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Increased spatial granularity of left brain activation and unique age/gender signatures: A 4D Frequency Domain Approach to Cerebral Lateralization at Rest

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Abstract

Cerebral lateralization is a well-studied topic. However most of the research to date in functional magnetic resonance imaging (fMRI) has been carried out on hemodynamic fluctuations of voxels, networks, or regions of interest (ROIs). For example, cerebral differences can be revealed by comparing the temporal activation of an ROI in one hemisphere with the corresponding homotopic region in the other hemisphere. While this approach can reveal significant information about cerebral organization, it does not provide information about the full spatiotemporal organization of the hemispheres. The cerebral differences revealed in literature suggests that hemispheres have different spatiotemporal organization in the resting state. In this study, we evaluate cerebral lateralization in the 4D spatiotemporal frequency domain to compare the hemispheres in the context of general activation patterns at different spatial and temporal scales. We use a gender-balanced resting fMRI dataset comprising over 600 healthy subjects ranging in age from 12 to 71, that have previously been studied with a network specific voxel-wise and global analysis of lateralization (Agcaoglu, Miller, Mayer, Hugdahl, & Calhoun, 2014). Our analysis elucidates significant differences in the spatiotemporal organization of brain activity between hemispheres, and generally more spatiotemporal fluctuation in the left hemisphere especially in the high spatial frequency regions, and more power in the right hemisphere in the low and middle spatial frequencies. [We also find significant gender and age effects in both hemispheres consistent with (Miller et al., 2015) which analyzed a different dataset but did not evaluate lateralization. Importantly, the identified effects are not visible in the context of a typical assessment of voxelwise, regional, or even global laterality, thus our study highlights the value of 4D spatiotemporal frequency domain analyses as a complementary and powerful tool for studying brain function.

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[†]Authors have the equal contribution on the method in this work.

Keywords

4D Fourier transform; frequency domain; laterality; resting state; gender differences; aging

Introduction

There has been a considerable amount of work studying the differences between cerebral hemispheres of the brain, starting with the seminal observations by Paul Broca (Broca, 1861) and Carl Wernicke (Wernicke, 1874), and later confirmed and extended by the work of Roger Sperry (Sperry, 1974) and numerous others. These studies have helped us understand brain laterality and revealed interesting results: the left hemisphere, for example, has been shown to be associated with grammar, vocabulary and other language skills, as well as being connected with analytical and logical functions, while the right hemisphere is associated with non-verbal functions such as visuospatial, intuitive and various sensory tasks (Breier, Simos, Zouridakis, & Papanicolaou, 1999; Cai, Van der Haegen, & Brysbaert, 2013; Clements et al., 2006; Gobbele et al., 2008; Gotts et al., 2013; Groen, Whitehouse, Badcock, & Bishop, 2012; Smith, Jonides, & Koeppel, 1996; Stephan et al., 2003; Thomason et al., 2009); see also (Hugdahl & Westerhausen, 2010) for updated overview of research on hemispheric asymmetry. (Plessen, Hugdahl, Bansal, Hao, & Peterson, 2014) reported several asymmetries in cortical thickness of the cortical mantle between hemispheres that were also correlated with age and gender. (Plessen et al., 2014) also found improved performance on working memory and vocabulary tasks with increasing normal asymmetries in the regions thought to be related to these cognitive tasks.

In the modern era, the invention of brain imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), provides a new set of tools to study cerebral lateralization (Hugdahl, 2011). There have been several studies related to cerebral lateralization using PET or fMRI, mostly using task-related data and more recently trending toward lateralization of brain activity at rest (Agcaoglu et al., 2014; Filippi et al., 2013; Gotts et al., 2013; Liu, Stufflebeam, Sepulcre, Hedden, & Buckner, 2009; Mazoyer et al., 2014; Nielsen, Zielinski, Ferguson, Lainhart, & Anderson, 2013; Swanson et al., 2011; Zhu et al., 2014; Zuo et al., 2010). All of these studies have approached lateralized brain function through either global measures of lateralized connectivity or comparison of hemodynamic fluctuations in homotopic regions or voxels of the two hemispheres. There has been some consideration of temporal frequencies in fMRI. For example, (Garrity et al., 2007) showed that schizophrenia patients have significantly more spectral power at high temporal frequencies (0.08 Hz to 0.24 Hz) and significantly less spectral power at low temporal frequencies in the default mode network comparing to healthy control and indicated that temporal frequencies of the default mode network could be used to distinguish schizophrenia patients from healthy controls. However, to our knowledge (with the exception of (Miller et al., 2015)), there have been no efforts to study spatial and temporal frequencies together in a 4D domain.

