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Estimating DSM accuracy for Attention Deficit Hyperactivity Disorder Based on Biological and Behavioral Correlates

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Abstract

To find objective evidence of accuracy of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in the diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), by comparing classifications of subjects based on behavioral (Attentional Network Test - ANT), psychological (Wechsler Intelligence Scale for Children - WISC-III), and neurophysiological (ANT-related potentials) data. Twenty typically developing (TD) boys and 19 boys diagnosed with ADHD according to DSM-IV-TR, aged 10-13 years, were examined using the ANT with simultaneous recording of the respective event-related potentials (ERPs). They also performed the Block Design, Digit Spam, Vocabulary and Arithmetic subtests of the WISC-III. A total of 815 variables of interest (VOI) obtained from the ANT, WISC-III scores, and ERP parameters were grouped by hierarchical clustering and integrated in 2 to 6 resultant vectors (RVs), from clusters at hierarchical levels 1 to 5. These RVs were used for the reclassification of subjects using the k-means method. Regarding DSM-IV-TR diagnostics, the RVs from behavioral and psychological data and ERPs from the mid-frontal, mid-parietal plus right frontal, right central, and right temporal channels showed accuracy rates from 0.64 to 0.82 using the k-means reclassification. Among reclassifications with higher agreement (0.82), six subjects were reclassified (4 from the TD group, and 2 from the ADHD group). Assuming the reclassification of these six subjects, the estimated agreement between DSM and biological data was 84.61% with kappa index of 0.69. The results suggest biological validity and efficiency of DSM as a tool for ADHD diagnostics.

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1. Introduction.

The validity of the Diagnostic and Statistical Manual of Mental Disorders (DSM, 1, 2) used to be questioned due to its subjective criteria and to the lack of laboratorial tests to define nosological entities (3); therefore, accuracy and biological validity of the DSM still need validation (4). This is particularly important in controversial mental diseases such as the Attentional Deficit Hyperactivity Disorder (ADHD) (5, 6). Similar to some other disorders, ADHD diagnosis is based on the quantification of normal behavior characteristics using DSM scores. Thus, the DSM presents a taxonomy of categories that are defined by dimensional phenomena based on normality, which could not be distinct and well-defined entities (7, 8). Correlations between biological alterations and ADHD still cannot support the diagnosis (8, 9).

Mental disorders are multidimensional complex entities that can be mostly associated with a pool of biological and neurobehavioral variables, many times with non-linear relationships (8, 10) rather than being defined by a single distinct biomarker such as an antibody or aberrant protein (11), what formally define their complexity. A complex nosological entity such as ADHD may be defined by a set of different quantitative variables. In this perspective, since the 70s, multivariate factor analysis techniques have been applied to electroencephalographic or biochemical data in order to develop high-sensitivity and accuracy models for the diagnosis of mental disorders (12-15).

The present study is an attempt to discuss whether the DSM provides an accurate diagnosis, if any, of the nosographic entity called ADHD. This is done by analyzing the large set of behavioral variables in the Attention Network Test (ANT)

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(16), and psychological (from WISC-III) and neurophysiological data (event-related potentials - ERPs recorded during ANT performance) in typically developing boys (TD) and boys diagnosed with ADHD using the DSM-IV-TR criteria.

Several neural findings related to ADHD were obtained via the late P3 (or P300) component of ERPs evoked during cognitive tasks such as detection of "rare events" in the 'odd-ball' paradigm (17). This component proved to be altered in children diagnosed with ADHD (18, 19). Other studies have pointed out that ANT is also sensitive to ADHD, in either behavioral or neurophysiological domains (20, 21). ANT is focused on different dimensions of attention, according to Posner's theory of attentional neural networks, and relates them to distinct independent cerebral systems responsible for vigilance, spatial orientation, and decision-making (16, 22-24).

Here, the relationships between ADHD manifestations, assessed using DSM-IV-TR, and the objective characteristics obtained by experimental measuring were analyzed in order to discuss taxonomic (i.e. classificatory) aspects of ADHD diagnosis using DSM, without considering the role of these characteristics in putative brain mechanisms underlying ADHD.

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2. Methodology.

2.1. Design and Volunteer Selection.

This transversal and exploratory study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the National Institute of Women, Children, and Adolescents Health Fernandes Figueira (CAAE 08340212.5.0000.5269). All the participants gave their oral assent in the presence of their caregivers, who provided written informed consent after receiving a complete description of the study.

