RESEARCH ARTICLE

Cortical thickness abnormalities in attention deficit hyperactivity disorder revealed by structural magnetic resonance imaging: Newborns to young adults

Jacob Levman[1,2,3] | Cynthia Forgeron[1] | Tadashi Shiohama[4] |
Patrick MacDonald[5] | Natalie Stewart[5] | Ashley Lim[5] | Lindsay Berrigan[6] |
Emi Takahashi[2,5,7]

[1]Department of Computer Science, St. Francis Xavier University, Antigonish, Nova Scotia, Canada

[2]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Department of Radiology, Harvard Medical School, Massachusetts Institute of Technology, Charlestown, Massachusetts, USA

[3]Nova Scotia Health Authority - Research, Innovation and Discovery Center for Clinical Research, Halifax, NS, USA

[4]Department of Pediatrics, Graduate School of Medicine, Chiba University, Chiba, Japan

[5]Division of Newborn Medicine, Department of Medicine, Boston Children's Hospital, Boston, Massachusetts, USA

[6]Department of Psychology, St. Francis Xavier University, Antigonish, Nova Scotia, Canada

[7]Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA

Correspondence
Jacob Levman, Department of Computer Science, St. Francis Xavier University, Antigonish, 5005 Chapel Square, Antigonish, NS, Canada, B2G 2K9.
Email: jlevman@stfx.ca

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental condition for which we have an incomplete understanding, and so brain imaging methods, such as magnetic resonance imaging (MRI), may be able to assist in characterising and understanding the presentation of the brain in an ADHD population. Statistical and computational methods were used to compare participants with ADHD and neurotypical controls at a variety of developmental stages to assess detectable abnormal neurodevelopment potentially associated with ADHD and to assess our ability to diagnose and characterise the condition from real-world clinical MRI examinations. T1-weighted structural MRI examinations ($n = 993$; 0–31 years old [YO]) were obtained from neurotypical controls, and 637 examinations were obtained from patients with ADHD (0–26 YO). Measures of average (mean) regional cortical thickness were acquired, alongside the first reporting of regional cortical thickness variability (as assessed with the standard deviation [SD]) in ADHD. A comparison between the inattentive and combined (inattentive and hyperactive) subtypes of ADHD is also provided. A preliminary independent validation was also performed on the publicly available ADHD200 dataset. Relative to controls, subjects with ADHD had, on

Jacob Levman and Cynthia Forgeron denote co-primary author.

average, lowered SD of cortical thicknesses and increased mean thicknesses across several key regions potentially linked with known symptoms of ADHD, including the precuneus and supramarginal gyrus.

1 | INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) defines attention deficit hyperactivity disorder (ADHD) as a chronic and consistent appearance of hyperactivity, impulsivity and inattention which interferes with the completion of daily tasks and overall patient development. ADHD is diagnosed in approximately 5.3% of children worldwide (Polanczyk et al., 2007). Several studies suggest that multiple types of structural abnormalities are prevalent in patients with ADHD (Baroni & Castellanos, 2015; Batty et al., 2010; Konrad et al., 2010; Konrad & Eickhoff, 2010); however, consensus is lacking in this field.

Magnetic resonance imaging (MRI) provides contrast between grey and white matter, which is critical in assessing brain structure in patients with a variety of neurological conditions (Wahlund et al., 2001). MRI contrast forms the basis for technologies that automate the extraction of biomarkers from a broad range of brain regions, such as grey/white matter volumetric measurements, cortical thicknesses and more (e.g. Fischl, 2012).

