

Distinct Cognitive and Neuroimaging Profiles in Later-Life Attention Deficit/Hyperactivity Disorder and Mild Cognitive Impairment

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Research

Keywords: neuropsychology, MRI, dementia, attention-deficit disorder, ADD, differential diagnosis, profiles, language

Posted Date: October 19th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-91495/v1>

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Abstract

Background: Attention deficit/hyperactivity disorder (ADHD) is increasingly being recognized in adults and older adults. Some of its behavioral features (e.g., distractibility, forgetfulness, impulsivity) may resemble those of mild cognitive impairment (MCI), which contributes to diagnostic uncertainty in later life. The present study aimed to systematically compare ADHD and MCI on measures of cognition and structural neuroimaging to clarify the extent of their overlap (i.e., cognitive features of ADHD that are most likely to be taken for signs of MCI) and identify potential features unique to each disorder (i.e., that may be used to guide diagnostic impressions).

Methods: One hundred and six adults aged 50 years or above were recruited from a Cognitive Neurology clinic (40 ADHD, 29 MCI and 37 controls) completed a comprehensive neuropsychological battery. A subsample (n=80) underwent structural neuroimaging.

Results: Memory was impaired in both patient groups, but reflected a storage deficit in MCI (supported by imaging findings of reduced hippocampal volumes) and an encoding deficit in ADHD (supported by frontal-lobe cortical thinning). Both groups performed normally on executive measures. Semantic retrieval was uniquely impaired in MCI.

Conclusions: Behavioral and structural imaging features strongly suggest that ADHD and MCI are similar manifestations of separate pathophysiological processes. Although ADHD has been proposed as a risk factor or prodromal stage of neurodegeneration, we propose it is rather acting as a phenotypic mimic of MCI via overlap in memory and executive performance.

Background

Despite its relatively high prevalence in later life (around 3%),⁽¹⁾ attention-deficit/hyperactivity disorder (ADHD) is not well-recognized in seniors.⁽²⁾ This may be because the subjective and objective cognitive difficulties reported by older adults with ADHD are taken as signs of mild cognitive impairment (MCI).⁽³⁾ MCI is a heterogeneous syndrome which we refer to inclusively here as the presumed incipient stage of any dementia, akin to the DSM-5 concept of 'mild neurocognitive disorder'. Many of the cognitive issues that characterize ADHD (e.g., difficulty multi-tasking or planning, absent-mindedness and forgetfulness) are also present in amnesic and non-amnesic MCI.

Though later-life ADHD may be difficult to distinguish behaviorally from MCI, the extent of phenotypic overlap has not been explored systematically. Direct group comparisons would clarify the extent of their overlap (i.e., cognitive features of ADHD that are most likely to be taken for signs of MCI) and identify potential features unique to each disorder (i.e., that may be used to guide diagnostic impressions). Some authors have additionally suggested that structural neuroimaging may help distinguish ADHD from MCI;⁽⁴⁾ however this recommendation has no empirical basis, because knowledge of structural neuroimaging profiles in ADHD aged > 50 is unavailable. That is, whether older adults with ADHD display sufficiently different neuroimaging profiles to distinguish them from MCI is unknown, as to our knowledge it has never been directly tested. Complicating matters further are epidemiological reports linking ADHD symptoms to subsequent neurodegeneration,^(5–9) suggesting the distinction between ADHD and MCI may not be as clear-cut as one might assume if the former is a risk factor or prodromal stage of the latter. Characterizing the profile of older adults with ADHD in relation to MCI is directly relevant to clinical practice, to inform diagnostic impressions and optimize the provision of clinical services to older adults.

This study aims to systematically compare the neuropsychological and neuroimaging characteristics of older adults with ADHD to those of MCI. We will first briefly summarize what is known about cognitive and structural brain features in these conditions. The extent and severity of neuropsychological impairments in later-life ADHD remain unclear. Only two studies have included samples aged > 50, and results were inconsistent: one reported deficits in frontal-lobe functions,⁽¹⁰⁾ while the other found grossly normal cognitive performance.⁽¹¹⁾ In younger adult cohorts, a recent review of neuropsychological performance reported impairments in attention, episodic memory and executive functions.⁽¹²⁾ Some studies have found no

deficits whatsoever in younger adults,(13) or have found that low performance on certain tasks is primarily accounted for by depressive symptoms.(11, 14) In MCI, cognitive deficits depend on the clinical subtype (i.e., single- vs. multi-domain amnesic or non-amnesic), but most commonly involve episodic memory, language and executive functioning.(15)

Regarding neuroimaging in ADHD, to our knowledge, no published work has involved older adults. In younger adult samples, abnormalities primarily involve regions involved in modulating attention and executive processes, including volumetric and cortical thickness reductions in superior frontal, anterior cingulate and orbitofrontal cortices.(16) In MCI, structural brain abnormalities depend on the clinical subtype but may include atrophy within the lateral and medial temporal lobes, prefrontal and inferior parietal cortices, and posterior cingulate gyrus,(17) and temporal and parietal cortical thinning.(18)

These individual bodies of literature lead us to expect possible overlap between ADHD and MCI in memory and executive functions, as well as in prefrontal cortical volumes. We take an inclusive approach to MCI as we have no *a priori* reason for focusing on any one clinical subtype.

