Published in final edited form as:

J Child Psychol Psychiatry. 2015 September ; 56(9): 958–965. doi:10.1111/jcpp.12434.

Latent profile analysis of neuropsychological measures to determine preschoolers' risk for ADHD

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Abstract

Background—Hyperactive/Inattentive preschool children show clear evidence of neuropsychological dysfunction. We examined whether patterns and severity of test scores could reliably identify subgroups of preschoolers with differential risk for ADHD during school-age.

Method—Typically-developing (TD: n=76) and Hyperactive/Inattentive (HI: n=138) 3–4 year-olds were assessed annually for 6 years (T1–T6). Latent profile analysis (LPA) was used to form subgroups among the HI group based on objective/neuropsychological measures (NEPSY, Actigraph and Continuous Performance Test). Logistic regression assessed the predictive validity of empirically-formed subgroups for risk for ADHD diagnosis relative to the TD group and to each other from T2–T6.

Results—LPA yielded 2 subgroups of HI preschoolers: 1) selectively weak Attention/Executive functions and 2) pervasive neuropsychological dysfunction across all measures. Both subgroups were more likely to have ADHD at all follow-up time-points relative to the TD group (OR range: 11.29–86.32), but there were no significant differences between the LPA-formed subgroups of HI children at any time-point.

Conclusions—Objective/neuropsychological measures distinguish HI preschoolers from their TD peers, but patterns and severity of neuropsychological dysfunction do not predict risk for ADHD during school-age. We hypothesize that trajectories in at-risk children are influenced by subsequent environmental and neurodevelopmental factors, raising the possibility that they are amenable to early intervention.

Keywords

Latent profile analysis; preschool; ADHD; neuropsychology

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Conflict of interest statement: No conflicts declared.

The authors have declared that they have no competing or potential conflicts of interest.

Introduction

ADHD is a prevalent neurodevelopmental disorder defined by excessive inattention, overactivity and impulsivity (APA, 2013). Symptoms are commonly first observed in early childhood and often persist through school-age and into adulthood, exacting substantial personal and societal burden. Those with persisting symptoms have more adverse health outcomes (Cortese et al., 2013); family and peer difficulties (Mrug et al., 2012); academic problems (Mannuzza, Klein, Bessler, Malloy, & Hynes, 1997); and elevated substance abuse (Sibley et al., 2014). Additionally, compared to their non-ADHD peers, children with ADHD are more likely to meet criteria for comorbid internalizing and externalizing disorders (Angold, Costello, & Erkanli, 1999).

Although the above symptoms and profiles characterize children with ADHD at a group level, considerable within-group heterogeneity has been observed vis-à-vis outcomes. Therefore, it is essential to determine which children are at disproportionately greater risk for adverse outcomes and, conversely, which youth profiles might suggest a more favorable trajectory. Moreover, as symptoms of ADHD often emerge during the preschool years, efforts to clarify such pathways early in development may have far-reaching therapeutic consequences on both individual and population-based levels.

The generally accepted method of arriving at diagnostic determinations of ADHD is through rating scales and clinical interviews that probe for core symptoms of the disorder. Yet, for young children, such methods can be problematic as only about half of preschoolers showing elevated inattention and/or hyperactivity/impulsivity and/or externalizing problems will go on to meet criteria for ADHD at school-age (Campbell, Ewing, Breaux, & Szumowski, 1986; Harvey, Lugo-Candelas & Breaux, 2014). Although rates of persistence are somewhat higher in cases where preschoolers meet full diagnostic criteria for ADHD, a significant minority of children experience remission of symptoms. In Lahey et al.'s (2005) longitudinal study of 4-6 year-olds, all of whom initially met DSM-IV criteria for ADHD, 65% continued to meet criteria for *any* DSM-IV ADHD subtype over a 7-year follow-up period. A 6-year follow-up of children from the Preschool ADHD Treatment Study (PATS; Riddle et al. 2013) found that 89% continued to meet criteria for ADHD. However, this was a particularly severe preschool sample with participants failing to respond to parent management training prior to enrollment in the medication trial. Notably, in the PATS study, the only significant correlate of persistence of ADHD at follow-up was *concurrent* comorbidity with ODD/CD; preschool classification via core symptoms of ADHD did not predict a persisting or remitting course.

Taken together, these data indicate that elevated levels of inattention, impulsivity and overactivity are readily identifiable during the preschool years, and that among those identified as symptomatic, a substantial portion go on to a persisting course of ADHD throughout childhood and early adolescence. Rates of ADHD during the school-age years are consistently reported to be higher in preschool children with behavioral problems (Harvey et al. 2014; Pierce, Ewing & Campbell, 1999) as compared to their typically-developing peers. Nevertheless, among those identified as having elevated levels of ADHD

symptoms in early childhood, a substantial minority do not have ADHD throughout the school-age years, and severity of ADHD symptoms appears to have limited predictive utility as to future course. Yet, with limited resources available for early intervention, it would be desirable to be able to identify those symptomatic preschoolers at greatest risk for, or resilience from, later adverse outcomes.