MRI has been used extensively to assess structural and functional differences in the brains of patients with ADHD. Several studies have reported that ADHD presents with reduced grey matter volumes (Batty et al., 2010; Bonath et al., 2016; Carmona et al., 2005; Hoogman et al., 2017; McAlonan et al., 2007; Nakao et al., 2011), structural connectivity issues (Konrad et al., 2010; Konrad & Eickhoff, 2010) and inconsistent findings in terms of cortical thicknesses (Almeida Montes et al., 2013; Ambrosino et al., 2017; Kumar et al., 2017; Shaw et al., 2007; Shaw, Lerch, et al., 2006; Silk et al., 2016; Sörös et al., 2017). Abnormalities in a variety of regions have been observed to be associated with populations with ADHD including, but not limited to, the basal ganglia (Aylward et al., 1996; Qiu et al., 2009), parietal lobes (Aman et al., 1998; Hart et al., 2012), lingual gyrus (Dibbets et al., 2010), prefrontal cortex (Schulz et al., 2005) and the cerebellum (Stoodley, 2014). Assessing imaging features of ADHD in a paediatric population comes with a multitude of challenges due to the structural changes between children and adults (Casey et al., 2000), rapidly changing anatomy and physiology (Shaw, Greenstein, et al., 2006), and significant variability in neuroanatomical structures in healthy children. In this study, we hypothesise that analysis of a large-scale ADHD population compared with neurotypical controls using MRI can help elucidate the clinical presentation of the brain in ADHD, may assist in diagnosis and characterisation and can help act as a clinical reference. We also hypothesise that regional cortical thickness variability, as assessed with the standard deviation (SD), may assist in characterising ADHD. We also hypothesise that differences can be detected between inattentive and combined (inattentive and hyperactive) subtypes of ADHD in terms of regional cortical thicknesses. This study is an analysis of a wide variety of regional cortical thickness measurements in control and ADHD participants extracted from volumetric T1 examinations compatible with the automated assessment of distributed cortical thickness measurements (Fischl, 2012).

2 | METHODS AND MATERIALS

2.1 | Participants

2.1.1 | Boston Children's Hospital (BCH)

Following approval from BCH's Institutional Review Board (informed consent was waived due to a lack of substantial risk to the patients), electronic patient medical records were reviewed between 01/01/2008 and 02/24/2016, and patients with an indication of ADHD, and for which subtype information was available, were selected for further analysis. All examinations were further analysed for imaging quality, such as excessive head movement and the presence of metal resulting in imaging artefacts, and were excluded if deemed of insufficient quality. The ADHD-affected sample size after the quality control was 637 examinations, and the sample includes patient examinations retrospectively identified after ADHD diagnosis later in life. This cohort included 406 MRI examinations from male participants and 231 examinations from female participants. The control group was selected based on an assessment by a BCH neuroradiologist that their MRI examination was normal and that their medical records indicated no neurological comorbidities, yielding 993 examinations used in previous analyses (Levman et al., 2017, 2018, 2019, 2021). Demographic information on our dataset is provided in Figure 1 and Table 1.
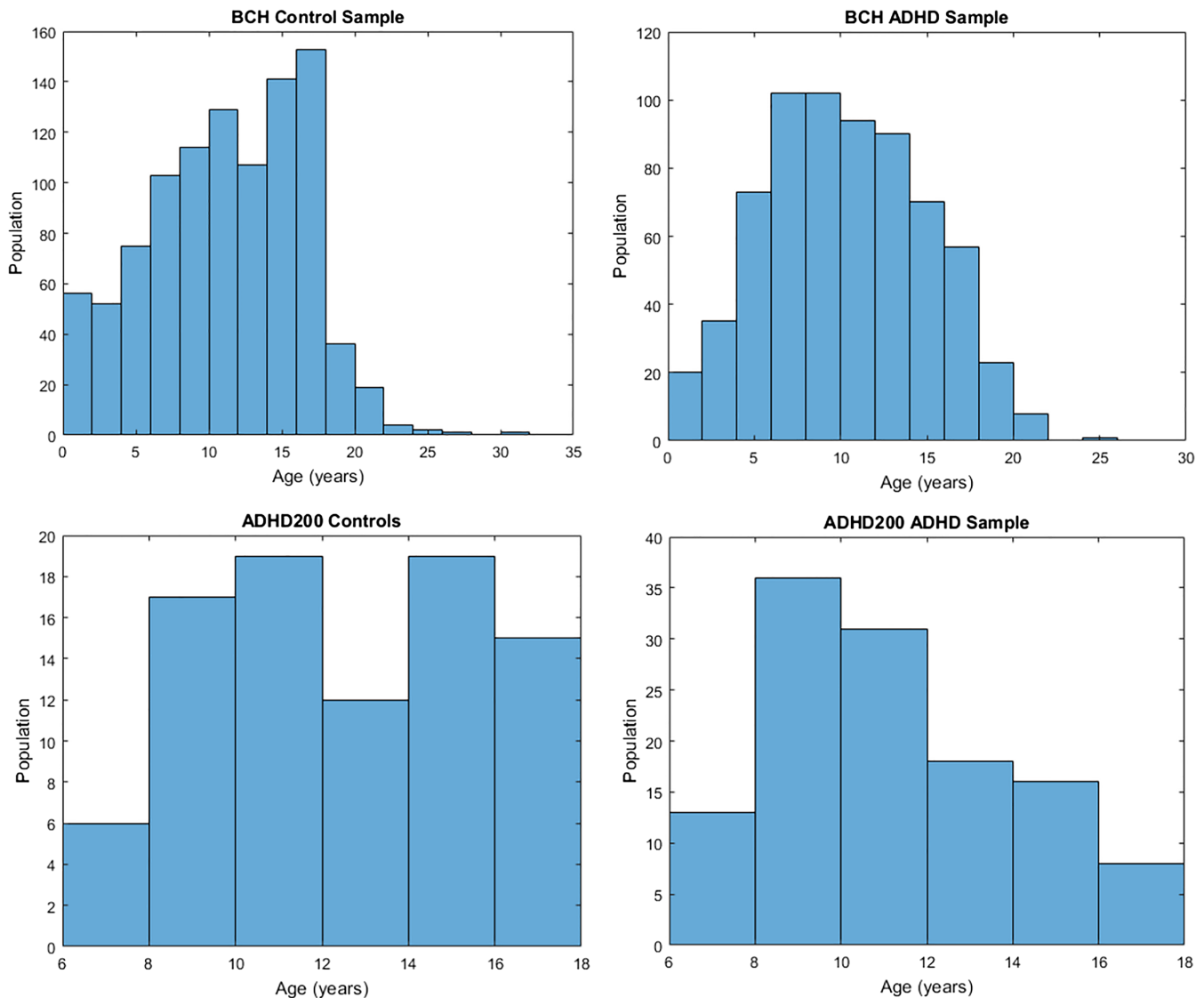
FIGURE 1 Age distribution among sample groups analysed

