Characterizing different cognitive and neurobiological profiles in a community sample of children using a non-parametric approach: An fMRI study

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ARTICLE INFO

Keywords:
- Inhibitory control
- Default Mode Network
- Latent Profiles
- Nonparametric approach
- Reading abilities

ABSTRACT

Executive Functions (EF) is an umbrella term for a set of mental processes geared towards goal-directed behavior supporting academic skills such as reading abilities. One of the brain’s functional networks implicated in EF is the Default Mode Network (DMN). The current study uses measures of inhibitory control, a main sub-function of EF, to create cognitive and neurobiological “inhibitory control profiles” and relate them to reading abilities in a large sample (N = 5055) of adolescents aged 9–10 from the Adolescent Brain Cognitive Development (ABCD) study. Using a Latent Profile Analysis (LPA) approach, data related to inhibitory control was divided into four inhibition classes. For each class, functional connectivity within the DMN was calculated from resting-state data, using a non-parametric algorithm for detecting group similarities. These inhibitory control profiles were then related to reading abilities. The four inhibitory control groups showed significantly different reading abilities, with neurobiologically different DMN segregation profiles for each class versus controls. The current study demonstrates that a community sample of children is not entirely homogeneous and is composed of different subgroups that can be differentiated both behaviorally/cognitively and neurobiologically, by focusing on inhibitory control and the DMN. Educational implications relating these results to reading abilities are noted.

1. Introduction

1.1. Cognitive development and inhibitory control across development

Executive Functions (EF) comprise a set of mental processes geared toward goal-directed behavior and self-control, problem-solving, and planning (Diamond, 2013). EF includes three main sub-functions: working memory, shifting, and inhibition (Diamond, 2013), with reports of inhibition abilities as related to academic abilities such as reading (Blair and Razza, 2007; Borella et al., 2010; Doyle et al., 2018; Meixner et al., 2019), math (Clark et al., 2010; Cragg and Gilmore, 2014; Espy et al., 2004), and emotional regulation (Bartholomew et al., 2021). According to Diamond, inhibition is one of the central EF, as it is also divided into cognitive inhibition (the ability to filter out unnecessary stimuli to stay tuned on the task and focus attention) and behavioral inhibition (the ability to control emotions and impulsivity) (Diamond, 2013; Fox et al., 2005).

The age window of 9–10 years is an interesting one, both from the EF and academic abilities (i.e. the reading) developmental perspectives. At this developmental age window, children achieve similar levels of EF to adults in several EF, which can be clustered under response speed (speed of processing), set maintenance, and planning (Welsh et al., 1991). However, a fine-grained developmental study pointed at the developmental trajectory of subcomponents of EF within a slightly extended age window (3–12 years old children), showing how inhibitory control develops first, followed by selective attention, and then more complex EFs...
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planning, fluency) develop into adolescence (Klenberg et al., 2001). As for reading achievement, according to Chall’s developmental model for milestones in reading development (Chall, 1983), by the age of 9 years, children are transitioning from “learning to read” to “reading to learn.” This phase requires automatic reading skills so attention and cognitive resources can be “released” for reading comprehension (see also (LaBerge and Samuels, 1974)).

1.2. Inhibitory control and reading skills

Notably, although inhibitory control is one of the first EF to develop, reading and comprehension rely heavily on this cognitive ability. It was suggested that inhibition is an important cognitive skill contributing to individual differences in cognitive, emotional, academic abilities and creativity (Harnishfeger and Bjorklund, 1994). Regarding academic outcomes, inhibition abilities play a role in several components underly reading; per the Simple View of the Reading model, language processing and word decoding development lead to reading comprehension (Gough and Tunmer, 1986). Inhibitory control was found to be related to different reading components (word decoding (Spencer and Cutting, 2021; Taboada Barberet et al., 2021); reading comprehension (Abo-Elhija et al., 2022; Butterfuss and Kendoue, 2018; Connors, 2009; Haft et al., 2019)), and although fluent reading is not officially part of the SVR model (Adlof et al., 2006; Kim, 2020), this foundational reading skill was also associated with inhibition (Johann et al., 2020).

Due to its central role in EF and especially inhibition in academic outcomes (Harnishfeger and Bjorklund, 1994), the current study’s goal was to distinguish groups of children based on inhibitory control and their reading measures using computational tools (i.e. Latent Profile Analysis; LPA (Pastor et al., 2007; G. A. Williams and Kibowski, 2016; Wurpts and Geiser, 2014).

1.3. The neurobiological profiles associated with inhibition skills

The neuroimaging literature converges on several functional networks associated with EF, e.g. the Frontotoparietal (Dosenbach et al., 2008; Ptak, 2012), Cingulo-opercular (Dosenbach et al., 2008; Neta et al., 2014), Dorsal Attention, Ventral attention (Vossel et al., 2014) and Salience networks (Seeley et al., 2007). Several papers focusing on typically and atypically developing individuals (e.g., those with attention deficit hyperactivity disorder or schizophrina), suggest intriguingly that the Default Mode Network (DMN), is implicated in EF as it may also be important for inhibitory function (Fryer et al., 2018; Hernández-Alvarez et al., 2020; Liddle et al., 2011). The DMN is mainly activated during rest in internally-directed cognitive processes such as feeling processing, future planning, and retrieving memories (Buckner, 2012). The DMN is also involved in performing different experimental tasks, including social processing (e.g. such as emotional perception, empathy, theory of mind, and morality) (Li et al., 2014), language (Horowitz-Kraus et al., 2017), semantic processing (Binder et al., 2005; Lanzoni et al., 2020; Seghier and Price, 2012; Wirth et al., 2011) and other EF processes such as attention (Leech et al., 2011; Rohr et al., 2018), planning (Spreng et al., 2010) and error monitoring (C. S. Li et al., 2007). A handful of papers have outlined an altered involvement of the DMN during rest in different clinical conditions such as Alzheimer’s disease (Buckner, 2012), Schizophrenia (Doucet et al., 2020; Fan et al., 2018), mood and anxiety disorders (Doucet et al., 2020) and Attention Deficit Hyperactivity Disorder (ADHD) (Sidlauskaite et al., 2016; Sripada et al., 2014b). Although there is a considerable amount of research on children with ADHD (Castellanos and Proal, 2012; Duffy et al., 2021; Harikumar et al., 2021; Kozial et al., 2013), fewer studies have focused on patterns of the DMN related to inhibitory control and academic abilities such as reading, in a community sample of children, which is the topic of the current study.

