RESEARCH ARTICLE

Progressive Voxel-Wise Homotopic Connectivity from childhood to adulthood: Age-related functional asymmetry in resting-state functional magnetic resonance imaging

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Abstract

Homotopic connectivity during resting state has been proposed as a risk marker for neurologic and psychiatric conditions, but a precise characterization of its trajectory through development is currently lacking. Voxel-Mirrored Homotopic Connectivity (VMHC) was evaluated in a sample of 85 neurotypical individuals aged 7–18 years. VMHC associations with age, handedness, sex, and motion were explored at the voxel-wise level. VMHC correlates were also explored within 14 functional networks. Primary and secondary outcomes were repeated in a sample of 107 adults aged 21–50 years. In adults, VMHC was negatively correlated with age only in the posterior insula (false discovery rate $p < .05$, >30-voxel clusters), while a distributed effect among the medial axis was observed in minors. Four out of 14 considered networks showed significant negative correlations between VMHC and age in minors (basal ganglia $r = −.280$, $p = .010$; anterior salience $r = −.245$, $p = .024$; language $r = −.222$, $p = .041$; primary visual $r = −.257$, $p = .017$), but not adults. In minors, a positive effect of motion on VMHC was observed only in the putamen. Sex did not significantly influence age effects on VMHC. The current study showed a specific decrease in VMHC for minors as a function of age, but not adults, supporting the notion that interhemispheric interactions can shape late neurodevelopment.

KEYWORDS
development cognitive neuroscience, fMRI, hemispheric lateralization, neurodevelopment, neuroimaging, VMHC

1 | INTRODUCTION

Historically, the brain topology of several cognitive functions has been identified studying focal lesions (Ratiu et al., 2004). These findings have highlighted the frequent predominance of one hemisphere over the other in determining a specific function, that is, hemispheric specialization. Most evidence concerns the hemispheric specialization of brain functions such as emotion recognition (Damasio et al., 1994), language processing (Mohr et al., 1978), or visuospatial discrimination

processes (Dell'Acqua et al., 2011). More recently, functional asymmetry has been appraised through multiple neuroimaging modalities in the human brain, and persuading evidence has been offered for the notion of an overall trend in hemispheric specialization for emotional processing (Fusar-Poli et al., 2009) and language tasks (Riès et al., 2016), although significant interindividual differences seem to be described. Further evidence corroborated functional asymmetry in the brain at the molecular and cellular level (Kantonen et al., 2020; Toga & Thompson, 2003), yet a high degree of hemispheric specialization

is not always advantageous at the individual, group, or population level (Paszulewicz et al., 2020). On the contrary, a high degree of hemispheric specialization has been observed as a predisposing factor for greater risks of performance deficits subsequent to structural lesions (Knecht et al., 2002). Similarly, the clinical relevance of increased or decreased hemispheric specialization in psychiatry has yet not been fully elucidated, despite multiple theories relying on atypical lateralization as a mechanism for the onset of neuropsychiatric disorders (Angrilli et al., 2009; Berretz et al., 2020; Vingerhoets, 2019).

For what concerns resting-state functional magnetic resonance imaging (fMRI), interhemispheric connectivity has been shown to be negatively associated with functional lateralization (Stark et al., 2008). In other words, the higher the interhemispheric connectivity in a brain region, the less likely its association with hemispheric specialization (Stark et al., 2008). However, this association seems to be complex, as regions consistently recognized as part of lateralized networks (eg, language processing areas) may exhibit a relatively high degree of interhemispheric connectivity during resting state (Dorsaint-Pierre et al., 2006; Stark et al., 2008). Recent studies described the longitudinal changes in brain structure across the life span (Brouwer et al., 2022; Mills et al., 2021), and similar approaches have only recently started to populate the scientific literature for what concerns functional connectivity and its association with age or development. More importantly, longitudinal approaches in neuroimaging studies are mostly focused on early infancy in order to characterize neurodevelopment (Dubois et al., 2014; Gao et al., 2015; Woodburn et al., 2021), or on senescence in order to examine neurodegeneration (Damoiseaux, 2017; Xu et al., 2021). However, novel evidence has highlighted the important modulation in the functional organization of the brain during late childhood, adolescence, and early adulthood (Kim-Spoon et al., 2021; Kundu et al., 2018; Mills et al., 2021; Woodburn et al., 2021). This evidence seems of primary importance considering how a high proportion of psychiatric disorders arise during this time period (Kessler et al., 2007), and how an earlier time of onset can be associated with a worse presentation or outcome (Cornelius et al., 2016).