Methods

Participants

Individuals were considered for inclusion if they were 50–85 years old. Fifty-nine participants suspected of ADHD were identified among patients presenting to a cognitive neurology clinic. All were screened using the Adult ADHD Self-Report Scale (ASRS), and a subset (n = 37) also agreed to complete the ADHD module of the Structured Clinical Interview for DSM-5 (SCID-5). The remaining 22 were unavailable or refused to complete the SCID-5.

Participants were classified as ‘ADHD’ if they met SCID-5 criteria for adult ADHD (n = 22), with the exception of the age-of-onset criterion (< age 12). Efforts were made to ascertain that symptoms had been longstanding; however, the age-of-onset criterion was not strictly applied due to concerns with relying on very remote retrospective recall (consistent with expert recommendations to exercise some flexibility in applying this criterion in adults(19, 20)). When SCID-5 had not been completed, ASRS scores were considered: 16 participants endorsed ≥ 4 items above a pre-specified threshold value on Part A or obtained a total summed score of ≥ 14 on Part A and were considered to have significant ADHD symptoms.(21) Thirteen suspected ADHD participants did not meet SCID-5 criteria, and six had no SCID-5 data available and screened negative on the ASRS; these 19 were excluded. Two participants reported longstanding issues with attention and executive functions and obtained ASRS ≥ 14 ; although they did not meet SCID-5 criteria at the time of enrollment because therapy had successfully helped them manage the functional impact of these symptoms, they were assumed to have underlying ADHD and were included in the final ADHD sample.

The Conners Adult ADHD Rating Scale (CAARS) Self-Report Long Form was administered to quantify ADHD symptom severity. Participants with children were also queried about their children’s early-life ADHD symptoms using the Barkley Adult ADHD Rating Scale-IV (BAARS-IV) Other-Report Childhood Scale. This served as additional corroborative evidence of ADHD, as heritability studies estimate that ADHD occurs in 40–50% of parents who have a diagnosed child.(22) The CAARS and BAARS scores were not used to exclude any participants. Three participants were taking stimulant medication and 32 were not. Current medication was unavailable for 5 ADHD participants.

Twenty-four MCI participants were drawn from the Sunnybrook Dementia Study (SDS) (ClinicalTrials.gov NCT01800214), a well-characterized cohort with varying cognitive impairment due to neurodegenerative or vascular disease. SDS participants are thoroughly screened to exclude secondary causes of impairment or concomitant illness; thus, any suspected cases of ADHD were not included, and participants were free from stroke. SDS diagnoses are determined by at least two experienced clinicians, based on neurological and cognitive examination. Data from an additional six MCI participants enrolled in another study were also used here, bringing the total MCI sample to n = 30. All were diagnosed based on Petersen’s(23) criteria (subjective and objective impairment in any cognitive domain, preserved functional independence, and no dementia).

Based on Jak and Bondi's comprehensive neuropsychological criteria,(24) three (10.3%) had single-domain amnesic MCI, 14 (48.3%) had multiple-domain amnesic MCI, two (6.9%) had single-domain non-amnesic MCI, and eight (27.6%) had multiple-domain non-amnesic MCI. Two had unclear neuropsychological profiles based on the Jak and Bondi criteria, but evidenced isolated impairments in California Verbal Learning Test (CVLT) learning and recognition and Stroop color-naming, or Wisconsin Card Sorting Test (WCST) set-loss errors. MCI participants who could be contacted (n = 17) also completed the ASRS, BAARS and CAARS.

Although cognitive tests were used to determine group status in the MCI group and as primary outcome measures in this study, their use in combination with ADHD symptom scales aimed to decrease circularity. Participants with cognitive impairment were not necessarily all classified as MCI; those who also screened positive on the SCID or the ASRS were classified as ADHD. ADHD classification was made agnostic to cognitive status.

An additional sample of 37 healthy controls was selected from the SDS. These participants reported no cognitive complaints, performed within normal limits on all cognitive measures, and were stroke-free. The final sample consisted of 40 participants with ADHD, 29 with MCI and 37 healthy controls.

Procedures

Cognitive and behavioral measures. Participants completed the Mini-Mental State Examination (MMSE) as an estimate of global cognitive function. To quantify depressive symptoms, participants completed either the 30-item Geriatric Depression Scale (GDS) (n = 85), the Beck Depression Inventory II (BDI-II) (n = 17) or an informant completed the Cornell Scale for Depression in Dementia (n = 4). In four ADHD participants, the MMSE was completed > 1 year after or prior to the rest of the neuropsychological assessment and was therefore coded 'missing'. One ADHD and two control participants did not complete any depressive symptom measure.

