



Effects of sex and age on presumed inhibitory interactions in 6 areas of the human cerebral cortex as revealed by the fMRI Human Connectome Project

Peka Christova^{1,2} · Lisa M. James^{1,2,3} · Apostolos P. Georgopoulos^{1,2,3,4,5}

Received: 5 November 2021 / Accepted: 20 December 2021 / Published online: 30 January 2022

This is a U.S. government work and not under copyright protection in the U.S.; foreign copyright protection may apply 2021

Abstract

Cortical inhibition is theorized to reflect an underlying property of human brain function, sharpening tuning and shaping connectivity. Although age and sex effects on large-scale resting-state brain connectivity have been well documented, effects on local cortical inhibition have received relatively limited attention. Here, we evaluated age and sex effects on presumed local inhibitory interactions in 6 lateral cortical areas using resting-state functional magnetic resonance imaging (fMRI) data acquired from 1054 young adults who participated in the Human Connectome Project. For each area, all possible pairwise crosscorrelations between prewhitened blood oxygenation level-dependent (BOLD) time series were calculated, and the highest value ($CC^{\max}$) was retained to determine the mean and percentage of negative and positive $CC^{\max}$. Here, we focused on the percentage of negative $CC^{\max}$ which we referred to as presumed “percent inhibition”. The results documented regional differences in percent inhibition as well as age and sex effects, such that women’s brains were characterized by significantly higher percent inhibition than men overall and in 4 of the 6 cortical areas, and the percent inhibition increased significantly with age in all 6 areas for women but in only one area for men. The findings from this young adult sample are presumed to reflect ongoing maturational processes involving local network connectivity that may be shaped by sex differences in brain structure, function, and neurochemistry.

Keywords Inhibition · Connectivity · Functional magnetic resonance imaging · Resting state · Sex · Maturation

Introduction

For decades, neuroimaging has provided an increasingly nuanced glimpse into the complexities of human brain activity. Although neuroimaging research was traditionally dominated by investigations of brain activity evoked by stimuli, functional magnetic resonance imaging (fMRI) studies documenting temporally correlated brain activity in the absence of stimuli (i.e., at rest) (Biswal et al. 1995; Greicius et al. 2003; Zhang et al. 2008; Fox and Raichle 2007; Smith et al. 2009) prompted a surge of investigations into resting-state brain function (for reviews, see Friston et al. 1993; Buckner et al. 2013; Van Den Heuvel et al. 2010). At-rest brain function is characterized by remarkably high energy consumption indicative of immense ongoing brain activity even in the absence of task performance (Raichle 2015). In the absence of task constraints, resting-state neuroimaging studies permit evaluation of dynamic brain activity reflecting intrinsic functional connections between and within brain regions.

Communicated by Francesco Lacquaniti.

✉ Apostolos P. Georgopoulos
omega@umn.edu

¹ The Neuroimaging Research Group, Brain Sciences Center, Department of Veterans Affairs Health Care System, Minneapolis, MN 55417, USA

² Department of Neuroscience, University of Minnesota Medical School, Minneapolis, MN 55455, USA

³ Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN 55455, USA

⁴ Department of Neurology, University of Minnesota Medical School, Minneapolis, MN 55455, USA

⁵ Brain Sciences Center (11B), Minneapolis VAHCS, One Veterans Drive, Minneapolis, MN 55417, USA

Human brain activity is facilitated by dynamic neuronal interactions shaped by the convergence of inhibitory and excitatory inputs, the output of which can be captured via fMRI. Substantial evidence indicates that cortical inhibition influences global brain dynamics (Deco et al. 2014), regulates activity of cortical neurons, and sharpens local cortical circuits (Stefanis and Jasper 1964; Georgopoulos and Stefanis 2007; Merchant et al. 2008, 2014; Georgopoulos and Stefanis 2010; Isaacson and Scanziani 2011; Lee et al. 2012; Li et al. 2012a, b; Georgopoulos 2014; Georgopoulos and Carpenter 2015; Merchant and Georgopoulos 2018). Inhibitory activity influences not only long-range (e.g., inter-hemispheric; Carson 2020) cortical activity but also local neuronal populations (Georgopoulos 2014; Lee et al. 2012; Li et al. 2012a, b; Merchant and Georgopoulos 2018). For example, by shaping the neuronal population vector, local cortical inhibition has been shown to play a critical role in enhancing movement accuracy (Mahan and Georgopoulos 2013; Georgopoulos 2014; Georgopoulos and Carpenter 2015) and improving visual perception (Lee et al. 2012; Li et al. 2012a, b). Moreover, local cortical inhibition is theorized to reflect an underlying property of human brain function (Georgopoulos 2014). Here, we used resting-state fMRI (rs-fMRI) to evaluate local inhibition in 6 cortical areas and to explore sex and age effects on inhibition in healthy participants.

Several prior fMRI studies have documented sex- and age-related differences in large-scale resting-state brain functional connectivity (Allen et al. 2011; Biswal et al. 2010; de Lacy et al. 2019; Fair et al. 2009; Filippi et al. 2013; Geerligs et al. 2015; Scheinost et al. 2015; Tomasi & Volkow 2012a, b; Zhang et al. 2018; Weissman-Fogel et al. 2010). Comparatively, the effects of age and sex on local networks have received relatively limited attention. One study reported age-related decreased connectivity limited to networks involved in higher level cognitive function (Geerligs et al. 2015). Another influential study documented nearly ubiquitous decrease in functional connectivity with age and modestly stronger within-network connectivity for females relative to males, particularly involving sensorimotor networks (Allen et al. 2011). Others have similarly found increased within-network resting-state functional connectivity in females and, conversely, increased resting-state functional connectivity between networks in males, that corresponded to sex differences on cognitive tasks (Satterthwaite et al. 2015). A recently developed technique, referred to as regional homogeneity, assesses the functional coherence of a given voxel with its nearest neighboring voxels, and is interpreted as an index of local connectivity (Zang et al. 2004). Investigations of age and sex differences in regional homogeneity have similarly documented decreased regional homogeneity with age in practically all brain regions (Wu et al. 2007; Lopez-Larson et al. 2011), whereas sex

differences in regional homogeneity were limited to medial temporal regions (Lopez-Larson et al. 2011). Here, we take an alternative approach, evaluating age and sex differences in local connectivity in terms of the relative influence of presumed excitatory and inhibitory interactions.