Since Voxel-Mirrored Homotopic Connectivity (VMHC) was implemented as a method for measuring interhemispheric connectivity in fMRI during resting state, contrasting results started to populate the scientific literature. Some studies suggested a marked and generalized lateralization/asymmetry during resting state among healthy individuals (Agcaoglu et al., 2015, 2021). Other studies described brain asymmetry as a localized property exclusively involving a small number of brain regions—in particular, default mode and language network (Nielsen et al., 2013; Raemaekers et al., 2018). Early results in the field of fMRI showed that the degree of symmetry between geometrically corresponding interhemispheric regions, that is, homotopic connectivity, actually followed a quadratic trajectory during development (Zuo et al., 2010). Agcaouglu and colleagues (2021) observed a complex association between functional lateralization and age in a sample of children between 6 and 10 years old. Sex and handedness were both significantly associated with functional lateralization in the same sample (increased lateralization in dorsolateral frontal cortex, decreased lateralization in auditory and sensorimotor regions), but no associa-

tion between functional lateralization and behavioral scores was found. Altogether, whether functional lateralization can be considered a protective proxy for typical development is currently disputed (Knecht et al., 2000; Szaflarski et al., 2002), and only a limited number of studies approached this topic considering the age-related trajectories.

Although a significant difference underlies spatial and functional homotopy, the current study addressed specifically the degree of connectivity between geometrically corresponding interhemispheric regions. In fact, brain regions seldom have their functional hemispheric correspondent in a spatially homotopic manner (Joliot et al., 2015). However, homotopic connectivity has been recently proposed as a risk marker for neurologic or psychiatric conditions (Chen et al., 2021; Fan et al., 2018; Hermesdorf et al., 2016), and the characterization of brain networks by degree of interhemispheric connectivity has been proposed as a reliable marker of disease (Cheung et al., 2021). The use of VMHC also seems supported by evidence of high test–retest stability (intraclass correlation coefficient $\geq$.8; Dai et al., 2020), in contrast with similar measurements (Hagemann et al., 2002). As descriptions of developmental trajectories for homotopic connectivity are currently lacking, the current study addressed resting-state VMHC in neurotypical children and adolescents. A first characterization of neurotypical development may also provide future insight on neuropsychiatric disorders. In fact, not only atypical development is often recognized as either their precipitating or maintaining factor (Kumar et al., 2019; Rice et al., 2019), but also early onsets of these conditions are strongly associated with worse prognosis (Cirone et al., 2021; Driver et al., 2020; Franke et al., 2018; Rice et al., 2019). Finally, the current study aimed at offering novel evidence on interhemispheric connectivity during resting state as assessed by fMRI.

1.1 | Aims

The primary aim of this study was to evaluate the role of age in the voxel-wise interhemispheric interaction of the brain (measured through VMHC) in a sample of 85 children/adolescents 7–18 years old. The potential interaction between individual factors (handedness, age, sex, motion) and results was evaluated. As secondary analysis, the voxel-wise-level results were assessed using a region-of-interest approach at the functional network level, the role of individual factors explored (handedness, age). Furthermore, control analyses were performed. Both voxel-wise and network-level analyses were repeated in a sample of adults (107 individuals, 21–50 years old), expecting that age-related VMHC modifications were specific for childhood/adolescence, changing their trajectory in adulthood.

2 | MATERIALS AND METHODS

2.1 | Sample description

The primary sample was obtained from the New York University dataset of the ADHD200 repository, specifically from the International

Neuroimaging Data-Sharing Initiative (for further information, please see Castellanos et al., 2008). Resting-state scans of 99 neurotypical participants were retrieved from the original sample; 85 included after motion and quality control. All subjects were right handed, but handedness was evaluated in a dimensional manner through the Edinburgh Handedness Inventory (Oldfield, 1971). Only the scans of neurotypical subjects were included in the analyses. MRI data were acquired on a 3T Siemens Magnetom Allegra scanner (syngo MR 2004A). Functional MRI scans were collected using a T2*-weighted echo-planar imaging (EPI) sequence with the following parameters: slice thickness, 4 mm; repetition time, 2 s; echo time, 15 ms; and flip angle, 90°. An anatomical scan was acquired for each participant, in order to align the functional data to the anatomical brain. All anatomical scans were defaced in order to preserve anonymity. The resting-state fMRI scan lasted 360 s. Participants were asked to remain still, close their eyes, and not fall asleep; they were not presented with any stimuli or asked to respond during the scan. Participants were exposed to a blank screen during scan.

The adult sample was gathered from an open-access neuroimaging dataset, specifically from the UCLA Consortium for Neuropsychiatric Phenomics (Poldrack et al., 2016). A total of 130 adults were retrieved from the original sample; 107 included after motion and quality control. Further details about recruiting can be found in Poldrack et al. (2016). All subjects were right handed, but handedness was evaluated in a dimensional manner through the Edinburgh Handedness Inventory (Oldfield, 1971). Only the scans of neurotypical subjects were included in the analyses. MRI data were acquired on one of two 3T Siemens Trio scanners. Functional MRI scans were collected using a T2*-weighted EPI sequence with the following parameters: slice thickness, 4 mm; repetition time, 2 s; echo time, 20 ms; and flip angle, 90°. An anatomical scan was acquired for each participant, in order to align the functional data to the anatomical brain. All anatomical scans were defaced in order to preserve anonymity. The resting-state fMRI scan lasted 304 s. Participants were asked to remain relaxed and keep their eyes open; they were not presented with any stimuli or asked to respond during the scan.

