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Patterns of Cerebellar–Cortical Structural Covariance Mirror Anatomical Connectivity of Sensorimotor and Cognitive Networks

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ABSTRACT

The cortex and cerebellum are densely connected through reciprocal input/output projections that form segregated circuits. These circuits are shown to differentially connect anterior lobules of the cerebellum to sensorimotor regions, and lobules Crus I and II to prefrontal regions. This differential connectivity pattern leads to the hypothesis that individual differences in structure should be related, especially for connected regions. To test this hypothesis, we examined covariation between the volumes of anterior sensorimotor and lateral cognitive lobules of the cerebellum and measures of cortical thickness (CT) and surface area (SA) across the whole brain in a sample of 270 young adults drawn from the HCP dataset. We observed that patterns of cerebellar–cortical covariance differed between sensorimotor and cognitive networks. Anterior motor lobules of the cerebellum showed greater covariance with sensorimotor regions of the cortex, while lobules Crus I and Crus II showed greater covariance with frontal and temporal regions. Interestingly, cerebellar volume showed predominantly negative relationships with CT and predominantly positive relationships with SA. Individual differences in SA are thought to be largely under genetic control while CT is thought to be more malleable by experience. This suggests that cerebellar–cortical covariation for SA may be a more stable feature, whereas covariation for CT may be more affected by development. Additionally, similarity metrics revealed that the pattern of covariance showed a gradual transition between sensorimotor and cognitive lobules, consistent with evidence of functional gradients within the cerebellum. Taken together, these findings are consistent with known patterns of structural and functional connectivity between the cerebellum and cortex. They also shed new light on possibly differing relationships between cerebellar volume and cortical thickness and surface area. Finally, our findings are consistent with the interactive specialization framework which proposes that structurally and functionally connected brain regions develop in concert.

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Summary

- Individual differences in structural features covary between connected regions of the cerebellum and cortex.
- Patterns of covariation differ for sensorimotor and cognitive loops.
- Patterns of covariation with cortical thickness and surface area suggest differing developmental influences.

1 | Introduction

Axonal tracing experiments in primates and neuroimaging studies in humans have revealed an intricate pattern of connectivity between the cerebellum and the cerebral cortex. These two brain structures are connected through reciprocal input/output projections that form circuits linking functionally related regions (Leiner, Leiner, and Dow 1987; Orioli and Strick 1989). For example, anterior lobules of the cerebellum exhibit denser connections to sensorimotor and parietal cortical regions than they do to prefrontal regions, while lobules Crus I and II are more heavily connected to the prefrontal regions (Palesi et al. 2017; Salmi et al. 2010). Functional magnetic resonance imaging (fMRI) studies have also revealed functional connectivity between the cortex and cerebellum that parallels structural connectivity, both during rest and during cognitive and motor tasks (Buckner et al. 2011; Kipping et al. 2013). Further, evidence from brain development has shown that the volumes of the cerebellum and cortex follow correlated developmental trajectories (Bethlehem et al. 2022; Kipping, Xie, and Qiu 2018; Mechelli et al. 2005). These cerebellar–cortical loop circuits form powerful networks that are thought to be involved in error processing and the development of forward models that optimize both movement and cognitive functions, such as working memory and language (Guell, Gabrieli, and Schmahmann 2018; Schmahmann 2019).

The pattern of correlations between structural measures can be compared across regions using an approach termed structural covariance (Alexander-Bloch, Giedd, and Bullmore 2013; Lerch et al. 2006). Structural covariance has been examined between structurally connected cortical regions (Mechelli et al. 2005), and between the cortex and subcortical structures (Colibazzi et al. 2007). In addition, recent work from our laboratory has found that the structure of cerebellar and cortical motor regions shows different patterns of covariance in people who began musical training before age seven compared to those who began later and non-musician controls (Shenker et al. 2022). In our previous work, we hypothesized that interactive specialization, such as music training, promoted changes in one region that may drive changes in connected regions (Johnson 2011). However, as far as we can determine, normative structural covariance between the cortex and the cerebellum has not yet been examined. Therefore, the goal of the current study was to investigate this relationship in a large sample of healthy young adults from The Human Connectome Project (HCP; van Essen et al. 2013). Using structural magnetic resonance imaging scans (MRI) of the human brain,

we examined the association between the thickness and surface area of the cortex and the volume of cerebellar lobules. We hypothesized that anatomically connected regions of the cerebellum and cortex would show stronger structural covariance compared to unconnected regions. In particular, we expected that structural covariance would be stronger between the thickness and surface area of posterior frontal and parietal regions with the volume of motor lobules of the cerebellum, namely hemispherical lobules III, IV, V, VI, VIIB, VIIIA, and VIIIB. We also expected that covariance between prefrontal cortical regions is stronger with lobules Crus I and Crus II, which have been implicated in cognitive functioning and are anatomically connected to frontal regions (Kelly and Strick 2003).

Using transneuronal tracing of fiber pathways in non-human primates, Kelly and Strick (2003) identified differential connectivity between sensorimotor and frontal cortical regions and the cerebellum. Axons from lobules III–VI as well as lobules VIIIA, and VIIIB were found to project to the primary motor cortex, the premotor cortex, and the supplementary motor cortex. Importantly, another set of axons projects back from these cortices to the cerebellum to form cerebellar–cortical loops. Similarly, Crus I and Crus II are connected to frontal regions, primarily the dorsal prefrontal cortex, through reciprocal loops.