Moreover, developmental changes in the functional connections within the DMN were reported in different stages along the life span. In adulthood (63–73 years) decreased intra-network connectivity within the DMN was observed as well as decreased segregation with additional EF networks associated with declined cognitive abilities (Ng et al., 2016). This decreased intra-network FC with age was also related to the speed of processing and episodic memory (Staffaroni et al., 2018), also supported by others in younger adults (Esposito et al., 2018).

Interestingly, prior studies have suggested that different parts of the DMN are potentially related unequally to a variety of developmental/maturational changes (Fair et al., 2008; Fan et al., 2021; Supukar et al., 2010), semantic processing differences (Seghier and Price, 2012), attention challenges (Fan et al., 2018; Rohr et al., 2018), cognitive disorders (Sripada et al., 2014b; Swanson et al., 2011) and the functionality of the motor system (Hanakawa et al., 2003; Malouni et al., 2003; Margulies et al., 2009; Uddin et al., 2009; Zhang et al., 2014; Zhang and Li, 2012). In relation to the activation/FC patterns of the DMN, an overall increased deactivation of this network was found in children ages 5–18 years old, while listening to stories, with more extensive deactivation in older children, associated with better task comprehension scores (Horowitz-Kraus et al., 2017). More specifically and concerning the range of the current study’s population, relations between the level of DMN and attention network (dorsal attention network) and emotional and EF abilities in 9–10 years old children were found (Owens et al., 2020).

An attempt to profile children based on their inhibition abilities has not been conducted before but has been conducted using EF profiles using LPA. Dajani et al. (2016) used LPA for creating “EF profiles” using different cognitive tests to evaluate sub-levels of EF, such as working memory, inhibitory control, and cognitive flexibility, as indicators (Dajani et al., 2016). Dajani and colleagues divided a mixed group of 8–13-year-old children identified as typically developing children, children with ADHD, or with Autism Spectrum Disorder (ASD), into three sub-groups distinguished by their general EF levels (low, average, and high). The result included three EF profiles, while each profile included a mix of children from different sub-groups (Dajani et al., 2016). In a follow-up study conducted by these researchers, no differences in FC between these EF sub-groups were observed (Dajani et al., 2019). The lack of findings in that study could be due to the use of parent reports only (BRIEF questionnaire) for creating the sub-profiles or the use of several EF components instead of one sub-component. This may cause more heterogeneous masks and mark the common patterns. Additionally, the number of participants may not have been large enough (N = 129, three groups of n = 43) to identify common functional patterns related to general EF ability strength.

Due to the involvement of inhibition in several emotional and cognitive deficits in childhood (Diamond, 2013; Fox et al., 2005), its central role in academic achievements (Blair and Razza, 2007; Borrella et al., 2010; Clark et al., 2010; Doyle et al., 2018; Eapy et al., 2004) and especially in reading (Doyl et al., 2018) and reading comprehension (Borella et al., 2010), it is essential to detect individual differences in inhibition abilities even among typically developing individuals.

Hence, the goal of the current study is to determine the neurobiological correlates to different inhibitory control profiles in association with reading abilities by focusing on the DMN and using a non-parametric approach in a community sample of children ages 9–10 years (from the Adolescent Brain Cognitive Development (ABCD) dataset). During this age range, proficient reading abilities should be achieved (Chall, 1983), and inhibition control is in its maturation period (Klenberg et al., 2001), so different profiles between children will not be attributed to psychiatric/developmental or neurological disorders. We hypothesized that different inhibition profiles would be revealed based on a variety of inhibition measures. We assumed divergent FC segregation patterns within the DMN would be found on each profile related to what was previously reported (Fair et al., 2008; Fan et al., 2021; Fan et al., 2018; Hanakawa et al., 2003; Rohr et al., 2018; Sripada et al., 2014a; Swanson et al., 2011; Uddin et al., 2009; Zhang et al., 2014). We also hypothesized that profiles demonstrating lower inhibitory control...
scores would also demonstrate lower reading abilities.

2. Methods

2.1. Participants

5055 children at ages 9–10 years (Mean (in months) = 119.83, SD = 7.45; 2626 females) were selected from a cohort of 11,880 in the curated annual release 2.0.1 of The Adolescent Brain Cognitive Development (ABCD) study (https://abcdstudy.org/). The 11,880 participants recruited across 22 sites in the U.S (2018–2019) reflect the U.S population of boys and girls with diverse races and ethnicities, education, income levels, and living environments. Inclusion criteria for the ABCD study were 9–10 years old children that are fluent in English, approved for MRI scanning, without a major neurological disorder, were born after 28 weeks, without a history of brain injuries and a diagnosis of schizophrenia, moderate and above ASD, mental retardation or alcohol/ substance use disorder (Karcher et al., 2019).

From the entire sample of 11,880 participants, the participants included in the current study met the following criteria: 1) at least 10 min usable resting-state scan; 2) no clinical diagnosis; 3) the stop-signal task measures (Logan, 1994); 4) t-score for CBCL ADHD DSMS Scale (Achenbach and Ruffle, 2000); and 5) the BIS-BAS questionnaire raw scores (Carver and White, 1994). The demographics and behavioral test statistics can be found in Tables 1 and 2, respectively. The project and hypothesis were not pre-registered.

2.2. Behavioral data

2.2.1. LPA Indicators

Several tasks were used for profiling the participants in the current study: Stop Signal Task (SST) (Logan, 1994), DSM-5 ADHD from the Child Behavior Checklist (CBCL) (Achenbach, 2009), and BIS-BAS questionnaire (Carver and White, 1994). The Flanker test (Eriksen and Eriksen, 1974) was also initially selected but removed due to a lack of contribution to profiling separation with the LPA algorithm due to relative homogenous scores across participants. Each test was related to a different aspect of inhibitory control ability, as can be shown in Table 2. Several variables were derived from each test, resulting in total eight indicators for the LPA algorithm.