2.1.2 | ADHD200

Preliminary validation of our primary findings from BCH was performed on the ADHD200 dataset (a publicly available dataset used in previous analysis competitions) acquired from New York University (NYU). NYU was selected as it was the ADHD200 imaging centre that exhibited the most overlap with our sample age ranges, with the NYU-ADHD200 dataset being inclusive of ages 7 to 21 years. All datasets are anonymous, with no protected health information included, in accordance with HIPAA guidelines, and all pathological patients had an official diagnosis of ADHD (Bellec et al., 2017). Histograms demonstrating the age distributions for both the healthy and control groups from both samples are provided in Figure 1. Table 1 provides demographic information that includes the number of patients with various

subtypes of ADHD, including inattentive type, hyperactive type and combined type. Age demographics are also provided for the total of all ADHD and control participants in both datasets.

2.2 | MRI data acquisition and preprocessing

All participants at BCH were imaged with clinical 3 Tesla MRI scanners (Skyra, Siemens Medical Systems, Erlangen, Germany) yielding T1 structural volumetric images accessed through the Children's Research and Integration System (Pienaar et al., 2014). Because of the clinical and retrospective nature of this study, there is variability in the pulse sequences employed to acquire these volumetric T1 examinations, including several

TABLE 1 Examination counts and demographics related to the BCH and ADHD200 datasets

	BCH					ADHD-200 (NYU)			
	Inattentive	Combined	Hyperactive	Other	Controls	Inattentive	Combined	Hyperactive	Controls
Count	275	347	3	12	993	44	77	0	88
Percentage (%)	43.17	54.47	0.47	1.88		36.37	63.63	0	
Mean ± SD age (years)	10.41 ± 4.55				11.02 ± 5.22	11.23 ± 2.81			12.46 ± 3.12

Abbreviations: ADHD, attention deficit hyperactivity disorder; BCH, Boston Children's Hospital.

types of magnetisation-prepared rapid gradient echo (MPRAGE) acquisitions and a few traditional T1 structural sequences and volumetric spoiled gradient recalled sequences, representing a cross-section of imaging examinations from a real-world clinical environment. Spatial resolution also slightly varied but was typically ~1 mm. Strengths and limitations of the large-scale varying MR protocol approach taken in this study are addressed in the discussion and associated citations. By selecting a single ADHD200 imaging centre (NYU), we are able to provide a preliminary validation of the results of our variable set of clinical MRI pulse sequence data (at BCH) with examinations all acquired by an identical pulse sequence. Motion correction was not performed, but examinations with substantial motion artefacts were carefully excluded based on visual assessment. T1 structural examinations were processed with FreeSurfer (Fischl, 2012). If FreeSurfer results substantially failed, they were excluded from this analysis (i.e. FreeSurfer regions of interest [ROIs] that do not align to the MRI and examinations where major problems were observed with an ROI such as a cerebellar segmentation extending far beyond the extent of the cerebellum).