As expected, cerebellar–cortical functional connectivity reflects the known structural connectivity, as observed in resting-state fMRI (rs-fMRI; Buckner et al. 2011) and latent functional gradients (Guell et al. 2018; Stoodley and Schmahmann 2010). Resting-state connectivity has been found between the lobules of the anterior cerebellum, VIIIA, and VIIIB and sensorimotor cortices, and between Crus I and Crus II and the prefrontal cortex (Kipping et al. 2013). Consistent with the results of structural and functional connectivity studies, task-based studies show that lobules III–VI, VIIB–VIIIB, and sensorimotor cortices are active during sensorimotor tasks and Crus I and Crus II and the prefrontal cortex are active during cognitive functions (Buckner et al. 2011; Salmi et al. 2010). Indeed, correlated activity between sensorimotor cortices and the cerebellum is related to motor task performance and motor learning (Penhune and Steele 2012; Stoodley and Schmahmann 2010), and correlated cerebellar–cortical activity has also been linked to executive functioning (Stoodley, Valera, and Schmahmann 2012). Gradient decomposition of cerebellar function also supports this conclusion by revealing motor versus nonmotor representations within the cerebellum (Guell et al. 2018). However, whether the associations between the structure of the cerebellum and that of the cortex show similar organization remains unclear.

We and others hypothesize that the structural and functional connectivity between the cortex and the cerebellum may be in part determined by a pattern of interactive changes during development (Johnson 2011). Johnson (2011) proposes that functionally connected brain regions develop in association and exert effects on each other throughout maturation and in response to experience. This framework for understanding brain development is termed interactive specialization. Based on the existence of structural and functional connections between regions

(Alexander-Bloch, Giedd, and Bullmore 2013), interactive specialization might be expected to lead to structural covariance. Structural connectivity has been suggested to mediate positive associations between variations in the structure of brain regions during development (Mechelli et al. 2005). Structural covariance between regions is also influenced by genetics and lifespan experiences and exhibits different patterns across sexes (Chen et al. 2011; Lv et al. 2010; Schmitt et al. 2008). It has been shown that dancers exhibit an association between reduced cortical thickness in the entire brain and cortical thickness in the middle frontal gyrus when compared to healthy controls (Karpati et al. 2018). Yee et al. (2018) observed an association between the transcriptomic similarity between regions and their structural covariance, reflecting a genetic influence on these patterns of variation. Since structural covariance is influenced by life experiences, we expect that experience could play a role in cerebellar–cortical structural associations as well. This is evident in our previous study with musicians showing that changes in cerebellar–cortical structural covariance were linked to musical training before the age of 7 (Shenker et al. 2022). The current study extends this work to investigate the patterns of normative cerebellar-cortical structural covariance in the healthy adult brain.

There are two primary and theoretically distinct measures of cortical structure that can be measured in humans from MRI: cortical thickness and surface area. Cortical thickness is defined as the depth/thickness of the grey matter ribbon, and surface area as the two-dimensional extent of a given region of cortex. Individual variation in these features is thought to reflect different contributions from genetic and environmental factors during development (Panizzon et al. 2009). Surface area undergoes rapid changes early in life and is thought to be under greater genetic control (Bishop, Goudreau, and O'Leary 2000; Sanabria-Diaz et al. 2010; Yoon, Perusse, and Evans 2012). Cortical thickness continues to change across development into young adulthood and is therefore more likely to be affected by the environment and experience (Amlien et al. 2016). While cortical thickness and surface area are routinely extracted from MRI images of cortex, measuring them in the cerebellum is problematic. The cerebellum has a relatively thin grey matter ribbon, very dense gyrification, and closely packed lobules. This means that white and grey matter tissue segmentation, the basis for estimating these metrics, is unreliable (Serenio et al. 2020). Therefore, lobular volume is a more reliable measure of cortical structure in the cerebellum that can be accurately measured. To measure the volumes of cerebellar lobules, we used a robust multi-atlas segmentation approach (Chakravarty et al. 2013) that has been applied in a number of previous studies of cerebellar structural variation (Park et al. 2014; Shenker et al. 2022; Steele and Chakravarty 2018).

Taken together, the existing literature suggests that there may be normative covariance between the structure of the cortex and cerebellum based on known anatomical and functional connectivity. Therefore, the current study examined cerebellar–cortical structural covariance in a large sample of healthy young adults controlling for age and sex. We hypothesized that the volumes of motor and cognitive lobules of the cerebellum would show greater covariance with cortical thickness and surface area of motor and cognitive regions of the cortex. Further, we expected

that these patterns of covariation might differ for cortical thickness and surface area, and between hemispheres.

2 | Methods

2.1 | Participants

Structural MRI images were obtained from the Human Connectome Project S1200 release [HCP; full protocol is described in van Essen et al. (2013)]. We conducted our analyses on a subsample of 270 right-handed young adults (age: M : 28.77 years, SD : 3.73; 157 female) who were selected based on the following criteria: no history of psychiatric, neurological, or neuropsychological disorders; no history of substance abuse; and full cerebellar coverage on T1w scans. Given the nature of the HCP data collection that included family members, we selected unrelated subjects. In our previous work, we reported the volumes of all cerebellar regions in this same sample, and here we extend the analysis to include cortical features (Steele and Chakravarty 2018).

