RESEARCH ARTICLE

Rostro-caudal organization of the human posterior superior temporal sulcus revealed by connectivity profiles

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Funding information

Beijing Municipal Science & Technology Commission, Grant/Award Numbers: Z171100000117002, Z161100000216139; Guangdong Pearl River Talents Plan Innovative and Entrepreneurial Team grant, Grant/Award Number: 2016ZT06S220; National Natural Science Foundation of China, Grant/Award Number: 31620103905, 81501179, 91132301, 91432302; Science Frontier Program of the Chinese Academy of Science, Grant/Award Number: QYZDJ-SSW-SMC019; Shenzhen Peacock Plan, Grant/Award Number: KQTD2015033016104926; McDonnell Center for Systems Neuroscience; NIH Blueprint for Neuroscience Research; Science Frontier Program of the Chinese Academy of Sciences, Grant/Award Number: QYZDJ-SSW-SMC019

Abstract

The posterior superior temporal sulcus (pSTS) plays an important role in biological motion perception but is also thought to be essential for speech and facial processing. However, although there are many previous investigations of distinct functional modules within the pSTS, the functional organization of the pSTS in its full functional heterogeneity has not yet been established. Here we applied a connectivity-based parcellation strategy to delineate the human pSTS subregions based on distinct anatomical connectivity profiles and divided it into rostral and caudal subregions using diffusion tensor imaging. Subsequent multimodal connection pattern analyses revealed distinct subregional connectivity profiles. From this we inferred that the two subregions are involved in distinct functional circuits, the language processing loop and the cognition attention network. These results indicate a convergent functional architecture of the pSTS that can be revealed based on different types of connectivity and is reflected in different functions and interactions. In addition, when the subregions were performing their processing in the different functional circuits, we found asymmetry in the bilateral pSTS. Our findings may improve the understanding of the functional organization of the pSTS and provide new insights into its interactions and integration of information at the subregional level.

KEYWORDS

connectivity-based parcellation, parcellation, pSTS, tractography

1 | INTRODUCTION

The posterior superior temporal sulcus (pSTS) integrates many types and sources of inputs and promotes multisensory integration

(Beauchamp, Nath, & Pasalar, 2010). Compared with the corresponding brain region in other mammals, the human pSTS has undergone great evolutionary expansion and exhibits a considerable increase in connections, especially with higher-order association areas (Fullerton & Pandya, 2007). Based on its cytoarchitecture and anatomical structure, Seltzer and Pandya (1978) parcellated the superior

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temporal sulcus into several subregions, which are correlated with the pattern of afferent cortical connections. Later, Munoz-Lopez et al. (2015) used a tracer technique to explore the projections from the subregions to other brain regions in nonhuman primates and showed that these areas integrate information with inputs from distinct cerebral cortex regions. Another research study explored the feasibility of functional subdivisions of the temporal lobe neocortex of a primate and showed that heterogeneity existed in the neuronal response properties in this area (Baylis, Rolls, & Leonard, 1987). All the above research suggests the possibility of parcellating the human pSTS based on anatomical connection patterns, although studies utilizing cytoarchitectonic and anatomical data from humans are lacking.

The human pSTS, a brain region commonly known to be important for language processing (Xiao, Friederici, Margulies, & Brauer, 2016), has a complex organization with some regions responding to an array of other tasks (Hein & Knight, 2008). Numerous neuroimaging studies have demonstrated that the pSTS also plays a vital role in social perception, which refers to the ability to recognize, manipulate, and behave with respect to socially relevant information (Jack & Morris, 2014; Lee, Gao, & McCarthy, 2014; Lieberman, 2007). The pSTS is also thought to be a key region in dynamic facial processing, such as changes in expression and gaze, which are important for social interactions (Engell & Haxby, 2007; Flack et al., 2015; Pelphrey, Morris, & McCarthy, 2004; Wang, Song, Zhen, & Liu, 2016). As a variety of studies have shown, the pSTS is more likely to be activated when both visual and auditory information are presented, whether they are related to speech processing or not (Beauchamp, Lee, Argall, & Martin, 2004; Hocking & Price, 2008; Watson, Latinus, Charest, Crabbe, & Belin, 2014). In addition, some diseases, such as autism spectrum disorders (ASD) (Alaerts et al., 2014; von dem Hagen et al., 2011), simultanagnosia (Sakurai, Hamada, Tsugawa, & Sugimoto, 2016), and conduction aphasia (Hickok, 2009), are highly related to lesions in the pSTS. Therefore, these converging results suggest that the pSTS is functionally complex, is related to multiple information processing circuits (Abrams et al., 2013; Dziura & Thompson, 2014), and is involved in several brain diseases (Redcay, 2008; Vallesi, 2016; Yang, Rosenblau, Keifer, & Pelphrey, 2015). These findings may, therefore, imply that the pSTS consists of more than one functional subregion, which contribute to a variety of functional processes. A key to understanding pSTS organization and function is to investigate its connection pattern specialization at a more granular level (Eickhoff, Constable, & Yeo, 2018). Consequently the pSTS existed as a hub appearing in the language network and in biological motion processing. Determining the parcellation of the pSTS and its connection modes across modalities could be very helpful for exploring the fundamental neural mechanisms underlying adaptation to these complex processes. In addition, analyzing the connection patterns of the subregions has potential implications for understanding the limitations in social perception associated with ASD (Rosenblau, Kliemann, Dziobek, & Heekeren, 2016).