All participants underwent neuropsychological assessment, but because data were drawn from different sources not everyone completed all tests. Table 2 summarizes the number of participants having completed each test. Domains assessed included attention (forward digit span, Trails A, digit-symbol coding, Stroop word-reading and color-naming), episodic memory (Logical Memory Short Story, CVLT, Rey-Osterrieth Complex Figure Task [ROCF]), language (Boston Naming Test [BNT], phonemic and semantic fluency), and executive abilities (WCST, backward digit span, Stroop interference). Total time obtained on Trails B was transformed to a B/A ratio to isolate a relative measure of switching.(25)

Neuroimaging measures. A subset of MCI (n = 21) and controls (n = 33) had usable brain magnetic resonance imaging (MRI) data collected as part of SDS, and imaging data were acquired on an additional subset of 26 ADHD participants using the same imaging protocol. The MRI protocol was acquired on a 1.5 T GE Signa scanner (Milwaukee, WI, USA) and included a T1-weighted axial three-dimensional spoiled gradient recalled echo (5 ms echo time [TE], 35 ms repetition time [TR], 1 number of excitations [NEX], 35° flip angle [FOV], 22 × 16.5 cm, 0.859 × 0.859 mm in-plane resolution, with 1.2–1.4 mm slice thickness depending on head size) and interleaved PD and T2 sequences (interleaved axial dual-echo spin echo: TEs of 30 and 80 ms, 3 s TR, 0.5 NEX, 20 × 20 cm FOV, 0.781 × 0.781 mm in-plane resolution, 3 mm slice thickness).

Cortical thickness analysis (described previously)(26, 27) was conducted using an enhanced modification of FreeSurfer software v.6.0 (<http://surfer.nmr.mgh.harvard.edu/>). Briefly, the pre-processing of T1-weighted scans included motion correction, skull-stripping, transformation to Talairach space, intensity normalization, hemispheric separation, and tissue segmentation and parcellation. We performed two additional stages to the conventional pipeline to improve accuracy and quality assessment based on the PD/T2 sequence which shows the subarachnoid enabling more accurate delineation of the cortical surface. Stage 1 involved replacing the skull-stripped brain in FreeSurfer with one generated using our in-house semi-automatic brain extraction pipeline (SABRE),(28) which enhances the overall downstream processes in FreeSurfer. This was done Stage 2 involved incorporating lesions masks from our in-house PD and T2 based lesion segmentation pipeline to account for small vessel disease such as white matter hyperintensities.(29, 30) Grey and white matter, and grey matter and cerebrospinal fluid (CSF) borders, were identified and modelled as surfaces. Cortical thickness was defined as the distance

between the grey and white matter surface boundaries and the grey and CSF boundaries along each point of the cortex in each hemisphere. After pre-processing, all participants' surface data were resampled to FreeSurfer's average surface map. A 15-mm full-width half-maximum Gaussian spatial smoothing kernel was applied to the surface maps. FreeSurfer outputs, based on the Desikan atlas parcellation,(31) were visually inspected for quality control.

T1 was segmented using a multi-feature histogram method to generate a tissue segmentation containing normal appearing grey matter (NAGM), normal appearing white matter (NAWM), sulcal and ventricular CSF.(32) SABRE was used to parcellate brain tissue into 26 standardized volumes of interest described elsewhere.(28) Hippocampal volumes were segmented using an in-house 3D convolutional neural network with a U-net architecture that is robust for populations with brain atrophy (<https://hippmapp3r.readthedocs.io>).(33)

Statistical Analyses

Cognitive and behavioral measures. Depressive symptoms were categorized as 'none' (GDS < 10; BDI-II < 14; Cornell < 8), 'mild/probable' (GDS 10–19; BDI-II 14–19; Cornell 8–12) or 'moderate/severe' (GDS > 19; BDI-II > 19; Cornell > 12). Age, education, and MMSE scores were non-normally distributed, therefore nonparametric Kruskal-Wallis H tests were applied. Sex and depression were compared using chi-square (χ^2). ASRS, CAARS and BAARS scores were compared using t-tests.

Raw cognitive scores were standardized to Z scores using published normative data. Z scores were entered into separate univariate analysis of variance models adjusted for age, sex, MMSE and depressive symptoms (because the groups differed on these measures; see Results below). Models were then adjusted to remove non-significant predictors except age. Pairwise comparisons were examined where the main effect was significant.

Neuroimaging measures. NAGM volumes in inferior, middle, and superior frontal regions, superior and inferior parietal regions, and anterior and posterior temporal regions were corrected for head size by dividing cubic millimeters in each region by total supratentorial intracranial volume. Corrected regional volumes were normally distributed and entered raw into univariate analysis of variance models adjusted for age, sex, MMSE and depressive symptoms. Models were individually adjusted to remove non-significant predictors except age. Pairwise comparisons were examined in models with a significant main effect.

For cortical thickness analyses, vertex-wise surface-based analysis was first performed within the frontal lobe only using the general linear model in FreeSurfer, based on cortical thickness alterations in young adults with ADHD(34). A second exploratory analysis was performed across the whole brain. Age, education, MMSE scores were included as regressors of no interest. Monte Carlo simulation with 5000 iterations using a cluster-wise probability ($p_{(cwp)}$) of $p < 0.05$ (two-sided) was used to correct for multiple comparisons. Bonferroni correction was applied across the two hemispheres.