2.2.1.1. Stop signal task. This task was held as part of fMRI task-based scans (Casey et al., 2018). In this task, the participants were required to press the right or the left button according to the arrow on the screen. If a “Stop” stimulus was presented, they needed to withhold their reaction and not press the button (Casey et al., 2018). They were instructed to react as quickly and accurately as possible. Incorrect go trial is defined as a late response, pressing an incorrect button (i.e., left instead of right), or no response. An incorrect stop trial is defined as responding to a stop screen by pressing the left or right button.

The following task-generated variables were included in this research: the proportion of incorrect go trials, the proportion of incorrect stop trials, and the mean response time for all incorrect “Stop” trials. The incorrect trial scores were selected so they would match in directionality with the other measures in this study.

2.2.1.2. Child’s ADHD symptom scale. The parents were asked to report the child’s behavior using the CBCL form (Achenbach, 2009). The DSM-5 ADHD t-scores were chosen from the CBCL, which are normalized to age and gender.

2.2.1.3. Behavioral inhibition and behavioral activation. The children filled out the BIS-BAS questionnaire (Carver and White, 1994), and a total of 4 raw scores variables were derived from this questionnaire: three aspects of the BAS system (drive, fun-seeking, and reward responsiveness) and one for the BIS system.

Additional information regarding these inhibition tasks is listed in Supplementary material 1.

2.2.2. Reading analysis

To determine differences in reading abilities between the subprofiles, a single-word reading recognition measure, the Oral Reading Recognition Task (Gershon et al., 2013; Luciana et al., 2018), from the NIH toolbox (NIH Toolbox (healthmeasures.net)) was used. In this task, participants were required to recognize words or letters presented on the screen. Each response was scored as correct or incorrect by the
examiner. A total score normalized by age (Casaletto et al., 2015) was derived from this test.

2.3. Neuroimaging data

Resting-state fMRI derivatives from the ABCD-BIDS dataset (https://collection3165.readthedocs.io/en/stable/derivatives/) were used to determine the DMN in the current study. In the resting state task, the participants were required to relax and stare at a fixation cross for a total time of 20 min (in sets of 5 min each). Before scanning, they trained for motion compliance in a mock scanner. During the scan, a real-time motion correction for structural scanning was applied. During the resting-state scan, another real-time motion monitoring was applied, called FIRMM (fMRI Integrated Real-Time Motion Monitor (Dosenbach et al., 2017) allows a live adjustment of the scanning paradigm (Casey et al., 2018).

2.4. Data acquisition and scan parameters

The ABCD neuroimaging data were acquired from three types of 3 T scanners: Siemens Prisma, General Electric (GE) 750, and Philips (Achieva and Ingenia) with multiband echo-planar imaging (EPI) acquisitions and adult-size coils acquired in 22 sites across the U.S (for the sites see https://abcdstudy.org/contact/). The scanning parameters for the fMRI images and structural images are summarized in Table S1 in the Supplemental materials. Due to an error in processing Philips scans in ABCD 2.0.1 collection (ABCD, 2019), these scans were omitted from this study.

2.5. Data analyses

2.5.1. The latent profile analysis (LPA)

The latent profile analysis (LPA) was run using the tidyLPA library in R version 4.0.2 software (Rosenberg et al., 2018) and rstatix library (Kassambara, 2020), using eight indicators representing inhibitory control in different aspects (Table 2). Different models with a different number of classes to identify the most suitable (1–6 latent classes) were tested. Each model was with equal variance and zero covariance. The model was selected based on the following criteria (Dajani et al., 2016; Nylund and Muthén, 2007; Tein et al., 2013): Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC), sample-adjusted BIC (SABIC), Entropy and Likelihood Ratio Test (BLRT). In all the information criteria (BIC, AIC, and SABIC), lower values indicate better model fit. In the Entropy index, higher values indicate better class
separation. The BLRT, a parametric bootstrap method, provides a p-value that can be used to compare the increase in model fit between the k-1 and k-class model and the ratio from the sample in the smallest class. To help the model selection decision, a graph of the BIC, AIC, and SABIC values was added (see Fig. 3). The gradient in the graph represented when the difference between the models was very small. After choosing the number of classes, the non-parametric Kruskal-Wallis test was run for each of the indicators to characterize the difference between the classes.

2.5.2. Covariate analysis

Socio-Economics Status (SES), and motion (average Framewise Displacement (FD)) variables were included in the LPA model and analyzed using the Mplus program version 8 (Muthén and Muthén, 1998–2017). Differences in age and grade between the classes were tested with appropriate statistical analysis and, due to insignificant findings, were excluded from the covariate analysis. Table 3 represents the descriptive statistics of demographic variables, together with motion, between the classes.

Fig. 2. An example of the effect size calculation. Fig. 2: (a) An example for effect size calculation for only one division. One effect size table was created with only positive correlations in both class1 and class2. ROI = Region Of Interest; Zxy = correlation value after fisher Z transformation between ROIx and ROIy. (b) An example of effect size calculation is the output for all divisions together. The effect size tables from (a) were calculated for each division and then merged. The output is a table of ten effect size values for each comparison. esx = effect size of x division.
2.5.3. Association of the different profiles with reading decoding scores

After creating the profiles, the Kruskal-Wallis test was conducted to explore the reading decoding scores (Gershon et al., 2013; Luciana et al., 2018) effect between the classes. The post-hoc Dunn test and a Bonferroni correction were conducted ($p < 0.05/6 = p < 0.008$).