Though the brain is not organized periodically, the spatiotemporal hemodynamic patterns can, like all signals, be decomposed into additive (in this case 4-dimensional) periodic

components. Our work indicates that the periodic constituents of resting state fMRI data contains interesting spatiotemporal patterns that differ between the hemispheres. Recently, we, (Miller et al., 2015), proposed a 4D frequency domain approach that considers the whole brain fMRI scan as a single 4D signal. A 4D approach reveals the global organizational differences between hemispheres while simultaneously accounting for temporal changes. This combined spatiotemporal information provides a broader perspective relative to conventional temporal spectral analysis. Because we are working with the amplitude spectra, such an approach allows us to consider patterns of change in brain imaging data which have similar spatiotemporal frequency content but which may have different delays or spatial locations. It thus provides a rather different, yet complementary, way to view the underlying resting fMRI information in contrast to typical approaches which focus on specific networks or solely focus on spectral information in the time domain.

Because there are well-known hemispheric differences in measures such as complexity, interaction, connectivity, intrinsic activity (Agcaoglu et al., 2014; Gotts et al., 2013; Liu et al., 2009; Nielsen et al., 2013), we were interested in evaluating whether the frequency characteristics vary in the left versus right hemisphere. To this end, we employ a 4D frequency domain approach to study cerebral lateralization. We treat left and right hemisphere fMRI scans as 4D signals and explore group-level differences in general spatiotemporal patterning of hemodynamic activation between left and right hemispheres. Results show strong and persistent differences in spatiotemporal power in left versus right hemisphere. [maybe speculate here as to what this might mean about the brain and why it might be important?] To the best of our knowledge, this is the first study that investigates cerebral lateralization in the 4D spatiotemporal domain.

Methods and Materials

Participants

An existing dataset consisting of a total of 603 subjects that combined from 34 different studies and the work of 18 principal investigators at the Mind Research Network (MRN) were used for this study. In accordance with institutional guidelines at the University of New Mexico, informed consent was obtained from all subjects. The data were all obtained using the same scanner with same parameters, and were anonymized prior to the group analysis. At the time of the scan, the subjects were not taking psychoactive medications, or did not any have a history of psychiatric or neurological disorders. Subjects whose functional scans showed obvious evidence of motion (maximum translation > 6mm, approximately 2 voxels) were also excluded from the study. The demographic information of the subjects is shown at Table 1, with 305 females and 298 males in the sample ranging in age 12 to 71 (only 7 subjects are over 50, so the sample predominantly encompasses teenagers through late middle age), gender is nearly balanced, and the age distributions for genders are also very similar. The sample is mostly right-handed (46 ambidextrous or left-handed individuals) and preliminary results did not point out any difference in results without these left handed or ambidextrous individuals, so handedness is not considered in this study.

Data Acquisition

All imaging was conducted using a 3-Tesla Siemens TIM Trio scanner. High resolution T1-weighted structural images were obtained using a 5-echo MPRAGE sequence with TE = [1.64, 3.5, 5.36, 7.22, 9.08] ms, TR = 2.53 s, TI = 1.2 s, flip angle = 7°, number of excitations = 1, slice thickness = 1 mm, field of view = 256 mm, resolution = 256 × 256. T2*-weighted functional images were obtained using a gradient-echo EPI sequence with TE = 29 ms, TR = 2 s, flip angle = 75°, slice thickness = 3.5 mm, slice gap = 1.05 mm, field of view = 240 mm, matrix size = 64×64, voxel size = 3.75×3.75×4.55 mm. Resting state scans had a minimum duration of 5 minutes (150 volumes). In order to match data quantity throughout participants, any additional volumes if collected, were excluded. During the scan, subjects were instructed to stare passively at a fixation cross and keep their eyes open both to ensure participants stayed awake and also because studies have shown this may help with network delineation (Van Dijk et al., 2010).

