]. The delay aversion questionnaire score was the only variable to predict group membership with a marginal effect for the letter-number sequencing score. The authors reran analyses with these last two variables and reported a higher sensitivity (75 %) but a lower specificity (66%). The three classification models developed in this study reflect the low discriminant power of neuropsychological measures and the absence of a consensual approach to the neuropsychological procedure for ADHD.

As reported by several authors, there is no neuropsychological test specific enough to confirm or rule out individual ADHD [29, 34, 35]. Despite the low specificity of these tests, a description of cognitive

status in clinical practice remains important for several reasons. Neuropsychological assessment appears to be an integrative approach that considers multiple data sources across multiple contexts and therefore helps to understand the severity of functional impairment in daily living. It also provides valuable information to determine a non-pharmacological approach to improve ADHD and adaptive functioning and academic and professional achievement. Neuropsychological assessment could be very useful in following the patient's disease course and monitor subsequent changes in cognitive abilities, mood and the effects of treatments. Finally, an analysis of cognitive functioning could be effective to increase metacognitive abilities [36] by providing a comprehensive view of the strengths and weaknesses as well as to increase empowerment.

6. Conclusions

Most of the studies confirmed cognitive impairment in adults with ADHD compared to healthy controls in a broad range of cognitive domains. However, normal cognitive scores cannot exclude a diagnosis of ADHD. The negative prediction of cognitive tests used in clinical practice for diagnosing ADHD is confusing with inconsistent cognitive results across studies. The importance of comorbidities, including substance abuse and possible compensation for cognitive deficits could partially explain this absence of specificity in cognitive pattern of adult ADHD. Cognitive impairment could be masked by the structured testing environment where interferences are erased, facilitating attentional engagement and therefore cognitive performance and by high within-subject cognitive fluctuations.

For futures studies, it seems important to address some methodological points regarding neuropsychological assessment. The ecological validity of neuropsychological assessment is low especially to capture attentional disengagements frequently observed in natural conditions. There is no specific cognitive test or consensual approach to cognitive testing that reveals the cognitive engagement of ADHD patients as expressed in daily living. Therefore, the development and optimization of tasks dedicated to neuropsychological research in ADHD is important and should

include rapid decisions with feedback, a motivational component and an increased complexity task. Moreover, given the psychological impact of ADHD on self-esteem, the positioning of each individual in a personal and social context and the limited data available in the memory domain, the study of episodic autobiographical memory seems to be particularly important in ADHD. The low specificity of cognitive pattern in relation to psychiatric and neurodevelopmental comorbidities should be investigated and included in statistical models. Cognitive performances are also dependent on the environmental context and rehabilitative care initiated in childhood. Therefore, it is essential to verify the effect of the type and degree of comorbidities as well as socio-demographic status on neuropsychological results. Medication intake should also be routinely verified at least 24 hours before assessment since psycho-stimulant treatment can increase cognitive performance. Further neuropsychological studies could be associated with clinical, biological and imaging data using new informatics technologies. In addition, a machine learning approach could improve the understanding of the connection between these parameters. Such an approach has already been used for neuroimaging in ADHD. Neuropsychological data should be provided by larger longitudinal studies that take into account ADHD presentations to reduce cognitive heterogeneity and examine the course of ADHD across lifespans. Methodological improvements in cognition assessment are now required.

Disclosures

The authors declare no conflict of interest.

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Table 1: Meta-analysis parameters and pooled effect sizes

Notes: Ctrl, controls; CADHD, childhood ADHD; N/A, not available
** Effect size indicates a better performance for ADHD group.*
The term "reported" indicates that the authors gave the number of studies with data without including the data in statistical models; "controlled" indicates that data were included as co-variable in statistical models; "investigated" indicates that data are included as statistical models as a dependent measure.
Search strategy: Literature searches were conducted using the PUBMED database. We used the following keywords: 'adult attention deficit disorder' and 'adult ADHD'. Each was associated with 'neuropsychological impairment', 'cognitive impairment', 'cognitive disorder', 'cognitive deficit', 'cognitive functioning' and 'cognition'.