Results

Participant Characteristics

The groups differed on age, sex, MMSE and depressive symptoms, but not education (Table 1). By design, participants with ADHD obtained higher ASRS and CAARS scores. Higher children's BAARS scores corroborate our ADHD classification.

Cognitive Measures

Cognitive performance is summarized in Table 2. Relative to controls, MCI participants performed worse on measures of attention (digit-symbol coding and Stroop color-naming), all measures of memory (except immediate Short Story recall, and CVLT recognition), language (BNT and semantic fluency), and one measure of executive functioning (Trails switching). CVLT free recall scores were also worse than those of ADHD participants. ADHD participants were impaired on digit-symbol coding, Stroop color-naming, and immediate and delayed recall of the Short Story. Performance on all other tasks was comparable between groups.

Neuroimaging Measures

Regional NAGM volumes are summarized by group in Table 3. The groups' mean volumes did not differ in any of the regions of interest, except hippocampal volumes which were marginally lower in MCI participants than controls.

In frontal lobe cortical thickness analyses (Table 4, **Fig. 1.1**), ADHD participants showed decreased cortical thickness in the right precentral, right pars opercularis, and bilateral lateral orbitofrontal cortices compared to controls after correcting for multiple comparisons. They also showed reduced cortical thickness in the right rostral middle frontal and left precentral cortices relative to MCI.

In whole-brain analyses (Table 5, **Fig. 1.2**), cortical thickness in the right lateral orbitofrontal, right lateral occipital, and right pars opercularis cortices were reduced in ADHD relative to controls. ADHD participants also had lower cortical thickness in the left postcentral and left superior parietal cortices compared to MCI.

Discussion

This study aimed to quantify the shared and unique cognitive and imaging characteristics of ADHD and MCI in later life. First, we found notable overlap in participants' recall of a short story. However, ADHD participants' performance was comparable to controls' in a context with added semantic structure (the CVLT), suggesting a frontally-mediated encoding deficit in ADHD and a temporally-mediated storage deficit in MCI. This interpretation is corroborated by compromised frontal and medial temporal lobe brain structures in our samples of ADHD and MCI, respectively, on neuroimaging.

Language abilities were impaired in MCI only, with robust semantic retrieval deficits (naming and semantic fluency) relative to controls. Semantic abilities have been normal in previous investigations of later-life ADHD(11) and in some younger adult cohorts(35) (but not all).(36, 37) These rely relatively more on anterior temporal than frontal brain regions(38) and may thus be most sensitive to the earliest stages of dementia due to AD,(39) which is known to begin in temporal regions.(40)

Both ADHD and MCI groups showed grossly normal executive performance. This is contrary to historical conceptualizations of ADHD as a dysexecutive disorder, although there is growing recognition that executive dysfunction is not universal in ADHD.(41) Two previous studies of ADHD in individuals aged > 50 found normal executive performance when considered on a standardized scale (i.e., scaled scores between 8.3–10.9)(10) and relative to controls.(11) Despite normal test scores, our ADHD group did endorse ASRS and CAARS items closely tied to executive functioning (e.g., wrapping up details of a project, organizing tasks, remembering appointments). This corroborates previous observations that 'executive' occupational impairments in ADHD are not adequately captured by formal testing.(42) Neuropsychological tasks with greater ecological validity might be explored in future work to determine whether these better reflect the self-reported impairments of these individuals. Fractionation of frontal-lobe functions – i.e., dissociation of individual processes linked to specific aspects of an executive task(43) – may reveal additional between-group differences, because our neuroimaging findings and others'(16, 17) indicate that the frontal regions associated with process-specific specialization are differentially affected in ADHD and MCI. Unfortunately, fractionation could not be carried out here because not all participants completed the same test versions, which required us to standardize all raw scores for comparison purposes, and many measures useful for fractionation (e.g., words generated in the first 15 seconds of a fluency task) had no available normative data and could not be standardized. This will be an area for future study.

Consistent with behavioral performance, hippocampal volumes were relatively reduced in MCI, supporting an interpretation of a primary (storage) memory deficit. The ADHD group showed cortical thinning in the middle frontal gyrus which mediates working memory abilities(44) and sustained mnemonic responses.(45) Cortical thinning in the pars opercularis may best be understood in the context of reduced verbal memory retrieval in our ADHD cohort, as right inferior frontal gyrus (which comprises the pars opercularis) has been linked to verbal learning and recall.(46) The lateral orbitofrontal cortex, which was

also thinner in our ADHD sample relative to controls, has been implicated in decision-making and judgement,(47) which were not explicitly assessed in the present study.

