Cerebellar Gray Matter Volume and its Role in Executive Function, and Attention: Sex Differences by Age in Adolescents

Hayeon Kim1,*, Bumhee Park2,3,*, Shin-Young Kim1, Jiyea Kim1, Bora Kim1, Kyu-In Jung1, Seung-Yup Lee1, Yerin Hyun1, Bung-Nyun Kim4, Subin Park5, Min-Hyeon Park1

1Department of Psychiatry, Eunpyeong St. Mary’s Hospital, The Catholic University of Korea, Seoul, 2Department of Biomedical Informatics, Ajou University School of Medicine, 3Office of Biostatistics, Ajou Research Institute for Innovative Medicine, Ajou University Medical Center, Suwon, 4Department of Psychiatry and Behavioral Science, Seoul National University College of Medicine, 5Department of Research Planning, National Center for Mental Health, Seoul, Korea

Objective: This research measures the regional GMV (rGMV) of the cerebellum, attention, Executive Function (EF) and we aimed to identify their correlation and sex differences in children and adolescents.

Methods: Subjects comprised 114 children (male = 62, female = 52, 12.44 ± 2.99 years old) from South Korea. Participants were divided into three groups by age (age 6−9, 10−13, and 14−17). The Stroop Color and Word Test (SCWT), Wisconsin Card Sorting Test (WCST), and Advanced Test of Attention (ATA) were used to estimate executive function. Magnetic resonance imaging (MRI) images were analyzed with Regional Voxel-Based Morphometry Analysis.

Results: The correlations between cerebellar rGMV and SCWT, WCST, and ATA subcategories showed difference by age and sex. In 6−9 age group, girls showed more overall correlations with cerebellar regions than boys, in WCST Categories Completed and ATA results. In age 10−13 group, more regions of cerebellum corresponded to SCWT subcategories in girls. Nevertheless, more correlation between cerebellar rGMV, WCST subcategories and some ATA subtests were observed in boys in the same age group. In the adolescent group, aged 14−17, boys showed more correlation with cerebellar rGMV, while girls showed little correlation.

Conclusion: This study highlights that sex-different cerebellum maturation in adolescence might be correlated with EF and attention. These results provides evidence that cerebellum modulates higher cognitive functioning during child development.

KEY WORDS: Adolescent; Child; Cerebellum; Executive function; Attention; Magnetic resonance imaging.

INTRODUCTION

The cerebellum is well established for its role in movement and motor skills. There is much evidence that the cerebellum is important in mental functions such as cognition, language, learning, social cognition, and affective function. Various neuroimaging, anatomical and clinical studies support the idea that the cerebellum is a critical site for executive functioning. In anatomical studies, the cerebellum has been shown to interact with prefrontal and parietal association cortices, areas that are well known to be related to cognition. Cerebello-thalamo-cortical and cortico-ponto-cerebellar loops are assumed to be associated with cognitive areas [1-3].

Additionally, Stoodley and Schmahmann [4] presented a meta-analysis study that provided neuroimaging evidence that supports the notion that the cerebellum is associated with cognitive function. Keren-Happuch et al. [5] assessed the literature that included positron emission tomography (PET) and functional MRI (fMRI) studies of cerebellar structures. Studies have consistently found that the left lobule VIIIB is activated more during executive function (EF) tasks than language, timing, and working memory tasks [5], even though EF overlaps with other domains, in-
cluding working memory, emotion and language. Greater activation of crus 1 and 2 regions during EF tasks compared to other cognitive domains establish an association of cerebellar regions with EF [1,6,7].

Clinical data have demonstrated that the cerebellum is related to EF and cognition. Cerebellar disorders in childhood and adolescence influence higher cognitive functions, including language, learning, visuospatial organization, and EF, and affective symptoms [8,9]. Cerebellar cognitive affective syndrome (CCAS) has been well studied: damage in the cerebellum results in impairments in EF, attention, behavior and personality [8]. The cerebellum is thought to be associated with cortical areas controlling the speed, timing, and attentional process [10,11]. In addition to higher cognition, the cerebellum is assumed to affect error processing and, therefore, modulate attention networks [12]. Attention is known to be associated with brain activity, supported by significant changes in event-related potential and quantitative electroencephalography in Attention Deficit-Hyperactivity Disorder (ADHD) children and adolescents [13,14]. Neuroimaging studies have found that reduced cerebellar vermal volume and decreased cerebellar activation are associated with inattention in children with ADHD [15-17]. Boys with ADHD showed significant cerebellar volume reductions mainly in the posterior inferior lobe (lobules VIII to X) after adjusting for total brain volume and IQ. Attention also improves with age. Studies have shown improvements in all areas of attention as children age, and development takes place faster at earlier ages [18].

Frontal lobe myelination occurs until the age of 15, and brain development continues as children grow older [19]. Additionally, brain morphometric measures are highly variable from person to person, and there is considerable overlap between male and female groups [20]. Tiemeier et al. [21] studied cerebellar development in a young population and showed that total cerebellar volume followed an inverted U-shaped curve with age; the trajectory peaked at 11.8 years of age in girls and 15.6 years in boys. This showed that males show later development in cerebellar volume than females.

Clinical reports have suggested that EF increases during childhood [22] and have shown sex differences. Girls initially scored lower in some subcategories of EF measures. However, in early adolescence, girls outperform boys, and this altered pattern was maintained through later adolescence.

As attention and executive functions develop by age with cerebellar maturation, the present study measured regional gray matter volume (rGMV) of the cerebellum, EF, and attention, and we aimed to identify the correlations among these variables and sex differences in children and adolescents.