2.2 | Procedure

2.2.1 | MRI Acquisition and Preprocessing

T1-weighted Structural MRI images were acquired for all participants on a 3T Connectome Skyra MRI scanner with a 32-channel head coil. Scanning parameters were as follows: voxel size = 0.7 mm^3 isotropic, repetition time = 2400 ms, inversion time = 1000 ms, echo time = 2.14 ms, field of view = $224 \times 224\text{ mm}$ (van Essen et al. 2012). All MRI scans were preprocessed by the HCP according to the minimal preprocessing pipeline (Glasser et al. 2013). This included registration to the common Montreal Neurological Institute 152 space (MNI-152) with a rigid body transformation. Then, FreeSurfer's recon-all was used to reconstruct white and grey matter surfaces that were then used in surface area (SA) and cortical thickness (CT) measurements (Dale, Fischl, and Sereno 1999). In this study, we used CT and SA which were provided by the HCP consortium (db.humanconnectome.org). We used CIFTI metric files to extract individual-level CT surface maps (i.e., corrThickness). We extracted the CT values and applied a smoothing kernel on the resulting vertex-wise data (using -metric-smoothing). For SA, we used the individual-level pial GIFTI surface meshes, and used the connectome workbench toolbox to calculate the surface area of each vertex (-surface-vertex-areas). Then, we applied the same smoothing kernel on the resulting SA maps (using -surface-smoothing). Details on CT and SA calculation and smoothing are described next.

2.2.2 | Thickness and Area Calculation

Thickness was measured as the distance between the white and gray matter surfaces in millimeters (mm). To extract the SA of the cortex at every vertex, the area of one-third of each triangle that the vertex was part of was assigned to that vertex, and it was measured in mm^2 . Surface area values for each participant were normalized at each vertex by total brain volume to account

for global differences in brain size. SA, but not CT values were normalized because variations in the cortical volume are mainly driven by changes in SA, therefore normalizing only SA corrects for brain size while preventing data contamination with noise (Im et al. 2008). Thickness and area measurements were then smoothed using a 12 mm full width at half maximum smoothing Gaussian kernel to maximize signal-to-noise ratio and minimize false positives as reported previously in structural covariance literature (Bernal-Rusiel, Atienza, and Cantero 2010; Mechelli et al. 2005).

2.2.3 | Cerebellar Lobule Identification

To label the hemispherical cerebellar lobules of interest, the Multiple Automatically Generated Templates Brain Segmentation Algorithm was used (MAGeTbrain: <https://github.com/CobraLab/MAGeTbrain>; Park et al. 2014). The algorithm first performs a nonlinear registration between multiple high-resolution, expert-labeled, atlases and a set of 21 randomly chosen scans from the subsample (Steele and Chakravarty 2018). Each of the 21 scans is segmented according to the five atlases, therefore each voxel in these scans would have five labels assigned to it. Then, a majority vote is conducted to determine the most frequent label out of the $5 \times 21 = 105$ possible labels that each voxel is assigned. Based on the votes, a sample template is created, and each participant's scan was then labeled according to that template. Following the identification of the nine hemispherical cerebellar lobules in each hemisphere (III, IV, V, VI, Crus I, Crus I, VIIB, VIIIA, and VIIIB), we normalized their volume by total brain volume to account for variation due to brain size.

2.3 | Statistical Analysis

2.3.1 | Cerebellar–Cortical Structural Covariance

Since our goal was to examine cerebellar–cortical structural covariance, regression analyses were used to investigate the relationships between measures of CT and SA at each vertex in the cortex and the volumes of contralateral hemispherical cerebellar lobules. That is, CT and SA of the vertices in the left cortex were the dependent variables while the volumes of right cerebellar lobules were the independent variables. The same was performed for the right cortex and the left cerebellum, such that each hemisphere's structural covariance was assessed with each of the nine lobules of the contralateral cerebellum. Age and sex were included as covariates. Standardized regression coefficients were extracted to indicate the specific association between the volumes of the lobules and vertex-wise CT or SA, which were then plotted on the cortex for visualization. In total, we conducted 18 regression analyses at each of the 326k cortical vertices (i.e., 9 lobules each for CT and SA, with each lobular volume serving as the independent variable). We performed 1000 permutations per vertex per lobule to assess significance, for CT and SA, setting a permutation-threshold p -value of 0.05. For the permutation analysis, we used Nilearn's `ols_permuted` in a mass univariate paradigm. First, an ordinary least squares model is fit at each vertex, estimating the relationship between the volume of cerebellar lobules and either CT or SA. Permutation of the cerebellar volumes provides the null distribution by recomputing

the OLS estimates for each permutation and the resulting p values are then corrected for multiple comparisons using family-wise error correction. All analyses were conducted in Python version 3.7 (<https://www.python.org/>), using the packages `statsmodels` and `scipy` for regression analysis, and `Nilearn` for permutation analysis and data visualization.

2.3.2 | Similarity Assessment

To assess similarity in patterns of associations between the cortex and the volumes of the different cerebellar lobules, we computed the correlation between the vertex-wise associations of each cortical hemisphere (for CT and SA separately) for each cerebellar lobule, using only statistically significant vertices after permutations. The correlation between each pair of brain maps was permuted 1000 times, with a 0.05 significance threshold. In this step, correlation coefficients represent the similarity in the pattern of covariance between each pair of lobules, and provide a comparative summary of the vertex-wise regression analyses. In this analysis, greater correlations between lobules are indicative of greater similarity, whereas lower values indicate less similar patterns of covariance of the lobules with CT/SA across the cortical hemisphere. We conducted 36 similarity assessments (each of the 9 lobules to every other lobule) per cortical measure per hemisphere. In total, there were $36 \times 4 = 144$ assessments, grouped by measure (CT/SA) and hemisphere. The similarity analysis was conducted in Python version 3.7 (<https://www.python.org/>), using the packages `scipy` for correlation and permutation analysis, and `seaborn` for data visualization (i.e., heatmaps of similarity).

