


Similar Subgroups Based on Cognitive Performance Parse Heterogeneity in Adults With ADHD and Healthy Controls

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Abstract

Objective: To characterize heterogeneity in adults with ADHD we aimed to identify subgroups within the adult ADHD spectrum, which differ in their cognitive profile. **Method:** Neuropsychological data from adults with ADHD ($n = 133$) and healthy control participants ($n = 132$) were used in a confirmatory factor analysis. The resulting six cognitive factors were correlated across participants to form networks. We used a community detection algorithm to cluster these networks into subgroups. **Results:** Both the ADHD and control group separated into three profiles that differed in cognitive performance. Profile 1 was characterized by aberrant attention and inhibition, profile 2 by increased delay discounting, and profile 3 by atypical working memory and verbal fluency. **Conclusion:** Our findings suggest that qualitative differences in neuropsychological performance exist in both control and ADHD adult individuals. This extends prior findings in children with and without ADHD and provides a framework to parse participants into well-defined subgroups. (*J. of Att. Dis.* 2018; 22(3) 281-292)

Keywords

adult ADHD, neuropsychology, executive functions, delay discounting, heterogeneity

Introduction

Although ADHD is classically known as a childhood disorder, the disease has increasingly become acknowledged as persisting into adulthood. Prevalence of the diagnosis of ADHD in adults is estimated between 2.5% and 4.9% (Simon, Czobor, Balint, Meszaros, & Bitter, 2009). Similar to ADHD in childhood, persistent ADHD in adults is characterized by age-inappropriate symptoms of inattention, and/or hyperactivity and impulsivity (American Psychiatric Association [APA], 2000, 2013). ADHD in children as well as in adults has been associated with cognitive (neuropsychological) deficits.

In an extensive meta-analysis, Hervey, Epstein, and Curry (2004) showed that adults with ADHD are impaired on a wide range of neuropsychological tasks. In contrast to theories stating that inhibition is the primary deficit in ADHD (Barkley, 1997; Boonstra, Kooij, Oosterlaan, Sergeant, & Buitelaar, 2010), the authors concluded that deficits in adults with ADHD are widespread, covering multiple cognitive domains including attention, memory, and processing speed. This ties in with studies on children with ADHD showing that there is no single, core deficit

causal to the disorder (de Zeeuw, Weusten, van Dijk, van Belle, & Durston, 2012; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Sonuga-Barke, 2005). Coghill, Seth, and Matthews (2014) recently extended these findings by demonstrating that on each cognitive domain (working memory, inhibition, delay aversion, decision making, timing, and

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variability), only a minority of children with ADHD performed deficiently, despite significant group-level effects on all domains. In line with these studies, our own work has shown that adult ADHD patients are impaired in multiple cognitive domains (attention, working memory, and delay discounting), but with moderate effect sizes and with large variability in the number of neuropsychological tasks on which patients performed deficiently (Mostert et al., in press). This indicates that cognitive heterogeneity is also apparent in adults with ADHD.

Acknowledging this heterogeneity in neuropsychological performance in ADHD, Fair, Bathula, Nikolas, and Nigg (2012) identified neuropsychological subgroups within a large sample of children with ADHD. Patients in one subgroup exhibited high response variability, while patients with low performance on memory, inhibition, and response speed formed another subgroup. A third subgroup was characterized by inaccurate temporal information processing and the fourth showed suboptimal arousal. Interestingly, the authors found that such subgroups exist both in the patient and in the typically developing population, and concluded that “heterogeneity in individuals with ADHD might be ‘nested’ in . . . normal variation” (Fair et al., 2012). Similarly, van Hulst, de Zeeuw, and Durston (2015) identified three neuropsychological subgroups within a sample of children with ADHD: a quick and accurate, a slow and variable reaction time, and a poor cognitive control subgroup. The first two of these subgroups were also present in the healthy control group, showing again that cognitive heterogeneity in childhood ADHD extends into the healthy population. The cognitive control subgroup, however, was only present in patients, indicating that this subtype may be more specific to ADHD.

Classification methods can be used to investigate within-group heterogeneity. One such method is community detection (CD), as was used by Fair and colleagues (2012). CD originates from graph theory and can be used to identify clusters within networks. In the current case, the network represents correlations between individuals in terms of neuropsychological performance. A modularity algorithm is then used to search for clusters of participants that are highly correlated with each other, and marginally correlated with participants from other clusters (Newman, 2006). These clusters can be interpreted as subgroups within the network, or in this case, the sample.

It is as yet unknown whether different subgroups, characterized by distinct cognitive profiles, exist in adult ADHD, and whether these profiles are similar to the ones found in childhood ADHD. Based on previous studies we hypothesized that adults with ADHD can be divided into subgroups based on their performance on a neuropsychological testing battery. Furthermore, we expected these cognitive profiles to also exist in the control sample. To investigate the clinical relevance of the cognitive profiles,

we explored their correspondence with clinical subtypes (inattentive, hyperactive/impulsive and combined type) as determined by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; APA, 1994) and with comorbid psychiatric disorders.

Method

Participants

A total of 265 participants between 18 and 65 years old were included in this study, of which 133 were ADHD patients and 132 were healthy controls. Demographics of the sample are described in Table 1. All participants were part of the Dutch chapter of the International Multicenter persistent ADHD CollaboraTion (IMpACT—<http://impactadhdgenomics.com>; Franke et al., 2010). Participants were recruited at the Department of Psychiatry of the Radboud University Medical Center in Nijmegen and through advertisements. Patients were included if they had previously been diagnosed with adult ADHD by a psychiatrist according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; *DSM-IV-TR*; APA, 2000). Exclusion criteria were psychosis, alcohol or substance addiction in the last 6 months, current major depression, full-scale IQ estimate <70 (assessed using the Wechsler Adult Intelligence Scale–III [WAIS-III], see *Neuropsychological testing battery*), neurological disorders, sensorimotor disabilities, non-Caucasian ethnicity, and medication use other than psychostimulants, atomoxetine, or bupropion. Additional exclusion criteria for healthy participants were a current or lifetime neurological or psychiatric disorder in either the participant or his or her first-degree relatives.