While the precise processes that lead to ADHD have remained elusive and likely vary across individuals, it is well-established that ADHD is a neurologically-based disorder. Data indicate deviant cortical development (Shaw et al., 2007), reduced neural connectivity involving both cortical and subcortical networks (Clerkin et al., 2013), as well as more circumscribed findings in an array of brain regions including the basal ganglia (Shaw et al., 2014), prefrontal cortex and cerebellum (Valera et al., 2007). Given the neural etiology for ADHD, it would stand to reason that among symptomatic preschoolers, measures of early brain function might provide an avenue for distinguishing hyperactive/inattentive preschoolers who go on to an adverse life-course of ADHD from phenocopies who “outgrow” the disorder.

One approach to assessing neural integrity during the preschool years is through neuropsychological testing. Studies of school-aged children with ADHD consistently indicate neuropsychological deficits across multiple domains, including both executive (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005) and non-executive (Frazier, Demaree, & Youngstrom, 2004) functions. Similarly, cognitive correlates of elevated ADHD symptoms in preschoolers include, but are not limited to, deficits in inhibitory control (Sjowall, Backman, & Thorell, 2014; Sonuga-Barke, Daley, Dalen, & Remington, 2002), working memory (Mariani & Barkley, 1997; Sjowall et al., 2014), delay aversion (Sjowall et al., 2014; Sonuga-Barke, Dalen, & Remington, 2003), response variability (Berwid et al., 2005), and motor control (Mariani & Barkley, 1997).

As with clinical outcomes for children with ADHD, significant inter-individual variability is observed with regard to profiles of neuropsychological functioning. Not all individuals with ADHD show deficits in the same area of cognitive function (Nigg, Willcutt, Doyle and Sonuga-Barke, 2005), and risk in one domain does not necessarily increase risk for poor performance in a second domain (Coghill, Seth, & Matthews, 2014; Willcutt et al., 2005). In light of such heterogeneity, several investigators (Castellanos & Tannock, 2002; Sonuga-Barke et al. 2002; 2003) have posited distinct neuropsychological subtypes, including a shortened delayed gradient, deficient temporal processing, impoverished working memory, diminished response inhibition, and elevated response variability. It has been hypothesized that neuropsychological subtypes of ADHD may inform clinical outcomes (Nigg et al. 2005).

Thus, neuropsychological factors are concurrently related to clinical presentation in young children with ADHD. However, little is known regarding their prognostic utility with regard to ADHD. Rajendran et al. (2013) found that *changes* in neuropsychological functioning over time was associated with variations in ADHD symptom severity, but preschool levels of *global* neuropsychological functioning did not predict changes in symptom severity and impairment over time. Distinct patterns of neuropsychological functioning were not

examined, and, to our knowledge, no study has used preschool neuropsychological measures to categorize children and test the likelihood of future ADHD diagnosis.

Given the limited ability of early ADHD severity to predict course and outcomes among hyperactive/inattentive preschoolers, and the potential utility of neurocognitive variables, a compelling rationale exists for using these objective, biologically-based parameters to form early subgroups and to determine their capacity to predict distinct trajectories. With such goals in mind, we used latent profile analysis (LPA) of preschool measures of neuropsychological functioning and objectively-assessed activity level followed by logistic regression to determine whether the emergent profiles differentially predicted ADHD diagnosis over five years of follow-up in a group of preschoolers characterized by hyperactivity and/or inattention. Due to our inability to know what patterns of neuropsychological functioning would emerge from the LPA, we did not have specific hypotheses regarding patterns of functioning that would be differentially associated with outcome. However, we hypothesized that poorer outcomes would, in general, be associated with more impaired neuropsychological performance, and that distinct patterns of neuropsychological strengths and weaknesses would have differential outcomes.

Method

Participants

Based on screening using the ADHD-RS-IV (DuPaul, Anastopoulos & Reid, 1998) preschool children were recruited for a longitudinal sample as either Typically-developing (TD; <3 items rated as Often or Very Often by both parents and teachers; n=76) or Hyperactive/Inattentive (HI; 6 symptoms within a domain rated as Often or Very Often by either parent or teacher; n=138). Among those in the HI group, 116 (84.7%) met diagnostic criteria for ADHD. By design, children with HI were oversampled. Children who had a Full-Scale IQ below 80, as measured by the Wechsler Preschool and Primary Scale of Intelligence– Third Edition (WPPSI-III; Wechsler, 2002); a pervasive developmental or neurological disorder; or whose parent was not fluent in English were excluded.

Mean (SD) age of the children at six annual assessments (T1, T2, T3, T4, T5, and T6) was 4.25 (0.48), 5.29 (0.50), 6.29 (0.49), 7.30 (0.52), 8.29 (0.49), and 9.29 (0.51) years respectively. The Mean (SD, range) socio-economic status (SES; see measures below) was 63.09 (17.88, 20-97), representing on average, a middle class sample. The sample was racially and ethnically diverse. Table 1 shows the demographic characteristics of the sample.

