# *Estimating DSM Validity for Attention Deficit/Hyperactivity Disorder Based on Neurophysiological, Psychological, and Behavioral Correlates*

Dimitri M. Abramov[1], Evelyne Vigneau[2], Saint-Clair Gomes-Junior[3], Carlos Alberto Mourão-Júnior[4], Monique Castro-Pontes[1], Carla Quero Cunha[1], Leonardo C. deAzevedo[1], Vladimir V. Lazarev[1]

1. Laboratory of Neurobiology and Clinical Neurophysiology, National Institute of Women, Children, and Adolescents Health Fernandes Figueira, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil;

2. StatSC, Oniris, INRA, Nantes, France;

3.Clinical Research Unit, National Institute of Women, Children, and Adolescents Health Fernandes Figueira, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil; and

4.Laboratory of Psychophysiology, Institute of Biological Sciences, Federal University of Juiz de Fora, Juiz de Fora, Brazil.

**Corresponding Author:**
Dimitri Marques Abramov
National Institute of Women, Children, and Adolescents Health Fernandes Figueira, Oswaldo Cruz Foundation
Avenida Ruy Barbosa, 716, Flamengo, Rio de Janeiro, RJ
Postal Code: 22.250-020
Phone: +55 21 2554-1955, +55 21 2554-1805
E-mail: dimitri.abramov@iff.fiocruz.br

**Short Title:** *Estimating DSM validity for ADHD diagnosis.*

# Abstract

**Background.** The psychiatric nosology lacks objective biological foundation, as well as characteristic biomarkers for the diagnoses, which raises questions about its validity. The problem is particularlly evident concerning the Attention Defict/Hyperactivity Disorder (ADHD). The objective of this study is estimate if the “Diagnostic and Statistical Manual of Mental Disorders” (DSM) is biologically valid for ADHD diagnosis, using a multivariate analysis of a large dataset concerning neurophysiological, behavioral, and psychological variables.

**Methods:** Twenty typically developing boys and 19 boys diagnosed with ADHD, aged 10-13 years, were examined using the Attentional Network Test (ANT) with records of event-related potentials (ERPs). From 815 variables, a reduced number of latent variables (LVs) were extracted with a clustering method for the reclassification of subjects using the k-means method.

**Results:** From datasets including ANT and WISC scores and ERPs from the mid-frontal, mid-parietal, right frontal, and central channels, only eight subjects were miss-reclassified by the LVs. In the reclassification, the estimated specificity of 75% and sensivity of 85% for DSM. The kappa index between DSM and

behavioral/psychological/neurophysiological data was 0.72, regarded as a “substantial level of agreement”.

**Discussion:** Results suggest the biological validity of DSM for ADHD diagnosis, in accordance to alteractions in fronto-striatal networks previously related to ADHD.

# Introduction

The validity of the *Diagnostic and Statistical Manual of Mental Disorders* -DSM (American Psychiatric Association, 1994 – 2013) [1,2] is usually questioned due to its subjective criteria and to the absence of objective tests to define nosological entities [3, 4]. Therefore, the lack of objective determinants opens the way to criticism and doubts about the nosological criteria itself [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, DSM has a taxonomy of categories that are defined by dimensional phenomena based on a variation from normality [7,8]. Correlations between biological alterations and ADHD are still not enough to support the diagnosis [8, 9].

Mental disorders are multidimensional complex entities that can be mostly associated with a pool of biological and neurobehavioral variables, often with non-linear relationships [8, 10], rather than being defined by a single distinct biomarker such as an antibody or aberrant protein [11], which formally defines their complexity. A complex nosological entity such as ADHD may be defined by a set of different quantitative variables. From this standpoint, multivariate factor analysis techniques have been applied to electroencephalographic or biochemical data since the 70's in order to develop high-sensitivity and accuracy models for the diagnosis of mental disorders [12-16].

The present study is an attempt to discuss whether DSM is valid for an accurate diagnosis of the nosological entity called ADHD, analyzing a small sample of subjects where the confounding variables and the bias were well controlled. Large datasets of (1) behavioral variables, and (2) neurophysiological data (event-related potentials – ERPs, including late cognitive component P3 or P300 [17,18]), both obtained while subjects performed the Attention Network Test - ANT [19,20], as well as (3) psychological characteristics (from WISC-III) have been collected from typically developing boys (TD) and boys diagnosed with ADHD using the DSM-IV-TR criteria.

However, high-dimensional datasets from relatively few observations or subjects usually appear to be statistically questionable and hamper unambiguous interpretation. In order to tackle this problem (the curse of the dimensionality), approaches based on

feature selection in a supervised context or on feature extraction in explorative data analysis (for instance, Principal Components Analysis, Canonical Correlation Analysis) have been investigated. In particular, we have considered a strategy of unsupervised clustering of variables that makes it possible to extract synthetic/latent variables through cluster analyses [21-23].

The relationships between ADHD manifestations, evaluated using DSM-IV-TR, and the objective characteristics obtained by the above-mentioned experimental measurements were here analyzed. The aim was to discuss the taxonomic (i.e. classificatory) aspects of ADHD diagnosis using DSM, compared with a data-driven statistical approach, without considering the role of these characteristics in putative brain mechanisms underlying ADHD. This study does not address controversial issues, as if the phenomenology of ADH actually configures a mental disorder or not. Here we seek to discuss the validity of the DSM as a tool to identify this phenomenology, inferring about its sensitivity and specificity.

