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Review

Reduced homotopic interhemispheric connectivity in psychiatric disorders: evidence for both transdiagnostic and disorder specific features

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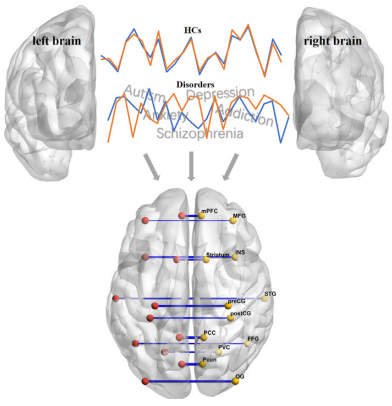
Abstract

There is considerable interest in the significance of structural and functional connections between the two brain hemispheres in terms of both normal function and in relation to psychiatric disorders. In recent years, many studies have used voxel mirrored homotopic connectivity analysis of resting state data to investigate the importance of connectivity between homotopic regions in the brain hemispheres in a range of neuropsychiatric disorders. The current review summarizes findings from these voxel mirrored homotopic connectivity studies in individuals with autism spectrum disorder, addiction, attention deficit hyperactivity disorder, anxiety and depression disorders, and schizophrenia, as well as disorders such as Alzheimer's disease, mild cognitive impairment, epilepsy, and insomnia. Overall, other than attention deficit hyperactivity disorder, studies across psychiatric disorders report decreased homotopic resting state functional connectivity in the default mode, attention, salience, sensorimotor, social cognition, visual recognition, primary visual processing, and reward networks, which are often associated with symptom severity and/or illness onset/duration. Decreased homotopic resting state functional connectivity may therefore represent a transdiagnostic marker for general psychopathology. In terms of disorder specificity, the extensive decreases in homotopic resting state functional connectivity in autism differ markedly from attention deficit hyperactivity disorder, despite both occurring during early childhood and showing extensive co-morbidity. A pattern of more posterior than anterior regions showing reductions in schizophrenia is also distinctive. Going forward, more studies are needed to elucidate the functions of these homotopic functional connections in both health and disorder and focusing on associations with general psychopathology, and not only on disorder specific symptoms.

Keywords: interhemispheric communication; resting state fMRI; voxel mirrored homotopic connectivity; psychiatric disorders; transdiagnostic marker; disorder specific marker

Graphical Abstract



Introduction

The functions of the two individual brain hemispheres and communication between them have been widely debated in neuroscience ever since the first human split-brain observations by Roger Sperry and Michael Gazzaniga 60 years ago (Gazzaniga *et al.*, 1962). While a major focus of research has been on what functions each hemisphere can perform alone, and whether each are capable of consciousness (Gazzaniga, 2000), the question of how the

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two hemispheres interact normally through their extensive interconnections to facilitate sensory, motor, and cognitive functions has also received considerable attention (Doron *et al.*, 2012). The potential importance of interhemispheric communication in the context of psychiatric disorders has also been suggested by studies of individuals where this communication is absent or reduced due to surgical interventions or congenital agenesis of the corpus callosum (CC), the main fiber tract connecting the two hemispheres. Findings have indicated higher incidence of autistic and schizophrenic type symptoms and social cognition impairment (Lábadi and Beke, 2017; Paul *et al.*, 2007; Siffredi *et al.*, 2018) leading to an increasing number of studies attempting to associate altered interhemispheric functional or structural connectivity with psychiatric disorders.

Over the last few decades, brain imaging approaches have been increasingly used to improve our understanding of the precise nature and function of interhemispheric communication and associations with psychiatric disorders. Particular emphasis has been placed on the importance of interhemispheric connectivity between homotopic regions in the two hemispheres (Jin *et al.*, 2020; Yao *et al.*, 2021a) and hemispheric asymmetry (Berretz *et al.*, 2020; Mundorf *et al.*, 2021), and in recent years there has been a substantial increase in the number of studies using voxel-mirrored homotopic connectivity (VMHC) analysis in a wide range of different disorders that selectively measures connectivity between individual voxels at the same location in each hemisphere. In this review, we will primarily focus on studies using structural and resting state-functional magnetic resonance imaging (rs-fMRI) approaches to investigate homotopic interhemispheric resting state functional connectivity (rsFC), and particularly those studies using the technique of VMHC. Studies have shown that these interhemispheric functional connections are the strongest in the brain and correspond to structural connections of the CC (Mollink *et al.*, 2019), with strength being dependent on distance between the left and right regions (Agcaoglu *et al.*, 2018). Their functional importance is well established and studies have increasingly revealed evidence for reduced connectivity across a range of psychiatric disorders, which is often associated with symptoms (see next). This raises the question as to whether altered VMHC may be an important transdiagnostic feature of psychiatric disorders.

VMHC methodology and functional importance of homotopic interhemispheric connections

Homotopic interhemispheric rsFC reflects the degree of temporal covariation of spontaneous fMRI blood-oxygen-level-dependent signal time series between homotopic brain regions of the two brain hemispheres (Stark *et al.*, 2008; Zuo *et al.*, 2010). It is mainly calculated based on a VMHC analysis, whereby rsFC is measured between each voxel in one hemisphere and its mirrored counterpart in the other side (Stark *et al.*, 2008; Zuo *et al.*, 2010) and has shown highly test–retest reliability (Dai et al., 2020; Zuo *et al.*, 2010). CC tracts interconnect most homotopic bilateral regions, especially those along the midline, and thus may structurally underpin homotopic rsFC (van den Heuvel *et al.*, 2009). Indeed, recent large-scale studies have confirmed that there is a consistent relationship between functional and structural connectivity involving interhemispheric homotopic regions (Shen *et al.*, 2015; Mollink *et al.*, 2019). As a key characteristic of the intrinsic functional architecture of the brain, homotopic rsFC is significantly stronger and more stable than rsFC between intra-hemispheric and the remaining inter-hemispheric heterotopic regions in healthy populations (Mollink *et al.*, 2019; Salvador *et al.*, 2005; Shen *et al.*, 2015; Stark *et al.*, 2008). This robust functional synchronization between widespread homotopic regions is negatively correlated with hemispheric asymmetry as defined by normalized difference of intra-hemispheric weighted degree (Gracia-Tabuenca *et al.*, 2018).

Previous studies have demonstrated close associations of homotopic interhemispheric rsFC with human behavior and consciousness. Homotopic interhemispheric rsFC of the occipital lobe has been found to be negatively associated with visual long-term memory performance in healthy children (6–10 years old; Gracia-Tabuenca *et al.*, 2018). In young adults, homotopic interhemispheric rsFC of the fronto-parietal network was positively correlated with task-switching performance (Vallesi *et al.*, 2022). Homotopic rsFC of the language network can also predict new language learning performance, although different regions correspond to different aspects of new language learning (Sander *et al.*, 2022). Strong homotopic rsFC has also been found in the middle occipital gyrus (MOG), inferior parietal lobule (IPL), precentral gyrus (preCG), middle frontal gyrus (MFG), inferior temporal gyrus (ITG), superior temporal gyrus (STG), and anterior insula (aINS) across different tasks (Toro *et al.*, 2008). Homotopic interhemispheric rsFC can be extensively reduced by traumatic brain injury (Li *et al.*, 2017a; Mäki-Marttunen *et al.*, 2013; Ovadia-Caro *et al.*, 2012; Raizman *et al.*, 2022; Song *et al.*, 2022) and predict the degree of consciousness or coma severity in disorders of consciousness (Mäki-Marttunen *et al.*, 2013; Ovadia-Caro *et al.*, 2012). Both animal model (Bukhari *et al.*, 2018) and human (Nir *et al.*, 2022) studies have also reported that loss of consciousness produced by general anesthesia reduces the strength of homotopic interhemispheric rsFC and correspondingly increases hemispheric lateralization.

Developmental trajectories of homotopic interhemispheric rsFC vary across regions in healthy populations, with sensorimotor regions showing increasing homotopic rsFC and higher-order processing regions such as the anterior cingulate cortex (ACC), striatum, and parietal and occipital areas showing a decreasing trend associated with age (Zuo *et al.*, 2010). More complex developmental curves such as quadratic trajectories have been found in regions including the INS and lingual gyrus (LG) and cubic trajectories in the superior frontal gyrus (SFG) and putamen. Sex differences in the developmental trajectory of homotopic rsFC have been found in the dorsolateral prefrontal cortex (dlPFC) and amygdala (Zuo *et al.*, 2010), and a sex difference in the dorsal medial prefrontal cortex (dmPFC) has been reported in 6–10-year-old children (Gracia-Tabuenca *et al.*, 2018). Homotopic interhemispheric rsFC can also be modulated by other factors. For example, sleep deprivation has been demonstrated to increase homotopic interhemispheric rsFC in regions including the thalamus, supplementary motor area (SMA), paracentral lobule (PCL), lingual, and postcentral gyrus (postCG), which could reflect compensatory involvement of bilateral brain regions to avoid possible deterioration of cognitive performance due to sleep loss (Zhu *et al.*, 2016). A similar argument has also been put forward for increased homotopic rsFC of the posterior cerebellum (PCe) and fusiform gyrus (FFG) in individuals with nonclinical depressive symptoms (Wei *et al.*, 2015).