Materials and methods

Participants

Data from the Human Connectome Project-Young Adults (HCP-YA 1200 Subjects Data Release March 1, 2017) were used in this study (Van Essen et al. 2013). Participants comprised 575 women and 479 men, for a total $N = 1054$. The age of participants was given in years; the handedness of the participants (Oldfield 1971; Schachter et al. 1987) ranged from -100 (most left handed) to 100 (most right handed). All subjects provided written informed consent and the Institutional Review Board of Washington University in St. Louis approved the research protocol. Our analyses were approved by a local IRB Committee.

fMRI data collection

fMRI data were collected at Washington University St. Louis using a 32-channel customized Siemens 3T scanner, with image acquisition methods described by Uğurbil et al. (2013). The structural scans include T1-weighted and T2-weighted images, acquired at high 0.7 mm isotropic resolution. Resting-state fMRI images were collected using a gradient-echo echo planar imaging (EPI) sequence with the following parameters: TR = 720 ms, flip angle = 52° , FOV = 208×180 mm, matrix = 104×90 , 2.0 mm isotropic voxels, 72 slices covering the entire brain, and multiband factor = 8. The HCP's main pipeline was implemented on the fMRI datasets for preprocessing (Glasser et al. 2013). This pipeline removes spatial artifacts and distortions, re-aligns volumes to compensate for subject motion, registers the fMRI data to the structural MRI, and spatially transforms to the standard Montreal Neurological Institute (MNI) space.

fMRI data preprocessing

We investigated neural interactions at rest in the following 6 cortical areas (Desikan-Killiany atlas; Desikan et al. 2006): superior frontal gyrus, precentral gyrus, postcentral gyrus, superior parietal cortex, inferior parietal cortex, and lateral occipital cortex. Resting-state fMRI time series of each vertex consisted of 1200 Blood Oxygenation Level-Dependent (BOLD) values acquired every 720 ms. These BOLD time series were prewhitened using an Autoregressive Integrative Moving Average (ARIMA) model of orders (15, 1, 1)

(Christova et al. 2011; Christova and Georgopoulos 2018) to obtain practically white noise residuals (innovations). This procedure removes the internal dependencies from within each series and paves the way for unbiased estimation of interactions between time series.

Data analysis

Crosscorrelations

All possible pairwise crosscorrelation functions (CCFs) between innovations within each of the 6 areas of the left and right hemispheres were calculated using ± 10 lags, corresponding to total ± 7.2 s; each CCF consisted of 21 cross-correlations (10 negative lags + 10 positive lags + zero lag). For each CCF, we located the highest absolute crosscorrelation ($|CC|^{\max}$), and retained its value and sign (negative, positive); an example is shown in Fig. 1. $CC^{\max}$ values were Fisher z -transformed (Fisher 1958) to normalize their distribution for statistical analyses

$$\pm zCC^{\max} = \operatorname{atanh}(\pm CC^{\max}). \quad (1)$$

For each area, we computed the mean $\pm zCC^{\max}$ and the percentage of positive and negative $CC^{\max}$. Thus, the dataset analyzed with regard to age and sex comprised $1054 \text{ brains} \times 2 \text{ hemispheres} \times 6 \text{ areas} = 12,648 - CC^{\max}$ values. Given that the positive and negative percentages add 100%, we will report on the analyses only of the percentage of negative $CC^{\max}$ which we call “percent inhibition”.

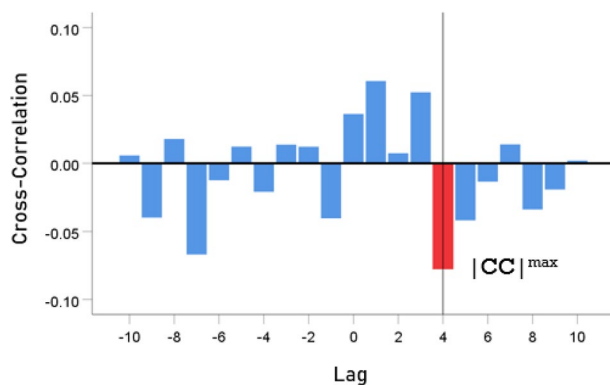


Fig. 1 An example of crosscorrelation function (CCF) calculated between 2 innovations from lag -10 to lag $+10$ including zero lag. The highest absolute crosscorrelation ($|CC|^{\max}$) (red color) was obtained, and its value and sign were retained

Statistical analyses

Standard statistical methods were used to analyze the data, including analysis of covariance (ANCOVA), linear regression, and Pearson correlation. Statistical analyses were performed using the IBM-SPSS package (IBM-SPSS Statistics for Windows, Version 27.0, 64-bit edition. Armonk, NY: IBM Corp; 2020).

Results

Age

The frequency distributions of age for women and men are shown in Fig. 2. Age-related statistics are given in Table 1. Women were statistically significantly older than men (Mann–Whitney U test, $z = 7.021$, $P < 0.001$).

Handedness

The frequency distributions of handedness for women and men are shown in Fig. 3. The handedness of the participants ranged from -100 (most left handed) to 100 (most right handed); handedness-related statistics are given in Table 2. Given the heavily skewed distributions of handedness (Fig. 3), they were compared using nonparametric statistics; women were statistically significantly more right handed than men (Mann–Whitney U test, $z = 6.658$, $P < 0.001$).

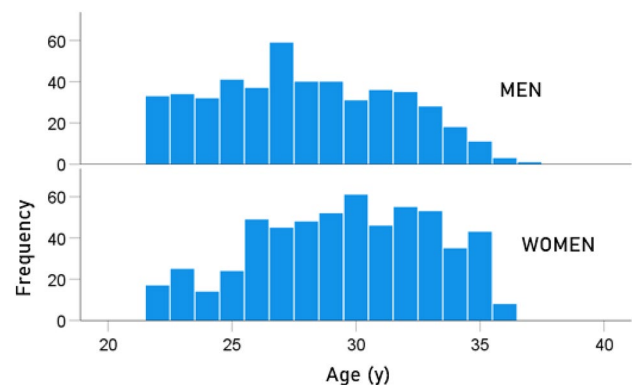
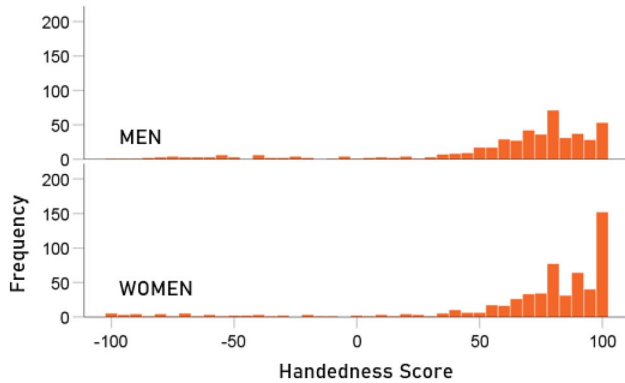


Fig. 2 Frequency distribution of participant's age in years: men (top) $N = 479$ and women (bottom) $N = 575$. For details, see Table 1

Table 1 Age statistics for the participants. SD, standard deviation; SEM, standard error of the mean; min, minimum; max, maximum

	<i>N</i>	Mean (y)	SD	SEM	Median	Min (y)	Max (y)
Women	575	29.5	3.59	0.15	30.0	22	36
Men	479	27.9	3.64	0.17	28.0	22	37
Total	1054	28.8	3.70	0.11	29.0	22	37

**Fig. 3** Frequency distribution of participant's handedness ranged from -100 (most left handed) and +100 (most right handed): men (top) *N* = 479 and women (bottom) *N* = 575. For details, see Table 2

shown in Fig. 4 and those for women and men are shown in Fig. 5. Descriptive statistics are given in Table 3. Women had statistically significantly higher percent inhibition than men (Mann–Whitney *U* test, $z = 12.52$, $P < 0.001$).