Hypothesis: ADHD as a phenotypic mimic of MCI

Previous studies have reported associations between ADHD symptoms and neurodegeneration in later life(5–9), leading some authors to speculate that ADHD may be a risk factor for dementia, or represent an early point along a neurodegenerative pathophysiological continuum, potentially characterized by hypodopaminergic brain disorders.(8) The present study indicates that, indeed, both disorders display broadly overlapping dementia-like features (i.e., impaired aspects of verbal episodic memory). However, careful examination was successful in teasing apart unique characteristics (i.e., separate storage and encoding impairments in MCI and ADHD, respectively). Considered alongside additional MCI-specific weaknesses (i.e., semantic impairment) and unique neuroimaging markers (i.e., frontal-lobe thinning in ADHD and marginally smaller hippocampi in MCI), these findings lead us to propose the hypothesis that the pathological processes underlying ADHD and MCI are fundamentally distinct, and that their putative association in prior work is more parsimoniously explained by ADHD mimicking the MCI phenotype.(3) Attentional processes play a central role in successful memory functioning through their role in facilitating encoding,(48) and deficits in some of these attentional processes appear to manifest as memory impairment in ADHD. Because memory deficits are considered the hallmark feature of MCI (particularly MCI due to AD), they may lead older adults with ADHD to seek assessment or treatment in memory clinics(49) and contribute to diagnostic confusion with MCI/early dementia.(4)

It follows from this hypothesis that, in addition to unique cognitive and neuroimaging profiles, ADHD and MCI should show specific physiological and pathological markers of disease, and distinct longitudinal cognitive trajectories. Some important next tests of this hypothesis, then, may include quantification of various neurodegenerative biomarkers (e.g., using functional and diffusion MRI data, molecular imaging, or emerging plasma biomarkers) and prospective follow-up of participants with ADHD to determine the extent to which their cognitive and structural trajectories resemble those of normal vs. abnormal aging.

In the present study, the possibility cannot be ruled out that ADHD and MCI may indeed be different points along a single neurodegenerative continuum as others have proposed(8) and that the between-group cognitive and structural differences seen here may be explained by differences in disease severity. We posit this is unlikely, because our neuroimaging results point to unique cortical thinning patterns only present in ADHD (that one would expect to see in MCI if it were a 'later' point on the same disease continuum), though this could be because we enrolled primarily participants with MCI due to AD. For example, early Parkinson's disease is associated with frontal-lobe thinning patterns similar to those observed in our ADHD group.(50) Thus, the hypothesis we propose should be tested in replication samples as well as other neurodegenerative disorders besides AD.

Limitations

It cannot be conclusively determined that MCI participants were in the initial stages of dementia or, conversely, that ADHD participants ADHD were not. Because MCI and control participants were drawn from secondary sources, not all completed ADHD measures and thus it cannot be concluded they did not have ADHD. However, the SDS includes thorough assessment by experienced neurologists, and all MCI participants reported recent, insidious onset of cognitive decline which was corroborated by a knowledgeable informant. Lastly, quantifiable structural imaging data were only available on a small subsample of participants, and we did not collect functional or diffusion MRI data. We therefore interpret these findings cautiously as a discovery sample requiring replication that will stimulate further research on this relatively common condition that can complicate brain aging and masquerade as neurodegeneration, and may benefit from cognitive rehabilitation.

Conclusions

Both later-life ADHD and MCI groups exhibit memory impairment, but frontal-lobe cortical thinning in ADHD versus hippocampal atrophy in MCI support process-specific impairments contributing to memory deficits (i.e., encoding in ADHD and storage in MCI). In contrast to previous reports of ADHD as possible risk factor or prodrome of dementia, we propose the hypothesis that this association may be more parsimoniously explained by ADHD 'mimicking' the MCI phenotype via distinct pathophysiological processes. Prospective follow-up of ADHD participants, particularly relative to non-Alzheimer disease groups, are necessary to ascertain whether ADHD is associated with accelerated cognitive decline (e.g., may be associated with an α -synucleinopathy, or increase risk for dementia through vascular burden accumulation).

Abbreviations

ADHD
attention-deficit/hyperactivity disorder
asrs
Adult ADHD Self-Report Scale
BAARS-IV
Barkley Adult ADHD Rating Scale, Fourth Edition
BDI-II
Beck Depression Inventory II
BNT
Boston Naming Test
CAARS
Conners Adult ADHD Rating Scale
CSF
cerebrospinal fluid
CVLT
California Verbal Learning Test
dsm-5
Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
FOV
flip angle
GDS
Geriatric Depression Scale
MCI
mild cognitive impairment
MMSE
Mini-Mental State Examination
MRI
magnetic resonance imaging
NAGM
normal appearing grey matter
NAWM
normal appearing white matter
NEX
number of excitations
ROCFT
Rey-Osterrieth Complex Figure Task
SABRE

semi-automatic brain extraction pipeline
SCID-5
Structured Clinical Interview for DSM-5
SDS
Sunnybrook Dementia Study
TE
echo time
TR
repetition time
WCST
Wisconsin Card Sorting Test

Declarations

Ethics approval and consent to participate: All participants consented to participate, and the protocol was approved by the Sunnybrook Institutional Review Board.