Preprocessing

Functional MRI data were preprocessed as in (Allen et al., 2011), using an automated preprocessing pipeline based on SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5/>) within the Collaborative Informatics and Neuroimaging Suite (COINS) neuroinformatics system (Scott et al., 2011) developed at the MRN. Scanned data were automatically copied and archived to an analysis directory, where they were then preprocessed. The first 4 time-points were excluded from the data to remove T1 history-effects. Images are also realigned using INRIalign (Freire, Roche, & Mangin, 2002) and slice-timing correction is performed with the middle slice used as the reference frame. Following, data were then spatially normalized into the standard Montreal Neurological Institute (MNI) space, resliced to 3 × 3 × 3 mm voxels.

Extracting Hemispheres

A common, symmetric, group-mask was used for all subjects to ensure the masking did not add subject variance to the spatiotemporal profile. Next, we divided the 4D fMRI data into left and right hemispheres. We also flipped the right hemisphere data along the left-right dimension to have an exact coordinate match with the other hemisphere, which provided data for each hemisphere for each subject.

Transforming to Frequency Domain

We used the Welch' method to estimate power spectral density of 4D fMRI data (Welch, 1967). To do so, we applied sliding windows on data with a 4D Hanning window of size [27, 64, 46, 64] and shifted 1 point each time. We removed the mean on each data segment and implemented an n-dimensional discrete Fourier transform using Matlab's *fftn.mat* function. In order to maintain the same scale of spatial frequencies across x, y, and z, we used a transform size of [64, 64, 64, 64] on the [27, 63, 46, 64] sized data segments. The result is a 4 dimensional array for each segment; we used the squared magnitudes of the Fourier coefficients. The squared magnitudes are divided into (64*64*64*64) in order to equalize frequency domain power to time domain power (Perceval's theorem). Next, the magnitudes were normalized so that each subject and each hemisphere and each segment has the same

total power. This normalization enables us to compare the distribution of the power in spatiotemporal regions among subjects. Finally, we average over each segment to estimate PSD of each subject's hemispheres.

Spatial Spherical Band Profiles (SSBPs)

In order to further reduce the dimensionality and provide an intuitive display; for each temporal frequency, we group the spatial frequencies from low to high into 32 spherical frequency bands and sum the squared magnitudes in each group. By doing so, for each subject and each hemisphere, we have a matrix of size 32 (temporal frequencies) by 32 (spatial frequencies). We called this matrix the spatial spherical band profiles (SSBPs). Finally, a logarithm transformation was applied to the SSBPs.

Paired t-test

We tested left and right hemisphere SSBPs differences with a paired t-test (left minus right) thresholded at $p < 0.01$ corrected for multiple comparison via a false discovery rate (FDR) correction [ref].

Modeling Age and Gender Effects

We also tested age and gender effects on the spatiotemporal organization using a linear regression model. Explanatory variables included *age* and *gender*. We also included motion covariates average scan to scan rotation, translation from INRIAAlign motion estimates and also spatial normalization accuracy, which is the Spearman correlation between the warped T2*-weighted image and the EPI template, in the regression model and since results were very similar with and without motion variables, we present the results without motion covariates for the sake of simplicity.

$$\sigma_{(i,j)} = \beta_o + \beta_{age}^{(i,j)} X_{age} + \beta_{gen}^{(i,j)} X_{gen} + \varepsilon_{(i,j)}$$

Where X_{gen} is a number indicating the gender of subject with 2 for males and 1 for females. The age (X_{age}) distribution ranges from 12 to 71, but it is right skewed with only 7 people older than 50 years, therefore we applied a logarithm transform to age, where X_{age} represents the log transformed age of the subject. All β 's are the parameter of the regression model with ε being the error parameter for the model, $\sigma_{(i,j)}$ is the combined SSBPs. This analysis gives us the regions on the SSBPs that are significantly ($p < 0.01$, following FDR correction for multiple comparisons) affected by age and gender (Genovese, Lazar, & Nichols, 2002).