**METHODS**

**Participants**

We recruited children and adolescents aged 6 to 17 years through a flyer posted in schools and libraries in Seoul and Gyeonggi-do Province. In addition to flyers, participants were recruited from one middle school and one senior high school in Seoul, South Korea. Children with any history of neurological disorders, including cerebral palsy, brain injury, and convulsive disorder, were excluded. Additionally, we excluded participants with psychiatric disorders (e.g., bipolar disorder, schizophrenia, or pediatric psychosis), developmental disorders (e.g., autism spectrum disorder or intellectual disability), language disorders, learning disabilities, or uncorrected sensory impairment.

A total of 150 participants (age = 11.9 ± 3.1; male [M] = 79, female [F] = 71) were enrolled in the study. This study was approved by the Institutional Review Board (IRB) for Human Subjects at Seoul National University Hospital (No. C-1412-081-633) and conducted in accordance with the Declaration of Helsinki. All participants and their parents or legal guardians provided written informed consent.

Of the 150 children who participated in the study, 36 subjects were excluded from the study because of failure to complete the questionnaires, executive function test, continuous performance task (CPT), or magnetic resonance imaging (MRI) scans. In this study, data for a total of 114 subjects (M = 62, F = 52; 12.44 ± 2.99 years) were finally analyzed.

We analyzed the data by dividing the participants into three age groups (6−9 years old, 10−13 years old, 14−17 years old), which was based on a previous study showing that cerebellar development differed by age and sex in adolescents [21].
Measures
We used the Stroop color and word test (SCWT) and Wisconsin card sorting test (WCST) to measure EF and the Advanced Test of Attention (ATA), a type of CPT, to measure attention. MRI images were acquired, and regional voxel-based morphometry (VBM) analysis was performed. The process resulted in 26 sites in the cerebellum (8 vermian regions and 9 lobular regions in each hemisphere).

Stroop Color and Word Test
The Stroop color and word test [23], also known as the Stroop test or the SCWT, was used to measure EF in this study. The stimuli were arranged in a 5 × 20 question matrix; the words ‘red’, ‘green’ and ‘blue’ were randomly arranged, and another page had 100 questions printed in red, green, and blue. The last color-word page included a mixture of the questions on the previous two pages, and the subjects were required to read along the rows or columns of each page.

The subjects were required to read the three different tables as quickly as they could. Two tables represented the ‘congruous condition’ in which the participant had to read the color name (called a color word) printed with black ink (W) and name the other color patch (C). In contrast, in the third table, color words were printed with incongruent color ink (for example, the word "red" is printed with green ink). This was named the color word (CW) condition. Under these unfavorable conditions, the participants had to name the color of the ink instead of reading the word.

The program calculated T scores (mean = 50, standard deviation [SD] = 10), i.e., WT, CT, and CWT, which represent the time to complete the W, C, and CW tables. Stroop_CWT indicates the converted T score from the CW raw score. Stroop_C_CW_T is an interference score, which is the T value of the raw score of C minus the raw score of CW.

Wisconsin Card Sorting Test
The WCST is an acknowledged measure of EF. In this study, we used a computerized version of the WCST. The participants had to match response cards to the four stimulus cards along three dimensions (color, form, and number). The computerized program calculated T scores (mean = 50, SD = 10) for total errors (TE), perseverative responses (PR), perseverative errors (PE), nonperseverative errors (NPE), raw scores for categories completed (CC), and failure to maintain set (FMS).

The total number of perseverative and nonperseverative errors was measured as TE. PR measured the number of responses that were perseverative, regardless of the feedback. PE indicated the inability to change responses patterns, suggesting a tendency towards perseveration. NPE reflected the number of errors that were not perseverative. CC was the number of times that there were 10 correct responses in succession. FMS was the number of times subjects made an error after 5−9 consecutive correct responses. FMS indicates the efficiency of sorting. With FMS, lower scores reflect higher function on each subscale, whereas with the other categories, including the subscales calculated by T scores, higher scores mean higher function on each subscale.

Continuous Performance Test
The ATA is a CPT consisting of auditory and visual stimulation tests and takes 15 minutes to complete. The ATA was developed to measure attention and response inhibition in Korean children over five years old. The presentation ratio of the target stimulus was 22% for the first section, 50% for the middle section, and 78% for the last section. The stimulus presentation time was 100 ms, and the interval between the presentations was 2,000 ms [24]. The ATA provides four variables as age-adjusted T scores: omission errors (OE), commission errors (CE), mean reaction time (RT), and response time variability (RTv). An omission error represents a patient not responding to a target stimulus that should have resulted in a response. This measures the patient’s sustained attention. A commission error indicates a patient responding to a nontarget stimulus, and this is an indication of impulsivity, self-regulation, and inhibitory control. The mean reaction time reflects the response preparation components of EF. The response time variability measures inconsistency in the patient’s responses.

Based on the ATA guidelines, a T score above 65 on these test variables indicates ADHD. Therefore, we used a T score of 65 as our cutoff score to distinguish between normal and abnormal performances.

Magnetic Resonance Imaging Data Acquisition
A 3.0 Tesla MRI scanner (MAGNETOM Tim Trio; Siemens Medical Solutions, Erlangen, Germany) was used
to obtain MRI images. High-resolution T1-weighted images were acquired from each participant using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) pulse sequence (repetition time = 1,900 ms; echo time = 3.13 ms; flip angle = 9°; matrix size = 256 × 256; field of view = 230 × 230 mm²; thickness = 0.9 mm). Artifacts related to head motion during scanning were minimized by using foam pads.