3 | Results

3.1 | Cerebellar–Cortical Structural Covariance

First, we assessed cerebellar–cortical structural covariance between motor and cognitive lobules of the cerebellum and either CT or SA using multiple regression accounting for age and sex. Results revealed a pattern of cerebellar–cortical covariance that differed for CT and SA, between sensorimotor versus cognitive regions, and between the left (Figure 1) and right hemispheres (Figure 2).

For CT, the covariance between left cortical sensorimotor regions and right lobules III, IV, V, VIIIA, and VIIIB were predominantly strong negative associations as seen by the large negative beta coefficients. This negative covariance was weaker for lobules Crus I and Crus II, and positive for lobules that are at the boundary of motor and cognitive transitions, namely VI and VIIB. CT of the left cortical cognitive regions in the frontal lobes exhibited sparsely distributed weaker negative associations with the motor lobules III, IV, V, VIIIA, and VIIIB. Overall, this pattern was weaker and less consistent for the right hemisphere. For CT of the right cortical sensorimotor regions, negative associations were found with lobules III, IV, V, while lobules VI–VIIIB show weak negative associations with premotor regions. CT of right frontal regions was positively associated with lobules VI–VIIIB. In contrast to the left cortex, CT of the right frontal regions was also negatively

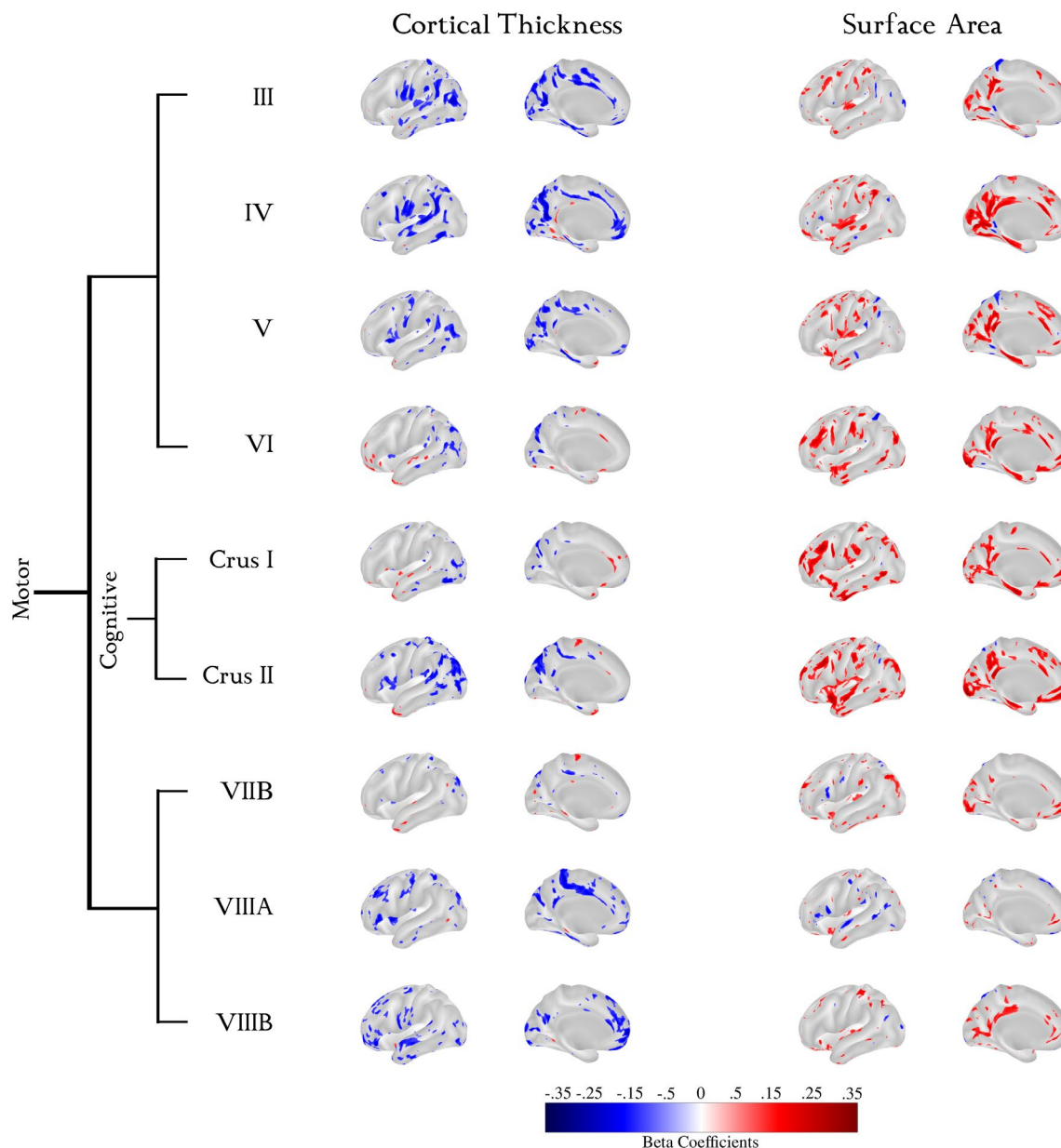


FIGURE 1 | Vertex-wise beta coefficients of the association between CT and SA of the left cortex and the volumes of right cerebellar lobules while accounting for age and sex. Each brain-plot represents the association between the cortical measure (top) of one hemisphere (lateral and medial view) and the volume of the contralateral cerebellar lobule (left). Blue indicates a negative association while red indicates a positive one. The unthresholded beta maps for left and right CT and SA are included as Figure S1.

associated with lobules III–VIIB, and this negative association is stronger with VIIIA and VIIIB.