A recent large-scale study has investigated genetic mechanisms underlying interhemispheric functional homotopy using a discovery dataset of 656 healthy participants and two independent validation datasets (103 and 329 healthy participants) where VMHC was calculated in combination with the Allen Human Brain Atlas (Zhao *et al.*, 2022). The study identified 1001 genes that were spatially associated with VMHC and were primarily involved in

protein kinase activity, ion channel regulation, and synaptic function. A temporal specificity analysis of these genes revealed that they were consistently preferentially expressed in nearly all developmental periods other than early fetal and late infancy. Importantly, in the context of the current review, many of the genes are also associated with neuropsychiatric disorders (including addiction, autism, bipolar disorder (BD), epilepsy, major depression, memory impairment disorders, and schizophrenia). The VMHC-associated genes were linked to a wide range of behavioral functions including vision, attention, and executive function, further supporting the importance of interhemispheric homotopic connections in the control of sensory and cognitive processing. Another large-scaled study using data from the UK Biobank has also reported several genes involved in brain development that are associated with concordance between functional and structural measures of homotopic interhemispheric connectivity (Mollink *et al.*, 2019).

Altered homotopic interhemispheric connectivity in psychiatric disorders

The main focus of the current review is to consider whether patterns of reduced, or sometimes increased, interhemispheric homotopic rsFCs reported in VMHC studies are similar across psychiatric disorders, and could therefore represent a transdiagnostic feature and/or exhibit a degree of disorder specificity. Associations between homotopic rsFC changes and symptoms, treatment effects, and structural connectivity will also be detailed. Table 1 provides a summary of all the VMHC studies in the domain of psychiatric disorders as well as in a few other disorders. There are insufficient numbers of studies and too much heterogeneity within and across disorders to undertake a meaningful formal meta-analysis at this stage and so commonly reported regions within (Fig. 1) and across (Fig. 2) psychiatric disorders are summarized based on the frequency with which a region is reported across studies. Potential future treatment interventions that may specifically be utilized to strengthen weakened homotopic interhemispheric connectivity in psychiatric disorders will also be discussed.

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is an early onset neurodevelopmental disorder with impairments in social interaction and communication behaviors, and restrictive and repetitive behaviors (DSM-V), which can generally be diagnosed by the age of 2 years (APA, 2013; Lord *et al.*, 2018). Individuals with autism have been reported to exhibit alterations of interhemispheric communications in extensive brain regions (Holiga *et al.*, 2019; King *et al.*, 2019). Based on a recent review of altered interhemispheric rsFC in ASD, reduced homotopic interhemispheric rsFC can be an important component among those altered interhemispheric rsFCs and has been demonstrated by previous studies using from moderate sample sizes to large databases, such as ABIDE, with the latter providing greater statistical power and thus more robust findings (see Yao *et al.*, 2021a for an overview) (Fig. 1).

Decreased homotopic interhemispheric rsFC, using VMHC, was first reported in a study on 53 ASD vs. 39 neurotypical (NT) adult males and included the aINS, superior parietal lobule (SPL), and preCG and postCG (Anderson *et al.*, 2011). Another early region of interest (ROI-)based study found decreased homotopic rsFC in the STG and inferior frontal gyrus (IFG) in naturally sleeping ASD toddlers (29 ASD vs. 30 controls), which was negatively associated with deficits in the social and communication subscale of the Autism Diagnostic Observation Schedule (ADOS) (Dinstein *et al.*, 2011). The first VMHC study using the large ABIDE I database (which includes data from children, adolescents, and adults) found decreased homotopic interhemispheric rsFC in the posterior cingulate cortex (PCC), aINS, and thalamus (Di Martino *et al.*, 2014). In a subsequent VMHC study also using the ABIDE I database, and which further controlled for gender, reduced homotopic rsFC was found in these three regions and additionally in large-scale brain networks including the default mode network (DMN), salience network, mirror neuron, sensorimotor, and auditory and visual systems, with strengths of homotopic rsFC in the PCC, aINS, and STG being negatively correlated with social and communication impairments as measured by ADOS (Li *et al.*, 2019) (see Fig. 1). Decreased homotopic rsFC in regions of the DMN including the PCC, precuneus (Pcun), and dmPFC were further replicated by a recent study using sub-datasets from ABIDE and the Gender Explorations of Neurogenetics and Development to Advance Autism Research (Floris *et al.*, 2021). This study additionally identified reduced homotopic rsFC in the superior lateral occipital cortex in ASD relative to NT females but not in males, with homotopic rsFC strengths of this region in females with ASD being negatively correlated with ADOS social-affect subscale scores (Floris *et al.*, 2021). In a study that only used data from children with ASD (5–10 years old) from both ABIDE I and II, and further controlled for center/scanner variability, a similar pattern of decreased homotopic rsFC was found to that reported by Li *et al.* (2019) across different ages in ABIDE I, but positive correlations between strengths of homotopic rsFC in regions of the DMN and visual cortex and ASD symptom severity (Yao *et al.*, 2021b). The positive correlation with symptoms in children may reflect abnormal developmental trajectories of homotopic interhemispheric rsFC in ASD (Kozhemiako *et al.*, 2019; Ma *et al.*, 2022). Similar decreased homotopic rsFC has also been found in a recent ROI-based functional near-infrared spectroscopy study in the temporal cortex (Wu *et al.*, 2021).

Although all these studies have reported decreased homotopic interhemispheric rsFC in ASD one, moderate sized one (68 ASD vs. 73 NT adult males) found decreased homotopic interhemispheric rsFC in the inferior occipital gyrus (IOG)/MOG and the postCG but increased in the ITG and MFG (Hahamy *et al.*, 2015).

Of these VMHC studies, only one has reported associations between homotopic rsFC and CC structure, with a trend for caudate rsFC being negatively correlated with volume of the anterior CC (Yao *et al.*, 2021b). Previous studies have consistently revealed reduced CC volume in ASD, although specific subregions vary across studies due to differences in sample size, analysis approaches, and age of participants (see Yao *et al.*, 2021a). An early meta-analysis also reported an overall reduction of CC volume in ASD, with reduction magnitude being greater in the anterior than posterior part (Frazier and Hardan, 2009). Structural CC differences in ASD have also been reported in DTI studies with a general pattern of decreased fractional anisotropy (FA) but increased mean diffusivity or radial diffusivity relative to typically developing controls, although different patterns have been found in very young ASD children (around 2–4 years old) (see Yao *et al.*, 2021a for an overview), which may be explained by an atypical developmental trajectory (Travers *et al.*, 2015).

Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is another highly prevalent neurodevelopmental disorder characterized by

Table 1: Overview of VMHC studies examining alterations in homotopic interhemispheric functional connectivity in mental disorders.

Study	Disorder	Patient		Control		Method	Decreased FC	Increased FC	Regions correlated with symptoms/illness duration
		N (F)	Age	N (F)	Age				
Anderson *et al.* (2011)	ASD	53 (0)	22.40 (7.20)	39 (0)	21.10 (6.50)	whole brain VMHC	aINS, SPL, preCG, postCG	/	IFG−
Di Martino *et al.* (2014)	ASD	360 (0)	16.30 (7.00)	403 (0)	16.30 (7.00)	whole brain VMHC	PCC, pINS, Thal	/	/
Dinstein *et al.* (2011)	ASD	29 (/)	29 mths (12–46)	30 (/)	28 mths (13–46)	ROI-based VMHC	STG, IFG	/	/
Floris *et al.* (2021)	ASD	444 (82)	11.75 (2.65)	575 (166)	11.6 (2.45)	whole brain VMHC	PCC, Pcun, dmPFC	/	/
Hahamy *et al.* (2015)	ASD	68 (6)	26.6 (1.87)	73 (14)	25.82 (2.02)	whole brain VMHC	IOG/MOG, postCG	ITG, MFG	
Li *et al.* (2019)	ASD	409 (47)	17.42 (8.56)	455 (72)	17.35 (7.76)	whole brain VMHC	PCC, Pcun, dmPFC, vmPFC, pINS, ACC, preCG, postCG, IFG, IPL, SMA, STG, LG, FFG, IOG, Thal, SMG, PCL, SOG, SFG, MFG	/	PCC, pINS, STG−
Yao *et al.* (2021b)	ASD	146 (25)	8.48 (1.07)	175 (47)	8.62 (0.84)	whole brain and ROI-based VMHC	PCC, Pcun, dmPFC, preCG, STG, caudate, MOG	/	PCC+; caudate[c−]
Jiang *et al.* (2019)	ADHD	30 (16)	9.20 (1.70)	33 (18)	9.70 (1.80)	whole brain VMHC	/	SFG, MOG, ACe	/
Tarchi *et al.* (2022)	ADHD	89 (23)	11.22 (2.76)	86 (46)	12.23 (3.10)	whole brain VMHC	/	/	/
Zhou *et al.* (2018)	ADHD[d]	45 (7)	8.49 (1.87)	26 (9)	9.04 (1.56)	whole brain VMHC	MOG	/	MOG+
Deng *et al.* (2019)	OCD	46 (20)	30.39 (10.68)	46 (20)	31.83 (10.27)	whole brain VMHC	FFG/IOG, LG, preCG/postCG, putamen, mOFC	/	AG/MOG+
Lai & Wu (2014a)	PD[d]	30 (19)	47.03 (10.63)	21 (11)	41.40 (13.94)	whole brain VMHC	PCC, Pcun	/	PCC−
Sun *et al.* (2015)	PTSD	15 (9)	40.20 (13.12)	14 (5)	36.29 (13.15)	whole brain VMHC	SFG, MFG	/	PHG, aINS−
Wang *et al.* (2019)	GAD[d]	28 (14)	32.93 (4.13)	28 (14)	33.21 (5.25)	whole brain VMHC	MCC, pINS, putamen, preCG	/	MCC−,[a]
Fan *et al.* (2018)	MDD	80 (54)	28.86 (9.57)	124 (87)	27.40 (8.29)	whole brain VMHC	PCC, Pcun	/	PCC−
Guo *et al.* (2013a)	TRD	23 (12)	27.35 (7.26)	19 (9)	24.37 (4.18)	whole brain VMHC	CCR	/	/
	TSD	22 (10)	28.09 (9.91)				/	/	/
Guo *et al.* (2018a)	MDD[d] sample 1	59 (39)	30.25 (6.97)	31 (17)	29.71 (5.04)	whole brain VMHC	PCC, cuneus	/	/
	MDD[d] sample 2	29 (14)	27.00 (8.89)	24 (11)	24.13 (3.97)		PCC, cuneus	/	/
Hermesdorf *et al.* (2016)	MDD	368 (211)	48.84 (7.37)	461 (224)	52.37 (8.00)	whole brain VMHC	Pcun, cuneus, putamen, aINS, STG	/	/
Lai & Wu (2014a) [d,e]	MDD	44 (23)	36.91 (5.31)	27 (15)	38.29 (11.80)	whole brain VMHC	ACC, MFG, PCe	/	ACC−
Liu *et al.* (2021)	MDD[d] with GI	35 (22)	30.86 (6.84)	28 (14)	30.14 (5.00)	whole brain VMHC	PCC, Pcun, MFG	PCe	MFG, SFG−
	MDD[d] without GI	17 (11)	30.29 (8.05)				pallidum, IPL, postCG	SFG	
Shan *et al.* (2021a)	M-MDD	31 (21)	28.65 (5.30)	32 (17)	29.59 (5.00)	whole brain VMHC	PCC, FFG, SOG, postCG, preCG	/	PCC−
	NM-MDD	28 (18)	32.04 (8.18)				PCC	/	/

