

# Intelligence-Related Differences in the Asymmetry of Spontaneous Cerebral Activity

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**Abstract:** Recent evidence suggests the spontaneous BOLD signal synchronization of corresponding inter-hemispheric, homotopic regions as a stable trait of human brain physiology, with emerging differences in such organization being also related to some pathological conditions. To understand whether such brain functional symmetries play a role into higher-order cognitive functioning, here we correlated the functional homotopy profiles of 119 healthy subjects with their intelligence level. Counterintuitively, reduced homotopic connectivity in above average-IQ versus average-IQ subjects was observed, with significant reductions in visual and somatosensory cortices, supplementary motor area, rolandic operculum, and middle temporal gyrus, possibly suggesting that a downgrading of interhemispheric talk at rest could be associated with higher cognitive functioning. These regions also showed an increased spontaneous synchrony with medial structures located in ipsi- and contralateral hemispheres, with such pattern being mostly detectable for regions placed in the left hemisphere. The interactions with age and gender have been also tested, with different patterns for subjects above and below 25 years old and less homotopic connectivity in the prefrontal cortex and posterior midline regions in female participants with higher IQ scores. These findings support prior evidence suggesting a functional role for homotopic connectivity in human cognitive expression, promoting the reduction of synchrony between primary sensory regions as a predictor of higher intelligence levels. *Hum Brain Mapp* 36:3586–3602, 2015. © 2015 Wiley Periodicals, Inc.

**Key words:** intelligence; brain asymmetry; resting state; connectivity; homotopy; individual differences

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## INTRODUCTION

Understanding the neurobiological underpinnings of higher order cognitive abilities is an intriguing topic of contemporary neuroscience, with increasing evidence for a multifactorial structure encompassing genetic, molecular, and environmental agents [Colom et al., 2010; Deary et al., 2010]. In this framework, one of the most influential contributor to functional optimization is regional specialization, a neocortical brain property slowly developed through human evolution [Geschwind, 1979]. Regional specializations thought to contribute, through the

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Additional Supporting Information may be found in the online version of this article.

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development of structural and functional asymmetries between the two hemispheres, to the genesis and development of human language [Geschwind, 1972], memory [Rossi et al., 2001; Rossi et al., 2004], and abstract reasoning abilities [Allen et al., 2007]. In this context, the degree of asymmetry has been considered a marker of physiologically adequate development, and thus it has been associated with enhanced cognition [Rogers et al., 2004], while an abnormal lateralization has been described in psychiatric disorders such as autism [Escalante-Mead et al., 2003; Kleinmans et al. 2008], depression [Herrington et al., 2010], and schizophrenia [Altamura et al., 2012; Ribolsi et al., 2009]. Interestingly, this regional specialization somehow contrasts with another, long-standing, brain property: functional homotopy (FH). As a matter of fact, corresponding neocortical regions are not only anatomically connected through a high proportion of callosal fibers [Innocenti, 1986], but also display coherent functional activity. Resting-state electroencephalographic evidence [Duffy et al., 1996] has been extended to a finer spatial resolution by functional magnetic resonance imaging (fMRI) studies that documented a high degree of functional connectivity (FC), expressed by coherence in spontaneous activity between corresponding, homotopic regions [Salvador et al., 2008; Stark et al., 2008]. However, remarkable regional variation exists, with sensorimotor cortex exhibiting stronger homotopic connectivity, while a weaker connection seems to be present between prefrontal and temporo-parietal homotopic association areas [Stark et al., 2008]. Moreover, FH appears to be age-dependent across the life span, with different patterns identified during development [Fair et al., 2008, 2007; Fransson et al., 2007; Supekar et al., 2009], adulthood [Biswal et al., 2010; Zuo et al., 2010], and aging [Andrews-Hanna et al., 2007]. Accordingly, such measures of homotopic connectivity have been implicitly interpreted as indices of physiological well-being, possibly explaining the deficit that accompanies pathological conditions associated with reduced regionally-specific homotopy, such as multiple sclerosis [Zhou et al., 2013]. The regional and interindividual variability in homotopic connectivity suggests that different FH patterns may modulate diverse cognitive expressions, possibly extending to intelligence quotient (IQ) profiles. While several studies have shown, for instance, associations between intelligence and brain total and regional volumes [Jung and Haier, 2007; Rushton and Ankney, 2009], structural connectivity [Chiang et al., 2008], networks interplay [Song et al., 2008], and efficiency of information processing [da Rocha et al., 2011; Neubauer and Fink, 2009; Santarnecchi et al., 2014a,b; van den Heuvel et al., 2009], investigations of the relation between homotopic connectivity and intelligence do not exist to date. Here, we analyzed resting-state fMRI data of 119 healthy adult individuals, correlating their FH maps with intelligence levels as assessed by validated instruments. The main goal was threefold: (i) identify differences in homotopic connectivity

between low and high IQ subjects, and (ii) characterize these differences in terms of their left or right-hemispheric localizations as well as (iii) unveil age and gender-related differences.

## MATERIALS AND METHODS

### Participants

Behavioral and neuroimaging data are included in the NKI-Rockland database ([www.fcon\\_1000.projects.nitrc.org](http://www.fcon_1000.projects.nitrc.org)). The institutional review boards of New York University Langone Medical Center and New Jersey Medical School approved the receipt and dissemination of the data [Song et al., 2012]. The original database includes 207 right/left-handed healthy volunteers with an age range 8–86 years. To rule out the effect of the “gender-intelligence” [Biswal et al., 2010; Haier et al., 2005] and “gender-brain structural/functional asymmetry” [Gong et al., 2011; Tomasi and Volkow, 2012] interactions, a selection was performed to obtain a subsample of solely right-handed subjects with (i) an equal number of males and females per decade (decades = 18–25 years, 26–35 years, 36–45 years, 46–55 years, 56–65 years) and (ii) an equal number of subjects belonging to each decade (~20). The selection resulted in a final sample of 119 subjects (59 males), with mean age of 33 years (range 18–62, SD = 13). The study protocol has been approved by the University of Siena Ethical committee.

### Intelligence Evaluation

IQ was estimated using the Wechsler abbreviated scale of intelligence (WASI) [Wechsler, 1999], a short version of both the Wechsler adult scale of intelligence (WAIS-III) [Wechsler, 1997], and the Wechsler intelligence scale for children (WISC-IV) [Wechsler, 2003]. The WASI consists of four subscales: Vocabulary, Similarities, Block Design, and Matrix Reasoning. Three different scores are obtained with WASI administration, (i) a standardized, full-scale intelligence quotient (FSIQ), (ii) a verbal IQ score (VIQ) which indexes word knowledge, verbal reasoning, and concept formation and a (iii) performance IQ score (PIQ) representing abstract reasoning skills, visual information processing, visual-motor coordination, simultaneous processing, and learning abilities. WASI demonstrated high concurrent validity (i.e., correlation with the WAIS-III FSIQ,  $r = 0.92$ ;  $n = 248$ ), as well as good reliability coefficients (0.92–0.98 for VIQ, 0.94–0.97 for PIQ, 0.96–0.98 for the full FSIQ) [Ryan et al., 2003]. Sample characteristics in terms of IQs, subtests scores and WASI correlational structures are reported in Table I. A median split approach was applied to obtain two groups reflecting high and low intelligence levels (i.e., IQ scores) within our sample, leading to an “Above Average” IQ group composed by participants with an overtly above average IQ score ( $n = 62$ ; mean

**TABLE I. Sample characteristics. IQs and subtests scores for the entire sample are reported, as well their correlational structure, computed through age and gender corrected partial correlation coefficients**

(A)								
	$M_{119}$	$SD_{119}$	VIQ	PIQ	BD	VOC	SIM	MAT
FSIQ	110	11	0.689**	0.845**	0.897**	0.412**	0.523**	0.902**
VIQ	108	13		0.821**	0.512**	0.917**	0.824**	0.456**
PIQ	109	11			0.834**	0.743**	0.745**	0.813**
BD	55	8				0.423**	0.536**	0.764**
VOC	54	7					0.577**	0.357**
SIM	55	8						0.472**
MAT	55	9						