Although no child was taking psychotropic medication at T1, 43 (20.1%) had taken such medication by the age of 9 years. Among those, most had taken stimulants (n=33; 76.7%) and/or atomoxetine (n=7; 16.3%) for ADHD, although some took other medications including SSRIs (n=3; 7.0%), antipsychotics (n=8; 18.6%) and/or alpha-2 agonists (n=4; 9.3%). Parents withheld stimulants and atomoxetine, but not other medications, on assessment days. This study was approved by the university's Institutional Review Board. Primary caregivers signed informed consent forms.

Measures

Class indicators: Objective/Neuropsychological measures

The Developmental Neuropsychological Assessment (NEPSY): The NEPSY (Korkman, Kirk, & Kemp, 1998) assesses neuropsychological functioning in five domains: Attention/Executive functioning, Language, Visuospatial, Sensorimotor, and Memory. In the normative sample, test-retest reliability for the five domains ranged from 0.70 to 0.91 for 3–4 year olds. The five domain scores were used as class determinants.

Kiddie CPT/Go-No-Go task (CPT/GNG; Berwid et al., 2005): The CPT/GNG is a computerized task with 4 blocks with different ratios of targets to non-targets (5:1, 2:1, 1:2, and 1:5). CPTs typically have a low target-probability, yielding higher rates of omission errors, while go/no-go tasks have a high target-probability, eliciting more commission errors. Therefore, some blocks elicited more commission errors, while others yielded higher rates of omission errors. Block order was counterbalanced across participants. Each block included 48 Microsoft clipart cartoon stimuli that were presented for 750ms, with a 1500ms inter-stimulus interval. Children were initially trained using 10 sample trials in a booklet and 8 practice computer trials. Once the test began, children were not provided feedback though they were encouraged to keep doing their best. Percent false alarms, percent misses and reaction time variability across all blocks were used as class determinants.

Actigraphs: Children's activity level at T1 was measured using solid state actigraphs (model # AM7164; ActiGraph, LLC, Fort Walton Beach, FL) worn around the waist and non-dominant ankle. This measure has been associated with teacher ratings of inattention and hyperactivity in non-referred school-age (Reichenbach, Halperin, Sharma, & Newcorn, 1992) and preschool (Marks et al. 2005) children. A mean of the waist and ankle activity during assessment was used as a class determinant.

Dependent variable

ADHD diagnosis: The Kiddie Schedule for Affective Disorders and Schizophrenia: Present and Lifetime Version (K-SADS-PL; Kaufman et al. 1996) was used to assess ADHD diagnosis (T2-T6). Parents of children taking medication for ADHD were asked to describe their child's behavior off medications. Interviewers were well-trained graduate students or Ph.D.-level psychologists who were blind to children's prior diagnostic status. Neuropsychological testing and parent interviews were conducted by different evaluators.

Covariates

Socio-economic status: The Nakao-Treas Socioeconomic Prestige Index (Nakao & Treas, 1994) was used to measure SES at T1 with greater scores reflecting higher SES. In two-parent families, scores for both parents were separately coded and the higher of the two served as the index of family SES.

Missing data—Retention rates at T2, T3, T4, T5, and T6 were 86.1%, 81%, 73.1%, 74.1%, and 68.1% respectively. Children not evaluated at T3 and T4 were from families with lower SES than those who were assessed ($p < .05$), but there were no significant

differences in SES other time-points. There were no significant differences in age, gender and T1 ADHD severity between those who came for follow up (T2-T6) and those who did not.

Data analysis—We examined descriptive statistics of all class indicators. Only Actigraph counts were non-normal and were log-transformed. A person-centered LPA using Mplus Version 4 (Muthén & Muthén, 2006) was employed to classify the HI children into categories based on objective/neuropsychological measures. LPA groups individuals based on shared characteristics or response patterns such that individuals in one group are more similar to each other than individuals in another group. This technique uses continuous variables as class determinants, provides probabilities of class membership, robustness to non-normality and access to fit statistics that help empirically determine the number of classes

The Akaike information criteria (AIC), Bayes Information Criteria (BIC), sample size adjusted BIC and Entropy, along with Lo-Mendell-Rubin Adjusted Likelihood Ratio Test (LRT) (Nylund, Asparouhov, & Muthén, 2007) were used to determine the number of classes that best fit the data. Smaller values of AIC and BIC indicate better fit. Entropy values close to 1 indicate class distinctiveness (Kline, 2005). LRT indicates the significance of improvement in model fit of the number of groups being tested versus one less group. Research supports the performance of BIC, along with the LRT test and Entropy (Nylund et al., 2007). We therefore favored models that had a combination of the lowest BIC with the highest LRT and Entropy.

We then tested the distinctiveness of classes relative to each other and relative to the TD group by conducting logistic regression to assess the predictive validity (T2-T6) of subgroups for ADHD diagnosis.

