Article

# ADHD Endophenotypes in Caribbean Families

Journal of Attention Disorders
1–15

DOI: 10.1177/1087054718763741
journals.sagepub.com/home/jad
SAGE

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## Abstract

**Objective:** The aim of this study is to contrast the genetics of neuropsychological tasks in individuals from nuclear families clustering ADHD in a Caribbean community. **Method:** We recruited and clinically characterized 408 individuals using an extensive battery of neuropsychological tasks. The genetic variance underpinning these tasks was estimated by heritability. A predictive framework for ADHD diagnosis was derived using these tasks. **Results:** We found that individuals with ADHD differed from controls in tasks of mental control, visuospatial ability, visuoverbal memory, phonological and verbal fluency, verbal and semantic fluency, cognitive flexibility, and cognitive ability. Among them, tasks of mental control, visuoverbal memory, phonological fluency, semantic verbal fluency, and intelligence had a significant heritability. A predictive model of ADHD diagnosis using these endophenotypes yields remarkable classification rate, sensitivity, specificity, and precision values (above 80%). **Conclusion:** We have dissected new cognitive endophenotypes in ADHD that can be suitable to assess the neurobiological and genetic basis of ADHD. (*J. of Att. Dis. XXXX; XX(X) XX-XX*)

**Keywords**
ADHD, endophenotypes, attention, memory, genetics, heritability

## Introduction

ADHD (OMIM 143465) is a phenotypically complex (Acosta, Arcos-Burgos, & Muenke, 2004) and highly prevalent neurodevelopmental disorder that affects 10% to 17% of children and adolescents worldwide (Acosta et al., 2011; Arcos-Burgos et al., 2010; Bukstein, 2012; Jain et al., 2012; Pelham & Fabiano, 2008; Visser, Bitsko, Danielson, & Perou, 2010), frequently persisting into adulthood (Sibley et al., 2012). Heritability estimates indicate that ADHD symptoms are highly heritable ($h^2$ = 0.85-0.90; Rhee, Waldman, Hay, & Levy, 1999), and that offspring of ADHD-affected individuals are 6 to 8 times more likely to develop the condition than those of unaffected individuals (Biederman & Faraone, 2005). Studies that have ascertained nuclear, extended, and multigenerational families from ADHD-affected probands, and clustering several ADHD-affected family members, have demonstrated that families are an effective resource to define the genetic basis of ADHD (Arcos-Burgos et al., 2002; Cannon, Gasperoni, van Erp, & Rosso, 2001; Castellanos & Tannock, 2002).

The term *endophenotypes* was first coined ~50 years ago to explain insects' evolution (John & Lewis, 1966) and

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introduced to psychiatry by Gottesman and Shields in 1967. In complex neuropsychiatric conditions such as ADHD, endophenotypes might be defined as neuropsychological, behavioral, cognitive, or neuroanatomical quantitative "measurable components" associated/correlated with the disorder (Castellanos & Tannock, 2002; Miller & Rockstroh, 2016; Walters & Owen, 2007) that occurs at a higher frequency in individuals with the disease than in the general population, are heritable, state-independent (i.e., manifest in individuals whether the illness is active), tend to co-segregate with the illness within families, and lie in the causal pathway between gene and disease (Flint & Munafo, 2007; Lee Gregory, Burton, Shapiro, Rowland, & Coyle, 2015; Walters & Owen, 2007). Given that endophenotypes are in general continuous variables instead of categorical traits, do not depend on the inherent difficulties of a symptoms-based clinical diagnosis, and have the ability to differentiate between potential diagnoses that present with similar symptoms (Brotman et al., 2008; Gottesman & Gould, 2003), it has been hypothesized that they are well suited to study the genetic and neurophysiological basis of psychiatric traits such as ADHD (Castellanos & Tannock, 2002; Mastronardi et al., 2016; Pineda et al., 2011; Sibley et al., 2012).

Several ADHD studies have identified potential cognitive endophenotypes in neuropsychological tasks such as continuous vigilance, inhibitory control, alteration of temporal perception, delay aversion, working memory alterations, interval timing deficits, fluid intelligence to sustained attention, and visual-motor skills (Acosta-López et al., 2010; Castellanos & Tannock, 2002; Henriquez-Henriquez et al., 2014; Hwang-Gu & Gau, 2015; Mastronardi et al., 2016; Pironti et al., 2014). Recently, we and others have identified ADHD endophenotypes in families ascertained from two well-characterized genetic isolates, the *Paisa* community in Antioquia, Colombia (Mastronardi et al., 2016; Pineda et al., 2011) and the Central Valley in Costa Rica (Arcos-Burgos & Muenke, 2002; Peskin et al., 2015). In these studies, several measures of cognitive intelligence, attention, visual and motor skills, verbal coefficient, sustained visual attention, and visuospatial problem resolution reported high heritability values and strong association to the ADHD status (Peskin et al., 2015; Pineda et al., 2011). These initial findings support and confirm both the heterogeneity and complexity of ADHD, as a syndrome and from the cognitive point of view (Acosta et al., 2004; Pennington, 2006; Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008; Willcutt, Pennington, et al., 2010), and the important role that genetic factors play in the etiology of this neuropsychiatric condition (Barkley., 1997; Doyle et al., 2005; Mastronardi et al., 2016; Nigg, 2001; Willcutt, Betjemann, et al., 2010; Willcutt, Pennington, et al., 2010).

The racial composition in Latin America is extremely complex and geographically heterogeneous as well as it is the cultural heritage (Sibley et al., 2012). It is well known that Colombia was colonized by Spaniards with variable geographical proportions of genetic admixture with the aboriginal Amerindian populations. This racial and genetic conundrum was later convoluted by the arrival of African populations as a consequence of the slave trading. The racial admixture in Colombia was more pronounced in communities inhabiting the Caribbean coast that had a strong influx of African populations arriving in Cartagena, one of the main trade centers of slaves (Sibley et al., 2012; Villalón, 2008). Furthermore, earlier in the 20th century, the arrival of Arabian populations to the Caribbean brought more diversity to these communities' gene pool. Thus, this differential pattern of admixture that happens in the Colombian Caribbean coast shaped the culture and genetic population structure in a particular and differential way when compared with other regions of the country (Barragán-Duarte, 2007; Sibley et al., 2012; Villalón, 2008).