Recent advances in diffusion tensor imaging (DTI) can portray fiber tractography in vivo. These techniques have been extensively used to parcellate heterogeneous brain regions based on their anatomical connection patterns (Bach, Behrens, Garrido, Weiskopf, & Dolan, 2011; Fan et al., 2014). Numerous investigations using methods based on connectivity-based parcellation (CBP) techniques have led to descriptions of the organization and functioning of the

human brain (Anwander, Tittgemeyer, von Cramon, Friederici, & Knosche, 2007; Kahnt, Chang, Park, Heinzle, & Haynes, 2012; Tungaraza, Mehta, Haynor, & Grabowski, 2015). CBP is based on the assumption that the voxels that belong to a given brain area share similar connectivity profiles and that brain areas can be defined by aggregating the voxels that show similar connectivity patterns into larger clusters (Eickhoff, Thirion, Varoquaux, & Bzdok, 2015; Fan et al., 2016; Johansen-Berg et al., 2004). This method has been widely combined with other multimodal data sources, such as combining functional magnetic resonance imaging (fMRI) with meta-analytic data, to explore the mechanisms of some regions of the brain, and even of the whole brain (Bzdok et al., 2013; Cloutman & Ralph, 2012; Holschneider, Wang, & Pang, 2014; Tziortzi et al., 2014). Therefore, in the present study we adopted a parcellation strategy based on diffusion MRI (dMRI) to search for subdivisions in the human pSTS. In addition, by combining dMRI with fMRI and a meta-analysis, we discovered the distinct anatomical organization and the functional interactions between each subarea and the whole brain.

In the current research, we employed CBP technology to parcellate the pSTS based on its structural connectivity and then calculated the probabilistic fiber tracking for each subregion to obtain the connection patterns. To clarify the functional connectivity model of each subregion, we analyzed resting-state functional MRI (rfMRI) and meta-analytic data. Finally, we used a behavioral domains analysis to verify the specific connectivity patterns of each subregion.

2 | MATERIALS AND METHODS

2.1 | Subjects and data acquisition

The MRI data used in our study were accessed from the Human Connectome Project (HCP, <http://humanconnectome.org/>) dataset. A total of 40 healthy, unrelated adults were accessed from the Q3 data to form a subject group that included 17 males and 23 females aged 22–35 years. None of the participants had ever had any psychiatric or neurological disease, and none had any contraindications for MRI scanning.

The entire multimodal MRI images, specifically, structural MRI, rfMRI, and dMRI, were captured on a 3T Siemens Skyra scanner with a 32-channel head coil. DTI data were acquired by a single-shot echo planar imaging sequence. For each participant, 111 slices were collected with repetition time (TR) = 5,520 ms, echo time (TE) = 89.5 ms, field of view (FOV) = 210 × 180 mm², acquisition matrix = 168 × 144, flip angle (FA) = 90°, six b = 0, three diffusion weightings of b = 1,000, 2,000, and 3,000 s/mm², 0 and isotropic spatial resolution = 1.25 × 1.25 × 1.25 mm with no gap. Resting-state fMRI data parameters were as follows: TR/TE = 720/33 ms, FOV = 208 × 180 mm², matrix = 104 × 90, FA = 52°, slice thickness = 2 mm, 72 slices covering the entire brain, and 1,200 volumes. We also acquired the T1-weighted image sets from the HCP dataset. These were obtained using 0.7 mm isotropic resolution, TR/TE = 2,400/2.14 ms, inversion time (TI) = 1,000 ms, FA = 8°, band width = 210 Hz per pixel, FOV = 224 × 224 mm², matrix = 320 × 256, and sagittal slices.

2.2 | DTI preprocessing

The multimodal MRI data were preprocessed in the HCP database by the minimal preprocessing pipeline (Glasser et al., 2013) using the FMRIB Software Library (FSL, <http://www.fmrib.ox.ac.uk/fsl>). The processing steps on the DTI data are described here briefly. The intensity of the mean b0 images was normalized across the six diffusion series. Echo-planar imaging distortions were removed using the TOPUP algorithm in FSL. Eddy current-induced distortions and subject motion were corrected with the EDDY algorithm in the FSL. All b0 images were registered to T1-weighted images using FSL's FLIRT algorithm, and the registration results were refined using Free Surfer's Bbregister algorithm. Registered images were imported into standard Montreal Neurological Institute (MNI) structural space.