Regional Voxel-Based Morphometry Analysis

In this study, we performed a VBM analysis using the SPM12 VBM-DARTEL procedure (SPM12, http://www.fil.ion.ucl.ac.uk/spm/; Wellcome Trust Centre for Neuroimaging, London, UK) [25]. This results in a clearer segmentation and better registration with regard to boundaries between different tissues compared with previous optimized VBM [25,26].

No artifacts or abnormalities from motion were found by T1-weighted images, which were inspected by a well-trained physician. The preprocessing procedure for T1-weighted images included (i) manual reorientation to the anterior commissure; (ii) gray matter segmentation based on a standard tissue probability map provided by SPM; (iii) creation of a study-specific template, spatial normalization with DARTEL to normalize individual images to the DARTEL template, and modulation to adjust for volume signal changes during spatial normalization; and (iv) spatial smoothing of the gray matter partitions with a Gaussian kernel of 8 mm full width at half maximum. After the preprocessing was performed, cerebellar rGMV values were extracted from 26 sites (8 vermal regions and 9 lobular regions in each hemisphere), which were defined by an automated anatomical labeling (AAL) atlas [27].

In this study, we introduced a standard adult SPM template instead of an age-specific template [28]. Previous neuroimaging studies of brain development have suggested that neuroanatomical differences between adults and children did not affect the results when adult templates were used [29-33]. The use of the standard adult SPM template allowed us to compare or combine the results from previous studies with adults or other age groups [34-36].

Statistical Analysis

Partial correlation analyses (covariates: age, total intracranial volume [TIV], and IQ) were conducted to investigate associations of each rGMV with 18 clinical variables for the three age groups (group 1: age ≤ 9, group 2: 10 ≤ age ≤ 13, group 3: age ≥ 14) of boys and girls separately. Then, we compared the partial correlation values between the values of boys and girls for each age group. For this analysis, correlation values for each group were transformed to normal distributed values (i.e., \( Z_{Boys} = 0.5 \times [\log(1 + R_{Boys}) - \log(1 - R_{Boys})] \) and \( Z_{Girls} = 0.5 \times [\log(1 + R_{Girls}) - \log(1 - R_{Girls})] \) as Fisher’s r-to-z transformation). After z-transformation, we compared them with \( Z = (Z_{Boys} - Z_{Girls}) / \sqrt{\frac{1}{N_{Boys} - 3 - M} + \frac{1}{N_{Girls} - 3 - M}} \), where \( N_{Boys}, N_{Girls}, \) and \( M \) each represent the sample size for each group and the number of covariates used in partial correlation analyses. Correlations between boys and girls for each age group were compared at 3 threshold levels: \( p < 0.001 \) (high difference), \( p < 0.01 \) (moderate difference), and \( p < 0.05 \) (weak difference or trend). All statistical analyses were performed using MATLAB-based custom software (Mathworks, Sherborn, MA, USA) and SPSS 20.0 for Windows (IBM Co., Armonk, NY, USA).

RESULTS

Demographic and Clinical Characteristics of the Participants

The participants were distributed into three age groups based on the well-known child/adolescent developmental trajectory of the cerebellum. There were no significant differences in IQ and TIV according to age among the three age groups. A total of 114 children completed the Stroop test and WCST for the assessment of executive function. Four subcategory results from the Stroop test were measured and are presented as T scores: Stroop_WT, Stroop_CT, Stroop_CWT, and Stroop_C_CW_T. Six items from the WCST were calculated as T scores: WCST_TE, WCST_PR, WCST_PE, WCST_NE, WCST_CC, and WCST_FMS. The participants performed ATA audio (ATAa) and visual (ATAv) assessments. Four variables from the ATA are presented as ATA_OE, ATA_CE, ATA_RT, and ATA_RTv in this article.

These data are illustrated in Table 1. Our regions of interest (ROIs) in the cerebellum included 26 regions (Fig. 1). In this study, we distinguished the cerebellum in 10 lobules (left and right) and 10 vermal...
Table 1. Demographic and clinical data according to age and sex

| Characteristics | Age 6−9 (n = 24) | Age 10−13 (n = 42) | Age 14−17 (n = 48) | Total (n = 114) |
|-----------------|------------------|--------------------|--------------------|----------------|
|                 | Male (n = 13)    | Female (n = 11)    | Male (n = 19)      | Female (n = 23) |
| Age             | 7.85 ± 1.21      | 8.18 ± 0.75        | 11.74 ± 1.33       | 11.74 ± 1.18    |
| IQ              | 97.85 ± 21.02    | 110.27 ± 13.17     | 103.21 ± 14.50     | 104.91 ± 18.53  |
| TIV             | 1.47 ± 0.12      | 1.37 ± 0.07        | 1.46 ± 0.12        | 1.41 ± 0.13     |
| Stroop_WT       | 42.08 ± 20.65    | 38.55 ± 23.52      | 54.47 ± 20.97      | 57.43 ± 19.47   |
| Stroop_CT       | 50.62 ± 17.10    | 46.00 ± 7.94       | 51.63 ± 14.64      | 60.09 ± 22.24   |
| Stroop_CWT      | 50.15 ± 24.38    | 55.45 ± 12.25      | 53.79 ± 20.84      | 60.26 ± 22.66   |
| Stroop_C_CW_T   | 50.85 ± 19.96    | 56.82 ± 10.58      | 58.21 ± 15.88      | 64.30 ± 15.53   |
| WCST_TE         | 40.15 ± 10.33    | 37.82 ± 22.59      | 49.16 ± 12.45      | 52.26 ± 14.06   |
| WCST_PR         | 48.23 ± 10.86    | 43.55 ± 23.29      | 50.21 ± 11.09      | 56.91 ± 11.42   |
| WCST_PE         | 44.00 ± 10.47    | 41.09 ± 21.85      | 47.42 ± 11.66      | 52.65 ± 12.90   |
| WCST_NPE        | 46.08 ± 9.45     | 40.82 ± 22.98      | 52.79 ± 9.09       | 53.32 ± 10.73   |
| WCST_CC         | 4.38 ± 1.61      | 3.82 ± 2.44        | 5.05 ± 1.54        | 5.26 ± 1.36     |
| WCST_FMS        | 2.92 ± 1.98      | 2.82 ± 1.99        | 1.37 ± 1.46        | 1.57 ± 1.56     |