Thirty nine boys, aged 10-13 years, were sampled according to DSM-IV-TR (see below): 19 with ADHD and 20 TD, paired for confounder variables (see table 1). All of them had been free of psychotropic medicines for at least 30 days, without history of chronic diseases and psychiatric disorders, as screened by K-SADS-PL (25), and with estimated intelligence quotient (I.Q.) > 80 (see below). They had at least 6 hours of regular sleep before experimental testing.

2.2. Clinical and psychological examination

Each subject was evaluated by a structured interview where their caregivers were shown the DSM-IV-TR criteria, and were instructed to point out carefully whether or not each specific criterion was an exact characteristic of their children's behavior. If there was any doubt or hesitation about any item, it was disregarded. Thus, subjects were classified in accordance with the DSM-IV-TR.

Intelligence Quotient (I.Q.) was estimated by Block Design, Vocabulary, Digit Spam, and Arithmetic subtests from the Wechsler Intelligence Scale for Children (WISC-III), (26, 27).

2.3. Experimental procedures

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The ANT version adapted for children was used, in line with Kratz et al. (20, 21). A forced two-choice test was performed, where the subject was instructed to observe the horizontal orientation of a target stimulus (yellow fish), which is (or not) preceded by a cue signal (a red star). The target appeared above or below the fixation point. There were three equiprobable cue conditions corresponding to this signal position or to its non-appearance: 1) at the subsequent upper or lower position of the target - spatial cue condition; 2) at the central fixation point - neutral cue condition; or 3) no cue condition. The subject had to promptly press the left or right arrow key on the keyboard, according to the horizontal orientation of the target. The test was organized in 8 test blocks, with 24 trials each, and one preceding training block. Reaction time (RT) was recorded. For the detailed ANT procedure, see Abramov et al, 2017 (28).

2.4. EEG acquisition

During the ANT performance, the subject's EEG was recorded using a Nihon Kohden NK1200 EEG System at 20 scalp points according to the International 10/20 system, with reference at the central leads (linked C3 and C4, the physical reference of the System). Impedance was below 10 kΩ, sampling rate was 1000 Hz with a resolution of 16 bits, and filters were: low-pass 0.5 Hz, high-pass 100 Hz, and notch 60 Hz

2.5. Data analysis

The following behavioral variables were obtained using ANT for each subject: average accuracy (AC) of task performance, i.e. the percentage of correct responses; mean RT and its standard deviation, called intraindividual variation of RT (IVRT), for each cue and target condition and their respective attentional network scores (alerting, orienting, and conflict resolution) according to (16), mean RT of

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errors and hits; and learning rates for RT and VIRTs, i.e. the mean scores of the first ANT trial block divided by those of the eight following experimental blocks

In each subject, for each cue and target condition, in each EEG derivation (except for C3 and C4, see below) the following ERP characteristics were estimated: (1) mean peak amplitude, (2) mean peak latency, and the (3) mean of the total amplitude under the wave (i.e. the sum of all amplitude values, proportional to mean amplitude) inside selected time windows, the regions of interest (see Figure 1-A, red squares, and Supplemental Table 1 for window measures), which include late P3-like components evoked by both the cue and the target stimuli, and the voltage variation between these two ERPs. The same ERP parameters were calculated for the difference between signals of the two central channels (C3 minus C4) instead of estimating the absolute signal values in each lead (see discussion).

The total number of variables of interest (VOI) was 815 (see Supplemental Table 2): four scores obtained from WISC-III subtests; 31 behavioral variables obtained from ANT; and 780 neurophysiological variables (39 for each channel).

The neurophysiological variables obtained represent topographically different parameters of regional (local) cerebral activity, while the variables from ANT and WISC provide the integral characteristics of the individual. We assumed that the activity in certain brain regions of subjects performing ANT would correlate with the phenomenology of ADHD (20, 21, 24), but we do not know yet which regions are most informative and sufficient to explain the phenomenology of ADHD in the ANT. For this reason, 42 different sets of channels (see Supplemental Table 3) were used for data mining, in an attempt to find the best agreement with DSM (if any).

Predictor (DSM scores for ADHD: total, for inattention and for hyperactivity/impulsivity) and confounder variables (family income, hours of sleep the night before, week time exposed to computers and videogames, estimated I.Q.