We did further processing on the preprocessed data using the FMRIB Diffusion Toolbox. First, the fiber orientation and the associated uncertainties for each voxel were estimated using FSL's BEDPOSTX algorithm, estimating the probability distributions for multiple fiber directions at each voxel. Second, the T1-weighted images were realigned to the nondiffusion b0 images using an affine transformation for head motion and eddy current-induced image distortion correction. We derived the nonlinear transformation between the diffusion space and the MNI 152 structural template brain based on each of the aligned T1 images. These transformations were then used to transform the seed masks into diffusion space for each subject.

2.3 | Definition of pSTS seed mask

For each subject, the bilateral pSTS masks were extracted from their T1w image based on the "Destrieux" cortical atlas which is based on a parcellation scheme that first divided the cortex into gyral and sulcal regions (Desikan et al., 2006). Then, all the individual seed masks were transformed into MNI space to create a group-averaged pSTS map. The final volumetric region of interest (ROI) was obtained by thresholding the group-averaged pSTS map at >25% probability and performing a subsequent binary conversion. After that, the ROI seed mask was transformed to the individual native DTI space using an inverse linear transformation and nonlinear deformations. As the curvature of the pSTS slightly varies with each individual, the ROI seed

masks were checked on the sagittal planes slice by slice to include all tissues commonly assigned to the pSTS. In brief, the superior temporal gyrus and middle temporal gyrus (MTG), respectively, were defined as the upper and lower borders for the pSTS. In the absence of detailed cytoarchitectonic measurements, we used the extension of the posterior superior temporal gyrus as the anterior border (Wang et al., 2015). The posterior border of the pSTS was defined as one slice posterior to the angular gyrus (Fullerton & Pandya, 2007). Due to the fact that various curves and branches exist in this area, we can find two different patterns of morphology of the sulcus in the subjects, as showed in Figure 1 below. One is a curved sulcus pattern in the seed mask and the other appears to be a branch of the sulcus in this area. To carry out the resting-state and coactivation analyses, the pSTS seed masks were resampled into 3 mm³ voxels in MNI space.

2.4 | Tractography-based parcellation of the pSTS

The FSL package was used to perform the tractography on the DTI dataset (Smith et al., 2004). First, to estimate the fiber connections, we applied probabilistic tractography by sampling 5,000 streamline fibers per voxel for each voxel in the seed region. The connection probability between a seed and each of the other voxels in the brain is defined by the total number of traces arriving at the target site (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). Then we used a small threshold, $p < .002$ (10 of 5,000 samples), to threshold the path distribution to reduce the false-positive connections. Finally, to facilitate the data storage, all the connectivity profiles for each voxel were downsampled to 5 mm isotropic voxels (Johansen-Berg et al., 2004). Based on the correlations in the connectivity profile, a cross-correlation matrix for the parcellation was obtained that showed all the cross-correlations between any pair of voxels in the seed mask (Johansen-Berg et al., 2004).

The cross-correlation matrix was then permuted using spectral clustering with an edge-weighted centroidal Voronoi tessellations method for image segmentation to define different clusters (Wang, Ju, & Wang, 2009). Specifically, we employed the split-half method where the data from each subject are excluded from the averaging. When using this method, the number of component clusters is chosen by the experimenter. Since the seed region was

FIGURE 1 Two different morphologies of the pSTS in native DTI space. The seed mask in DTI space in the left hemisphere (green) and right hemisphere (red). The top row is the curve sulcus pattern and the bottom row is the branch pattern in this area

relatively small, the number of potential clusters was set to range from 2 to 5. The Dice coefficient was used to measure the similarity between the parcellation results for the various subjects (Dice, 1945). The values of this index range from 1.0 to 0.0, where high values indicate reasonable consistency; in our case the highest number was chosen. In addition, we evaluated the topological distance (TpD) to quantify the similarity in the topological arrangement of the putative homologous areas in either hemisphere (Tungaraza et al., 2015). To this end, we computed a $K \times K$ topology matrix for a given parcellation. The (i, j) entry of this matrix was the number of voxels from region i that were spatially in contact (26-nearest neighbor) with voxels from region j . The TpD between the given left and right subregions in each hemisphere was defined as the cosine distance of the two matrices (normalized to a sum of 1 and vectorized). The TpD score ranges from 0 to 1. A score close to 0 suggests that the two hemispheres have similar topologies.