Values are presented as mean ± standard deviation.

TIV, total intracranial volume; WT, word T score; CT, color T score; CWT, color word T score; C_CW_T, interference score, which is the T value of the raw score of C minus the raw score of CW; TE, total errors; PR, perseverative responses; PE, perseverative errors; NPE, nonperseverative errors; CC, categories completed; FMS, failure to maintain set; ATAA, advanced test of attention-auditory; OE, omission errors; CE, commission errors; RT, mean of response time; RTv, response time variability; ATAv, advanced test of attention-visual.

regions. Lobules 4 and 5, vermis 1 and 2 and vermis 4 and 5 were analyzed as groups. The mean volume of cerebellar gray matter ROIs according to age group and sex are described in Table 2. Then, each cerebellar region volume was analyzed in relation to each subscale of the cognitive tests.

Correlation Analysis of Regional Gray Matter Volume, Executive Function and Attention

First, we analyzed sex differences in each age group regarding participants’ regional cerebellar volume, while controlling for age, TIV, and FSIQ (Fig. 2). In the 6−9-year-old group, the boys had a greater volume in lobule 3 (left) and vermis 1−2, 3, and 10 than girls (p < 0.05). The age 10−13 group showed no significant differences. In the adolescents aged 14−17, boys’ rGMV was larger in crus 1 (left, right), crus 2 (left, right), lobule 6 (left, right), lobule 10 (right) (p < 0.05), and lobule 4−5 (right) (p < 0.01) than in girls.
Table 2. Mean volume of cerebellar gray matter regions of interest (ROIs) according to age and sex