2.5.4. Neuroimaging data processing

The derivative neuroimaging data went through preprocessing steps previously detailed in Hagler Jr et al. (2019). Average time courses of 333 Regions of Interest (ROI) were created according to Gordon atlas (Gordon et al., 2016). Following the parcellation of the data, the current study employed the 333 cortical ROIs from Gordon’s atlas and then focused the analysis only on DMN per our study aims. To deal with excessive motion, Framewise Displacement (FD) was calculated (Power et al., 2014), then frames with FD of more than 0.2 were excluded. We used the Gordon atlas parcellation time series of the best 10 min scan frames, i.e. frames with the lower FD (see documentation: Collection 3165 - ABCD-BIDS Community Collection (ABCC)).

2.6. Accounting for subject-specific noise factors in functional connectivity analysis

The current study used a non-parametric approach which has fewer prior assumptions about a given population compared to parametric methods (Corder and Foreman, 2009, p. 1–2). This non-parametric approach assumes no prior knowledge of the distribution of the data and can be used to determine common patterns in functional MRI data (Zhitnikov et al., 2018). Specifically, assuming that the covariance matrix of the j-the subject is given by

$$
\Sigma_j = \Sigma_c + \Sigma_{\epsilon_j}
$$

(1)

where $\Sigma_c$ is a component common to all subjects and $\Sigma_{\epsilon_j}$ is a subject-specific component, the method provides an estimate for $\Sigma_c$.

Five correlation matrices were created for all 5055 subjects (one representing all subjects and one for each class derived from the LPA analysis, see Results), using the Zhiltsov et al. algorithm (Zhiltsov et al., 2018). Second, to reinforce reproducibility as recently encouraged (Botvinik-Nezer et al., 2020; Klapwijk et al., 2021; Marek et al., 2020), the full cohort was randomly divided into two groups. Then, the two groups were matched by the following descriptive criteria: class distribution (following the LPA analysis), age, gender, race, handedness, parent’s education, and household income) similar to the ABCD reproducible matched samples (ARMS) (Feczko et al., 2020)). This process was performed five times and at the end, ten divisions were created (Fig. 1). In each division, the Zhiltsov algorithm was run on the time-courses data. For each subject, a covariance matrix of the 333 ROIs was calculated using the Ledoit-Wolf estimator (Ledoit and Wolf, 1996).

### Table 3

Descriptive statistics of demographic and motion variables among classes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Class1 – Behavioral Inhibition n = 1716</th>
<th>Class2 – Controls n = 2661</th>
<th>Class3 – Cognitive Inhibition n = 332</th>
<th>Class4 – Inattention\Hyperactivity n = 346</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>119.78 (7.46)</td>
<td>119.89 (7.47)</td>
<td>119.94 (7.30)</td>
<td>119.49 (7.42)</td>
</tr>
<tr>
<td>Motion (average FD)</td>
<td>0.159 (0.105)</td>
<td>0.148 (0.093)</td>
<td>0.171 (0.099)</td>
<td>0.161 (0.098)</td>
</tr>
<tr>
<td>Sex</td>
<td>Female 861 (50.17%)</td>
<td>1476 (55.46%)</td>
<td>127 (38.25%)</td>
<td>162 (46.82%)</td>
</tr>
<tr>
<td>Grade, age in months (mean, SD)</td>
<td>2nd grade (110.92, 2.57)</td>
<td>11 (0.64%)</td>
<td>1 (0.3%)</td>
<td>4 (1.16%)</td>
</tr>
<tr>
<td></td>
<td>3rd grade (110.81, 3.58)</td>
<td>377 (14.17%)</td>
<td>60 (18.07%)</td>
<td>51 (14.74%)</td>
</tr>
<tr>
<td></td>
<td>4th grade (116.75, 5.39)</td>
<td>1164 (43.74%)</td>
<td>134 (40.36%)</td>
<td>156 (45.09%)</td>
</tr>
<tr>
<td></td>
<td>5th grade (126.11, 3.97)</td>
<td>1003 (37.69%)</td>
<td>124 (37.35%)</td>
<td>122 (35.26%)</td>
</tr>
<tr>
<td></td>
<td>6th grade (129.56, 1.92)</td>
<td>105 (3.95%)</td>
<td>13 (3.92%)</td>
<td>13 (3.76%)</td>
</tr>
<tr>
<td></td>
<td>7th grade (129.00, 0)</td>
<td>1 (0.04%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Handedness</td>
<td>Right 1393 (81.18%)</td>
<td>2163 (81.29%)</td>
<td>270 (81.33%)</td>
<td>273 (78.90%)</td>
</tr>
<tr>
<td></td>
<td>Mixed 215 (12.53%)</td>
<td>300 (11.27%)</td>
<td>44 (13.25%)</td>
<td>44 (12.72%)</td>
</tr>
<tr>
<td></td>
<td>Left 108 (6.29%)</td>
<td>198 (7.44%)</td>
<td>18 (5.42%)</td>
<td>29 (8.38%)</td>
</tr>
<tr>
<td>Ethnicity/Race</td>
<td>White/Non-Hispanic 905 (52.80%)</td>
<td>1687 (63.44%)</td>
<td>206 (62.24%)</td>
<td>174 (50.58%)</td>
</tr>
<tr>
<td></td>
<td>Hispanic 371 (21.65%)</td>
<td>426 (16.02%)</td>
<td>24 (16.31%)</td>
<td>45 (18.60%)</td>
</tr>
<tr>
<td></td>
<td>Black 241 (14.06%)</td>
<td>225 (8.46%)</td>
<td>36 (10.88%)</td>
<td>57 (16.57%)</td>
</tr>
<tr>
<td></td>
<td>Asian 36 (2.10%)</td>
<td>48 (1.81%)</td>
<td>1 (0.3%)</td>
<td>4 (1.16%)</td>
</tr>
<tr>
<td></td>
<td>Other 161 (9.39%)</td>
<td>273 (10.27%)</td>
<td>34 (10.27%)</td>
<td>45 (13.08%)</td>
</tr>
<tr>
<td>Family Income (in U.S. dollars)</td>
<td>&gt; 100 K 618 (39.64%)</td>
<td>1298 (51.88%)</td>
<td>140 (45.45%)</td>
<td>93 (29.25%)</td>
</tr>
<tr>
<td></td>
<td>50k &lt; 100 K 489 (31.37%)</td>
<td>724 (28.94%)</td>
<td>100 (31.45%)</td>
<td>100 (31.45%)</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 K 452 (28.99%)</td>
<td>480 (19.18%)</td>
<td>68 (22.08%)</td>
<td>125 (39.31%)</td>
</tr>
<tr>
<td>Parental Education</td>
<td>Post graduate degree 570 (33.26%)</td>
<td>1112 (41.80%)</td>
<td>124 (37.35%)</td>
<td>87 (25.14%)</td>
</tr>
<tr>
<td></td>
<td>Bachelor’s degree 472 (27.54%)</td>
<td>753 (28.31%)</td>
<td>98 (29.52%)</td>
<td>83 (23.99%)</td>
</tr>
<tr>
<td></td>
<td>Some college 470 (27.42%)</td>
<td>571 (21.47%)</td>
<td>77 (23.19%)</td>
<td>127 (36.71%)</td>
</tr>
<tr>
<td></td>
<td>High school diploma or GED 137 (7.99%)</td>
<td>160 (6.02%)</td>
<td>29 (8.73%)</td>
<td>34 (9.83%)</td>
</tr>
<tr>
<td></td>
<td>Didn’t finish high school 65 (3.79%)</td>
<td>64 (2.41%)</td>
<td>4 (1.20%)</td>
<td>15 (4.34%)</td>
</tr>
</tbody>
</table>