2.2 | Preprocessing

fMRI data preprocessing steps were implemented in Analysis of Functional NeuroImages (AFNI) (Cox, 1996; Cox & Hyde, 1997; Taylor & Saad, 2013). First, the structural and functional reference images were co-registered (Saad et al., 2013). The first four frames of each fMRI run were removed in order to discard the transient effects in amplitude observed until magnetization achieves steady state (Caballero-Gaudes & Reynolds, 2017). Slice timing correction (Konstantareas & Hewitt, 2001) and despike methods (Satterthwaite et al., 2013) were applied. Rigid-body alignment of the structural and functional image was performed. The anatomical image was then warped using the Montreal Neurological Institute standard space template (MNI152). The "2009c" symmetric template of the MNI152 initiative was chosen as the

template of choice. Volume registration was then used to align the functional data to the base volume, warping it to the stereotactic space of choice. Spatial blurring was performed, with a kernel of full width at half maximum of 6 mm. Bandpass (0.01–0.1 Hz) was performed (Shirer et al., 2015). Each of the voxel time series was then scaled to have a mean of 100. To control for nonneural noise, regression based on the rigid body motion parameters and their derivatives was applied, as well as mean time series from cerebrospinal fluid masks (Fox et al., 2005; Vovk et al., 2011) eroded by one voxel (Chai et al., 2012). Regression of white matter artifacts was performed through the fast ANATICOR technique as included in AFNI (Jo et al., 2010). To further improve motion correction, censoring of voxels with a framewise displacement (FD) above 0.5 mm was applied (Power et al., 2014) to the time series. Subjects with excessive motion were excluded; excessive motion was defined as >2 mm translation or >2° rotation and/or more than 20% of time points above FD 0.5 mm. The same preprocessing steps were applied to the adult sample.

2.3 | Voxel-Wise Homotopic Connectivity

VMHC is a measure of interhemispheric connectivity between corresponding areas in fMRI (Wei et al., 2018). VMHC measures the level of symmetry, or correlation, between left/right pairs of voxels or brain areas. VMHC values were computed by calculating the Pearson's correlation coefficients between each voxel and its interhemispheric counterpart in the mirrored symmetrical brain space. Thereafter, the correlation values were z-transformed to improve normality: whole-brain, voxel-wise VMHC maps were computed for each participant, then normalized using Fisher z-transformation (Zuo et al., 2010). The adopted formula for computing Z-transformed VMHC values was as follows:

$$\frac{1}{2} \ln \frac{(1 + \rho)}{(1 - \rho)},$$

where ρ represents voxel-wise VMHC values.

2.4 | VMHC, voxel-wise analyses

The main effect of age was estimated through the 3dttest++ function as implemented by AFNI (Cox, 1996), including handedness and sex as covariates. A false discovery rate-corrected threshold (FDR-p) of .05 was set as statistical significance for voxel-wise t-tests. Significant voxels after thresholding were reported after clustering in order to remove potential, isolated, artifacts. A minimum cluster of 30 voxels with three nearest neighbors (NNs) was selected in accordance with previous literature (Damiani et al., 2020). The resulting mask was compared to the CA_ML_18_MNI atlas of AFNI, through the whereami function. The CA_ML_18_MNI was developed from maximum probability maps of cytoarchitectonic atlases. Please see Eickhoff et al. (2005, 2006, 2007) for further details.

2.5 | VMHC, network-based analyses

Fourteen reference networks were obtained from the Functional Imaging in Neuropsychiatric Disorder Lab website—University of Stanford (Shirer et al., 2012). In accordance with the original publication by Shirer et al. (2012), and with the literature using the template (Hall et al., 2013; Tarchi et al., 2022), the atlas was composed by the following networks: anterior salience, auditory, basal ganglia, dorsal and ventral default mode, language, left and right executive control, posterior salience, precuneus, sensorimotor, high and primary visual, and visuospatial. Mean VMHC values per network and their variance were calculated by averaging results per network mask. Normality was tested with the Kolmogorov–Smirnov test; data were assumed as normally distributed if p-value was greater than .05. Correlation coefficients were calculated for each network between age and mean VMHC value through Pearson's r. The role of handedness in VMHC was estimated. Estimated correlation coefficients for handedness were reported. Results were considered significant if p-value was below .05. Finally, as VMHC is a dimensionless variable, the degree of homotopy as measured by different scanning procedures could not be directly compared between the adult and minor samples.