Considering inter-individual differences in the pSTS parcellation, we calculated a maximum probability map (MPM) to show the final results (Caspers et al., 2008). For this result, each individual parcellation result was transformed from diffusion space to the MNI template. The MPM was calculated in MNI space by assigning each voxel to the subregion to which it was most likely to belong. We also calculated the probabilistic map and distributions of the probability values for each pSTS subregion.

2.5 | Anatomical connectivity patterns of the pSTS subregions

To show the different anatomical connection patterns of the pSTS subregions, a whole brain probabilistic tractography for each subject was run from each subregion of the pSTS in individual diffusion space by estimating the fiber orientations for each voxel (Behrens et al., 2007). First, we drew 5,000 samples from the connectivity distribution of each voxel to all the other voxels of the whole brain for each subregion. Second, to reduce the noise in the fiber tracking, the threshold for the connectivity probability was set at $p > 2.0$ ($>0.04\%$ of the 5,000 samples generated from each seed voxel) (Fan et al., 2014). Then, the fiber tracts were binarized and warped into standard MNI space according to the

corresponding estimated transformations. Last, the population maps were obtained by averaging the warped fiber tracts and were thresholded at 50% across the subjects. Moreover, we used the Johns Hopkins University (JHU) WM tractography atlas to label the fiber pathways (Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004).

Next, we computed the connectivity probability between each subregion and each of the brain areas in the automated anatomical labeling template (Tzourio-Mazoyer et al., 2002). The averaged connectivity probability values between each pSTS subregion and all the target regions were calculated across all the subjects. We selected those target brain regions with a connection strength >0.5 to estimate the anatomical connectivity fingerprints. In addition, for each target area in the fingerprints, paired t tests were used to test the significance of the anatomical connective differences between the results for each pair of subregions.

Finally, permutation testing was used to test for significant differences in the Manhattan distance between fingerprints of the two subregions, as described in Mars et al. (2016). For each hemisphere we tested the hypothesis that the difference between the anatomical connectivity fingerprints to be compared would be larger (or smaller) than expected by chance. The null hypothesis to reject is that the difference is the same independent of how we permute the target areas of the fingerprint. As such, the Manhattan distance was calculated for 25,000 different permutations of each hemisphere fingerprints, using 95% confidence intervals.

2.6 | Resting-state fMRI data preprocessing

The resting-state fMRI data came from the same scanning of the 40 subjects in the HCP database ($TR = 720$ ms, 1,200 frames in each scanning). The preprocessing of the fMRI data included the following steps: (a) gradient distortion correction (Jovicich et al., 2006); (b) motion correction; (c) distortion correction; (d) registration to the T1 scan; (e) spline resampling to FSL MNI152 2 mm space using FSL FNIRT (Smith et al., 2004); (f) intensity normalization to mean of 10,000 and bias field correction. In the end, the functional data were resampled into MNI space.

FIGURE 2 (a) Dice coefficient for different numbers of clusters. The polylines indicate the mean dice coefficient for each number of clusters. Error bars show the variance. (b) The TpD showed the similarity of the four solutions for the topological arrangement between the two hemispheres. The two-cluster solution had the highest mean dice coefficient and lowest TpD values

FIGURE 3 Tractography-based parcellation of the pSTS. The human pSTS can be reproducibly subdivided into rostral (yellow) and caudal (blue) subregions. The brains show the location of these areas. Abbreviations: L = left; R = right; rpSTS = rostral pSTS; cpSTS = caudal pSTS

2.7 | Whole brain resting-state functional connectivity (rsFC) patterns

To obtain the whole brain rsFC patterns, the Pearson's correlation coefficients between the mean time series for the given subregion, and the time series for each voxel in the rest of the brain were calculated in function space for each subject. The correlation coefficients were then normalized using Fisher's z-transform to improve normality. Next, a one-sample *t* test was performed to identify the voxels that showed significantly positive or negative correlations with the seed region in these normalized correlation maps. Moreover, paired *t* tests were used to identify the precise regions that differed in their rsFC strengths between each pair of pSTS subregions ipsilaterally (Supporting Information Figure S2). For all the above voxel-wise comparisons, the false discovery rate method was used for multiple comparisons correction ($p < .01$), and only clusters that contained a minimum of 100 voxels are reported here (Figure 5).