2.3 | Statistical analysis

This study included the acquisition of 662 cortical thickness measurements per imaging examination, as extracted by FreeSurfer (Fischl, 2012) using recon-all to extract measurements from all available atlases (aparc, aparc.a2009, aparc. DKTatlas40, BA, BA.thresh, entorhinal_exvivo), in order to support a thorough assessment of group-wise differences in cortical thickness. Thus, our analysis reports on overlapping ROIs, including measurements across a region's cortex as well as localised gyral, sulcal and lobular measurements when available. Data were analysed in the following age groups: 0–5, 5–10, 10–15 and 15–20 years old. BCH's data included very few patients over the age of 20 years, and so these samples were not included as part of this statistical analysis; however, the scatter plot in Figure 2 presents all samples vs. age for ease of visual comparison. This resulted in $m = 3310$ group-wise comparisons, yielding a Bonferroni-corrected threshold for statistical significance of $p < 0.05/m = 1.51e^{-5}$. Statistical testing was performed using the standard t test (Student, 1908) for two groups of samples. Age-dependent receiver operating characteristic curve (ROC) analysis allows us to assess the diagnostic potential of any given FreeSurfer biomarker at a wide variety of developmental stages. The area under the ROC curve (AUC) was used as a

diagnostic statistic for evaluation. Cohen's *d* statistic was also calculated in each age group (Cohen, 1992) for each cortical thickness measurement produced by FreeSurfer, providing a convenient method to assess group-wise differences between healthy and ADHD patients at a variety of developmental stages. Scatter plots were created to visually present biomarkers-of-interest as they vary with age. A preliminary analysis comparing this large-scale study's findings with the ADHD200 dataset's NYU imaging results is also provided. Since the NYU dataset has no patients in the 0–5 age group, direct comparison with BCH in this age bracket is not possible. Additionally, FreeSurfer (Fischl, 2012) is not validated for children below the age of 5 years, so findings from this cohort that lack validation with the independent ADHD200 dataset are relegated to the supplementary materials for reference.

In order to confirm that the findings reported are the result of group-wise differences between the ADHD and typically developing patients, a statistical model was constructed based on multivariate regression, adjusting each measurement within each age range to control for group-wise differences in age, gender and estimated total intracranial volume (using MATLAB's mvregress function). This model was used to adjust each cortical thickness measurement, in order to evaluate whether group-wise differences between our ADHD and typically developing populations are the result of age, gender or intracranial volume effects.

In this study, we hypothesise that brain MRI analysis combined with advanced analytic techniques can help characterise ADHD and potentially provide insights towards better understanding the condition.