2.6 | Analyses in adult sample

The primary analyses were repeated in a resting-state fMRI sample of adults aged between 21 and 50 years. The sample was chosen in a reduced window of age as to exclude the potential effect of pathological aging in the characterization of brain laterality (Li et al., 2018; Zhao et al., 2020). Correlations of VMHC with age, handedness, and motion were calculated. Significant voxels after thresholding were reported after clustering in order to remove potential, isolated, artifacts. A minimum cluster of 30 voxels with thee NNs was selected. Boxplot distributions of VMHC values per network were plotted. Potential group differences in VMHC values between adults and minors at the network level were not directly calculated as differences in scanning parameters and equipment could inflate Type I statistical errors (Friedman et al., 2008; Sutton et al., 2008).

2.7 | Control analysis, the role of motion

The effect of motion in the samples was evaluated through voxel-wise associations between VMHC and motion (mean FD value per run) both for the sample of minors and adults. Correlations between VMHC network values and motion (mean FD value per run) were also evaluated both for the sample of minors and adults.

3 | RESULTS

3.1 | Descriptive statistics

In the sample of NYU minors, five participants were excluded as no information was retrievable about handedness. A final count of 85 participants were included in the study. The age in the sample ranged from 7 to 18 years; the mean age at the time of the scan was 12.39 years ($SD = 3.12$). Forty-six participants were female and 39 male. The average handedness quotient was 0.62 ($SD = 0.23$).

In the sample of UCLA adults, 23 participants were excluded after quality checks and motion control, finally including 107 individuals. Age ranged from 21 to 50 years (mean = 30.85, $SD = 8.6$). Fifty-one participants were female and 56 male. The average handedness quotient in the sample of adults was 0.95 ($SD = 0.12$).

3.2 | VMHC, age effect and interactions

Age was negatively correlated with VMHC in 1184 voxels (Figure 1) bilaterally in the basal ganglia, anterior and posterior cingulate cortex, superior and medial prefrontal cortex, primary motor cortex, medial and inferior temporal cortex, and superior and middle orbital gyri, indicating a decrease in interhemispheric interaction in these areas from late childhood to adolescence. A list of overlapping regions between results and the CA_ML_18_MNI atlas (as implemented in AFNI) is offered in Table S1.

At the voxel-wise level, handedness did not significantly influence the age effect, as expected as all individuals were right-hand dominant, with no surviving voxel at FDR-$p < .10$. Sex also did not significantly influence the observed age effect, with no surviving voxel at FDR-$p < .10$.

3.3 | VMHC, network-based analyses

All variables were assumed as normally distributed, as all variables showed a p-value greater than .05 at the Kolmogorov–Smirnov test. The primary visual network (mean VMHC = 10.182, $SD = 2.214$) and the precuneus showed the highest mean VMHC values (9.789, $SD = 1.461$), indicating a high degree of interhemispheric interaction. The left and right executive networks (3.525, $SD = 0.803$ and 3.195, $SD = 0.723$, respectively), as well as the language network (3.254, $SD = 0.861$), showed the lowest mean VMHC (Table 1).

Analyses of correlations between age and network-level VMHC showed significant negative correlations for the anterior salience ($r = -.245$, $p = .024$), basal ganglia ($r = -.280$, $p = .010$), dorsal default mode ($r = -.289$, $p = .007$), language ($r = -.222$, $p = .041$), and primary visual ($r = -.257$, $p = .017$) networks, indicating a lower degree of interhemispheric interaction in these regions with increasing age from childhood to adolescence (Table 2). No network was significantly correlated with handedness.