2.8 | Whole brain coactivation connectivity

The whole brain co-activation connectivity pattern for each individual seed voxel was computed using the meta-analytic connectivity modeling (MACM) approach in the BrainMap database (Eickhoff et al., 2010; Laird et al., 2013). The co-activation pattern for each subregion was obtained by first identifying all the experiments in the BrainMap database that featured at least one focus of activation in the particular CBP-derived cluster. Then a meta-analysis was performed using the revised version of the activation likelihood estimation (ALE) approach. Modeled activation (MA) maps were computed by pooling all the probability distributions for the activation foci reported in a given experiment (Turkeltaub et al., 2012). The MA maps contained the probability of an activation's being located at exactly that position in a given experiment for each voxel. Then the ALE scores were calculated on a voxel-by-voxel basis by taking the union of these individual MA maps and were tested for significance in a random-effects analysis against a null distribution (Eickhoff, Bzdok, Laird, Kurth, &

Fox, 2012). The resulting ALE maps that included only foci with a cluster-level threshold of $p < .05$ (cluster-level FWE-corrected, cluster forming threshold at a voxel-level $p < .001$, converted to z-scores) were obtained.

2.9 | Functional characterization of each subregion

The functional characterization of the CBP-derived subregions was based on the "Behavioral Domain" and "Paradigm Class" meta-data categories available for each neuroimaging experiment included in the BrainMap database. Behavioral domains include the main categories of cognition, action, perception, emotion, and interoception, as well as their related sub-categories. Paradigm classes categorize the specific task employed (<http://brainmap.org/subscribe/>). Forward inference is the probability of observing activity in a brain region given knowledge of the psychological process, whereas reverse inference is the probability of a psychological process being present given knowledge of activation in a particular brain region. When using the forward inference approach, a subregion's functional profile was determined by identifying the taxonomic labels (domains or subdomains) for which the probability of finding activation in a specific subregion was significantly higher than the overall chance (across the entire database) of finding activation in that particular subregion. Significance was established using a binomial test ($p < .05$). For the reverse inference approach, the functional profile of a subregion was determined by identifying the most likely behavioral domains and paradigm classes associated with activation in a particular subregion using Bayes' rule. Significance ($p < .05$ corrected for multiple comparisons using Bonferroni's method) was then assessed by means of a chi-squared test. In sum, forward inference assessed the probability of activation given a psychological term, while reverse inference assessed the probability of a psychological term given activation.

Next, to examine the specificity of the functional profiles of different seed regions ipsilaterally, we performed contrast analyses, which were restricted to those experiments in BrainMap that

FIGURE 4 Anatomical connectivity patterns and fingerprints of the pSTS subregions. The subregions are shown in different colors (rpSTS: Yellow; cpSTS: Blue). (a) Population maps of the probabilistic tractography results from the two pSTS subregions in the bilateral hemispheres were thresholded at 70% and are portrayed on the MNI152 standard brain in 3D and multislice presentations, respectively. We used the JHU white matter tractography atlas to label the main fiber pathways, and the overlap pathway is marked in red. (b) Anatomical connectivity fingerprints of the pSTS subregions. The target regions naming convention is based on Tzourio-Mazoyer et al. (2002). For each target area, the connective differences between the two subregions with this target area were tested using a paired samples *t* test. “n.s.” indicates that no significant difference was found. (c) Permutation distribution of the differences between the two subregions, showing the criterion values in red and the actual statistics from the data in green. This indicates a significant difference in the connectivity fingerprint for the two areas

activated either set of seeds. The results of these quantitative comparisons were thresholded at $p < .05$ (corrected for multiple comparisons using Bonferroni's method). For the differential forward inference, we compared the activation probabilities between the

two seeds given a particular behavioral domain; for the differential reverse inference, we compared the probabilities of a particular behavioral domain's being present given activation in one or the other seed.

FIGURE 5 Resting-state functional connectivity patterns for the bilateral pSTS subregions. Statistical parametric maps using a voxel-level statistical threshold of $p < .01$ corrected for false discovery

3 | RESULTS

3.1 | Tractography-based parcellation of pSTS

In this study, we used in vivo probabilistic tractography and a spectral clustering algorithm to parcellate the human pSTS into two to five subregions to establish their functional organization. To determine the optimum number of clusters, the consistency, as characterized by the Dice coefficient, and the interhemispheric consistency of topological relationships between clusters, characterized by the TpD, were calculated for each number of subregions. Thus, the two parcellation clusters of the left and right pSTS with the highest mean Dice coefficient and lowest TpD values across all the subjects were selected for further analyses (Figure 2). Furthermore, the two different patterns of

the pSTS were also highly coincident with the forward and backward trends of the two clusters from the parcellation result (see Supporting Information Figure S1). The parcellation of the pSTS based on the above results indicated the presence of a rostral pSTS (rpSTS) and a caudal pSTS (cpSTS). The probability maps for the bilateral pSTS are shown in Figure 3. In addition, we show the details of the subregions of the pSTS along the ventral and dorsal banks of these areas (Figure 3).