Table 1: Continued

Study	Disorder	Patient		Control		Method	Decreased FC	Increased FC	Regions correlated with symptoms/illness duration
		N (F)	Age	N (F)	Age				
Wang *et al.* (2015a)	UD	32 (18)	31.97 (10.55)	40 (22)	29.15 (9.56)	whole brain VMHC	PCC, FFG, LG, PCe	/	/
	BD II	36 (20)	28.22 (10.20)				FFG, LG, ACe, PCe	/	/
Wang *et al.* (2015b)	BD II	26 (11)	26.12 (10.30)	40 (18)	28.97 (9.17)	whole brain VMHC	dmPFC, ITG	/	/
Zhang *et al.* (2022)	Postpartum MDD	31 (31)	31.50 (3.40)	31 (31)	31.7 (6.30)	whole brain VMHC	aINS, amygdala, MFG, ACC, MCC, putamen, pallidum	/	/
Chang *et al.* (2015)	AVH SCZ[d]	18 (8)	22.56 (6.73)	20 (9)	23.43 (6.48)	whole brain VMHC	ACC, Pcun, SPL, ACe	IFG	ACC, SPL, preCG–
	Non-AVH SCZ[d]	18 (9)	22.67 (3.85)				preCG	STG	
Guo *et al.* (2014a)	paranoid SCZ[d]	49 (19)	22.69 (4.62)	50 (27)	23.48 (2.49)	whole brain VMHC	Pcun, preCG, STG, MOG, FFG/PCe	/	preCG, STG–
Guo *et al.* (2017)	SCZ[d]	28 (10)	22.93 (3.92)	40 (20)[HC]	23.28 (2.60)	whole brain VMHC	Pcun	/	/
				28 (7)[FBC]	22.86 (3.14)		Pcun, FFG/ACe, LG/PCe	/	/
Guo *et al.* (2018b)	SCZ	17 (9)	33.12 (7.61)	24 (13)	30.67 (5.36)	whole brain VMHC	MTG, FFG/PCe, IOG/MOG, STG/preCG/postCG, LG, Pcun, IPL	/	LG, Pcun–
Hoptman *et al.* (2012)	SCZ	25 (3)	35.50 (10.90)	23 (7)	41.60 (11.40)	whole brain VMHC	LG/ACe, cuneus, Thal, PCe	/	pre/postCG–
Lang *et al.* (2016)	SCZ with CR	36 (15)	32.80 (6.20)	55 (22)	33.10 (9.80)	ROI-based VMHC	IOG, FFG, PCL	/	/
	SCZ with ICR	58 (23)	34.00 (9.60)				IOG, FFG, PCL	/	/
Li *et al.* (2015)	SCZ[d]	26 (13)	14.50 (1.94)	25 (12)	14.40 (2.97)	whole brain VMHC	STG/postCG	/	STG/postCG–
Liu *et al.* (2018)	SCZ[d]	48 (27)	15.79 (1.64)	31 (17)	15.42 (1.52)	whole brain VMHC	FFG, STG/pINS, preCG, Pcun	/	FFG, preCG, STG/insula–
Shan *et al.* (2021b)	SCZ	20 (5)	22.75 (4.38)	20 (6)	25.70 (4.90)	whole brain VMHC	IFG, FFG/ACe, STG, MTG/AG, dmPFC, MFG, preCG, postCG, Pcun, mOFC	MCC	/
Yang *et al.* (2022)	SCZ[d]	107 (62)	15.33 (1.62)	67 (39)	15.43 (1.91)	whole brain VMHC	putamen/caudate	/	/
Zhu *et al.* (2018)	SCZ	88 (21)	35.00 (10.20)	116 (40)	35.30 (10.70)	whole brain VMHC	postCG, pINS, STG, MTG, CCR	/	pINS–
Bi *et al.* (2015)	Internet	21 (5)	18.90 (1.55)	21 (5)	19.29 (2.24)	whole brain VMHC	MFG	/	MFG–
Dai *et al.* (2021)	Alcohol	30 (0)	47.33 (8.30)	30 (0)	47.20 (6.17)	whole brain VMHC	STG, MTG, IFG, aINS, PCC/Pcun	/	/
Guo *et al.* (2019)[e]	Alcohol	24 (1)	49.80 (9.80)	35 (1)	47.40 (9.80)	whole brain VMHC	PCe	MFG	MFG–
	Alcohol and nicotine	30 (0)	50.40 (8.50)				/	PCe, Pcun, MFG, SFG	/
Kelly *et al.* (2011)	Cocaine	25 (2)	35.00 (8.0)	24 (4)	35.10 (7.50)	whole brain & ROI-based VMHC	IFG, MFG, preCG	/	IFG–
Qiu *et al.* (2017a)	Heroin	45 (7)	37.10 (6.49)	35 (5)	35.10 (6.73)	whole brain VMHC	MFG, mOFC, FFG, ITG, Pcun/PCC, putamen/NAcc	/	MFG–,[b+]; putamen/NAcc–
Qiu *et al.* (2017b)	Codeine	33 (0)	24.09 (3.28)	38 (0)	24.21 (3.08)	whole brain VMHC	mOFC	/	mOFC–

Table 1: Continued

Study	Disorder	Patient		Control		Method	Decreased FC	Increased FC	Regions correlated with symptoms/illness duration
		N (F)	Age	N (F)	Age				
Yu *et al.* (2018)	Nicotine	27 (0)	19.40 (2.30)	27 (0)	19.50 (2.30)	whole brain VMHC	aINS, putamen	SFG	SFG+; aINS−
Cheung *et al.* (2021)	AD	16 (13)	74.81 (7.93)	25	68.84 (6.27)	whole brain VMHC	preCG, SFG, mOFC, lOFC, MFG, dmPFC, IFG, RO, GR, aINS, ACC, PCC, HI, PHG, amygdala, calcarine, cuneus, LG, SOG, MOG, IOG, FFG, postCG, SPL, IPL, SMG, AG, Pcun, caudate, Thal, STG, MTG, ITG	/	/
	MCI	29 (14)	74.95 (6.84)				lOFC, mOFC, GR, olfactory cortex	preCG, SFG, RO, SMA, aINS, MCC, postCG, PCL, caudate, putamen, Thal	/
Li *et al.* (2022)	GTCS	24 (9)	69.94 (46.36)	34 (10)	69.38 (28.82)	whole brain VMHC	SOG, HI, FFG, putamen, amygdala, AG, MTG, IFG, MFG	/	MTG/HI−
Lu *et al.* (2021)	CD	18 (0)	17.06 (0.54)	18 (0)	16.89 (0.32)	whole brain VMHC	MOG, postCG, RO, preCG, PCL	/	MOG, PCL−
Ji *et al.* (2014)	GTCS	52 (19)	24.27 (7.04)	65 (29)	25.49 (7.15)	whole brain VMHC	olfactory cortex, IFG, SMG, MTP	cuneus, ACC	/
Chu *et al.* (2022)	rTLE	59 (32)	28.97 (7.73)	60 (29)	26.54 (4.96)	whole brain VMHC	STP, MTP, ITG, IFG	preCG, postCG, SMA	/
Liu *et al.* (2016)	lTLE	21 (9)	27.48 (7.94)	20 (9)	26.35 (8.09)	whole brain VMHC	SMA, MTG, vmPFC, IPL	AG, IOG, SPL	/
	rTLE	22 (8)	25.55 (6.11)				MTG, preCG/IFG	IOG, PHG, PCe	/
Shi *et al.* (2021)	uTLE	36 (20)	29.64 (6.55)	37 (21)	29.03 (6.65)	whole brain VMHC	ITG	LG	ITG+
Dai *et al.* (2020)	Insomnia	48 (32)	46.48 (12.60)	48 (25)	45.69 (12.53)	whole brain VMHC	dmPFC, ITG	postCG	dmPFC−
Li *et al.* (2017b)	Insomnia	27 (15)	38.37 (11.87)	27 (10)	38.15 (11.68)	whole brain VMHC	/	Thal/aINS/pINS, FFG, MCC, IPL, postCG	ACC/SFG+