# Methods

## Design and Subject 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 provided their oral consent in the presence of their caregivers, who provided written informed consent after receiving a complete description of the study.

Sixty boys, aged 10-13 years, were included according to DSM-IV-TR: 35 with ADHD (coded as T001 to T035) and 25 TD (coded as C001 to C025). The exclusion criteria were: (1) history of chronic diseases, and any suspicion of psychiatric disorders other than ADHD (psychosis, affective, obsessive-compulsive and tic disorders, phobic and post-traumatic stress conditions, anorexia, bulimia, encopresis or enuresis) as screened by K-SADS-PL [23]; (2) use of any psychotropic medicines for at least 30 days; (3) estimated I.Q. equal or lower than 80; and (4) less than 6 hours of regular sleep and (5) report of somnolence before the ANT testing.

We considered as confounding variables years in school, monthly family income (in Brazilian Reals), sleep hours the night before, and mean weekly time which the boy dedicated to computer activities and videogames (ranked as follows: 1, less than 2h/week; 2, 2-4h; 3, 5-8h; 5, more than 15 h/week), learning rate (see below) in the experimental procedure, as well as age.

After applying the exclusion criteria, the behavioral analysis of accuracy (AC) and speed-accuracy tradeoff (see below), and also after excluding confounding outliers, there remained 19 ADHD and 20 TD boys in the sample, whose data were considered as experimental results.

## Clinical and Psychological Examination

Each subject was evaluated using 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 on 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 and Vocabulary subtests from the Wechsler Intelligence Scale for Children, WISC-III [24, 25]. We also performed the Arithmetic and Digit Spam subtests to the pool of variables used in the multivariate analysis.

## Experimental Procedures

The ANT version adapted for children was used [20, 26]. 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's 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) and accuracy (AC, rate of hits) were recorded.

Subjects with both AC lower than 70% and speed-accuracy tradeoff (estimated as AC × RT) lower than the mean sample value minus two standard deviations were excluded.

## EEG Acquisition

During the ANT, the subject's EEG was recorded using a Nihon Kohden NK1200 EEG System at 20 scalp points according to the International 10/20 System (Figure 1), with reference at the lateral central leads (linked C3 and C4, the physical reference of the System). Impedance was below 10 kΩ, sampling rate was 1000 Hz with a 16-bit resolution, and the filters were: low-pass 0.5 Hz, high-pass 100 Hz, and notch 60 Hz.

**Figure 1. Electrical potentials related to Attention Network Test.** (A) Cue- and target-related potentials and inter-stimulus voltage variation during Attention Network Test performance (averaged over all ANT conditions and all subjects). Overview of the ERPs for all channels, including 'C3 minus C4' (normalized amplitudes, μV), with waves of interest (in dotted squares) to calculate the mean square of the total area under each wave and peak amplitudes/latencies. In the grey box, C and T stand for cue and target onsets; the trigger signal is identified by dotted lines. Above the ERP graphs, scalp areas are marked with letters with even (right), odd (left) or z (midline) indices: occipital – O, parietal – P, central – C, frontal – F, frontopolar – Fp, mid-temporal – T, posterior temporal – T5 and T6, and anterior temporal – F7 and F8. Scalp scheme for 10-20 montage at the bottom left. (B) ERPs for selected channels, in different colors, showing wave amplitudes (μV).

# Data Analysis

Predictor (i.e. DSM score for ADHD as the sum for inattention and hyperactivity/impulsivity scores) and confounding variables were compared between the groups using Student's t-test, after normality and heteroscedasticity assessments were performed using the Shapiro-Wilk and Levene's tests, respectively.

Several behavioral variables were gathered from the ANT for each subject: mean AC of task performance, i.e. the percentage of correct responses; mean Reaction Time (RT) and its standard deviation, called intra-individual variation of RT (IVRT), for each cue and target condition. Additionally, data included the ANT scores of the subjects: alerting, orienting, and conflict resolution, mean RT for correct and incorrect responses,

and learning rates (the mean scores of the first ANT trial block divided by those of the last experimental block evaluated for RTs and IVRTs).

The following ERP characteristics were estimated inside time intervals of interest (see dotted squares in Figure 1 and their measures in S1 Table) for each subject, in each cue and target condition and in each EEG derivation (except for C3 and C4): (1) peak amplitude, (2) peak latency, and (3) the total amplitude under the wave (i.e. the sum of all amplitude values, proportional to the mean amplitude). These three time intervals included late ERPs evoked by 1) the cue, 2) the target stimuli, and 3) 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 of these leads, observing the EEG reference used here (C3+C4).

Thus, the total number of variables of interest (VOI) was 774: four scores obtained from the above mentioned WISC-III subtests, 29 behavioral variables obtained from ANT, and 741 neurophysiological variables (39 for each of the 18 channels and C3-C4).

The neurophysiological variables obtained represent topographical parameters of regional (local) cerebral activity, while the variables from ANT and WISC provide the integral characteristics of the subject. For analysis, we assumed that the activity in

certain brain regions of the subjects performing ANT (but not all) would best correlate with the phenomenology of ADHD. For this reason, 40 different sets of channels (Table 2) were used for data mining, in an attempt to find the best agreement with DSM (if any).

