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Shared grey matter correlates of reading and attention

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Abstract

Disorders of reading (developmental dyslexia) and attention (ADHD) have a high rate of comorbidity (25–40%), yet little is known about the neural underpinnings of this phenomenon. The current study investigated the shared and unique neural correlates of reading and attention in 330 typically developing children ages 8–18 from the Philadelphia Neurodevelopmental Cohort. Multiple regression analyses were used to identify regions of the brain where grey matter (GM) volume was associated with reading or attention scores ($p < 0.001$, cluster FDR $p < 0.05$). Better attention scores correlated with increased GM in the precuneus and higher reading scores were associated with greater thalamic GM. An exploratory conjunction analysis ($p < 0.05$, $k > 239$) found that GM in the caudate and precuneus correlated with both reading and attention scores. These results are consistent with a recent meta-analysis which identified GM reductions in the caudate in both dyslexia and ADHD and reveal potential shared neural correlates of reading and attention.

Keywords

Attention-deficit/hyperactivity disorder (ADHD); Developmental dyslexia; Reading; Behavioral attention; Caudate; Precuneus; Voxel-based morphometry

1. Introduction

Reading disability (RD; also known as Specific Learning Disorder with impairment in Reading or Developmental Dyslexia) and Attention-Deficit/Hyperactivity Disorder (ADHD) are prevalent developmental disorders, each affecting approximately 5–10% of children

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bandl.2023.105230>.

(American Psychiatric Association, 2013; Willcutt & Pennington, 2000). RD and ADHD co-occur more often than chance, with approximately 25%–40% of children with either RD or ADHD diagnosed with comorbid RD-ADHD (for review, Boada, Willcutt, & Pennington, 2012; Willcutt, Pennington, Olson, Chhabildas & Hulslander, 2005). Children who are diagnosed with comorbid RD-ADHD tend to have poorer responses to treatment (Gray & Climie, 2016) and experience more functional impairment, including lower grades in school (Turker et al., 2019) and higher rates of substance use (Chang, Lichtenstein, & Larsson, 2012) and stressful life events (i.e. job loss, financial issues; Friedrichs, Igl, Larsson, & Larsson, 2012; for review, see Sexton, Gelhorn, Bell, & Classi, 2011). This highlights the importance of understanding the potential factors (genetic, environmental, neural, cognitive) underpinning comorbid RD-ADHD.

The multiple factors model (MFM; also known as the multiple deficit model) framework for understanding the comorbidity of developmental disorders has been applied specifically to RD-ADHD comorbidity (Pennington, 2006; McGrath et al., 2019). This model suggests comorbidity arises from disorders sharing multiple risk factors that can span various levels of analysis, e.g., etiological, neural, and neuropsychological. Studies based on the MFM framework have focused mostly on the neuropsychological level (see review in McGrath et al., 2019), with less work in neuroimaging. If the MFM is correct, we should be able to identify shared neural correlates for reading and attention disorders that contribute to their comorbidity.

In neuroimaging research, most studies investigating RD or ADHD have not focused on shared risk factors. The majority of studies use single-disorder groups, in which inclusion requires individuals who *only* meet criteria for RD or *only* ADHD, setting up statistical analyses that determine differences (contrasts) rather than overlap. An extensive neuroimaging literature exists that focuses on single-disorder group analyses, at both the structural and functional levels (for reviews of RD, see Linkersdörfer et al., 2012; Li, Hu, & Liang, 2022; Reis, Araújo, Morais, & Faisca, 2020; for reviews of ADHD, see Frodl & Skokauskas, 2012; Hoogman et al., 2017; McCarthy, Skokauskas, & Frodl, 2014; Sutubasi et al., 2020; Valera et al., 2007). Most of this work has been conducted based on categorical designations of each disorder, although some studies have focused on identifying regions and networks of interest from investigations of reading and attention in neurotypical populations (for reviews, see Child et al., 2019; McCandliss & Noble, 2003; Raichle, 2015). Such a dimensional approach can be valuable because RD and ADHD are thought to be categorical cut-off points on a continuous distribution (Peters & Ansari, 2019) and so a categorical approach necessarily neglects subclinical variation in reading and attention. Here, we adopt a dimensional approach in a large, population-based sample to investigate the convergence of brain regions where grey matter is associated with both reading and attention. We use the term “reading” as shorthand to refer to single-word reading skills, which are distinguishable from more complex reading processes, such as reading comprehension. We use the term “attention” to refer to behavioral ratings of attention symptoms that contribute to the DSM diagnosis of ADHD (American Psychiatric Association, 2013). Such behavioral ratings of attention differ from cognitive measures of attention, which are correlated with ADHD but do not entirely overlap with clinical ADHD diagnosis (Willcutt et al., 2005).

1.1. Neural correlates of reading and attention

The neural correlates of reading and attention are the subject of extensive investigation in the field of cognitive neuroscience. Here, we focus on findings emerging from voxel-based morphometry (VBM) analyses of the grey matter (GM) correlates of reading and attention.

Structural GM correlates of reading in neurotypical populations are mostly left-lateralized (e.g. left frontal, temporo-parietal, and occipito-temporal regions; He et al., 2013; Torre & Eden, 2019), but also include right hemisphere regions (e.g. right superior and middle frontal gyrus, right inferior and middle temporal gyrus; He et al., 2013) along with bilateral cerebellar lobules VIIb-IX and left lobule VI (Moore et al., 2017). These findings largely map to regions where GM alterations have been reported in the RD literature. When compared with typical readers, volumetric differences have been found in areas associated with the left hemisphere reading network, as well as right hemisphere regions, including bilateral temporo-parietal, occipito-temporal, and cerebellar cortices, and the caudate nucleus (Ligges et al., 2022; for VBM meta-analyses see McGrath & Stoodley, 2019; Eckert et al., 2016; Linkersdörfer et al., 2012; Richlan et al., 2013). There is also evidence of increased GM volume in RD groups compared to typical readers in left supramarginal gyrus/inferior parietal lobule, left middle temporal gyrus, left cerebellum (Crus I), right precuneus, right supplementary motor area, right precentral gyrus, and right medial frontal regions (McGrath & Stoodley, 2019).

Executive attention networks include fronto-parietal cortices (for meta-analysis see McKenna, Rushe, & Woodcock, 2017; Smolker et al., 2015; Weise et al., 2019), thalamus, and basal ganglia (including caudate, putamen, and globus pallidus; Weise et al., 2019). These findings closely correspond with GM structural differences reported in ADHD, which report volumetric alterations in basal ganglia (McGrath & Stoodley, 2019; Ellison-Wright et al., 2008; Hoogman et al., 2017; Valera et al., 2007), orbitofrontal regions (Lukito et al., 2020), cuneus (Zhao et al., 2020), fronto-parietal regions, and thalamus (McGrath & Stoodley, 2019). Additional regions showing structural differences include temporal regions (e.g. superior temporal gyrus), amygdala (McGrath & Stoodley, 2019; Hoogman et al., 2019), and bilateral cerebellum, as well as reduced total cerebral volume (McGrath & Stoodley, 2019; Valera et al., 2007).

Therefore, VBM studies in both neurotypical and clinical populations identify multiple regions where GM is associated with both reading and attention skills. While there are some areas of commonality (e.g. basal ganglia, temporal cortices), determining shared correlates of reading and attention requires examining both measures in the same dataset.

1.2. Neural correlates of comorbid reading and attention problems

The few studies that have examined comorbidity at the neural level have revealed both overlapping and unique brain areas associated with RD, ADHD, and comorbid RD-ADHD (Jagger-Rickels, Kibby, & Constance, 2018; Langer, Benjamin, Becker, & Gaab, 2019; McGrath & Stoodley, 2019). Brain regions showing volumetric differences in both the comorbid group *and* single disorder groups include areas associated with the reading network (e.g. right superior frontal gyrus [Jagger-Rickels, Kibby, & Constance, 2018],

left inferior frontal gyrus, and left planum temporale [Langer et al., 2019]) and regions associated with executive attention (e.g. left thalamus [Jagger-Rickels, Kibby, & Constance, 2018], left and right caudate [Goradia et al., 2016], and left anterior cingulate cortex [Langer et al., 2019]). Unique regions showing volumetric alterations in *only* the comorbid group have varied between studies (e.g. left medial frontal gyrus [Jagger-Rickels, Kibby, & Constance, 2018], right thalamus, and left middle temporal gyrus [Langer, et al., 2019]). Therefore, while there is a consensus that there are both overlapping and unique GM correlates associated with RD, ADHD, and comorbid RD-ADHD, there is no consensus yet on shared GM differences or regions that are uniquely implicated in RD-ADHD compared to the single disorders.