Note: FD = Framewise Displacement.
2.6.1. Calculating the differences in DMN between classes

A comparison between each class to the group characterized by the higher inhibition control abilities (class2) referred to as the "control" in the current study (e.g. class1-class2, class3-class2, class4-class2) was conducted in each division. The effect size was calculated, $z_1 - z_2$ (Cohen, 1977), of the difference in each ROI (see example in Fig. 2a). This process was repeated for each division, with an overall of ten effect size values for each ROI in each comparison (e.g. class1-class2, class3-class2, class4-class2) (Fig. 2b). After conducting a significance test for comparing two correlation coefficients (Diedenhofen and Musch, 2015; Lenhard and Lenhard, 2014), ROIs with effect sizes smaller than 0.1 were marked as significant, which is ordinary for a large sample size (Khalilzadeh and Tasei, 2017; Marek et al., 2020). To give importance to replicable results, only results that repeated at least in 90% of the divisions were chosen. Thresholds of 0.1, 0.2, and 0.3 were tested, but only with a threshold of 0.1, a variety of replicable results were demonstrated. Moreover, negative correlations were also included in the analysis, but the results were not replicable among the subdivisions; hence, only the positive correlations are presented in this study. In conclusion, ROIs with an effect size greater than 0.1 repeated at least in 90% of the divisions were selected.

3. Results

3.1. Behavioral results

3.1.1. Latent profile analysis results

According to the BLRT significance parameter, all six models tested were significant (Table 4). The information criterion AIC/BIS/SABIC values decreased as the number of classes increased. The gradients from models 4–5 and from models 5–6, were the smallest (Fig. 3), and hence models 4 and 5 were marked as the best choices. The entropy values of models 4 and 5 were 0.815 and 0.840, respectively, indicating a better class separation for model 5. The sample ratio in the smallest class in (Khalilzadeh and Tasei, 2017; Marek et al., 2020). To give importance to replicable results, only results that repeated at least in 90% of the divisions were chosen.

3.1.2. Covariate analysis results

Covariate analysis results are presented in Table 5 when each class is tested against class2 – controls.

3.1.3. Reading ability effect between the classes

Statistically significant differences in reading scores between the four classes were found ($F(3) = 55.719$, $r^2 = 0.0105$, $p < 0.001$). The highest reading scores were found for the control group (class2), whereas the lowest scores were found for the inattentive/hyperactive group (class4). Post-hoc Dunn tests using a Bonferroni adjustment were conducted to compare all pairs of classes. The difference between the control class (class2) and the behavioral inhibition class (class1) was significant. The inattention/hyperactivity class (class4) was different from all other classes. Classes 1 and 3 and classes 2 and 3 did not show significant differences in their reading abilities. The means, standard scores (including age-normalized reading scores), and post-hoc test results are described in Fig. 6 (For the full scores, see Table S4 and S5).

3.2. Neuroimaging results

3.2.1. Comparison of the DMN ROIs in each class vs controls

Further investigate the characteristics that uniquely differentiate each class from the others, each class was compared to the control class, as described in the Methods section. Then, ROIs with effect size values that were greater than 0.1 and repeated in at least 90% of the divisions were selected. See Fig. 7 for the common correlation matrices composed of all Gordon networks and Fig. 8 for the DMN’s sub-matrices. In class1, which was associated with lower behavioral inhibition ability, greater FC was found between the anterior and the posterior parts of the brain in the left hemisphere (Fig. 9a and 56 and Table S7). In class3, which was associated with lower cognitive inhibition ability, greater FC was found in the anterior part of the brain in both the left and right hemispheres (Fig. 9b, Table S8 and S9). In class4, which was associated with lower attention, hyperactivity, and lower inhibition abilities (ADHD characteristics), greater FC was detected mostly with the precuneus: left dorsal precuneus (parcel 94, Brodmann area 7), left ventral precuneus (parcel 1, Brodmann area 23, 31) and right ventral precuneus (parcel 162, Brodmann area 23, 31) with other regions within the DMN: left mPFC, right Middle temporal gyrus, right Cingulate Gyrus and right Superior Frontal Gyrus (Fig. 9c, Table S10, and Table S11). Greater connectivity was also shown within the right hemisphere (Fig. 9c, Table S12).
The goal of the current study was to demonstrate, in a community sample of children, the relationship between heterogeneity in inhibitory control, reading abilities, and connectivity features of a brain system linked to inhibition and executive function. We focused on behavioral measures associated with inhibition and the DMN, a functional network implicated in EF and inhibitory control (Fryer et al., 2018; Hernández-Alvarez et al., 2020; Liddle et al., 2011) and linguistic/semantic processing (Binder et al., 2005; Lanzoni et al., 2020; Seghier and Price, 2012; Wirth et al., 2011). The results supported our hypotheses showing different sub-profiles of inhibitory control and related neurobiological differences in DMN. More specifically, high FC between anterior and posterior DMN is related to the behavioral inhibition class, low FC within anterior DMN is related to the cognitive inhibition class, and higher FC of the precuneus together with high FC in the right hemisphere related to the inattention/hyperactivity class. As postulated, different reading abilities were also found for the four profiles: the control class showed the highest reading scores, whereas the inattentive/hyperactive class showed the lowest scores.