3.2 | Anatomical connectivity patterns of the pSTS subregions

In this study, diffusion tractography was used to estimate the probability of connections between each subregion and other brain regions for each subject. The anatomical connectivity pattern for each pSTS

FIGURE 6 The whole-brain co-activation connectivity patterns for each subregion of the pSTS. The patterns were obtained using MACM analyses. (cluster-level FWE corrected $p < .05$)

FIGURE 7 Behavioral domains and paradigm classes for the pSTS subregions. Forward inference and reverse inference were used to determine the functional organization of each subregion. The significant activation probabilities for each subregion with respect to a given domain or paradigm and the significant probability of a domain's or paradigm's occurrence given activation in a cluster are depicted separately. Color code: yellow = rpSTS; blue = cpSTS

subregion is illustrated in Figure 4(a). The population probability of a voxel's belonging to the pathway of each subregion was >50% for each pattern. We used the JHU white matter tractography atlas to distinguish the main fiber pathways in the result. These primarily included the anterior thalamic radiation, forceps major, corticospinal tract (CST), inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus, and cingulum. Most of these fibers connected the pSTS and other brain areas to implement a system for language and communication.

To quantify the differences in the anatomical connections between the two pSTS subregions, the average normalized connection strengths between each pSTS subregion and the other areas of each hemisphere are shown in Figure 4(b). Through the fingerprint, it is easy to observe that the rpSTS showed connections with the insula (INS), precuneus (PCUN), median cingulate and paracingulate gyri (DCG), inferior parietal lobule (IPL), thalamus (THA), and the temporal lobe and that the cpSTS showed connections with the angular gyrus (ANG), superior temporal gyrus (STG), and precentral gyrus. Moreover, we found that the left rpSTS was relatively strongly connected with the IPL, while the middle occipital gyrus (MOG) connections appear relatively strongly connected with the

right rpSTS. In addition, there were some differences between the bilateral hemispheres. The right subregions showed relatively stronger connections with the inferior temporal gyrus (ITG), but the left hemisphere had relatively weaker connections. Also, the left subregions had relatively stronger connections with the language areas than the right side (Supporting Information Table S1).

The permutation distribution and criterion are indicated in Figure 4(c); the observed value was greater than the criterion in the right tail for both sides of the brain. Furthermore, the p values of the actual distance for each side region were both <.005, so we rejected the null hypothesis as not being a likely explanation for such an observed difference; that is, the two fingerprints were "far" from each other in that the rpSTS and cpSTS subdivisions had clearly distinct anatomical connectivity profiles.

3.3 | Whole brain rsFC pattern

The rsFC results for each pSTS subregion are displayed in Figure 5. Overall, these two pSTS subregions showed different rsFC patterns, indicating that they are involved in different neural networks. The

FIGURE 8 Differences in behavioral domains and paradigm classes between the two subregions. The base rate denotes the general probability of the BrainMap activations for the given seeds. Color code: yellow = rpSTS; blue = cpSTS

results shown in the figure did not include the cerebellum (for the peak coordinates see Supporting Information Table S2).

3.3.1 | Positively correlated networks

From the resting-state FC pattern for each subregion, we found that the rpSTS was positively correlated with the anterior part of the superior and middle temporal gyri, temporal pole, inferior frontal gyrus, medial orbito-frontal gyrus, precentral gyrus, and insula, most of which belong to the auditory and language cortex. Contrarily, the cpSTS was primarily correlated with the superior temporal gyrus, superior frontal gyrus, posterior part of the middle frontal gyrus (MFG), and inferior frontal gyrus. Specifically, the bilateral pSTS subregions showed similar functional connectivity patterns for both the positively and negatively correlated brain regions except for the following: (a) the left pSTS showed stronger positive correlations with the inferior frontal gyrus, and (b) the right pSTS showed less positive correlations with the frontal lobe. In addition, paired *t* tests were used to reveal significant differences in functional connectivity between each pair of pSTS subregions on one side of the brain (see Supporting Information Figure S2). In brief, the differences in rsFC between the subregions were in the posterior part of the MFG, temporal pole, superior frontal gyrus, and inferior frontal gyrus, resulting in the two pSTS subregions being involved in different functional networks.

3.3.2 | Negatively correlated networks

The left rpSTS was primarily negatively correlated with the parietal lobe, visual association cortex, somatosensory association cortex, anterior entorhinal cortex, ventral posterior cingulate cortex, dorsolateral prefrontal cortex, and frontal eye field. The right rpSTS was primarily negatively correlated with the superior parietal lobule, ventral posterior cingulate cortex, inferior frontal gyrus, frontal eye field, and supramarginal gyrus. However, there was no significant negative connectivity of the cpSTS subregions on either side.