One emerging point of convergence is the caudate nucleus (Goradia et al., 2016; Jagger-Rickels, Kibby, & Constance, 2018; McGrath & Stoodley, 2019). The bilateral caudate shows evidence of compression on the surface in comorbid RD-ADHD and ADHD-only boys compared to age- and IQ-matched controls (Goradia et al., 2016), and GM volumes in the right caudate of comorbid RD-ADHD, RD-only, and ADHD-only children tend to be smaller compared to age-, gender-, and SES-matched children (Jagger-Rickels, Kibby, & Constance, 2018). The only meta-analysis to date of VBM studies of RD and ADHD also reported the right caudate as an area of overlap for reduced GM in both conditions (McGrath & Stoodley, 2019).

1.3. Current study

The current study's goals were twofold: (1) to determine the GM correlates of dimensional measures of reading and attention in a large, population-based sample of youth; and (2) to determine whether these GM correlates of reading and attention are shared or unique. Only one other study to date has investigated the conjunction of regions associated with reading and attention in a neurotypical sample, though only children aged 6–12 were included (Wang et al., 2022). The current study thus expands on Wang and colleagues by including an overlapping and older sample of youths that encompass the full range of reading and attention skills. We hypothesized that regions within the reading network (e.g. left occipito-temporal cortex, left inferior frontal gyrus [Kearns et al., 2019; Ramus et al., 2018]) would correlate with reading scores and areas within attention networks (e.g. prefrontal cortex and striatum [Frodl & Skokauskas, 2012; McCarthy, Skokauskas, & Frodl, 2014; Sutubasi et al., 2020]) would correlate with behavioral attention scores. We also predicted that GM associations with both reading and attention scores would be evident in regions where shared GM differences were identified in clinical populations, specifically in the right caudate (McGrath & Stoodley, 2019).

2. Materials and methods

2.1. Participants

The current study used data from the Philadelphia Neurodevelopmental Cohort (PNC; described in Satterthwaite et al., 2014), a large-scale, publicly available dataset aimed at understanding the impact of genetics on brain maturation and cognitive development in a population-based sample of youth, aged 8–21 at the time of enrollment. The current study

used the version 2 dataset release from dbGAP (<https://www.ncbi.nlm.nih.gov/gap/>) (see Acknowledgements).

The PNC dataset (N = 9428) is composed of youth originally enrolled in a genetic study at the Center for Applied Genomics (CAG) at clinics associated with Children's Hospital of Philadelphia (CHOP) serving the Delaware Valley (Philadelphia and surrounding area, southwest New Jersey, and Northern Delaware) who were invited back for psychiatric and cognitive phenotyping (Calkins et al., 2014; Calkins et al., 2015; Gur et al., 2014). Researchers used the following inclusion criteria for cognitive testing: parents able to provide a signed consent form, English proficiency, and youth able to participate in neurocognitive testing. Cognitive testing used the Penn Computerized Neurocognitive Battery (CNB), which took approximately one hour to administer. Tasks were administered in a fixed order that was determined based on prior testing experience and included strategically placed breaks to avoid fatigue (e.g. a break following a particularly challenging task; Gur et al., 2012). The CNB included 14 tasks designed to evaluate a broad range of cognitive domains, including executive control, episodic memory, complex cognition, social cognition, sensorimotor speed, and motor speed (Gur et al., 2014; Gur et al., 2012). The WRAT4, a single-word reading measure, was also administered as part of the cognitive testing (further details below). In addition to the cognitive testing, researchers administered a computerized version of GOASSESS, a structured clinical interview modified from the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997), to parents or legal guardians (youth 8–10 years old), to youth and parents/legal guardians (youth 11–17 years old), or youth (18 years or older) to measure psychiatric symptoms, including ADHD symptoms listed in the DSM-IV (Calkins et al., 2014; Calkins et al., 2015).

Researchers invited back a subset of participants (n = 1594) who completed the cognitive and psychiatric testing to participate in neuroimaging (Satterthwaite et al., 2014). In some families, multiple siblings participated in neuroimaging. When that was the case, one sibling was randomly selected from each family to preserve statistical assumptions of independence for the present analyses. Exclusion criteria for this study included a moderate, significant, or major health condition (designated by the PNC study team) that could impact the central nervous system, such as cerebral meningitis, cystic fibrosis, severe liver or kidney problems, or sickle cell anemia. Additional exclusion criteria for the current study were: participants younger than 8 or older than 18 years of age, history of genetic disorders, history of epilepsy, history of a serious head injury with loss of consciousness, history of cancer, impaired vision or hearing, history of lead poisoning, missing data for behavioral measures of reading or attention, and participants without a T1-weighted MRI scan that passed quality control (see below).

After applying these criteria, we analyzed data from 330 participants (Fig. 1; 156 male participants, 174 female participants; Mean age = 13.4 years, SD = 3.1 years). Participants or their parents reported on sex (male or female; no intersex option was provided) and gender was not assessed. The participants predominantly identified as European American (51.2%) or African American (38.2%), with 8.2% identifying as multiracial (defined as any endorsement of more than one race) and 1.8% did not report on race. Participants who

passed imaging quality measures did not differ from those who were excluded on age ($t(858) = -0.74, p = 0.46$) or attention scores ($t(858) = -0.34, p = 0.73$). Participants who did and did not pass imaging quality measures did differ on reading scores ($t(858) = 2.82, p < 0.01$), such that those who passed quality control had higher mean reading scores ($M = 104.3, SD = 15.9$) than those who did not ($M = 101.1, SD = 16.5$; Table S3).

2.2. Reading and attention tasks

Participants completed the word reading subtest of the Wide Range Achievement Test-4 (WRAT-4; Wilkinson & Robertson, 2006), a widely-used standardized academic measure in which the child reads a list of real words that increasingly become more phonologically complex (English, not timed). Scores were calculated by adding the number of words read correctly. Raw scores were used in analyses because the standard scores were not normally distributed. We and others have found that the standard scores showed a bimodal distribution with a second enrichment of scores at the highest standard score (see Price et al., 2020). To account for age effects in the raw scores, age was used as a covariate in the regression model (described in section 2.5). Raw scores were centered and entered into the analyses.

As part of the GOASSESS psychopathology screen (Calkins et al., 2015; Calkins et al., 2014), parents/legal guardians (youth 8–10 years old), parents/legal guardians and participants (youth 11–17 years old), or participants (youth 18 years old) completed a structured clinical interview which included six inattention symptoms from the DSM-IV ADHD criteria (of 9 total) (American Psychiatric Association, 1994). Because there should be two reports for youths 11–17 years old (their own and their parent or legal guardian), the parent's or legal guardian's report was used unless it was missing. In that case, the participant's report was used instead. The number of symptom endorsements was summed to index inattention, ranging from 0 (no inattention symptoms) to 6 (all inattention symptoms selected), and then the scores were multiplied by -1 so that higher scores reflected stronger skills. These values were then centered and entered into data analyses.

We chose to focus on the inattention symptoms of ADHD for theoretical and practical reasons. Theoretically, previous work demonstrated that inattentive ADHD symptoms significantly account for the relationship between ADHD and reading, and that hyperactive/impulsive symptoms do not add any unique variance to this relationship once inattention is accounted for (Chhabildas, Pennington, & Willcutt, 2001; Willcutt & Pennington, 2000). Practically, only three of nine hyperactive-impulsive symptoms from DSM-IV ADHD criteria were assessed, which limited our ability to analyze these symptoms separately.

2.3. MRI acquisition

Magnetic resonance images (MRIs) were acquired on a single 3T Siemens TIM Trio whole-body scanner with a 32-channel head coil at the Hospital of the University of Pennsylvania. An MPRAGE was acquired for each participant, with a TR of 1810 ms, TE of 3.5 ms, flip angle of 9, voxel resolution of 1 mm^3 , and 160 1-mm thick slices with no gaps. For more details, see Satterthwaite et al. (2014).