This study was approved by the regional ethics committee (Centrale Commissie Mensgebonden Onderzoek: CMO Regio Arnhem–Nijmegen; Protocol Number III.04.0403). Written informed consent was obtained from all participants

Psychiatric Assessment

Both patients and controls were assessed using the Structured Diagnostic Interview for Adult ADHD (DIVA; <http://www.divacenter.eu>; Kooij, 2010). This interview focuses on the 18 *DSM-IV* symptoms of ADHD and uses concrete and realistic examples to thoroughly investigate whether a symptom is currently present or was present in childhood. In addition, a self-report questionnaire on current symptoms was obtained using the ADHD Rating Scale–IV (Kooij et al., 2005). Further measurements included the Structured Clinical Interview for DSM Disorders (SCID) to identify lifetime Axes I and II disorders, a magnetic resonance imaging (MRI) scanning

Table 1. Characteristics of Participants.

	Healthy controls (<i>n</i> = 132)	ADHD patients (<i>n</i> = 133)	Total sample (<i>N</i> = 265)
Gender	53 (40.2%) male	56 (42%) male	109 (41.1%) male
<i>M</i> age (<i>SD</i>)	36.30 (11.75)	35.56 (10.40)	35.93 (11.08)
<i>M</i> IQ ^a (<i>SD</i>)	109.97 (14.90)	107.84 (14.34)	108.90 (14.63)
<i>M</i> education ^b (<i>SD</i>)	5.16 (0.81)	4.70 (0.80)	4.93 (0.83)
Profile 1	<i>n</i> = 46 (35%)	<i>n</i> = 52 (39%)	<i>n</i> = 100 (46 C; 54 A)
Profile 2	<i>n</i> = 31 (23%)	<i>n</i> = 31 (23%)	<i>n</i> = 49 (28 C; 21 A)
Profile 3	<i>n</i> = 55 (42%)	<i>n</i> = 50 (38%)	<i>n</i> = 116 (58 C; 58 A)
<i>Q</i> -value	.46	.47	.47
Differences between profiles			
Gender	$\chi^2 = 3.85$	$\chi^2 = 1.95$	$\chi^2 = 0.99$
IQ ^a	$F = 2.40$	$F = 0.45$	$F = 1.52$
DIVA			
Inattentive symptoms	$F = 1.68$	$F = 1.05$	$F = 1.48$
Hyperactive symptoms	$F = 0.77$	$F = 2.70$	$F = 0.54$
Self-report			
Inattentive symptoms	$F = 0.65$	$F = 1.59$	$F = 2.49$
Hyperactive symptoms	$F = 0.34$	$F = 4.81^{**}$	$F = 2.00$

Note. C = control participants, A = ADHD patients; DIVA = Diagnostic Interview for Adult ADHD.

^aEstimated IQ based on performance on the WAIS-III block pattern and vocabulary tasks.

^bEducation level was coded from 1 (unfinished primary school) to 7 (post-university).

***p* < .01.

session and blood withdrawal for DNA analysis. These data are described elsewhere (Franke et al., 2008; Franke et al., 2010; Hoogman et al., 2011; Hoogman et al., 2013; Onnink et al., 2014) and are not part of the current analysis.

Neuropsychological Testing Battery

Neuropsychological performance was measured by means of a test battery that included measures tapping into executive functioning (working memory, attention, inhibition, set-shifting, fluency) and delay discounting. Detailed group comparisons between adult ADHD patients and healthy controls on the separate measurements have been reported elsewhere (Mostert et al., in press). Details about tasks and main outcome measures are described in Supplementary Table 1. The tasks were always administered in the same order. In total, we analyzed 21 variables from seven tasks. Outliers were defined as having a score more extreme than four times the standard deviation above or below the mean per group (Leth-Steensen, Elbaz, & Douglas, 2000; Nigg, Stavro, Ettenhofer, Hambrick, Miller, & Henderson, 2005). This threshold guarded against artifacts, while still including participants performing at the extremes of the normal distribution (i.e., including low performing cases that might have more severe ADHD symptoms). If a participant's score was an outlier on one outcome variable of a task, his or her scores on all outcome variables from that task were excluded. All data were transformed in such a way that higher values indicated worse performance. To estimate IQ,

subtests of the WAIS were administered (vocabulary and block design; Wechsler, 1997).

Confirmatory Factor Analysis (CFA) for Data Reduction

CFA was used to reduce the neuropsychological data by modeling latent factors, using the program *Mplus* (Muthen & Muthen, Version 6.11). CFA requires an a priori model specifying which variables load onto which latent factors. The model fit reflects how well the data support the model. We considered a CFA more suitable for our analyses than a model-free approach (e.g., principal components analysis), as we had a rationale based on the literature for the latent factors measured by the variables (see Supplementary Table 1). In our initial model, the latent factors reflected the cognitive domains that the measured variables are theorized to tap into (i.e., the delay discounting task variables should all reflect delay discounting and hence load onto the same factor). We compared this model with several competing models (see supplementary text). Model fit was evaluated by comparing the tested models based on their chi-square statistic, comparative fit index (CFI), Tucker–Lewis index (TLI), and the root mean square error of approximation (RMSEA). As CFA requires complete data, missing data points were first estimated using the full information maximum likelihood approach. For the model with the best fit, factor scores were estimated for each participant. These factor scores were regressed on age and normalized across the entire sample (patients and controls combined).