The data from each investigated set of EEG channels was analyzed either with or without behavioral (ANT) and psychological (WISC) variables. They were submitted to an unsupervised method called Clustering of Variables around Latent Variables (CLV) [21,22]. The aim was to reduce the number of dimensions in the variables space by extracting latent variables (LVs), each of them associated with a cluster of the VOI variables. This clustering approach is based on correlation similarity indices between variables and aims to identify directional clusters of variables. As it is, each extracted LV, associated with a specific cluster of variables, is defined as the first (standardized) principal component of the variables assigned to this cluster [21]. In our study, the clusters of variables around one to four LVs was systematically considered and the best number of LVs was determined according to the classification of subjects.

Indeed, our ultimate purpose was to reindex the subjects into two groups according to the objective behavioral, psychological, and neurophysiological data, all of which were summarized around the extracted LVs. A k-means clustering method [27] was performed on the subjects using the LVs. Each reclassification obtained (named “output”) was checked for agreement compared to the classification of subjects using the DSM-IV-TR (called “DSM agreement”). The probability that the DSM agreement could

be observed under randomness was checked using the Chi-Square test for categorical variables, with one degree of freedon, where the expected value was 20 (absolute randomness). The kappa index [28] was also evaluated to estimate the DSM agreement level (S2 method).

In order to determine reclassification consistency, we analyzed which subjects were reclassified into the other group than his/her original DSM group ("miss-reclassification"). This was done for each specified DSM agreement rate, on the basis of the outputs providing this level of agreement. By dividing the DSM agreement level and the number of miss-reclassified subjects in any output with that DSM agreement, we suggested a measure for the "classifier power".

Subsequently, we considered that the outputs with the highest classifier power were the most representative to estimate the validity of the DSM. From these most representative outputs, we suggested a sensitivity and specificity analysis for DSM criteria for ADHD

The dataset with variables used in multivariate analysis is available as supplementary material (S3 Dataset).

# Results

## Evaluating predictor and confounding variables

Control and ADHD groups showed significant differences in the quantitative scores from DSM-IV-TR ($p < 0.05$) (Table 1). The significance level of the difference between the two groups was higher for the inattention score than for the hyperactivity/impulsivity score. Among variables considered as confounders, the I.Q. scores in ADHD group were lower than in TD boys ($p = 0.006$), although they were always higher than 80. All other variables, including learning rate, were not significantly different between the two groups according to the Student's t-test (normality and homoscedasticity were not statistically rejected).

**Table 1.** Predictor and Confounding Variables Between Groups

| | **Typically Developing (n = 20)** | | **ADHD (n = 19)** | | | |
|---|---|---|---|---|---|---|
| | *M* | *SD* | *M* | *SD* | T-value[a] | *p*-value |
| Predictor Variables (DSM scores) | | | | | | |
| **Inattention** | **2.40** | **1.66** | **7.21** | **1.27** | **-10.09** | **< 0.001** |
| **Hyperactive+Impulsive** | **2.60** | **1.63** | **4.36** | **2.90** | **-2.36** | **0.023** |
| **Total** | **5.00** | **2.75** | **11.63** | **3.00** | **-7.19** | **< 0.001** |
| Confounding Variables | | | | | | |
| Age (years) | 11.30 | 0.86 | 11.52 | 1.07 | -0.73 | 471 |
| **Estimated I.Q.** | **109.35** | **13.53** | **97.36** | **12.53** | **2.86** | **0.006** |
| Hours of Sleep (last night) | 7.25 | 2.12 | 7.68 | 1.73 | -0.70 | 0.490 |
| Videogame [b] | 3.40 | 1.23 | 2.89 | 1.66 | 1.08 | 0.286 |
| Computer handling [c] | 3.30 | 1.26 | 2.94 | 1.68 | 0.74 | 0.462 |
| Years in school | 6.05 | 1.14 | 6.10 | 1.32 | -0.14 | 0.889 |
| Family Incomes [d] | 6355.00 | 5643.57 | 3978.94 | 4436.91 | 1.46 | 0.153 |
| Learning Index [e] | 1.22 | 0.34 | 1.26 | 0.30 | -0.36 | 0.721 |

[a] Inference by Student's t-test for independent samples, significant differences (*p* value < 0.05) in bold.

[b, c] Videogame and computer handling were scored as: 1 = less than 2h/week; 2 = 2-4h/wk, 3 = 5-8 h/wk, 4 = 8-15 h/wk, 5 = more than 15h/wk.

[d] in brazilian reals (R$), per month

[e] Learning Index in the ANT: reaction time (RT) (ms) of last trial block / mean RT (ms) of the first experimental blocks**.**

## Overview of Event-Related Potentials

Cue and target-related potentials with late peak latency (> 200ms, corresponding to parietal P3) were observed in all channels. Peak amplitude varied from the maximum value of 18µV for the frontopolar target ERP to the minimum value of 1µV for the difference between C3 and C4 (Fig 1).

## Data Mining and Reclassification of subjects

For all 40 channel sets and LV sets (extracting 1 to 4 LVs), with and without behavioral variables enclosed (Table 2), we found that the DSM agreement rates ranging from 0.51 (20 subjects, p = 0.125, $\chi^2$ = 0.00, p = 1.000) to 0.82 (32 subjects, $\chi^2$ = 7.20, p = 0.004). The *worst* mean agreement level between DSM and K-means reclassification was 23.25 for channel set [F7, T3, T5, Fp1, F3, C3-C4, P3, O1, Fz, Pz] ($\chi^2$ = 0.43, p = 0.528); and the best mean DSM agreement was 30.62 for channel set [C3-C4, F8, F4, Fz, Pz] $\chi^2$ = 5.63, p = 0.010).