2.4. Voxel based morphometry

Voxel based morphometry (VBM; Ashburner & Friston, 2000; Mechelli et al., 2005) was conducted using the CAT12 toolbox (CAT12.3; <https://www.neuro.uni-jena.de/cat/>) and SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/>) implemented in MATLAB 2018 (Math-works, Inc., 2018). Each T1 structural image was visually inspected for motion artifacts or poor grey matter (GM)/white matter (WM) differentiation. During this step, a large number of images were removed because of ringing, a common motion artifact caused by movement within the scanner which leads to poor definition of GM/WM boundaries, which is problematic for VBM analyses (Reuter et al., 2015). This degree of data loss was expected due to the age of the sample (8–18 years) and is consistent with previous studies (e.g. Moore et al., 2017). A second, automated quality assessment was also conducted using the CAT12 sample homogeneity check to determine if any additional images were flagged compared to visual inspection, but no additional images were excluded based on this quality control step. Preprocessing consisted of reslicing the T1 images to 1.5 mm³ voxels, normalizing to Montreal Neurological Institute (MNI) space using DARTEL registration, and modulating the tissue to reflect volume rather than concentration. These normalized and modulated images were segmented into GM, WM, and cerebrospinal fluid (CSF) that were then used to estimate total intracranial volume (TIV), which was entered as a covariate in the statistical analyses. Segmented images were smoothed with an 8 mm full width-half maximum (FWHM) Gaussian kernel. The normalized, modulated, segmented, and smoothed images were entered into multiple regression models in SPM12. Data were visualized using MRICroGL (<https://www.mccauslandcenter.sc.edu/mricrogl/home>) and anatomical localization was based on the Automated Anatomical Labeling (aal; <https://www.gin.cnrs.fr/en/tools/aal-aal2/>) atlas in xjView (<https://www.alivelearn.net/xjview/>).

2.5. Statistical analyses

Separate whole-brain multiple regression analyses were used to test the relationships between GM volume and reading scores and GM volume and attention scores. Centered reading or attention scores were used, with age, age², sex, handedness, and total intracranial volume (TIV) as covariates. Age was included because the current study aimed to explore risk factors that persisted across age and also to correct for any age-related effects on scores. Age² was included as a covariate to account for GM developmental trajectory. GM volume across development increases and then decreases, with the timepoint of the peaks depending on the brain region, causing an inverted-U shape which can be modeled with a quadratic age variable (Bethlehem et al., 2022). An absolute threshold mask of 0.2 was used to control for edge effects at the border of GM and WM. Results were thresholded at a height threshold of $p < 0.001$ and an FDR-corrected cluster-level threshold of $p < 0.05$.

A conjunction analysis was performed in SPM12 to determine potential overlap of brain regions associated with both reading and attention scores. Results were thresholded at $p < 0.001$ with an FDR-corrected cluster-level threshold of $p < 0.05$.

3. Results

For distribution of attention and reading scores in the final cohort, see Table 1, Fig. S1, and Fig. S2.

3.1. Grey matter correlates of attention scores

Higher attention scores were associated with increased GM in the precuneus ($r = 0.21$; $p < 0.001$, FDR-corrected cluster $p < 0.05$; Fig. 2a). Peak coordinates were located in the left precuneus, but the cluster extended bilaterally (Table 2, Fig. 2c).

No regions showed a statistically significant negative relationship with attention scores, where increased GM was associated with lower attention scores.

3.2. Grey matter correlates of reading scores

Higher scores on the word reading subtest of the WRAT-4 were associated with increased thalamic GM ($r = 0.39$; $p < 0.001$, FDR-corrected cluster $p < 0.05$; Fig. 2b). Peak coordinates were located in the left thalamus, but the cluster extended bilaterally (Table 2, Fig. 2c).

No regions showed a statistically significant negative relationship with reading scores, where increased GM was associated with lower reading scores.

3.3. Reading and attention conjunction analysis

We performed a conjunction analysis to identify regions that showed statistically significant relationships with both reading and attention. There were no significant regions of conjunction at our *a priori* statistical threshold ($p < 0.001$, FDR-corrected cluster $p < 0.05$). Because this study is one of the first of its kind examining convergence of GM correlates of reading and attention, we conducted an exploratory analysis at a more liberal voxel-level threshold of $p < 0.05$. Clusters with 239 voxels or more met the cluster-level threshold of $p < 0.05$ based on 1000 Monte Carlo simulations (3dClustSim; Cox et al., 2017a, Cox et al., 2017b). This conjunction analysis revealed that the GM correlates of both reading and attention overlapped in the bilateral precuneus and the right caudate (Table 2, Fig. 3; see Table S4 for the results of additional conjunction analyses at a range of voxel-level thresholds).

We did not conduct a conjunction analysis of the regions showing a negative relationship between task scores and GM volume, as there were no findings that reached statistical significance in the individual attention and reading analyses.

3.4. Neurosynth meta-analytic coactivation map

The conjunction analysis results indicated two areas of overlap for reading and attention at our more liberal thresholds. These regions might also be areas of shared neural risk in reading and attention disorders. It is also possible that the caudate and precuneus are not contributing to reading and attention separately, but instead could be part of a functional network that supports both reading and attention. Aberrant functional connectivity has been

associated with both poor reading (e.g. Mateu-Estivill et al., 2021; Schurz et al., 2015) and ADHD (e.g. Gonzalez-Madruga et al., 2022). Therefore, it is important to examine the relationship between the precuneus and caudate more closely.

To determine whether these two brain regions are functionally connected to each other, we examined the meta-analytic coactivation maps with the caudate coordinates in the Neurosynth database (<https://neurosynth.org/>; Yarkoni et al., 2011), an online repository of >14,000 studies reporting over 150,000 brain regions, to create meta-analytic coactivation maps. A previous functional connectivity study found that the caudate region identified in the current study showed resting-state functional connectivity with the precuneus, along with other regions often associated with reading (inferior frontal gyrus, inferior parietal lobule) and attention (anterior cingulate; Di Martino et al., 2008). The co-activation map from the caudate coordinates included the precuneus cluster found in the conjunction analysis, indicating that these regions are part of the same functional network (Fig. 4).

3.5. Developmental effects on grey matter correlates of reading and attention

While the goal of the current study was to determine neural overlap(s) between reading and attention that persisted across age, the sample spanned a wide age range, and therefore the regression and conjunction results may be driven by a certain age group. To evaluate this, we split the sample into two age groups: 8–12 years old ($n = 124$; referred to as “younger”) and 13–18 years old ($n = 206$; referred to as “older”). We performed the same reading and attention multiple regression models and subsequent conjunction analysis (described in section 2.5) for each age group to see if results were consistent between the younger and older youths.

In the younger sample, higher reading scores were associated with increased GM in the thalamus ($r = 0.48$; Fig. 5a). Peak coordinates were located in the left thalamus (Table 3, Fig. 5d), similar to the whole-group findings. No brain regions associated with increased attention survived FDR cluster correction. A conjunction analysis at the stringent threshold of $p < 0.001$ with an FDR-corrected cluster-level threshold of $p < 0.05$ did not result in any significant brain regions. No significant brain regions survived a more liberal conjunction threshold of $p < 0.05$, $k > 138$ (cluster-level threshold of $p < 0.05$ based on 1000 Monte-Carlo simulations, 3dClustSim; Cox et al., 2017a; Cox et al., 2017b).

In the older sample, no brain regions that were associated with higher reading scores survived FDR cluster correction, but the left thalamus could be considered marginally significant (FDR cluster corrected $p = 0.069$, $r = 0.40$; Fig. 5c, 5e). Higher attention scores were associated with increased GM in the precuneus ($r = 0.20$, Fig. 5b, 5e, Table 3), similar to the whole-group findings. A conjunction analysis at the stringent threshold of $p < 0.001$ with an FDR-corrected cluster-level threshold of $p < 0.05$ did not result in any significant brain regions. We therefore explored the conjunction at a more liberal threshold, mimicking our whole-sample conjunction analysis (voxel-level threshold $p < 0.05$, $k > 74$; cluster-level threshold of $p < 0.05$ based on 1000 Monte-Carlo simulations, 3dClustSim; Cox et al., 2017a; Cox et al., 2017b). The more liberally thresholded analysis revealed conjunction between the GM associated with reading and attention scores in the bilateral precuneus and bilateral caudate, replicating our whole-group findings. Additional identified regions were

bilateral middle temporal gyrus, right inferior temporal gyrus, right fusiform gyrus, and right superior parietal lobule (Table 3).