3 | RESULTS

It is noteworthy that our clinical cohort from BCH included 231 MRI examinations from female participants and 406 MRI examinations from male participants aged 0 to 31 years old, whereas the ADHD200 public dataset, relied upon to provide a degree of cross dataset validation, only included participants aged 7 to 21 years old. This is, in part, related to the difficulty in imaging the youngest ADHD patients, especially those who have not yet received an ADHD diagnosis. It is noteworthy that our large-scale retrospective analysis of BCH patients included the identification of MRI examinations from many young patients who would go on to receive an ADHD diagnosis later in life. As such, this study demonstrates the potential for large-scale multiyear retrospective analyses to identify patients with clinical data acquired prior to their diagnosis of ADHD and thus can potentially provide valuable information with respect to
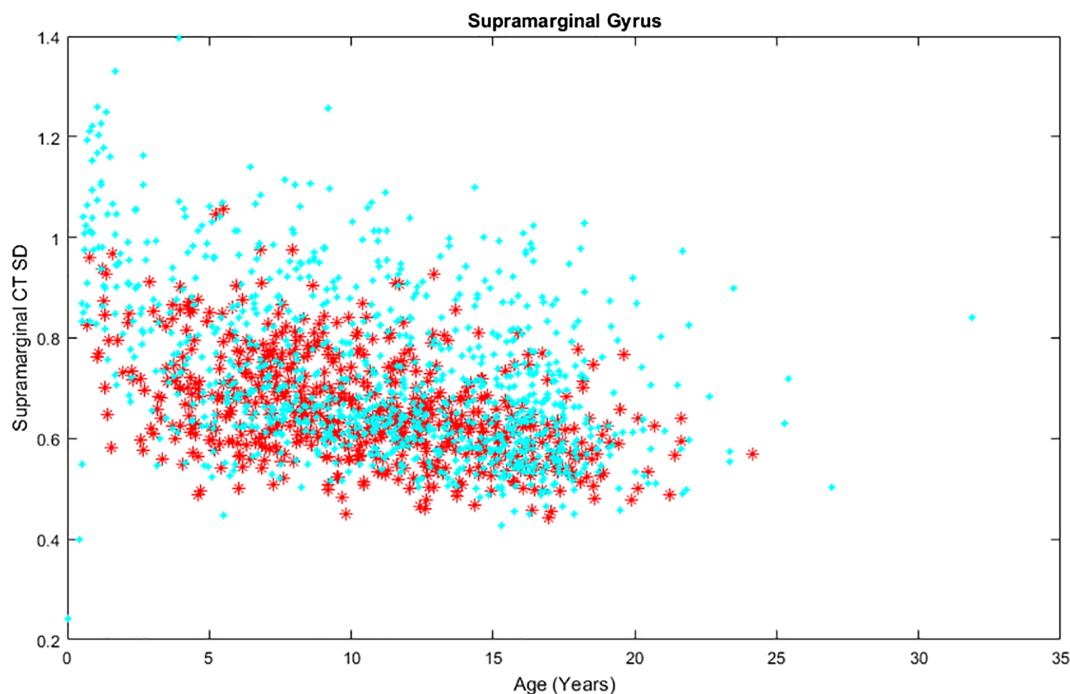

FIGURE 2 The supramarginal gyrus cortical thickness (CT) variability as measured with the standard deviation (SD) demonstrating patients with ADHD (red) vs. neurotypical controls (blue) as varying with age

the aetiology and development of the condition. This finding extends previous research demonstrating that large-scale retrospective analyses can identify MRI examinations acquired prior to diagnosis in autism as well (Levman et al., 2018, 2019). Although we are not able to confirm/validate our ADHD findings from this youngest cohort with the public ADHD200 dataset, we are able to compare findings across these two datasets in later age groups.

Our primary findings sorted by the largest observed effect size (Cohen's d value) across age groups are provided in Table 2, presenting brain regions exhibiting the largest effect sizes that were also statistically significant (Bonferroni-corrected $p < 1.51e^{-5}$) in at least one age range when comparing neurotypical with ADHD patients from our main BCH dataset. The largest positive effect sizes are located at the top of the table. Findings demonstrate several cortical regions that exhibit increased mean cortical thicknesses in the ADHD cohort. The largest mean cortical thickness differences were found in regions such as the right cuneus gyrus, the left precuneus and the right superior occipital region. Table S1 is the equivalent table inclusive of the 0–5 years old cohort, demonstrating mean cortical thickness differences in early years

ADHD patients in the right angular gyrus and the left supramarginal gyrus, findings that require additional validation in future studies.

Table 3 presents brain regions exhibiting the most negative effect sizes that were also statistically significant (Bonferroni-corrected $p < 1.51e^{-5}$) in at least one age range when comparing neurotypical with ADHD patients from our main BCH dataset. The most negative effect sizes are located at the top of the table. Negative effect sizes imply, on average, smaller cortical thickness variability (SD) values in the ADHD group. The largest cortical thickness variability differences were found in the superior frontal gyrus, the caudal middle frontal region and the middle frontal gyrus. Table S2 is the equivalent table inclusive of the 0–5 years old cohort, demonstrating abnormal reductions in cortical thickness variability in the right supramarginal gyrus, the right intraparietal sulcus and Brodmann's Area (BA) 1 in the right hemisphere in the ADHD cohort.