(B)	Above average ( $n = 62$ )		Average ( $n = 57$ )		(C)	ANCOVA	
	$M_{119}$	$SD_{119}$	$M_{119}$	$SD_{119}$		$F$	Sig.
	122	3	92	7		161.1	<0.001
	116	4	91	4		52.1	<0.001
	117	5	89	4		84.2	<0.001
	63	4	40	6		123.5	<0.001
	59	7	49	10		9.8	<0.013
	60	6	48	6		14.7	<0.008
	63	4	44	9		63.2	<0.001

\*\*Correlation is significant at the 0.01 level (two-tailed).

age =  $33 \pm 11$ ; males = 33; mean FSIQ =  $122 \pm 3$ ; mean VIQ =  $116 \pm 4$ ; mean PIQ =  $116 \pm 5$ ; referred to as AA-IQ hereafter), and a “Average” (A-IQ hereafter) one ( $n = 57$ ; mean age =  $32 \pm 11$ ; males = 26; mean FSIQ =  $92 \pm 7$ ; mean VIQ =  $91 \pm 4$ ; mean PIQ =  $89 \pm 4$ ). Groups did not differ for age ( $t = 0.184$ ,  $P = 0.882$ ) or gender distribution ( $\chi^2 = 0.405$ ,  $P = 0.5498$ ).

### Resting State fMRI: Theory, Data Acquisition, and Processing

Our brain is a complex system of interconnected regions spontaneously organized into distinct networks [Hagmann et al., 2008; Sporns, 2014]. The integration of information between and within these specialized, spatially distributed but functionally linked brain regions is a continuous process that can be observed even when the brain is in a quiescent state, that is, not engaged in any particular task [Greicius et al., 2003; Raichle et al., 2001; Stam, 2004]. Such intrinsic organization of spontaneous brain activity is captured within the framework of brain connectivity analysis, a novel approach based on resting-state fMRI analysis [Achard et al., 2006]. Differently from the canonical task-fMRI paradigm, where the signal is derived by contrasting subject’s activity during an active and a passive states, this novel approach relies on the endogenous brain oscillations recorded during spontaneous rest, with the activity of each brain regions being correlated with each others, giving rise

to a complex pattern of temporally and spatially independent resting state networks [Biswal et al., 2010]. Such methodology has been proven to hold enough information not only to allow the identification of pathological conditions (like multiple sclerosis [Bonavita et al., 2011], schizophrenia [Bassett et al., 2008], and Alzheimer [Agosta et al., 2012]) but also to identify the correlates of several cognitive [Santarnecchi et al., 2014a; Yuan et al., 2012] and psychological individual traits [Adelstein et al., 2011] in healthy subjects.

The analysis of homotopic connectivity, therefore, requires the acquisition of resting-state fMRI data, and the computation of the temporal dependency between symmetrical brain regions located in the two hemispheres. Neuroimaging data were acquired on a 3.0 T Siemens MAGNETOM TrioTim (Siemens Medical Solutions, Erlangen, Germany). A three-dimensional T1-weighted MPRAGE image was acquired in the axial plane (TR/TE 2500/3.5 ms; 192 slices; slice thickness 1 mm; flip angle 8°; voxel size  $1.0 \times 1.0 \times 1.0$  mm). Resting-state fMRI data were acquired using T2-weighted BOLD images (TR/TE 2500/30 ms; 38 interleaved slices; slice thickness 3 mm; 260 volumes; flip angle 80°; voxel size  $3.0 \times 3.0 \times 3.0$  mm). Data were preprocessed and analyzed at the Department of Medicine, Surgery and Neuroscience at University of Siena. Functional image preprocessing was performed using SPM8 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London; <http://www.fil.ion.ucl.ac.uk/spm/>) within the MATLAB scientific computing environment ([◆ 3588 ◆](http://www.</a></p>
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mathworks.com, MathWorks, MA). The first five volumes of functional images were discarded for each subject to allow for steady-state magnetization. EPI images were then corrected for inhomogeneity using fieldmap regression; stripped of skull and other noncerebral tissues; slice-timed using interleaved descending acquisition; manually realigned and subsequently resliced. Importantly, two recent studies suggested that head motion during MRI scanning may produce significant changes in FC estimates [Power et al., 2012; Van Dijk et al., 2012]. Controlling for such a confounding factor is particularly important in the context of homotopic connectivity, as head motion correction procedure might apply similar transformations to couples of correspondent voxels in the two hemispheres. To address this issue, we proceeded with an interpolation procedure based on the displacement indexes proposed by Power et al. [2012], that is, frame-wise displacement (FD) and the RMS variance of the temporal derivative (DVARS). Time points showing  $FD > 0.5$  mm and  $DVARS > 0.5$  have been interpolated using a cubic spline function [Power et al., 2012]. Structural images were coregistered to the mean volume of functional images and subsequently segmented using the NewSegment routine in SPM8. A Hidden Markov Random Field model was applied to remove isolated voxels. Moreover, to obtain a more accurate spatial normalization, we applied the SPM8 DARTEL (Diffeomorphic Anatomical Registration Through Exponential Lie algebra) module, creating a customized gray matter template from all subjects' segmented images [Ashburner, 2007]. A nonlinear normalization procedure with subsequent affine-only normalization to the Montreal neurological institute (MNI) template brain, and voxel resampling to an isotropic  $3 \times 3 \times 3$  mm voxel size, were then applied to functional images. Linear trends were removed to reduce the possible influence of the rising temperature of the MRI scanner and all functional volumes were band-pass filtered at  $0.01 \text{ Hz} < f < 0.08 \text{ Hz}$  to reduce low-frequency drifts. Finally, the potential contribution of nuisance sources of variability to gray matter BOLD time courses were controlled by regressing out the head motion parameters as well as the signal derived from four regions-of-interest (ROIs) placed in the white matter and cerebro-spinal fluid, an approach that has been shown to significantly enhance within-subject and test-retest reliability [Liang et al., 2012; Schwarz and McGonigle, 2011].

### Homotopic Connectivity

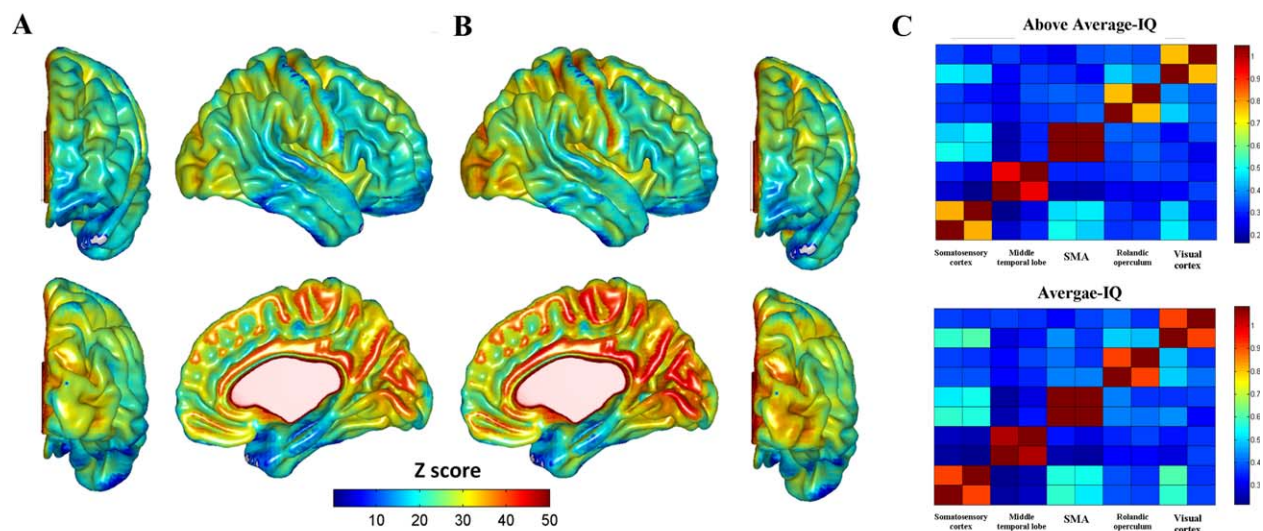
>Homotopic Resting-State functional connectivity was computed as the Pearson correlation (Fisher's  $Z$ -transformed) between every pair of symmetric interhemispheric voxels' time-series. The resultant correlation maps define voxel-mirrored homotopic connectivity (VMHC) as described by Zuo et al. [2010]. To account for interhemispheric anatomical variability, individual structural images were normalized to MNI space using a group-specific sym-