4. Discussion

This study presents the first structural analysis exploring the potential neural overlaps of single-word reading and behavioral attention skills in a population-based sample of youth. This dimensional approach is relatively new in the neuroimaging literature (Perdue et al., 2020) and allows for the identification of potential regions of focus for studies in clinical populations. Further, this approach better reflects the conceptualization of clinical disorders as occupying the tail of a continuous distribution of behavior (Peters & Ansari, 2019). The study was motivated by the multiple factors model (also known as the multiple deficit model) which hypothesizes that shared risk factors contribute to the comorbidity of reading and attention difficulties (Pennington, 2006; Willcutt et al., 2010; McGrath et al., 2011; McGrath et al., 2019). Reading scores were positively correlated with GM volume in the thalamus, while attention scores were positively associated with GM in the precuneus. The same GM correlates of reading and attention were found in the older age group, while in the younger age group the thalamus was associated with reading scores but there were no significant neural correlates of attention scores. While the conjunction models were not statistically significant at our *a priori* statistical threshold, exploratory analyses at a more lenient threshold identified regions in the precuneus and basal ganglia (caudate) where GM correlated with both reading and attention scores. As overlapping neural correlates of reading and attention in an unselected sample, these regions warrant further follow-up and indicate areas of interest for future research investigating shared neural risk factors for RD and ADHD.

Here we discuss (1) how the GM correlates of reading and attention scores in this sample fit into the vast imaging literature of reading and attention abilities; (2) whether the regions highlighted in the exploratory conjunction analysis are consistent with studies of RD-ADHD comorbidity; and (3) potential reasons for the lack of neural overlap at *a priori*-defined thresholds between the GM correlates of reading and attention.

4.1. Neural correlates of attention scores: The precuneus

The current study found an association between higher attention scores and increased GM in the left ventral precuneus extending bilaterally, though this association was driven by the older youth in our sample (13–18 years). The precuneus is associated with various aspects of cognitive control and executive function, such as task-switching (Worringer, Langner, Koch, Eickhoff, Eickhoff, & Binkofski, 2019), inhibition (Lei et al., 2015), and working memory (Mencarelli et al., 2019). GM alterations in the precuneus have previously been reported in ADHD populations compared to typically-developing controls (Wu et al., 2019; Vilgis et al., 2016; Carmona et al., 2005). Furthermore, a higher number of reported ADHD symptoms correlated with decreasing GM volume in the precuneus (Wu et al., 2019), the same directionality as reported in the current study.

Several studies have reported atypical activation patterns in the precuneus during executive function tasks in ADHD participants. Lei and colleagues (2015) reported precuneus

hyperactivation in their ADHD sample when performing inhibition tasks. Adults with ADHD have also exhibited hyperactivation in the precuneus during a task-switching paradigm compared to age- and education-matched controls (Dibbets, Evers, Hurks, Bakker, & Jolles, 2010). Conversely, children and adolescents with ADHD displayed less activation in the precuneus during executive function tasks compared to controls, as shown by a meta-analysis from Dickstein et al. (2006).

The ventral precuneus is also considered part of the Default Mode Network (DMN), a set of brain regions that show increased activation during times of mind wandering or passive mental states (Buckner, Andrews-Hanna, & Schacter, 2008; Margulies et al., 2009; Raichle, 2015; Uddin et al., 2008; Utevsky, Smith, & Huettel, 2014). Resting state fMRI studies indicate that the ventral precuneus is functionally connected to all other regions associated with the DMN, i.e. medial prefrontal cortex, posterior cingulate, and angular gyrus (Cauda et al., 2010; Zhang & Li, 2012). Functional connectivity between the ventral precuneus and other DMN brain regions is often disrupted in clinical disorders including ADHD (Broyd et al., 2009). Functional connectivity within the DMN, specifically with the precuneus, is often associated with directed attention and working memory, coinciding with attention weaknesses in ADHD. Moreover, there is evidence of altered functional connections between the precuneus and frontal regions in individuals with ADHD when compared to age-matched controls (e.g. Castellanos et al., 2008; Wu et al., 2019), consistent with the relationship between precuneus GM and attention scores in the current study.

VBM analyses comparing clinical ADHD samples and typically-developing controls have also reported converging GM differences in frontal regions of the brain, including superior frontal gyrus, orbitofrontal cortex, dorsolateral prefrontal cortex, and anterior cingulate cortex (e.g. Hoogman et al., 2019; Makris et al., 2013), as would be predicted from regions that support executive attention in neuroimaging studies (Smolker et al., 2015; Weise et al., 2019). While we did not find that GM in frontal regions correlated with attention scores at our *a-priori* defined threshold, at a more lenient, exploratory threshold ($p < 0.05$, $k > 239$) a cluster of GM in the middle frontal gyrus correlated with attention scores (Fig. 3).

4.2. Neural correlates of reading scores: The thalamus

We found an association between higher reading scores and increased GM volume in the thalamus bilaterally. While not traditionally considered part of the reading network, the thalamus is thought to support reading by relaying reading-relevant sensory information to cortical regions (Simon et al., 2013; Hoeft et al., 2007) and may also be associated with visual attention during reading (Koyama et al., 2011). The relationship between thalamic GM volume and reading scores was also present in both the younger (8–12 years) and older (13–18 years) cohorts when the whole group was subdivided by age.

Thalamic differences have been reported in reading disorders at different levels of analysis, from post-mortem studies (e.g. Galaburda, 1999) to neuroimaging analyses. In a recent meta-analysis, the left medial dorsal nucleus of the thalamus showed reduced GM in RD (McGrath & Stoodley, 2019). Decreased thalamic GM volume has been demonstrated in adult men diagnosed with RD compared to typical readers (Brown et al., 2001). Jednoróg et al. (2015) also found evidence of decreased thalamic GM volume in children with dyslexia

compared to typical readers across many languages. Interestingly, the latter thalamic coordinates overlap with the current study's thalamic cluster findings. Functional imaging studies also report thalamic activation differences in RD, though these findings are mixed. A meta-analysis reported hyperactivation in the left thalamus (pulvinar) in individuals with RD compared to a control group, and hypoactivation in the right lateral posterior thalamus (Maisog et al., 2008). Another meta-analysis by Richlan and colleagues (2009) reported hyperactivation in the left lateral dorsal thalamus of the RD group compared to controls. A more recent meta-analysis did not report any thalamic activation differences between the RD and control groups (Linkersdörfer et al., 2012).

In the current study, the peak thalamic coordinates were in the left medial pulvinar (PuM), which has been previously connected to phonological processing (Crosson, 1999), a cognitive-linguistic skill which is associated with RD (for reviews see D'Mello & Gabrieli, 2018; Peterson & Pennington, 2015). Consistent with this, the pulvinar is functionally connected with widespread areas in the superior temporal cortex (Guedj & Vuilleumier, 2020; Hwang et al., 2017; Johansen-Berg et al., 2005), which is often implicated in phonological processing weaknesses in individuals with RD (e.g. Linkersdorfer et al., 2012; Pugh et al., 2001; Temple et al., 2001).

The current study did not identify a relationship between reading scores and GM in other regions often implicated in RD, such as left temporoparietal and occipitotemporal cortices and bilateral cerebellum (Linkersdörfer et al., 2012; Richlan et al., 2013). This discrepancy might arise because previous studies have primarily focused on individuals meeting clinical criteria for RD, which sets up analyses to discover differences between groups rather than regions associated with dimensional variations in reading performance. Indeed, there is preliminary evidence that canonical regions associated with RD might not show linear associations with reading in unselected samples (Torre & Eden, 2019). That said, the largest VBM analysis of GM volumes in RD compared to typically-developing individuals (Eckert et al., 2016) also found no regions of reduced GM in RD when controlling for total GM volume. Similarly, Jagger-Rickels and colleagues (2018) also did not find many canonical reading brain regions in their VBM analysis when using a more lenient threshold for characterizing RD. Dimensional analyses including readers of a wide range of abilities might shed light on the discrepancies across studies analyzing the GM correlates of reading and RD (Torre & Eden, 2019).