CD

A graph theoretical measure to optimize clustering, so called *community detection*, was used to identify cognitive profiles based on the neuropsychological data (Newman, 2006; Rubinov & Sporns, 2011). Weighted, undirected networks were created by correlating participants with each other based on their normalized factor scores. This was done in the total sample and in the control and ADHD samples separately, hence resulting in three correlation matrices (networks): a 265×265 network of the total sample, a 133×133 network of patients, and a 132×132 network of control participants. A weight-conserving modularity algorithm (Rubinov & Sporns, 2011) was used to identify distinct communities of participants within each of the three networks. Details about this algorithm can be found elsewhere (Fair et al., 2012; Karalunas et al., 2014; Rubinov & Sporns, 2011). Briefly, the algorithm searches for the most optimal partitioning of the network by iteratively sorting nodes (in this case, participants) into communities until the modularity (Q) reaches a maximum. Modularity is calculated as the number of edges (correlations between participants) falling within communities minus the expected number in a random network with an equivalent degree distribution, and can range between -1 and 1 . Values larger than zero indicate that there are stronger within-community edges than expected in random data (Fair et al., 2012; Newman, 2006). A positive Q -value therefore indicates that the strength of edges within communities is larger than expected at random. In the community structure with the highest Q , that is, the most optimal partitioning, nodes within communities have strong correlations between them and weak correlations with nodes from other communities.

The most optimal modularity, however, does not necessarily mean that there is a strong community structure (Karrer, Levina, & Newman, 2008). Especially with large networks, there is a risk that purely by chance a certain division reaches a high modularity. We therefore performed several analyses to assess the quality and robustness of the community structure. First, we computed the group assignment for each participant across ten runs. Final group assignment for each participant was based on the median of the ten runs. We also computed the average Q -value across these ten runs. Second, we compared our findings with the community structure created from random data, to check whether the community structure was not due to certain random structures in the data. For this, we created a null model in which the original network is randomized while preserving weight, degree, and strength distributions (Rubinov & Sporns, 2011). As a third step, we evaluated the robustness of the community structure by computing the variation of information (VOI; Karrer et al., 2008; Meila, 2007). Here, a proportion (α) of edges in the network is randomly rewired. In other words, when α is zero, no edges are

rewired, and when α is one, all edges are rewired. Although random graphs show large changes in community structure even when only rewiring a small proportion of edges, robust community structures remain the same until a larger proportion of edges is rewired (Karrer et al., 2008). As the rewiring of edges required some edges to be zero, graphs for the VOI computations were thresholded at $-0.5 < r < 0.5$ (i.e., removing weak correlations between participants). The community structure after thresholding remained highly similar to the original community structure.

All CD analyses were performed using Matlab (Mathworks, R2011b) and the functions provided by Olaf Sporns, Mikail Runov, and collaborators (<https://sites.google.com/site/bctnet/>).

Statistical Analyses

Patients and controls were compared on age, estimated IQ, and education level using separate independent-samples t tests; they were compared on gender using a Pearson chi-square test. Within the group of patients and controls, as well as in the total sample, we compared participants between profiles on gender, IQ, and ADHD symptoms (from both the DIVA interview and the self-report questionnaire). In addition, within the ADHD patient group, we tested for differential distributions of comorbid psychiatric disorders (as measured by the SCID I interview) between the profiles using Pearson chi-square tests. We investigated this for the total number of comorbid disorders the patient had experienced, and more specifically for whether major depressive disorder (MDD) and substance use disorder (SUD) had been experienced in the past as these were the most prevalent comorbidities in the sample. Data from the SCID interview were missing for ten patients.

Per profile, we compared factor scores between patients and controls using a MANOVA. Furthermore, we computed the average score of all six factors combined per participant, and compared patients and controls on this total factor score using an independent-samples t test per profile.

Focusing on only the patients with ADHD, we investigated whether clinical subtypes of ADHD were differentially distributed between the profiles. For this, we used the Pearson chi-square test on subtype (both the subtype determined by the DIVA interview and by the self-report questionnaire) and profile.

Results

Adults with ADHD and healthy controls did not differ in terms of age ($T = 0.54$), gender ($\chi^2 = 0.10$), or IQ ($T = 1.19$), but controls were higher educated ($T = 4.66$, $p < .001$). Sixty-one patients were identified by the DIVA interview as having combined type ADHD, 38 as having the inattentive subtype, and eight as having the hyperactive/impulsive