metrical template. This was created by first averaging individual images, and then averaging the mean image across hemispheres. Each subject's image was nonlinearly registered to this symmetrical template and the resulting transformation matrices were applied to their respective preprocessed functional datasets. This led to complete correspondence between left and right hemispheres' voxels, allowing for the computation of meaningful voxel-wise interhemispheric correlations. Considering that template creation procedures may lead to blurring and artifactual increases of VMHC values for mesial regions, voxels within 3 mm from the midline were not included in the analysis [Kelly et al., 2011]. Moreover, to address potential confounds associated with interhemispheric structural asymmetry, we calculated both unsmoothed and 6-mm smoothed images and compared VMHC values before entering the between-group analyses. H-IQ and A-IQ group VMHC maps were compared through a voxel-wise  $F$ -test controlling for age, total brain volume (TBV) and gender. Moreover, given that homotopic connectivity plausibly relies on the integrity and efficiency of corpus callosum (CC) connections linking mirrored regions in the two hemispheres [Innocenti, 1986], we use segmented T1-weighted images to derive the volume of the CC for each participant and include such values as additional covariate in each ANCOVA analysis. Corrections for multiple comparisons were performed using Gaussian Random Field theory (two-tailed,  $\min Z > 2.239$ , voxel level  $P < 0.01$ , cluster level  $P < 0.05$ , corrected).

### Hierarchical Functional Classification

VMHC has been shown to follow a hierarchical subdivision of brain regions [Stark et al., 2008] which mainly reflect the functional classification as a primary sensory-motor, unimodal association, or heteromodal association areas, as described by Mesulam [Mesulam, 2000]. This leads to different degrees of homotopic connectivity between voxels belonging to each of these classes, in agreement with anatomical, electrophysiological, lesion, and functional imaging studies in humans and nonhuman primates [Hopkins et al., 2007; Stark et al., 2008; Zhang et al., 2010]. Consequently, to test the hypothesis that VMHC levels within this hierarchy might show differences related to intelligence, we parcellated functional data using the Harvard-Oxford Structural Atlas, a probabilistic atlas comprised of 112 regions (56 per hemisphere) [Kennedy et al., 1998; Makris et al., 1999]. Briefly, hierarchical subdivisions define (i) primary sensory-motor cortices as the postcentralgyrus (somatosensory), intracalcarine cortex and occipital pole (visual), Heschl'sgyrus (auditory), and precentralgyrus (motor), (ii) unimodal association areas, adjacent to primary sensory cortices, and (iii) heteromodal association areas, located primarily in prefrontal and temporoparietal cortices, responsible for integration of information across multiple sensory domains and sensory-motor integration. Additionally, we also parcellated





**Figure 1.**

VHMC maps, seed-based FC and hierarchical homotopic connectivity. Whole-brain voxelwise mirrored homotopic connectivity patterns in AA-IQ (**A**) and A-IQ subjects (**B**). VHMC is reported using four surfaces representing the right hemisphere. Subjects with lower IQs show an increased synchronization between structures located in visual and somatosensory cortices, temporal lobe, rolandic operculum, and supplementary motor area. (**C**) Time series have been extracted from spherical

ROIS (5 mm diameter) placed in correspondence to the local maxima of clusters obtained through the voxel-wise comparisons of AA-IQ versus A-IQ subjects VHMC maps. Seed regions correspond to both left and right-sided representations of aforementioned brain regions. Decreased homotopic interhemispheric connectivity is evident in high IQ subjects' connectivity matrices (upper panel).

subcortical structures into three main categories, (i) limbic, (ii) paralimbic, and (iii) subcortical regions [Mesulam, 2000] (see Supporting Information Table S1 for a complete listing of each region's functional classification). Mean values for each of six categories were compared between H-IQ and A-IQ groups using a *t*-test ( $P < 0.05$ , Bonferroni corrected).

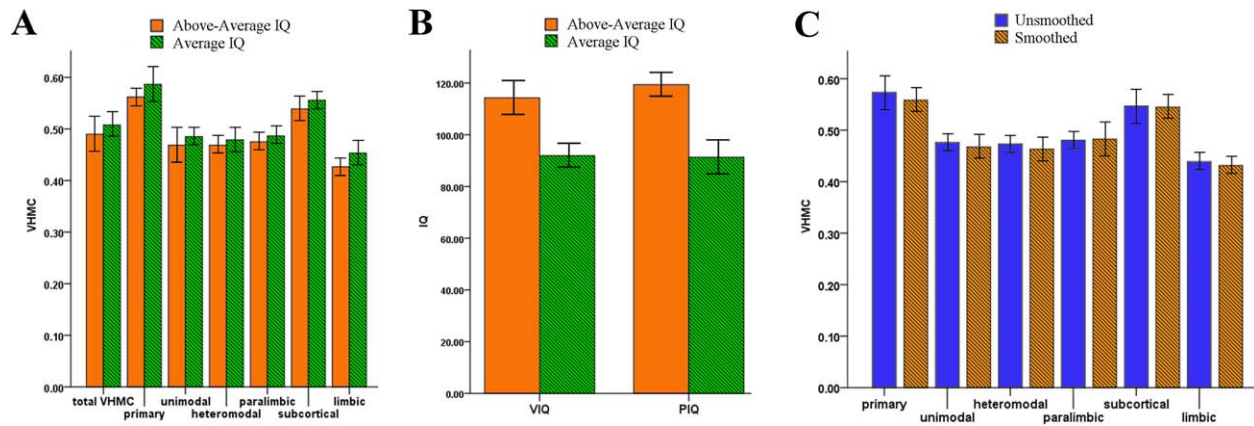
### Seed-Based Functional Connectivity Analysis

Apart from the reference to "symmetry," differences in VHMC are basically expressions of differences in voxels' connectivity profile. For instance, a VHMC map which shows voxels belonging to motor cortex having different homotopic connectivity values between two groups of individuals (i.e., high vs average IQ or male vs female) practically means that one of these voxels, or both, are differently "connected" to the rest of the brain and consequently also to their mirrored counterpart. Critically, the speculative nature of VHMC maps does not allow us to identify which voxel (right and left) mostly contributes to this observed between-group difference. To determine if bilateral or side-specific voxels' connectivity profile variation contributes to differences into intelligence levels, we computed a seed-based FC analysis using regions showing different VHMC values. We created spherical ROIs (diameter = 5 mm) over each significant clus-

ters' local maxima, obtaining corresponding right (MNI coordinate  $x = +$ ) and left (MNI coordinate  $x = -$ ) ROIs which were used to compute whole-brain FC maps. Consequently, a statistical comparison has been performed by entering high and low IQ subjects' FC maps into a group-level voxel-wise ANCOVA, controlling for age, TBV, gender, and CC volume. Multiple comparisons corrections were performed using Gaussian Random Field theory (two-tailed,  $\min Z > 2.239$ , voxel level  $P < 0.01$ , cluster level  $P < 0.05$ , corrected).