3.4 | Results in adult sample

When the analyses were repeated on the adult sample, in order to control for the specificity of our findings as for what concerns adolescence—UCLA sample—the effect of age on the interhemispheric interaction of the brain at the voxel-wise level resulted in 148 voxels in
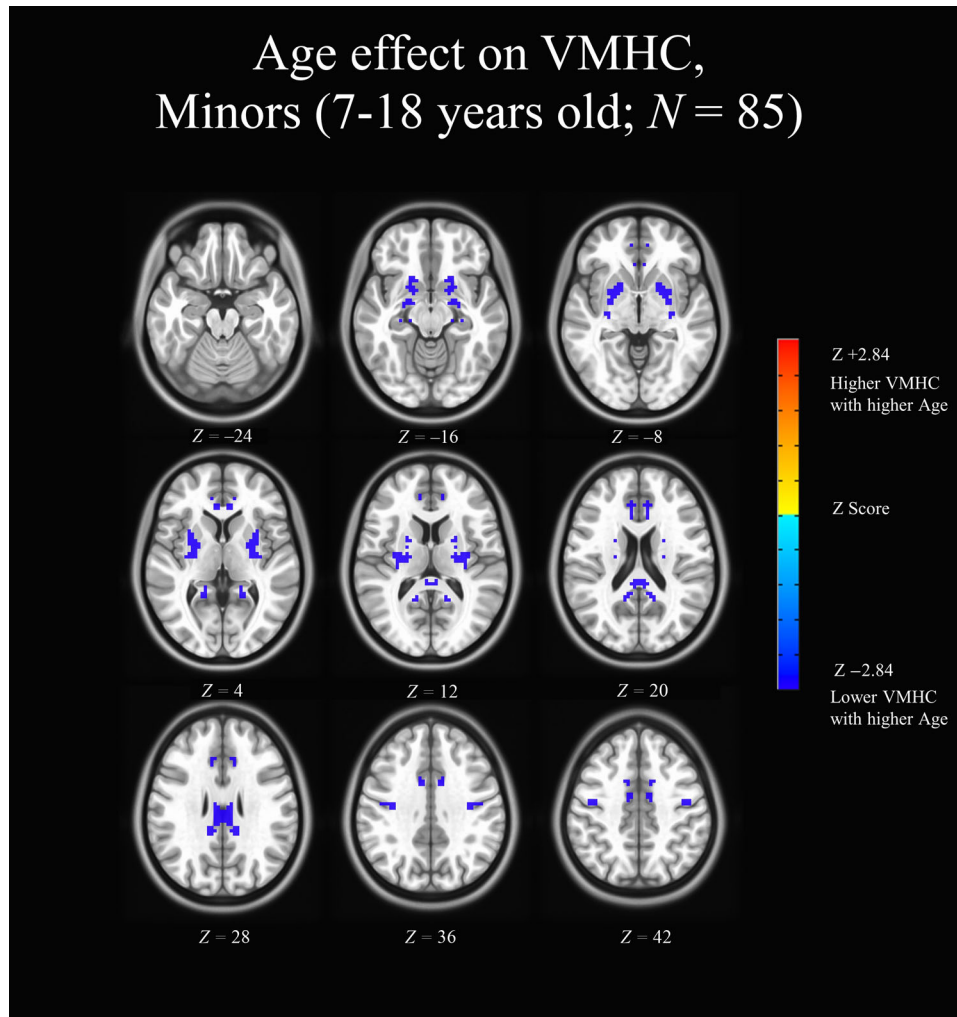
FIGURE 1 Age effect on interhemispheric connectivity. VMHC decreases with age in minors in the basal ganglia, anterior and posterior cingulate cortex, superior and medial prefrontal cortex, primary motor cortex, medial and inferior temporal cortex, and superior and middle orbital gyri. Surviving voxel at FDR-p = .05—clustered for minimum 30 voxels, NN 3. Results displayed on the MNI 152 symmetric template, resolution 1 mm^3. Surviving voxels after thresholding: 1184 (functional image resolution: 3 mm^3)

the posterior insula surviving FDR correction of 0 (see Figure 2). The effect of motion was also evaluated in the sample of adult participants, with no surviving voxel at FDR-$p < .10$. For network-level VMHC, similar to the sample of minors, VMHC showed the highest mean values for the primary visual network and precuneus (mean VMHC = 11.547, SD = 2.136 and mean VMHC = 11.106, SD = 1.385, respectively) and the lowest for the left and right executive network (4.562, SD = 0.855 and 4.493, SD = 0.814, respectively) and the language Network (4.565, SD = 1.212; see Table 2). Network-level correlation analyses showed an effect for age on VMHC in the dorsal default mode ($r = -.335$, $p < .001$), high visual ($r = -.303$, $p = .001$), posterior salience ($r = -.233$, $p = .013$), and visuospatial networks ($r = -.266$, $p = .004$). A borderline-significant negative correlation between VMHC and handedness was observed in the posterior salience ($r = -.184$, $p = .050$; see Table 2). Boxplot distributions, for both samples, are offered in Figure S2.

3.5 | Control analysis, the role of motion

In minors, motion was positively correlated to VMHC in the putamen with 238 surviving voxels at FDR-$p < .05$ (Figure S1). As the relationship between age and VMHC was negative, and, conversely, positive between VMHC and motion, the effect of motion could potentially mitigate the size effect of previously shown results.

For what concerns network-level analyses among minors, the left executive ($r = .233$, $p = .032$) and right executive ($r = .264$, $p = .014$) networks were positively correlated with motion (see Table S1). Motion had a positive correlation with VMHC value in the sensorimotor ($r = .234$, $p = .015$) network among adults (see Table S2). As in the voxel-wise analyses, motion was positively correlated with VMHC, thus inducing a potential mitigating effect on previously shown results.