| ROIs       | Age 6–9 (n = 24) | Age 10–13 (n = 42) | Age 14–17 (n = 48) |
|------------|------------------|---------------------|-------------------|
|            | Male (n = 13)    | Female (n = 11)     | Male (n = 19)     | Female (n = 23) | Male (n = 30) | Female (n = 18) |
| Crus 1 (L) | 0.60 ± 0.05      | 0.58 ± 0.03         | 0.55 ± 0.05       | 0.55 ± 0.06     | 0.54 ± 0.06   | 0.51 ± 0.03     |
| Crus 1 (R) | 0.53 ± 0.04      | 0.50 ± 0.03         | 0.48 ± 0.05       | 0.48 ± 0.05     | 0.47 ± 0.07   | 0.45 ± 0.03     |
| Crus 2 (L) | 0.64 ± 0.06      | 0.61 ± 0.04         | 0.55 ± 0.08       | 0.56 ± 0.09     | 0.53 ± 0.11   | 0.51 ± 0.06     |
| Crus 2 (R) | 0.50 ± 0.04      | 0.48 ± 0.03         | 0.44 ± 0.08       | 0.44 ± 0.07     | 0.43 ± 0.09   | 0.41 ± 0.05     |
| Lobule 3 (L) | 0.35 ± 0.03    | 0.32 ± 0.02         | 0.37 ± 0.05       | 0.35 ± 0.07     | 0.40 ± 0.05   | 0.37 ± 0.05     |
| Lobule 3 (R) | 0.44 ± 0.03    | 0.40 ± 0.04         | 0.44 ± 0.04       | 0.43 ± 0.05     | 0.46 ± 0.03   | 0.42 ± 0.04     |
| Lobule 4–5 (L) | 0.57 ± 0.04 | 0.53 ± 0.03         | 0.56 ± 0.04       | 0.54 ± 0.06     | 0.57 ± 0.04   | 0.54 ± 0.05     |
| Lobule 4–5 (R) | 0.66 ± 0.04 | 0.62 ± 0.05         | 0.65 ± 0.06       | 0.63 ± 0.06     | 0.64 ± 0.05   | 0.60 ± 0.05     |
| Lobule 6 (L) | 0.70 ± 0.05      | 0.67 ± 0.04         | 0.66 ± 0.06       | 0.65 ± 0.06     | 0.66 ± 0.06   | 0.63 ± 0.03     |
| Lobule 6 (R) | 0.70 ± 0.05      | 0.66 ± 0.04         | 0.66 ± 0.07       | 0.65 ± 0.06     | 0.65 ± 0.07   | 0.62 ± 0.05     |
| Lobule 7b (L) | 0.35 ± 0.03     | 0.32 ± 0.02         | 0.37 ± 0.05       | 0.35 ± 0.07     | 0.40 ± 0.05   | 0.37 ± 0.05     |
| Lobule 7b (R) | 0.44 ± 0.03     | 0.40 ± 0.04         | 0.44 ± 0.04       | 0.43 ± 0.05     | 0.46 ± 0.03   | 0.42 ± 0.04     |
| Lobule 8 (L) | 0.58 ± 0.06      | 0.55 ± 0.05         | 0.54 ± 0.08       | 0.53 ± 0.11     | 0.40 ± 0.13   | 0.39 ± 0.08     |
| Lobule 8 (R) | 0.55 ± 0.05      | 0.50 ± 0.06         | 0.43 ± 0.11       | 0.45 ± 0.11     | 0.40 ± 0.13   | 0.39 ± 0.08     |
| Lobule 9 (L) | 0.58 ± 0.06      | 0.52 ± 0.05         | 0.46 ± 0.13       | 0.47 ± 0.12     | 0.42 ± 0.14   | 0.41 ± 0.08     |
| Lobule 9 (R) | 0.61 ± 0.05      | 0.52 ± 0.06         | 0.18 ± 0.03       | 0.18 ± 0.03     | 0.18 ± 0.03   | 0.17 ± 0.02     |
| Lobule 10 (L) | 0.21 ± 0.03      | 0.20 ± 0.02         | 0.21 ± 0.04       | 0.21 ± 0.03     | 0.20 ± 0.03   | 0.19 ± 0.02     |
| Lobule 10 (R) | 0.22 ± 0.03      | 0.21 ± 0.01         | 0.37 ± 0.04       | 0.34 ± 0.04     | 0.40 ± 0.08   | 0.39 ± 0.10     |
| Vermis 1−2 | 0.48 ± 0.03      | 0.45 ± 0.03         | 0.37 ± 0.05       | 0.35 ± 0.08     | 0.39 ± 0.04   | 0.37 ± 0.05     |
| Vermis 3    | 0.48 ± 0.03      | 0.45 ± 0.03         | 0.48 ± 0.04       | 0.46 ± 0.05     | 0.49 ± 0.03   | 0.47 ± 0.05     |
| Vermis 4−5 | 0.48 ± 0.03      | 0.45 ± 0.03         | 0.56 ± 0.05       | 0.55 ± 0.05     | 0.57 ± 0.04   | 0.55 ± 0.05     |
| Vermis 6    | 0.65 ± 0.06      | 0.62 ± 0.04         | 0.59 ± 0.07       | 0.60 ± 0.06     | 0.60 ± 0.07   | 0.59 ± 0.05     |
| Vermis 8    | 0.63 ± 0.05      | 0.59 ± 0.04         | 0.56 ± 0.07       | 0.57 ± 0.08     | 0.55 ± 0.09   | 0.54 ± 0.06     |
| Vermis 9    | 0.56 ± 0.04      | 0.51 ± 0.06         | 0.48 ± 0.09       | 0.50 ± 0.10     | 0.47 ± 0.11   | 0.46 ± 0.07     |
| Vermis 10   | 0.21 ± 0.01      | 0.19 ± 0.02         | 0.19 ± 0.02       | 0.19 ± 0.03     | 0.20 ± 0.03   | 0.19 ± 0.02     |

Values are presented as mean ± standard deviation.
L, left; R, right.
Volume unit: liters.

We determined the cerebellar regions with significant correlations ($p < 0.05$, controlling for age, IQ, and TIV) between each subcategory score on the Stroop test, WCST, and ATA and rGMV in each age group (Fig. 3).

In the 6- to 9-year-old boys, negative correlations were observed in the following SCWT and WCST results: Stroop CT with lobule 7 (left) and lobule 8 (left); WCST_NPE with lobule 10 (left); WSCT_FMS with verm 4–5, lobule 6 (right), lobule 4–5 (right), and crus 1 (right). Positive correlations were observed between WCST_TE and lobule 4–5 (right) and lobule 6 (right). Additionally, negative correlations were observed in the following ATAv results: ATAv_RT with verm 6, 7, and 8 and lobule 6 (left). Positive correlations were found in the ATAv results: ATAv_CE with verm 7, verm 8, and lobule 3 (left) ($p < 0.05$).

In the girls in the same age group, the differences were prominent in the EF test results. The girls showed only one positive correlation between Stroop_CWT and verm 8 with the SCWT. Otherwise, WCST_FMS and various regions (crus 1 [right] [$p < 0.005$]; crus 2 [right], lobule 4–5 [left], lobule 6 [left], and lobule 6 [right] [$p < 0.05$]) showed highly positive correlations. There were positive correlations between ATAv_OE and verm 1–2 and 3 lobule 3 (left) and between ATAv_RT and verm 4–5, lobule 3 (right), crus 2 (right), and crus 1 (right). Vermis 1–2 and 3 were also markedly correlated with ATAv_OE and ATAv_RT.

In the 10- to 13-year-old children, both sexes showed various levels of correlations with EF and attention. In boys, negative correlations were prominent between Stroop_CT and crus 1 (right), lobule 4–5 (right), lobule 6 (left), lobule 6 (right), and verm 6. Few positive correlations were seen between Stroop_CWT and lobule 7 (left, right) or lobule 8 (left, right). WCST items were not correlated with cerebellar GMV with the exception of WCST_PR and
lobule 10 (left).