**Table 2.** DSM Agreement (Number of Subjects) by Channel Set and Number of Latent Vectors for Variables of Interest

| Channel Sets [a] | ERPs variables only | | | | All variables of Interest | | | | MEAN |
|---|---|---|---|---|---|---|---|---|---|
| | 1 LV | 2 LV | 3 LV | 4 LV | 1 LV | 2 LV | 3 LV | 4 LV | |
| *All Channels* | 20 | 24 | 24 | 25 | 20 | 24 | 24 | 28 | 23.63 |
| *Fz Cz Pz Oz* | 23 | 25 | 23 | 22 | 27 | 28 | 29 | 29 | 25.75 |
| *F7 T3 T5 Fp1 F3 C3-C4 P3 O1 Fz Pz* | 21 | 22 | 22 | 24 | 20 | 22 | 27 | 28 | 23.25 |
| *C3-C4 F8 T4 T6 Fp2 F4 P4 O2 Fz Pz* | 24 | 24 | 24 | 24 | 24 | 24 | 24 | 24 | 24.00 |
| *F7 T3 T5 F8 T4 T6 Fz Cz Pz* | 20 | 25 | 25 | 24 | 23 | 25 | 29 | 28 | 24.88 |
| *F7 T3 T5 C3-C4 F8 T4 T6 Fz Cz Pz* | 22 | 20 | 22 | 24 | 22 | 28 | 28 | 28 | 24.25 |
| *F7 T3 T5 Fp1 C3-C4 F8 T4 T6 Fp2 Fz Cz Pz* | 21 | 23 | 24 | 24 | 23 | 28 | 25 | 28 | 24.50 |
| *C3-C4 Fz Cz Pz* | 27 | 27 | 27 | 26 | 30 | 30 | 30 | 30 | 28.38 |
| *F7 T3 T5 C3-C4 Fz Pz* | 22 | 28 | 23 | 22 | 22 | 30 | 28 | 29 | 25.50 |
| *C3-C4 F8 T4 T6 Fz Pz* | 20 | 25 | 24 | 22 | 31 | 31 | 29 | 28 | 26.25 |
| *F7 T3 C3-C4 Fz Pz* | 23 | 27 | 20 | 31 | 26 | 29 | 31 | 29 | 27.00 |
| *C3-C4 F8 T4 Fz Pz* | 31 | 30 | 28 | 29 | 30 | 30 | 31 | 28 | 29.63 |
| *C3-C4 Fz Pz* | 30 | 30 | 29 | 30 | 29 | 28 | 30 | 29 | 29.38 |
| *F7 T3 T5 C3-C4 F8 T4 T6 Fz Pz* | 21 | 20 | 23 | 22 | 22 | 26 | 28 | 29 | 23.88 |
| *F7 C3-C4 F8 Fz Pz* | 23 | 29 | 29 | 27 | 30 | 28 | 31 | 29 | 28.25 |
| *F7 F3 F8 F4 Fz Pz* | 27 | 25 | 31 | 30 | 29 | 29 | 30 | 31 | 29.00 |
| *F7 F3 C3-C4 F8 F4 Fz Pz* | 27 | 27 | 28 | 30 | 28 | 30 | 31 | 30 | 28.88 |
| *F7 F3 F8 F4 Fz* | 25 | 26 | 27 | 27 | 27 | 29 | 29 | 28 | 27.25 |
| *F7 F3 F8 T4 F4 Fz Pz* | 28 | 25 | 29 | 29 | 28 | 29 | 30 | 29 | 28.38 |
| *F7 F3 C3-C4 F8 F4 Fz* | 27 | 26 | 23 | 28 | 27 | 29 | 29 | 28 | 27.13 |
| *F7 Fp1 F3 C3-C4 F8 Fp2 F4 Fz Pz* | 27 | 29 | 29 | 30 | 28 | 29 | 29 | 26 | 28.38 |
| *F7 Fp1 F3 F8 Fp2 F4 Fz Pz* | 29 | 29 | 29 | 29 | 28 | 29 | 29 | 28 | 28.75 |
| *F7 Fp1 F3 C3-C4 F8 Fp2 F4 Fz* | 28 | 28 | 28 | 28 | 28 | 28 | 27 | 28 | 27.88 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *F7 Fp1 F3 F8 Fp2 F4 Fz* | 27 | 28 | 28 | 28 | 28 | 28 | 28 | 29 | 28.00 |
| *F7 F3 C3-C4 P3 F8 F4 P4 Fz Pz* | 27 | 28 | 27 | 21 | 29 | 29 | 29 | 29 | 27.38 |
| *F7 F3 P3 F8 F4 P4 Fz Pz* | 25 | 29 | 29 | 24 | 26 | 29 | 29 | 28 | 27.38 |
| *F7 F3 C3-C4 P3 Fz Pz* | 23 | 22 | 20 | 25 | 27 | 25 | 30 | 27 | 24.88 |
| *F7 F3 P3 Fz Pz* | 26 | 21 | 25 | 22 | 28 | 23 | 28 | 24 | 24.63 |
| ***C3-C4 F8 F4 P4 Fz Pz*** | **28** | **31** | **29** | **27** | **30** | **32** | **31** | **29** | **29.63** |
| *F8 F4 P4 Fz Pz* | 27 | 29 | 27 | 24 | 28 | 27 | 27 | 27 | 27.00 |
| *F7 F3 C3-C4 Fz Pz* | 26 | 27 | 28 | 22 | 29 | 29 | 30 | 29 | 27.50 |
| *F7 F3 Fz Pz* | 25 | 28 | 27 | 27 | 29 | 28 | 31 | 29 | 28.00 |
| ***C3-C4 F8 F4 Fz Pz*** | **32** | **31** | **31** | **31** | **29** | **31** | **31** | **29** | **30.63** |
| *F8 F4 Fz Pz* | 30 | 29 | 29 | 29 | 30 | 30 | 30 | 31 | 29.75 |
| *C3-C4 F8 T4 F4 P4 Fz Pz* | 28 | 30 | 27 | 23 | 31 | 30 | 31 | 27 | 28.38 |
| *F7 T3 F3 C3-C4 P3 Fz Pz* | 23 | 22 | 26 | 26 | 23 | 25 | 29 | 29 | 25.38 |
| *C3-C4 F8 T4 F4 Fz Pz* | 31 | 31 | 28 | 28 | 29 | 31 | 31 | 30 | 29.88 |
| *F7 T3 F3 C3-C4 Fz Pz* | 25 | 27 | 26 | 28 | 26 | 30 | 30 | 28 | 27.50 |
| *Fz Pz* | 27 | 29 | 29 | 29 | 29 | 27 | 28 | 30 | 28.50 |
| *Fz Cz Pz* | 27 | 27 | 22 | 26 | 28 | 28 | 28 | 27 | 26.63 |