First author	Year of publication	Design	Diagnostic criteria	N	Minimum age at inclusion	Unweighted mean age or unweighted mean range (years)	Control for comorbidities	Control for Presentations of ADHD	Control for medication	Cognitive functions investigated	Neuropsychological results (Cohen's d or Hedges' g reported values)	Conclusions
Hervey et al. [7]	2004	ADHD vs. Ctrl.	DSM-, Wender-Utah criteria	N/A	18	ADHD: 32; Ctrl: 32	No	N/A	Reported	Intelligence, Decision-making, Fluency, Memory, Planning, Reaction time, Reaction time variability, Inhibition, Flexibility, Shifting, Vigilance, Working memory, Creativity	Verbal Memory (d=0.90, d=0.60, and d=0.46), Inhibition (d=0.85 and d=0.63), Vigilance (d=0.76, d=0.65 and d=0.51) Working memory (d=0.83 and d=0.31), Flexibility (d=0.68), Fluency (d=0.60), Reaction time variability (d=0.53), Intelligence (d=0.39), Decision-making (d=0.33), Visual memory (d=0.25 and d=0.12), Selective attention (d=0.15), Reaction time (d=0.04*), Creativity (d=0.08)	Neuropsychological impairment is multi-domain in ADHD. Higher disorders are in attention, behavioral inhibition, and memory whereas simple reaction time is normal.
Schoechlin & Engel [37]	2005	ADHD vs. Ctrl or psychiatric ctrl.	DSM-IV, DSM-IV-R, DSM-III-R, CADHD,	867 ADHD; 808 Ctrl	16	ADHD: 31; Ctrl: 31	Controlled	Reported	Reported	Intelligence, Executive, Memory, Fluency, Vigilance, Working memory, Attention	Verbal memory (d=0.56), Visual/verbal fluency (d=0.52), Sustained attention (d=0.52), Focused attention (d=0.52), Abstract problem solving and memory (d=0.51), Simple attention (d=0.38), Intelligence (d=0.27), Visual/figural problem solving (d=0.26), Planning (d=0.21), Figural memory (d=0.18)	Complex attention and verbal memory functions are the most discriminating functions between ADHD and control subjects. Executive functions were not reduced in ADHD patients.
Boonstra et al. [21]	2005	ADHD vs. Ctrl.	DSM-IV, DSM-III-R	662 ADHD; 417 Ctrl	18	ADHD: 22-36 (2-16); Ctrl: 22-41 (2-13)	No	No	Reported	Decision-making, Fluency, Reaction time, Reaction time variability, Inhibition, Flexibility, Shifting, Vigilance, Working memory	Flexibility (d=0.65), Inhibition (d=0.64 and d=0.13), Verbal fluency (d=0.62), Color naming (d=0.62), Word reading (d=0.60), Reaction time variability (d=0.57), Vigilance (d=0.55), Working memory (d=0.44 and d=0.29), Decision-making (d=0.22*)	Neuropsychological disorders in ADHD are multi-domain.

Bridgett & Walker [38]	2006	ADHD vs. Ctrl.	DSM -IV, DSM-III-R	1031 ADHD; 928 Ctrl	16	N/A	Reported	N/A	N/A	Intelligence	Wechsler Adult Intelligence Scale Full Scale IQ (d=0.26)	Adults with ADHD scored lower than non-ADHD adults on the WAIS intelligence tests but the difference was small and mainly explained by some ADHD patients with comorbid disorders.
Balint et al. [22]	2009	ADHD vs. Ctrl.	DSM-III-R, DSM-IV	1711 ADHD; 1731 Ctrl	18	ADHD: 34; Ctrl: 33	No	No	No	Intelligence, Reaction time, Inhibition, Flexibility, Vigilance, Selective attention	Flexibility (d=0.72), Inhibition (d=0.61 and d=0.47), Vigilance (d=0.49), Selective attention (d=0.46), Intelligence (d=0.25), Reaction time (d=0.05)	ADHD patients had poorer performance on complex but not on simple tasks of attention.
Alderson et al. [39]	2013	ADHD vs. Ctrl.	N/A	1015 ADHD; 1103 Ctrl	18	ADHD: 19-47; Ctrl: 19-44	N/A	N/A	N/A	Working memory	Phonological working memory (d=0.55), Visuo-spatial working memory (d=0.49)	Moderate magnitude effect sizes were observed between ADHD and controls on verbal and non-verbal working memory.
Mostert et al. [23]	2015	ADHD vs. Ctrl.	DSM-IV-TR	133 ADHD; 132 Ctrl	N/A	ADHD: 36; Ctrl: 36	Investigated	Reported	Investigated	Intelligence, Working memory, Attention, Inhibition, Set-Sifting, Fluency, Delay discounting, Time estimation	Sustained attention (d=0.71 and d=0.52 and d=0.28), Delay discounting (d=0.48), Working memory (d=0.40* and d=0.37*), Fluency (d=0.32* and d=0.10*), Flexibility (d=0.30), Time estimation (d=0.30 and d=0.14*), Inhibition (d=0.18 and d=0.14* and d=0.05*)	ADHD patients are impaired in several cognitive domains and neuropsychological performances are heterogeneous.
Mowinckel et al. [25]	2015	ADHD vs. Ctrl.	N/A	1971 ADHD; 1899 Ctrl	N/A	ADHD: 19-42; Ctrl: 19-46	Reported	Reported	Reported	Decision-making, Reaction time, Reaction time variability, Inhibition, Vigilance	Decision-making [Instrumental learning (g=0.55), Risky decision making (g=0.23), temporal discounting (g=0.14)]; Attention [Vigilance (g=0.41), Inhibition (g=0.41), Reaction time variability (g=0.40), Reaction time (g=0.09*)]	Decision-making disorders are of similar magnitude to attention disorders.
Skodzik et al. [24]	2016	ADHD vs. Ctrl.	DMS-III-R, DSM-IV, DSM-IV-TR	827 ADHD; 771 Ctrl	18	ADHD: 19-47; Ctrl: 19-44	Yes	N/A	Investigated	Learning and Memory	Verbal memory [Memory acquisition baseline (d=0.58), Delayed free recall (d=0.49), Recognition (d=0.51)]; Visual memory [Delayed free recall (d=0.36), Memory acquisition baseline (d=0.12)]	Memory deficits reflect learning deficits induced at the stage of encoding.