4.3. Conjunction analysis: Regions where grey matter correlated with both reading and attention

The conjunction analysis did not reveal any brain regions associated with both reading and attention scores at our *a priori* statistical threshold ($p < 0.001$, FDR-corrected cluster $p < 0.05$), which was not surprising given the lack of overlap in the individual regression analyses. Because the goal of the study was to evaluate the overlap between GM correlates of reading and attention, we conducted an exploratory conjunction analysis for the purposes of hypothesis generation for future research. This exploratory conjunction analysis at a more liberal threshold revealed regions in the precuneus and right caudate where GM was associated with both reading and attention scores.

The only other study looking at overlapping GM correlates of typical reading and attention in a sample of 6–12 year-old children did not report similar results, but rather identified regional overlap in the left middle frontal gyrus that was associated with both reading and attention scores (Wang et al., 2022). This discrepancy could be due to a variety of reasons, such as the different age ranges, participants' language (logo-graphic vs alphabetic), how attention was quantified, or range of abilities in the samples. In this study, at the more lenient thresholds in the whole group analysis, we also see visual overlap between the GM correlates of reading and attention in the middle frontal gyrus, though in a region inferior to that reported in Wang et al. (2022). When we visualize the overlap within the younger cohort, which is more closely matched in age with the Wang et al. (2022) study, we see convergence in a similar region of the middle frontal gyrus, albeit with unthresholded maps. It is notable that neither study identified extensive overlap between the GM correlates of reading and attention at the corrected statistical thresholds used in the primary analyses.

We reported some developmental differences in the conjunction results in the younger (8–12 years old) and older (13–18 years old) cohorts. While findings in the older group reflected our whole-group conjunction results, the younger group did not show any regions of reading/attention overlap, even at a more lenient threshold. This could be an issue of statistical power, since there were more participants in the older age group than the younger ($n = 206$ vs 124). When we look at unthresholded maps, the younger group shows overlap in the left caudate and the precuneus, similar to the whole-group results. Alternatively, attention- and reading-related brain networks include regions that are among the latest to develop and mature (Bethlehem et al., 2022) which may account for the differences in the current study's conjunction results between the younger and older groups.

While there is limited research investigating the overlapping neural correlates of RD and ADHD, the few existing studies have pointed to the caudate as a region of shared neural differences. A recent VBM meta-analysis from our group revealed the right caudate as the only area of conjunction between regions of reduced GM in RD and ADHD (McGrath & Stoodley, 2019). Additionally, Jagger-Rickels and colleagues (2018) compared RD children, ADHD children, and comorbid RD-ADHD children to age-matched typically-developing children and found reduced GM in the right caudate of each clinical group. Further, Goradia and colleagues (2016) found evidence of surface compression of the caudate in comorbid RD-ADHD boys and ADHD-only boys compared to typically developing controls, though this result was not seen in the RD-only boys.

In the current study, the peak coordinates for the conjunction analysis were in the head of the caudate, an area which has repeatedly been associated with cognitive tasks, such as executive function and working memory tasks (for meta-analyses see Arsalidou, Deuren, & Taylor, 2012; Robinson et al., 2012). This region also has anatomical projections to the prefrontal cortex, an area important for executive function (Robinson et al., 2012). In line with analyses of comorbidity at the cognitive level, it has been proposed that executive functions represent potential shared cognitive risk factors for RD and ADHD (Kibby et al., 2021; McGrath et al., 2011; Willcutt et al., 2005). The head of the caudate is therefore a potential area of interest in the investigation of the neural correlates of both RD and ADHD.

The exploratory conjunction analysis also revealed conjunction of the GM correlates of reading and attention in the precuneus. Structural imaging studies of comorbid RD and ADHD have not reported GM differences in the precuneus, although functional imaging studies have implicated the precuneus in both reading and attention (e.g. in reading, Bonhage et al., 2015; Maisog et al., 2008; in attention, Dibbets et al., 2010; McKenna et al., 2017), and both RD and ADHD groups compared to controls showed increased GM volumes in the right precuneus (McGrath & Stoodley, 2019). Another group has reported decreased white matter (WM) volumes in the right precuneus of children with RD compared to age- and reading-level matched children (Xia, Hoeft, Zhang, & Shu, 2016). The precuneus shows increased activation when reading words compared to reading pseudowords in typical readers (Taylor, Rastle, & Davis, 2013) and hypoactivation of a network involving the precuneus was seen in readers with dyslexia during semantic processing (Paz-Alonso et al., 2018). Furthermore, the precuneus is engaged when performing executive function tasks (McKenna, Rushe, & Woodcock, 2017), and has also been implicated in ADHD. It is possible that the precuneus supports shared cognitive processes (e.g. executive function) that are relevant to both reading and attention.

Interestingly, the regions implicated in the conjunction analysis have been shown to be functionally linked (Di Martino et al., 2008). Using the peak caudate coordinates from the conjunction analysis, we generated a meta-analytic coactivation map in the Neurosynth database (<https://neurosynth.org>; Yarkoni et al., 2011). Our precuneus cluster from the conjunction analysis overlapped with the meta-analytic coactivation map from the right caudate coordinates. The correlations between GM and reading *and* attention scores in this network indicate that these structural differences might reflect functional differences in a basal ganglia-cortical network critical for both reading and attention. Future work should determine if there is a link between this network, shared cognitive components of reading and attention skills, and RD-ADHD comorbidity.

4.4. Limited overlap between correlates of reading and attention

Several factors might explain the lack of overlap between the neural correlates of reading and attention at our *a priori* statistical threshold. The VBM analysis provided a metric of GM volume, and it is possible that the neural overlap between reading and attention is better measured by another imaging modality, such as functional neuroimaging, including task-based and functional connectivity approaches. Visual inspections of meta-analyses separately investigating functional neural correlates of task-based attention and reading suggest overlap in the middle frontal gyrus, precuneus, and cerebellum (for reading, see Martin et al., 2015; Pugh et al., 2001; Taylor et al., 2013; Turkeltaub et al., 2002; for attention, see Kerren-Happuch et al., 2014; McKenna et al., 2017; Niendam et al., 2012), only one of which (precuneus) was found in the current VBM analysis. Also, while there is moderate agreement between reports of structural and functional alterations in the reading and attention disorder literature, there is not complete agreement in the findings emerging from these different modalities (for reading, see Linkersdorfer et al., 2012; for attention, see Wu et al. 2019).

Overlap in regional GM associated with reading and attention also might have been limited by the behavioral measures used in the current study. For example, the PNC dataset used a clinical interview assessing inattention symptoms which included six of nine inattention symptoms from the DSM-IV. In addition, the reading measure consisted of only the untimed, single-word reading subtest of the WRAT-4 which does not capture the full spectrum of reading skills, such as reading speed or comprehension.

4.5. Limitations

The current results should be considered in the context of several limitations. First, strict quality control for motion artifacts led to the exclusion of a large portion of participants from the original dataset (see Fig. 1). Motion artifacts are a common feature of imaging in pediatric populations and can lead to false positives in VBM analysis (Reuter et al., 2015). This amount of exclusion is consistent with image removal in other developmental imaging studies (e.g. Koldewyn et al., 2014; Moore, D’Mello, McGrath, & Stoodley, 2017), and is a limitation of VBM analyses in developmental populations.

Second, the conjunction analysis must be considered exploratory, given that the results are reported at a more lenient threshold. Our goal here was to determine any potential regions of neural overlap in this cohort to establish a starting point for future investigations into overlapping neural correlates of single-word reading and behavioral attention.

The current study also did not identify a relationship between behavioral performance and GM in regions traditionally associated with reading or attention. As mentioned previously, this could be related to the dimensional measurement of reading and attention, rather than the more typical group-based comparisons of children with and without a clinical disorder. It is also important to note that most network mapping stems from functional neuroimaging studies, and, while there is some overlap, these results do not necessarily map one-to-one with brain regions identified in anatomical neuroimaging (e.g. Yan et al., 2021).

Finally, our analyses did not extensively examine the effects of age on the relationship between GM and behavioral performance. It is possible that this relationship differs throughout development (e.g. Moore et al., 2017), reflecting the nonlinear patterns of GM volume throughout the age range of our participants (e.g. Giedd, 2004). While we controlled for age and age² in our regression models and also ran the same analyses in two age subgroups of our full sample, further investigation into developmental effects is needed. Given that there can be differences in the structural correlates of RD and ADHD in youth vs adults (e.g. Frodl & Skokauskas, 2012; Martin et al., 2015), this is an important direction for future research.