[a] Channel sets according to the International 10-20 system for EEG leads; C3-C4, the channel of difference between two leads.

In bold and gray shading, higher DSM agreement.

ERPs = event-related potentials; LV = latent variables.

The two channel sets that manifested the highest DSM agreement were [C3-C4, F8, F4, Fz, Pz] (using 1 LV from ERP variables alone) and [C3-C4, F8, F4, P4, Fz, Pz] (using 3 LVs from ERP and behavioral variables together). Table 2 shows all the observed agreement rates for all channel sets.

As expected, we observed an inverse relationship between the DSM agreements (from 20 to 32, according to the trial) and the total number of miss-reclassified subjects (Fig 2). We observed that the highest agreement rate found (32 subjects) corresponded to the highest classifier power (4.00). Eight subjects in these outputs were miss-reclassified: C005, C009, C012, C020, C023 (control subjects miss-reclassified to the ADHD group) and T010, T012, T026 (ADHD subjects miss-reclassified to the Control group). From these results, the estimated specificity and sensitivity of the DSM-IVTR regarding biological variables were 75% and 84%, respectively, with an accuracy of 79.48% corresponding to the kappa index of 0.72, i.e. *a substantial strength of agreement* [28].

**Figure 2. Classifier Power of the MVA analysis.** Number of miss-reclassified subjects by DSM agreement (number of subjects), in all 320 outputs, and the corresponding classifier power (numbers at graph marks). See methods.

# Discussion

Our study tackled the possibility of examining attention defict/hyperactivity disorderusing the DSM manual, whose criteria seemed to be biologically justified for ADHD diagnosis with “substantial strength of agreement” in relation to a specific pool of behavioral, psychological, and neurophysiological variables. We found in the ANT the

larger source of behavioral and neurophysiological data related to ADHD phenomenology, since this test is suitable to access in the same setting the three dimensions of attention [19, 29].

To classify subjects as normal or ADHD according to DSM criteria, we asked caregivers what criteria were well-defined characteristics of their children. In both scientific research and clinical practice, for ADHD diagnosis it is appropriate that we also use other assessment methodologies besides the DSM. Moreover,in clinical practice the manual should not be applied as a questionnaire. However, in this case, the object of evaluation is the DSM itself, thus it was the only clinical diagnostic tool used for subjects classification as ADHD or not-ADHD. It was the most objective and controlled way to obtain the scores without interference of any other clinical impression. Supporting the present methodology, we observed that the ASRS, the WHO questionnaire for adult ADHD screening, is applied through self-evaluation [30].

The most informative neurophysiological variables in this pool proved to be topographically asymmetrical and represented the binded information from ERPs in the three time intervals of interest from mid-frontal, mid-parietal, right frontal, and right anterior temporal sites (channels Fz, Pz, F4, and F8), as well as early ERP components (45 to 290ms after target onset) from the ‘C3 minus C4’ channel. This asymmetry has already been shown to correlate with DSM scores, mainly with hyperactivity/impulsivity [31]. It was not the focus of the present investigation to establish models for ADHD or its

neural mechanisms. However, our results revealed certain biological aspects of ADHD regarding alterations in the frontal control over executive functions [18, 32, 33]. Several studies have shown  brain asymmetries related to ADHD phenomenology, spetially in frontal-striatal network [33-35]. By spectral and coherence analyses of the resting EEG, we also have showed asymmetrical topographic patterns, with signs of relative inactivation of the frontal and *left* temporal cortex, known to be responsible for voluntary attention, and impaired in ADHD patients [36]. These observations could partially explain the leading role of ERP data from the right frontal regions in discriminating between patients and controls in the present research.

The present results suggest that DSM-IV-TR is actually an effective and biologically justified tool for ADHD diagnosis.  Although a Kappa index of 0.72 should be considered with reservations for some clinical settings, a clinical method such as DSM, with sensitivity of 84% and specificity of 75% with regard to objective behavioral, psychological, and neurophysiological measures, should be considered as particularly relevant considering the complexity of mental disorders, spetially those whose clinical phenomenology is dimensional, and without any validated biomarkers, So much so that 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. Furthermore, the ADHD has been regarded as a heterogeneous condition with inattentive, hyperactive, and combined subtypes, which

could be the answer for this level of agreement since these subtypes were not predicted for reclassification. The existence of three discrete subtypes could lead to flawed reclassification.