In contrast to CT, SA was generally positively related to cerebellar volumes, but with a similar pattern in the shift of covariance across cognitive versus motor lobules and hemispheres. SA of the left sensorimotor regions of the cortex were strongly positively associated with right lobules III, IV, and V. This positive association extended to lobules VI, Crus I, Crus II, unlike CT where the direction of association switched from negative to positive between motor and cognitive lobules. We observed negative associations between left SA and right lobules VIIIB and VIIIA similarly to lobules III and IV. However, the associations between right VIIIB and SA were predominantly positive. SA of left frontal regions was strongly positively associated

with lobules Crus I and Crus II, with weaker associations with other lobules. A similar pattern of associations was observed for the right hemisphere, where SA was positively associated with volumes of lobules III–Crus II as well as VIIIB, and negatively associated with VIIIB and VIIIA.

3.2 | Similarity Assessment

To quantify similarity in cerebellar–cortical structural covariance between motor and cognitive regions, we investigated whether the distributions of covariance were correlated across lobules for CT and SA. As a measure of similarity, we calculated the correlation between hemispherical covariance maps for each pair of lobules (Figure 3). Each association map is compared to

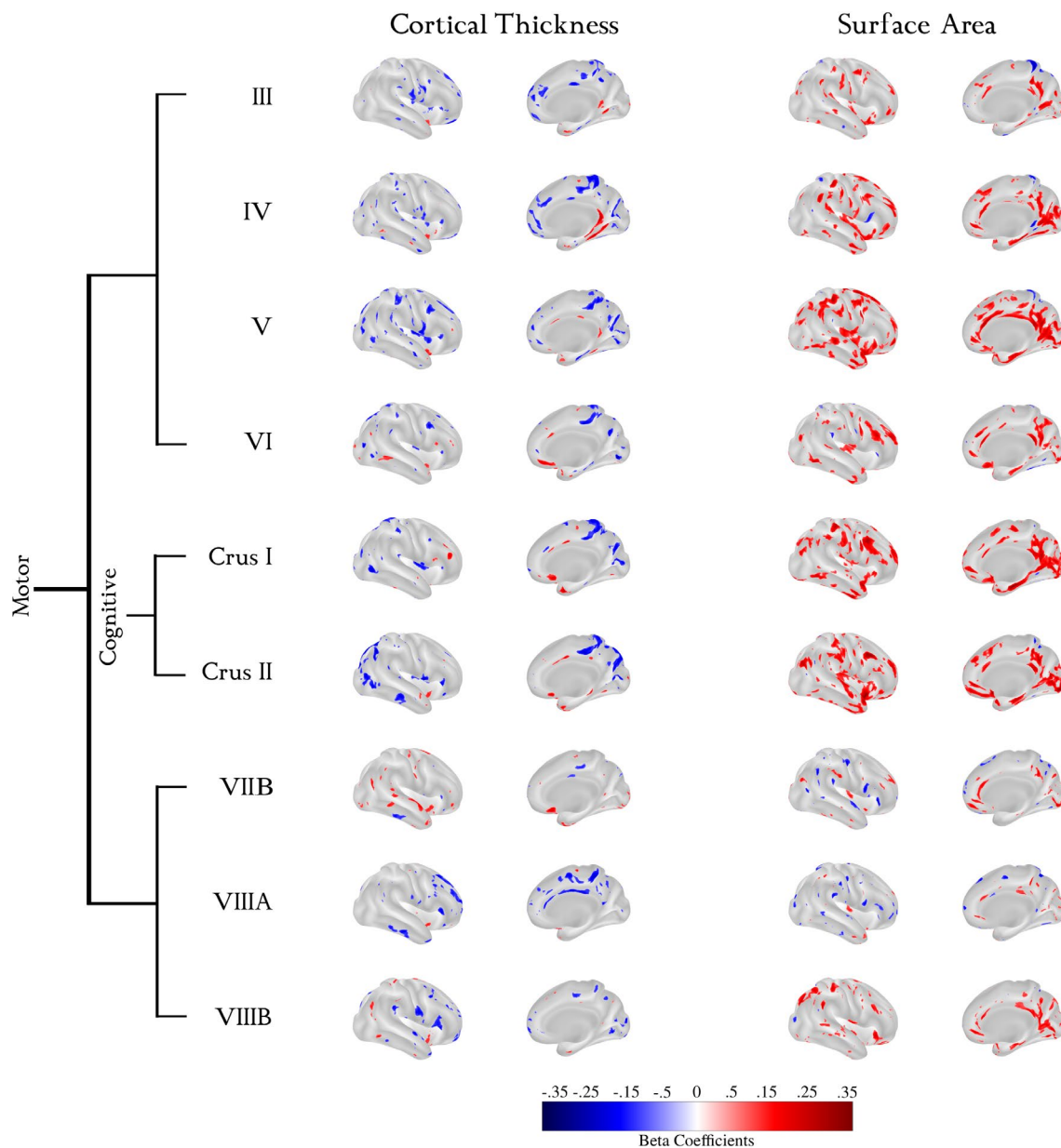


FIGURE 2 | Vertex-wise beta coefficients of the association between CT and SA of the right cortex and the volumes of left cerebellar lobules while accounting for age and sex. Each brain-plot represents the association between the cortical measure (top) of one hemisphere (lateral and medial view) and the volume of the contralateral cerebellar lobule (left). Blue indicates a negative association while red indicates a positive one. The unthresholded beta maps for left and right CT and SA are included as Figure S1.

other maps in the same hemisphere for either CT or SA, summarizing vertex-wise similarity between each pair of lobules in one score.

We observed a clear delineation of motor versus cognitive cerebellar lobules in their associations with the cortex (Figure 3). Except for the comparisons between lobules VII B with VI and Crus II, and VIII A with IV in their association with left CT, all correlations were statistically significant (permuted p values < 0.05). For CT, motor lobules III–V showed higher similarity among themselves and lower similarity with lobules VI, Crus I and VII B. Cognitive lobules Crus I and II also showed higher similarity with each other and greater dissimilarity with lobules III–V and VIII A and VII B. Lobule VI appears to be a transitional area, showing higher

similarity with Crus I and III (than the other motor lobules) and lower similarity with other motor lobules. Similarity was generally lower in the left than the right hemisphere.

The similarity between cognitive and motor lobules was overall lower for SA. Motor lobules III–V again showed higher similarity with each other and greater dissimilarity with lobules Crus I and II, and VIII A. Cognitive lobules Crus I and II were more similar to each other and showed lower similarity with lobules VII B and VIII A. Lobule VI again was found to be more similar to Crus II and more dissimilar to lobules VII B and VIII A. Inferior motor lobules VII B and VIII A also showed marked lower similarity from all other regions. For SA, lobular similarities appear to be more pronounced for the left, compared to the right hemisphere.