4.6. Future directions

The results of this study identified regions where GM correlates with single-word reading and behavioral attention scores in a population-based sample of youth and reveal several regions that might be relevant in the future investigation of the neural underpinnings of comorbid reading and attention disorders. The functional connectivity between the caudate and precuneus is of interest for future imaging studies of comorbid RD and ADHD, as these regions were associated with both reading and attention scores in the exploratory

conjunction analysis. Future work should aim to connect these neuroimaging findings with existing cognitive work on the shared neural underpinnings of reading and attention and RD-ADHD comorbidity. For example, processing speed and executive functions have been identified as shared cognitive risk factors for RD and ADHD that explain a portion of their comorbidity (McGrath et al., 2011; Moura et al., 2017; Peterson, et al., 2017; Shanahan et al., 2006; Willcutt et al., 2005). Future studies should assess whether the structural and/or functional integrity of the regions implicated by the conjunction analysis (precuneus and right caudate) are significantly associated with these cognitive constructs. Given that RD and ADHD share genetic risk factors (Willcutt et al., 2007; Willcutt et al., 2010), another future direction is to consider imaging genetic approaches that link polygenic scores with shared cognitive and neural correlates of reading and attention skills (McGrath, 2018). The publicly-available PNC dataset is particularly well-positioned for such analyses because of its large size and the availability of high-quality cognitive, behavioral, imaging, and genetic information. Together, these future directions would advance our understanding of the relationship between reading and attention at multiple levels of analysis.

5. Conclusions

This is the first study utilizing a population-based, dimensional dataset of youth to investigate the shared GM correlates of single-word reading and behavioral attention scores to elucidate potential neural underpinnings contributing to comorbid reading and attention disorders. There was a lack of overlap between neural correlates of reading and attention with conservative thresholding, but exploratory analyses revealed overlap in the right caudate and precuneus. There is converging evidence across studies that the caudate is a shared region of interest implicated in both RD and ADHD that may contribute to their comorbidity. The precuneus awaits further replication, but is functionally connected to the caudate, and this network could underpin shared cognitive factors associated with both reading and attention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Data will be made available on request.

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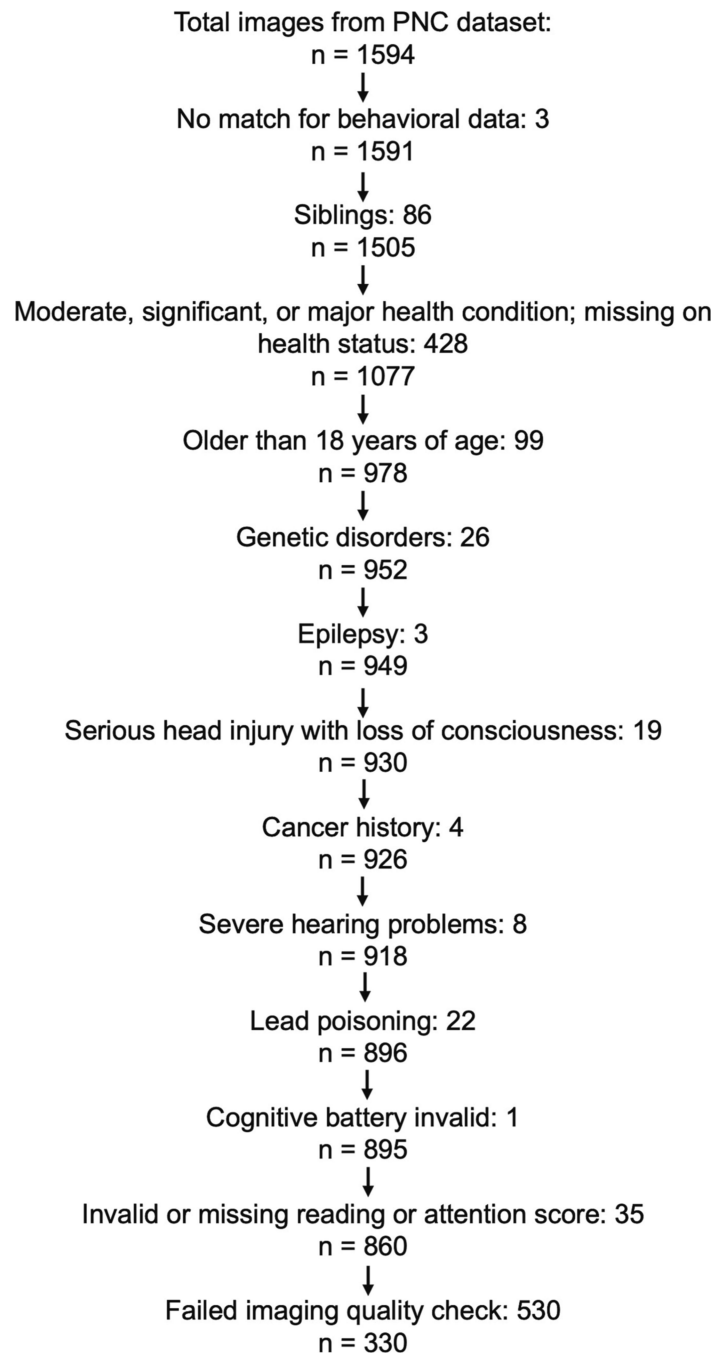


Fig. 1. Final study sample.

Imaging quality check exclusions were based on a visual inspection to determine if there was consistent and clear differentiation of white matter (WM) and grey matter (GM).