Results

Identification of latent classes

At T1, children in the HI group performed significantly poorer on all five NEPSY and all three CPT/GNG measures, and were more active as measured by actigraphs, as compared to the TD group (all $p < .01$; Cohen's d range = 0.43–1.00). Using all nine measures we tested the fit of the sample to 2, 3, and 4 groups, beyond which the indices did not improve (see Table 2). The two-class solution showed by far the highest LRT and the only one that was significant ($p < .0001$), along with a BIC that was similar to the 4-class solution and Entropy identical to the 3-class solution. Although the 4-class solution showed slightly lower BIC and higher Entropy, its LRT did not approach significance ($p = .64$). We therefore chose the 2-class solution as best fitting the data.

As shown in Table 3, Group 1 showed a selective deficit, relative to the TD group, as measured by the Attention/Executive Domain of the NEPSY. Further, consistent with their classification as HI, they were significantly more active than the TD group as measured by actigraphs. In contrast, Group 2 had neuropsychological deficits across all nine domains relative to the TD group and all but one domain (Memory) relative to Group 1.

External validation of latent classes with future ADHD diagnosis

After controlling for SES, logistic regression indicated that both Groups 1 and 2 were significantly more likely to be diagnosed with ADHD at all five follow-up time-points relative to the TD group with odds ratios (ORs) ranging from 11.29 – 86.32 (all $p < .001$; see Table 4). While ORs tended to be higher for Group 2 relative to Group 1, chi-square tests indicated no significant differences in rates of ADHD diagnoses between those groups at any time-point (all $p > .10$), with rates of ADHD at follow-up ranging from 60.0 – 77.5% in Group 1 and 71.9 – 81.8% in Group 2 (see Figure 1) ¹.

Secondary analyses

Because the latent classes did not distinguish HI children who did and did not have a diagnosis of ADHD throughout the subsequent five years, follow-up analyses examined whether any of the nine individual indicators might have better predictive utility. As such, using only the HI children and controlling for SES, all 9 dimensional measures were entered simultaneously into a logistic regression at each time-point to see if any emerged as a consistent predictor of ADHD outcome after controlling for the other variables. Only one marginal (RTSD at T4: OR = 1.01; 95% C.I. = 1.00 – 1.01) and two significant (Actigraph at T5: OR = 2.86; 95% C.I. = 1.35 – 6.21 and T6: OR = 2.48; 95% C.I. = 1.18 – 5.23) predictors emerged.

As we found no significant differences between Groups 1 and 2 for ADHD diagnoses, we examined dimensional ADHD severity scores on the K-SADS as outcomes using linear regression. Similar to the diagnostic findings, symptom severity was significantly greater at all time-points in Groups 1 and 2 relative to the TD group (all $p < .001$). However, the groups did not differ at any time-point beyond T1 (all $p > .07$).

Discussion

This prospective longitudinal study employed LPA to examine whether neuropsychological data derived during the preschool years in HI children could be used to form subgroups of children based upon patterns of neurocognitive functioning and whether such groupings would have prognostic utility with regard to ADHD diagnosis. LPA yielded two distinct classes of HI children; one with selective impairment in Attention/Executive functioning as measured by the NEPSY, and one with more severe and pervasive neuropsychological dysfunction. However, contrary to our hypothesis, the nature/severity of neuropsychological dysfunction in HI preschoolers was not predictive of later ADHD diagnosis. Relative to the TD group, both subgroups of HI children had significantly higher rates of ADHD throughout the 5-year follow-up period, but they did not differ from each other at any time-point.

¹Given that the 2- and 4 class solutions among HI children showed comparable Information Criteria, we also tested the external validity of the 4 classes in relation to ADHD diagnosis (available on request). All 4 groups were more likely to have ADHD than the TD group at all follow-up time-points. However, the likelihood of later ADHD diagnosis did not differ among the 4 HI groups at any later time-point. Thus the findings from the 4 group solution were in line with those from the 2 group solution.

Further, when examined individually, all nine objective/neuropsychological measures significantly distinguished TD from HI preschoolers, with effect sizes in the medium to large range. Yet, among HI children these measures had minimal prognostic utility as to who would or would not have ADHD during the school-age years. Only preschool actigraph recordings, perhaps an index of early symptom severity, predicted ADHD outcome 4 and 5 years later.

Taken together, these data suggest that early neural dysfunction, as measured by neuropsychological tests administered during the preschool years, do not provide a useful prognostic indicator of outcome among children with early signs of ADHD. Clearly, these measures provide evidence of concurrent validity, separating HI children from their non-behaviorally-disturbed peers, but they do not provide predictive utility among this subgroup of children. As such, like many other psychological measures administered during early childhood, they appear to accurately reflect current functioning, and may predict later cognitive/academic status, but are limited in their ability to predict future ADHD status.