Findings comparing patients with inattentive ADHD to those with combined (inattentive and hyperactive) ADHD are summarised in Table 4. The largest mean thickness differences were observed in BA 44, the middle temporal visual area and the superior occipital gyrus. The

TABLE 2 Regions exhibiting the largest effect sizes when comparing neurotypical with ADHD patients (Cohen's d statistic), illustrating mean/average cortical thicknesses

Measurements	5–10 years	10–15 years	15–20 years
Cuneus MT	L (0.208) R (0.19573)	L (0.57924) R (0.30097)	L (0.70391) R (0.43711)
Precuneus MT	L (0.3256) R (0.26954)	L (0.39703) R (0.48893)	L (0.5782) R (0.41833)
Superior occipital gyrus MT	L (0.21983) R (0.28695)	L (0.52089) R (0.56299)	L (0.4656) R (0.51978)
Caudal anterior cingulate MT	L (0.55613) R (0.20656)	L (0.012222) R (0.068613)	L (0.26524) R (0.23203)
Brodmanns area V1 MT	L (0.13829) R (0.043418)	L (0.3773) R (0.24909)	L (0.53418) R (0.36508)
Mid anterior cingulate gyrus and sulcus MT	L (0.52108) R (0.37795)	L (−0.010935) R (0.070428)	L (0.34088) R (0.44908)
Inferior segment of circular sulcus of insula MT	L (0.11456) R (0.19509)	L (0.17759) R (−0.011332)	L (0.50899) R (0.07347)
Brodmanns area V2 MT	L (−0.017042) R (0.01982)	L (0.36163) R (0.32778)	L (0.50549) R (0.42899)
Precentral gyrus MT	L (0.29421) R (0.39039)	L (0.50249) R (0.42588)	L (0.39802) R (0.4156)
Posterior dorsal cingulate gyrus MT	L (0.4731) R (0.38634)	L (0.12538) R (0.34505)	L (0.33579) R (0.38721)
Superior parietal MT	L (0.17479) R (0.16953)	L (0.42717) R (0.46606)	L (0.45615) R (0.41117)
Calcarine sulcus MT	L (−0.01169) R (−0.14384)	L (0.44597) R (0.44545)	L (0.35923) R (0.46166)
Middle frontal gyrus MT	L (0.34943) R (0.4063)	L (0.31668) R (0.34337)	L (0.45215) R (0.40653)
Mid anterior cingulate gyrus and sulcus MT	L (0.52108) R (0.37795)	L (−0.010935) R (0.070428)	L (0.34088) R (0.44908)
Supramarginal MT	L (0.43274) R (0.25785)	L (0.23892) R (0.3883)	L (0.2449) R (0.36196)
Posterior cingulate MT	L (0.42845) R (0.34639)	L (0.055881) R (0.12522)	L (0.37571) R (0.42042)
Brodmanns area 4p MT	L (0.094934) R (0.12678)	L (0.38713) R (0.42602)	L (0.31312) R (0.37097)
Superior frontal gyrus MT	L (0.4137) R (0.30261)	L (0.38128) R (0.37691)	L (0.42096) R (0.40866)
Brodmanns area 6 MT	L (0.27664) R (0.32912)	L (0.39256) R (0.28098)	L (0.37321) R (0.38583)

Abbreviations: ADHD, attention deficit hyperactivity disorder; L, left; MT, mean thickness; R, right.

TABLE 3 Regions exhibiting the most negative effect sizes when comparing neurotypical with ADHD patients (Cohen's d statistic), illustrating variability (SD) of cortical thicknesses

Measurements	5–10 years	10–15 years	15–20 years
Superior frontal gyrus SD	L (-0.72244) R (-0.62267)	L (-0.5852) R (-0.5486)	L (-0.52109) R (-0.47633)
Caudal middle frontal SD	L (-0.65326) R (-0.60526)	L (-0.50459) R (-0.46089)	L (-0.51557) R (-0.37783)
Middle frontal gyrus SD	L (-0.64394) R (-0.513)	L (-0.47795) R (-0.45232)	L (-0.46457) R (-0.31461)
Middle anterior cingulate gyrus SD	L (-0.64205) R (-0.53876)	L (-0.43096) R (-0.23743)	L (-0.41101) R (-0.13445)
Inferior part of the precentral sulcus SD	L (-0.54443) R (-0.62209)	L (-0.44059) R (-0.47752)	L (-0.34493) R (-0.47532)
Supramarginal gyrus SD	L (-0.54942) R (-0.41614)	L (-0.33462) R (-0.45428)	L (-0.31574) R (-0.47952)
Intraparietal sulcus and transverse parietal sulci SD	L (-0.53539) R (-0.42819)	L (-0.30003) R (-0.41938)	L (-0.5214) R (-0.42734)
Rostral middle frontal SD	L (-0.49766) R (-0.39153)	L (-0.35611) R (-0.45357)	L (-0.31183) R (-0.14872)
Subparietal sulcus SD	L (-0.48036) R (-0.37187)	L (-0.37862) R (-0.36196)	L (-0.44022) R (-0.49891)
Precentral SD	L (-0.4864) R (-0.48769)	L (-0.52487) R (-0.60473)	L (-0.48555) R (-0.54611)
Postcentral sulcus SD	L (-0.46624) R (-0.27524)	L (-0.39139) R (-0.41848)	L (-0.36656) R (-0.51288)
Brodmanns area 2 SD	L (-0.46502) R (-0.37819)	L (-0.40473) R (-0.31792)	L (-0.22899) R (-0.4681)
Caudal anterior cingulate SD	L (-0.44189) R (-0.26985)	L (-0.30337) R (-0.039436)	L (-0.29426) R (-0.31257)
Paracentral gyrus and sulcus SD	L (-0.32587) R (-0.26933)	L (-0.42105) R (-0.32279)	L (-0.37066) R (-0.31771)