In this study, we explored the definition of ADHD cognitive endophenotypes in a family-based sample of 408 individuals ascertained from a community inhabiting the city of Barranquilla, Colombia. With a population of ~2.4 million where many populations that settled in the Atlantic coast converge (Villalón, 2008), Barranquilla is the biggest city in the Colombian Caribbean coast. Our overarching hypothesis was that there were racial and community-specific endophenotypes able to represent a significant variance of the ADHD symptomatology and subtypes, and of the genetics underpinning ADHD susceptibility.

## Participants and Methods

### *Participants*

Four hundred eight individuals belonging to 120 nuclear families from Barranquilla, Colombia and its metropolitan area, with at least a single ADHD-affected individual, were recruited in this study. Barranquilla is a modern city of ~2.4 million people located in the Atlántico state at the northern Caribbean coast. The Barranquilla population is the result of a racial admixture between Aboriginal Amerindian communities with Spaniards and Africans, and later with other communities (i.e., Syrian-Lebanese, Sephardi Jews, Germans, Italians, and Britons; Villalón, 2008). Most of the families belonged to a medium socioeconomic stratum with an average monthly family income of ~US$1,000 to US$3,000. All individuals in this study participated voluntarily and provided informed written consent either directly or from their parents (in the case of children; <18 years old). This study was approved by The Ethics Committee of Universidad Simón Bolívar at Barranquilla, Colombia (Approval No. 00032 of October 13, 2011).

### *Clinical Assessment*

*ADHD diagnosis.* The Diagnostic Interview for Children and Adolescents–Version IV (DICA-IV; Palacio et al., 2004;

Reich, 2000) was used as the Gold Standard to assess the ADHD diagnosis in children and adults. This interview gathers information about patients from a systematic examination of symptoms, making use of a binary classification system of symptoms (0 = *absence*, 1 = *presence*) to explore their commencement and end, to allow an optimal clinical evaluation. Among others, the DICA-IV covers childhood disorders, mood, anxiety, nutritional behavior, psychotic disorders, and psychosocial stress—in conjunction, these areas allow the identification of ADHD and its inattentive, hyperactive, and inattentive/hyperactive (combined) subtypes. In the case of children and adolescents, the DICA-IV structure interview was completed by children's parents who reported children's symptoms and consequences in the academic, legal, and work-related areas, as well as alcohol and tobacco consumption and its consequences (Palacio et al., 2004; Reich, 2000; Tacchini, Coppola, Musazzi, Altamura, & Invernizzi, 1994). This information was subsequently used to define the index case (proband). Presumptive ADHD diagnosis in children was assessed by DICA-IV with a self-report evaluating, retrospectively, parents' behavior during Grades 1 to 11 (Acosta-Lopez et al., 2013). Persistent symptoms affecting family, social, and work-related environments were also recorded.

The DICA-IV interview has successfully been used in Colombia by the Grupo de Neurociencias de Antioquia in clinical and genetic studies of ADHD in the Paisa genetic isolate (Palacio et al., 2004). ADHD diagnoses were performed by two experienced neuropsychologists (P.P.-R. and J.A.-L.), who were trained by a Child Psychiatrist (DAP) from the Grupo de Neurociencias de Antioquia until a $\kappa$ concordance coefficient >.9 was reached for ADHD, oppositional defiant disorder (ODD), and conduct disorder (CD) diagnoses, and $\kappa$ >.75 for other psychiatric diagnosis of the A criterion in the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association [APA], 1994). The DICA-IV is highly reliable for each diagnostic category (Cronbach's $\alpha$ >.75) as it has questions, counterquestions, validation questions, and skip questions regarding every symptom of each criterion in every diagnostic category, in addition to a series of standardized examples in each category, specially designed to determine burden criteria. Following the C criteria of *DSM-IV*, ADHD symptoms in children and adolescents were evaluated by their parents and teachers using the ADHD diagnosis with Colombian version of the Behavioral Assessment System for Children (BASC; Pineda, Kamphaus, et al., 1999) and the ADHD checklist (APA, 2000; DSM-IV, 2002).

*Neurological evaluation.* Anamnesis of personal and familiar pathological events was assessed using a neurological interview, which included prenatal, perinatal, childhood, and language anomalies. First, mothers accompanied children during the neurological interview to facilitate the interaction with the examiner during the physical/neurological evaluation. Next, information about the child's behavior at home and at other scenarios (social events, parties, birthdays, etc.) is obtained from the mother. Subsequently, a new evaluation involving both parents is performed; information about parents' behavior is obtained from the child's grandparents by telephonic interview to retrospectively assess parents' hyperactivity, inattention, and impulsivity symptoms. Finally, a physical examination of senses, joints, and cardiopulmonary, digestive, reproductive, and nervous systems is further performed for every child, together with a neurological evaluation assessing cranial pairs, visual auditory syndromes, motor-sensitive skills, muscular tone, reflexes, and soft neurological signs (Puentes Rozo et al., 2018).

*Neuropsychological tests.* We used the mental control subtests of an adapted version of the Wechsler Memory Scale, Third Edition (WMS-III; Wechsler, 2004) in addition to the Wechsler Intelligence Scale for Children, Third Edition (WISC-III; Wechsler, 1991) for children aged between 6 and 16 years, the short version of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III; Wechsler, 2003), the Trail Making Test Parts A and B (Reitan, 1955, 1958; Reitan & Wolfson, 1985, 1995, 2004), visuoverbal memory test, the Rey–Osterrieth Complex Figure Test (ROCFT) for copy and immediate recall (Osterrieth, 1944), the Token Test, phonological and semantic fluency verbal tests (Franke et al., 2010), and the Wisconsin Card Sorting Test (WCST; Heaton, Avitable, Grant, & Matthews, 1999) and Stroop's Color and Word Test (Golden, 1999). The full neuropsychological protocol is presented in Supplementary Table 2. The vocabulary, comprehension, arithmetic, digits, and analogies subtests of the WISC-III/WAIS-III were used to assess verbal intelligence quotient (VIQ) and rule out mental retardation, and the incomplete figures, block design, and symbol search and puzzle tests were used to assess the performance intelligence quotient (Khodiyar et al., 2007). A prorated full-scale intelligence quotient (FSIQ) was estimated (Wechsler, 1955, 2004).

Neurological and neuropsychological evaluations were performed at the Unit of Cognitive Neurosciences of the Caribbean Group of Neurosciences, Simon Bolivar University, Barranquilla, Colombia, in two sections of ~1.5 hr long each. To avoid any potential distraction or interference during the clinical evaluation period, participants were evaluated in a room with constant illumination, a temperature of 18°C, and isolated from external noise.