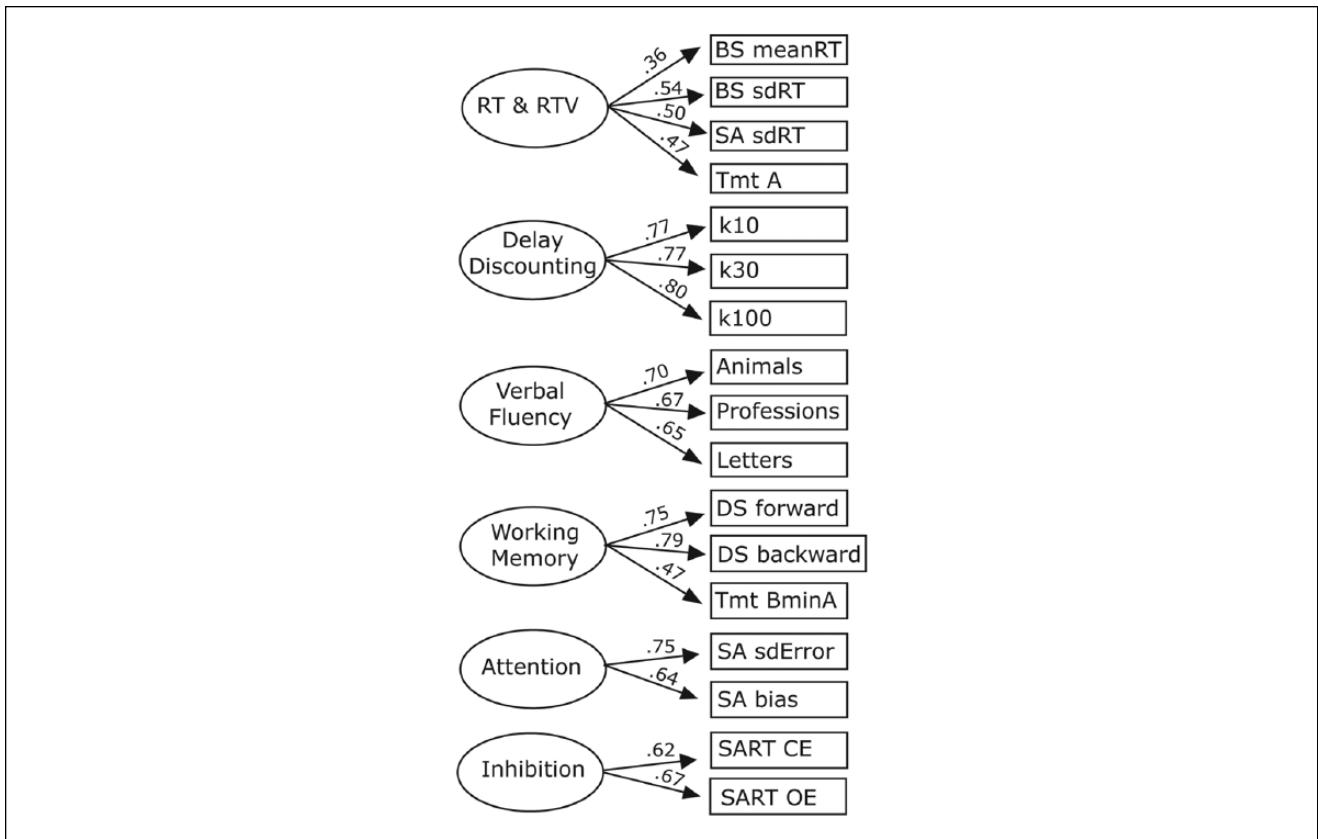


Figure 1. The best-fitting six-factor model that was tested with the CFA for data reduction.

Note. Shown are the standardized loadings of variables onto the factors. Not shown are cross-loadings, error terms, and correlations between factors. Factor names are arbitrary labels based on the theorized underlying measure of the variables loading onto the factor. CFA = confirmatory factor analysis; RT = reaction time; RTV = reaction time variability; BS mean RT = Baseline speed task mean reaction time; BS sd RT = Baseline speed task standard deviation of reaction time; SA sd RT = SA-dots task standard deviation of reaction time; Tmt A = Trailmaking task time to complete Part A; k10 / k30 / k100 = Delay discounting task impulsivity parameter for 10 / 30 / 100 euros; Animals / professions / letters = number of animals / professions / letters listed in fluency task; DS forward = digit span in the forward condition; DS backward = digit span in the backward condition; SA sdError = standard deviation in errors made across the blocks on the SA-dots task; SA bias = response bias on the SA-dots task; SART CE = commission errors made on the SART; SART OE = omission errors made on the SART. Details about the tasks and variables can be found in Supplementary Table 1.

subtype. Five patients had less than four or five instead of six inattention or hyperactivity/impulsivity symptoms, which we classified as “subthreshold ADHD.” Thirty-three participants (11 controls, 21 patients) did not participate in the clinical interviews (but did fill out the self-report questionnaires). Self-report identified 55 patients as combined type, 39 as inattentive, 13 as hyperactive/impulsive subtype, and 26 as subthreshold ADHD (less than six symptoms).

CFA

Out of the 21 analyzed variables, of which the original case-control comparison has been published elsewhere (Mostert et al., in press), 17 were included in the final models investigated in the current study. The variable Trailmaking–Part B was highly correlated with the other Trailmaking variables and was therefore excluded from the CFA models. In

addition, removing the variables Sustained Attention (SA)-dots mean reaction time (RT), Sustained Attention to Response Task (SART) mean RT, and SART SD of RT improved the model fit. The best-fitting six-factor solution produced a superior fit over competing models: $\chi^2(104) = 167.81$, CFI = 0.925, TLI = 0.901, RMSEA = 0.048, 66 free parameters (Figure 1; supplementary text). We labeled the six factors “reaction time and reaction time variability,” “delay discounting,” “verbal fluency,” “working memory,” “attention,” and “inhibition.” As can be seen from Table 2, patients with ADHD performed significantly worse than healthy controls on all six factors.

On the seven tasks that were included in the final six-factor model, there were missing data for 32 controls and 50 ADHD patients. Although covariance coverage for the model including missing data was sufficient (minimal 77%), excluding participants with missing data from the CFA resulted in a slightly improved model fit,

Table 2. Factor Scores per Diagnostic Group and per Cognitive Profile.