3.4 | Whole-brain co-activation connectivity

Next, the whole-brain co-activation connectivity pattern (cluster-level FWE corrected $p < .05$) for each subregion was obtained from the

MACM analysis (Figure 6). The co-activation connectivity pattern for each subregion was quite similar to each resting-state FC pattern. For the rpSTS, co-activation connectivity was primarily found in the inferior frontal gyrus, superior temporal gyri, precentral gyrus, posterior part of the MFG, and fusiform gyrus. Meanwhile, the cpSTS primarily coactivated with the inferior frontal gyrus, precentral gyrus, superior temporal gyri, and supramarginal gyrus. However, on the right side, the cpSTS did not connect with the inferior frontal gyrus, which is a critical brain region for language and speech processing (for the peak coordinates see Supporting Information Table S3).

3.5 | Functional characterization: Behavioral domain and paradigm analysis

Quantitative forward and reverse inferences were employed on the behavioral domains and paradigm classes to detect the functional role for each of the two subregions. The significant activation probabilities within a cluster given a certain taxonomic label (forward inference) and the significant probability of domain and paradigm occurrence given activation in a certain cluster (reverse inference) are shown in Figure 7. Note that the taxonomic terms displayed in Figure 7 are taken from the BrainMap database and that this individual functional characterization shows which behavioral domains and paradigm classes are significantly associated with a particular cluster. Through these results, we found that the rpSTS was significantly associated with cognition language, speech, phonological discrimination, and word generation, and the cpSTS was primarily involved in language phonology, tone monitoring, audition perception, and vision motion. In addition, further exploration of the result showed that the left pSTS was primarily responsible for language production and processing while the right part was involved in saccades, cognition attention, and perception of biological motion.

To further examine the differences between the two subregions in the same hemisphere of the brain, we compared the functional profiles of each subregion of the pSTS (Figure 8). On the left side, the rpSTS principally supported language, speech, passive viewing, phonology discrimination, and word generation tasks, while the cpSTS was more associated with action, vision perception, distraction, and

reward tasks. In contrast, the right side of the rpSTS showed a high activation probability for social cognition, action observation, speech, and cognition attention, while the cpSTS was more involved in perception of vision motion, saccades, visual distraction, and pitch monitoring.

4 | DISCUSSION

To the best of our knowledge, this is the first study to parcellate the human pSTS based on probabilistic fiber tractography with DTI and to elucidate the anatomical and functional connectivity patterns of the human pSTS at the subregional level. The results of this study show that the human pSTS can be subdivided into rostral and caudal subregions because of the clear superiority of this subdivision in the data metrics and in showing significant heterogeneity. Furthermore, each of the pSTS subregions has its own specific anatomical and functional connectivity patterns. Combined with the behavioral domain and paradigm analysis, we can infer that these subregions are involved in different brain functions.

The pSTS parcellation described in this study may be supported by studies reporting that the pSTS is a part of the association cortex involved in multimodal sensory integration (Saxe, 2006). Many task-based fMRI studies have demonstrated that different parts of the pSTS respond to distinct stimuli, such as that the activation in response to biological motion was primarily centered in the back part of the pSTS (Redcay, 2008). Candidi, Stienen, Aglioti, and de Gelder (2011) applied event-related repetitive transcranial magnetic stimulation over the posterior portion of the pSTS and found that this area is crucially devoted to the detection of socially relevant information about others' actions, fostering the notion that amygdalo-temporo-cortical modulatory connections mediate the perception of emotionally salient body postures. Furthermore, Maldonado et al. (2011) found that semantic paraphasias were observed during subcortical stimulation of the white matter under the anterior part of the pSTS. These studies are consistent with our results in this study in that they also indicate that the pSTS is subdivided into two subregions and that each subregion is predominately involved in two distinct networks. One is the dorsal language processing pathway in humans, which has been suggested to support auditory-motor integration; the other is the perception of social interaction as well as cortical sensorimotor simulative mechanisms. These findings improve our understanding of the pSTS connectivity and functions at the subregion level.

Only a few studies of the subdivisions of the pSTS have been conducted. Shih et al. (2011) identified three functional subdivisions in the pSTS using a data-driven approach. Based on anatomical connection patterns, we parcellated the human pSTS into the rostral and caudal subregions. Comparing the two different parcellation schemes, the distribution of the subareas and the direction of the boundary are basically analogous. The fact that our parcellation results are not completely consistent with those results of Shih et al. may be ascribable to the following: First, an obvious difference exists between the DTI and fMRI data that we and they, respectively, employed. Thus, the imaging measurements were not completely matched. Second, a CBP using dMRI and a data-driven

approach using an fMRI subdivision analysis may not show complete correspondence. In addition, De Winter et al. (2015) used the responding clusters in their experiment to make subdivisions of the pSTS that are consistent with those found in our study. These studies indicated that investigating the pSTS at a fine-grained level is important and urgently needed, and we need to try to understand how these subregions' specific functions are indicated by their unique connections. Meanwhile, considering the finer subregions as the individual nodes of the brain organization will most likely be helpful for studying the information exchange between the pSTS and other brain nodes of functional networks. Furthermore, research at a fine-grained level may help in more accurately positioning the abnormal subarea of the pSTS in patients with conditions such as simultanagnosia or ASD (Jaimes et al., 2017; Plantinga et al., 2018).