TABLE 1 Network-based VMHC, mean values and standard deviations

Network	Minors (7–18 years; N = 85)	Adults (21–50 years; N = 107)
Anterior salience	6.916 (SD = 0.942)	7.450 (SD = 1.182)
Auditory	5.543 (SD = 1.637)	6.764 (SD = 2.029)
Basal ganglia	4.341 (SD = 1.331)	5.170 (SD = 1.356)
Dorsal default mode	9.086 (SD = 1.082)	9.761 (SD = 1.172)
High visual	5.171 (SD = 1.934)	6.596 (SD = 2.132)
Language	3.254 (SD = 0.861)	4.565 (SD = 1.212)
Left executive control	3.525 (SD = 0.803)	4.562 (SD = 0.855)
Posterior salience	4.573 (SD = 1.052)	6.042 (SD = 1.175)
Precuneus	9.789 (SD = 1.461)	11.106 (SD = 1.385)
Primary visual	10.182 (SD = 2.214)	11.547 (SD = 2.136)
Right executive	3.195 (SD = 0.723)	4.493 (SD = 0.814)
Sensorimotor	4.634 (SD = 1.161)	6.770 (SD = 1.576)
Ventral default mode	6.353 (SD = 1.128)	7.943 (SD = 1.063)
Visuospatial	3.849 (SD = 1.057)	5.496 (SD = 1.169)

Note: Precuneus and primary visual network were observed to report the highest mean VMHC values among both minors and adults. Conversely, left and right executive control and language networks were observed to report the lowest mean VMHC values among both samples.

4 | DISCUSSION

The current study addressed resting-state interhemispheric interactions during late childhood and adolescence. Both voxel-wise and network-based methods were used and both approaches showed a gradual decline in interhemispheric interactions with age, indicating increasing hemispheric specialization. VMHC was negatively correlated with age in basal ganglia, anterior and posterior cingulate cortex, superior and medial prefrontal cortex, primary motor cortex, medial and inferior temporal cortex, and superior and middle orbital gyri—as to indicate a higher degree of asymmetry in these areas after adolescence. Network-based analyses confirmed the voxel-wise findings, highlighting an age effect from late childhood to adolescence in the basal ganglia, salience, default mode, and language networks.

Brain areas shown to be interested by significant age effects on VMHC overlap with significant results at the network-level analyses. In fact, the superior and middle orbital gyri, as well as the medial and inferior temporal cortex, have been previously described as pertaining to the language network (Tie et al., 2014), for which left-specialization in the general population has been well characterized (Ocklenburg et al., 2014; Sommer et al., 2008). Both basal ganglia and medial prefrontal cortex—through its dorsal medial components—contribute to form the salience network (Peters et al., 2016; Yeo et al., 2011). Additionally, the medial prefrontal cortex—through its ventral medial components—and the posterior cingulate modulate default mode network (DMN) activity (Bluhm et al., 2008).

Current results enrich and expand the previous literature on resting-state activity, neurodevelopment, and interhemispheric connectivity. For instance, previous studies described specific alterations in resting-state activity for the salience network during development in response to early trauma and in relation to ADHD (Rogers et al., 2021; Zhao et al., 2021). Moreover, DMN development during late childhood and adolescence has been previously described as influencing both physiological growth (Lei et al., 2022; Spencer-Smith & Anderson, 2009) and abnormal psychopathology (Via et al., 2021), dynamically integrating with the salience network during typical development in order to modulate cognitive or social responsiveness (Chen et al., 2022; Valera-Bermejo et al., 2021). A small effect for age was previously shown for the resting-state activity of the DMN—in a sample of adults (Bluhm et al., 2008)—while the current study indicates medium age effects in the same region from 7 to 18 years of age. The crucial role of DMN in typical neurodevelopment was also shown to be observable by a variety of dimensions, as network connectivity and centrality (Davey et al., 2019; Gu et al., 2015; Sato et al., 2014; Tarchi et al., 2021). DMN shows increasing intra- and inter-network connectivity during childhood (Gu et al., 2015) and increasing centrality through early adolescence (Sato et al., 2014). Conversely, interactions between ventral and dorsal DMN progressively reduce through age—as measured in a sample between 15 and 25 years old (Davey et al., 2019). The current authors suggest further studies on the progressive functional segregation of DMN, postulating that it may be mirrored at the regional level, and characterized by a gradual hemispheric specialization through late development. In fact, in clinical samples of individuals with ADHD, children and adolescents exhibit a reduced connectivity between default mode and executive control or salience networks (Sutcubasi et al., 2020). These findings may be interpreted in light of a conceptualization of psychiatric disorder arising during late childhood or adolescence as probably driven by neurodivergence or brain maturation factors (Franke et al., 2018; Rice et al., 2019), with ADHD to be considered along autism spectrum disorder and schizophrenia among this category.