	RT and RTV	DD	VF	WM	Attention	Inhibition	All factors
Profile 1							
Controls (<i>n</i> = 46)	-0.76 (0.65)	-0.37 (0.84)	0.77 (0.91)	-0.77 (1.07)	0.14 (0.69)	0.16 (0.85)	-0.39
ADHD (<i>n</i> = 52)	0.29 (1.14)	0.26 (0.87)	-0.26 (0.94)	-0.15 (0.97)	1.14 (0.95)	0.88 (1.09)	0.36
Difference	30.21***	13.07***	7.33**	8.84**	34.99***	12.79***	-5.70***
Profile 2							
Controls (<i>n</i> = 31)	-0.51 (0.81)	0.67 (0.63)	-0.37 (0.74)	-0.29 (0.81)	-0.70 (0.63)	-0.51 (0.78)	-0.28
ADHD (<i>n</i> = 31)	0.39 (1.07)	0.90 (0.94)	-0.15 (0.96)	0.41 (0.80)	-0.02 (0.79)	0.06 (0.83)	0.26
Difference	13.91***	1.33	1.02	11.79**	13.78***	7.69**	-3.56
Profile 3							
Controls (<i>n</i> = 55)	0.12 (0.74)	-0.56 (0.91)	0.41 (0.85)	0.19 (0.79)	-0.60 (0.64)	-0.50 (0.80)	0.55
ADHD (<i>n</i> = 50)	0.35 (0.94)	-0.29 (0.89)	0.85 (0.58)	0.58 (0.85)	-0.21 (0.87)	-0.23 (0.80)	0.61
Difference	1.92	2.41	9.24**	5.72*	7.10**	3.13	-2.92
All profiles							
Controls (<i>n</i> = 132)	-0.34 (0.82)	-0.20 (0.96)	-0.18 (0.99)	-0.25 (0.99)	-0.37 (0.75)	-0.27 (0.87)	
ADHD (<i>n</i> = 133)	0.33 (1.05)	0.20 (1.00)	0.18 (0.97)	0.25 (0.94)	0.36 (1.08)	0.27 (1.05)	
Difference	-5.78***	-3.40**	-3.02**	-4.26***	-6.38***	-4.59***	

Note. For each profile, values in the first two rows indicate mean (*SD*) factor scores per group, and those in the third row show the *F* value for the difference between the groups on that factor (*T* value for the total factor scores comparisons). As factor scores were normalized across the entire sample, positive scores indicate worse than average performance, negative scores indicate better than average performance. RT = reaction time; RTV = reaction time variability; DD = delay discounting; VF = verbal fluency; WM = working memory.

p* < .05. *p* < .01. ****p* < .001.

$\chi^2(104) = 142.575$, CFI = 0.939, TLI = 0.920, RMSEA = 0.045, 66 free parameters. The differences between patients and controls on the factor scores remained when only taking into account the participants with complete data.

CD to Identify Cognitive Profiles

Using the CD algorithm on the complete group, the controls, and the ADHD sample resulted in three cognitive profiles per sample. These profiles were highly similar across the samples (Table 1; Figure 2). Per sample (total, control, and ADHD), participants did not differ between profiles in terms of gender distribution and estimated IQ. Quality checks showed that these profiles were markedly different from profiles generated from random networks (Supplementary Figure 2), and that the networks were robust against chance variations (Supplementary Figure 3). CD on only those participants with complete data gave very similar results, indicating that the profiles were not influenced by estimated data points in the CFA (not shown).

As performing the CD on the total sample did not add additional information beyond analysis of the control and ADHD samples separately, we focus on the latter two in the remainder of this section. Profile 1 was characterized by lower performance on attention and inhibition as compared with the other factors. Patients within this profile performed worse than controls on all six factors (Table 2; Figure 3). Profile 2 stood out through high scores for impulsive behavior captured in the delay discounting factor. Patients and

controls within this profile performed similar on this factor as well as on working memory, while the patients showed worse performance on the other four factors. Profile 3 was marked by aberrant working memory and verbal fluency. Here, patients performed worse than controls on those two factors and on attention, but not on delay discounting, reaction time, and reaction time variability or inhibition.

Association Between Cognitive Profiles and Clinical ADHD Symptoms

Based on self-report, there was a slightly unequal distribution across profiles of patients with predominantly hyperactivity/impulsivity symptoms, predominantly inattention symptoms, and those with high scores in both symptom domains (combined type; Pearson $\chi^2 = 14.29$, *p* < .03; see Supplementary Table 2). The self-reported combined type was most prevalent in our sample (*n* = 55), and about half were in Profile 1 (*n* = 25). Patients with the inattentive subtype (*n* = 39) were predominant in Profiles 1 and 3 (14 out of 52 Profile 1 patients and 16 out of 50 Profile 3 patients). The hyperactive/impulsive subtype was least common in our sample (*n* = 13), and these patients were mainly found in Profiles 1 and 2 (5 out of 52 and 7 out of 31 patients, respectively). Such differential distributions were not found when symptom severity scored using the DIVA interview was investigated (Pearson $\chi^2 = 7.14$, *p* = .31).

Based on the self-report scores, patients differed between profiles in the number of hyperactivity/impulsivity (*F* = 4.81,