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and analysed during the current study are not publicly available in order to protect the privacy and confidentiality of participants and their health data, but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: This work was supported by a grant from the Alzheimer's Association awarded to Drs. Callahan, Stuss and Black (#AACF-16-443540) and by a Canada Research Chair to Dr. Callahan. Dr. Bierstone received funding from the Comprehensive Research Experience for Medical Students (CREMS) program and the LC Campbell foundation during this work. The Sunnybrook Dementia Study (ClinicalTrials.gov NCT01800214) is supported through the Canadian Institutes of Health Research (MOP-13129; FDN 159910). We graciously thank the Department of Medicine, Sunnybrook Health Sciences Centre, Hurvitz Brain Sciences Program at the Sunnybrook Research Institute, inaugural Brill Chair in Neurology, and the Toronto Dementia Research Alliance, the University of Toronto for financial and salary support to Dr. Black.

Authors' contributions: BLC conceptualized the study, analyzed and interpreted behavioral data, and drafted the manuscript. NR and RT compiled all data and assisted with drafting the manuscript. PS and DB collected behavioral data and assisted with drafting the manuscript. MO and MG analyzed all neuroimaging data and assisted with drafting the manuscript. DTS conceptualized the study, interpreted behavioral data and assisted with drafting the manuscript. SEB conceptualized the study, interpreted all data and assisted with drafting the manuscript.

Acknowledgements: We gratefully acknowledge the research participants who generously donated their time and efforts to this research. We are also grateful to Sabrina Adamo for assistance with neuroimaging data processing and to Audrey Schnell for statistical expertise.

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Tables

Table 1
Participant characteristics.

	Controls			ADHD			MCI			Test statistic	P value	Effect size
	N	Mean (SD)		N	Mean (SD)		N	Mean (SD)				
Age (years)	37	67.3 (7.1)		40	64.0 (8.9)		29	73.7 (6.5)		$\chi^2 = 22.212$	<.001	$\varphi = 0.458$
Sex (% women)	37	78.4%		40	52.5%		29	72.4%		$\chi^2 = 6.353$.042	$\varphi = 0.245$
Education (years)	37	15.9 (2.4)		40	16.2 (3.7)		29	15.2 (3.1)		$\chi^2 = 2.030$.362	$\varphi = 0.138$
Depressive symptoms	35			39			29			$\chi^2 = 14.666$.005	$\varphi = 0.377$
% None (GDS < 10; BDI-II < 14)		91.9%			62.5%			82.8%				
% Mild/probable (GDS 10–19; BDI-II 14–19)		2.7%			30.0%			10.3%				
% Moderate/severe (GDS > 19; BDI-II > 19)		0.0%			5.0%			6.9%				
MMSE (total score)	37	29.1 (0.9)		36	28.2 (1.6)		29	27.2 (1.8)		$\chi^2 = 22.020$	<.001	$\varphi = 0.465$
ASRS (total score, Part A)		N/A		40	15.3 (4.2)		14	7.1 (3.5)		$t = 6.483$	<.001	$d = 2.070$
CAARS (ADHD Index T-score)		N/A		39	57.1 (10.1)		15	46.3 (7.4)		$t = 3.724$	<.001	$d = 1.165$
BAARS (score for highest-scoring child)		N/A		30	34.4 (12.3)		10	23.0 (6.1)		$t = 3.880$	<.001	$d = 1.049$
<p><i>Notes.</i> ADHD: Attention-deficit/hyperactivity disorder. ASRS: Adult ADHD Self-Report Scale. BAARS: Barkley Adult ADHD Rating Scale IV. CAARS: Conners Adult ADHD Rating Scale Self-Report Long Form. MCI: Mild cognitive impairment. MMSE: Mini Mental State Examination. SD: Standard deviation. Effect sizes refer to phi (φ) where 0.1, 0.3 and 0.5 indicate small, medium and large effect sizes, and to Cohen's d where 0.2, 0.5 and 0.8 indicate small, medium and large effect sizes. Because data were drawn from different sources, not all of the participants completed the ASRS, CAARS and BAARS; the N columns summarize the number of participants having completed each questionnaire. The ASRS has a maximum score of 24, where higher values indicate more severe ADHD symptoms and scores ≥ 14 are generally indicative of clinically significant ADHD symptoms. CAARS values have been transformed to T-scores, where scores ≥ 65 are generally indicative of clinically significant ADHD symptoms.</p>												

Table 2
Cognitive performance.