In the 10–13-year-old girl group, SCWT items and cerebellar GMV tended to be generally positively correlated. Significant correlations appeared in following results: Stroop_WT with crus 1 (left, right) \( (p < 0.01) \), crus 2 (left, right), lobule 7 (right), lobule 8 (right), and lobule 10 (right) \( (p < 0.05) \); Stroop_CT with crus 1 (left, right) and lobule 10 (right) \( (p < 0.05) \); Stroop_CWT with crus 1 (right) and lobule 10 (right) \( (p < 0.05) \); Stroop_C_CWT with crus 1 (right) \( (p < 0.01) \), crus 2 (right), and lobule 10 (right) \( (p < 0.05) \). WCST subcategories were correlated with volumes in fewer regions but showed strong positive correlations: WCST_PR with lobule 3 (left), vermis 3 \( (p < 0.05) \), and vermis 4–6 \( (p < 0.01) \); WCST_PE with lobule 3 (left) \( (p < 0.05) \) and vermis 3, 4, and 5 \( (p < 0.005) \); WCST_FMS with lobule 6 (left), lobule 9 (left, right) \( (p < 0.05) \), and lobule 10 (left, right) \( (p < 0.01) \). The girls did not show correlations with ATA performance. Nevertheless, they showed negative correlations between ATA subcategories and cerebellar GMV: ATAa_OE with lobule 3 (left, right), vermis 1–2 \( (p < 0.05) \), vermis 3 \( (p < 0.01) \), lobule 4–5 \( (p < 0.05) \), and vermis 6 \( (p < 0.01) \). ATAa_CE with lobule 4–5 (left), vermis 4–5 \( (p < 0.05) \), and vermis 6 \( (p < 0.01) \).

In 14–17-year-old group, the boys show marked positive correlations with SCWT performance: Stroop_WT with crus 1 (right) \( (p < 0.05) \); Stroop_CT with lobule 7 (left), lobule 8 (left, right), lobule 9 (left, right), lobule 10 (left, right), vermis 3–9 \( (p < 0.05) \), crus 1 (left, right), crus 2 (right), and lobule 7 (right) \( (p < 0.01) \); Stroop_CWT with crus 3 \( (p < 0.05) \); Stroop_C_CWT with crus 2 (right), lobule 4–5 (right), lobule 7 (left), lobule 8 (left, right), lobule 9 (right), vermis 8 \( (p < 0.05) \), crus 1 (right), lobule 6 (right), lobule 7 (right), lobule 9 (left), and vermis 9 \( (p < 0.01) \). ATAv results showed no correlations. ATAa showed correlations. ATAa_CE and lobule 3 (right), vermis 3 \( (p < 0.05) \), lobule 4–5 \( (p < 0.05) \), and vermis 6 \( (p < 0.005) \) showed negative correlations, which indicates fewer commission errors, which means that greater attention was related to the regions’ volumes. ATA_RTv and lobule 7 (right), lobule 8 (left, right), lobule 9 (left, right), and vermis 9 were positively correlated \( (p < 0.05) \).

The EF test and ATA results of the 14–17 aged girls showed few correlations with cerebellar GMV. Stroop_C_
CW_T and vermis 9 was negatively correlated ($p < 0.05$).
In the WCST, WCST_NPE and crus 1 (right) and crus 2 (left, right) were positively correlated ($p < 0.05$). ATAta_RT and crus 1 (left, right), lobule 10 (right), vermis 8 ($p < 0.05$), and lobule 6 (left, right) ($p < 0.01$) had positive correlations. ATAt showed no correlations with cerebellar volumes.

In each age group, we observed differences between boys and girls in association with GMVs, attention tests, and cognitive function tests for each cerebellar region (covariates = age, IQ, TIV). It was also seen that there was an overall tendency in the correlations that was associated with the cerebellum developmental trajectory. We analyzed the partial correlations of differences in cerebellar rGMV and SCWT, WCST, and ATA subscale scores between girls and boys by age group (Fig. 4).

In the 6−9 age group, the boys showed more correlations than the girls between WCST_TE and WCST_CC and

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**Fig. 3.** Partial correlations between cerebellar gray matter volumes and ATA and WCST scores by age group (controlling for age, IQ, and TIV). ATA, advanced test of attention; WCST, Wisconsin card sorting test; TIV, total intracranial volume.
lobule 4−5 (right) and lobule 6 (right) (p < 0.05); between ATAa_RT and vermis 1−2 and 3 (p < 0.001); between ATAa_RTv and vermis 6 (p < 0.05) and vermis 7 (p < 0.01). The girls showed greater correlations than the boys in the following: between WCST_FMS and crus 1 (right) (FDR < 0.02), crus 2 (right) (p < 0.05), lobule 4−5 (left, right), lobule 6 (left) (p < 0.01), lobule 6 (right) (p < 0.001), lobule 7 (right) (p < 0.05), vermis 4−5 (p < 0.01), and vermis 6 (p < 0.05). ATAv_RT was a distinctive category in which girls showed greater correlations: crus 1 (right) (p < 0.01), crus 2 (right), lobule 3 (right), lobule 6 (left), and vermis 4−5, and 8 (p < 0.05).

In the 10−13-year-old group, the boys showed greater correlations in between WCST_PR, WCST_PE, and WCST_NPE and lobule 10 (left) (p < 0.05). Additionally, correlations between ATAA_OE and vermis 4−5 (p < 0.05) and ATAA_CE and vermis 6 (p < 0.001) and vermis 7 (p < 0.05) correlations were greater in the boys. In this age group, female cerebellar rGMV was more closely associated with SCWT performance. In particular, Stroop_CT was related to various regions: crus 1 (left, right) (p < 0.01), crus 2 (right), lobule 4−5 (right) (p < 0.05), lobule 6 (left, right) (p < 0.01), and vermis 6, 7 (p < 0.05). Other subcategories also showed greater correlations in the girls: Stroop_CW and lobule 4−5 (right) and Stroop_C_CW_T and crus 1 (right) and crus 2 (right), ATAv_OE and lobule 9 (left), lobule 9 (right), and lobule 10 (left) were also more correlated in the girls in this group.