There are several possibilities as to why early neuropsychological functioning does not predict ADHD outcome among HI children. First, early childhood is a time of rapid cognitive development with considerable between-child variability. Therefore, testing at one time-point may not capture stable between-child differences. Second, given the short attention span and disinhibition characteristic of HI preschoolers, testing them at this age may yield somewhat unreliable scores. While clinicians conducting individual evaluations integrate test scores with behavioral observations, and generally make statements whether scores likely reflect the child's ability or level of functioning, such individualized statements are not readily integrated into group analyses such as these. Nevertheless, arguing against the unreliability of scores is the fact that all of our measures distinguished the HI children from their TD peers.

It is also possible that early neuropsychological test scores are reliable among HI preschoolers, but, as suggested by our findings, do not predict ADHD outcomes. Several factors likely influence neurodevelopmental pathways leading to and from ADHD in children at risk for the disorder including the presence of comorbid psychiatric disorders, academic failure, poor social relationships, low self-esteem, and negative parent/family relationships (Sonuga-Barke & Halperin, 2010). As such, early neural status may only account for a small amount of variance influencing ADHD outcomes and may be moderated by intervening factors influencing development. Further, from a neurobiological perspective, it has been proposed that changes in cortical development over time, and not the starting point, may be the primary driver of ADHD trajectory and outcomes (Giedd & Rapoport, 2010; Halperin & Schulz, 2006; Rajendran et al. 2013). Thus, early behavioral and neural dysfunction may place children at elevated risk for ADHD, but many factors influence outcomes. Given that TD and Group 1 children differed significantly only on Attention/Executive and actigraph measures, it is possible that early executive dysfunction in hyperactive/inattentive children, irrespective of additional/broader neuropsychological deficits, is sufficient for predicting later ADHD, and that more widespread neuropsychological impairments do not increase risk further for ADHD. Our data are consistent with the notion of equifinality; both HI groups, irrespective of neuropsychological

status, were at very high risk for ADHD outcomes, suggesting that it may be important to monitor such children from early on.

This study has several strengths including annually-collected prospective, longitudinal data for HI and TD children from 3-4 years through 9 years. Thus, the reliability of significant findings could be readily determined by monitoring persistence over years. In addition, by limiting the LPA to HI children, we enhanced the clinical utility of the study. Had we included in the LPA, TD children, who rarely receive neuropsychological evaluations, it would be difficult to interpret our findings as they apply to symptomatic preschoolers who are often referred for such assessments. Furthermore, staff who conducted T2-T6 ADHD evaluations were blind to T1 neuropsychological status, eliminating evaluator bias. Finally, we used a dimensional LPA approach which helped provide a range of possible objective factors rather than artificial cut-offs. While other studies (e.g., Althoff et al. 2006; Martel et al. 2010) have used Latent Class or Profile Analysis, this has mostly been used in school-aged children and has generally considered only ADHD symptoms or other informant ratings as class determinants, and then tested for correspondence with concurrent diagnoses. Our study was unique because variables that determined classes did not include symptom counts. Moreover, it included external validation over several years. Notably, there was a low likelihood of rater bias because class determinants were objective measures while outcomes were based on parent reports.

Despite strengths, the study also had limitations. First, the sample size of only 138 HI children may have limited our ability to detect a wider array of differential classes. With a larger sample, greater differentiation based on patterns of neuropsychological functioning may have emerged. Second, our results were likely influenced by the specific neuropsychological measures administered. We used the five Domain scores from the NEPSY, three measures from a CPT/GNG task developed specifically for preschoolers, and objective measures of movement from actigraphs. While all nine measures distinguished HI children from the TD comparison group, recent data have raised questions regarding the validity of the NEPSY Domain scores (Korkman, Kirk, & Kemp, 2007), which was among the very few standardized neuropsychological test batteries that went down to the preschool age when this study was initiated. Third, none of our measures assessed key areas of functioning such as working memory and set shifting. Had we used newer and potentially better measures, such as those in the Early Childhood Battery of the NIH Toolbox for the Assessment of Neurological and Behavior Function (2013), our results may have been different. Additionally, we did not have longitudinal data for all of our neuropsychological measures, and were thus unable to use latent class growth modeling to identify distinct subgroups based on changing neuropsychological profiles. Further, attrition is always a problem in longitudinal research and by our final follow-up year was greater than 30%. However, there was little evidence of differential attrition based on key baseline measures. Finally, it should be noted that the information criteria did not conclusively show that the 2-class solution was preferable over the 4-class solution. Therefore, we tested the 4-class solution and found results similar to the 2-class solution; the groups could be distinguished at T1 via objective measures, and were significantly different from TD children, but not from each other, with regard to ADHD at all follow-up time-points (available on request).

Taken together, our data indicate that HI preschool children are clearly distinguishable from their TD peers on neuropsychological measures spanning a wide array of cognitive domains. Yet, patterns and severity of impairment on these measures do not predict future ADHD outcome. As such, we hypothesize that early, potentially non-specific, neural dysfunction that varies across individuals, places children at risk for a life-course of ADHD and its varied outcomes. However, trajectories in at-risk children are likely influenced by an array of subsequent environmental and neurodevelopmental factors that may be amenable to early intervention (Halperin, Bedard & Curchack-Lichtin, 2012). The challenge is to identify these factors and to develop interventions that facilitate more optimal trajectories and outcomes.