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assessment, mean age of group individuals and learning rate for RT) were compared between the groups using the Student's T-test or Mann-Whitney U-test, after estimating normality and scedasticity using the Shapiro-Wilk and Levene's tests, respectively.

The selected VOIs (ANT, WISC-III and ERP variables of the above-mentioned 42 channel sets) were clustered into the Resultant Vectors (RVs), reducing data dimensionality. As the Principal Component Analysis is not suitable to handle samples smaller than the number of variables, clusterization using the hierarchical method was proposed to classify the VOIs into their clusters and calculate RVs by transposing the data matrix (variables as cases and vice-versa). Pearson's linear correlation was used as distance metrics (see algorithms in Supplemental Information 1), since variables are of distinct dimensions while the shape of relationships among different biological dimensions should be preserved (29), and Ward's minimum variances was adopted as an agglomerative method (29, 30, Supplemental Information 1). RVs are the grand average from z-scores of variables inside each emergent cluster. Two to six RVs were obtained integrating clusters of variables from the first to fifth levels of the tree, respectively.

Subsequently, subjects were reindexed in two new groups according to channel set and RV set using the K-means clustering method, in order to check the agreement between classification of subjects using DSM-IV-TR and their reclassification based on objective behavioral, psychological, and neurophysiological data. The K-Means algorithm was iterated until complete convergence. The mean number of concordant subjects after reindexation was calculated among all RV sets for each channel set, and the respective probability that agreement was random was verified using the Binomial probability mass function. The probability of classification of each subject in one of the two groups was considered equal to 0.5 (Supplemental Information 2). Subjects' indices after reclassification with agreement higher than

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80% in the original classification by DSM, where applicable, were further analyzed to check whether reclassification of subjects was consistent among index sets. Agreement was measured by estimating the kappa index (31).

3. Results

3.1. Evaluating predictor and confounder variables by diagnostic group.

Control and ADHD groups showed significant differences regarding quantitative scores from DSM-IV-TR ($p < 0.001$; Table 1). There was a somewhat higher probability of equality related to hyperactivity/impulsivity between the two groups ($p = 0.023$) here. Among variables considered as confounder, there were significant differences only in I.Q. scores ($p = 0.006$), although the I.Q. of all children were higher than 80. All other variables, including Learning Index, were not significantly different according to the Student's T-test. Normality and homoscedascity were not statistically rejected.

3.2. Overview of Event-Related Potentials.

Cue and target-related potentials with late peak latency (> 200ms, corresponding to parietal P3) were observed at all channels using the current reference system; however, voltage variation between cue and target responses did not appear in the occipital and frontopolar leads (Figure 1-A). Peak amplitude varied from the maximum of 18µV for the frontopolar target ERP to the minimum of 1µV for the difference between C3 and C4 (Figure 1-B).

3.3. Data Mining and Reclassification of subjects

For all the above 42 channel sets and RV sets (from the first to the fifth Hierarchical tree levels), mean agreement between the original classification and K-means reclassification was 61.04 ± 4% (mean ± std. deviation), which was close to

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randomness (50%). Among all channel sets considered, the three sets: [C3-C4, Fz (midfrontal), F8 (right anterior temporal), F4 (right frontal), and Pz (midparietal)], [C3-C4, Fz, and Pz], and [C3-C4, Fz, F8, T4 (right midtemporal), T6 (right posttemporal), Pz] had the highest mean agreements of 79.48%, 78.97%, and 77.43%, respectively. Six RV/Channel sets manifested highest reindexation agreement of 82% (32 concordant subjects), with high probability of not being random ($p < 0.0001$, Table 2). The Supplemental Figure 1 shows the hierarchical tree of variables from the channel set [C3-C4, Fz, F8, F4, Pz], where the six clusters from the first five levels are indicated. The lowest reindexation agreement, with high probability of random reclassification (agreement = 0.52, $p = 0.125$), was observed for the set with all 20 channels (Supplemental Table 4).

The above-mentioned six reclassifications with high agreement (> 0.82%) included the same six reindexed subjects. Four of them were originally classified by the DSM-IV-TR as controls (coded as C009, C012, C020, C023) and two of them were classified as ADHD (T010, T026) (Supplemental Table 5). They seemed to be the definite non-concordant cases between DSM and biological classifications, which indicates agreement between DSM and biological variables equal to 84.61% in 33 subjects. The Kappa Index was 0.69, i.e., “substantial strength of agreement” (29). Considering DSM-IV-TR as “the alternative test” and biological experimental data as the “standard test”, DSM sensitivity and specificity were estimated as 88% and 89%, respectively (see supplemental information 4).