### Age and gender-Related Differences in Homotopic Connectivity

All previous analyses were corrected by age and represent a net evaluation of the interplay between homotopic connectivity and intelligence. To understand how the interaction between VHMC and intelligence may change over time, we additionally split the overall sample into five decades (18–25 years; 26–35 years; 36–45 years; 46–55 years; 56–65 years) and thus compared VHMC maps of AA-IQ and A-IQ individuals belonging to each decade (voxel-wise *F*-test controlling for age, TBV, gender, and CC volume). To ease results interpretation, resulting maps, representing the average cortical VHMC values distribution in each different decade, have been parcellated using both (i) hierarchical and (ii) lobar schemes. Moreover, given the existence of



**Figure 2.**

Confounding factors. Hierarchical analysis showed an overall pattern for reduced VHM in AA-IQ group (A), encompassing primary, unimodal, heteromodal, and subcortical brain regions. Several possible confounding factors have been taken into account to explain the IQ-related effect on VHM values. In this context, such differ-

ences do not depend to unbalanced verbal and performance IQ levels (B) or to the impact of smoothing on VHM maps (C) (0 mm vs 6 mm kernel). Note: VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

potentially interesting gender-related differences in the interaction between IQ and mirrored connectivity, we split our sample in male and female participants and computed the correlation between their VHM maps and their FSIQ, VIQ, and PIQ scores. A comparison of the average VHM values in male/female and High/Average participants have been also tested, running a two way between-subjects ANOVA including factor Gender and Intelligence. All analyses have been corrected for TBV and Age values. Corrections for multiple comparisons were performed using Gaussian Random Field theory (two-tailed, min  $Z > 2.239$ , voxel level  $P < 0.01$ , cluster level  $P < 0.05$ , corrected).

## RESULTS

### Intelligence Related Differences in Mirrored Connectivity

Both A-IQ and H-IQ participants showed the already documented trend for stronger VHM between primary cortical regions including visual, motor, and somatosensory cortices as well cingulate cortex, whereas prefrontal and temporoparietal, association cortices showed relatively weaker VHM (Fig. 1A,B). Group comparisons revealed a set of regions where A-IQ subjects exhibited stronger VHM than H-IQ ones, as expressed in the connectivity matrix (Fig. 1C). These regions correspond to primary somatosensory cortex (Brodmann area 3, MNI  $x = \pm 24$ ,  $y = -30$ ,  $z = 62$ ), premotor cortex and supplementary motor area (Brodmann area 6, MNI  $x = \pm 23$ ,  $y = -3$ ,  $z = 60$ ), visual cortex (Brodmann areas 23 and 31, MNI  $x = \pm 15$ ,  $y = -69$ ,  $z = 12$ ), rolandic operculum (Brodmann area 43, MNI  $x = \pm 56$ ,  $y = -8$ ,  $z = 20$ ), middle temporal

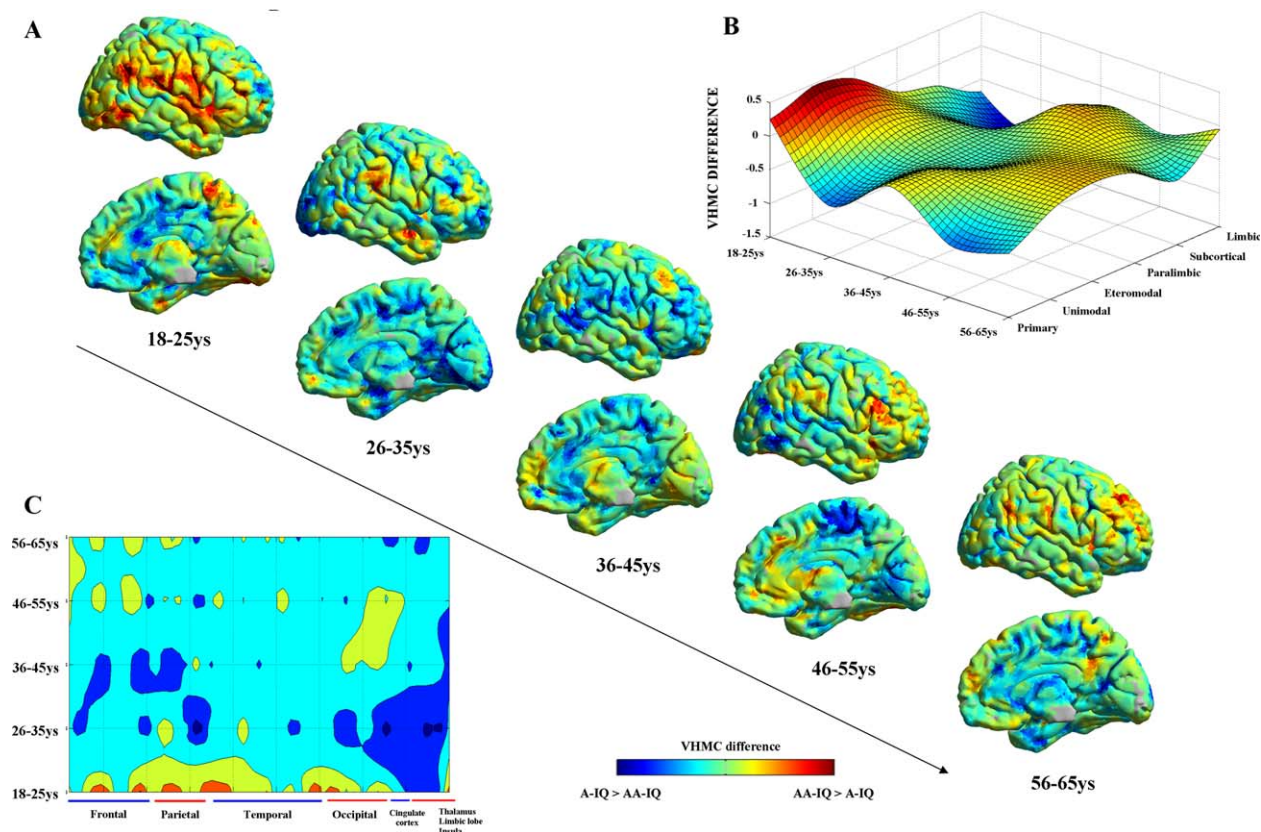
gyrus (Brodmann area 21, MNI  $x = \pm 59$ ,  $y = -30$ ,  $z = -2$ ). Clusters' cytoarchitectonic mapping is reported in Supporting Information Figure S1. None of the regions exhibited stronger VHM in H-IQ subjects respect to A-IQ ones. Connectivity matrices derived from ROIs-to-ROIs (right and left) Pearson correlations (Fig. 1C) showed increased connectivity between ROIs pairs in A-IQ group. Total VHM values did not differ between groups ( $F_{(118)} = 1.732$ ,  $P = 0.191$ ) or as a function of the smoothing kernel applied ( $F_{(118)} = 0.178$ ,  $P = 0.652$ ; Fig. 2A,C).

### Hierarchical Classes Comparison

The overall pattern of VHM globally reflected previous evidence using this technique [Gee et al., 2011; Stark et al., 2008; Zuo et al., 2010], showing a trend for higher FH in primary sensory regions, that is, visual, motor, somatosensory, with heteromodal brain area (involved into multisensory integration) showing lower interhemispheric synchronization. ANCOVA analysis revealed no between-groups significant differences in VHM values for any of the functional classes (primary  $F_{(118)} = 2.308$ ,  $P = 0.131$ ; unimodal  $F_{(118)} = 1.196$ ,  $P = 0.276$ ; heteromodal  $F_{(118)} = 0.645$ ,  $P = 0.424$ ; limbic  $F_{(118)} = 1.887$ ,  $P = 0.172$ ; paralimbic  $F_{(118)} = 0.746$ ,  $P = 0.389$ ; subcortical  $F_{(118)} = 1.139$ ,  $P = 0.288$ ). However, an overall trend of lower VHM in A-IQ subjects can be observed (Fig. 2A).