## Procedure

Eleven Spanish-speaking public schools located at disparate areas of Barranquilla, Colombia and its metropolitan area were visited. These schools provide educational services to a population of medium (three to five) socioeconomic strata. This study was advertised in the Grupo

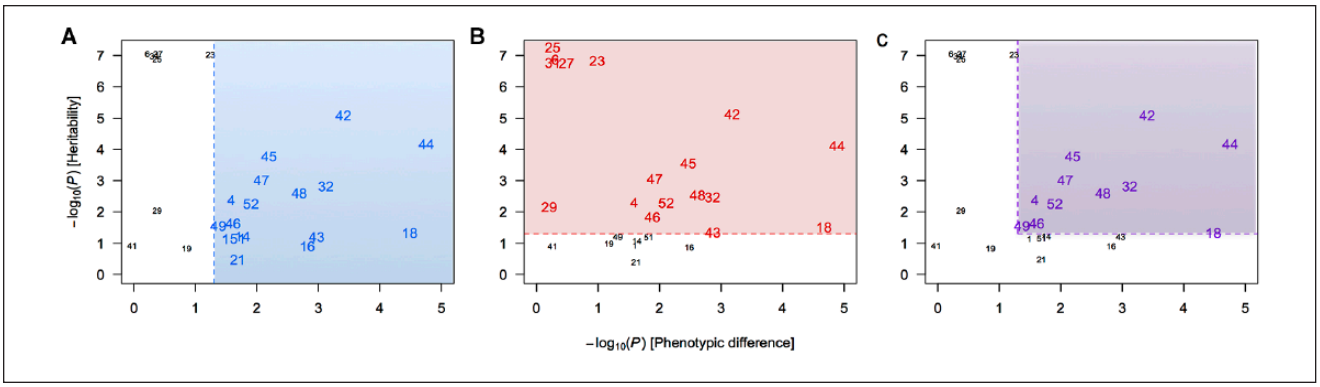


**Figure 1.** Neurological and neuropsychological where (a) ADHD affected individuals differed from *unaffected individuals*, (b) genetic effects and hereditary transmission are present, and (c) fulfill the requirements to be considered as potential endophenotypes.
*Note*. Displayed numbers correspond to task numbers in Table 2.

Neurociencias del Caribe's website. Out of the schools visited, seven agreed to participate in our study. Once their participation was approved by delegated authorities, an informative meeting with teachers from each school to explain the objectives and dynamic of the study took place. Subsequently, teachers provided a complete list of children 6 to 11 years old (first to sixth grades) attending their classes for the last 6 months, and who they would think could have any issue that may affect their academic performance or their behavior at school. Out of this list, we administered 845 checklist questionnaires (Pineda, Henao, et al., 1999) to children, children's parents, and teachers from these seven ascertained schools. A georeferenced map showing the location of ascertained families is shown in Supplementary Figure 1. Parents and other family members of children with scores higher than the 85th percentile in the checklist (this value is an indicator of an ADHD positive diagnosis; Pineda, Henao, et al., 1999) were further assessed and provided with all relevant information about the study. ADHD diagnosis in family members was assessed using the DICA-IV interview and the *DSM-IV* criteria (Pineda, Henao, et al., 1999). After reviewing both the clinical evaluation and the psychiatric interview, each individual's diagnosis was discussed among a staff of well-experienced clinicians for confirmation. Our full neuropsychological evaluation protocol is presented in Supplementary Table 2.

## Statistical Analysis

Measures of location and dispersion were employed to summarize continuous variables. Those variables meeting the assumptions of normality and homogeneity of variance were compared using the *t* test for independent samples or the nonparametric Mann–Whitney *U* test otherwise. Normality and homogeneity of variance were tested with the Shapiro–Wilk and the Bartlett tests, respectively. Uncorrected Cohen's *d* was calculated to measure the effect size for all variables. To avoid the effect of potential confounding variables such as age and gender, *p* values were corrected using ANCOVA. Frequencies and proportions were estimated for categorical variables. Categorical variables were compared using a $\chi^2$ test.

We used Advanced Recursive Partitioning Approach (ARPA) to construct a predictive tree-based model of ADHD status in our cohort. Gender, age, and potential cognitive endophenotypes were used as predictors. ARPA offers fast solutions to reveal hidden complex substructures and provides nonbiased statistical analyses of high-dimensional seemingly unrelated data, and is widely used in predictive analyses as it accounts for nonlinear hidden interactions better than alternative methods and is independent of the type of data and of the data distribution type (Rao, 1998). ARPA was applied using the Classification and Regression Tree (CART; Breiman, Friedman, Olshen, & Stone, 1984), Random Forest (Breiman, 2001; Satterfield, Cantwell, & Satterfield, 1974), and TreeNet (Friedman, 1999) modules implemented in the Salford Predictive Modeler® software suite (Salford Systems, San Diego, CA, USA). A short description of CART, random forest (RF), and TreeNet is provided in the Supplementary Material. The final model was chosen based on a battery performance measure presented in Supplementary Table 1.

## Heritability Estimation

To estimate heritability of neurological and neuropsychological variables in our sample, the ASSOC module in the Statistical Analysis of Genetic Epidemiology (SAGE) software (Elston & Gray-McGuire, 2004) was used. Briefly, ASSOC evaluates the association between a continuous trait and one or more covariates from pedigree data in the presence of familial correlations and simultaneously estimates familial variance components (and hence familial

**Table 1.** Demographic Characteristics of 408 Individuals Included in This Study.

| | Affected | Unaffected | | | |
|---|---|---|---|---|---|
| | *n* = 236 | *n* = 172 | | | |
| Gender | Frequency (%) | Frequency (%) | Statistic index $\chi^2$ | *p* | Effect size |
| Male | 161 (68.22) | 72 (41.86) | 27.156 | <.00001 | — |
| Female | 75 (31.78) | 100 (58.14) | | | |
| | *M* (*SD*) | *M* (*SD*) | Mann–Whitney's *U* | | |
| Age | 21.14 (12.15) | 34.19 (15.4) | 29,746 | <.0001 | 0.941 |

correlations and heritability; Elston & Gray-McGuire, 2004). Parameters in the segregation model evaluated by ASSOC are estimated by maximum likelihood under the assumption that parameters follow multivariate normality (Bochud, 2012; Elston & Gray-McGuire, 2004; Elston, Satagopan, & Sun, 2012a, 2012b).