Hemispheres

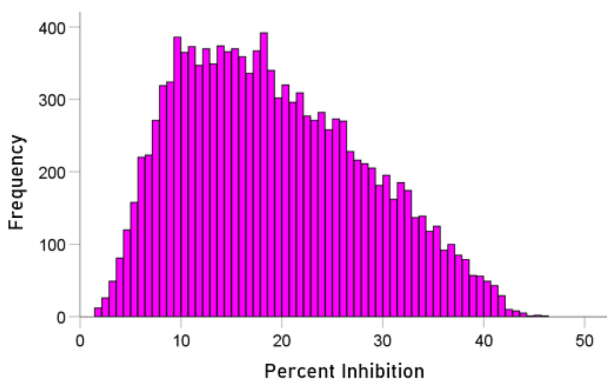
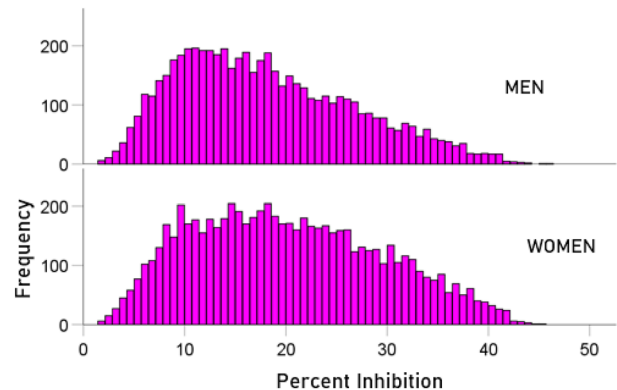
The percent inhibition was highly correlated between the left and right hemispheres in all 6 areas (Figs. 6, 7, 8, $P < 0.001$ for all areas).

Areas

The frequency distributions of percent inhibition are shown in Fig. 9. It can be seen that percent inhibition tended to be more frequent in anterior than in posterior areas. This aspect

Table 2 Handedness statistics for the participants. SD, standard deviation; SEM, standard error of the mean; min, minimum; max, maximum

	<i>N</i>	Mean	SD	SEM	Median	Min	Max
Men	479	60.9	43.78	2.00	75.0	– 100	100
Women	575	70.6	43.42	1.81	80.0	– 100	100

**Fig. 4** Frequency distribution of percent inhibition in 1054 participants $\times$ 2 hemispheres $\times$ 6 cortical areas = 12,648**Fig. 5** Frequency distribution of percent inhibition: men (top) 479 participants $\times$ 2 hemispheres $\times$ 6 cortical areas *N* = 5748 and women (bottom) 575 participants $\times$ 2 hemispheres $\times$ 6 cortical areas *N* = 6900. For details, see Table 3

Percent inhibition

Descriptives

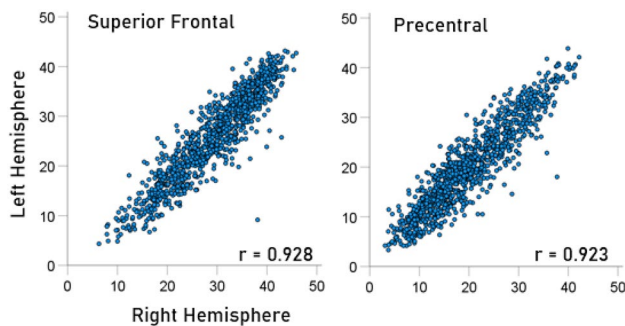
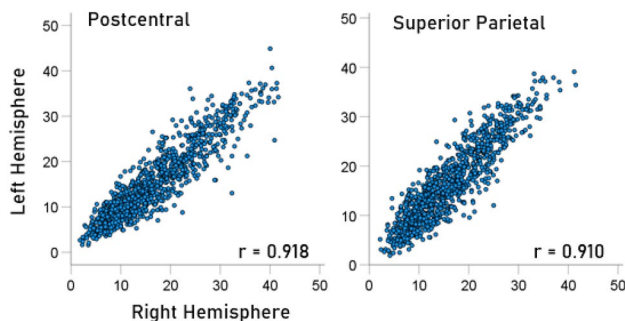
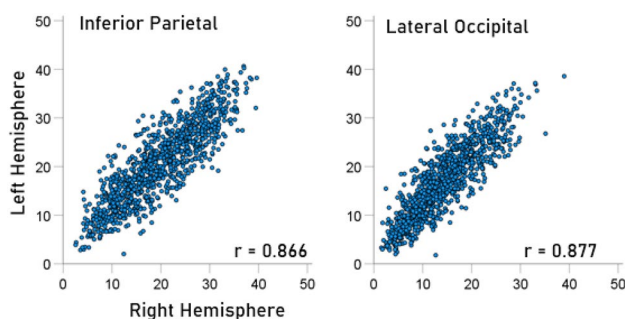
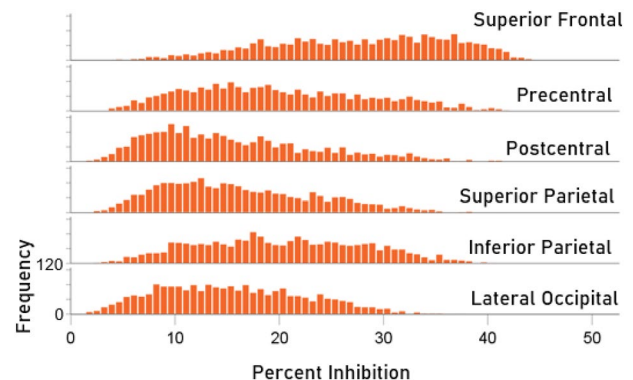
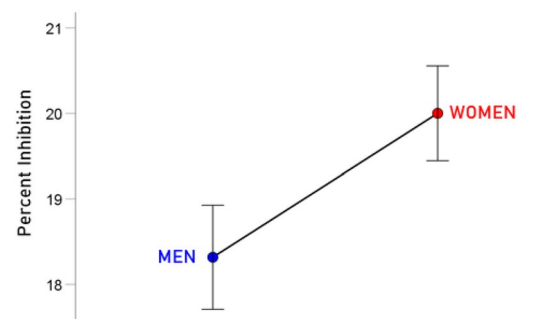
The overall frequency distribution of percent inhibition is

was analyzed quantitatively using an ANCOVA (see Methods), as follows. In an initial repeated-measures ANCOVA, we evaluated the effects on percent inhibition (averaged over

Table 3 Percent inhibition statistics for the participants

	N	Mean	SD	SEM	Median	Min	Max
Women	6,900	20.17	9.25	0.111	19.36	1.63	45.17
Men	5,748	18.12	8.68	0.114	16.81	1.55	45.87
Total	12,648	19.24	9.05	0.080	18.14	1.55	45.87