Cortical Thickness

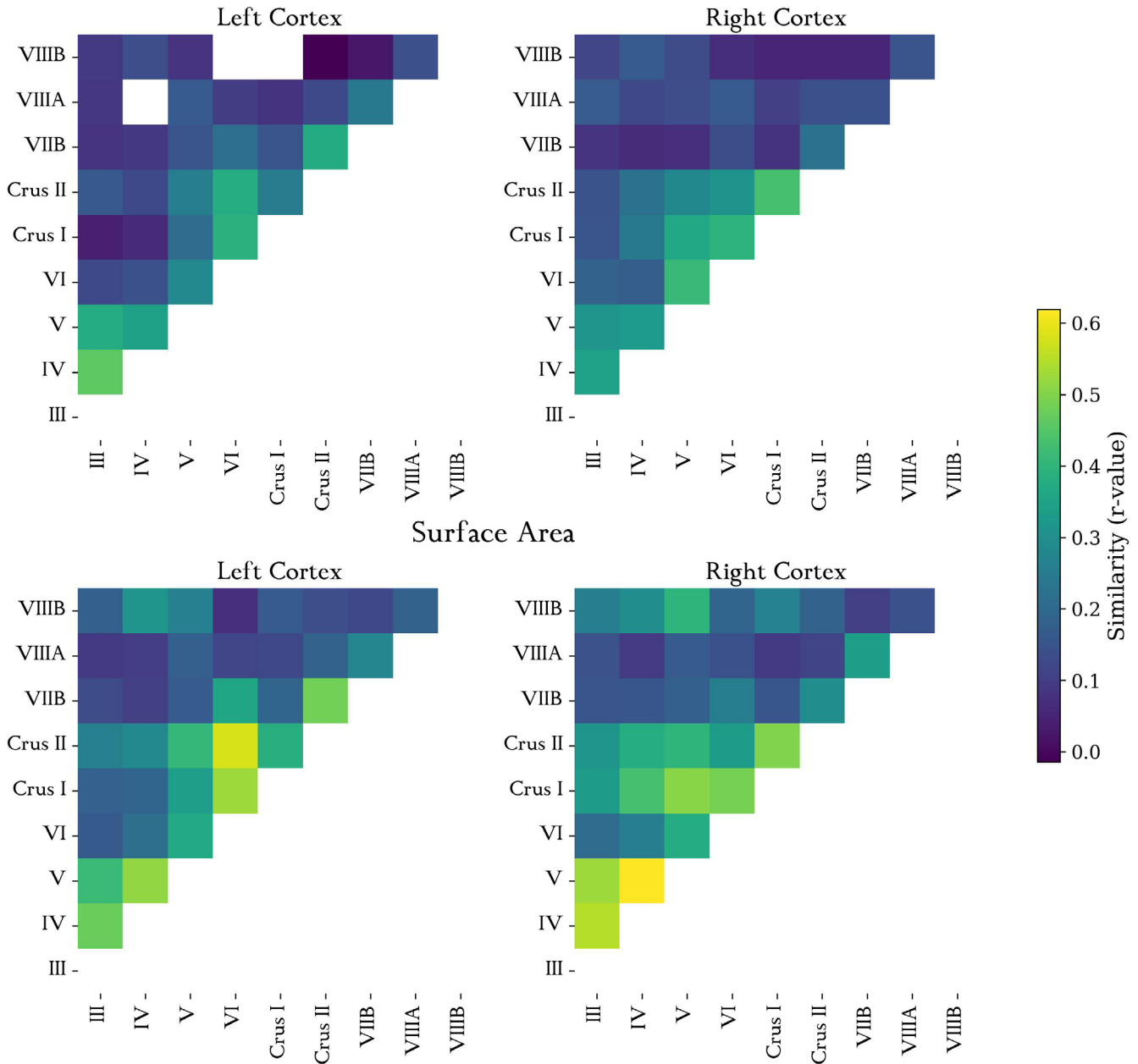


FIGURE 3 | Statistically significant correlation coefficients between each pair of cerebellar–cortical associations, for each structural measure of each hemisphere. The color represents the similarity between each brain-plot in Figures 1 and 2 and all the other plots below it, for all possible pairs. White square represents nonstatistically significant similarity.

4 | Discussion

The goal of the current study was to examine the pattern of cerebellar–cortical structural covariance in motor and cognitive networks. Overall, our findings revealed a pattern of cerebellar–cortical covariance that differed between sensorimotor versus cognitive regions, for cortical thickness and surface area, and between the left and right hemispheres. Cortical thickness showed predominantly negative relationships with cerebellar volume, particularly in sensorimotor, parietal, and frontal regions of the left hemisphere. Surface area showed a predominantly positive relationship with cerebellar volumes, particularly in sensorimotor, parietal, frontal, and temporal lobe regions bilaterally.

Motor lobules (III–VI and VII B–VIII B) of the cerebellum showed greater covariance with sensorimotor regions of the cortex, and cognitive lobules (Crus I and Crus II) showed greater positive covariance with frontal and temporal regions. The pattern of cerebellar–cortical covariance for both cortical thickness and surface area differed across regions, with covariance being more similar within sensorimotor and cognitive networks and more dissimilar between them. Similarity in the pattern of covariance of each lobule with the cortex showed a gradual transition between sensorimotor and cognitive lobules, with lobules III–V showing the greatest dissimilarity with lobules VI, and VII B showing greater similarity to Crus I and II. Taken together, these findings are consistent with the known pattern of anatomical connectivity

between different cerebellar lobules and the cortex. In addition, they shed new light on the relationship between cerebellar volumes and different cortical features, showing that larger cerebellar volumes are related to reduced cortical thickness but greater surface area. Surface area has been hypothesized to be under greater genetic control (Bishop, Goudreau, and O'Leary 2000; Sanabria-Diaz et al. 2010; Yoon, Perusse, and Evans 2012) while cortical thickness is thought to be more malleable by experience (Amlien et al. 2016). This suggests that covariance between cerebellar volumes and surface may be a more stable feature, whereas covariance with cortical thickness may be more affected by development. This is consistent with the interactive specialization framework which proposes that functionally connected brain regions develop in tandem (Johnson 2011).