When analyses were repeated in a sample of adults, voxel-wise VMHC resulted significantly and negatively correlated with age only in the posterior insula. The specificity of the findings was therefore supported for the age window of evaluation. Previous studies observed age-related reductions of VMHC for the ventromedial prefrontal cortex, hippocampus, dorsal anterior cingulate, insula, and inferior parietal lobule in a range from 7 to 85 years old (Zuo et al., 2010). However, increased hemispheric asymmetry in elders may reflect neurodegenerative processes rather than physiological neural plasticity (Dai et al., 2021; Wang et al., 2015), as a polynomial rather than linear trend was observed in multiple regions after 50 years old (Zuo et al., 2010). For these reasons, VMHC reductions between 7 and 85 years old might include heterogenous factors (such as neurodevelopment vs. neurodegeneration). Besides, the current study did not observe a significant generalized reorganization in functional lateralization during adulthood, with only the posterior insula progressively reducing its interhemispheric connectivity with age (21–50 years old). At the network level, a concordant negative correlation between age and VMHC was observed for both minors and adults in the dorsal DMN. Interestingly, motion was positively correlated with VMHC in the left and right

TABLE 2 Network-based VMHC, role of age and handedness

| Network | Minors (7–18 years; N = 85) | | Adults (21–50 years; N = 107) | |
	Age	Handedness	Age	Handedness
Anterior salience	**r = −.245* (p = .024)**	r = −.032 (p = .772)	r = −.125 (p = .185)	r = −.175 (p = .063)
Auditory	r = −.109 (p = .372)	r = −.105 (p = .338)	r = −.125 (p = .186)	r = −.146 (p = .120)
Basal ganglia	**r = −.280* (p = .010)**	r = −.032 (p = .774)	r = −.034 (p = .722)	r = .047 (p = .620)
Dorsal default mode	**r = −.289* (p = .007)**	r = .001 (p = .996)	**r = −.335* (p < .001)**	r = −.086 (p = .364)
High visual	r = −.102 (p = .354)	r = −.062 (p = .575)	**r = −.303* (p = .001)**	r = −.072 (p = .447)
Language	**r = −.222* (p = .041)**	r = −.134 (p = .223)	r = −.007 (p = .942)	r = −.122 (p = .195)
Left executive control	r = −.164 (p = .133)	r = −.084 (p = .442)	r = .039 (p = .683)	r = −.007 (p = .942)
Posterior salience	r = −.048 (p = .662)	r = .032 (p = .768)	**r = −.233* (p = .013)**	**r = −.184 * (p = .050)**
Precuneus	r = −.131 (p = .233)	r = .033 (p = .766)	r = −.125 (p = .185)	r = −.027 (p = .775)
primary visual	**r = −.257* (p = .017)**	r = −.065 (p = .554)	r = −.121 (p = .201)	r = .047 (p = .620)
Right executive control	r = −.138 (p = .208)	r = −.087 (p = .431)	r = .025 (p = .793)	r = .002 (p = .986)
Sensorimotor	r = −.125 (p = .253)	r = .079 (p = .470)	r = −.069 (p = .464)	r = .070 (p = .457)
Ventral default mode	r = −.203 (p = .062)	r = −.041 (p = .709)	r = −.157 (p = .096)	r = −.029 (p = .755)
Visuospatial	r = −.198 (p = .070)	r = −.057 (p = .603)	**r = −.266* (p = .004)**	r = −.080 (p = .399)

Note: Significant r values (Pearson's correlation coefficients) were marked in bold and visually marked with an asterisk.
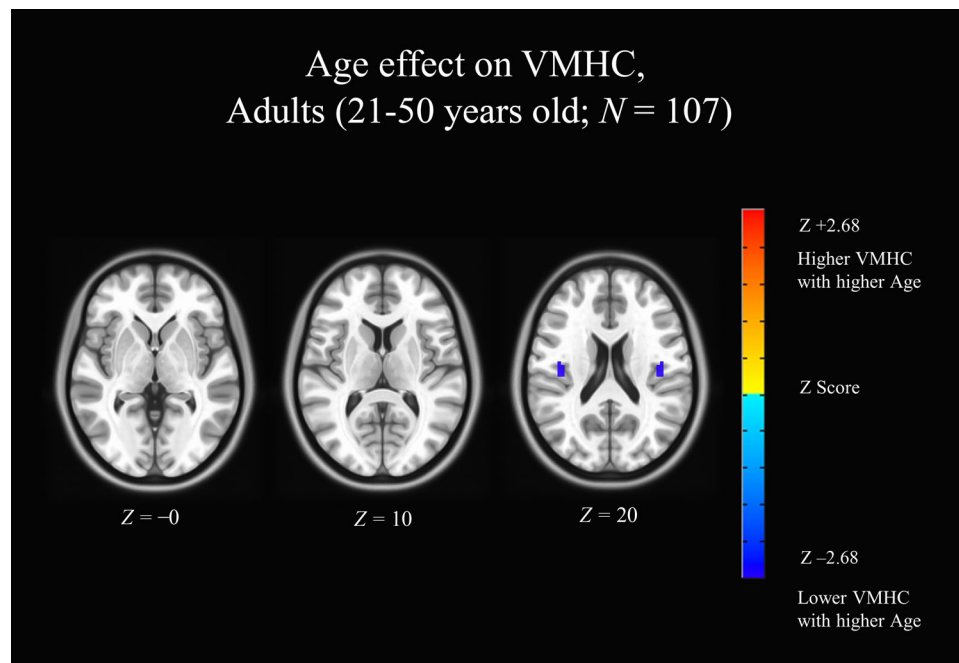