## Results

### Participants

Four hundred eight individuals (175 [43%] females and 233 [57%] males) from 120 nuclear families were included in this study (Table 1). Of those, 236 (57.84%) individuals were diagnosed as ADHD affected (161 [68.2%] males, 75 [31.8%] females; 105 [44.5%] were diagnosed as ADHD inattentive, 32 [13.6%] as ADHD hyperactive, and 99 [41.9%] as ADHD combined type). No children or adults were under medication. Among affected individuals, the estimated male-to-female ratio was 2.146 confidence interval (CI) = [1.65, 2.85], $p < .001$. As expected, the ADHD diagnosis distribution differed by gender ($\chi^2 = 27.16$, degrees of freedom [*df*] = 1, $p = 1.87 \times 10^{-7}$). The average age at diagnosis in the whole sample was 26.64 ± 15.5 (range = 6-60), and no statistically significant difference was found by gender (females: 25.34 ± 16.77 years; males: 28.37 ± 13.5 years; $W = 18{,}707$, $p = .1537$). The average family size in the 120 nuclear families was 3.4 ± 0.64 individuals (range = 3-6), with 80 (66.7%) trios, 34 (28.3%) quartets, four (3.3%) families with five members and two (1.7%) families with six members (Pineda et al., 2016; Puentes Rozo et al., 2018). Furthermore, 32 (26.7%) families had one affected individual, 63 (52.5%) had two, 21 (17.5%) families had three, and four (3.3%) families had four affected individuals; 88 (73.3%) families had more than one member affected with ADHD. Analyses of the probands' relatives ($n = 288$) indicate that 120 of them are diagnosed with ADHD (77 males, 43 females, 41.6%), with an age at diagnosis of 34.11 ± 12.04, which differed between males and females (35.34 ± 13.05 vs. 32.83 ± 10.78, $p < .0001$).

### Neuropsychological Differences Between Affected and Unaffected Individuals

We found statistically significant differences between ADHD affected and unaffected individuals after controlling for age and gender in neurological and neuropsychological tasks measuring mental control, visuospatial ability (i.e., ROCFT), visuoverbal memory, verbal fluency tasks (VFTs) by phonological and semantic guidance, planning and abstraction (i.e., WCST), and intelligence (i.e., IQ in the WISC-III and WAIS-III; see Table 2 and Figure 1a). ADHD-affected individuals had a lower score than unaffected individuals in the Total 9/9 test (4.44 ± 2.54 vs. 5.93 ± 2.17, $p = .028$) and in the numbers from 20 to 1 test (2.13 ± 0.99 vs. 2.55 ± 0.7, $p = .034$) of the mental control subtest. Likewise, ADHD-affected individuals had a lower score than unaffected individuals in the ROCFT copy (20.65 ± 8.49 vs. 26.31 ± 6.5, $p = .002$) and ROCFT evocation (immediate recall; 9.15 ± 6.05 vs. 13.38 ± 6.16, $p = 2.4\text{x}10^{-5}$) subtests but not in the ROCFT type (2.64 ± 1.53 vs. 1.62 ± 0.94, $p = .018$) subtest or in the number of attempts needed to accomplish the visuoverbal memory test (3.18 ± 1.77 vs. 2.7 ± 0.91, $p = .027$). Conversely, unaffected individuals obtained an average score higher than affected individuals in the phonological VFTs (12.34 ± 9.84 vs. 16.81 ± 13.65, $p = .024$), the 36/36 Token Test (30.46 ± 3.66 vs. 32.04 ± 4.21, $p = .001$), and correct answers (73.46 ± 23.69 vs. 80.9 ± 20.42, $p = .014$) of the WCST (i.e., planning and abstraction cognitive domain; see Supplementary Table 2). As expected, ADHD affected individuals performed poorer than ADHD unaffected individuals in the number of errors (53.6 ± 23.21 vs. 46.58 ± 20.34, $p = .031$) and the number of correct answers at the conceptual level (58.26 ± 29.81 vs. 66.56 ± 27.4, $p = .044$) of the WCST. Analogously, ADHD-affected individuals had lower performance than unaffected individuals in the FSIQ of the WISC-III (children) and WAIS-III (adults) with low-to-high effect sizes (Table 2 and Figure 1a).

### Heritability Estimates

Strong statistical evidence supporting genetics effects and hereditary transmission (measured by the heritability