For both the left and right hemisphere, cerebellar motor lobules III–V and VIIIA and VIIIB showed primarily negative associations with sensorimotor and parietal cortical regions in cortical thickness. In contrast, lobules VI and Crus I showed positive associations with frontal regions, with those in Crus I exhibiting larger spatial extent in the right hemisphere. In a parallel finding, but with reversed direction, motor lobules III–V and VIIIB, VIIIA, and B showed predominantly positive associations with cortical surface area in sensorimotor regions of the cortex, and with more frontal regions that appeared to increase in coverage from lobules III–VI. This culminated in Crus I and II, which were found to be more strongly positively associated with surface area of cortical frontal regions. The patterns of observed differences in structural covariance were supported by their similarity which shows clearly that cerebellar–cortical covariance within motor and cognitive regions is more similar than covariance across these regions, and that similarity decreased at the transition from motor (III and IV) to cognitive (Crus I and Crus II) and back to motor (VIIIA and VIIIB) lobules.

In line with our hypotheses, these differing patterns of cerebellar–cortical structural covariance are consistent with known anatomical connectivity in primates (Kelly and Strick 2003), with studies in humans using diffusion-weighted imaging (Habas and Cabanis 2007; Rousseau, Chakravarty, and Steele 2022; Steele and Chakravarty 2018) and with evidence from resting-state functional connectivity (Bernard et al. 2012; Krienen and Buckner 2009; Stoodley and Schmahmann 2010). In primates, lobules III–VI as well as VIIIA and VIIIB project primarily to motor cortical regions, while Crus I and II connect primarily to prefrontal regions (Kelly and Strick 2003). Evidence for a similar pattern of connectivity has been found using diffusion imaging in humans, showing distinct motor and nonmotor divisions in the dentate nucleus and the pons (Rousseau, Chakravarty, and Steele 2022; Steele et al. 2017). In parallel, patterns of resting-state functional connectivity between the cerebellum and sensorimotor and prefrontal regions match the anatomical connections between the regions described above (Buckner et al. 2011; Ji et al. 2019; Marek et al. 2018; O'Reilly et al. 2010). Finally, task-based studies show specific activation of sensorimotor regions of the cerebellum and cortex for sensorimotor tasks and lobules Crus I and Crus II and the prefrontal cortex for cognitive tasks (King et al. 2019, 2023; Salmi et al. 2010; Stoodley, Valera, and Schmahmann 2012).