For age and IQs, mean and standard deviation are reported (age range is provided instead in Dinstein *et al.*, 2011). N (F): number of participants and female participants. AG: angular gyrus; CCR: calcarine cortex; HI: hippocampus; lOFC: lateral OFC; mOFC: medial orbitofrontal cortex; MTP: middle temporal pole; NAcc: nucleus accumbens; pINS: posterior insula; SMG: supramarginal gyrus; STP: superior temporal pole; AVH: auditory verbal hallucinations; CR: complete remission; FBC: family-based controls; GTCS: generalized tonic-clonic seizures; ICR: incomplete remission; M-MDD: melancholic MDD; NM-MDD: nonmelancholic MDD; SCZ: schizophrenia; Thal: thalamus; lTLE: left TLE; rTLE: right TLE; uTLE: unilateral TLE.. Minus (−) indicates negative correlations. + indicates positive correlations. [a] indicates positive correlations between changes of homotopic FC and FA of CC. [b+] indicates negative correlations between changes of homotopic FC and CC volumes; [c−] indicates negative correlations between changes of homotopic FC and CC volumes. [d] indicates first-episode, drug-naive disorder. [e] indicates homotopic rsFC changes that cannot survive multiple comparison correction. Note that names of some regions reported in the table were further adjusted based on coordinates reported in corresponding studies such that regions are comparable across studies. For example, dlPFC was changed as SFG or MFG according to their coordinates in the MNI space. Subregions of the cerebellum were also categorized into anterior and PCe given the heterogeneity of finding.

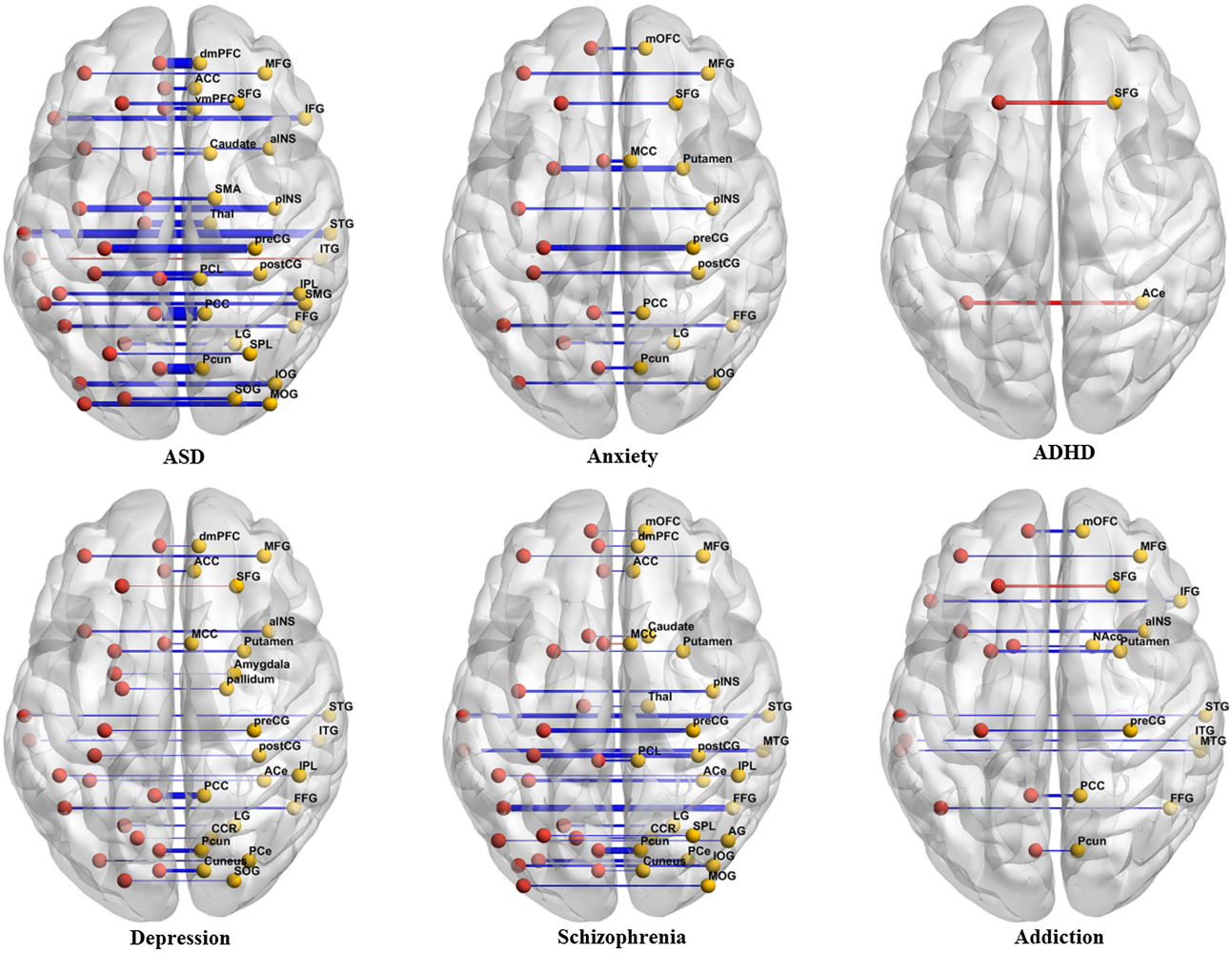

Figure 1: Altered homotopic interhemispheric rsFC in ASD, ADHD, depression, schizophrenia, and addiction. Blue connections indicate decreased homotopic rsFC and red ones indicate increased homotopic rsFC in disorders compared with HCs. The size of the lines indicates the proportion of studies (relative to all studies) showing significant changes of specific homotopic rsFCs in each psychiatric disorder.

symptoms of inattention, hyperactivity, and impulsivity (DSM-V) that generally occur before the age of 12 years but can sometimes be detected as early as 3 years of age (APA, 2013). ADHD children tend to exhibit hyper mirror overflow, as defined by unintentional movements that mimic intentional ones in corresponding homologous muscles on the other side of the body (MacNeil *et al.*, 2011). Based on a ROI analysis, Chen *et al.* (2021) has recently demonstrated that altered homotopic interhemispheric connectivity of the sensorimotor network may underpin such an abnormal motor overflow in ADHD children (8–12 years old), as reflected by increased homotopic rsFC in the preCG and postCG and their correlations with severity of mirror overflow. A previous whole brain-based VMHC study has shown that increased homotopic rsFC in ADHD children (7–13 years old) occurs in the SFG, MOG, and anterior cerebellar lobes (Jiang *et al.*, 2019). However, in medication-free children (8.5–9.1 years old) decreased homotopic rsFC of the MOG has been found based on a whole brain VMHC analysis with homotopic rsFC being negatively correlated with anxiety levels rated by parents (Zhou *et al.*, 2018). There is also one study reporting no homotopic rsFC changes in ADHD children/adolescents (7–18 years old; Tarchi *et al.*, 2022) (see Fig. 1 for summary). Finally, an functional near-infrared spectroscopy-based study has reported decreased homotopic FC in the mPFC, parietal, and occipital lobes (Wang *et al.*, 2020). Thus, the overall situation in ADHD is unclear but suggests that some limited homotopic rsFC changes are present. However, further larger scale studies that control for other co-morbid symptoms, notably ASD and anxiety, and stimulant medications such as methylphenidate (Ritalin) are required.

Anxiety and related disorders

In DSM-V there are a number of anxiety and anxiety-related disorders that all feature individuals experiencing excessive fear or anxiety and have a wide range for ages of onset (APA, 2013). Abnormalities of homotopic interhemispheric rsFC have also been investigated in anxiety disorders including generalized anxiety disorder (GAD) and panic disorder (PD), as well as related disorders such as obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) although few studies have been conducted on each of these (see Fig. 1). In first-episode, treatment-naïve GAD, decreased homotopic rsFC has been found in regions including the middle cingulate cortex (MCC), aINS, putamen, and preCG based on a whole brain VMHC analysis (Wang *et al.*, 2019). GAD

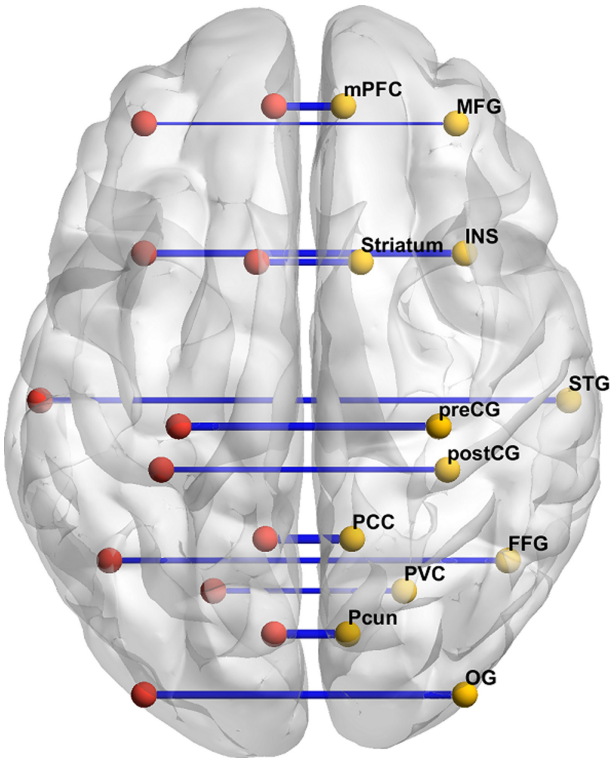

Figure 2: Decreased homotopic interhemispheric rsFC common to either four or five different disorders (ASD, anxiety, depression, schizophrenia, and addiction) are summarized. Blue connections indicate decreased homotopic rsFC. The size of the lines indicates the overall mean proportion of studies across the five disorders reporting changes in a specific homotopic connection. Given the opposite pattern in ADHD based on very few studies, it was not included in this combined figure. INS: insula; PVC: primary visual cortex.