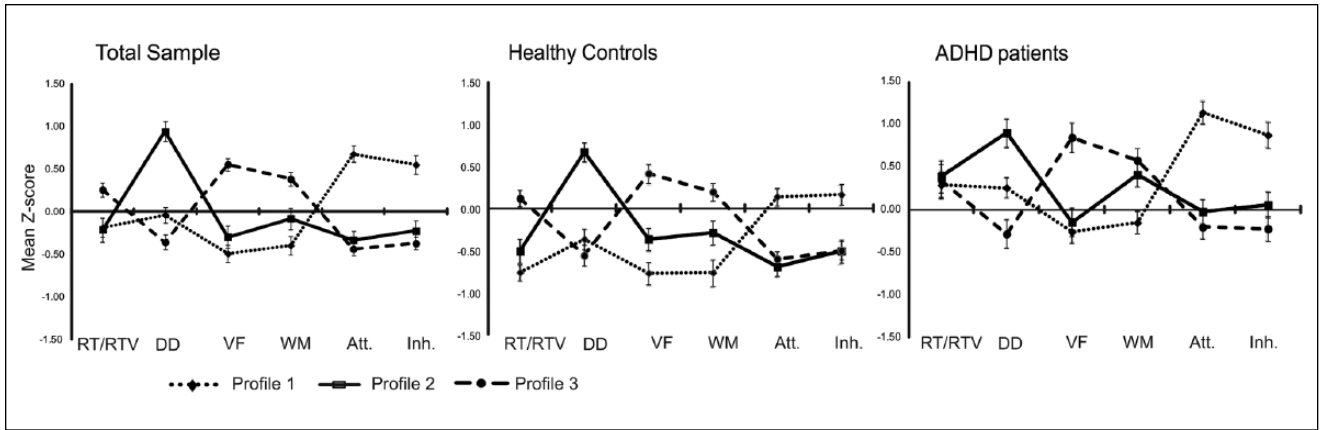


Figure 2. Profiles from community detection.

Note. For each sample (total sample, healthy controls, and ADHD patients), lines represent participants in each profile from the community detection. Lines indicate the mean z score (y-axis) for each factor (x-axis); error bars indicate standard error of the mean. As factor scores were normalized across the entire sample, positive scores indicate worse than average performance, negative scores indicate better than average performance. Diamond-dashed lines represent participants in Profile 1, full lines Profile 2, and stripe-dashed lines Profile 3. RT/RTV = reaction time and reaction time variability, DD = delay discounting, VF = verbal fluency, WM = working memory, Att. = attention, Inh. = inhibition.

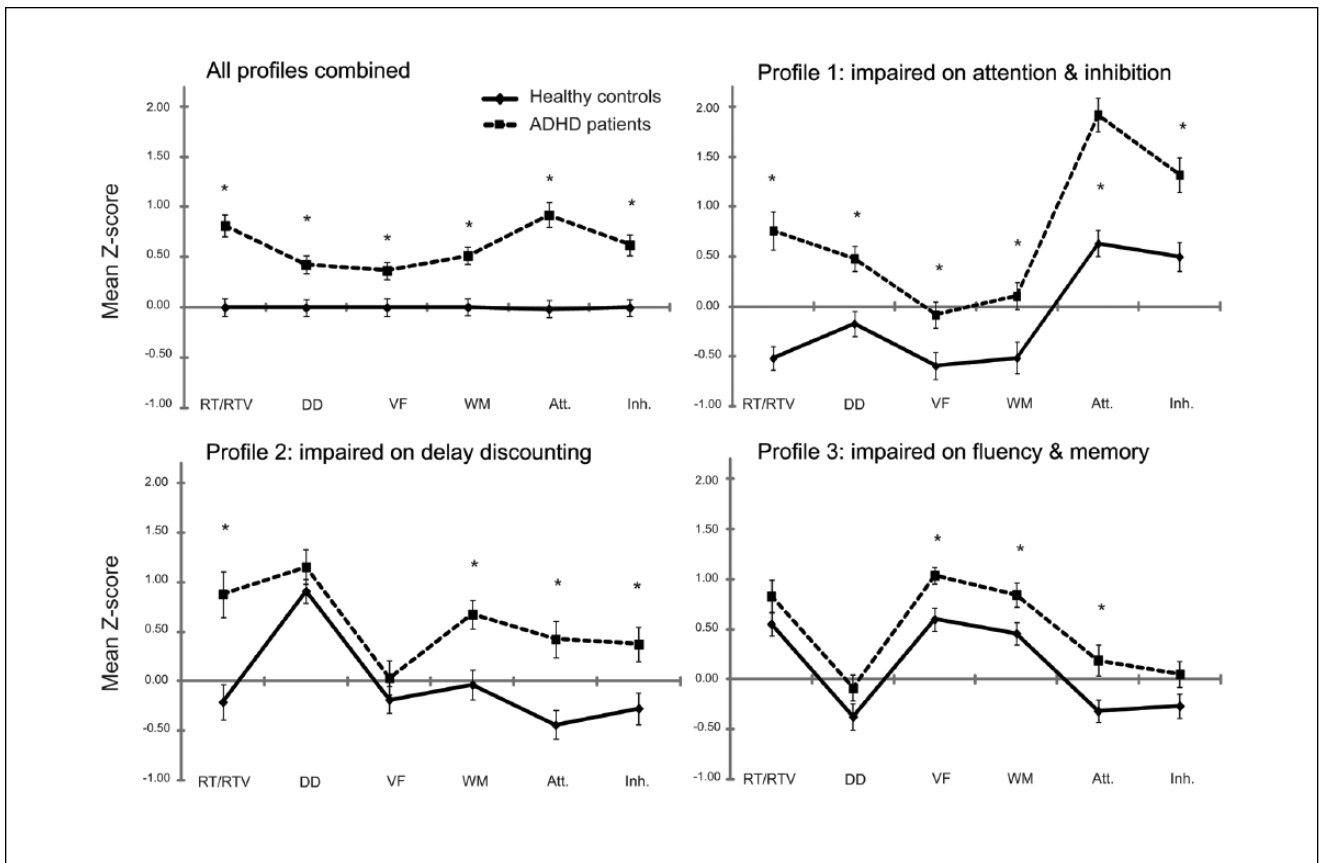


Figure 3. Comparing patients with ADHD and healthy controls within each profile.