	Controls		ADHD		MCI		F value	P value	Partial eta ²	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)				
Attention & Processing speed										
Forward Span	37	0.08 (0.87)	40	-0.41 (1.10)	29	-0.36 (0.86)	1.163	.317	.023	
Trails A time	37	-0.18 (0.66)	40	-0.66 (1.27)	29	-0.38 (0.98)	1.921	.152	.036	
Coding	37	0.62 (0.92)	27	-0.33 (0.87)	22	0.08 (0.91)	9.661 ^{a,b}	< .001	.191	
Stroop Color Naming time	36	0.14 (0.74)	25	-0.69 (1.07)	26	-0.65 (0.85)	9.417 ^{a,b}	< .001	.185	
Stroop Word Reading time	36	-0.12 (0.75)	25	-0.68 (1.01)	26	-0.70 (0.76)	1.941	.150	.046	
Episodic memory										
Logical Memory immediate recall	35	0.39 (0.74)	26	-0.59 (1.24)	20	-0.52 (0.99)	4.439 ^b	.015	.110	
Logical Memory delayed recall	35	0.51 (0.77)	26	-0.57 (1.16)	20	-0.70 (1.20)	5.792 ^{a,b}	.005	.139	
CVLT Short Delay free recall	36	0.33 (0.83)	29	-0.43 (1.42)	23	-1.52 (1.30)	7.559 ^{a,c}	.001	.161	
CVLT Short Delay cued recall	36	0.33 (0.68)	29	-0.67 (1.50)	23	-1.28 (1.12)	6.240 ^a	.003	.136	
CVLT Long Delay free recall	36	0.36 (0.80)	29	-0.40 (1.31)	23	-1.74 (1.29)	16.781 ^{a,c}	< .001	.309	
CVLT Long Delay cued recall	36	0.17 (0.77)	29	-0.53 (1.51)	23	-1.46 (1.24)	5.006 ^a	.009	.112	
CVLT Recognition hits	36	0.28 (0.74)	29	-0.60 (1.23)	23	-0.48 (0.91)	2.595	.081	.062	
CVLT Recognition false positives	36	-0.25 (0.94)	29	0.38 (1.32)	23	1.07 (1.64)	2.583	.082	.062	
ROCFT immediate recall	37	0.92 (1.27)	26	0.34 (1.45)	22	-0.41 (1.21)	9.346 ^{a,c}	< .001	.188	
ROCFT delayed recall	37	0.79 (1.29)	26	0.16 (1.47)	21	-0.73 (1.42)	5.469 ^{a,c}	.006	.127	
Language										
BNT	37	-0.09 (0.55)	29	-0.39 (0.84)	23	-1.13 (1.69)	6.214 ^a	.003	.128	
Semantic fluency	37	-0.10 (0.81)	38	-0.53 (0.97)	29	-1.15 (0.72)	10.304 ^a	< .001	.171	

Notes. ADHD: Attention-deficit/hyperactivity disorder. BNT: Boston Naming Test. CVLT: California Verbal Learning Test. MCI: Mild cognitive impairment. ROCFT: Rey-Osterrieth Complex Figure Test. SD: Standard deviation. WCST: Wisconsin Card Sorting Test. Because data were drawn from different sources, not all participants completed the full battery of cognitive measures; the *N* column summarizes the number of participants having completed each test. Bolded values highlight statistically significant main effects of Group. ^aMCI different from Controls. ^bADHD different from Controls. ^cADHD different from MCI.

	Controls			ADHD			MCI			F value	P value	Partial eta ²
Phonemic fluency	37	0.79	(0.75)	31	0.37	(1.12)	29	0.28	(0.96)	0.537	.587	.012
Executive functions												
Backward Span	37	0.12	(1.14)	40	-0.14	(0.95)	29	0.01	(0.80)	0.393	.676	.008
Trails B/A ratio	37	-0.78	(0.66)	40	-0.05	(1.68)	28	0.09	(1.01)	5.340 ^a	.006	.096
WCST category completion	37	-1.08	(0.22)	40	-1.19	(0.33)	29	-1.08	(0.23)	0.866	.424	.017
WCST set loss errors	37	-1.14	(0.42)	39	-1.10	(0.32)	29	-1.29	(0.54)	1.173	.314	.024
Stroop Interference time	36	0.51	(0.78)	25	-0.24	(1.00)	26	-0.10	(1.04)	2.077	.132	.049
<p><i>Notes.</i> ADHD: Attention-deficit/hyperactivity disorder. BNT: Boston Naming Test. CVLT: California Verbal Learning Test. MCI: Mild cognitive impairment. ROCFT: Rey-Osterrieth Complex Figure Test. SD: Standard deviation. WCST: Wisconsin Card Sorting Test. Because data were drawn from different sources, not all participants completed the full battery of cognitive measures; the <i>N</i> column summarizes the number of participants having completed each test. Bolded values highlight statistically significant main effects of Group. ^aMCI different from Controls. ^bADHD different from Controls. ^cADHD different from MCI.</p>												

Table 3
Regional brain volumes (in mm³), corrected for total intracranial volume.

	Controls		ADHD		MCI		<i>F</i> statistic	P value	Partial η^2
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)			
Total NAGM	33	0.464 (0.022)	22	0.458 (0.023)	20	0.447 (0.025)	2.768	.070	.073
Superior frontal NAGM	33	0.024 (0.002)	22	0.023 (0.003)	20	0.023 (0.003)	1.766	.178	.047
Anterior cingulate NAGM	33	0.024 (0.002)	22	0.024 (0.002)	20	0.023 (0.003)	0.554	.577	.016
Inferior frontal NAGM	33	0.030 (0.005)	22	0.030 (0.006)	20	0.028 (0.005)	0.546	.582	.015
Inferior parietal NAGM	33	0.059 (0.009)	22	0.057 (0.010)	20	0.060 (0.007)	0.823	.443	.023
Posterior cingulate NAGM	33	0.049 (0.006)	22	0.050 (0.008)	20	0.046 (0.007)	2.078	.133	.056
Anterior temporal NAGM	33	0.026 (0.003)	22	0.025 (0.002)	20	0.025 (0.004)	0.973	.383	.027
Posterior temporal NAGM	33	0.099 (0.008)	22	0.099 (0.008)	20	0.094 (0.006)	0.788	.459	.022
Hippocampal volumes	31	0.006 (0.001)	11	0.005 (0.001)	14	0.005 (0.001)	3.318	.044^a	.115