Acknowledgments

This original article was invited by the journal as part of a special issue, it has undergone full, external peer review. This research was supported by grant# R01MH68286 from the National Institute of Mental Health.

References

- Althoff RR, Copeland WE, Stanger C, Derks EM, Todd RD, Neuman RJ, et al. Hudziak JJ. The Latent class structure of ADHD is stable across informants. *Twin Research & Human Genetics*. 2006; 9(4): 507–522. [PubMed: 16899158]
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5. Arlington, VA: American Psychiatric Publishing; 2013.
- Angold A, Costello EJ, Erkanli A. Comorbidity. *Journal of Child Psychology and Psychiatry*. 1999; 40(1):57–87. [PubMed: 10102726]
- Berwid OG, Curko Kera EA, Marks DJ, Santra A, Bender HA, Halperin JM. Sustained attention and response inhibition in young children at risk for Attention Deficit/Hyperactivity Disorder. *Journal of Child Psychology and Psychiatry*. 2005; 46(11):1219–29. [PubMed: 16238669]
- Campbell SB, Ewing LJ, Breaux AM, Szumowski EK. Parent-referred problem three-year-olds: follow-up at school entry. *Journal of Child Psychology and Psychiatry*. 1986; 27(4):473–488. [PubMed: 3745347]
- Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nature Reviews Neuroscience*. 2002; 3(8):617–628. [PubMed: 12154363]
- Clerkin SM, Schulz KP, Berwid OG, Fan J, Newcorn JH, Tang CY, Halperin JM. Thalamo-cortical activation and connectivity during response preparation in adults with persistent and remitted ADHD. *American Journal of Psychiatry*. 2013; 170(9):1011–1019.
- Coghill DR, Seth S, Matthews K. A comprehensive assessment of memory, delay aversion, timing, inhibition, decision making and variability in attention deficit hyperactivity disorder: advancing beyond the three-pathway models. *Psychological Medicine*. 2014; 44(9):1989–2001. [PubMed: 24176104]
- Cortese S, Ramos Olazagasti MA, Klein RG, Castellanos FX, Proal E, Mannuzza S. Obesity in men with childhood ADHD: a 33-year controlled, prospective, follow-up study. *Pediatrics*. 2013; 131(6):e1731–1738.10.1542/peds.2012-0540 [PubMed: 23690516]
- DuPaul, GJ.; Power, TJ.; Anastopoulos, AD.; Reid, R. ADHD Rating Scale IV: Checklists, norms, and clinical interpretation. New York: Guilford; 1998.
- Frazier TW, Demaree HA, Youngstrom EA. Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. *Neuropsychology*. 2004; 18(3):543–55. [PubMed: 15291732]
- Giedd JN, Rapoport JL. Structural MRI of pediatric brain development: What have we learned and where are we going? *Neuron*. 2010; 67(5):728–734. [PubMed: 20826305]
- Halperin JM, Bedard ACV, Curchack-Lichtin J. Preventive interventions for ADHD: A neurodevelopmental perspective. *Neurotherapeutics*. 2012; 9:531–541. [PubMed: 22692794]