SD standard deviation; *SEM* standard error of the mean; *min* minimum; *max* maximum. *N* for women = 575 participants $\times$ 6 areas $\times$ 2 hemispheres = 6900; *N* for men = 479 $\times$ 6 $\times$ 2 = 5,748; *N* total = 1054 $\times$ 6 $\times$ 2 = 12,648

**Fig. 6** Scatter plot of percent inhibition in the left hemisphere vs the right hemisphere in superior frontal gyrus ($N=1054$) and precentral gyrus ($N=1054$)**Fig. 7** Scatter plot of percent inhibition in the left hemisphere vs the right hemisphere in postcentral gyrus ($N=1054$) and superior parietal cortex ($N=1054$)**Fig. 8** Scatter plot of percent inhibition in the left hemisphere vs the right hemisphere in inferior parietal cortex ($N=1054$) and lateral occipital cortex ($N=1054$)**Fig. 9** Frequency distribution of percent inhibition of 1054 participants (average of left and right hemisphere) of 6 cortical areas, as shown**Fig. 10** Main effect of sex. Mean $\pm$ 95% confidence intervals (CI) of percent inhibition for women (red) 575 participants $\times$ 2 hemispheres $\times$ 6 cortical areas ($N=6900$) and men (blue) 479 participants $\times$ 2 hemispheres $\times$ 6 cortical areas ($N=5748$)

the two hemispheres) of repeated measure Area (6 cortical areas; “Within Subjects Effect”) and fixed factor Sex (male, female; “Between-Subjects Effect”), with Age and Handedness as covariates. Handedness did not have a statistically significant effect (F test, $F_{[1,1050]}=0.032$, $P=0.858$) and was eliminated from further analyses. In contrast, Area, Sex, and Age had highly significant effects and were retained for the next ANCOVA. This yielded the following results.

(a) The main effect of Sex was highly significant (Fig. 10; F test, $F_{[1,1050]}=15.65$, $P<0.001$); more specifically,

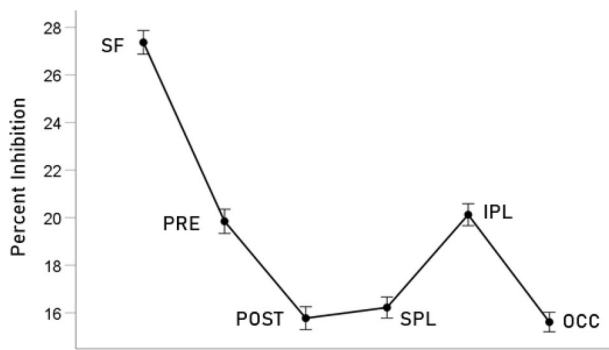


Fig. 11 Main effect of area. Mean $\pm$ 95% CI of percent inhibition in the areas indicated; superior frontal gyrus (SF), precentral gyrus (PRE), postcentral gyrus (POST), superior parietal cortex (SPL), inferior parietal cortex (IPL), and lateral occipital cortex (OCC)

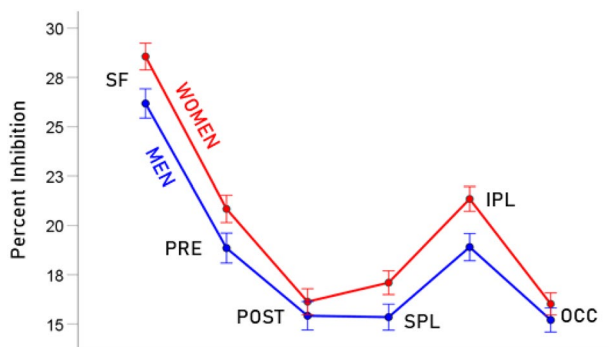


Fig. 12 Mean $\pm$ 95% CI of percent inhibition in the 6 areas in women (red) and men (blue). Abbreviations as in Fig. 11

women had a higher percent inhibition (20.001 ± 0.283 , mean $\pm$ SEM) than men (18.318 ± 0.311) by a mean difference of 1.682 ± 0.428 ($P < 0.001$, as the F test above).

(b) The main effect of Area was highly significant (Fig. 11; Greenhouse–Geisser test, $P < 0.001$; sphericity not assumed, since Mauchy’s test of sphericity was highly significant, $P < 0.001$); superior frontal had the highest percent inhibition (27.3%), whereas postcentral and lateral occipital had the lowest (15.8% and 15.6%, respectively). There were 15 possible pairwise comparisons between the mean percent inhibition of the 6 areas; all comparisons yielded statistically

significant differences ($P < 0.05$, pairwise tests in ANCOVA, Bonferroni corrected), except for the postcentral vs. lateral occipital difference which was not significant.

(c) The Sex $\times$ Area interaction term was highly significant (Fig. 12; Greenhouse–Geisser test, $P < 0.001$). We investigated this further by performing 6 univariate ANCOVAs with percent inhibition of each area as the dependent variable, sex as a fixed factor, and age as a covariate. Women had significantly higher ($P < 0.001$) percent inhibition than men in all areas except for postcentral and lateral occipital, for which the difference was not statistically significant.

(d) The overall effect of Age was highly statistically significant (F test, repeated-measures ANCOVA, $P < 0.001$). The Area $\times$ Age interaction term was not statistically significant ($P = 0.147$; Greenhouse–Geisser test). Indeed, the percent inhibition increased significantly with age in all 6 areas. We investigated this finding further by performing 6 linear regressions of percent inhibition vs. age, i.e., a regression for each one of the 6 areas. The results are shown in Table 4 and plotted in Figs. 13, 14, 15. In addition, we investigated whether the dependence of percent inhibition on age differed between women and men by performing the same regressions separately for women and men. Indeed, we found that percent inhibition increased highly significantly with age in women, in all 6 areas; in contrast, in men, this effect was marginally significant for superior frontal but not statistically significant for any of the remaining 5 areas (Table 5). Finally, we averaged percent inhibition across all 6 areas and regressed it against age separately for men and women (Fig. 16). We found that there was no significant dependence of overall percent inhibition in men (b (slope) = 0.133, $t = 1.613$, $P = 0.107$) but a strong one in women ($b = 0.308$, $t = 3.886$, $P < 0.001$).