FIGURE 2 Age effect on interhemispheric connectivity, analyses repeated in a sample of adults between 21 and 50 years old. Surviving voxels at FDR-p = .05—clustered for minimum 30 voxels, NN3. The only significant effect for age was in the posterior insula. Results displayed on the MNI 152 symmetric template, resolution 1 mm^3. Surviving voxels after thresholding: 148 (functional image resolution: 3 mm^3)

executive network for minors and in the sensorimotor network for adults. This observation might be derived from the significant synaptic plasticity in adolescents for the development of executive functions (Selemon, 2013), and the fact that instructions to be followed during a fMRI study may prove more taxing for children and adolescents than adults (Evans et al., 2010), requiring more cognitive control in order to achieve motion inhibition during image acquisition (Jor'dan et al., 2017; Kim et al., 2017).

Significant reshaping in interhemispheric connectivity during late childhood, adolescence, and early adulthood may be driven by a variety of factors, including synaptic pruning and neuronal regulation (Chechik et al., 1999; Giedd et al., 1999; Mallya et al., 2019; Paolicelli et al., 2011; Selemon, 2013; Sowell et al., 1999). While more commonly investigated for their role in driving early-life development, synaptic pruning and neuronal regulation may be highly expressed during adolescence, suggesting a potential alteration in those neurodevelopmental

disorders arising in this time window such as autism or schizophrenia (Petanjek et al., 2011; Selemon & Zecevic, 2015). Emerging evidence highlights the contribution of glial cells in controlling the maturation of brain circuitry (Neniskyte & Gross, 2017). Indeed, glial alterations have recently been proposed to contribute to instigating and maintaining several neurodevelopmental disorders—as autism or schizophrenia (Germann et al., 2021; Haroutunian et al., 2014; Hong et al., 2016; Neniskyte & Gross, 2017). As synaptic pruning and neuronal regulation may undergo a second critical phase during adolescence (Selemon & Zecevic, 2015), future research may focus on the role of microglia in interhemispheric connectivity, while early evidence shows that microglia may actually significantly reshape interhemispheric connectivity (Bütefisch et al., 2008; Rehme & Grefkes, 2013; Sandvig et al., 2018; Yu et al., 2021). However, the role of pruning or neuronal regulation in shaping neurotypical development through interhemispheric connectivity is less known, and may be of primary interest to the field of clinical neurosciences. For these reasons, a better description of neurotypical development in this age window may also provide a trend against which to compare patterns of neurodivergence in future research (Kumar et al., 2019; Rice et al., 2019).

VMHC during resting state was not correlated with handedness. Previously, contrasting evidence either supported or criticized a correlation between handedness and hemispheric dominance (Packheiser et al., 2020; Rolinski et al., 2020; Szaflarski et al., 2002). In the current study, a small effect for handedness on VMHC was expected but not observed. No significant difference in VMHC trajectories was observed between sexes. This result was in partial disagreement with the scientific literature on sex differences, which suggests subtle but consistent interactions when studies enroll tight age ranges (Etchell et al., 2018; Packheiser et al., 2020).

4.1 | Limitations

The sample of minors had their eyes closed during scan, while adults had eyes open. VMHC has been correlated to significant differences between eyes open or closed conditions during scan (Wei et al., 2018). However, the current study did not appraise direct differences between groups, but rather explored VMHC associations with age. Nonetheless, this difference during image acquisition might influence similarities between age groups. Analyses describing network-level correlations with age confirmed voxel-wise results, but no correction was performed for multiple comparisons. For network-level results, statistical significance was indeed primarily directed at confirming primary results, and exploring a potential clinical relevance for the structures involved in a specific lateralization during late childhood and adolescence.

5 | CONCLUSIONS

Interhemispheric connectivity during late childhood and adolescence undergoes specific and localized reorganization. In particular, lower interhemispheric connectivity with age (7–18 years) was found in the basal ganglia, anterior salience, primary visual, dorsal default mode, and language networks. The results indicate that neurotypical development involves increasing hemispheric lateralization and may be used in future studies to examine the role of interhemispheric connectivity in the development of psychopathology.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data supporting the present study will be shared upon reasonable request to the corresponding author.

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