Thus the observed pattern of structural covariance is consistent with known segregation of the sensorimotor and cognitive cortico-cerebellar networks. This segregation is also supported by the similarity results, which showed that covariation was more similar within the motor and cognitive networks than between them. Despite this broad segregation into motor and cognitive domains, we also observed a transitional zone at the border of motor to cognitive representations for lobules VI and VIIIB. This is consistent with the observation of multiple gradients of functionally defined continuous representations that do not strictly match lobular structural boundaries (Guell and Schmahmann 2020; King et al. 2019).

An intriguing finding from this study is the differing relationship between cerebellar volumes and the cortical metrics; while cerebellar volumes exhibited largely negative relationships with cortical thickness, they showed largely positive relationships with surface area. These opposite relationships may be due to differing developmental trajectories: surface area increases up until age 12 with little change thereafter, while cortical thickness peaks in infancy and then decreases until the third decade of life (Amlien et al. 2016; Bethlehem et al. 2022). Based on this, variation in surface area is thought to be largely under genetic control, while variation in cortical thickness is thought to reflect a combination of accumulated genetic and environmental effects (Roe et al. 2023). Together with our findings, this suggests that interactions between cerebellar and cortical regions across development may lead to correlated structural plasticity, although it is not clear what underlying mechanisms would lead to positively correlated versus negatively correlated changes.

Structural covariance is thought to be driven by structural and functional connectivity (Alexander-Bloch, Giedd, and Bullmore 2013). Therefore, covariation between cerebellar and cortical regions is consistent with the idea that functionally and structurally connected regions may develop in tandem, a concept known as interactive specialization (Johnson 2011). Developmental data show that GM volume of anterior motor regions, including M1 and PMC has a peak rate of change between the ages of 6 and 8 (Bethlehem et al. 2022; Giedd et al. 1999). In contrast, peak maturation in the cerebellum occurs later, between the ages of 12 and 18 (Bethlehem et al. 2022; Tiemeier et al. 2010). The interactive specialization framework proposes that connected brain regions or networks interact during development to reciprocally influence maturation (Johnson 2011). In the case of the cortex and cerebellum, we propose that dense connectivity drives plasticity, and that the structure of these regions changes interactively (Fjell et al. 2019; Penhune 2020). The cerebellum has been hypothesized to support the optimization of both motor and cognitive functions through its loop circuits with different cortical regions (Bostan, Dum, and Strick 2013), possibly through encoding of predictions and error correction (Sokolov, Miall, and Ivry 2017). Thus optimal functioning is contingent on the co-development of the cortex and the cerebellum. This idea is supported both by correlated cerebellar and cortical structural changes in early-trained musicians (Shenker et al. 2022) and in rodents exposed to an enriched environment (Scholz, Allemang-Grand, et al. 2015; Scholz, Niibori, et al. 2015). Earlier-maturing sensorimotor cortical networks may modulate the development of later-maturing cerebellar networks. Later in development, however, cerebellar mechanisms related to forward models and

optimization may contribute to the fine-tuning of motor and cognitive functions observed in adolescence and early adulthood (Fuhrmann, Knoll, and Blakemore 2015).

Finally, our results also show that the degree of covariance was overall stronger for the left compared to the right hemisphere. This may be due to typical left-hemisphere dominance for control of the right hand and language functions. It may also be due to differences in intra- and inter-hemispheric connectivity where the left hemisphere is characterized by stronger within-hemisphere networks and the right by broader, more distributed connections (Iturria-Medina et al. 2011).

Although we aimed to decompose cortical volumes into more basic elements by using cortical thickness and surface area, it remains difficult to attribute the patterns of structural covariance that we observed to specific molecular or physiological causes. Further research is needed to examine the mechanisms that drive structural covariance or determine the direction of correlated change. One approach that could address this would be to look at covariance in a longitudinal sample of children where patterns of change in cerebellar volume could be related to changes in cortical metrics across development. It is also likely that the observed patterns of cerebellar–cortical structural covariance would differ with aging since surface area and cortical thickness follow different trajectories (Lemaitre et al. 2012). Another direction for future work would be to decompose cerebellar volumes into surface area and cortical thickness in order to examine covariation with cortex for each metric separately. While we were able to estimate lobular volumes with high accuracy, the cerebellar cortex is a dense and highly gyrified structure, rendering results from commonly used tools to measure cortical thickness and surface unreliable (Lundell and Steele 2024; Sereno et al. 2020). In the future, the use of high-field strength scanners may resolve these limitations.

5 | Conclusion

The observed pattern of cerebellar–cortical structural covariance largely mirrors known structural and functional connectivity, where sensorimotor and cognitive regions are connected in partially separate loops. Similarity metrics also identified transitional regions at the boundaries of motor and cognitive lobules, consistent with evidence of functional gradients, rather than sharp boundaries within the cerebellum. Patterns of structural covariation differed for surface area and cortical thickness, consistent with evidence that individual variation in these features results from either greater genetic or environmental influences. Together, these findings support the interactive specialization framework which proposes that structurally and functionally connected regions mutually influence each other during development.

Data Availability Statement

The data that support the findings of this study are available in Human Connectome Project at <https://www.humanconnectome.org/study/hcp-young-adult>. These data were derived from the following resources

available in the public domain: - Human Connectome Database, <https://db.humanconnectome.org/app/template/Login.vm?sessionId=98B4357A64C4CFAF607FC18F3AA4506E>.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.