Discussion

Methodological considerations

Here, we evaluated age and sex effects on resting-state presumed cortical inhibition in healthy young adults. Our basic measure was negative crosscorrelation of prewhitened BOLD time series within a cortical area. We use

Table 4 Linear regression statistics of percent inhibition vs. age. $N = 1054$

	<i>b</i>	SE	Correlation	<i>t</i> value	<i>P</i> value	Figure #
Superior frontal	0.386	0.069	0.170	5.604	<0.001	13
Precentral	0.296	0.070	0.129	4.222	<0.001	13
Postcentral	0.232	0.066	0.107	3.498	<0.001	14
Superior parietal	0.235	0.061	0.118	3.857	<0.001	14
Inferior parietal	0.279	0.064	0.134	4.374	<0.001	15
Lateral occipital	0.231	0.056	0.126	4.113	<0.001	15

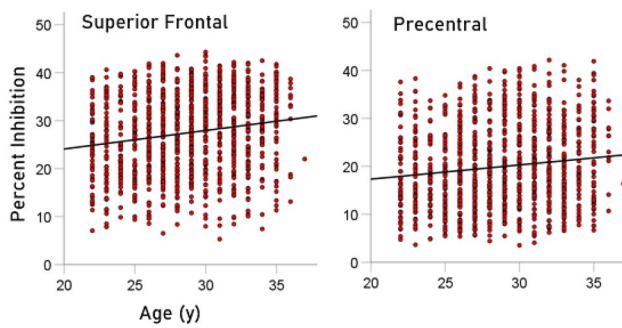


Fig. 13 Scatter plot of percent inhibition (averaged between hemispheres) vs age in years for superior frontal and precentral areas. See Table 4 for detailed results

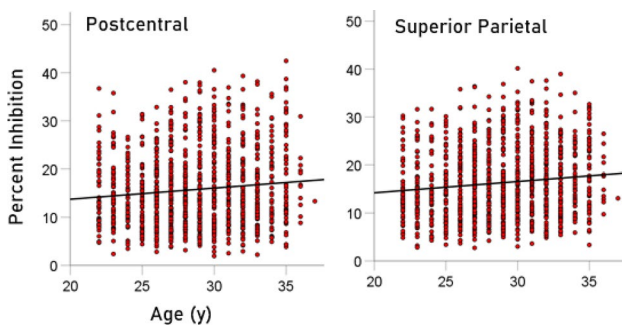


Fig. 14 Scatter plot of percent inhibition (averaged between hemispheres) vs age in years for postcentral and superior parietal areas. See Table 4 for detailed results

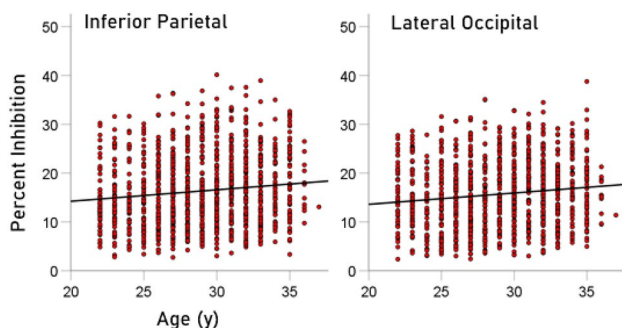


Fig. 15 Scatter plot of percent inhibition (averaged between hemispheres) vs age in years for inferior parietal and lateral occipital areas. See Table 4 for detailed results

the term “presumed inhibition” in an operational sense, to denote a negative interaction between two time series. “True” inhibition can only be ascertained by intracellular recording, a method not feasible in humans and used in animal studies under special circumstances (e.g., Stefanis and Jasper 1964). And yet, even in extracellular electrophysiological studies, positive and negative peaks in the crosscorrelogram between two spike trains (Perkel et al.

1967) or local field potentials (LFP) (Merchant et al. 2014) are referred to as denoting excitation and inhibition, respectively. Our use in this study of the term “presumed inhibition” to label negative crosscorrelations between BOLD time series is based on (a) the well-documented association and dependence of the BOLD signal on LFP (Logothetis 2002), and (b) the interpretation of LFP positive and negative crosscorrelations as denoting excitatory and inhibitory neural interactions, respectively (Merchant et al. 2014); the qualification “presumed” in the title of the paper signifies the uncertainty associated with assessing inhibitory effects in the absence of intracellular recordings.

Cortical areas studied

In this study, we focused on 6 areas located on the lateral surface of the cortical hemispheres and spanning 3 lobes (frontal, parietal, and occipital). These areas are interconnected (Caminiti et al. 1999), they are involved in visuomotor coordination, including visual control of reaching and eye movements (Johnson et al. 1996; Battaglia-Mayer et al. 2000), and the local excitatory interactions in them have been thoroughly analyzed (Christova and Georgopoulos 2018). In the present study, we extend the investigation of these areas to include presumed local inhibitory interactions and the effects of sex and age on them.

Local cortical inhibitory mechanisms

Cortical inhibition has been purported to shape brain activity through several mechanisms, including influencing excitatory activity, impacting the pacing and synchronization of spontaneous and evoked oscillations, and sharpening tuning (Isaacson and Scanziani 2011; Georgopoulos 2014). For instance, inhibition in the motor cortex has been shown to play a prominent role in the tuning of the neuronal population vector, thereby shaping accuracy and precision of behavioral outputs (Georgopoulos 2014). Here, we documented regional variation in cortical inhibition with the highest percent inhibition found in the superior frontal areas and the lowest percent inhibition found in postcentral and lateral occipital areas. This is consistent with the previous studies documenting regional differences in cortical connectivity profiles (Sepulcre et al. 2010), and stronger positive within-network correlations within the motor, visual, and auditory cortex than within frontal regions (Allen et al. 2011). Those findings coupled with evidence of regional variation in inhibition observed here highlight important differences in local cortical interactions in brain regions underlying higher order cognitive processes such as the superior frontal region versus primary sensory and motor regions.

Table 5 Linear regression statistics of percent inhibition vs. age for women (W; $N=575$) and men (M; $N=479$)

	Sex	<i>b</i>	SE	Correlation	<i>t</i> value	<i>P</i> value
Superior frontal	W	0.388	0.093	0.171	4.163	<0.001
	M	0.231	0.105	0.100	2.199	0.028
Precentral	W	0.301	0.100	0.125	3.017	0.003
	M	0.165	0.102	0.074	1.615	NS
Postcentral	W	0.276	0.098	0.117	2.815	0.005
	M	0.135	0.092	0.067	1.465	NS
Superior parietal	W	0.267	0.087	0.127	3.058	0.002
	M	0.087	0.088	0.045	0.993	NS
Inferior parietal	W	0.306	0.087	0.146	3.524	<0.001
	M	0.094	0.097	0.044	0.967	NS
Lateral occipital	W	0.309	0.080	0.159	3.850	<0.001
	M	0.089	0.082	0.050	1.088	NS

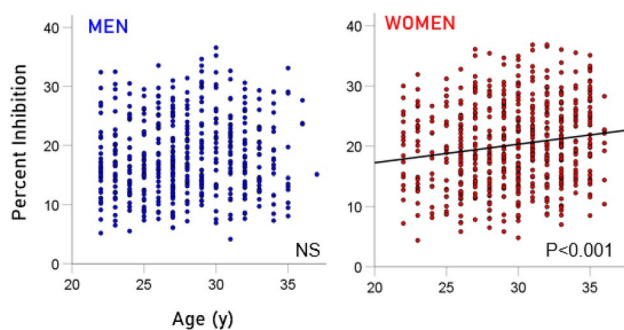


Fig. 16 Scatter plot of percent inhibition (averaged between hemispheres and 6 areas) vs age in years for men (blue; $N=479$) and women (red; $N=575$). See Table 5 for detailed results