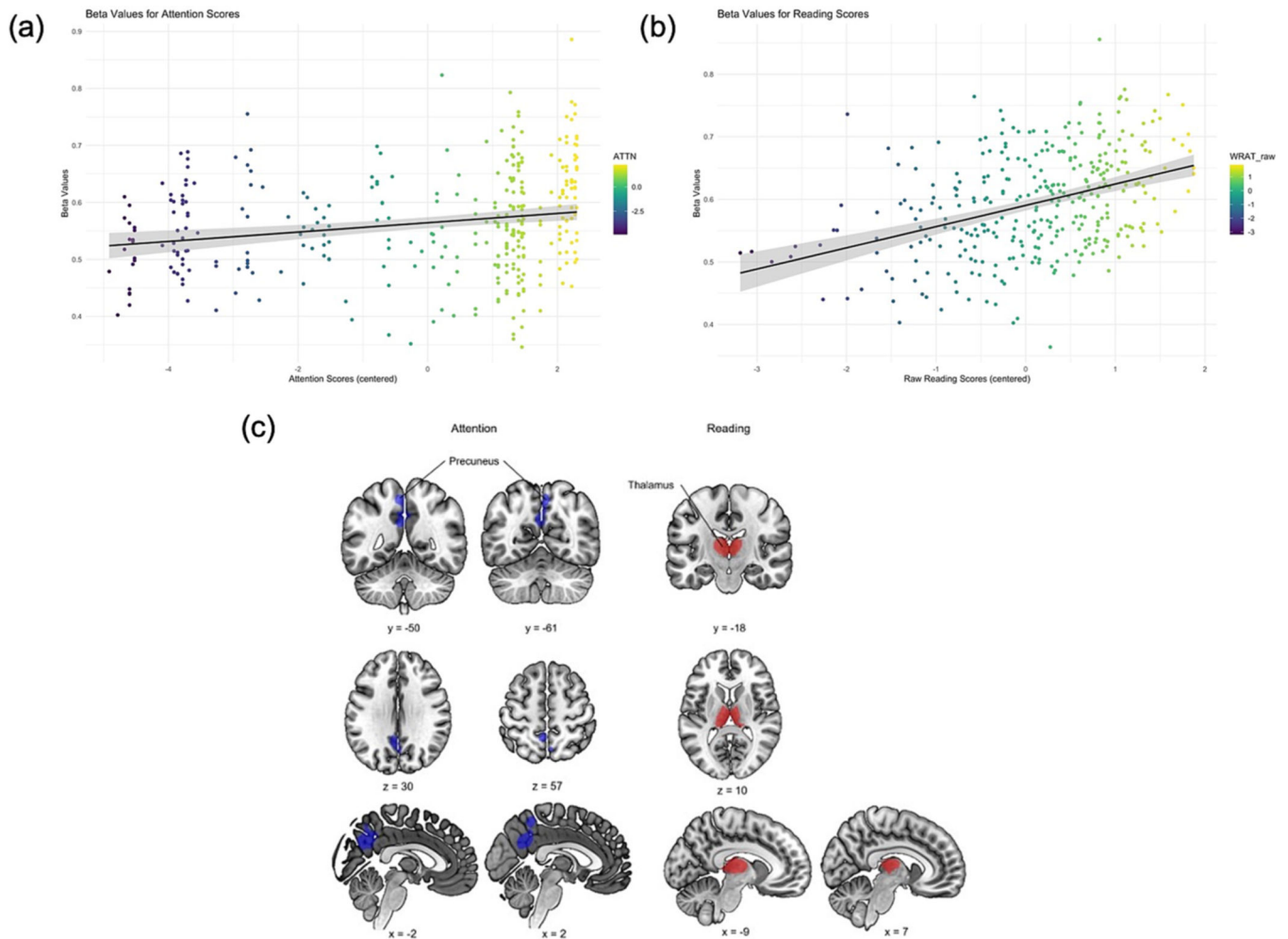


Fig. 2. VBM analyses of attention and reading.

(a) Correlation between attention scores and GM volume in left precuneus ($-4, -57, 28$), $r = 0.21$. (b) Correlation between reading scores and GM volume in left thalamus ($-6, -24, 15$), $r = 0.39$. (c) Regions where higher attention and reading scores were associated with greater GM. Better attention scores were associated with greater GM in the precuneus (blue) and higher reading scores were associated with greater GM in the thalamus (red), $p < 0.001$, FDR corrected $p < 0.05$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

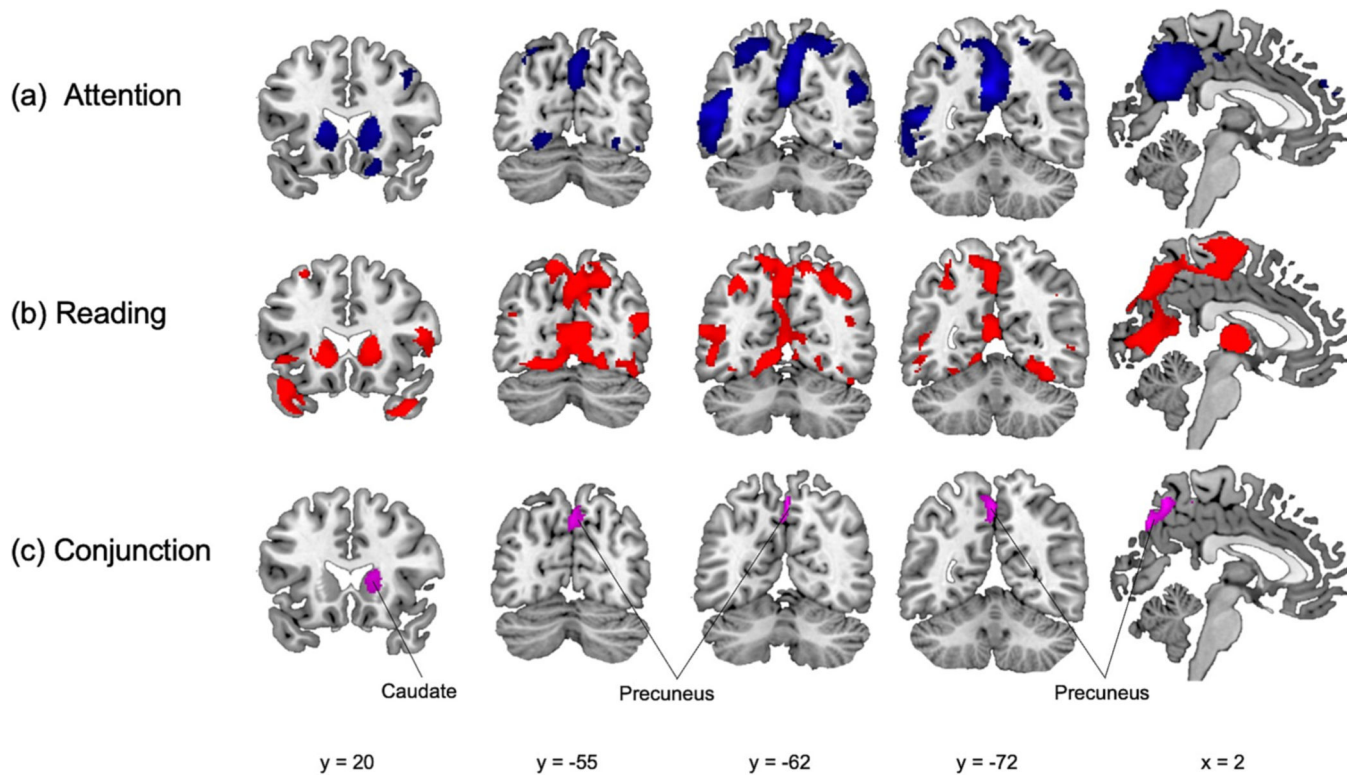


Fig. 3. Conjunction analysis: Regions showing GM associated with reading scores \cap GM associated with attention scores. (a) and (b) GM regions showing significant relationships with attention (a) and reading scores (b) are shown at an exploratory threshold of $p < 0.05$, $k > 239$. (c) Conjunction analysis revealed statistical convergence in the right caudate and right precuneus, $p < 0.05$, $k > 239$.

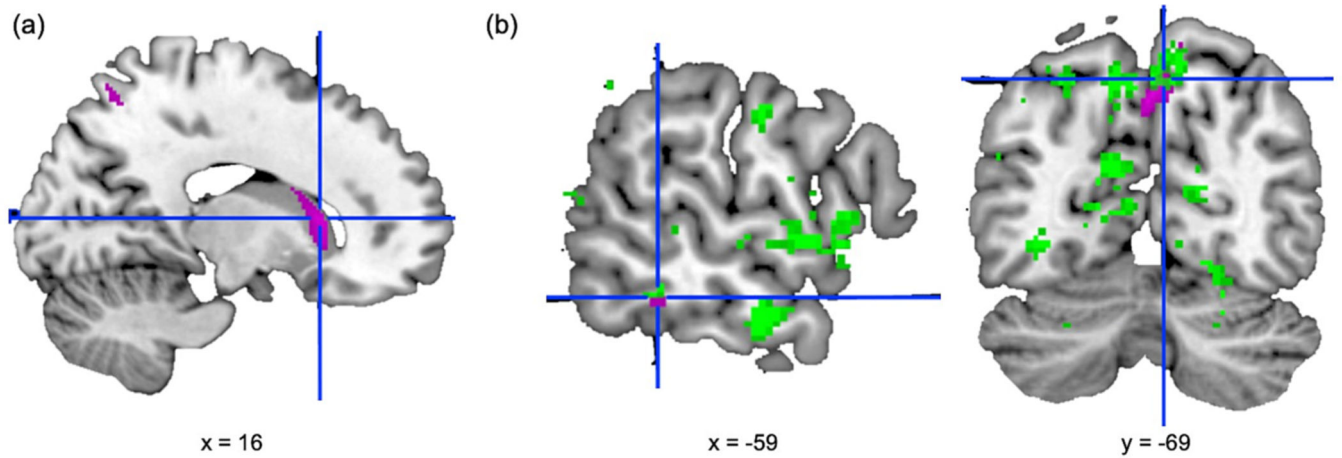


Fig. 4. Neurosynth meta-analytic co-activation map reveals that the caudate and precuneus are part of a functional network.