**Table 2.** Performance on Neurological and Neuropsychological Tasks of 408 Individuals From the Colombian Caribbean.

| No. | Task | Affected (n = 236) | Unaffected (n = 172) | | | Heritability | |
|---|---|---|---|---|---|---|---|
| | | *M (SD)* | *M (SD)* | *d* | *p* | $h^2$(*SE*) | *p* |
| Mental control | | | | | | | |
| 1 | Total score 9/9 | 4.44 (2.54) | 5.93 (2.17) | 0.624 | **.028** | 0.182 (0.117) | .059 |
| 2 | Time—Numbers from 20 to 1 | 16.68 (14.49) | 11.29 (6.28) | 0.459 | .147 | [a] | [a] |
| 3 | Errors—Numbers from 20 to 1 | 0.25 (1.56) | 0.13 (0.47) | 0.103 | .817 | [a] | [a] |
| 4 | Score—Numbers from 20 to 1 | 2.13 (0.99) | 2.55 (0.7) | 0.483 | **.034** | 0.351 (0.138) | .006 |
| 5 | Time—Abecedary | 15.14 (15.78) | 10.73 (9.18) | 0.329 | .420 | [a] | [a] |
| 6 | Errors—Abecedary | 0.78 (2.06) | 0.48 (1.36) | 0.171 | .443 | 0.546 (0.089) | **$1.0 \times 10^{-7}$** |
| 7 | Score—Abecedary | 1.43 (1.37) | 2.12 (1.23) | 0.525 | .192 | [a] | [a] |
| 8 | Time—Counting | 29.49 (24.42) | 22 (12.18) | 0.371 | .054 | [a] | [a] |
| 9 | Errors—Counting | 1.44 (2.84) | 1.52 (2.99) | 0.026 | .941 | [a] | [a] |
| 10 | Score—Counting | 0.84 (1.14) | 1.22 (1.27) | 0.319 | .237 | [a] | [a] |
| A Continuous Auditory Performance Test | | | | | | | |
| 11 | Correct answers | 13.53 (3.01) | 15.15 (1.53) | 0.649 | .062 | [a] | [a] |
| 12 | Omissions | 2.32 (2.8) | 0.85 (1.53) | 0.626 | .083 | [a] | [a] |
| 13 | Commissions | 1.94 (2.03) | 1.22 (1.59) | 0.385 | .246 | [a] | [a] |
| Rey–Osterrieth Complex Figure Test | | | | | | | |
| 14 | Copy (type) | 2.64 (1.53) | 1.62 (0.94) | 0.770 | **.018** | 0.172 (0.119) | .075 |
| 15 | Copy (time) | 192.02 (85.41) | 165.08 (88.97) | 0.310 | .855 | [a] | [a] |
| 16 | Copy (score) | 20.65 (8.49) | 26.31 (6.5) | 0.734 | .002 | 0.142 (0.137) | .150 |
| 17 | Evocation (time) | 115.81 (53.56) | 129.66 (56.92) | 0.252 | .058 | [a] | [a] |
| 18 | Evocation (score) | 9.15 (6.05) | 13.38 (6.16) | 0.694 | **$2.4 \times 10^{-5}$** | 0.185 (0.115) | .055 |
| Visuoverbal memory | | | | | | | |
| 19 | Initial volume | 6.44 (1.64) | 6.66 (1.41) | 0.142 | .123 | 0.141 (0.113) | .105 |
| 20 | Maximum volume 10/10 | 9.98 (0.16) | 9.91 (0.81) | 0.131 | .469 | [a] | [a] |
| 21 | Number of trials | 3.21 (1.69) | 2.81 (1.09) | 0.275 | **.027** | 0.065 (0.109) | .274 |
| 22 | Organizational index | 0.64 (0.35) | 0.79 (0.77) | 0.267 | .115 | [a] | [a] |
| 23 | Differed evocation at 20 | 8.67 (1.82) | 9.44 (1.32) | 0.478 | .063 | 0.773 (0.064) | **$1.0 \times 10^{-7}$** |
| Phonetic fluency tasks | | | | | | | |
| 24 | Total score | 16.07 (14.02) | 24.15 (17.99) | 0.511 | **.024** | [a] | [a] |
| 25 | Total errors | 2.57 (3.06) | 2.76 (2.99) | 0.065 | .466 | 0.765 (0.050) | **$1.0 \times 10^{-7}$** |
| 26 | Missing categories | 11.6 (13.03) | 13.53 (16.09) | 0.134 | .768 | [a] | [a] |
| 27 | Perseverance | 0.92 (1.53) | 1.18 (1.39) | 0.177 | .418 | 0.653 (0.079) | **$1.0 \times 10^{-7}$** |
| Semantic Verbal Fluency Test | | | | | | | |
| 28 | Total score | 18.28 (15.27) | 24.84 (18.4) | 0.394 | **.032** | [a] | [a] |
| 29 | Total errors | 1.44 (1.66) | 1.49 (1.58) | 0.033 | .362 | 0.264 (0.115) | **.011** |
| 30 | Missing categories | 22.8 (36.52) | 18.55 (28.52) | 0.128 | .305 | [a] | [a] |
| 31 | Perseverance | 0.8 (1.36) | 0.81 (1.26) | 0.013 | .640 | 0.669 (0.057) | **$1.0 \times 10^{-7}$** |
| 32 | Token Test 36/36 | 31.36 (3.8) | 33.51 (2.68) | 0.637 | .001 | 0.355 (0.124) | .002 |
| Wisconsin Card Sorting Test | | | | | | | |
| 33 | Correct responses | 73.46 (23.69) | 80.9 (20.42) | 0.333 | **.014** | [a] | [a] |
| 34 | Total errors | 53.6 (23.21) | 46.58 (20.34) | 0.318 | **.031** | [a] | [a] |
| 35 | Nonperseverative errors | 29.6 (20.17) | 24.05 (15.64) | 0.302 | .073 | [a] | [a] |
| 36 | Perseverative errors | 25.15 (22.58) | 23.24 (13.33) | 0.100 | .234 | [a] | [a] |
| 37 | Categories | 5.26 (18.6) | 4.89 (2.92) | 0.026 | .174 | [a] | [a] |
| 38 | Perseverative errors (%) | 21.41 (33.89) | 19.43 (15.05) | 0.072 | .885 | [a] | [a] |
| 39 | Conceptual-level responses | 58.26 (29.81) | 66.56 (27.4) | 0.288 | **.044** | [a] | [a] |
| 40 | Conceptual-level responses (%) | 46.8 (23.67) | 53.01 (20.91) | 0.276 | .083 | [a] | [a] |
| 41 | Failures to keep the principle | 1.43 (1.52) | 1.39 (1.28) | 0.028 | .832 | 0.138 (0.107) | .099 |

*(continued)*

**Table 2. (continued)**

| No. | Task | Affected (n = 236) *M (SD)* | Unaffected (n = 172) *M (SD)* | *d* | *p* | Heritability $h^2$(*SE*) | Heritability *p* |
|---|---|---|---|---|---|---|---|
| WISC-III and WAIS-III subtests | | | | | | | |
| 42 | Digit span total—Forward | 6.84 (1.73) | 7.8 (1.92) | 0.526 | **$3.7 \times 10^{-4}$** | 0.492 (0.107) | **$1.0 \times 10^{-5}$** |
| 43 | Digit span total—Backward | 4.53 (1.88) | 5.24 (1.87) | 0.375 | **.001** | 0.171 (0.102) | **.048** |
| 44 | Total | 11.32 (3.06) | 13.12 (3.33) | 0.564 | **$1.6 \times 10^{-5}$** | 0.416 (0.109) | **$6.8 \times 10^{-5}$** |
| 45 | Vocabulary | 28.28 (10.63) | 35.51 (10.99) | 0.670 | **.005** | 0.452 (0.126) | **$1.7 \times 10^{-4}$** |
| 46 | Comprehension | 17.75 (6.27) | 21.01 (5.88) | 0.533 | **.019** | 0.210 (0.107) | **.025** |
| 47 | Arithmetic | 12.94 (4.52) | 12.87 (3.87) | 0.016 | **.007** | 0.365 (0.116) | **.001** |
| 48 | Similarities | 16.16 (6.98) | 20.55 (5.89) | 0.671 | **.002** | 0.366 (0.130) | **.003** |
| 49 | Figure completion | 18.81 (4.86) | 20.58 (3.45) | 0.410 | **.036** | 0.235 (0.133) | **.039** |
| 50 | Block design | 30.89 (14.28) | 37.99 (12.86) | 0.518 | **$1.8 \times 10^{-4}$** | [a] | [a] |
| 51 | Symbol search | 21.45 (8.73) | 25.96 (8.81) | 0.514 | **.015** | 0.176 (0.133) | .094 |
| 52 | Objects assembly | 25.56 (8.8) | 29.92 (9.13) | 0.488 | **.012** | 0.323 (0.132) | **.007** |
| IQ | | | | | | | |
| 53 | Verbal | 98.51 (16.81) | 97.44 (12.33) | 0.071 | .078 | [a] | [a] |
| 54 | Performance | 100.98 (16.69) | 101.42 (11.45) | 0.030 | .128 | [a] | [a] |
| 55 | Full scale | 99.15 (16.85) | 98.86 (12.14) | 0.019 | **.040** | [a] | [a] |

*Note. d* = Cohen's effect size; $h^2$ = heritability estimated value. Potential endophenotypes are highlighted in blue. *p* values <.05 are shown in bold. Task numbers highlighted in red are included in the predictive model for ADHD status (see Figure 2). WISC-III = Wechsler Intelligence Scale for Children, Third Edition; WAIS-III = Wechsler Adult Intelligence Scale, Third Edition.
[a]Parameter could not be maximized in SAGE.
[b]Corrected for gender and age.
[c]Corrected for ADHD status, gender, and age.