Effects of sex

Here, we documented sex differences in local connectivity characterized by higher percent inhibition in women than men both globally and in 4 of the 6 areas evaluated—superior frontal gyrus, precentral gyrus, superior parietal, and inferior parietal cortices. Numerous sex differences in brain structure and function have been documented. In women, these include reduced brain volume, higher percentage of gray matter, and lower percentage of white matter (Cosgrove et al. 2007), higher processing efficiency (Christova et al. 2008), greater functional segregation (Satterthwaite et al. 2015), greater local functional connectivity density (Tomasi and Volkow 2012b), and greater cortical complexity (Luders et al. 2004). Sex differences in resting-state functional connectivity (Biswal et al. 2010; Lopez-Larson et al. 2011; Zhang et al. 2018) have also been shown to underlie sex differences in cognitive performance (Satterthwaite et al. 2015). In addition, women's brains are characterized by greater cerebral blood flow and neurochemical differences relative to men (Cosgrove et al. 2007). Recent evidence has

documented sex differences in gamma-aminobutyric acid (GABA), the primary neurotransmitter involved in inhibition, although methodological differences have resulted in inconsistent findings (Sanacora et al. 1999; O'Gorman et al. 2011). GABA has been shown to vary across the menstrual cycle, suggesting that it is at least partially regulated by sex hormones (Epperson et al. 2002). Indeed, estradiol, progesterone, testosterone, and other neuroreactive steroids have been shown to modulate multiple neurotransmitters including GABA, with regionally specific effects (Zheng 2009; McEwen and Milner 2017). In addition to sex differences in GABA, regional differences in GABA concentrations across the cortex have been reported (Greenhouse et al. 2016). Such sex and regional differences in GABA may contribute to the global and regional sex differences in percent inhibition observed here.

Effects of age

Percent inhibition was also highly associated with age. Specifically, percent inhibition increased with age globally and in all 6 areas. This age dependence is consistent with an extensive body of research documenting maturational brain changes including age-related changes in local connectivity (Allen et al. 2011; Wu et al. 2007; Lopez-Larson et al. 2011). For instance, it has previously been shown that brain networks progress from local, short-range connections to distributed long-range networks with age, presumably resulting in increased efficiency and reduced redundancy, before likely continuing inversely with advanced age (Fair et al. 2009). Throughout early development and into adulthood, brain maturation occurs sequentially starting in sensorimotor areas and progressing into areas supporting successively higher order cognitive functions (Marsh et al. 2008). Since the participants included in the present study were young adults within a relatively narrow age range (22–37 years), our findings regarding age-related changes in cortical inhibition

may reflect ongoing maturational processes involving local network connectivity, presumably facilitating tuning of the local circuitry. Notably, the dependence of percent inhibition on age differed between women and men in our study. In women, percent inhibition increased highly significantly with age in all 6 areas, whereas percent inhibition increased modestly for men only in the superior frontal area. Others have similarly reported sex differences in-related trajectories of functional connectivity (Scheinost et al. 2015). Taken together, our findings and those of others highlight the importance of considering independent and interacting age and sex effects on resting-state connectivity.

Overall, the current study documents a strong dependence of percent inhibition on age in women, but not in men, consistently within all studied cortical areas. These findings dovetail with other studies documenting sex and age as moderators of functional connectivity and highlight the relative influence of excitatory and inhibitory interactions as a useful index of local connectivity. Strengths of the study include a large sample with relatively equal numbers of men and women and state-of-the-art data collected on a customized 3T scanner using advanced acquisition methods (Uğurbil et al. 2013). However, the findings must also be considered within the context of study limitations and qualifications. The study sample evaluated here was comprised of healthy young adults ranging in age from 22 to 37 years. In light of well-established brain maturational changes, the findings of the present study may not generalize to individuals outside of this age range—for instance, to older adults. To that end, a recent study found significantly lower GABAergic cortical inhibition in older healthy adults compared to younger adults (Lissemore et al. 2018). That finding, coupled with the findings of the present study, raises the possibility that local cortical inhibition, particularly in women, increases with age, peaks, and then decreases again with advancing age, following a maturational trajectory similar to maturational changes in local vs distributed networks (Fair et al. 2009). Evaluation of local inhibitory interactions across the lifespan and with regard to sex, age, and their interacting effects (e.g., changes in estrogen across the lifespan) remain to be investigated.

Acknowledgements Data were provided by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 National Institutes of Health (NIH) institutes and centers that support the NIH Blueprint for Neuroscience Research and by the McDonnell Center for Systems Neuroscience at Washington University.

Author contributions APG conceived research; PC and APG designed research and analyzed data; LMJ, APG, and PK wrote the paper and approved final version of manuscript.

Funding Partial funding for this study was provided by the University of Minnesota (the Anita Kunin Chair in Women's Healthy Brain Aging, the Brain and Genomics Fund, the McKnight Presidential Chair of Cognitive Neuroscience, and the American Legion Brain Sciences Chair) and the U.S. Department of Veterans Affairs. The sponsors had no role in the current study design, analysis, or interpretation, or in the writing of this paper. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

Data availability Data are available from the Human Connectome Project (<http://www.humanconnectome.org/>).

Code availability Not applicable.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethics approval The Institutional Review Board of Washington University in St. Louis approved the HCP research protocol. The present analyses were approved by the Minneapolis VAHCS Research and Development Committee.

Consent to participate All participants in the present study gave informed written consent to participate in this study.

Consent for publication All participants in the present study gave consent for the publication of the result of this study.

References

- Allen EA, Erhardt EB, Damaraju E et al (2011) A base-line for the multivariate comparison of resting-state networks. *Front Syst Neurosci* 5:2. <https://doi.org/10.3389/fnsys.2011.00002>
- Battaglia-Mayer A, Ferraina S, Mitsuda T, Marconi B, Genovesio A, Onorati P, Lacquaniti F, Caminiti R (2000) Early coding of reaching in the parietooccipital cortex. *J Neurophysiol* 83(4):2374–2391. <https://doi.org/10.1152/jn.2000.83.4.2374>
- Biswal BB, Yetkin FZ, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med* 34:537–541. <https://doi.org/10.1002/mrm.1910340409>
- Biswal BB, Mennes M, Zuo XN et al (2010) Toward discovery science of human brain function. *Proc Natl Acad Sci USA* 107(10):4734–4739. <https://doi.org/10.1073/pnas.0911855107>
- Buckner RL, Krienen FM, Yeo BT (2013) Opportunities and limitations of intrinsic functional connectivity MRI. *Nat Neurosci* 16(7):832–837. <https://doi.org/10.1038/nm.3423>
- Caminiti R, Genovesio A, Marconi B, Mayer AB, Onorati P, Ferraina S, Mitsuda T, Giannetti S, Squatrito S, Maioli MG, Molinari M (1999) Early coding of reaching: frontal and parietal association connections of parieto-occipital cortex. *Eur J Neurosci*