4.1. Neurobiological differences between cognitive profiles

Our results demonstrate that neurobiological profiles can be identified for groups that were created solely on behavioral measurements. These results, though encouraging, are different from previous findings (Dajani et al., 2019), although there are several main differences between the studies. It may be that categorical differences between EF abilities (“Low”, “Average”, and “Above Average”) reported in (Dajani et al., 2019) are based solely on parental reports (rather than on performance tasks). In the current study, in addition to a parental questionnaire (CBCL ADHD DSM5), a child questionnaire (BIS-BAS questionnaire) and performance task (SST) were used as well, providing a multi-informant and multi-method assessment of inhibitory control.

### Table 5

<table>
<thead>
<tr>
<th>Variable</th>
<th>Class1 – Behavioral Inhibition</th>
<th>Class3 – Cognitive Inhibition</th>
<th>Class4 – Inattention/Hyperactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent education</td>
<td>-0.113</td>
<td>-0.076</td>
<td>0.174</td>
</tr>
<tr>
<td>Household income</td>
<td>-0.345 * **</td>
<td>-0.103</td>
<td>-0.580 * **</td>
</tr>
<tr>
<td>Motion (FD)</td>
<td>1.143 *</td>
<td>2.201 * **</td>
<td>1.554 * **</td>
</tr>
</tbody>
</table>

Note. Class 2 (Controls) served as a reference class. FD = Framewise Displacement.

* *p < 0.001,  * p < 0.001,  * p < 0.01

(Fig. 4. LPA four classes separation. (a) This graph represents model 4 class separation. The X-axis represents the measures. The Y-axis represents the mean of each measure, normalized. The red color stands for class1 (self-reported motivated inhibition), the green line stands for class2 (which we referred to as “controls”), the light blue stands for class3 (task-based cognitive inhibition), and the purple color stands for class4 (parent-rated problems with inattention/hyperactivity). BAS_DRIVE = BAS (behavioral activation system) score for Drive scale (pursuing after the desired goal); BAS_FS = BAS (behavioral activation system) score for Fun-seeking scale (desire for new rewards and spontaneity); BAS_RR = BAS (behavioral activation system) score for Reward responsiveness (positive reactions to an event or expectation of reward); BIS_SUM = BIS (behavioral inhibition system) score; CBCL_ADHD = DSM-5 ADHD t-scores from the CBCL questionnaire; SST_INCRGO_RT = rate of GO trials that were answered incorrectly in the Stop Signal Task; SST_INCRS_MRT = incorrect STOP trials mean response time (in ms) in the Stop Signal Task; SST_INCRS_RT = rate of STOP trials that were answered incorrectly in the Stop Signal Task. (b) Classes distribution. X-axis represents the classes. Y-axis represents the number of subjects in each class. The red color stands for class1 (behavioral inhibition), the green line stands for class2 (controls), the light blue stands for class3 (cognitive inhibition), and the purple color stands for class4 (inattention/hyperactivity). )
Also, while Dajani’s study used the BRIEF general EF questionnaire, here we used only the inhibition EF sub-component, which likely created more homogenous profiles. Lastly, the current study used a novel non-parametric analysis (Zhitnikov et al., 2018) aiming to reveal common phenomena that are masked in traditional analyses such as ICA. The benefits of this analysis (Zhitnikov et al., 2018) need to be tested further on different datasets to strengthen this claim.

4.2. Maturation of the DMN and inhibition profiles: early maturation is related to a greater behavioral inhibition in response to punishment and reward abilities

Our results suggest that children with greater behavioral inhibition in response to punishment and a greater behavioral approach in reward than controls demonstrate higher FC between anterior and posterior DMN. Previous studies suggested those connections as a signature of brain maturation (Fair et al., 2008; F. Fan et al., 2021; Supekar et al., 2010). Brain maturation can suggest a reduced brain plasticity, i.e. a lower ability to adjust to different environments (Kolb and Gibb, 2011), as brain plasticity is known to decline with age (Kolb and Gibb, 2011; La et al., 2004).

Amongst the four groups, the group of children with lower cognitive inhibition ability demonstrated a lower FC in the anterior DMN compared to controls. In contrast to the group with lower behavioral inhibition abilities, it can reflect an immature brain development. Studies investigating the development of DMN found that overall DMN FC increases with age (Fair et al., 2008; F. Fan et al., 2021) and particularly in anterior regions (F. Fan et al., 2021). Cognitive inhibition ability improves with age (Harnishfeger, 1995) and its improvement is connected with frontal lobe development (Harnishfeger, 1995). Hence, one of the reasons for delayed brain maturation may derive from frontal lobe FC which may explain the low performance in this group.

Other researchers found that lower FC in anterior DMN is associated with attention difficulties in different attention domains (executive attention and sustained attention) (J. Fan et al., 2018; Rohr et al., 2018). Attention and inhibitory control are related to each other, as to maintain attention and to direct attention to the relevant stimulus, the brain needs to inhibit attention towards unnecessary external distractors (Diamond, 2013). Hence, we suggest that children in this class may also be categorized with low attention abilities and a future study including attention measures needs to be conducted in this class to strengthen the connection between inhibitory control and attention-related neurobiological profiles.