Results

Our analysis provides insight into the spatiotemporal organization of the hemispheres while revealing the differences between the hemispheres, and age and gender effects on this spatiotemporal organization. Group summaries of the spatiotemporal organization for each hemisphere are shown in Figure 2; units are decibel-Watt due to log transformation. Visual inspection indicates similar spatiotemporal trends of activation for both hemispheres, though

some differences can easily be recognized. We observe the highest power in low spatial and low temporal frequencies, though zero temporal and zero spatial frequency (index [1,1]) has no power due to the mean removal. We have sharp borders from temporal frequencies 0.008 (index 2) Hz to 0.0016 (index 3) Hz and spatial frequencies from 0 (index 1) cycles/mm to 0.005 (index 2) cycles/mm. Overall variance is small in most of the low spatial frequencies. Generally power decreases as spatial or temporal frequencies increases.

Hemispheric Differences

Paired t-test results for left hemisphere SSBPs and right hemisphere SSBPs are displayed in Figure 3. Frequencies shows significant (0.01 level FDR corrected) differences between two hemispheres. Left hemisphere has more power in high spatial and low temporal frequencies comparing to right hemisphere. On the other hand, the frequencies favor right hemisphere occupies a larger area that covers low and middle spatial and almost all temporal frequencies.

Age Effects

Regression result for age effects for both left and right hemispheres are presented in Figure 4 and Figure 5. Age effects are very similar for both hemisphere and a separate analysis did not reveal any significant interaction effects of hemisphere and age, indicating that spatiotemporal organization of hemispheres is affected by aging similarly. We mainly see three regions that have reverse directional age effects and the border is mostly determined by temporal frequencies. The first region covers very low temporal frequencies (lower than 0.16 (3rd index) Hz) and almost all spatial frequencies (except 0.01 cycles/mm) and shows an increase in power with aging. The second region contains almost all spatial frequencies and temporal frequencies from 0.016 (3rd index) Hz to 0.137 (18th index) Hz; showing a decrease in spectral power with increasing age. The third region also increase in power with aging and covers almost all spatial frequencies and temporal frequencies greater than 0.137 (18th index) Hz. Most of the region survives after FDR correction (0.01 levels). Our findings are also consistent with (Miller et al., 2015) where age effects are investigated on the spatiotemporal organization of whole brain. We found significant age effects on lateralization in several regions using a network-based approach on the same data set (Agcaoglu et al., 2014). Therefore, though age is an important factor affecting the lateralization of certain local features of specific functional networks, the broader difference in spatiotemporal organization of the two hemispheres does not appear to be affected by age.

Gender Effects

Regression results on gender effects for left and right hemispheres are presented in Figure 6 and Figure 7. Gender effects are very similar for both hemisphere and a separate analysis did not reveal any significant interaction effects of hemisphere and gender, indicating that spatiotemporal organization of hemispheres is affected by gender similarly. Gender has a more complicated pattern; males have higher power in almost all spatial and temporal frequencies except the vertical region on very low temporal and high spatial frequencies. After the FDR correction (0.01 levels), these regions get smaller to the middle spatial frequencies. These middle spatial frequencies get larger in low and high temporal frequencies, and gets narrower in the middle temporal frequencies. Females have higher

spectral power in spatial frequencies (greater than 0.11 (22nd index) cycles/mm) and low temporal frequencies (less than 0.016 (3rd index) Hz). Our results are generally consistent with (Miller et al., 2015) pattern wise, however the specific FDR survival areas are not identical.

Discussion

We analyzed cerebral lateralization in the 4D frequency domain using a resting state fMRI dataset including 603 subjects, and also studied age and gender effects. Results indicate significant differences in the spatiotemporal organization of cerebral hemispheres, while age and gender showed significant associations with the spatiotemporal organization of each hemisphere. Age and gender effects on the two hemispheres did not differ in a statistically significant way.

In general, low spatial frequencies reflect mostly the global patterns of brain spatial organization while high spatial frequencies provide more information about the differences at a more spatially granular scale. In this context, we found that globally, the right hemisphere is slightly more active than left hemisphere, however the left hemisphere has more focal or distributed focal areas implicated in the spatial fluctuation. In other words the right hemisphere has smoother activation (spatially) while the left hemisphere has more of a hill-valley fluctuation pattern. An interpretation of these could be that the left hemisphere process information on various small regions intensely while the right hemisphere has the tendency to process information on a collaborative wider region.