- 11(9):3339–3345. <https://doi.org/10.1046/j.1460-9568.1999.00801>
- Carson RG (2020) Inter-hemispheric inhibition sculpts the output of neural circuits by co-opting the two cerebral hemispheres. *J Physiol* 598(21):4781–4802. <https://doi.org/10.1113/JP279793>
- Christova P, Georgopoulos AP (2018) Invariant and heritable local cortical organization as revealed by fMRI. *J Neurophysiol* 120(2):760–764. <https://doi.org/10.1152/jn.00137.2018>
- Christova P, Lewis SM, Tagaris GA, Uğurbil K, Georgopoulos AP (2008) A voxel-by-voxel parametric fMRI study of motor mental rotation: hemispheric specialization and gender differences in neural processing efficiency. *Exp Brain Res* 189(1):79–90. <https://doi.org/10.1007/s00221-008-1405-x>
- Christova P, Lewis SM, Jerde TA, Lynch JK, Georgopoulos AP (2011) True associations between resting fMRI time series based on innovations. *J Neural Eng* 8(4):046025. <https://doi.org/10.1088/1741-2560/8/4/046025>
- Cosgrove KP, Mazure CM, Staley JK (2007) Evolving knowledge of sex differences in brain structure, function, and chemistry. *Biol Psychiat* 62(8):847–855. <https://doi.org/10.1016/j.biopsych.2007.03.001>
- de Lacy N, McCauley E, Kutz JN, Calhoun VD (2019) Sex-related differences in intrinsic brain dynamism and their neurocognitive correlates. *Neuroimage* 202:116116. <https://doi.org/10.1016/j.neuroimage.2019.116116>
- Deco G, Ponce-Alvarez A, Hagmann P, Romani GL, Mantini D, Corbetta M (2014) How local excitation–inhibition ratio impacts the whole brain dynamics. *J Neurosci* 34(23):7886–7898. <https://doi.org/10.1523/JNEUROSCI.5068-13.2014>
- Desikan RS, Ségonne F, Fischl B et al (2006) An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage* 31:968–980. <https://doi.org/10.1016/j.neuroimage.2006.01.021>
- Epperson C, Haga K, Mason G et al (2002) Cortical-aminobutyric acid levels across the menstrual cycle in healthy women and those with premenstrual dysphoric disorder. *Arch Gen Psychiat* 59:851–858. <https://doi.org/10.1001/archpsyc.59.9.851>
- Fair DA, Cohen AL, Power JD et al (2009) Functional brain networks develop from a “local to distributed” organization. *PLoS Comput Biol* 5:e1000381. <https://doi.org/10.1371/journal.pcbi.1000381>
- Filippi M, Valsasina P, Misci P, Falini A, Comi G, Rocca MA (2013) The organization of intrinsic brain activity differs between genders: a resting-state fMRI study in a large cohort of young healthy subjects. *Hum Brain Mapp* 34:1330–1343. <https://doi.org/10.1002/hbm.21514>
- Fisher RA (1958) Statistical methods for research workers. Hafner, New York
- Fox MD, Raichle M (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 8:700–711. <https://doi.org/10.1038/nrn2201>
- Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ (1993) Functional connectivity: the principal component analysis of large (PET) data sets. *J Cereb Blood Flow Metab* 3:5–14. <https://doi.org/10.1038/jcbfm.1993.4>
- Geerligs L, Renken RJ, Saliassi E, Maurits NM, Lorist MM (2015) A brain-wide study of age-related changes in functional connectivity. *Cereb Cortex* 25(7):1987–1999. <https://doi.org/10.1093/cercor/bhu012>
- Georgopoulos AP (2014) Cell directional spread determines accuracy, precision, and length of the neuronal population vector. *Exp Brain Res* 232(7):2391–2405. <https://doi.org/10.1007/s00221-014-3936-7>
- Georgopoulos AP, Carpenter AF (2015) Coding of movements in the motor cortex. *Curr Opin Neurobiol* 33:34–39. <https://doi.org/10.1016/j.conb.2015.01.012>
- Georgopoulos AP, Stefanis CN (2007) Local shaping of function in the motor cortex: motor contrast, directional tuning. *Brain Res Rev* 55:383–389
- Georgopoulos AP, Stefanis C (2010) The motor cortical circuit. In: Shepherd G, Grillner S (eds) *Brain microcircuits*. Oxford University Press, New York, pp 39–45
- Glasser MF, Sotiropoulos SN, Wilson JA et al (2013) The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage* 80:105–124. <https://doi.org/10.1016/j.neuroimage.2013.04.127>
- Greenhouse I, Noah S, Maddock RJ, Ivry RB (2016) Individual differences in GABA content are reliable but are not uniform across the human cortex. *Neuroimage* 139:1–7. <https://doi.org/10.1016/j.neuroimage.2016.06.007>
- Greicius MD, Krasnow B, Reiss AL, Menon V (2003) Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *PNAS* 100(1):253–258. <https://doi.org/10.1073/pnas.0135058100>
- Isaacson JS, Scanziani M (2011) How inhibition shapes cortical activity. *Neuron* 72(2):231–243. <https://doi.org/10.1016/j.neuron.2011.09.027>
- Johnson PB, Ferraina S, Bianchi L, Caminiti R (1996) Cortical networks for visual reaching: physiological and anatomical organization of frontal and parietal lobe arm regions. *Cereb Cortex* 6(2):102–119. <https://doi.org/10.1093/cercor/6.2.102>
- Lee S-H, Kwan AC, Zhang S et al (2012) Activation of specific interneurons improves V1 feature selectivity and visual perception. *Nature* 488(7411):379–383. <https://doi.org/10.1038/nature11312>
- Li YT, Ma WP, Pan CJ, Zhang LI, Tao HW (2012a) Broadening of cortical inhibition mediates developmental sharpening of orientation selectivity. *J Neurosci* 32:3981–3991. <https://doi.org/10.1523/JNEUROSCI.5514-11.2012>
- Li YT, Ma WP, Li LY, Ibrahim LA, Wang SZ, Tao HW (2012b) Broadening of inhibitory tuning underlies contrast-dependent sharpening of orientation selectivity in mouse visual cortex. *J Neurosci* 32:16466–16477. <https://doi.org/10.1523/JNEUROSCI.3221-12.2012>
- Lissemore JJ, Bhandari A, Mulsant BH et al (2018) Reduced GABAergic cortical inhibition in aging and depression. *Neuropsychopharmacol* 43(11):2277–2284. <https://doi.org/10.1038/s41386-018-0093-x>
- Logothetis NK (2002) The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philos Trans R Soc Lond B Biol Sci* 357(1424):1003–1037. <https://doi.org/10.1098/rstb.2002.1114>
- Lopez-Larson MP, Anderson JS, Ferguson MA, Yurgelun-Todd D (2011) Local brain connectivity and associations with gender and age. *Dev Cogn Neurosci* 1(2):187–197. <https://doi.org/10.1016/j.dcn.2010.10.001>
- Luders E, Narr KL, Thompson PM et al (2004) Gender differences in cortical complexity. *Nat Neurosci* 7(8):799–800. <https://doi.org/10.1038/nn1277>
- Mahan M, Georgopoulos A (2013) Motor directional tuning across brain areas: directional resonance and the role of inhibition for directional accuracy. *Front Neural Circuits* 7:92. <https://doi.org/10.3389/fncir.2013.00092>
- Marsh R, Gerber AJ, Peterson BS (2008) Neuroimaging studies of normal brain development and their relevance for understanding childhood neuropsychiatric disorders. *J Amer Acad Child Psy*