participants also show decreased FA in the middle part of the CC, with FA of the middle part being positively correlated with homotopic rsFC of the MCC but negatively correlated with anxiety severity, with decreased homotopic rsFC of the MCC partly mediating the correlation between FA of the middle CC and anxiety severity (Wang *et al.*, 2019). Decreased homotopic rsFC has been consistently found in the preCG, putamen, and additionally in the medial orbitofrontal cortex (medial OFC) and postCG and visual areas including the FFG, IOG, and LG in OCD (Deng *et al.*, 2019). Homotopic rsFC of the angular/MOG (AG/MOG) is positively correlated with OCD illness duration (Deng *et al.*, 2019). In comparison to individuals who do not develop PTSD after trauma experience, individuals who develop PTSD show decreased homotopic interhemispheric rsFC in the SFG and MFG and decreased FA in the genu of CC whose commissural tracts connect bilateral SFG and MFG (Sun *et al.*, 2015). This study also found that both the homotopic rsFC of the parahippocampal gyrus (PHG) and aINS and FA of CC genu are negatively correlated with symptom severity as measure by the clinician-administered PTSD Scale (Sun *et al.*, 2015). For PD, decreased homotopic rsFC has been observed in the posterior DMN including the PCC and Pcun, with homotopic rsFC of the PCC being negatively correlated with symptom severity measured by the Panic Disorder Symptom Severity Scale (Lai and Wu, 2014a). Thus, anxiety disorders show a consistent pattern of reduced homotopic interhemispheric rsFC associated with symptom severity, although specific regions may vary across different subtypes of anxiety disorders.

Depression and bipolar disorder

In DSM-V major depressive disorder (MDD) primarily involves symptoms or depressed mood and anhedonia whereas in BD alternating periods of MDD symptoms and of mania (BD I) or hypomania (BD II) occur (APA, 2013). Changes in homotopic rsFC in MDD and BD-II are also illustrated in Fig. 1. In an early study investigating alterations of homotopic rsFC in MDD, Guo *et al.* (2013a) demonstrated that while treatment-resistant depression (TRD) patients show decreased homotopic rsFC in the calcarine cortex, treatment-sensitive depression (TSD) patients exhibit no alterations compared to healthy control participants (HCs), suggesting specificity of homotopic changes in subtypes of MDD. Homotopic rsFC in the calcarine cortex can discriminate TRD from TSD and HCs with a relatively high accuracy (>0.76 AUC) (Guo *et al.*, 2013a). Comparisons between unipolar depression (UD) and BD II during a depressive episode have been employed and found similar patterns of decreased homotopic interhemispheric rsFC in UD and BD in the FFG, LG, and PCe compared to HCs (Wang *et al.*, 2015a). Additional regions showing decreased homotopic rsFC have been found in the PCC for UD and in the anterior cerebellum (ACe) for BD, and no significant differences between UD and BD groups have been observed (Wang *et al.*, 2015a). However, in this last study no associations with Hamilton depression scores or disorder onset or duration were found. Another study on umedicated BD II patients also reported decreased homotopic rsFC in the dmPFC and ITG, again with no association with symptom severity (Wang *et al.*, 2015b).

Based on a large database (368 MDD vs. 461 HC), a VMHC study has reported decreased homotopic rsFC in the precuneus, cuneus, putamen, aINS, and STG in middle-aged MDD adults, whereas no group differences have been found for callosal FA and homotopic gray matter volumes, although there were positive correlations between homotopic rsFC of these regions and callosal FA across the two groups (Hermesdorf *et al.*, 2016). In medication-free, current-episode MDD patients, decreased homotopic rsFC has also been found in the precuneus and additionally the PCC, with a negative correlation between homotopic rsFC of the PCC and illness duration (Fan *et al.*, 2018). Similarly, in medication-free, first-episode MDD patients from two independent samples, decreased homotopic rsFC was found in the PCC and cuneus in both samples and could also differentiate MDD patients from HCs (sample 1 >0.91 AUC; sample 2 >0.76 AUC) (Guo *et al.*, 2018). An earlier study on first-episode, medication naïve MDD patients also found decreased homotopic rsFC in the MFG, ACC, and PCe compared to HCs. Furthermore, homotopic rsFC values of the ACC were strongly negatively correlated ($r = -0.65$) with Hamilton depression scores (Lai and Wu, 2014b). In a recent study focusing on first-episode, drug-naïve MDD patients with and without gastrointestinal (GI) symptoms, relative to HCs, while MDD patients with GI symptoms show decreased homotopic rsFC in the PCC, Pcun, and MFG but increased connectivity in the PCe MDD patients without GI symptoms show decreased homotopic rsFC in the pallidum, IPL, and postCG, but increased connectivity in the SFG. Decreased homotopic rsFC in the MFG and SFG and homotopic rsFC of the MFG and SFG were negatively correlated with weight loss in all the MDD patients (Liu *et al.*, 2021). There are also common and distinct patterns between melancholic and nonmelancholic MDD such that both show decreased homotopic rsFC in the PCC and patients with melancholic MDD further exhibit decreased connectivity in the FFG, superior occipital gyrus (SOG), preCG, and postCG (Shan *et al.*, 2021a). In comparison with nonmelancholic MDD, melancholic MDD patients show lower

homotopic rsFC in the preCG and postCG. Negative correlations have been found between homotopic rsFC of the PCC (melancholic vs. HCs) and scores of Snaith–Hamilton Pleasure Scale in melancholic MDD patients and between homotopic rsFC of the preCG and postCG (melancholic vs. nonmelancholic) and illness duration in nonmelancholic MDD patients (Shan *et al.*, 2021a). Finally, in women with postpartum depression, regions showing decreased homotopic rsFC are mainly involved in the emotional (regulation) network (aINS, amygdala, MFG, ACC, and MCC) and the reward system (putamen, pallidum) (Zhang *et al.*, 2022). In summary, although participants and sample sizes are highly heterogenous in these MDD, post-partum depression and BD studies, most have demonstrated a consistent reduced pattern of homotopic rsFC most frequently in the posterior midline regions of the DMN, especially the PCC and Pcun.

Schizophrenia

In the DSM-V, schizophrenia diagnosis requires the presence of two out of five main symptoms including delusions, hallucinations, disorganized or incoherent speaking, disorganized or unusual movements, and negative symptoms. It is considered as a neurodevelopmental disorder with full symptoms not usually occurring until the early 20s. However, some individuals develop symptoms during adolescence (APA, 2013). An initial regional brain wide study was the first to suggest that homotopic interhemispheric rsFC (not VMHC) was particularly weakened globally in schizophrenia and that this was associated with symptom severity measured by the Positive and Negative Symptom Scale (PANSS) (Guo *et al.*, 2013b). A more recent study also reported an overall decrease in homotopic interhemispheric connectivity in schizophrenia that was, interestingly, associated with reduced hemispheric asymmetry (Agcaoglu *et al.*, 2018), again underlining the links between these two measures. A number of studies have additionally reported reduced structural connectivity between the two brain hemispheres in schizophrenia patients (see Kuswanto *et al.*, 2012; Shahab *et al.*, 2018), which are improved by antipsychotic treatment (Tao *et al.*, 2021).

Studies with more fine-grained analysis using VMHC have identified a number of specific regions that show significantly reduced functional connectivity. Unfortunately, to date, no VMHC studies on schizophrenia have additionally measured structural changes in the CC, and so it is unclear to what extent functional and structural changes are correlated, although DTI studies of the CC report reduced FA even at the earliest stages of the disorder and this is associated with cognitive deficits and PANSS scores (Kuswanto *et al.*, 2012). In adult-onset schizophrenia, homotopic rsFC is most consistently reported in the posterior part of the DMN (Pcun), and the sensorimotor (preCG, postCG, PCL, cerebellum) and visual (occipital cortex and FFG) systems (Chang *et al.*, 2015; Guo *et al.*, 2014a; 2018; Hoptman *et al.*, 2012; Lang *et al.*, 2016; Shan *et al.*, 2021b). Other regions frequently reported to have decreased homotopic rsFC are the IFG and ACC (Chang *et al.*, 2015; Lang *et al.*, 2016; Shan *et al.*, 2021b) and MTG and STG (Chang *et al.*, 2015; Guo *et al.*, 2018; Shan *et al.*, 2021b; Zhu *et al.*, 2018) (see Fig. 1). Importantly, many of these studies report associations with PANSS scores or illness onset or duration, although correlations are not generally very strong (Chang *et al.*, 2015; Guo *et al.*, 2014a, 2018; Hoptman *et al.*, 2012; Zhu *et al.*, 2018).

One study comparing 20 first-episode patients with 28 family-based controls and 40 HCs reported reduced homotopic rsFC in the relatives of patients in the posterior DMN (Pcun), motor (cerebellum), and visual (FFG and LG) systems. However, combined FC for the Pcun, cerebellum, and LG could reliably discriminate between them and patients (>0.8 AUC) (Guo *et al.*, 2017). The same group also previously reported that unaffected siblings of schizophrenia patients had significantly reduced homotopic rsFC compared to HCs in the AG, LG, and cerebellum (Guo *et al.*, 2014b). Another study not using VMHC, but comparing inter- and intra-hemispheric regional differences between schizophrenia patients and their unaffected siblings and HCs, found that patients had reduced homotopic rsFC in the preCG, postCG, SMG, and subcallosal cortex compared to unaffected individuals. Furthermore, they reported that patients had increased hemispheric specialization, again providing further support for reduced homotopic rsFC being associated with increased asymmetry (Chang *et al.*, 2019). Overall, these studies suggest that some small or limited reductions in homotopic rsFC may occur in at risk individuals prior to onset of any symptoms, although they become greater and more extensive following disorder onset.