Statistical comparison considering the predictor variables in the control versus ADHD groups before ($n = 20$, $n = 19$) and after ($n = 16$, $n = 17$) reindexation (Table 3) revealed that the difference in predictor variables between groups was slightly higher for all cases studied, even when new groups proved to have a lower number of

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subjects than the original groups (Student's T-test for independent samples, regarding only true-positive and negative subjects, n=16 and 17, respectively).

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4. Discussion and Conclusion.

Our study explored the possibility of examining human behavior using the DSM manual. We showed that DSM criteria seemed to be biologically justified for ADHD diagnostics by using "substantial strength of agreement" with a specific pool of behavioral, psychological, and neurophysiological variables. In this pool, the most informative neurophysiological variables proved to be topographically asymmetrical and represent the binded information from parietal and frontal regions linked to right frontal sites and the early (45 to 290ms after target) 'C3 minus C4' asymmetry. This asymmetry has already been shown to correlate with DSM scores, mainly with hyperactivity/impulsivity (32). Our results are evidence that some people could be biologically classified as "inattentive and hyperactive".

It was not the focus of the present investigation to establish models for ADHD or its neural mechanisms. However, the high degree of agreement between reclassification by the K-means and original grouping by DMS revealed certain biological aspects of ADHD regarding alterations in the frontal control over executive functions (18, 20, 33, 34). Some studies have shown that right frontal processing is altered in ADHD patients (35) and right caudate volume positively correlates with ADHD symptomatology (36). In our results, right frontal (F4) and right anterior temporal (F8) ERP characteristics were present in the channel sets related to the first and third most concordant reclassifications. Moreover, the right midtemporal (F4) and right posterior temporal (T6) channels appeared in the third channel set. This is in accordance with the role of right temporal cortex in visuospatial memory (37-39), which is particularly involved in ANT performance based on visuospatial tasks. In our previous work, spectral and coherence analyses of the resting EEG also showed asymmetrical topographic patterns, with signs of relative inactivation of the frontal and *left* temporal cortex, known to be responsible for voluntary attention in norm, and

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impaired in ADHD patients. This left-side 'inactivation' may be compensated by the relatively higher activation of the contralateral cortex and can partially explain the leading role of ERP data from the right frontal-temporal regions in discriminating between patients and controls in the present research (40).

As a matter of fact, some of the above-mentioned VOI sets seem to be quite close to current neural models for ADHD and related experimental findings (34-37). They are consistent with DSM-IV-TR classification, with accuracy of 84%. The present analysis suggests that DSM-IV-TR is actually an effective and biologically justified tool for ADHD diagnosis. It is noteworthy that a discrepancy between DSM and biological classification in our data was observed only in 2 ADHD patients versus 4 TD subjects. This may reflect a probably less determined status of "normal" population as evaluated by DSM, and the existence of some unaccounted factors is quite possible.

Although a Kappa index of 0.69 should be considered with reservations for some clinical settings, a clinical method such as DSM-IV-TR, with sensitivity of 89% and specificity of 88% with regard to objective behavioral, psychological, and neurophysiological measures, should be considered as particularly relevant regarding the complexity of mental disorders without validated biomarkers. Unfortunately, the only psychiatric tool for diagnosis and intervention is still phenomenological examination, which must be systematically (although qualitatively) performed based on manuals such as the DSM.

The small sample size due to exclusion criteria and control of confounder variables, such as age, is an important limitation in this study. Any subject with the slightest suspicion of comorbidity was excluded. Among confounder variables, only the estimated I.Q. scores were different between the groups diagnosed using DSM-IV-TR. However, literature has shown that intelligence tests are sensitive to ADHD,

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and scores in patients are generally lower than in controls (40). Even taking into account the above restrictions, there is no doubt that the data obtained seem to be quite consistent.