### Age and Gender Related Differences

Regards the comparison between different decades, results referring to the mean VHM difference between H-IQ and A-IQ individuals at voxel, hierarchical, and



**Figure 3.**

Age-related changes into homotopic connectivity versus intelligence level. Panel **A**, **B**, and **C**, respectively, report the results of AA-IQ and A-IQ subjects VHM comparisons at voxel, hierarchical, and lobar levels for five different decades. Panel **A** shows the voxel-wise distribution of differences in VHM over the entire brain (right-hemisphere is shown only for visualization purposes, as VHM analysis produces specular results for both

lobar level have been plotted across time (decades) in Figure 3A–C, respectively. Despite the overall differences in homotopic connectivity depicted in Figure 1, subsamples analysis supports an interesting opposite pattern between AA-IQ and A-IQ subjects in the 18–25 years decade, where an increase in homotopic connectivity is observable for primary and unimodal brain regions in H-IQ subjects. However, given the relatively small sample size of each subsample, further evaluations are needed to confirm and possibly deepen such potentially interesting longitudinal fluctuations.

The ANCOVA model for gender-related differences did show a trending to significance interaction between Gender and Intelligence ( $F_{(117)} = 2.356$ ,  $P = 0.083$ ), which did not reach statistical significance possibly due to the small sample size of each subgroup. As shown in Figure 4, the correlation maps between mirrored connectivity and FSIQ, PIQ, and VIQ scores highlighted a different

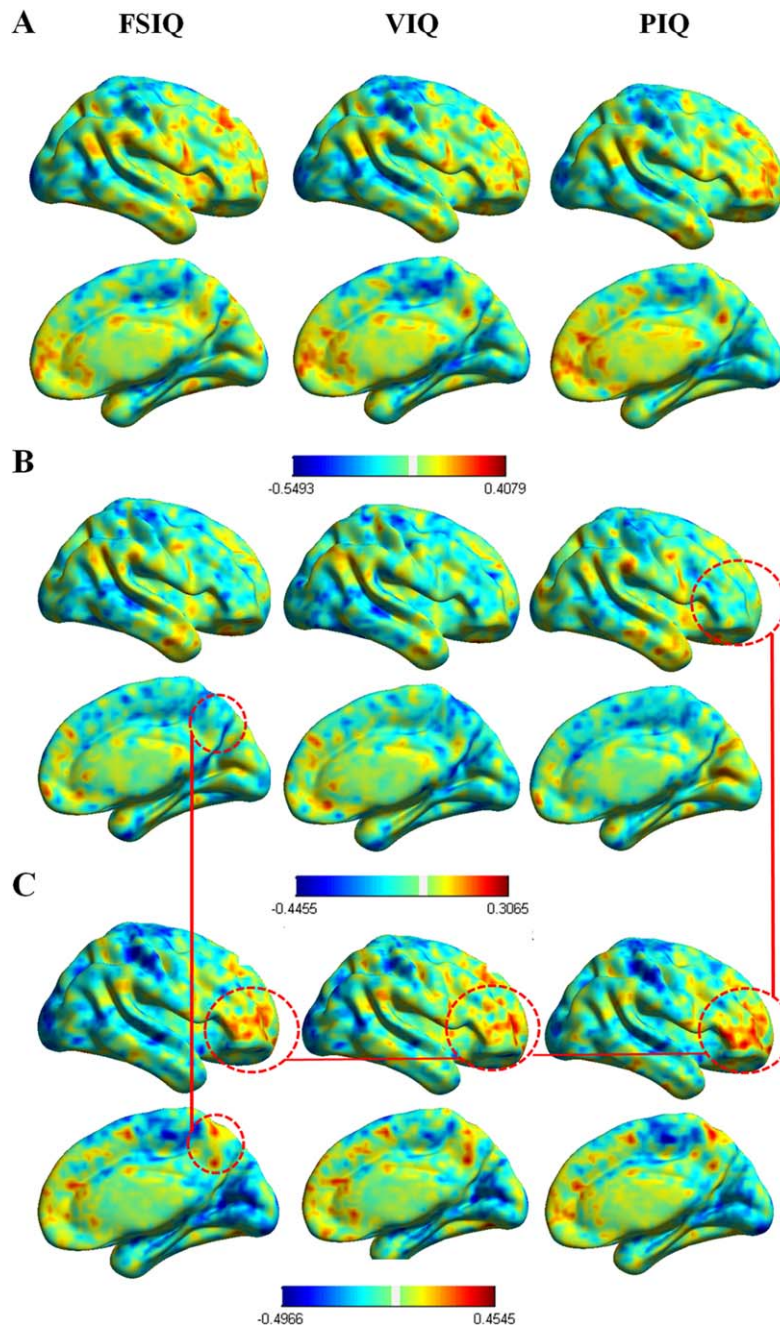
pattern for male and female located in the prefrontal cortex (mostly in the fronto-polar cortex—BA10) and precuneus/cuneus regions, where an increased correlation with intelligence level in female participants is visible. Panels **B** and **C** highlight a suggestive interaction between IQ, homotopic connectivity, and age where an increased homotopic connectivity in primary and unimodal brain regions is visible for H-IQ subjects for subjects in the first decade (18–25 years), with a switch to an opposite pattern for the remaining decades (26–65 years). [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

pattern for male and female located in the prefrontal cortex (mostly in the fronto-polar cortex—BA10) and precuneus/cuneus regions, where an increased correlation with intelligence level in female participants is visible.

### Seed-Based Connectivity and the Left Hemisphere

Seed-based connectivity analysis were performed using BOLD signal time series extracted from 5 mm spheres centered on seed regions obtained from VHM group comparison, namely 10 regions corresponding to left and right: (i) somatosensory and (ii) premotor/supplementary motor cortices, (iii) middle temporal gyrus, (iv) rolandic operculum, and (v) visual cortex (Fig. 5). ANCOVA results showed an overall pattern of increased connectivity exclusively for A-IQ subjects. Comparison of left and right seed





**Figure 4.**

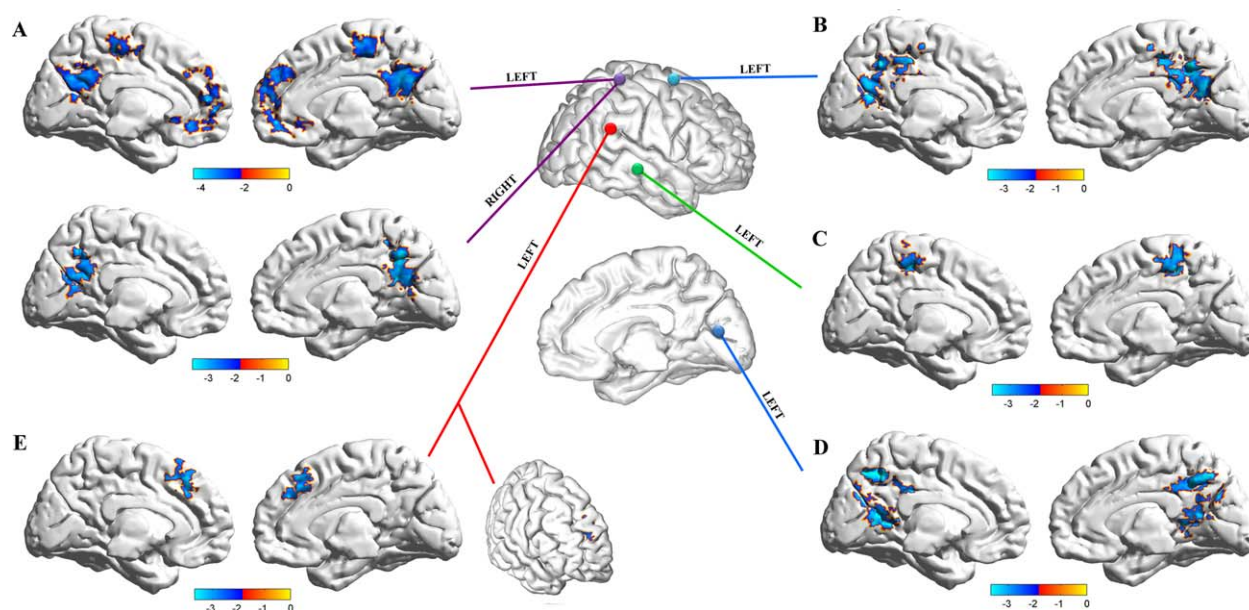
Gender related differences. Panel **A**, **B**, and **C**, respectively, report the correlation between Intelligence level (FSIQ, VIQ, PIQ) and brain FH in the overall sample, male ( $n = 59$ ) and female participants ( $n = 60$ ). As highlighted in the red circle, voxel-wise results show gender-related differences in the prefrontal lobe—mostly in the pars triangularis and opercularis of