Three studies on adolescent onset schizophrenia report somewhat contrasting findings with one finding decreased homotopic rsFC in the STG and postCG, with the latter associated with negative PANSS scores (Li *et al.*, 2015), whereas another found decreased rsFCs for the Pcun, FFG, pINS, preCG, and STG that were not correlated with PANSS scores but for the pINS, preCG, and STG were negatively correlated with a test of cognitive function (Liu *et al.*, 2018). The most recent study on the other hand found increased homotopic rsFC in the putamen and caudate in patients but no association with symptoms (Yang *et al.*, 2022).

It is worth mentioning findings from two other recent studies that, while not using VMHC, further support the importance of altered interhemispheric connectivity in schizophrenia. The first used a combination of 7-T rs-fMRI and magnetoencephalography in 19 patients with schizophrenia and 24 HCs to demonstrate converging evidence for reduced homotopic rsFC in sensorimotor networks from both reduced rsFC and delta-band-derived FC in sensorimotor networks in patients (Lottman *et al.*, 2019). Another task-based study reported altered FC and activation during the N-back task for working memory in schizophrenia patients relative to HCs. Importantly, while no associations with PANSS were found, FC of homotopic regions derived from healthy participants was the strongest in predicting working memory performance deficits in schizophrenia patients (Tik *et al.*, 2021). Only one VMHC study in adolescent onset schizophrenia patients has specifically included tests of cognitive function and that also reported a negative association between homotopic rsFC and cognitive performance (Liu *et al.*, 2018). Thus, future studies that attempt to establish the functional significance of homotopic rsFC reductions in schizophrenia may need to include tasks that specifically assess aspects of cognitive dysfunction. However, given that both sensorimotor and visual processing systems also consistently exhibit reduced homotopic rsFC in schizophrenia, tasks assessing visuomotor tasks and possibly social recognition (given involvement of FFG FC) might also reveal potential associations.

Addiction

In DSM-V addiction disorders include compulsive cravings and use of substances, but also now extends to compulsive use of facilities such as the internet (APA, 2013). A number of VMHC studies on homotopic interhemispheric rsFC have been carried out across a range of substance addictions, including cocaine (Kelly *et al.*, 2011), heroin (Qiu *et al.*, 2017a), codeine (Qiu *et al.*, 2017b), alcohol (Dai *et al.*, 2021), and nicotine (Yu *et al.*, 2018), as well as internet addiction (Bi *et al.*, 2015) (see Table 1). As with other disorders, the

predominant finding was for a reduced interhemispheric homotopic rsFC in addicted individuals although studies have generally only been on relatively small numbers of participants.

Regions most commonly found with reduced homotopic rsFC were in the frontal cortex (MFG and IFG) and in brain reward regions (OFC and putamen). Several studies also found reduced homotopic rsFC in the posterior part of the DMN (Pcun and PCC—Heroin addicts, Qiu *et al.*, 2017a and Alcoholics, Dai *et al.*, 2021). In contrast to many other disorders, no changes were reported in visual processing regions and only one study on cocaine addicts found reduced homotopic rsFC in sensorimotor regions (the preCG–Kelly *et al.*, 2011) (see Fig. 1). A study on heroin addicts reported a negative correlation between homotopic rsFC in the putamen and MFG and impulsivity scores and for the putamen also use duration (Qiu *et al.*, 2017a). For codeine addicts, homotopic rsFC for the medial OFC was also negatively correlated with impulsive behavior and use duration (Qiu *et al.*, 2017b). For internet addicts, the homotopic rsFC of the MFG was negatively correlated with addition duration (Bi *et al.*, 2015). One study on nicotine addicts (smokers) found both decreased (aINS and putamen) and increased (SFG) homotopic rsFC with that of the aINS being negatively correlated with smoking duration while for the SFG the correlation was positive (Yu *et al.*, 2018). In terms of the relationship between homotopic rsFC and CC structure in heroin addicts, there was a correlation between homotopic rsFC of the MFG and anterior CC volume (Qiu *et al.*, 2017a). In internet addicts there was also reduced FA in the CC although correlations between homotopic rsFC of the MFG and CC FA were only significant in HCs (Bi *et al.*, 2015). The study on cocaine addicts did not find any correlations between homotopic rsFC and FA of the CC (Kelly *et al.*, 2011). Thus, while there is some evidence for associations of homotopic rsFC changes with symptoms, addiction duration, and structure of the CC, findings across the different addictions are not consistent.

Neurological disorders

A number of other VMHC studies have investigated a range of behavioral, neurodegenerative and neurological, mental, and motor disorders [including amyotrophic lateral sclerosis, Zhang *et al.*, 2017; amblyopia and strabismus, Peng *et al.*, 2021; blepharospasm, Wei *et al.*, 2018; conduct disorder, Lu *et al.*, 2021; Alzheimer's disease (AD), vascular dementia (VD), and mild cognitive impairment (MCI), Cheung *et al.*, 2021; Shi *et al.*, 2020; Insomnia, Dai *et al.*, 2020; Li *et al.*, 2017b; irritable bowel syndrome, Qi *et al.*, 2016; Lupus–Wang *et al.*, 2022; Somatization disorder, Su *et al.*, 2016; Tourettes, Liao *et al.*, 2017]. Although individuals with these disorders often show additional psychiatric disturbances, these are rarely taken into account and overall it is perhaps not surprising that a range of heterogeneous findings have been reported with a small number of both decreased and increased homotopic interhemispheric rsFC. Indeed, a study on children with amblyopia and strabismus reporting significantly decreased homotopic rsFC in the SFG and ITG (Peng *et al.*, 2021) and one reporting decreases in the ITG in temporal lobe epilepsy (TLE) found changes were strongly negatively correlated with scores on the Hamilton anxiety scale (Shi *et al.*, 2021). Another study showing both increases and decreases of homotopic rsFC in systemic lupus erythematosus patients also found negative correlations of changes in the postCG, IPL, and MOG with Hamilton anxiety scores (Wang *et al.*, 2022).

The only conditions where multiple studies have been conducted are epilepsy, insomnia, and AD/VD/MCI. In patients with generalized epilepsy, a study reported decreased homotopic interhemispheric rsFC in the olfactory cortex, IFG, SMG, and middle temporal pole, but increased in the cuneus and ACC, although none correlated with clinical measures (Ji *et al.*, 2014). Three VMHC studies on TLE also showed both increased and decreased (Chu *et al.*, 2022; Liu *et al.*, 2016; Shi *et al.*, 2021) homotopic interhemispheric rsFC. One study included groups with either left or right hemisphere TLE, with increased homotopic rsFC being observed in the AG, SPL, and IOG and decreased in the SMA, ventral medial prefrontal cortex (vmPFC), IPL, and MTG in patients with left TLE; and with increases in the IOG, PHG, and PCe and decreases in the IFG, preCG, and MTG in the right TLE (Liu *et al.*, 2016). Thus, there may be differences in patterns of homotopic rsFC changes dependent on whether epilepsy is focused in the right or left temporal lobe. The two other studies only included patients with right/unilateral TLE. One study reported increased homotopic rsFC in the preCG and postCG and SMA, and decreased in the IFG, middle, and superior TPs, ITG, and MTG in the right TLE (Chu *et al.*, 2022). The other one found increased homotopic rsFC in the LG and decreased in the ITG in unilateral TLE, although the latter was positively associated with Hamilton anxiety scores (Shi *et al.*, 2021). One recent regional-based study has also reported increased rsFC in the bilateral Pcun in right TLE (Huang *et al.*, 2022). Thus overall, while findings for epilepsy are not very consistent from a regional point of view, there is a consistent pattern of increased homotopic rsFC, particularly in parts of the visual cortex, although some regions also exhibited decreased rsFC in most studies. Possibly some of the latter may have been due to co-morbid anxiety or depression.

As regards individuals with insomnia symptoms one VMHC study reported increased homotopic rsFC in the FFG, thalamus, aINS and pINS, MCC, IPL, and postCG. However, the insomnia group had higher Hamilton anxiety and depression scores, and when these were regressed out changes in the aINS, IPL, and postCG were no longer significant (Li *et al.*, 2017b). In another study on clinical insomnia while increases were also reported in the postCG, decreases were found in the ITG and dmPFC. Consistently, the dmPFC homotopic rsFC was negatively correlated with the insomnia index, indicating that participants with greater insomnia symptoms actually had lower rsFC (Dai *et al.*, 2020). Thus overall, while both increased and decreased homotopic rsFC has been found in clinical insomnia, only increased homotopic rsFC was reported in healthy individuals with insomnia symptoms, which may possibly reflect compensatory changes in hemispheric communication in response to the behavioral effects of sleep loss in healthy individuals.