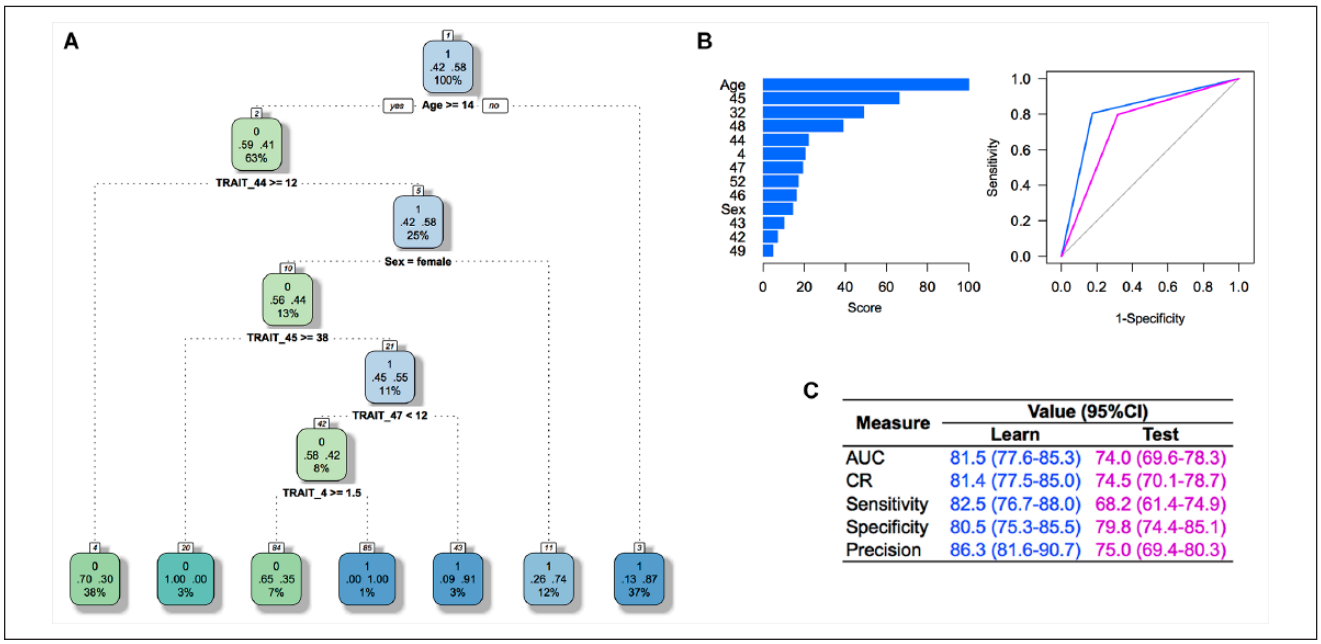


**Figure 2.** Classification tree for predicting ADHD status in individuals from the Colombian Caribbean.
*Note.* (a) Numbers within white squares represent the node number, the first line corresponds to the most frequent class (0 = *unaffected*; 1 = *ADHD affected*), the second line to the probability of each class within the node, and the third line to the percentage of the total sample size (*n* = 408) within each node. Nodes where ADHD-affected individuals are more likely to be classified are shown in blue. (b) Variable importance (left) and ROC curve (Ando, Ono, & Wright, 2001) for the CART strategy. Displayed numbers correspond to task numbers in Table 2. (c) Performance measures for the learning (blue) and test (pink) data sets. CI = confidence interval; AUC = area under the curve; CR = classification rate; ROC = receiver operating characteristic; CART = classification and regression tree.

parameter, $h^2$) was found in several neuropsychological variables (tasks) used to clinically characterize our sample (Table 2 and Figure 1b). These variables include the score in the numbers 1 to 20 ($h^2 = 0.351$, $p = .006$) and alphabet errors ($h^2 = 0.546$, $p < .00001$) measuring mental control; the differed evocation at 20 test ($h^2 = 0.546$, $p < .00001$) assessing visuoverbal memory; *the total number of errors* ($h^2 = 0.765$, $p < .00001$) and perseverance ($h^2 = 0.546$, $p < .00001$) assessing phonological fluency; *the total number of errors* ($h^2 = 0.264$, $p = .01$) and perseverance ($h^2 = 0.669$, $p < .00001$) subtests assessing semantic verbal fluency; the Token 36/36 Test ($h^2 = 0.355$, $p = .002$); and all but the *figure completion test* ($h^2 = 0.176$, $p = .094$) in the WAIS subtests, indicating that most of the measures assessing FSIQ had significant heritability. Within the WAIS-III subtests, the highest heritability value was estimated in the vocabulary test ($h^2 = 0.452$, $p = 1.7 \times 10^{-4}$) and the minimum in the reverse digits test ($h^2 = 0.171$, $p = .048$). No significant genetic effects and hereditary transmission were found in neuropsychological variables assessing ROCFT, continuous auditory execution, or the verbal semantics (Table 2 and Figure 1b). Our results suggest both a simultaneous differential pattern in ADHD diagnosis and genetic effects and hereditary transmission (significant heritability) in the numbers from 20 to 1 mental control subtest, the 36/36 Token Test, and in most of the WAIS-III subtests (see Table 2 and Figure 1c).

### *Predictive Model for ADHD Diagnosis*

Based on the performance measures presented in Supplementary Table 1, a five-level tree with seven terminal nodes was derived by CART to differentiate ADHD-affected individuals from unaffected in our cohort of 120 nuclear families. Splitting nodes involved age at diagnosis, sex, and traits 4 (numbers from 20 to 1; Table 2), 44 (digits; Table 2), 45 (vocabulary; Table 2) and 47 (arithmetic; Table 2) (Figure 2a). This predictive model was validated via RF and TreeNet, producing comparable results (data not shown). Interestingly, these last four variables defining splitting nodes were also found to be associated with ADHD and exhibited a significant heritability (i.e., constitute endophenotypes; see Table 2 and Figure 1c).