Abbreviations: ADHD, attention deficit hyperactivity disorder; L, left; R, right; SD, standard deviation (variability of thicknesses).

regions exhibiting the largest differences in cortical thickness variability were the calcarine sulcus, the middle occipital region, the lunatus sulci and the paracentral region. Table S3 is the equivalent table with the 0–5 years old age group included. Note that when comparing the combined and inattentive types of ADHD, differences in the 0–5 years old age group were modest.

Our results illustrate a common trend of lowered cortical thickness variability across all age ranges, as well as higher mean cortical thicknesses in a variety of brain regions in ADHD. Figure 2 illustrates the distribution of the SD of the cortical thicknesses in the supramarginal gyrus vs. age for both the healthy and ADHD participants from BCH. Comparison of our results from the public ADHD200 dataset with our primary clinical cohort from BCH is provided in the supporting information results.

4 | DISCUSSION

We performed a large-scale cortical thickness analysis of structural MRI examinations of the brain in ADHD and neurotypical individuals and demonstrated a variety of imaging features exhibiting differences between the two groups. Our findings include several unreported measurements demonstrating group-wise differences between ADHD and neurotypical participants, including abnormally reduced cortical thickness variability in key regions of the brain. To the best of our knowledge, this is the first study to report on regional cortical thickness variability biomarkers.

Age-dependent cortical thinning has been observed repeatedly in healthy populations (Levman et al., 2017), autism (Levman et al., 2019), Down syndrome (Romano et al., 2016) as well as in the ADHD population reported

in the current study. Cortical thicknesses could be linked with neural fibre tract development; however, the exact mechanism linking the two remains unknown. If fibre tract development does influence cortical thickness, one might expect that those tracts that extend from the white matter into neighbouring grey matter may play a structural role in support of cortical thickness. If neural fibre tracts play a structural role in the cortex and are linked with cortical thickness, one of the possible mechanisms linking age-related thickness decreases with known healthy neurodevelopment is through the process of pruning. Axon pruning is the process by which a branching fibre tract has some of its branches removed (or pruned) after an initial period of synaptic overgrowth (Chechik et al., 1998). This pruning procedure represents a critical component of brain maturation, is associated with maximising memory performance, and has been shown to continue into at least the third decade of life (Chechik et al., 1998). Thus, as neuronal pruning proceeds, the total size of the fibre tracts and all of their branches gets smaller, and in turn, their reduced size might result in reduced structural support to the cortex, leading to decreased cortical thicknesses. It should also be noted that the concentration of dendrites follows a pattern of nonlinear reductions with age (Chechik et al., 1998), with reductions also becoming smaller at later ages. Nonlinear reduction with age with smaller reductions at later ages is a pattern that is also observed in the distribution of cortical thicknesses with age (see Figure 2 for an example profile for a variability measurement; mean measurements have a similar age-dependent nonlinear reduction profile). This theory connecting pruning with cortical thickness might imply delayed/ reduced pruning in the ADHD population, leading to delayed/lessened age-dependent reductions in cortical thicknesses, which was observed in our study in a variety of brain regions (see Table 2 and S1). While the theory of accelerated pruning in ADHD has been discounted (Vaidya, 2012), the possibility of delayed/decelerated pruning in ADHD remains an open question. Delayed/ reduced pruning may also give rise to cortical thickness variability abnormalities (see Tables 3 and S2) depending on the distribution of the locations of the sites of pruning within a given cortical subregion. This is a similar hypothesis to that previously presented (Almeida Montes et al., 2012), whereby disordered pruning/maturation in the occipital cortex was considered as a possible explanation for observed cortical thickness abnormalities.