To date, only two VMHC studies have investigated altered homotopic rsFCs in AD, VD, and MCI. One study compared small groups of individuals with all three conditions with HCs (Cheung *et al.*, 2021). Patients with AD compared with HCs showed very extensive decreased homotopic rsFC in the preCG, SFG, medial and lateral OFC, gyrus rectus (GR), IFG, Rolandic operculum (RO), ACC, PCC, insula, supramarginal gyrus, SPL and IPL, postCG, AG, Pcun, MTG, STG, FFG, IOG, MOG and SOG, LG, caudate, and thalamus. A discrimination accuracy of 92% was achieved between AD and HC individuals by combining VMHC changes for all these regions. By contrast, patients with VD showed a slightly different pattern with mainly increased homotopic rsFC in the IFG (opercular), RO, SMA, ACC, MCC, PCC, hippocampus, PHG, amygdala, and caudate but decreased in the preCG, IFG (triangular), medial OFC, and GR. Combining VMHC changes in the SMA, LG, calcarine, and GR achieved 87% accuracy in discriminating VD from HCs. Individuals with MCI also primarily showed increased homotopic rsFC in the SFG, RO, aINS, MCC, preCG, postCG, SMA, caudate, putamen, and thalamus but decreases in the medial and lateral OFC,

olfactory cortex, and GR. Combining VMHC changes for both increased and decreased regions achieved an accuracy of 83% in discriminating MCI from HCs. As previously argued, it is possible that increased homotopic interhemispheric rsFC may reflect attempts at compensation in milder conditions such as MCI and possibly also VD, whereas in the more serious condition of established AD a consistent pattern of widespread decreased homotopic rsFC is seen. Interestingly, one other study only on individuals with MCI found increased homotopic rsFC primarily in frontal regions (IFG, MFG, SFG, and aINS) in carriers of the apolipoprotein E (APOE) $\varepsilon 4$ risk allele for developing AD (Shi *et al.*, 2020).

Common and distinct features of interhemispheric functional connectivity changes across disorders

From the details provided in Table 1 and representation of altered regional homotopic rsFC in Figs 1 and 2, it is clear that while the extent of decreased rsFC varies across five psychiatric disorders (ASD, addiction, attention, depression, and schizophrenia), although not ADHD, there are a number of common networks involved. In Fig. 2, reductions common to either four or five different disorders are summarized (ADHD is excluded given the opposite pattern based on very few studies). It can be seen that these common changes are particularly in regions involved in attention/executive (MFG), DMN (mPFC, PCC, Pcun), salience (INS), sensorimotor (preCG and postCG), visual recognition [(FFG, occipital gyrus (OG)], and primary visual processing (cuneus/LG) and subcortical reward (striatum) networks, and also social cognition networks (STG). Thus, weakened homotopic interhemispheric connectivity is occurring in brain networks involved in attentional, executive, self-processing, social cognition, motor, sensory, and reward processing networks frequently associated with a range of different psychiatric disorders. These altered networks also correspondingly map on to the five domains of the Research Domain Criteria (Morris and Cuthbert, 2022). The DMN is perhaps the most notable network involved including dorsal, core, and ventral components (i.e. mPFC, PCC, Pcun). Associations with severity of disorder specific symptoms tend to be limited to a relatively small number of homotopic regions, being most commonly reported for the PCC and insula. This may possibly suggest that the weakening of rsFC in many other homotopic regions observed across disorders may be more indicative of general psychopathology common to many of them rather than to disorder-specific symptoms.

Decreased homotopic rsFC has been reported in all five psychiatric disorders in only seven regions, the MFG, preCG, Pcun, FFG, insula, mPFC, and striatum, with decreases in additional regions being found in four of the five disorders and including PCC, postCG, STG, and visual processing regions (i.e. cuneus, LG or IOG, MOG, or SOG). There has been growing support for the presence of transdiagnostic general psychopathology factors, most recently in terms of a so called "p factor" that is proposed in particular as an index of psychiatric vulnerability, and is notably associated with dysfunction in the same DMN and sensorimotor networks where reduced homotopic rsFC occurs (Caspi *et al.*, 2014; Vanes and Dolan, 2021). In accordance with altered homotopic rsFC in the primary sensorimotor networks (preCG and postCG), motor dysfunction has also been proposed as a transdiagnostic feature across neuropsychiatric disorders (Peralta and Cuesta, 2017). Impaired bimanual coordination (Bellgrove *et al.*, 2001; Isenhower *et al.*, 2012) and sense of agency (Garbarini *et al.*, 2016; Zalla and Sperduti, 2015) found in ASD and schizophrenia may, for example, be contributed to by homotopic rsFC changes in the preCG and postCG. Altered early trajectories of motor skills found in children with ASD have even been reported in their unaffected infant siblings (Patterson *et al.*, 2022). Thus, altered homotopic rsFC in the preCG and postCG may underpin transdiagnostic motor abnormalities. Additionally, the interactions between motor and cognitive systems are well established, and therefore changes in the preCG and postCG homotopic rsFC may reflect general impairment in learning dependent on these interactions (Leisman *et al.*, 2016). Transdiagnostic impairment of cognitive control has also been a focus of interest with a so called "multiple demand" network considered important for aspects of self-regulation, which is essential for adapting to the demands of everyday life and involves frontal, salience, and parietal networks that are dysfunctional in many psychiatric disorders (McTeague *et al.*, 2016). Given that the networks proposed to be involved in transdiagnostic aspects of general psychopathology and in cognitive control map closely on to those where reductions in homotopic rsFC occur across psychiatric disorders, this suggests that their weakened interhemispheric connectivity may contribute to general aspects of psychopathology. However, it is important to emphasize at this point that it is unclear what specific contributions reduced homotopic rsFC in these networks might be making to psychopathology.

Both studies on healthy participants (Berretz *et al.*, 2020; Krupnik *et al.*, 2021; Mundorf *et al.*, 2021) and a small number on psychiatric patients suggest a general inverse relationship between homotopic rsFC and intra-hemispheric connectivity/hemispheric lateralization, although there are exceptions to this and asymmetries often show an atypical pattern rather than increases or decreases in disorders (Berretz *et al.*, 2020). Interestingly, one study on healthy participants has reported that weak homotopic rsFC and greater lateralization was present in a subgroup of individuals with higher IQ relative to an average IQ group, suggesting that the balance between homotopic functional connectivity and lateralization may have implications for psychopathology as well as for higher intellectual ability (Santarnecchi *et al.*, 2015).

While the majority of VMHC studies on psychiatric disorders have not additionally included structural measures, some have reported parallel decreases in CC structure using volumetric analyses (Hermesdorf *et al.*, 2016; Qiu *et al.*, 2017a; Sun *et al.*, 2015). Thus, in psychiatric patients, homotopic rsFC changes tend to be associated with structural ones in the same way as has been reported in healthy participants (Shen *et al.*, 2015; Mollink *et al.*, 2019), although the relationship between them is not always clear. Given that not all homotopic regions show altered rsFC, a crude analysis of volumetric changes in the CC, even when it is divided into subregions, might not be sensitive enough to show significant functional and structural associations and analyzing specific structural connectivity between homotopic regions using DTI might be more informative.

Although there may be common patterns of reduced homotopic rsFC across disorders, there is also a degree of disorder specificity. In particular, reductions in homotopic rsFC changes are most extensive in ASD and this has previously been proposed as a neural biomarker for this disorder (Yao *et al.*, 2021a). Intriguingly, the two major early onset developmental disorders, ASD and ADHD differ considerably in terms of altered homotopic rsFC even though there is substantial co-morbidity between them (60–70%; Hours *et al.*, 2022). The widespread pattern of reduced homotopic rsFC across multiple networks in ASD is in marked contrast to ADHD where only increased rsFC has been reported in the SFG, MOG, and ACe in one study (Jiang *et al.*, 2019). As such reduced

homotopic rsFC may represent a biomarker to distinguish between these two childhood onset disorders, although there have, so far, been relatively fewer VMHC-based studies of homotopic rsFC in ADHD. Notably, structural changes have been reported in the CC in both ASD (see Yao *et al.*, 2021a) and ADHD (Gehricke *et al.*, 2017), which raises the possibility that in some disorders there may be less correspondence between homotopic rsFC changes and structural ones in the CC.

In terms of the extent of homotopic rsFC changes, Fig. 1 shows that this is greatest in both ASD and schizophrenia, with those in anxiety, depression, and addiction disorders being less marked. A further notable difference between ASD and schizophrenia is that, while in ASD both anterior and posterior brain homotopic regions show consistently reduced homotopic rsFC, in schizophrenia reductions are mainly in posterior regions. Parietal lobe dysfunction contributes to many specific and general symptoms of schizophrenia (Chieffi *et al.*, 2018; Leech and Sharp, 2014), and there is some evidence that structural changes occurring early in schizophrenia tend to be more in parietal and occipital regions and progress later to involve the frontal ones (Yildiz *et al.*, 2011). The majority of VMHC studies to date have included first-episode, medication free adult or adolescent patients with schizophrenia and this may possibly have resulted in relatively fewer homotopic rsFC changes in frontal compared to parietal, occipital, and temporal regions.

Another notable difference between schizophrenia and the other disorders is the absence of reduced homotopic rsFC in the PCC. Whereas reductions in PCC homotopic rsFC are consistently found in ASD and addiction, anxiety, and depression disorders, they have not been observed in any schizophrenia studies to date. Reduced PCC homotopic rsFC is also frequently associated with symptom severity in ASD, anxiety, and depression (see Table 1). There is some evidence for an anterior to posterior shift in DMN responses during self-reflection in schizophrenia with enhanced responsivity occurring in the PCC (Holt *et al.*, 2011), so it is possible that this prevents reduced homotopic rsFC in this region.

For the remaining disorders (anxiety, depression, and addition) there is quite a lot of overlap, as well as with ASD and schizophrenia, in terms of regions with reduced homotopic rsFC (particularly in terms of the MFG, mPFC, preCG, postCG, PCC, Pcun, FFG, OG, insula, and striatum). While there may also be some specific differences, given the relatively small number of studies involved and that a number of different addictions (internet, cocaine, codeine, heroin, alcohol, and nicotine), anxiety (General, PTSD, OCD) and depression (MDD, BD-II, and post-partum depression) disorders have been combined it is premature to consider discussing them at this stage.