Age was found to have a strong association with the spatiotemporal organization of the brain, though no significant interaction between aging and hemisphere was found, suggesting both hemispheres are affected similarly by aging. Temporal frequencies were key determinants of the direction of the effects: we observed positive age effects in high temporal frequencies and negative age effects in low temporal frequencies covering a wider band comparing to the positively related high frequency band. The power decrease in the low temporal frequencies may be related to the increase in reaction time with aging. (Thompson, Blair, & Henrey, 2014) found that age-related slowing of the reaction time begins at the age of 24, in their task study of playing video games. Our result is also consistent with (Allen et al., 2011) which found a significant decrease in low frequency (0.01–0.15 Hz) power spectra of all RSN networks with aging, and included speculation that this could be due to decrease in gray matter concentration along with the influence of other factors such as vascular compliance or decrease in neural activity. We were unable to do a more detailed comparison with (Allen et al., 2011) results for higher temporal frequencies since the time series were low pass filtered in their study. There are some other age related cognitive differences in the literature, such as processing speed, reasoning, memory and executive functions (Deary et al., 2009), and also response inhibition; (Hong, Sun, Bengson, & Tong, 2014) presented evidence of age-related spatiotemporal dynamics reorganization during response inhibition; and found that in older adults (18 participants ranging 50–70), brain current densities showed an increase and also more distributed comparing to younger adults (23 participants between age 18–25) during the N2d and P3d periods. More distributed brain currents in older adults can be related to higher temporal and spatial

frequencies, which is consistent with our finding of increased power in higher temporal frequencies. Another factor could be related to functional consequences of age-related changes in the gyral and sulcal structure of the cortex. (Kochunov et al., 2005) reported that for each ten years, the average sulci width increased about 0.7 mm, while the average sulci depth decreased at a rate of about 0.4 mm/10 years. (Kochunov et al., 2005) also reported gender has significant influence on aging effect of sulcus in regions of the superior temporal, collateral, and cingulate sulci with males showing more pronounced age-related change in sulci width than females. However in our study, which was focused on function, we did not find any significant gender-age cross effect.

Gender effects show a more complex pattern than did age. Significant associations with gender were observed within each hemisphere though no significant interactions between gender-hemisphere were found. (Cosgrove, Mazure, & Staley, 2007) that reported females having higher cerebral global blood flow and cognitive activity comparing to males at rest, our technique was able to relate these differences to specific spatiotemporal frequencies. Even though, due the fact that we are working with rest fMRI data, it is not possible to make a direct inverse transform, these complicated patterns may be related to differences between gender on certain tasks such as verbal fluency, facial emotion recognition or emotional memory (Wang, Shen, Tang, Zang, & Hu, 2012).

Our SSBP approach differs meaningfully from the typical brain lateralization studies, (Agcaoglu et al., 2014; Gotts et al., 2013; Liu et al., 2009; Nielsen et al., 2013; Swanson et al., 2011; Zuo et al., 2010), with the fact that our approach reveals a global comparison of hemispheres in the frequency domain, rather than revealing specific regions. For example, the temporal activation of an ROI in one hemisphere with the corresponding homotopic region may have similar average activation value but different fluctuation rate (spatially or/and temporally), in this case, typical lateralization approaches would not reveal the differences; however our method can identify such differences. Moreover, our method can also detect significant spatiotemporal patterns regardless of when and where they actually change.

Significant hemisphere effects were quite strong, and no significant interaction between hemisphere and gender or age is found. In many previous studies, the left hemisphere has been shown to facilitate functions associated with language such as grammar and vocabulary, as well as analytical and logical functions (Breier et al., 1999; Cai et al., 2013; Clements et al., 2006; Gobbele et al., 2008; Gotts et al., 2013; Groen et al., 2012; Smith et al., 1996; Stephan et al., 2003; Thomason et al., 2009). In future work we how to evaluate the relationship of spatiotemporal frequencies to variables related to language processing in future work.

Limitations

Some limitations should be considered while interpreting the results. No cognitive or behavioral data were available for our subjects; thus we were unable to evaluate hemispheric differences due to cognitive function. In addition, as mentioned before, the ages in our dataset range from 12 to 71 with all but 7 subjects between ages 12 and 50, thus it does not fully cover the most rapidly changing ages of childhood and of old age, and though we log

transformed the age to work with a more uniform distribution, age was not uniformly distributed. Age effects were strong throughout both hemispheres, but no significant changes in left versus right hemisphere were identified. Finally, our method involves a significant data reduction, though it also provides a concise and useful summary of the spatiotemporal information. Based on the significant finding we show, this approach appears to provide a new and useful way to query fMRI data which is different, but complementary, to the typical approach of creating connectivity maps. In future work we will focus on capturing additional information that may not be fully captured by the proposed approach. For example, we can also incorporate the phase information in order to identify patterns of spatiotemporal signals that shift in time-space, in order to provide some additional information about where in the brain these signals might be localized.