Out of the 408 individuals clinically assessed, 58% of them were diagnosed as ADHD affected and 42% as unaffected (node 1, Figure 2a). In the first split, children <14 years old have 87% chance of being diagnosed with ADHD regardless of gender (terminal node 3, 37% of all sample), while those ≥14 years have a 59% change of being diagnosed as ADHD unaffected (node 2, 63% of total sample). Within this node, individuals with more than 12 points in trait 44 (digits; Table 2) have a 70% chance of being classified as ADHD unaffected (node 4; 38% of total sample), compared with 58% of being ADHD affected (node 5, 25%). On the contrary, males with <12 points in trait 44 (digits; Table 2) and <14 years old have a 74% (terminal node 11, 12% of total sample) of being diagnosed as ADHD affected. Likewise, females with <12 points in trait 44 (digits; Table 2), <38 points in trait 45 (vocabulary; Table 2) and ≥12 points in trait 47 (arithmetic; Table 2) have a 91% chance of being diagnosed as ADHD affected (terminal node 43; 3% of total sample) (Figure 2a; bottom). Finally, females with <38 points in trait 45 (vocabulary; Table 2), ≥12 points in trait 47 (arithmetic; Table 2), and <1.5 points in trait 4 (numbers from 20 to 1; Table 2) are classified as ADHD affected (terminal node 85, 1% of all sample) (Figure 2a; bottom).

Figure 2b depicts the variable importance and receiver operating characteristic (ROC) curves for the CART strategy for the learn and test data sets. Although similar results were obtained with all strategies, CART performed better than RF and TreeNet (Supplementary Figure 2). The performance measures for the testing and learning data sets using the CART strategy are shown in Figure 2c (see also Supplementary Table 1). For the learning data set, the estimated area under the curve (AUC) was 81.5 (95% CI = [77.6, 85.3]), with values of 81.4 (95% CI = [77.5, 85.0]) for the classification rate, a sensitivity of 82.5 (95% CI = [76.7, 88.0]), specificity of 80.5 (95% CI = [75.3, 85.5]), and precision of 86.1 (95% CI = [81.6, 90.7]), with overlapping 95% CI in most of these measures for the learning data set based on tenfold cross-validation (Figure 2c). Further analysis indicated that this predictive model outperforms that including sex and gender only (Supplementary Figure 3). Altogether, these measures indicate substantial predictive power of these cognitive endophenotypes to differentiate ADHD affected from ADHD unaffected individuals.

## Discussion

The purpose of this study was to define cognitive endophenotypes in a set of nuclear families ascertained from ADHD probands recruited from Barranquilla, Colombia. We characterized, by clinical neuropsychology methods, visuoconstructional skills, visuoverbal memory, language, executive function, and intelligence domains. We found strong evidence that tasks of mental control, language, and intelligence meet the criteria for endophenotypes. Despite the well-known limitations of CART (i.e., being a nonparametric technique, lacking the ability of forcing variables into the model, and high variance across samples; Breiman et al., 1984; Gordon, 2013; Hayes, Usami, Jacobucci, & McArdle, 2015; Ojha, 2018), these clinical variables accurately predict the ADHD status in this community (Figure 2 and Supplementary Figure 3). While we replicated endophenotypes described for other Colombian—and in general Latino—communities, there were new neuropsychological endophenotypes that perform as new major players in

outlining ADHD and its neurobiological basis. These newly discovered endophenotypes might be specific, but the role they might play in other ADHD cohorts and studies in other communities will define their importance.

The findings in this study can be framed from two perspectives. First, there is strong evidence supporting significant phenotypic differences between ADHD-affected and unaffected individuals in the cognitive domains of mental control (total score and numbers from 20 to 1 of the Mental Control Test), visuomotor skills (copy type and scores of copy and evocation in ROCFT), visuoverbal memory (number of trials in the visuoverbal memory test), phonological and semantic verbal fluency (total score of the verbal fluency test), as well as in language comprehension (Token Test total score), abstraction and problem solving (number of correct responses, total errors, and conceptual-level responses in the WCST), comprehension and verbal reasoning (analogies, vocabulary, digits span, and arithmetic, and comprehension subtests of the WISC-III/WAIS-III), and execution and perceptive reasoning (figure completion, block design, symbol search, and objects assembly subtests of the WISC-III/WAIS-III) (Table 2 and Figure 1a). These results are not only consistent with other studies evaluating potential ADHD cognitive endophenotypes (Peskin et al., 2015; Pineda et al., 2011) but also show how heterogeneous the ADHD phenotype is. In the mid- to long term, these phenotypic differences might allow researchers to dissect the spectrum of cognitive and behavioral phenotypes in ADHD (Cervantes-Henríquez, Acosta-López, Aguirre-Acevedo, Pineda-Álvarez, & Puentes Rozo, 2008; Puentes Rozo, 2009; Puentes-Rozo, Barcelo-Martinez, & Pineda, 2008) and contribute to the better understanding of the etiology, subtypes, and severity of this neuropsychiatric condition (Sonuga-Barke, Dalen, Daley, & Remington, 2002).

Second, we also identified statistically significant heritability indexes in the domains of mental control (numbers from 20 to 1 and abecedary errors), visuoverbal memory (differed evocation at 20), phonological and semantic verbal fluency (total errors and perseverance), language comprehension (Token Test), verbal comprehension (vocabulary, analogies, arithmetic and digits span subtests of the WISC-III/WAIS-III), and execution (incomplete figures and objects assembly subtests of the WISC-III/WAIS-III) (Table 2 and Figure 1b). Although these findings are closely related to previous findings (Doyle et al., 2005; Peskin et al., 2015; Pineda et al., 2011; Pineda et al., 2007; Rommelse, 2008; Rommelse et al., 2008) and provide supporting evidence regarding the genetic component of ADHD and how the offspring from parents affected with ADHD inherit this condition (Ramos-Quiroga, Ribases-Haro, Bosch-Munso, Cormand-Rifa, & Casas, 2007), only the domains of attention, tasks of verbal comprehension, and some tasks of the execution scale in this Caribbean community are similar to the findings in the Paisa genetic isolate (Pineda et al., 2011; Pineda et al., 2007) and those of a recent study in the Central Valley of Costa Rica (Peskin et al., 2015), which reported high heritability values for attention and verbal IQ. In this study, we found that not only verbal comprehension tasks but also verbal IQ are highly heritable. It is intriguing how closely related the findings in the Paisa and this Costa Rican communities are compared with those in our Caribbean families, and that, unlike endophenotypes that were highly heritable in our sample, only two symptoms of the *DSM-IV* were so (Supplementary Table 3). This latter result supports the hypothesis that symptoms are not sufficient to determine genetic effects and hereditary transmission in ADHD, and that other approaches are needed (Acosta et al., 2011).