In the above-14 age adolescent group, the boys showed greater correlations between cerebellar rGMV and EF tests: Stroop_WT and lobule 10 (left) (p < 0.01); Stroop_CT and lobule 10 (left) (p < 0.05); and Stroop_C_CW_T and lobule 4−5 (right) (p < 0.05), lobule 9 (left) (p < 0.01), lobule 9 (right), lobule 10 (left), vermis 8 (p < 0.05), vermis 9 (p < 0.001), and vermis 10 (p < 0.05). The girls showed greater correlations than boys between ATAA_RT and crus 1 (left) (p < 0.05), lobule 6 (left) (p < 0.01), lobule 6 (right), and lobule 10 (right) (p < 0.05).

**DISCUSSION**

This study highlights that sex-specific cerebellar maturation in adolescence might be correlated with EF and attention. In our study, the cerebellar volume was always greater in the boys than in the girls regardless of age, which is consistent with previous studies [37,38]. Cerebellar
rGMV increased with age, although the trajectory varied by sex. We attempted to identify correlations between attention/EF and GMV by developmental stage by dividing the participants into three age groups. We used the AAL-based division to anatomically classify each region of the cerebellum, which is a commonly used method in brain imaging-based research. Many cerebellar regions in boys had greater correlations with EF than girls, especially in the 6–9-year-old and above-14 age adolescent group. In the female participants, cerebellar rGMV in the 10–13-year-old group showed a positive correlation with EF. We also performed the ATA to measure attention. While the boys showed many cerebellar regions that were significantly correlated with performance in ATAa subcategories, girls’ attention was correlated to a greater extent in the visual tests. At ages 10–13, the boys showed more correlations with ATAAa stimulation values.

When divided into three age groups, boys showed many correlation of cerebellar rGMV with EF function in 14–17 age, and girls showed many correlation in 10–13 age. This result corresponds to the well-known developmental trajectory [21] that the cerebellar volume peaked at 11.8 years in girls and 15.6 years in boys. This result revealed that the correlation of cerebellar rGMV and attention/EF also follows the well-known developmental trajectory.

These outcomes provided evidence that the cerebellum modulates higher cognitive functioning during child development. This is thought to be consistent with the results of previous studies that cerebellum maturity takes place earlier in girls than boys, and larger cerebellar rGMV is associated with better EF in adolescents. Furthermore, the correlation of cerebellar rGMV and EF follows the developmental trajectory. These data provide evidence that as cerebellar volume increases, it becomes more relevant to EF.

EF is well known for its development over the lifespan. Age-related increases in EF are most noticeable in middle childhood [39], and growth slows down from 11 to 14 years [40]. Boeleva et al. [41] measured sex differences in six EF subcomponents (focused attention, inhibition, sustained attention, speed of processing, working memory, and shift attention). In this study, girls showed better performance on the inhibition, sustained attention, and working memory subscales of baseline tests and reported smaller slopes than boys, which indicated that girls show slower improvement during development. Boys underperformed working memory and sustained attention in early adolescence but showed larger improvements in late adolescence. However, there have been various perspectives related to these results. Other studies have shown that children, adolescents and young adults have no sex differences in spatial working memory [42-48]. On the other hand, a meta-analysis identified sex differences in visual-spatial working memory that first appeared in the 13–17-year-old group, and males performed better in most of the visual-spatial working memory tasks [49]. Compared to adolescents who show various differences, attention in adults has been known to relatively consistently show no sex differences [50].

Most of the previous studies regarding associations of the developing brain, sex, and EF have focused on whole brain or frontal lobe maturation. As studies have expanded to other regions of the brain, researchers have gradually become interested in the correlations between the cerebellum and EF. Therefore, several studies have shown that the cerebellum has an important role in EF in the development period. EF and attention tests conducted in our study involve various regions of brain to perform tasks [51-53]. Previous studies have revealed associations of cerebellum regions and cerebral associative area in the developing brain. EF shows differences in cerebellum regions, and is suggested to be affected by frontal gray matter development [21]. There has been scarce research on the correlation between EF test subcategories and rGMV in developing brain.

Synaptogenesis and pruning simultaneously occur during childhood and adolescence, which results in adjusting brain regional gray matter volumes. The process also develops neurocircuitry and consequently strengthens adolescents’ cognitive and social function [54].

The remainder of lobule VI and all of lobule VII (which includes lobule VIIA in the vermis and crus I and crus II in the hemispheres, lobule VIIIB and most of lobule IX) has no connections with the cerebral cortical sensorimotor areas [55,56]. However, these areas are related to associative areas in the cerebral cortex, which are the prefrontal cortex, posterior parietal cortex, superior temporal polymodal regions, cingulate gyrus, and posterior parahippocampal area [1-3,57-59].

There are studies showing that cerebellar neuroanatomical abnormalities interact with frontal lobe function and
consequently affect cognitive function. Purkinje cells are the only efferent projections from the cerebellar cortex, and their death results in functional abnormal lesions of the cerebellum [60]. Carper and Courchesne [61] suggested that a reduced number of cerebellar Purkinje cells at a young age would cause poor development of the frontal lobe and other brain areas receiving the input. They discovered abnormal neural activity in cerebello-thalamo-cortical projections in autistic patients. Likewise, the posterior lobe of the cerebellum in autistic patients has been suggested to be hypoplastic; in particular, autistic participants showed smaller lobules VI and VII [62-64] and vermis of lobules VIII-X [65,66].