- Halperin JM, Schulz KP. Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. *Psychological Bulletin*. 2006; 132:560–581. [PubMed: 16822167]
- Harvey EA, Lugo-Candelas CI, Breaux RP. Longitudinal changes in individual symptoms across the preschool years in children with ADHD. *Journal of Clinical Child and Adolescent Psychology*. 2014 Apr 3. 2014. Epub ahead of print.
- Kaufman, J.; Birmaher, B.; Brent, D.; Rao, U.; Ryan, N. The schedule for affective disorders and schizophrenia for school-age children present and lifetime version (version 1.0). Pittsburgh, PA: Dept of Psychiatry, University of Pittsburgh School of Medicine; 1996.
- Kline, RB. Principles and practice of Structural Equation Modeling. Guilford Press; New York: 2005.
- Korkman, M.; Kirk, U.; Kemp, S. NEPSY: A developmental neuropsychological assessment. San Antonio, TX: The Psychological Corporation; 1998.
- Korkman, M.; Kirk, U.; Kemp, S. NEPSY-II: Clinical and interpretive scoring manual. San Antonio, TX: The Psychological Corporation; 2007.
- Lahey BB, Pelham WE, Loney J, Lee SS, Willcutt E. Instability of the DSM IV subtypes of ADHD from preschool through elementary school. *Archives of General Psychiatry*. 2005; 62(8):896–902. [PubMed: 16061767]
- Mannuzza S, Klein RG, Bessler A, Malloy P, Hynes ME. Educational and occupational outcome of hyperactive boys grown up. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997; 36(9):1222–1227. [PubMed: 9291723]
- Mariani MA, Barkley RA. Neuropsychological and academic functioning in preschool boys with attention deficit hyperactivity disorder. *Developmental Neuropsychology*. 1997; 13:111–129.
- Marks DJ, Berwid OG, Santra A, Kera EA, Cyrluk SE, Halperin JM. Neuropsychological correlates of AD/HD symptoms in preschoolers. *Neuropsychology*. 2005; 19:446–455. [PubMed: 16060819]
- Martel MM, Goth-Owens T, Martinez-Torteya C, Nigg JT. A person-centered personality approach to heterogeneity in attention-deficit/hyperactivity disorder (ADHD). *Journal of Abnormal Psychology*. 2010; 119(1):186–196. [PubMed: 20141255]
- Muthén, LK.; Muthén, BO. Mplus version 4 user's guide. Los Angeles (CA): Muthén & Muthén; 2006.
- Mrug S, Molina BS, Hoza B, Gerdes AC, Hinshaw SP, Hechtman L, Arnold LE. Peer rejection and friendships in children with Attention-Deficit/Hyperactivity Disorder: contributions to long-term outcomes. *Journal of Abnormal Child Psychology*. 2012; 40(6):1013–1026. [PubMed: 22331455]
- Nakao K, Treas J. Updating occupational prestige and socioeconomic scores: How the new measures measure up. *Sociological Methodology*. 1994; 24:1–72.
- NIH Toolbox for Assessment of Neurological and Behavioral Function. *Neurology*. 2013; 80(Supplement 3):S1–S92.
- Nigg JT, Willcutt EG, Doyle AE, Sonuga-Barke EJ. Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes? *Biological Psychiatry*. 2005; 57(11):1224–1230. [PubMed: 15949992]
- Nylund KL, Asparouhov T, Muthén B. Deciding on the number of classes in latent class analysis and growth mixture modeling: A Monte Carlo simulation study. *Structural Equation Modeling: A Multidisciplinary Journal*. 2007; 14:535–569.
- Pierce EW, Ewing LJ, Campbell SB. Diagnostic status and symptomatic behavior of hard-to-manage preschool children in middle childhood and early adolescence. *Journal of Clinical Child Psychology*. 1999; 28(1):44–57. [PubMed: 10070606]
- Rajendran K, Trampush JW, Rindskopf D, Marks DJ, O'Neill S, Halperin JM. Association between variation in neuropsychological development and trajectory of ADHD severity in early childhood. *American Journal of Psychiatry*. 2013; 170(10):1205–1211. [PubMed: 23897408]
- Reichenbach LC, Halperin JM, Sharma V, Newcorn JH. Children's motor activity: reliability and relationship to attention and behavior. *Developmental Neuropsychology*. 1992; 8:87–97.
- Riddle MA, Yershova K, Lazzaretto D, Paykina N, Yenokyan G, Greenhill L, et al. Posner K. The Preschool Attention-Deficit/Hyperactivity Disorder Treatment Study (PATS) 6-year follow-up. *Journal of American Academy of Child Adolescent Psychiatry*. 2013; 52(3):264–278.
- Shaw P, De Rossi P, Watson B, Wharton A, Greenstein D, Raznahan A, et al. Chakravarty MM. Mapping the development of the basal ganglia in children with attention-deficit/hyperactivity

- disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2014; 53(7):780–789 e711. [PubMed: 24954827]
- Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, et al. Rapoport JL. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of National Academy of Sciences*. 2007; 104(49):19649–19654.
- Sibley MH, Pelham WE, Molina BS, Coxe S, Kipp H, Gnagy EM, et al. Lahey BB. The role of early childhood ADHD and subsequent CD in the initiation and escalation of adolescent cigarette, alcohol, and marijuana use. *Journal of Abnormal Psychology*. 2014; 123(2):362–74. [PubMed: 24886010]
- Sjöwall D, Backman A, Thorell LB. Neuropsychological heterogeneity in preschool ADHD: Investigating the interplay between cognitive, affective and motivation-based forms of regulation. *Journal of Abnormal Child Psychology*. 2014 Epub ahead of print.
- Sonuga-Barke EJ, Dalen L, Daley D, et al. Remington B. Are planning, working memory, and inhibition associated with individual differences in preschool ADHD symptoms? *Developmental Neuropsychology*. 2002; 21(3):255–272. [PubMed: 12233938]
- Sonuga-Barke EJ, Dalen L, Remington B. Do executive deficits and delay aversion make independent contributions to preschool attention-deficit/hyperactivity disorder symptoms? *Journal of the American Academy of Child and Adolescent Psychiatry*. 2003; 42(11):1335–1342. [PubMed: 14566171]
- Sonuga-Barke EJS, Halperin JM. Developmental phenotypes and causal pathways in attention-deficit/hyperactivity disorder: Potential targets for early intervention? *Journal of Child Psychology and Psychiatry*. 2010; 51(4):368–389. [PubMed: 20015192]
- Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biological Psychiatry*. 2007; 61(12):1361–1369. [PubMed: 16950217]
- Wechsler, D. *The Wechsler Preschool and Primary Scale of Intelligence*. 3rd. San Antonio, TX: The Psychological Corporation; 2002.
- Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. *Biological Psychiatry*. 2005; 57(11):1336–1346. [PubMed: 15950006]