The fact that several tasks of the WISC (Table 2) but not the IQ were found to be potential endophenotypes suggests the existence of different IQ profiles among ADHD subtypes (Pennington, 2006; Sonuga-Barke, Bitsakou, & Thompson, 2010; Sonuga-Barke et al., 2002; Sonuga-Barke et al., 2008) and a potential association mainly with attention as a processing system, with temporal processing (Castellanos & Tannock, 2002), and with working memory, thus interfering with the normal learning processes and limiting the ability of individuals to easily adapt to the environment. In this sense, intelligence may not be critically compromised but diminished due to the aforementioned difficulties and lead to learning disorders (Castellanos & Tannock, 2002; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Temporal-processing and working memory deficits are associated with ADHD (Castellanos & Tannock, 2002), which may partially explain why some attention and working memory tasks and not IQ resulted to be potential endophenotypes in our sample. Tulsky, Saklofske, and Zhu (2003) suggest that the IQ can be determined not only by cognitive aspects, but also by other motivational factors. Thus, difficulties in attention and working memory are related to the cognitive and academic impairment cluster observed in individuals with severe inattention than in individuals with hyperactivity/impulsivity (Castellanos & Tannock, 2002), which is consistent with the inattention profile of our sample.

Although genetic factors are implicated in the etiology of ADHD and its comorbidities (Acosta et al., 2011; Arcos-Burgos et al., 2002; Arcos-Burgos et al., 2010; Jain et al., 2012; Palacio et al., 2004), environmental, epigenetic, cultural, and educational factors may offer an explanation about the heterogeneity of the disorder (Acosta et al., 2004). The fact that the number of endophenotypes compromising several cognitive domains in our sample is considerably less than the phenotypes evaluated (Table 2) puts us one step closer to genetic factors explaining ADHD variability (Doyle et al., 2005). Studying distinctive ADHD profiles, such as the inattentive type in our sample, may potentially lead to the identification of genetic factors and physiopathological

processes underlying ADHD. However, it is important to acknowledge that, given the multifactorial nature of ADHD, our approach of comparing cognitive impairments in individuals with ADHD with impairments in unaffected relatives is limited. As a complementary approach, we conducted a factor analysis and studied the heritability of the derived factors (Supplementary Table 4 and Supplementary Figure 4). Interestingly, only factors constructed from phonetic fluency tasks, semantic verbal fluency, WCST, and WISC-III/WAIS-III were found to be heritable.

The finding that some tasks of the WISC test were found to be heritable (Table 2 and Figure 1b) is consistent with the postulate that individuals having a family history of ADHD increase susceptibility to develop the condition as well as presenting major social and vocational difficulties than individuals with no family history (Arcos-Burgos et al., 2002; Bochud, 2012; Faraone et al., 1993; Lopera et al., 1999; Lopez-Campo, Gomez-Betancur, Aguirre-Acevedo, Puerta, & Pineda, 2005; Peskin et al., 2015; Pineda et al., 2011; Willcutt et al., 2005). We found significant heritability values in sustained visual attention, speed of information processing, and resolution of visuospatial subtests of the Wechsler scale that might be used in genetic research of ADHD (i.e., fine-mapping and genomewide linkage and association studies) as efficient phenotypic indicators. Following this approach, new neurobiological and genetic markers for ADHD can be defined and subsequently increase the power to detect genetic loci conferring susceptibility to the disorder (Mastronardi et al., 2016).

The importance of our findings can be summarized as follows. First, the study was performed in a sample of 120 nuclear families from the metropolitan area of Barranquilla, Colombia, with at least one individual affected with ADHD. These families have been clinically characterized using extensive neuropsychological batteries during the past 5 years (Pineda et al., 2016; Puentes Rozo et al., 2018) and constitute, to the best of our knowledge, the largest collection of nuclear families with ADHD in South America today. Because of their structure and admixture composition (~63% African descendants are with a vast Amerindian contribution; Barragán-Duarte, 2007), these families constitute a powerful resource for genetic studies of ADHD. Second, this is one of few studies examining the heritability of cognitive measures as probable endophenotypes (Kuntsi et al., 2010) and might be useful to support future molecular studies aiming to uncover the final causes of ADHD. Future studies will include conducting linkage and association genetic analysis between common, rare, and functional exomic variants to these cognitive endophenotypes, and possibly deep sequencing of genes harboring these variants in this set of families. This will be crucial for accurate diagnosis and treatment, to improve long-term outcomes, and for outlining public health policies (Arango-Dávila, Rojas, & Moreno, 2008; Posada, 2013).

## Authors' Note

M. L. Cervantes-Henríquez (M.L.C.-H.), J. E. Acosta-López (J.A.-L.), M. L. Martínez-Banfi (M.L.M-B), and J. I. Vélez (J.I.V.) contributed equally to this work. M.L.C.-H., J.A.-L., and E. Mejía-Segura (E.M.-S.) are doctoral students at Universidad del Norte, Barranquilla, Colombia, Universidad Maimónides in Buenos Aires, Argentina and Universidad de Flores in Buenos Aires, Argentina. Some of this work is to be presented in partial fulfillment of the requirements for the PhD degree. The sponsor of the study has no role in the study design, data collection, data analysis, data interpretation, or writing of the article. M.L.C.-H., J.A.-L., J.I.V., and P. J. Puentes-Rozo (P.P.-R.) have full access to all the data in the study and are responsible for submitting this work for publication. The authors assert that all procedures contributing to this work have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The views and opinions expressed in this article are those of the authors and should not be construed to represent the views of any of the sponsoring organizations, agencies, or governments. None of the authors of this article has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the article.

## Acknowledgments

We express our highest appreciation to all families enrolled in this study.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was financed by COLCIENCIAS, project "*Fenotipos Complejos y Endofenotipos del Trastorno por Déficit de Atención e Hiperactividad y su Asociación con Genes Mayores y de Susceptibilidad*," Grant 1253-5453-1644, contract RC 384-2011, conferred to Grupo de Neurociencias del Caribe, Universidad Simón Bolívar, Barranquilla.

## Supplemental Material

Supplementary material for this article is available online.

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