In conclusion, we have found that there is a consistent complex of biological information which is in accordance with previous knowledge on ADHD, and it shows substantial agreement with DSM-IV-TR, which emphasizes the validity of this manual. We expect further studies with larger samples of both genders and different ages to elucidate and biologically validate more detailed aspects of DSM diagnostics, such as ADHD subtypes. In the present research, our objective was to draw attention to psychiatric approaches based on diverse and multiple factors intervening in the biological mechanisms of human behavior and its disorders.

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Figure Title and Legend

Figure 1. Cue and Target-Related Potentials and Interstimuli Voltage Variation from Attentional Network Test

Figure 1. Cue- and target-related potentials and interstimulus voltage variation during Attention Network Test performance (averaged over all ANT conditions and all subjects). (A) Overview of the ERPs for all channels, including 'C3 minus C4' (normalized amplitudes, µV), with waves of interest (in red dotted squares) to calculate the mean square of the total area under each wave and peak amplitudes/latencies. In the grey box: C, cue and T, target onsets; blue dotted line, trigger signal. (B) ERPs for selected channels, in different colors, showing wave amplitudes (µV).

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Tables

Table 1

Description and statistical comparisons of predictor and confounder variables between groups

	Typically Developing (n = 20)		ADHD (n=19)		
Predictor Variables (DSM IV scores)	**Mean**	**Std. Dev**	**Mean**	**Std. Dev**	**p-value [a]**
Inattention	**2.40**	**1.66**	**7.21**	**1.27**	**< 0.001**
Hyperactive+Impulsive	2.60	1.63	4.36	2.90	0.023
Total	**5.00**	**2.75**	**11.63**	**3.00**	**< 0.001**
Confounder Variables					
Age (years)	11.30	0.86	11.52	1.07	0.471
Estimated I.Q.	**109.35**	**13.53**	**97.36**	**12.53**	**0.006**
Hours of Sleep (last night)	7.25	2.12	7.68	1.73	0.490
Videogame (hours/week)	3.40	1.23	2.89	1.66	0.286
Computer handling (hours/week)	3.30	1.26	2.94	1.68	0.462
Years in the school	6.05	1.14	6.10	1.32	0.889
Familiar Incomes (monthly, BR Reals)	6355.00	5643.57	3978.94	4436.91	0.153
Learning Index [b]	1.22	0.34	1.26	0.30	0.456

[a] Student's T-test for independent samples
[b] Learning Index in the ANT: mean reaction time (RT) (ms) of first trial block / mean RT(ms) of the eighth experimental blocks

Table 2

Reclassification indices of subjects by the K-Means method with highest mean agreement to DSM classification

	Sets of Resultant Vectors in Clusters by tree level							
Channel Set[a]	2 RVs(1st L)	3 RVs (2nd L)	4 RVs (3rd L)	5 RVs (4th L)	6 RVs (5th L)	**Mean**	Conc Subjects[b]	p-value[c]
C3-C4, F8, F4, Fz, Pz	0,7948	0,8205	0,8205	0,7692	0,7692	**0,7948**	31	0,0001
C3-C4, Fz, Pz	0,7435	0,8205	0,7692	0,8205	0,7948	**0,7897**	30	0,0003
C3-C4, F8, T4, T6, Fz, Pz	0,7435	0,6923	0,8205	0,7948	0,8205	**0,7743**	30	0,0003

[a] according to the International 10-20 system for EEG leads; C3-C4, the channel of difference between two leads;
[b] number of "concordant" subjects (between original DSM classification and final reclassification) equivalent to the mean agreement (truncated values).
[c] Probability that reclassification is random, binomial probability mass function, regarding the probability that a subject is classified in one of the two groups = 0.5

Table 3

Statistics of the Predictor Variables before and after reindexation by Resultant Vectors of Variables of Interest

	Control by DSM		ADHD by DSM		**TRUE NEGATIVE (Control) n = 16**		**TRUE POSITIVE (ADHD) n = 17**		
DSM Scores	Mean	Std. Dev	Mean	Std. Dev	**Mean**	**Std. Dev**	**Mean**	**Std. Dev**	p-value [a]
Inattention	2.40	1.66	7.21	1.27	2,19	1,68	7,24	1,35	< 0,001
Hyperactivity/impulsivity	2.60	1.63	4.36	2.90	2,31	1,40	4,47	3,02	0,014
Total	5.00	2.75	11.63	3.00	4,56	2,53	11,76	3,11	< 0,001

[a] significance comparing True Negative and True Positive subject's classifications; Student's T-test for Independent measures.