4.3. Right lateralised functional connectivity of the DMN and attention challenges

The group with increased inattention\hyperactivity demonstrated...
Fig. 7. Common correlation matrices for all brain networks (based on the Gordon Atlas). **Fig. 7:** (a) Correlation matrix of all 5055 subjects. (b) Separate correlation matrix for each class.
stronger FC in the right hemisphere compared to controls (hyperconnectivity of the DMN in ADHD was also recently found in (Duffy et al., 2021)). These results are in line with previous research claiming that the DMN is mostly left-lateralized (Agcaoglu et al., 2015; Nielsen et al., 2013), and connects lower attention abilities with right lateralization of the DMN (Sripada et al., 2014b). In general, the right side of the brain was previously found to be associated with attention and inhibition (Aron, 2007; Aron et al., 2004; Corbetta et al., 2008; Corbetta and

Fig. 8. Common correlation matrices of the default mode network. Fig. 8: (a) Correlation matrix of all 5055 subjects. (b) Separate correlation matrix for each class.
The right Inferior Parietal Lobule (IPL), which is part of the DMN, is associated with both maintaining attention and reorienting attention to new stimuli (Corbetta et al., 2008; Husain and Nachev, 2007; Singh-Curry and Husain, 2009). Another network that is related to reorienting attention is the right ventral Frontoparietal network (Corbetta and Shulman, 2002). The right Inferior Frontal Gyrus (IFG), on the other hand, was related to inhibition control (Aron, 2007; Aron et al., 2004). Hence, we suggest that higher FC in the right hemisphere is due to compensation with deficits in attention and inhibitory control, which characterized this class. A future study involving the DMN along with other brain regions related to attention and inhibition can be conducted to determine the connection in this class with attention and inhibition control symptoms.

4.4. Higher involvement of the precuneus is related to the motor system, and its deactivation is related to visual attention abilities

This inattention/hyperactivity class demonstrated a greater FC between the left dorsal, left ventral, and right ventral Precuneuses (parcel 94, parcel 1, and parcel 162, respectively), and brain regions associated with...
with EF and language processing (e.g. left mPFC, right Middle Temporal Gyrus, right Cingulate Gyrus, and right Superior Frontal Gyrus). The ventral part of the precuneus was previously reported as negatively correlated with the motor network (Uddin et al., 2009; Zhang and Li, 2012), in contrast to the dorsal precuneus, which was positively correlated with the motor system (Margulies et al., 2009; Zhang et al., 2014; Zhang and Li, 2012). In the context of this class, it may be that greater involvement of this part of the DMN may be related to an altered ability to control the motor network as part of the higher hyperactive symptoms characterizing this group.

In addition to the FC pattern related to the motor system, the dorsal part of the precuneus was found to be triggered by motor-imaginary tasks (Hamakawa et al., 2003; Malouin et al., 2003). Lower performance in these tasks was found to be related to ADHD symptomatology (Williams et al., 2013). Hence, a greater involvement of the dorsal part of the precuneus may be used as a compensating mechanism for this lower performance mentioned above. This is in line with findings showing that greater deactivation of the posterior precuneus during a perceptual matching task compared to speech production is related to an engagement of visual attention (Seghier and Price, 2012). The authors also state that the relation between age (maturation) and the level of deactivation of this region is affected by the level of visual attention and perceptual processing demands of the task. This may be a possible explanation also for the lower reading ability observed in this group of children in the current study.

### 4.5. What is the inhibitory profile of children characterized by ADHD patterns?

Note that class 4 is characterized by ADHD patterns (i.e., parent-rated problems with attention, hyperactivity, and lower inhibitory control abilities), but the children in this class were not recruited as a clinical sample with a diagnosis of ADHD. The t-scores of the CBCL ADHD DSM5 in this class are varied, as 104 (30%) are in the normal range (64 and below), 131 (37%) are in the borderline clinical range (65 – 69), and 111 (32%) are in the clinical range (70 and above) (Achenbach, 2009; Achenbach and Ruffle, 2000). In addition to the CBCL questionnaire, the parents also completed the Kiddie Schedule for Affective Disorders and Schizophrenia for DSM-5 (KSADS-5) diagnostic questionnaire (Kaufman et al., 2021), which includes a diagnostic criterion for ADHD. According to the results, 180 (52%) children in this group were diagnosed with ADHD. Interestingly, as a group, neurobiological patterns related to ADHD were demonstrated.

Following the higher comorbidity of this class, other scales from the CBCL questionnaire were also tested (Table S12 and S13). The attention problems scale also showed high comorbidity: 112 (32.46%) are in the normal range, 128 (36.99%) are in the clinical borderline clinical range, and 106 (30.63%), as was expected. In all other scales, most of the class was in the normal range, but unexpectedly more subjects were in the clinical range compared to other classes.

### 4.6. Do higher inhibition abilities characterize children with high socio-economic status?

In the current study, we have created the four groups using the latent profile analysis, which was based on the inhibition behavioral tasks. The data demonstrate how a higher number of females also characterizes children in the “control” group (aka class 2), a higher number of Caucasian individuals, higher income, higher parental education, and less motion inside the scanner compared to the other classes (see also Table 3). An interesting question can be raised regarding the overall profile of children with high inhibition abilities- are these the characteristics of children from a high socio-economic status, i.e. affluent population? On the one hand, this group’s high demographic profile may result in higher inhibition test scores (per(Moilanen et al., 2010)). On the other hand, even within the low SES group, children’s inhibition ability was found to vary depending on different parameters that may not be evaluated when traditionally examining SES (i.e. children from a low SES background with a single parent showed lower inhibition abilities than children from a comparable low SES background who have two parents(Sarsour et al., 2011)). In addition, variable inhibition abilities (and developmental trajectories in inhibition abilities) were found in children from a low socio-economic background (Pacheco et al., 2018). It is, therefore, possible that the fact that the demographic background of class 2 is high is incidental. Hence, to determine if high inhibition abilities and specific profiles of DMN are truly characterized by higher SES, a future study examining the differences in neurobiological signature for DMN in children matched for their inhibition profiles from high vs low socio-economic status should be conducted.