The study was designed with a relatively small sample size. Any subject with the slightest suspicion of comorbidity was excluded. We monitor potentially confounding factors commonly ignored (such as manipulating technologies that could lead to the development of specific skills that would interfere with test performance and the socioeconomic niche, that could determine the psychological development).. Thus, our sample should be regarded as well consistent with and representative of ADHD. On the other hand, in order to classify the subjects according to their mental condition (a multidimensional phenomenological complex) it would seem reasonable to gather a considerable number of objective variables (as many as possible). Brain processing during the ANT test as well as ADHD neurophysiology and its behavioral correlates in this study were considered as potentially relevant features requiring further investigation. Thus, we had to deal with a dataset with a much smaller number of observations than variables, since it did not seem feasible to collect a sample with thousands of subjects evaluating hundreds of variables in an experiment with ideal control of confounders and bias. A small but strictly controlled and well exploited sample was considered preferable, even in conditions of high prevalence such as the ADHD. It is well established that multivariate statistical modeling, such as Linear Regression, Discriminant Analysis, or

Factor Analysis, are not suitable for this situation. Thus,in order to tackle a frequently encountered problem, often designated as the curse of the dimensionality, we have adopted an explorative data analysis suitable for small samples, to identify a small number of synthetic latent variables. Instead of the Principal Component Analysis, which does not always provide easily interpretable latent variables (the principal components), we have chosen an approach with clustering of variables to reduce data dimensionality to a small number of new latent variables. The CLV method [21,22] has been applied in a wide range of research domains among which are sensory analysis [37], chemometrics [38], image analysis [39], and analysis scorecards in health sector [40].

The estimated I.Q. scores were different between the groups diagnosed using DSM-IV-TR, but this was not regarded as bias. Literature has shown that intelligence tests are sensitive to ADHD, and patient scores are generally lower than in controls [41]. Even taking into account the above restrictions, there is no doubt that the data obtained seem to be quite consistent.

A major limitation of this study is the impossibility of testing all possible combinations among variables. Since consistency of our paradigm depends on not considering any biological / behavioral assumptions in the grouping of variables, it is necessary to test them randomly grouped. But there are more than one million possible combinations of EEG channels. The number of combinations grows exponentially if we include the other variables individually. For computational feasibility, we had arbitrarily

choose sets of variables to analize. With the eighty sets studied, we can assume that DSM has at least "substantial level of agreement" with biological determinants. Perhaps some untested set of variables may manifest greater agreement with the DSM, but the results found already satisfy our objective of testing the validity of the DSM criteria for ADHD.

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. In this way, we have found that there is a consistent complex of biological information which is in accordance with previous knowledge on ADHD, that confers biological validity for DSM criteria for ADHD.

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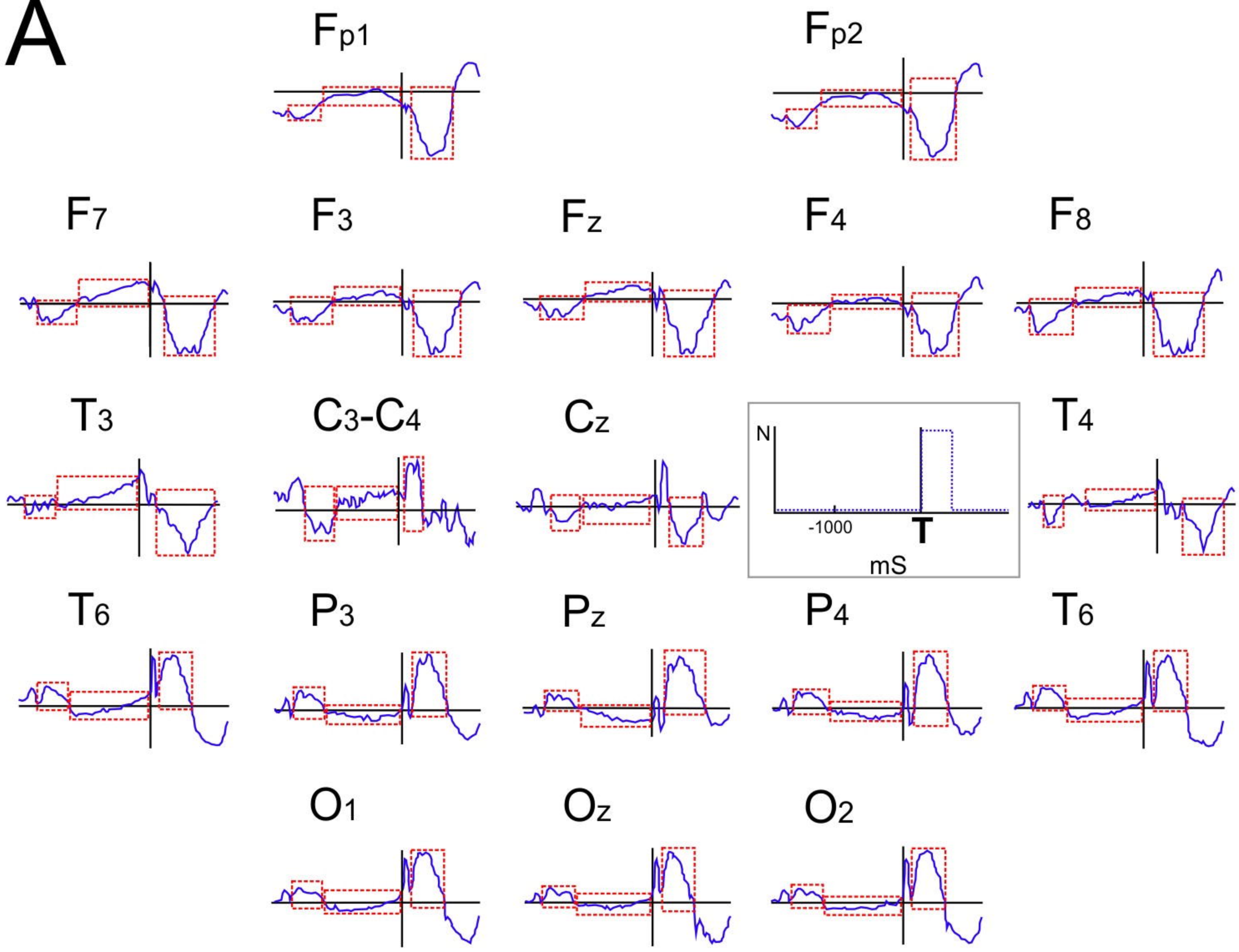
**S1 Table. Time intervals of Interest.** Windows holding Cue-related potentials (CUE), contigent voltage variation (CVV) and Target-related potentials (TGT), for each channel (ms), for calculation of peak amplitude, peak latency and mean amplitude. Zero ms refers to Target onset (see Figure 1).