regions connectivity profiles supports the existence of a left-lateralized tendency for connectivity increase, with 4 out of 5 ROIs showing significant connectivity alterations

the inferior prefrontal lobe (Broca's area, BA44-45) and the frontopolar cortex (BA10)—, the precuneus (BA7) and posterior cingulate cortex (BA31). Note: BA, Brodmann area. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

limited to seeds placed in the left hemisphere, while only the somatosensory cortex showed a bilateral FC increase, which is, however, wider for the left counterpart (Fig. 5,





**Figure 5.**

Lateralization of VHM differences between High and Average IQ subjects. The specular nature of VHM maps does not allow for the identification of which voxel (right and left) mostly contributes to the differences observed between AA-IQ and A-IQ subjects. To overcome this limitation, we computed a seed-based FC analysis using regions showing different VHM values. Seed-based FC maps have been calculated for spherical ROIs placed in left and right somatosensory (A), SMA (B), middle temporal gyrus (C), visual cortex (D), and rolandic operculum (E). FC maps have been compared using a voxel-wise ANCOVA, controlling for age, TBV, and gender. Multiple comparisons cor-

rections were performed using Gaussian Random Field theory (two-tailed,  $\min Z > 2.239$ , voxel level  $P < 0.01$ , cluster level  $P < 0.05$ , corrected). Results show an overall pattern of increased connectivity for subjects in the A-IQ group. Comparison of left and right seed regions supports the existence of a left-lateralized tendency for increased connectivity, with 4 out of 5 ROIs showing significant connectivity alterations limited to the seed placed in the left hemisphere, while I (somatosensory cortex) showed a bilateral FC increase, which is, however, wider for left somatosensory cortex. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

for cluster anatomical mappings see Table II). Such leftward increase in the connectivity level of LA-IQ subjects may be possibly induced by an inhomogeneous balancing of verbal and PIQs in the two groups. On the contrary, between-groups comparisons of VIQ and PIQ did not show significant differences ( $F_{(118)} = 0.245$ ,  $P = 0.458$ ; Fig. 2A).

Interestingly, it should be noted that all seed regions report an increase of their FC toward regions belonging to anterior and posterior cingulate cortex, midprefrontal, and parietal regions, which are nodes of the default mode network (DMN) [Fox et al., 2005].

## DISCUSSION

The first evidence of robust interhemispheric connectivity during spontaneous rest has been provided within the motor system [Biswal et al., 1995]. This finding opened a new era in brain imaging, expanding the idea of brain spontaneous activity as a highly informative tool for the exploration of both sensorimotor and cognitive functions

[Fox et al., 2005], providing new insights regarding both the architecture of the healthy brain [van den Heuvel et al., 2009] and the signature of diverse pathological conditions [Agosta et al., 2013; Madhavan et al., 2013; Santarnecchi et al., 2013]. Specifically, further studies have confirmed such generalized tendency for interhemispheric synchronization, that is homotopic connectivity, mainly for every pair of homologous brain regions [Hagmann et al., 2008; Salvador et al., 2005; Stark et al., 2008]. With the aim at understanding whether and how interhemispheric connectivity could be related to individual cognitive functioning, in the current investigation we analyzed resting-state fMRI data of 119 healthy adults by correlating their individual VHM maps with global intelligence levels (IQ). We detected a trend for reduced VHM in subjects with higher intelligence levels versus those with an average IQ, with significant decreases in visual and somatosensory cortices, SMA, rolandic operculum, and middle temporal gyrus. Moreover, an additional seed-based FC analysis revealed these regions as having an increased spontaneous synchronization with medial structures located in ipsi-

**TABLE II. Seed-based connectivity analysis results**

Seed regions	Clusters dimension (voxels)	MNI coordinates			Peak <i>t</i> -value	<i>p</i>
		<i>x</i>	<i>y</i>	<i>z</i>		
Left somatosensory cortex						
<i>Cluster 1</i>	<b>696</b>					
Right superior medial gyrus		12	57	36	4.34	0.024
Right anterior cingulate cortex		3	51	12	4.28	0.027
Right mid orbital gyrus		9	51	-6	4.15	0.029
Right superior medial gyrus		6	54	36	4.12	0.029
Left superior medial gyrus		-3	57	3	3.95	0.032
Left superior frontal gyrus		-15	54	30	3.66	0.033
Right precuneus		3	-60	33	4.24	0.035
<i>Cluster 2</i>	<b>542</b>					
Left precuneus		-9	-54	24	4.09	0.022
Left posterior cingulate cortex		-6	-48	21	3.8	0.029
Right middle cingulate cortex		3	-42	33	3.51	0.034
Left calcarine gyrus		0	-60	15	3.4	0.034
Right cuneus		15	-72	30	2.87	0.036
Left cuneus		-12	-66	27	2.84	0.039
<i>Cluster 3</i>	<b>397</b>					
Left paracentral lobule		-6	-27	54	4.42	0.022
Right paracentral lobule		9	-30	54	4.07	0.025
Right SMA		6	-21	60	4.03	0.025
Left postcentral gyrus		-33	-27	69	3.48	0.028
Right postcentral gyrus		12	-36	72	3.47	0.033
Left Precuneus		-12	-39	66	3.41	0.034
Left SMA		-3	-9	54	3.31	0.038
Right superior frontal gyrus		21	-12	66	3.26	0.039
Right somatosensory cortex						
<i>Cluster 1</i>	<b>624</b>					
Left posterior cingulate cortex		-6	-48	21	3.68	0.021
Right supramarginal gyrus		60	-24	39	3.67	0.024
Right precuneus		3	-57	42	3.64	0.024
Left Precuneus		-9	-48	45	3.52	0.026
Right posterior cingulate cortex		3	-54	30	3.3	0.029
Left rolandic operculum						
<i>Cluster 1</i>	<b>275</b>					
Right SMA		12	21	45	3.66	0.021
Right superior medial gyrus		15	51	30	3.61	0.027
Right middle frontal gyrus		21	57	27	3.53	0.028
Left superior medial gyrus		3	42	33	3.29	0.029
Right superior medial gyrus		12	42	42	3.19	0.032
Left SMA		-3	24	48	3.18	0.034
Left SMA-premotoc cortex						
<i>Cluster 1</i>	<b>853</b>					
Right SMA		9	-24	51	4.42	0.019
Right posterior cingulate cortex		9	-42	27	4.3	0.022
Right precuneus		3	-48	45	3.99	0.024
Left calcarine gyrus		0	-60	15	3.91	0.026
Left precuneus		-12	-51	39	3.8	0.027
Right Middle Cingulate Cortex		6	-36	36	3.61	0.029
Left precentral gyrus		-33	-6	63	3.52	0.030
Left middle temporal gyrus						
<i>Cluster 1</i>	<b>391</b>					
Left paracentral lobule		-9	-30	54	4.38	0.023
Right middle cingulate cortex		3	-33	51	4.05	0.024
Right paracentral lobule		6	-36	63	3.62	0.026
Right postcentral gyrus		15	-36	60	3.62	0.028

TABLE II. (continued).