(a) Location of our R caudate cluster from conjunction analysis; seed was placed at peak R caudate coordinates (15, 20, 9). (b) Overlap of the current study's R Precuneus conjunction results (pink) and Neurosynth's meta-analytic coactivation map with the R caudate cluster (green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

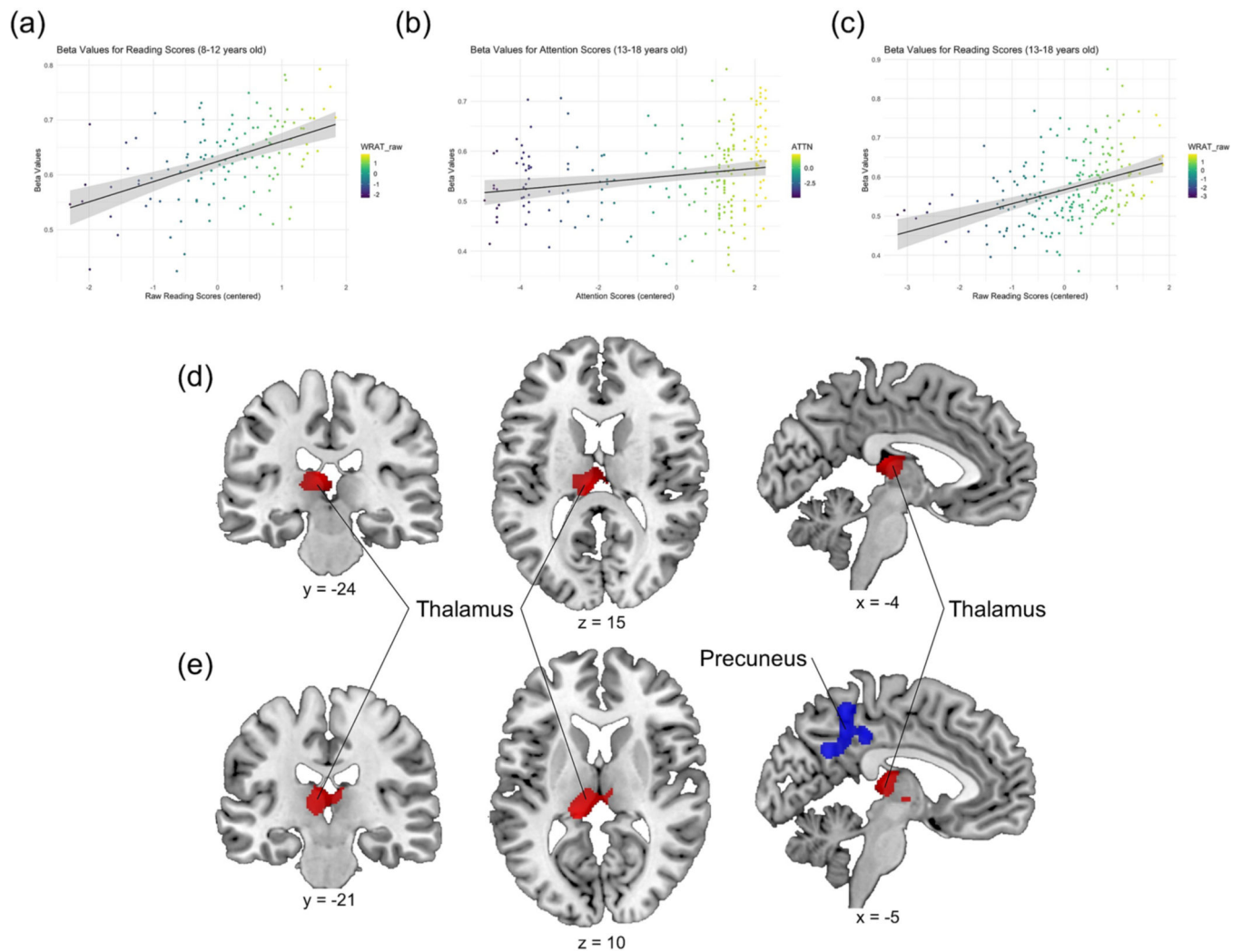


Fig. 5. VBM analyses of attention and reading in younger and older age groups.

(a) Correlation between reading scores and GM volume in left thalamus (peak at $-4, -24, 15$) in the younger age group, $r = 0.48$. (b) Correlation between attention scores and GM volume in left precuneus (peak at $-3, -36, 40$) in the older age group, $r = 0.20$. (c) Correlation between reading scores and GM volume in left thalamus (peak at $-14, -33, 9$) in the older age group, $r = 0.40$. Note that this cluster was marginally significant (uncorrected voxel-level $p < 0.001$, cluster-level FDR corrected $p = 0.069$). (d) Younger age group results; regions where higher reading scores were associated with GM volume in the thalamus, $p < 0.001$, FDR corrected $p < 0.05$. (e) Older age group results; regions where higher reading scores were associated with GM volume in the thalamus (red), $p < 0.001$, FDR corrected $p = 0.069$, and regions where higher attention scores were associated with GM volume in the precuneus (blue), $p < 0.001$, FDR corrected $p < 0.05$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Participant demographics.

	N		
Total	330		
	Mean	SD	Range
Age (years)	13.4	3.06	8–18
	N	%	
Sex			
Male	156	47.3 %	
Female	174	52.7 %	
Race			
European American	169	51.2 %	
African American	126	38.2 %	
Multiracial *	27	8.2 %	
Chose to self-describe race	6	1.8 %	
Missing	2	0.6 %	
Highest parental education			
High school or less	71	21.5 %	
Some college	73	22.1 %	
College graduate	101	30.6 %	
Greater than college	82	24.8 %	
Missing	3	1 %	
Handedness **			
Right	284	86.1 %	
Left	44	13.3 %	
No response	2	0.6 %	
	Mean	SD	Range
Task scores			
WRAT-4 Reading subscale ***	104.3	15.9	71–145
Number of clinically significant symptoms of inattention ****	1.9	2.3	0–6

* Participant was considered multiracial if they identified as any combination of African American, American Indian or Alaska Native, Asian, European American, Hispanic/Latino, Native Hawaiian/Pacific Islander, or Other.

** Handedness was determined through the Finger Tapping Test in which participants had to press a spacebar with their dominant and non-dominant hand. Reported here are the dominant hands.

*** Standardized scores based on a mean of 100 and SD of 15. Standardized scores are presented here for ease of interpretation, but raw scores were used in analyses.

**** Participant could have up to six clinical symptoms of inattention.

Table 2

GM correlates of reading and attention scores.

	Region	Cluster size (k)	Max <i>T</i> -value	Cluster <i>p</i> -value (FDR corrected)	Peak voxel <i>p</i> -value (uncorrected)	Peak MNI coordinates (x y z)
Regression with attention *	L Precuneus	1461	4.66	0.007	< 0.001	-4 -57 28
Regression with reading *	L Thalamus	2733	5.73	0.001	< 0.001	-6 -24 15
Conjunction: reading and attention **	R Precuneus	604	2.50	0.987	0.006	2 -62 52
	R Caudate	334	2.06	0.987	0.020	15 20 9

* $p < 0.001$, FDR cluster corrected $p < 0.05$.** $p < 0.05$, $k > 239$.

Table 3

GM correlates of reading and attention scores in younger and older age groups.

Region	Cluster size (k)	Max <i>T</i> -value	Cluster <i>p</i> -value (FDR corrected)	Peak voxel <i>p</i> -value (uncorrected)	Peak MNI coordinates (x y z)
8–12 years old					
Regression with attention*	None				
Regression with reading*	L Thalamus	5.02	0.035	< 0.001	-4 -24 15
Conjunction****	None				
13–18 years old					
Regression with attention*	L Precuneus	4.17	0.005	< 0.001	-3 -36 40
Regression with reading**	L Thalamus	4.22	0.069	< 0.001	-14 -33 9
Conjunction***	L Precuneus	2.67		0.004	-8 -60 30
	L Middle Temporal Gyrus	2.54		0.006	-54 -58 9
	L Middle Temporal Gyrus	2.47		0.007	-66 -48 -6
	R Middle Temporal Gyrus	2.39		0.009	62 -40 -15
	R Precuneus	2.29		0.011	2 -62 54
	L Precuneus	2.18		0.015	-3 -69 -45
	R Superior Parietal Lobule	2.09		0.019	28 -62 58
	R Fusiform	2.09		0.019	33 -69 -10
	R Inferior Temporal Gyrus	2.02		0.022	62 -6 -32
	L Caudate	1.96		0.025	-16 22 2
	R Caudate	1.89		0.029	14 16 12

* $p < 0.001$, FDR cluster corrected $p < 0.05$.** $p < 0.001$, FDR cluster corrected $p = 0.069$.*** $p < 0.05$, $k > 78$.**** $p < 0.001$, FDR cluster corrected $p < 0.05$ AND $p < 0.05$, $k > 138$.