Posterior lobe lesions in the cerebellum also result in CCAS. After cerebellar tumor resection, mutism, emotional lability, cognitive and affective deficits appear [67]. In a study that measured cerebellar volume in participants with ADHD and in age- and sex-matched controls, cerebellar volume was significantly smaller in the ADHD group than in the healthy control group, particularly in boys with ADHD [68]. This result was consistent with previous studies [15]. Reductions in cerebellar volume principally involved the posterior inferior lobe (lobules VIII to X). Our study was in accordance with the results of these described studies in that the associations between cognition and rGMV were prominent in posterior regions of the cerebellum.

There are a few studies that may explain the reasons for sex differences in cerebellar GMV and EF. The fact that girls show earlier brain maturation suggests that the pruning process appears to be working at different points in time. Another assumption is the difference in sex hormones. There have been several studies of sex differences in gene and protein expression during cerebellar maturation. Neurosteroids develop and regulate cerebellar function through estrogen and progesterone receptors [69,70]. Estrogen is well known for its protective effects in the nervous system. Postmenopausal women who received estrogen replacement therapy manifested larger cerebellar rGMV and advanced cognitive functions such as attention and planning skills [71]. In study with males, high endogenous testosterone levels showed a positive correlation with larger cerebellar rGMV. Steroid hormones play a role in sexual maturation, and the fact that females physically develop earlier than males suggests sex differences in the correlations between cerebellar rGMV and attention/EF.

Additionally, Purkinje cells in the cerebellum have been examined as having a major role in neurosteroid formation [72]. Vawter et al. [73] reported that different patterns of gene expression might lead to sex differences in the human brain. In this study, significantly distinctive gene expression of sex chromosomes was found in cerebellar regions as well as the cerebrum. However, findings at the molecular level have not been largely explored. In our study, subjects’ pubertal status was not estimated but followed the inverted-U-shaped developmental trajectory. Generally, puberty in males starts at a later age than in girls, and the cerebellar volume peaks at a later age. This suggests that the onset of cerebellar volume decrease may be associated with pubertal maturation [21].

This study has a few limitations. First, this study was a cross-sectional study. It cannot determine the causal relationship between cerebellar rGMV and EF. Second, moderate number of samples for each age group were used. Particularly, the size of the 6–9 age group was smaller than that of the other two groups. We originally conducted multiple comparison correction over all correlations with FDR approach. However, we did not find any relationship except for WCST_FMS and crus 1 (right) with FDR correction and believe this is due to not large samples. Nonetheless, we found consistent results with all marginal p values with p < 0.05, and we reported them. Given the consensus that the brain develops rapidly in younger age, further research could supplement the group size. Third, we used standard adult SPM template instead of an age-specific template. Age specific templates in previous studies were mainly based on western teenagers, and there were no researches that were divided into three age groups. Future studies could use East Asian child and adolescents’ age-specific template.

Nevertheless, this study has many implications. There have been previous studies that studied cerebellar GMV by sex or age, and studies that investigated specific cerebellar regions related to EF, but the number of studies was small. The demographic characteristics of our study were consistent with the results of previous studies. We subdivided children and adolescents by sex and age and subdivided the cerebellum to examine the relationship between cerebellar GMV and EF in each region.

Further neurobiological studies are required to de-
termine how cerebellar rGMV differs by sex and how it is related to cognitive development in children. As the cerebellum rapidly develops at an early age and has a large association with EF, this information can be used in the study of neurodevelopmental disorders with cognitive deficits. Numerous previous findings have shown that cerebellar dysfunction is related to neurodevelopmental disorders such as ADHD, autism, and dyslexia [74,75]. It is also important to see a sex difference in that the prevalence of neurodevelopmental disorders is greater in males. The relationships of cerebellar volume and EF that show sex differences could be a topic of future research.

In future studies, we can expand from the cerebellum to other areas of the brain that are connected to the cerebellum or other regions that are known to be related to higher cognitive function.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Hayeon Kim, Bumhee Park, Min-Hyeon Park. Data acquisition: Shin-Young Kim, Jiyea Kim, Bora Kim, Yerin Hyun, Bung-Nyun Kim, Subin Park. Formal analysis: Shin-Young Kim, Jiyea Kim, Bora Kim, Yerin Hyun, Bumhee Park. Funding: Bung-Nyun Kim, Min-Hyeon Park. Supervision: Min-Hyeon Park. Writing—original draft: Hayeon Kim. Writing—review & editing: Hayeon Kim, Bumhee Park, Kyu-In Jung, Seung-Yup Lee, Min-Hyeon Park.

■ ORCID

Hayeon Kim https://orcid.org/0000-0002-7739-7152
Bumhee Park https://orcid.org/0000-0002-5271-1571
Shin-Young Kim https://orcid.org/0000-0002-3827-3413
Jiyea Kim https://orcid.org/0000-0003-1463-762X
Bora Kim https://orcid.org/0000-0003-2827-6888
Kyu-In Jung https://orcid.org/0000-0003-2509-8377
Seung-Yup Lee https://orcid.org/0000-0001-5635-8958
Yerin Hyun https://orcid.org/0000-0003-1515-3352
Bung-Nyun Kim https://orcid.org/0000-0002-2403-3291
Subin Park https://orcid.org/0000-0002-4623-9899
Min-Hyeon Park https://orcid.org/0000-0002-1731-1388

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