Note. Similar to Figure 2, lines represent the mean z scores (y-axes) per factor (x-axes). Full lines indicate healthy control participants, dashed lines patients with ADHD. Mean factor scores per group are shown for the total sample and for each profile separately. For visualization purposes, factor scores were normalized to the control sample mean (instead of to the total sample mean, which was used for the analyses). Positive scores indicate worse than control average performance, negative scores indicate performance below the control sample average. Asterisks (*) indicate a significant difference between patients and controls. RT/RTV = reaction time and reaction time variability, DD = delay discounting, VF = verbal fluency, WM = working memory, Att. = attention, Inh. = inhibition.

$p < .01$), but not inattention ($F = 1.59, p = .21$) symptoms (Table 1). Patients in Profiles 1 and 2 had significantly more hyperactivity/impulsivity symptoms than patients in Profile 3. Again, no differences between profiles were observed when considering ADHD symptoms as measured by the DIVA interview (inattention: $F = 1.05, p = .35$; hyperactivity/impulsivity: $F = 2.70, p = .07$).

Association Between Cognitive Profiles and a History of Comorbid Psychiatric Disorders

Past episodes of MDD and SUD were present in 42% and 20% of patients with ADHD, respectively. Neither disorder did occur more frequently in one of the cognitive profiles compared with the other profiles (MDD: $\chi^2 = 0.44, p = .81$; SUD: $\chi^2 = 1.94, p = .38$). The same was true for the total number of comorbid psychiatric disorders experienced by a patient: There were no differences between the profiles ($\chi^2 = 7.71, p = .66$). On average, patients had one comorbid disorder ($SD = 1, \text{range} = 0-5$).

Discussion

In this article, we have shown that using CD, both adults with ADHD and healthy controls can be separated into different subgroups, or cognitive profiles, based on their neuropsychological performance. Both in the control and ADHD sample, some individuals were characterized by aberrant attention and inhibition (Profile 1), whereas others were impulsive in delay discounting (Profile 2), or performed relatively poorly on working memory and verbal fluency (Profile 3). These profiles thus represent qualitative differences in performance. Within profiles however, quantitative differences were observed, as patients performed worse than controls on most, although not all, neuropsychological factors. Furthermore, there was a weak association between self-reported current ADHD symptoms and the cognitive profiles.

Although the patient group as a whole performed worse on all neuropsychological domains defined by CFA, individual patients were not necessarily impaired on each of these. Rather, they could be separated into different groups based on their performance. Our findings clearly reject the null hypothesis that adult ADHD can be characterized by a single cognitive profile that is typical for the entire patient group. This confirms recent findings reported in the childhood ADHD literature and extends the theory that there is no single, core causal deficit underlying ADHD (Coghill, Seth, et al., 2014; de Zeeuw et al., 2012; Nigg, Willcutt, et al., 2005) in adults. The current results also add to our previous findings of cognitive heterogeneity in the same sample by showing that this heterogeneity is not random, but can be parsed into three qualitatively different cognitive profiles. We show a dissociation between patients with high

delay aversion (Profile 2) and those with poor inhibitory control (Profile 1). This finding is in line with the dual pathway model proposed by Sonuga-Barke that argues for two distinct pathways to ADHD: one of a motivational style with delay aversion as one of its characteristics, and one of disordered regulation of thought and actions, characterized by inhibitory dysfunction (Sonuga-Barke, 2002). Hence, the dual pathway model proposes a distinction between executive dysfunction and delay aversion; those arise from distinct biological pathways, but result in the same ADHD symptoms (Sonuga-Barke, 2005). The unifying theory of ADHD, however, that puts inhibitory deficits as the core deficit, would predict that all patients with ADHD were impaired on the factor inhibition, which would underlie secondary deficits in executive functions and delay aversion (Barkley, 1997). This was clearly not the case. Our data also show an additional distinction of executive functions, with inhibition and attention on the one hand (Profile 1) and verbal fluency and working memory, on the other hand (Profile 3). This suggests that also within the domain of executive functioning, impairments are not homogeneous and affect distinct cognitive functions in subsets of patients.

Heterogeneity in performance was apparent not only in patients with ADHD, but also in healthy controls. In line with previous studies, similar cognitive profiles were found in the ADHD and control groups (Fair et al., 2012; van Hulst et al., 2015). As can be seen from Table 1, even the distribution of patients across the different profiles was strikingly similar to that of control participants. This was further supported by our findings for the analysis of the total sample, where the same cognitive profiles emerged (Figure 2). Alternatively, one might have expected this sample to split into two profiles that separated patients from controls. We interpret these findings as an indication that ADHD is not characterized by a single deficient cognitive profile, but rather as performance at the extreme of normal variation.

One premise of the dual pathway theory is that deficiencies in distinct domains result in the same ADHD symptoms and diagnosis (Sonuga-Barke, 2003). Based on the DIVA interview, we found no differences in subtype or ADHD symptom distribution across the profiles. Although the DIVA interview has a lifelong, pervasive perspective, a self-report questionnaire likely reflects the more actual symptom perception by the patient. Using this measurement, we observed that patients in Profiles 1 and 2 had slightly more hyperactivity/impulsivity symptoms as compared with those in Profile 3. There was also a small but significant difference in the distribution of *DSM-IV* ADHD subtypes across the profiles, although there was no profile in which a particular subtype was strongly overrepresented (see Supplementary Table 2). We therefore conclude that there does not seem to be a strong relationship between pervasive ADHD symptoms and cognitive subtypes, supporting the

model that ADHD symptoms can arise from dysfunction in distinct behavioral domains with distinct neurobiological underpinnings (Sonuga-Barke, 2005).