Key points

- This study used a latent profile analysis (LPA) to determine the extent to which laboratory measures of ADHD symptoms and neuropsychological functioning, administered to hyperactive/inattentive preschool youth, map onto differential ADHD trajectories over the succeeding five years.
- Two subgroups of hyperactive/inattentive preschoolers emerged: one with a relative weakness in Attention/Executive Functioning, and the other with pervasive neuropsychological dysfunction across measures.
- The above-referenced groups did not show differential risk for ADHD during school age, but were more likely to have a diagnosis than their typically developing peers.
- When viewed alongside previously reported findings, these data suggest that environmentally and neurodevelopmentally mediated changes in neurocognitive functioning, rather than early profiles of neuropsychological functioning, may most closely influence the trajectories of at risk preschool youth.

Figure 1. Percentage of Children with ADHD at 5 follow-up time-points

Table 1
Demographic characteristics

Variable	Typically-developing N=76	Hyperactive Inattentive N=138	Total Sample N=214
Male, N (%)	51 (67.10)	105 (76.10)	156 (73.90)
Age, Mean (SD)	4.20 (0.48)	4.36 (0.46)	4.30 (0.47) *
Race, N (%)			
White	42 (55.30)	82 (59.40)	124 (57.90)
Black	5 (6.60)	22 (15.90)	27 (12.60) *
Asian	15 (19.70)	8 (5.80)	23 (10.70) **
Other/Mixed	14 (18.40)	26 (18.80)	40 (18.70)
Hispanic, N (%)	19 (25.00)	49 (35.50)	68 (31.80)
SES score, Mean (SD)	68.60 (15.68)	60.06 (18.35)	63.09 (17.88) **

**
p<.01,

*
p<.05

Table 2
Results of Latent Profile analysis HI children (N=137)

Model fit indices	2 class	3 class	4 class
AIC	6884.32	6872.73	6825.36
BIC	6966.07	6983.69	6965.52
Adjusted BIC	6877.49	6863.48	6813.67
Entropy	0.77	0.77	0.79
LRT; p	148.86; <.0001	30.95; 0.28	40.13; 0.64
N for each class	65, 72	27, 78, 32	31, 13, 28, 65
Probability of being in each class	0.93, 0.94	0.86, 0.93, 0.88	0.88, 0.91, 0.89, 0.88

Table 3

Means of class indicators

Variable	TD	Group 1		Group 2		F*	Post hoc
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Attention/Executive	107.27 (12.48)	99.92 (10.42)	90.72 (11.39)	37.68	TD> 1>2		
Language	105.40 (11.17)	101.43 (12.36)	95.10 (11.83)	14.15	TD & 1>2		
Sensorimotor	98.15 (14.64)	99.09 (11.98)	81.53 (11.06)	42.93	TD & 1>2		
Visuospatial	111.64 (11.77)	108.12 (12.17)	98.63 (10.00)	24.33	TD & 1>2		
Memory	97.93 (13.95)	93.26 (16.30)	88.08 (13.54)	8.26	TD>2		
CPT/GNG %misses	17.04 (15.60)	14.29 (10.09)	34.11 (17.28)	32.30	TD & 1<2		
CPT/GNG %FA	16.70 (16.31)	13.61 (7.74)	36.00 (16.84)	43.40	TD & 1<2		
CPT RTSD	350.87 (116.06)	344.38 (94.78)	526.04 (83.85)	64.34	TD & 1<2		
Actigraph (log)	6.14 (0.63)	6.40 (0.62)	6.70 (0.56)	15.18	TD<1<2		

* all p<.001

Table 4
Logistic Regression Predicting ADHD Diagnosis at each of 5 follow-up years relative to TD children

	B	S.E.	Wald	OR[*]	95% C.I.
T2: Group 1	3.91	.78	25.34	49.80	10.88 – 228.08
T2: Group 2	4.46	.77	33.23	86.32	18.96 – 393.02
T3: Group 1	2.96	.52	31.90	19.22	6.89 - 53.61
T3: Group 2	3.22	.52	38.00	25.12	9.01 – 70.00
T4: Group 1	3.14	.54	33.53	23.12	7.98 – 66.90
T4: Group 2	3.38	.55	38.01	29.40	10.04 – 86.12
T5: Group 1	2.77	.51	29.70	15.90	5.88 – 43.01
T5: Group 2	2.94	.49	36.21	18.88	7.25 – 49.16
T6: Group 1	2.46	.52	22.70	11.71	4.26 – 32.23
T6: Group 2	2.42	.48	25.31	11.29	4.39 – 29.02

* All p<.001