Seed regions	Clusters dimension (voxels)	MNI coordinates			Peak <i>t</i> -value	<i>p</i>
		<i>x</i>	<i>y</i>	<i>z</i>		
Left precuneus		-15	-42	66	3.52	0.029
Left postcentral gyrus		-30	-30	72	3.42	0.029
Left postcentral gyrus		-30	-36	63	3.42	0.029
Left paracentral lobule		-15	-21	78	3.39	0.030
Left Paracentral Lobule		0	-27	57	3.27	0.032
Right SMA		9	-24	51	3.26	0.033
Left paracentral lobule		-6	-30	72	3.25	0.033
Left posterior cingulate cortex						
<i>Cluster 1</i>	<b>720</b>					
Left precuneus		-3	-66	48	4.36	0.009
Left cuneus		-9	-66	27	4	0.013
Right precuneus		9	-60	45	3.99	0.019
Left calcarine gyrus		-3	-60	9	3.92	0.022
Left posterior cingulate cortex		-9	-42	24	3.59	0.026
<i>Cluster 2</i>	<b>474</b>					
Left precentral gyrus		-51	12	36	4.33	0.019
Left middle frontal gyrus		-39	12	39	3.93	0.020
Left inferior frontal gyrus (p. Triangularis)		-39	21	27	3.83	0.021
Left superior frontal gyrus		-21	30	48	3.41	0.024
<i>Cluster 3</i>	<b>379</b>					
Left inferior parietal lobule		-42	-51	45	4.16	0.020
Left supramarginal gyrus		-54	-48	30	3.41	0.023
Left angular gyrus		-51	-57	33	3.32	0.024

Four regions in the left hemisphere and one bilateral region have been identified as having a different connectivity profile between H-IQ and LA-IQ subjects. Table reports cluster dimensions, MNI coordinates and *t*-statistics of the brain areas showing a stronger connectivity with seed regions in LA-IQ subjects with respect to H-IQ ones

and contralateral hemispheres, with this pattern being mostly detectable for left hemisphere regions. Finally, an increase in the symmetry of the FC pattern have been identified in the prefrontal cortex of female participants, with a minor effect also detectable in the posterior midline regions. These results indirectly confirm recent evidences about the importance of basic sensory processes into explaining individual differences in IQ, also corroborating a relevant role for left hemisphere connectivity profiles in determining intelligence levels, at least in right-handed subjects.

Theories about the importance of hemispheric lateralization rely on two different schools of thought. Integrative models suggest that interhemispheric interaction aids information processing by coordinating parallel processing between the hemispheres [Banich and Brown, 2000], while other models conceptualize the lateralization of brain function as a mechanism allowing the isolation of competing processes [Kosslyn et al., 1995; Liederman and Meehan, 1986]. Consistent with models promoting FC as a reflection of coordinated, that is integrated, processing within functional systems [Fair et al., 2007; Fox et al., 2005], the ubiquitous finding of homotopic connectivity would validate the notion of a physiological interhemispheric processing

[Banich and Brown, 2000]. Additionally, recent evidence of a reduction in VHMC found in patients with multiple sclerosis [Zhou et al., 2013], cocaine addiction [Kelly et al., 2011], schizophrenia [Hoptman et al., 2012], and first major depressive episode [Guo et al., 2013] concur to indirectly support the association between interhemispheric synchronization at rest and brain optimal functioning.

In this context, the explanation of interhemispheric communication dynamics has been reasonably associated with the CC [Geschwind, 1972], with several models postulating different roles for the information flow through the callosal fibers [Nowicka and Tacikowski, 2011]. Excitatory models of callosal function postulate that the CC mediates the sharing of information between the two hemispheres [Berlucchi et al., 1995; Gazzaniga et al., 1962], allowing each hemisphere to access information that might have initially been lateralized. Moreover, as even simple tasks do not exclusively involve one hemisphere, cerebral functions often rely on dynamic cooperation between the two hemispheres, which obviously requires considerable interhemispheric transmissions of information [Houzel and Milleret, 1999]. Interestingly, this hypothesis has been functionally supported by the decrease of interhemispheric coherence observed in patients with agenesis of CC [Koeda et al.,



1995] and in those who underwent callosotomy [Johnston et al., 2008].

Conversely, several studies have put forward the idea that interhemispheric communication may not necessarily be conceptualized as an exclusively cooperative process [Denenberg, 1983], with CC playing an important role in maintaining independent processing in the two hemispheres through inhibitory actions [Cook, 1984]. Generally, it has been postulated that the activation in a region within a hemisphere may induce an inhibition of homologous regions in the contralateral hemisphere, with experimental confirmation observed during speech processing using positron emission tomography (PET) in humans [Karbe et al., 1998], and by looking at the interaction between somatosensory cortices in rats [Marcano-Reik and Blumberg, 2008].

Indeed, brain imaging and transcranial magnetic stimulation studies in patients with neglect have supported this hemispheric rivalry model too, by showing how transcallosal inhibition operates between brain homotopic regions, with patients showing an increased excitability of the intact hemisphere especially in regions homotopic to the lesion [Fink et al., 2000; Koch et al., 2008]. All these observations highlight the challenge in interpreting the possible relationship, and its direction, between (i) spontaneous homotopic connectivity, (ii) the optimization of brain functioning, and (iii) its cognitive correlates.

First of all, the pattern of VMHC demonstrated by our analysis is consistent with all other previous evidence [Gee et al., 2011; Stark et al., 2008; Zuo et al., 2010], showing an overall trend for higher VMHC with regard to primary sensory regions, that is, visual, motor, and somatosensory, while heteromodal brain areas involved in multisensorial integration show reduced interhemispheric synchronization (see Fig. 1). This spontaneous functional brain architecture possibly suggests that higher levels of interhemispheric synchrony may be required for low-level processing of sensory inputs, while the tendency of associative and higher order regions to be less coordinated may reflect their greater flexibility [Gee et al., 2011]. Interestingly, this medial-to-distal decrease of interhemispheric synchrony also reflects the temporal development of such connections in the developing brain, as shown by studies on preterm infants where networks composed of medial regions appear earlier with respect to those involving homotopic regions placed at greater anatomical distance [Smyser et al., 2010].

In light of the aforementioned models, our finding about the overall trend for VMHC decreases in subjects with higher intellectual functioning level seems to support the idea of hemispheric segregation as a marker of better cognitive functioning. Accordingly, in their recent work about patterns of intrahemispheric and interhemispheric connectivity at rest, Gee et al. [2011] supported the idea of increased intrahemispheric connectivity in healthy humans as evidence of hemispheric segregation, which finds a grounding in the enhanced performance in tasks involving

the two hemispheres performing independently observed in both split-brain patients [Holtzman and Gazzaniga, 1985] and healthy subjects (Banich and Belger, 1990). From an evolutionary point of view, Rilling and Insel [1999] have intriguingly concluded that the CC may have contributed to the spread of interhemispheric synchrony, but beyond a given brain size, the transmission of information between hemispheres might have become problematic, leading to the development of strong, intrahemispheric circuits and the genesis of a more efficient solution (i.e., brain lateralization and hemispheric independence [Rilling and Insel, 1999]). Therefore, the enhancement of cognitive functioning, expressed as a higher IQ, might be representative of different developmental trajectories involving both hemispheres, in the context of a global downgrading of interhemispheric talk.