The relationship between clinical symptoms and cognitive functioning is a complex one (Coghill, Hayward, Rhodes, Grimmer, & Matthews, 2014). In a longitudinal study on boys with ADHD, changes in symptoms over time were not associated with changes in cognitive performance (Coghill, Hayward, et al., 2014). Similarly, clinical response to chronic methylphenidate treatment was not associated with improvements in cognitive performance on the majority of tasks with a strong executive component (Coghill, Rhodes, & Matthews, 2007). Clinical symptoms are also weakly associated with functional impairments—which are the consequences that an individual experiences as a result of behavioral symptoms—such as low grades (= functional impairment) due to distractibility at school (= symptom; Barkley et al., 2006; Gordon et al., 2006). The cognitive profiles we observed may be more closely related to functional impairments than to symptoms. It has, for example, been shown that deficits in executive functioning are strongly associated with poor academic outcome in children with ADHD and with occupational functioning in adults with ADHD (Barkley & Murphy, 2010). However, for the latter it should be noted that self-ratings of executive functioning impairments were more predictive than scores on tests measuring executive functioning. From a clinical perspective, it would be of interest to investigate whether patients from different cognitive profiles show different functional impairments. Unfortunately, such data were unavailable in the present study.

Across the cognitive profiles, patients did not differ in the number of comorbid disorders they had been diagnosed with. Similarly, past episodes of MDD or SUD were also not more frequent in a particular profile. This finding is in accordance with previous studies reporting that deficits in cognitive performance cannot be accounted for by comorbid disorders (Nigg, Stavro, et al., 2005; Silva et al., 2013). Our work extends earlier findings on neuropsychological subgroups in children with ADHD and typically developing controls (Fair et al., 2012). It should be noted, however, that we did not find identical cognitive profiles as were reported in children. Although Fair and coworkers found four and six cognitive profiles in typically developing and ADHD children respectively, we identified three profiles in each sample. In addition, characteristics of the cognitive profiles were different between the two studies. Importantly, we did not study the exact same cognitive domains. For example, in contrast to Fair and coworkers we measured delay discounting and verbal fluency, but we did not include measures of temporal information processing and arousal. It is therefore difficult to compare the cognitive profiles between the studies. Despite this, some interesting aspects do stand out. First, we did not observe a distinct profile for reaction

time variability in adults. Instead, patients in all three profiles were impaired on this measure, consistent with our earlier findings showing that reaction time variability is consistently increased in adults with ADHD, and has the largest effect size for distinguishing patients from controls (Mostert et al., in press). This also ties in with a recent meta-analysis showing moderate-to-large effect sizes for reaction time variability in children, adolescents, and adults with ADHD (Kofler et al., 2013). Second, whereas children who performed poorly on working memory also showed low inhibition and response speed, in adults, poor working memory and poor inhibition were part of distinct profiles (Profiles 3 and 1, respectively). This is in line with a previous study showing that working memory and inhibition become more distinct during development (Tsujiyama, Kuwajima, & Sawaguchi, 2007). Longitudinal analyses are needed to confirm whether the differences in cognitive profiles between children and adults with ADHD are due to developmental neuropsychological differences.

From a clinical perspective, the identification of cognitive subtypes creates possibilities for more individual-based treatments (Sonuga-Barke, 2005). For this, it is essential to know more about the neurobiological mechanisms that are associated with the observed behavior. It would therefore be of interest to investigate whether patients from distinct cognitive profiles show different neural activity patterns during a task or resting state. This would provide evidence for impairments in distinct neurobiological pathways leading to ADHD. In addition, it would be of interest to investigate whether these profiles predict response to treatment or associations with certain genes. Taken together, such studies are in line with the recently proposed Research Domain Criteria (RDoC) strategy from the National Institute of Mental Health (NIMH) to investigate mental disorders not as homogeneous categories, but as constructs overarching multiple domains (Insel et al., 2010).

The current findings should be seen in the context of several strengths and limitations. Using data from a large sample of adults with persistent ADHD and healthy controls tested on a wide range of cognitive tasks, we were able to follow a similar rationale as was previously described by Fair and colleagues in their study of children with and without ADHD (Fair et al., 2012). Our findings hence extend the notion of distinct cognitive subgroups to adult ADHD. As mentioned, a limitation of the current study is that the neuropsychological measurements did not completely match the measurements of the Fair study. We therefore do not interpret our findings as being the only possible distinction of adults with ADHD into cognitive profiles. Second, we have focused on a single method of clustering using graph theory. Other studies have used latent class analysis (LCA) to answer similar questions (e.g., van Hulst et al., 2015), which provides a similar type of output (class membership). However, whereas the CD

algorithm looks for clusters of highly correlated individuals, LCA uses structural equation modeling (McCutcheon, 1987). Different clustering methods may therefore give different solutions. Third, as not all participants completed all tasks, missing data points were estimated to prevent exclusion of participants. As missing scores were estimated based on the available data of that participant, within-subject differences in performance across tasks will be reduced. However, we confirmed that when excluding participants with missing data points, the same three profiles were identified. Therefore, this limitation did not bias our findings, although it may have reduced power.

To conclude, in this study, we have shown that there is no single, core cognitive impairment in adult ADHD. Instead, patients can be parsed into three qualitatively distinct cognitive profiles. Such cognitive heterogeneity is also present in the non-ADHD population, supporting the notion that ADHD is the extreme of traits that are normally distributed in the population. Distinguishing patients into well-characterized subgroups based on cognitive performance may advance our understanding of the biological causes underlying the disorder and ultimately improve treatment efficacy.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Jan K. Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Janssen Cilag BV, Eli Lilly, Shire, Novartis, Roche, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, and royalties. All other authors report no conflict of interest.

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Supplemental Material

The supplementary materials are available at <http://jad.sagepub.com/supplemental>

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