**S2 Method. Calculating the Kappa Index.** Inference of the magnitude of agreement between two categorical data (in this case, the subjects' classification by DSM and by biological/behavioral variables in the dataset).

**S3 Dataset. DSM scores and variables of interest.** *In the first sheet:* innatention, hyperactive+impulsive and total scores for ADHD by DSM-IV-TR; *second sheet:* all data concerning (1) scores of the WISC-III subtests, (2) ANT performance (AC: accuracy, RT: reaction time and IVRT: intraindividual variation of reaction time, what is the standard deviation of RT for each subject) for each experimental condition (Allcon: mean of all conditions, NtCue: neutral Cue condition, SpCue: spatial cue condition, ConTg: congruent target condition, IncTg: incongruent target condition) and attentional network (alerting, orienting, and executive) plus learning indexes (IVRT or RT at the last ANT block/first ANT block), and (3) the neurophysiological measures (peak amplitudes and latencies, and mean amplitudes inside each time interval of interest in S1) for EEG channel set.

A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Fp2
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C3-C4
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P3
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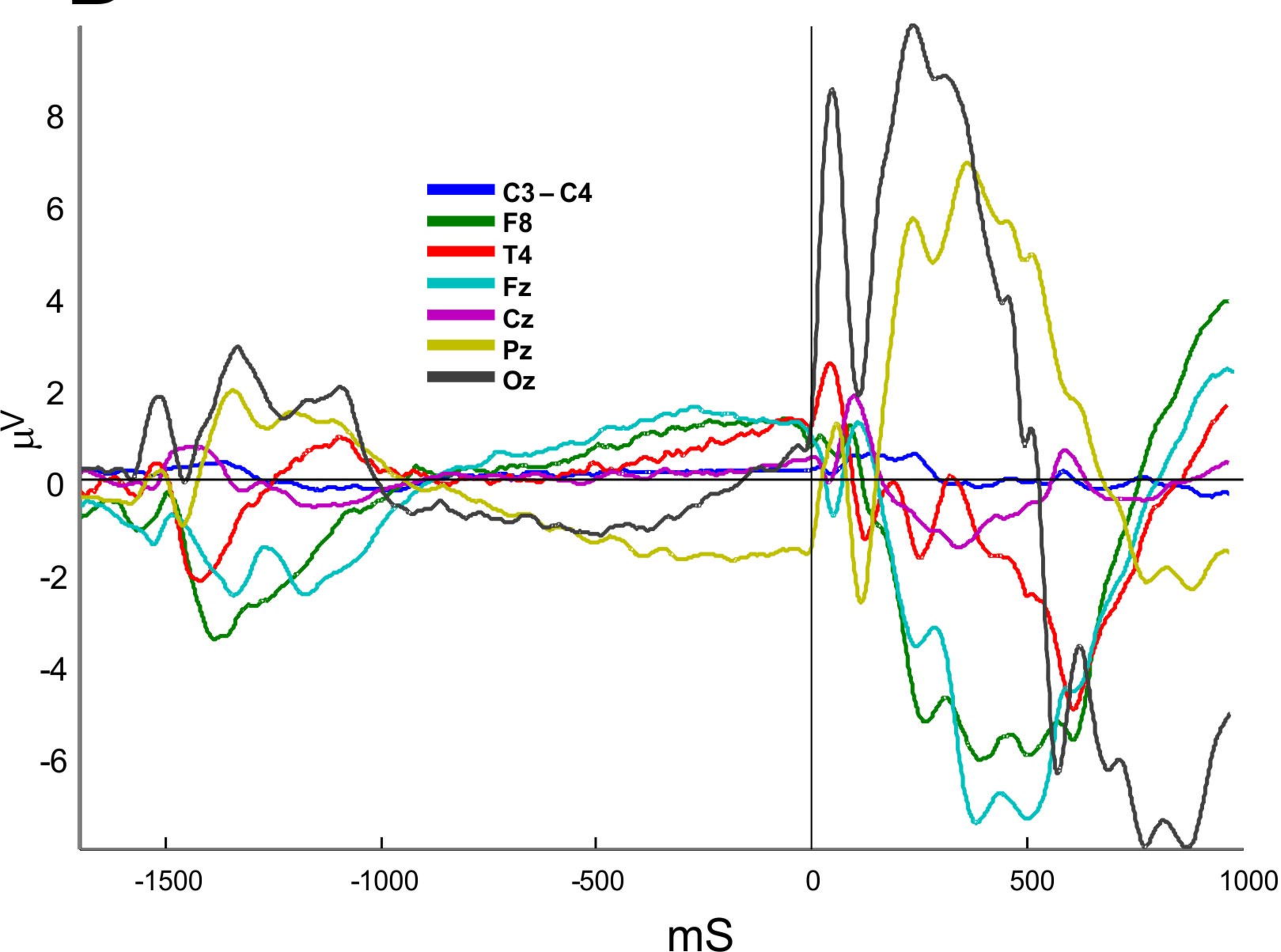
C3 – C4
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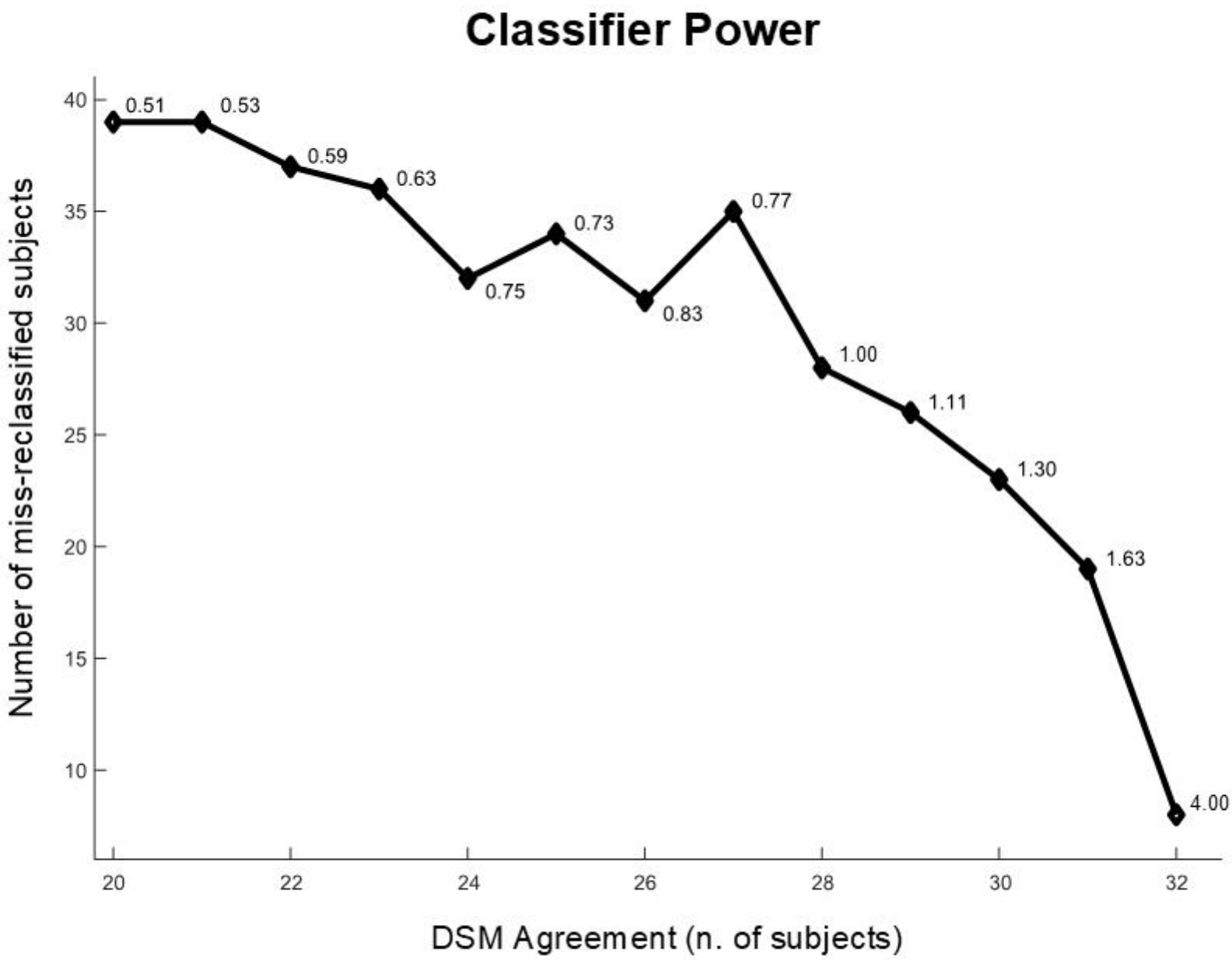
Classifier Power
Number of miss-reclassified subjects
DSM Agreement (n. of subjects)
40
35
30
25
20
15
10
20
22
24
26
28
30
32
0.51
0.53
0.59
0.63
0.75
0.73
0.83
0.77
1.00
1.11
1.30
1.63
4.00