Our study's shortcomings include that our consistent set of MRI scanners at BCH employed a variety of acquisition protocols, shortcomings of which have been discussed previously (Levman et al., 2017, 2018, 2019). Detailed information on severity of ADHD and medication status were not available for the analysis of the BCH data nor were official DSM diagnoses available. In order to perform a study of this size, we relied on ADHD being indicated in the patient's electronic medical records. This was a retrospective analysis of clinical data, so there were a variety of reasons for the referral to MRI. In our ADHD cohort, 20.2% were referred to MRI because of seizure(s), 14.6% because of headaches and 8.4% because of an abnormal EEG. In our neurotypical cohort, the leading reasons for the MRI examinations were headaches (60%), to rule out intracranial pathologies (13%) and vomiting (11%). An additional limitation of this study is that FreeSurfer is not optimised for the

TABLE 4 Regions exhibiting the largest magnitude of the effect sizes when comparing inattentive with combined-type ADHD patients (Cohen's *d* statistic)

Measurements	5–10 years	10–15 years	15–20 years
Brodmanns area 44 MT	L (0.029698) R (0.21701)	L (−0.2525) R (0.039978)	L (−0.22936) R (−0.97734)
Brodmanns middle temporal visual area MT	L (0.11376) R (0.1244)	L (−0.12683) R (−0.013673)	L (−0.8916) R (−0.51059)
Superior occipital gyrus MT	L (−0.15647) R (0.24207)	L (−0.22609) R (−0.092917)	L (−0.87132) R (−0.47546)
Anterior transverse temporal gyrus MT	L (0.06483) R (0.0048776)	L (0.072517) R (−0.077125)	L (−0.85598) R (−0.43902)
Medial occipito-temporal gyrus and lingual sulcus MT	L (0.28447) R (0.14237)	L (0.34717) R (0.26923)	L (−0.85548) R (−0.6201)
Calcarine sulcus SD	L (−0.31599) R (−0.46459)	L (−0.34025) R (−0.22626)	L (−0.56997) R (−0.85201)
Pars opercularis MT	L (0.095689) R (0.15692)	L (−0.14959) R (0.0041407)	L (−0.27997) R (−0.84685)
Inferior occipital sulcus MT	L (0.27123) R (0.27069)	L (−0.22564) R (−0.068119)	L (−0.84657) R (−0.55378)
Middle occipital and lunatus sulci SD	L (−0.75022) R (0.074661)	L (−0.10747) R (0.18183)	L (−0.059342) R (0.070836)
Paracentral SD	L (−0.11333) R (−0.41133)	L (−0.58893) R (−0.37251)	L (−0.15984) R (−0.25385)

Abbreviations: ADHD, attention deficit hyperactivity disorder; L, left; MT, mean thickness; R, right; SD, standard deviation (variability of thicknesses).

youngest study participants. As such, the rate at which FreeSurfer fails to extract measurements from clinical MRI examinations increases substantially for participants aged 0 to 8 months, and the reliability of the results produced by FreeSurfer on participants from this age range is uncertain. FreeSurfer's reliability was assessed as reasonable for participants 8 months old and later (considering this is beyond the validated age range for the technology), at which point myelination contrast patterns have inverted so as to match the general pattern exhibited through the rest of life (with grey contrast located on the brain's periphery and white contrast occupying central regions). Research towards overcoming FreeSurfer's reliability in very young populations is ongoing (de Macedo Rodrigues et al., 2015; Zollei et al., 2017), and developments will be incorporated into future work.

Supporting information contain additional discussion.

CONFLICTS OF INTEREST
Dr. Levman is founder of the technology startup company *Time Will Tell Technologies, Inc*. The authors have no additional conflicts of interest to report.

ETHICS STATEMENT
This retrospective study was approved by Boston Children's Hospital's (BCH) Institutional Review Board.

INFORMED CONSENT
Informed consent was waived for this retrospective analysis due to a lack of risk to study participants.

DATA AVAILABILITY STATEMENT
The data from the ADHD200 website is publicly available. The data from Boston Children's Hospital is private and thus not publicly available.

ORCID
Jacob Levman 🄳 https://orcid.org/0000-0002-9604-3157
Tadashi Shiohama 🄳 https://orcid.org/0000-0003-0076-5882

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