Conclusion

In summary, we analyzed hemispheric differences in the spatiotemporal domain using a large fMRI dataset. We found significant local and global spatiotemporal difference between the hemispheres, as well as age and gender effects. Age and gender were found to be affecting both hemisphere spatiotemporal organizations the same degree with no significant interaction effect. Hemisphere effects were quite robust and favored the left hemisphere for high spatial frequencies; favored right hemisphere for low and middle spatial frequencies. Age effects were mainly determined by temporal frequencies and consistent with previous studies. Gender effects were more complex and favoring males for mid-range spatial frequencies, which could be related to that male in general, perform better on visuospatial tasks. Overall, our 4D frequency domain approach appears to be a promising method to investigate brain organization in general and hemispheric specialization in particular.

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Figure 1.
Flowchart of data processing.

Figure 2.

Group averages of hemisphere SSBPs, Left hemisphere (on left) and Right hemisphere (on right) displayed in log10 format (unit is decibel-Watt). In each image; left bottom represents the low temporal and low spatial frequencies; on the x-axis from left to right, temporal frequencies increase from 0 Hz to 0.25 Hz; on the y-axis from bottom to top, spatial frequencies increases from 0 cycles/mm to 0.17 cycles/mm.

Figure 3.

Paired t-test results for hemisphere SSBPs, P-values (on left) and 0.01 level FDR corrected p-values (on right [maybe indicate FDR corrected in the figure titles as well, so its easy to see without reading the caption, same for figs below...also for this one would say “Left – Right (paired T-test)” or something like this in the figure titles]) are presented in – $sign(t)*log(p)$ format (where $sign(t)$ is the sign of corresponding beta value). Red color represents the regions favoring left hemisphere, while blue color represents region favoring right hemisphere. Overall, regions favoring right hemisphere occupies a larger area and includes low and middle spatial frequencies, left hemisphere has more power in high spatial frequencies.

Figure 4.

Regression analysis result on subject SSBPs for age effects on Left hemisphere. P-values (on left) and 0.01 level FDR corrected p-values (on right) are presented in $-sign(t)*log(p)$ format (where $sign(t)$ is the sign of corresponding beta value). Overall, temporal frequencies determine the direction of the age effects, from 0.016 (3rd index) Hz to 0.14 (19th index) Hz and in all spatial frequencies, show a decrease in power with increasing age, while other temporal and spatial frequencies increases in power with aging.

Figure 5.

Regression analysis result on subject SSBPs for age effects on Right hemisphere. P-values (on left) and 0.01 level FDR corrected p-values (on right) are presented in $-sign(t)*log(p)$ format (where $sign(t)$ is the sign of corresponding beta value). Generally, the age effects on right hemisphere are very similar to the effect on left hemisphere.

Figure 6.

Regression analysis result on subject SSBPs for gender effects on Left hemisphere. P-values (on left) and 0.01 level FDR corrected p-values (on right) are presented in $-sign(t)*log(p)$ format (where $sign(t)$ is the sign of corresponding beta value); blue color shows the region favors males while red color shows the region favors females. Gender patterns are complicated and dependent on both spatial and temporal frequencies.

Figure 7.

Regression analysis result on subject SSBPs for gender effects on Right hemisphere. P-values (on left) and 0.01 level FDR corrected p-values (on right) are presented in $-sign(t)*log(p)$ format (where $sign(t)$ is the sign of corresponding beta value); blue color shows the region favors males while red color shows the region favors females. Overall, the gender effects on right hemisphere are very similar to the effect on left hemisphere.

Table 1

Demographic information of the subjects. Gender and age distribution.

	N	%					
Gender	603	100					
Male	298	49.4					
Female	305	50.6					

	Mean	SD	Min	25%	50%	75%	Max
Age(year)	23.4	9.2	12	17	21	27	71
Male	23.8	9.1	12	17	21	26	71
Female	23.1	9.3	12	16	21	27	55