### 4.7. Reading abilities are related to patterns of inhibitory control

Our results provide a strong link between inhibitory control and reading abilities in early adolescents. These findings, by themselves, are not surprising and echo previous literature demonstrating the link between reading abilities (Allan et al., 2014) and reading comprehension and inhibitory control (Borella et al., 2010). The link to alterations of different parts of the DMN is also not surprising in light of the studies supporting its role in semantic processing (Binder et al., 2005; Lanzoni et al., 2020; Seghier and Price, 2012; Wirth et al., 2011). However, the results show different reading abilities across the sub-profiles found in the latent profile analyses. The control group showed the highest reading scores, and the inattentive/hyperactivity group showed the lowest. Also, significant differences were found between the controls and the behavioral inhibition group (class 1). A possible explanation for these lower reading scores may derive from the neuroimaging data and are related to the FC changes found in left-hemispheric regions within the DMN in classes 1 and 4 compared to the control group. Previous studies did suggest a connection between the recruitment of regions within the DMN and reading comprehension (Buckner et al., 2008) and discourse (Aboud et al., 2016). It was also suggested that the deactivation of sub-parts of the DMN is related to different cognitive/linguistic functions tightly linked to reading, such as visual attention (anterior PCC), speech production (posterior ventral Medial Prefrontal Cortex), perception and naming of objects (right inferior parietal cortex) (Seghier and Price, 2012). It may be that this over-recruitment of the left hemisphere, which is generally related to reading ability and changes in engagement of subregions within the DMN associated with semantic processing (Seghier and Price, 2012) in these groups, interferes with its role also in technical reading as was measured in the current study.

### 4.8. Big data in neuroimaging studies

One of the caveats in neuroimaging studies is the difficulty reproducing study procedures and results (Botvinik-Nezar et al., 2020; Klapwijk et al., 2021), especially for brain-wide association studies (Marek et al., 2022) as most studies are done using a limited number of participants (Klapwijk et al., 2021; Marek et al., 2022). Decreased results variability can be achieved using a large sample size which diminishes the variability with a sample size greater than 2000 participants (Marek et al., 2020). In the current study, we used the data from the Adolescent Brain Cognitive Development (ABCD) (https://abcdstudy.org/) study, the largest children dataset aiming at collecting various measures and assessments (neurocognition tasks, neuroimaging scans, culture and environment questionnaires, physical and mental health, and biospecimens data) from pre-adolescents into adulthood. One of the advantages of using large datasets like the ABCD is the ability to detect associations with many developmental outcomes (Dick et al., 2020; Klapwijk et al., 2021), even if these large datasets are usually associated with small effect sizes (Dick et al., 2020). Additional studies using this or similar large datasets have the potential to fuel prediction models associated with emotional and cognitive outcomes for
children.

5. Limitations

The results of the current study should be taken into consideration with the following limitations: first, minor variations of tests related to inhibition were included in the analysis. Other tests that measure additional aspects of inhibitory control may reveal more fine-tuned classes, especially in class1 (which includes the behavioral inhibition children), which comprised a large portion of the sample. Second, the recently developed algorithm for revealing the common correlation matrix was validated and tested on a smaller sample (n = 458). It is unknown to what extent the execution of the algorithm on large samples, as in our study, affects the results. Third, the interpretation of the results was based solely on the differences between the control group and the other groups generated from the analysis, and therefore, the actual values of the FC per group were not discussed. That is, there was no difference if the values in the two compared classes were high (e.g. close to 1) or low (close to zero). Lastly, to ensure that children in 2nd, 6th and 7th grades (outliers) do not affect the cognitive profiles, these children were removed from the analysis, and the profiles were recreated. The cognitive profiles remained similar to the original analysis as well as the differences in reading measures between the groups. However, when examining the FC differences within the DMN between the four classes, different results from the original analysis were found (see Supplemental material 1 in appendix B). One possibility for this difference in DMN profiles is the multiple seeds ranging between lobes that are part of the DMN (41 ROIs), which probably also contribute to the multiple roles this network plays in numerous cognitive and emotional processes (Mak et al., 2017). As such, it may be that changes in the number of participants within each group increase the variability within the network and hence result in different profiles. Therefore, choosing a different network with a more restricted function (i.e. sensory network, the cingulo-opercular or fronto-parietal ones) might have resulted in more homogenous profiles even in the case of changing the number of participants. However, choosing these networks will disable the ability to discuss the results in both emotional and cognitive contexts, as can be done when examining the DMN. Last but not least, failing to respond correctly to the SST used in the current study is traditionally related to inhibition challenges (Verbruggen and Logan, 2008) but also to challenges in attention and cognitive control (more broadly) (Matzke et al., 2017). Therefore, the groups showing challenges in the SST may also share an overall challenge in attention and cognitive control.

6. Conclusions

This study demonstrated how in a community sample of children, different subgroups could be found with inhibitory control difficulties and how each of them had a different neurobiological signature within the DMN. These findings can contribute to the understanding of the children’s variety of difficulties, which are not necessarily diagnosed with a particular learning disability, and the development of more precise teaching methods. In addition, the findings can contribute to the understanding of the neural basis of inhibitory control and aim to assist in objective neuroimaging diagnosis in the future. As we examined only the DMN, additional studies are needed to examine the involvement of other networks in inhibition, in addition to studies involving other aspects of inhibitory control. Finally, as the current study found different profiles for children with inhibition abilities linked to reading skills (for example, see (Fuchs et al., 2020; Horowitz-Kraus et al., 2015a, 2015b; Horowitz-Kraus and Holland, 2015; Peng and Goodrich, 2020), it will be interesting to examine whether reading interventions with embedded elements of EF, especially inhibitory control, are helpful for reading improvement in particular profiles.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data from this manuscript was downloaded from the ABCD dataset, which is publicly available. Scripts used for the analyses will be made available upon request.

Acknowledgments

Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multi-site, longitudinal study designed to recruit more than 10,000 children age 9–10 and follow them over 10 years into early adulthood. The ABCD Study® is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members/. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators.

The ABCD data repository grows and changes over time. The ABCD data used in this report came from ABCD collection 3165 and the Annual Release 2.0.1, DOI https://doi.org/https://doi.org/10.15154/1503209.

Funding

This work was supported by the National Institute of Child Health and Human Development (NICHD) [grant numbers 5R01HD086011, PI: Horowitz-Kraus].

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2023.101198.

References