- 47(11):1233–1251. <https://doi.org/10.1097/CHI.0b013e318185e703>
- McEwen BS, Milner TA (2017) Understanding the broad influence of sex hormones and sex differences in the brain. *J Neurosci Res* 95(1–2):24–39. <https://doi.org/10.1002/jnr.23809>
- Merchant H, Georgopoulos AP (2018) Inhibitory mechanisms in the motor cortical circuit (MCC). In: Shepherd GM, Grillner S (eds) *Handbook of brain microcircuits*. Oxford/Academic Press, NY
- Merchant H, Naselaris T, Georgopoulos AP (2008) Dynamic sculpting of directional tuning in the primate motor cortex during three-dimensional reaching. *J Neurosci* 28:9164–9172
- Merchant H, Crowe DA, Fortes AF, Georgopoulos AP (2014) Cognitive modulation of local and callosal neural interactions in decision making. *Front Neurosci* 8:245. <https://doi.org/10.3389/fnins.2014.00245>
- O’Gorman RL, Michels L, Edden RA, Murdoch JB, Martin E (2011) In vivo detection of GABA and glutamate with MEGA-PRESS: reproducibility and gender effects. *J Magn Res Imag* 33(5):1262–1267. <https://doi.org/10.1002/jmri.22520>
- Oldfield RC (1971) The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia* 9(1):97–113. [https://doi.org/10.1016/0028-3932\(71\)90067-4](https://doi.org/10.1016/0028-3932(71)90067-4)
- Perkel DH, Gerstein GL, Moore GP (1967) Neuronal spike trains and stochastic point processes II Simultaneous spike trains. *Biophys J* 7:419–440. [https://doi.org/10.1016/S0006-3495\(67\)86597-4](https://doi.org/10.1016/S0006-3495(67)86597-4)
- Raichle ME (2015) The restless brain: how intrinsic activity organizes brain function. *Phil Trans R Soc B* 370:20140172. <https://doi.org/10.1098/rstb.2014.0172>
- Sanacora G, Mason GF, Rothman DL et al (1999) Reduced cortical γ -aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. *Arch Gen Psychiat* 56(11):1043–1047. <https://doi.org/10.1001/archpsyc.56.11.1043>
- Satterthwaite TD, Wolf DH, Roalf DR et al (2015) Linked sex differences in cognition and functional connectivity in youth. *Cereb Cortex* 25(9):2383–2394. <https://doi.org/10.1093/cercor/bhu036>
- Schachter SC, Ransil BJ, Geschwind N (1987) Associations of handedness with hair color and learning disabilities. *Neuropsychologia* 25(1, Part 2):269–276. [https://doi.org/10.1016/0028-3932\(87\)90137-0](https://doi.org/10.1016/0028-3932(87)90137-0)
- Scheinost D, Finn ES, Tokoglu F et al (2015) Sex differences in normal age trajectories of functional brain networks. *Hum Brain Mapp* 36(4):1524–1535. <https://doi.org/10.1002/hbm.22720>
- Sepulcre J, Liu H, Talukdar T, Martincorena I, Yeo BT, Buckner RL (2010) The organization of local and distant functional connectivity in the human brain. *PLoS Comput Biol* 6(6):e1000808. <https://doi.org/10.1371/journal.pcbi.1000808>
- Smith SM, Fox PT, Miller KL et al (2009) Correspondence of the brain’s functional architecture during activation and rest. *Proc Natl Acad Sci USA* 106:13040–13045. <https://doi.org/10.1073/pnas.0905267106>
- Stefanis C, Jasper H (1964) Recurrent collateral inhibition in pyramidal tract neurons. *J Neurophysiol* 27:855–877
- Tomasi D, Volkow ND (2012a) Aging and functional brain networks. *Mol Psychiatry* 17(471):549–558. <https://doi.org/10.1038/mp.2011.81>
- Tomasi D, Volkow ND (2012b) Gender differences in brain functional connectivity density. *Hum Brain Mapp* 33:849–860. <https://doi.org/10.1002/hbm.21252>
- Uğurbil K, Xu J, Auerbach EJ, Moeller S et al (2013) Pushing spatial and temporal resolution for functional and diffusion MRI in the Human Connectome Project. *Neuroimage* 80:80–104. <https://doi.org/10.1016/j.neuroimage.2013.05.012>
- Van Essen DC, Smith SM, Barch DM, Behrens TEJ, Yacoub E, Ugurbil K (2013) The WU-Minn **human** Connectome Project: an overview. *Neuroimage* 80:62–79. <https://doi.org/10.1016/j.neuroimage.2013.05.041>
- Van Den Heuvel MP, Pol HE, Pol HE (2010) Exploring the brain network: a review on resting-state fMRI functional connectivity. *Eur Neuropsychopharm* 20(8):519–534. <https://doi.org/10.1016/j.euroneuro.2010.03.008>
- Weissman-Fogel I, Moayed M, Taylor KS, Pope G, Davis KD (2010) Cognitive and default-mode resting state networks: do male and female brains “rest” differently? *Hum Brain Mapp* 31:1713–1726. <https://doi.org/10.1002/hbm.20968>
- Wu T, Zang Y, Wang L, Long X, Li K, Chan P (2007) Normal aging decreases regional homogeneity of the motor areas in the resting state. *Neurosci Lett* 423(3):189–193. <https://doi.org/10.1016/j.neulet.2007.06.057>
- Zang YF, Jiang TZ, Lu YL, He Y, Tian LX (2004) Regional homogeneity approach to fMRI data analysis. *Neuroimage* 22:394–400. <https://doi.org/10.1016/j.neuroimage.2003.12.030>
- Zhang D, Snyder AZ, Fox MD, Sansbury MW, Shimony JS, Raichle ME (2008) Intrinsic functional relations between human cerebral cortex and thalamus. *J Neurophysiol* 100:1740–1748. <https://doi.org/10.1152/jn.90463.2008>
- Zhang C, Dougherty CC, Baum SA, White T, Michael AM (2018) Functional connectivity predicts gender: evidence for gender differences in resting brain connectivity. *Hum Brain Mapp* 39(4):1765–1776. <https://doi.org/10.1002/hbm.23950>
- Zheng P (2009) Neuroactive steroid regulation of neurotransmitter release in the CNS: action, mechanism and possible significance. *Prog Neurobiol* 89:134–152. <https://doi.org/10.1016/j.pneurobio.2009.07.001>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.