Notes. ADHD: Attention-deficit/hyperactivity disorder. MCI: Mild cognitive impairment. NAGM: Normal-appearing gray matter. SD: Standard deviation. Effect sizes refer to partial eta squared (η^2_p), where .01, .06 and .14 indicate small, medium and large effect sizes. All volumes are reported in mm³ and have been corrected for total intracranial volume. Because data were drawn from different sources, not all participants completed neuroimaging; the *N* column summarizes the number of participants with available imaging data. ^aMCI marginally different from Controls ($p = .053$).

Table 4

Frontal lobe analysis showing significant clusters with cortical thinning corrected for multiple comparisons.

	Anatomical regions	Max-log10 (<i>p</i> -value)	Surface area of cluster (mm ²)	Talairach (MNI305) coordinates (x,y,z)	LowCWP - HiCWP	<i>p</i> (<i>cwp</i>)
ADHD < NC	Right Precentral	3.164	594.62	47.2, 0.4, 32.9	0.003–0.007	0.005
	Right pars opercularis	3.189	756.69	38.9, 17.8, 20.5	0.000–0.001	< 0.001
	Right lateral orbitofrontal	3.928	1147.90	27.2, 34.3, -7.8	0.000–0.001	< 0.001
	Left lateral orbitofrontal	4.866	561.65	-28.7, 28.2, -16.0	0.009–0.015	0.012
ADHD < MCI	Right rostral middle frontal	-3.751	617.16	42.4, 21.5, 32.6	0.003–0.007	0.005
	Left precentral	-3.137	761.69	-35.9, -16.3, 53.7	0.000–0.016	< 0.001
<i>Notes.</i> LowCWP = Lower clusterwise p-value 90% confidence interval; HiCWP = Upper clusterwise p-value 90% confidence; MCI = Mild cognitive impairment; NC = Normal control; ADHD = Attention-deficit/hyperactivity disorder; <i>p</i> (<i>cwp</i>)=clusterwise p-value						

Table 5

Whole brain analysis showing significant clusters with cortical thinning corrected for multiple comparisons

	Anatomical regions	Max-log10 (<i>p</i> -value)	Surface area of cluster (mm ²)	Talairach (MNI305) coordinates (x,y,z)	LowCWP - HiCWP	<i>p</i> (<i>cwp</i>)
ADHD < NC	Right lateral orbitofrontal	3.927	1149.61	27.2, 34.3, -7.8	0.002–0.005	0.003
	Right lateral occipital	4.461	2482.53	43.8, -73.8, -7.7	0.000–0.001	< 0.001
	Right pars opercularis	3.189	756.69	38.9, 17.8, 20.5	0.035–0.045	0.039
ADHD < MCI	Left postcentral	-3.566	1023.82	-51.0, -17.9, 52.9	0.006–0.010	0.008
	Left superior parietal	-3.873	1003.53	-26.9, -60.5, 45.2	0.008–0.012	0.009
<i>Notes.</i> LowCWP = Lower clusterwise p-value 90% confidence interval; HiCWP = Upper clusterwise p-value 90% confidence; MCI = Mild cognitive impairment; NC = Normal control; ADHD = Attention-deficit/hyperactivity disorder; <i>p</i> (<i>cwp</i>)=clusterwise p-value						

Figures

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Figure 1

Frontal lobe (1) and whole-brain (2) cortical thickness analysis showing frontal regions with decreased cortical thickness in (A) ADHD relative to controls and (B) ADHD relative to MCI. Notes. ADHD=Attention-deficit/hyperactivity disorder. LLOF=Left lateral orbitofrontal. LP=Left precentral. LPos=Left postcentral. LSP=Left superior parietal. MCI=Mild cognitive impairment. RLO=Right lateral occipital. RLOF = Right lateral orbitofrontal. RP=Right precentral. RPars=Right pars opercularis. RRMF=Right rostral middle frontal.

Image not available with this version

Figure 1

Frontal lobe (1) and whole-brain (2) cortical thickness analysis showing frontal regions with decreased cortical thickness in (A) ADHD relative to controls and (B) ADHD relative to MCI. Notes. ADHD=Attention-deficit/hyperactivity disorder. LLOF=Left lateral orbitofrontal. LP=Left precentral. LPos=Left postcentral. LSP=Left superior parietal. MCI=Mild cognitive impairment. RLO=Right lateral occipital. RLOF = Right lateral orbitofrontal. RP=Right precentral. RPars=Right pars opercularis. RRMF=Right rostral middle frontal.