As far as other disorders are concerned, it is clear that a major neurodegenerative condition such as AD is associated with very extensive reductions in homotopic rsFC and in addition to cognitive dysfunction is known to include many aspects of general psychopathology (Holtzer *et al.*, 2003). However, reduced homotopic rsFC has also been reported in a small number of regions in a bewildering range of other physical and behavioral disorders. It seems likely that in most of these other disorders it is not the disorders themselves that are promoting the changes but concomitant general psychopathology, most likely in terms of anxiety and/or depression. Indeed, in studies where additional measures of anxiety and depression have been taken, these have often been shown to be associated with the reported decreases in homotopic rsFC (Peng *et al.*, 2021; Shi *et al.*, 2021; Wang *et al.*, 2022).

Although this review has primarily focused on patterns of reduced homotopic rsFC across psychiatric disorders, and as a potential transdiagnostic marker of general psychopathology, it is worth considering what distinguishes conditions where increased rsFC is often reported. Thus, ADHD and alcohol addiction to some extent, and MCI, epilepsy, and insomnia are noteworthy in often having regional increases in homotopic rsFC. Interestingly, almost all the regions reported to have increased homotopic rsFC are similar to those with decreased rsFC in most psychiatric disorders, although this conclusion could be biased by the number of regions reported. Several possible factors may have contributed to this pattern of increased rather than decreased homotopic rsFC. The first is under circumstances where individuals are actively attempting to compensate for problems caused by the disorder, which has been proposed in the case of insomnia (Dai *et al.*, 2020) but could easily additionally be applied in the case of MCI. A study has also reported increased homotopic rsFC in several brain regions (STG and PCC) in individuals with congenital amusia (a neurodevelopmental disorder with impaired perception of music) (Jin *et al.*, 2021) might also reflect attempts at compensation for impairment. In the case of epilepsy, increased homotopic rsFC may reflect the consequence of increased neural activity during seizures and in ADHD it is possible that increases might be contributed to by a proportion of participants taking stimulant medications such as methylphenidate (Ritalin). Clearly, more investigation of possible contributors to increased homotopic rsFC is required and may indeed be of potential therapeutic use in conditions characterized by decreases.

Potential therapeutic interventions

Relatively few studies have investigated the effects of different treatments on homotopic interhemispheric rsFC and psychiatric disorder symptoms. A small study on 17 schizophrenia patients and 24 HCs reported that a 6-week anti-psychotic treatment with olanzapine significantly increased connectivity in most regions with pretreatment decreases compared with HCs (Guo *et al.*, 2018). These regions included those involved in sensorimotor (preCG, postCG, cerebellum) and visual (FFG, LG, MOG) functions as well as temporal regions (ITG and STG). However, another small study on 20 patients and 20 HCs only found significant effects of an 8-week treatment with olanzapine on increasing homotopic connectivity in the mPFC and not in the sensorimotor, visual, or temporal regions (Shan *et al.*, 2021b). While both studies provide support for improved symptoms following anti-psychotic treatment being associated with increased homotopic rsFC, this needs to be confirmed in larger scale ones where specific improvements in symptoms can be correlated with functional connectivity changes. Another structural MRI study has also reported that treatment of schizophrenia patients with clozapine or risperidone increased the volume of the anterior CC, although no correlations between volume and clinical symptoms were found (Tao *et al.*, 2021).

Another potential pharmacological intervention that could normalize reduced homotopic rsFC is the hypothalamic neuropeptide oxytocin. Intranasal administration of oxytocin in healthy individuals has been demonstrated by a larger number of studies to facilitate social cognition and reward (Kendrick *et al.*, 2018), and has a wide distribution of receptors in the brain (Quintana *et al.*, 2019). Chronic administration of oxytocin has also been reported by some studies to improve social dysfunction in individuals with ASD and to reduce symptom severity (PANSS scores) in schizophrenia patients (see Kendrick *et al.*, 2018; Le *et al.*, 2022). Intranasal oxytocin has also been reported to have extensive effects on altering neural responses and functional

connectivity both in task and resting-state contexts (see Kendrick *et al.*, 2018; Jiang *et al.*, 2021). However, only one large scale study on 200 participants has reported effective rsFC changes following intranasal oxytocin administration and notably this found that out of a total of 54 links showing increased rsFC, 11 were homotopic interhemispheric connections. These included the medial and lateral OFC, ventral and dorsal mPFC, dorsal ACC, aINS and pINS, PCC, Pcun, and dorsal and ventral striatum (Jiang *et al.*, 2021). Most of these same homotopic regions have reduced rsFC in psychiatric disorders and thus exogenous oxytocin treatment might potentially have general therapeutic effects.

While no studies have specifically assessed the effects of psychostimulants on homotopic rsFC, some studies have suggested that methlyphenidate (Ritalin) can increase rsFC in individuals with decreased FC in ADHD, notably in the sensorimotor, visual and salience networks, and putamen (Rosenberg *et al.*, 2016; Ulrich *et al.*, 2022).

Noninvasive stimulation of the brain using transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tcDS) might seem to have considerable potential for influencing homotopic interhemispheric rsFC, however, to date only a few studies have been carried out. One study on women with postpartum depression has reported that theta burst repetitive TMS of the dlPFC normalized reduced homotopic rsFC in the amygdala, aINS, and MFG with effects in the aINS being correlated with symptom improvements (Zhang *et al.*, 2022). Another study in unmedicated schizophrenia patients using dlPFC repetitive TMS was also reported to alter homotopic rsFC for the dlPFC (Webler *et al.*, 2020).

Another intervention with potential to strengthen interhemispheric homotopic rsFC would be using real-time fMRI neurofeedback training. This approach has already been used to permit either healthy or clinical participants to voluntarily increase or decrease activity in specific brain regions or to increase or decrease functional connectivity between pairs of regions and also to promote behavioral changes and reductions in clinical symptoms (Pindi *et al.*, 2022; Weiskopf *et al.*, 2012). Future studies could therefore be considered where patients are trained to increase functional connectivity strength between homotopic pairs or regions.

Conclusions

Numerous studies have highlighted the importance of communication between the two brain hemispheres, both in terms of normal cognitive, emotional, and behavioral functions, as well as for dysfunction in many psychiatric disorders. Traditionally, brain imaging studies have quantified structural and resting-state interhemispheric connections in fairly global terms but increasingly they have focused on a subset of connections between mirror-regions in the two hemispheres. These so called "homotopic" regions have the strongest FCs in the brain, which in itself underlines their potential importance for coordinating the activities of the two hemispheres, and VMHC is a highly sensitive and robust methodology for quantifying differences in homotopic rsFC. Most studies have been conducted on groups of individuals with a wide range of psychiatric disorders compared to HC groups and the contents of this review have indicated that for psychiatric disorders, with the exception of ADHD, there appears to be a common pattern of reduced homotopic rsFC suggesting the possibility that it may be a potential brain biomarker for general psychopathology. However, patterns of reduced homotopic rsFC do also differ between disorders, most notably between ASD and ADHD and also ASD and schizophrenia, suggesting that they may also have utility in distinguishing between specific disorders.

Future research

Despite the large increase in VMHC-based studies, particularly over the last 5 years or so, there are some key questions that remain to be addressed before further progress can be made in establishing the importance of homotopic rsFC as either a transdiagnostic or disorder specific biomarker. First, very few studies have specifically examined the functional importance of homotopic rsFC for different aspects of behavior, and increasing our knowledge in this area will also help better interpret the significance of changes observed in psychiatric or other disorders. Second, a better understanding of the relationship between rsFC-based changes and measures of structural connectivity will also help us to interpret the likely mechanisms involved, as will establishing key molecular genetics contributions and pharmacological or other interventions that can reliably increase the strength of FCs. Third, it is still unclear at what point homotopic rsFC changes occur in the context of psychiatric disorders. While it is clear that they are present to varying degrees in the early stages of disorders (i.e. they occur in first-episode, unmedicated patients), we do not know clearly whether they represent potential risk factors and may predate the occurrence of disorder symptoms. Several studies on siblings and other family members of schizophrenia patients suggest that they may perhaps represent risk factors (Guo *et al.*, 2014b; 2017). However, more studies investigating individuals at higher risk of psychopathology using, for example, dimensional approaches in healthy populations, could be informative in this respect. Furthermore, there are very few studies having investigated the altered patterns of developmental trajectories of homotopic interhemispheric rsFC in various psychiatric disorders. A comparison between the developmental trajectories in healthy and psychiatric populations is informative to determine whether the reduced homotopic interhemispheric rsFC in psychiatric disorders is derived from slower development or faster decline. For example in ASD, one study has shown both slower and faster developmental trajectories before 10 years of age in ASD depending on regions or gender (Kozhemiako *et al.*, 2019). Fourth, going forward it is important to determine the extent to which changes in homotopic rsFC may be indicative of more general psychopathology than disorder specific symptoms. It is therefore important that future studies, whether on healthy or clinical populations, incorporate robust assessments of general psychopathology in addition to more disorder-specific measures. Finally, it will undoubtedly benefit the future impact of findings in this field if future studies include larger sample sizes in order to be sufficiently powered to allow confidence in the robustness of reported results.

Author Contributions

S.Y. and K.M.K. conceptualized and drafted the manuscript together.

Conflict of Interests

K.M.K. is an editor-in-chief of *Psychoradiology* is not involved in the review or decisions on the manuscript. S.Y. declares no conflict of interests.

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