Such interpretation may find some confirmation in the analysis of the specific brain regions showing a VMHC reduction, as well as the tendency to be more widely connected with areas located in the left hemisphere. Seed-based FC analyses showed that VMHC differences may be related to a difference in the FC profiles of regions placed in the left hemisphere, mainly involving heteromodal (MTG, ROL) and unimodal (visual and somatosensory cortex, SMA) regions. Interestingly, it must be noticed that 2 out of 5 regions are highly involved in language processing (MTG, ROL), while another is part of the visual network. Consistently, Liu et al. [2009] have described four factors that accounted for a vast part of interindividual variance in healthy brain functional asymmetry, with two of them highly loading on visual and language systems [Liu et al., 2009]. Moreover, Haier et al. [2003] have shown a specific significant correlation between brain metabolism in the visual cortex and fluid intelligence level using PET during resting-state, corroborating the idea about the important role played by primary sensory regions—and not high-order, prefrontal ones—into explaining variability in individual intelligence level.

Overall, our data suggest how a better cognitive profile may be an expression of less interhemispheric coordination at rest, with major differences involving left hemisphere connectivity. As a first level interpretation, this supports the idea that a correct pathway for interhemispheric dynamics maturation naturally leads to their segregation, a thesis which has been already supported [Rogers et al., 2004]. More specifically, the persistence of a diffuse left hemisphere connectivity in right-handed subjects with lower IQ suggests dominant hemisphere segregation as a final step into cognitive development, which could be the result of a physiological “pruning” process.

Furthermore, it must be noticed that these regions showing increased connectivity in A-IQ subjects are connected with midline regions mostly covering the well-known DMN [Fox et al., 2005]. Evidences support the idea of a physiological between-networks anticorrelation as a marker of brain healthy functioning [Kelly et al., 2008],

and an altered anticorrelation between the DMN and other resting-state networks have been associated with pathological conditions like Alzheimer's disease [Balthazar et al., 2013], autism [Lynch et al., 2013], schizophrenia [Moran et al., 2013], and antisocial disorder [Tang et al., 2013]. More interestingly, studies on infant brain have shown how, with respect to other resting-state networks encompassing visual, motor, and somatosensory systems, the DMN shows an unorganized structure till early school age (7–9 years old), with an interesting later increase of its intrinsic connectivity mostly involving regions placed in the left hemisphere [Fair et al., 2008]. Given such later development, these regions may also plausibly develop a different connectivity profile toward other networks, suggesting this time-window as a possible context for an initial interaction between connectivity, left–right hemispheres coupling and cognitive development.

Our results should be also discussed in light of other prominent theories about the neurophysiological underpinnings of human intelligence, like the Parieto-frontal integration theory (P-FIT) [Jung and Haier, 2007]. In the last few years, the P-FIT has received large experimental support using different imaging techniques, such as structural [Narr et al., 2007], diffusion weighted [Chiang et al., 2009], and functional MRI [Choi et al., 2008; Yuan et al., 2012], circumscribing the individual variability in intelligence level to the functional coupling between prefrontal, parietal, and temporal lobes regions. First of all, looking at interhemispheric coupling as a correlate of intelligence clearly does not allow to find easy overlap between our findings and those ones promoted in the context of the P-FIT. It must be noticed though that, while the P-FIT is mostly based on structural and evoked activity data, our findings are the first based on the exploration of resting-state brain homotopic organization and its correlation with intelligence at the voxel level, that is without any a priori selection of regions of interest and/or networks. While the P-FIT mostly supports the interhemispheric coupling between associative regions (e.g., fronto-parietal interaction) as a substrate for higher cognitive functioning, our approach completely disregards these connections, putting more emphasis on homotopic connectivity. This could partly explain why we observed significant correlations in unimodal—sensory—regions, a finding which is gaining consensus in the literature about behavioral correlates of intelligence. Indeed, a recent work by Melnick et al. supports a robust correlation between intelligence level and sensory discrimination in the visuo-motor domain [Melnick et al., 2013], suggesting the optimization of low-level processes as the first marker of a more globally efficient system, with a cascade of effects on more complex functions and, ultimately, IQ. It may be that variability in the low level—intermodality—components of intelligence may be captured by homotopic interactions, even at rest, while more complex behaviors may be better addressed by the investigation of inter-intra hemispheric connectivity

between different regions/systems. Further studies should address the role of both P-FIT-like and FH dynamics into explaining the variance of simple and complex cognitive tasks rather than comprehensive scores like IQs.

Furthermore, the apparently inverse role of interhemispheric connectivity—as proposed here in relation to intelligence level—partially differs from what have been already observed in pathological conditions [Kelly et al., 2011; Zhou et al., 2013] and thus must be considered as a different phenomenon. While a decrease in VHMC in neurological and psychiatric patients should be interpreted as a deviation from a normal baseline, intended as the result of a presumably optimal development prior the pathology onset, the same analysis in healthy subjects must consider the degree of symmetry as the optimum achieved by each subject within the boundaries of a nonpathological functioning. More specifically, any possible deviation induced by a pathological condition plausibly does imply a worsening of the overall system performance (i.e., cognition), whatever the goodness of the premorbid “brain symmetry-cognition” interplay. In this framework, as patients' higher-order cognitive profile has not been related to function symmetry changes in previous studies about pathology, further investigations testing this hypothesis are needed.

### Gender and Age Related Differences

Gender related differences in the correlation between intelligence and FH are not surprising, given the literature about cognitive as well as structural and functional differences between men and women [Bell et al., 2006; Goh et al., 2011; Gur et al., 1999; Narr et al., 2007; Witelson et al., 2006]. More specifically, our finding is in line with the work by Luders et al. [2008], which found a gender-related difference in the correlation between cortical folding and intelligence, with female participants showing significantly higher correlation with prefrontal regions convolution respect to males, which actually showed a trend for a negative correlation like the one observed in our data. Changes in cortical folding may be expression of a different development trajectory for male and female, which in turn could interact with cognitive functioning and possibly be also reflected in resting-state connectivity. Moreover, these results are also in line with structural studies by Haier et al. [2005] showing a significant interaction between gender, intelligence, and brain volumes, with the most pronounced differences being located in the prefrontal lobe and closely resembling the cluster of increased correlation in female we have identified [Haier et al., 2005].

As anticipated for gender-related effects, our finding related to differences in the correlation between intelligence and FH as a function of age is not entirely surprising. A vast literature about the structural changes observable during the lifespan is available, with specific patterns of correlation between cortical thickness/volume and intelligence level

being demonstrated in childhood and adolescence [Shaw et al., 2006] as well as adulthood and ageing [Staff et al., 2006; Witelson et al., 2006]. Our results suggest a different pattern of interaction during and right after late adolescence, with the main difference being linked to the FH of primary and unimodal brain regions, whose increased interplay could somehow provide some advantage during this specific time frame, where education-related learning processes are more actively engaged. Considering how the decrease in FH in these regions seems to constitute a persisting pattern for the rest of adult life (till 65 years old), the pattern observed for 18–25 years old participants could possibly reflect a distinctive connectivity profile as well, which could be maybe applied—at the theoretical level—to early adolescence and late infancy years which we did not monitor in our study. However, no causal relationship can be drawn from our data and further investigation with bigger samples encompassing infancy and early adulthood are needed.

### Future Directions

Given the exclusive inclusion of right-handed subjects, future investigations should deepen the interaction between cognition and FH by taking into account brain-lateralization and thus including left-handed subjects. Moreover, considering the IQ as a phenotype resulting from both genetic predisposition and a shaping process operated during early development, the interplay between intelligence and FH should be also disentangled through the creation of a unified model including individual genetic characterization. Finally, given recent evidence about the interaction between brain weak functional connections and intelligence [Santarnecchi et al., 2014a], an analysis based on the strength of functional homotopic connections and its relationship with IQ might interestingly expand the present results.

In conclusion, our findings promote the reduction of synchrony between primary sensory regions at rest, as well as the connectivity of left primary sensory areas and the rest of the brain, as two important factors supporting higher intelligence levels in humans, also contributing to the debate about the evolutionary benefits of brain asymmetry.

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