4.1 | Connectivity patterns of the pSTS subregions

According to its anatomical connectivity pattern, the rpSTS is strongly connected with the prefrontal cortex via the IFOF, which has been demonstrated to play an essential role in semantic processing and subserves the direct ventral pathway of language (Almairac, Herbert, Moritz-Gasser, de Champfleury, & Duffau, 2015; Catani & Bambini, 2014). Compared to macaque monkey brain anatomy, the IFOF is corresponding to the extreme capsule, which plays a significant role in high level language comprehension (Makris & Pandya, 2009). At a similar level of importance, the ILF projects from the rpSTS to the anterior temporal region, which serves as an indirect pathway for the ventral semantic stream (Duffau, Herbert, & Moritz-Gasser, 2013). An interesting observation is that in macaque monkeys, the ILF connects the occipital to the temporal region, due to the absence of the MTG, and leads from there to a less developed ventral route (Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012). This might match the lexical and semantic abilities of primates, but the size of their vocabulary is limited (Tamura et al., 2017). An obvious vital function of the rpSTS is to process different functions in the language stream. Good converging evidence was also evident from the whole brain functional connectivity map, in that the rpSTS was also strongly co-activated with the posterior part of the IFG (the so-called Broca's area), the posterior part of the STG (the so-called Wernicke's area) and the angular gyrus. These regions work together in the production of language or language outputs, the transmission of information, and the interpretation of words, as has been found in many previous studies (Flinker et al., 2015; Rilling, 2014). Thus, it could be postulated that the rpSTS plays a core role as a "computational hub" in the language information processing stream. Furthermore, many studies have found that the rpSTS is activated by audiovisual binding stimuli and, in particular, that the left hemisphere is more activated during audiovisual processing, findings which are consistent with ours (Beauchamp et al., 2010; Hocking & Price, 2008) and with previous task fMRI results in monkeys (Grossman, Battelli, & Pascual-Leone, 2005; Orban, Van Essen, & Vanduffel, 2004). Exploring the coactivation pattern with behavior analyses, we also found that the rpSTS was implicated in the process of word generation, which, obviously, does not appear as a monkey brain function (Crozier et al., 1999; Edwards et al., 2010). In future

studies it may be helpful to further explore the pSTS from the perspective of evolution between humans and nonhumans.

Even though the bilateral rpSTS is a hub for language semantic processing, patients with semantic dementia have relatively more severe symptoms and their disease progresses more rapidly when the atrophy is lateralized to the left, whereas the right rpSTS is more important for semantic retrieval (Binder et al., 2011; Tian, Zarate, & Poeppel, 2016). In addition, according to the behavioral domain analysis, face monitoring was activated more strongly in the right rpSTS, which is consistent with a previously reported role in analyzing facial expressions (Candidi, Stienen, Aglioti, & de Gelder, 2015; Flack et al., 2015). Watson et al. (2014), in another task-based fMRI study, also found asymmetric activation between the left and right hemispheres in the rpSTS. This asymmetry may result from a stronger anatomical connection between the right rpSTS and the MOG. In addition, a neuropsychological study reported that patients with a lesion in this region exhibited difficulty in discriminating facial identities (Fox, Hanif, Iaria, Duchaine, & Barton, 2011). Considering these findings in light of the results in our study, our work may shed new light on the underlying mechanism of these kinds of diseases.

In the diffusion data results, the cpSTS was connected with the precentral gyrus (PreCG) through the CST, which primarily responds to motor functions and the detection of intentionality. Consistent with this, a recent study observed that the connection between the cpSTS and the PreCG was indirectly served for the action understanding as they both play a role in motor imagery (Rajmohan & Mohandas, 2007). In macaques, as in humans, these areas were triggered by any action that involves the interaction between a biological effector and an object (Rizzolatti & Craighero, 2004). Our results also show clear evidence for connectivity between the cpSTS and IPL, which is consistent with previous findings (Calder et al., 2007; Yoshie, Nagai, Critchley, & Harrison, 2016). This region is sensitive to different gaze directions (Calder et al., 2007; Otsuka, Osaka, Ikeda, & Osaka, 2009) and is, therefore, a candidate for message processing delivered from the cpSTS. An analogous pattern was observed in monkeys (Aboitiz, 2012). The functional connectivity data also show clear connectivity with the fusiform gyrus. This brain region is associated with object processing on a pre-semantic level (Amedi, Malach, Hendler, Peled, & Zohary, 2001), shape processing (Amedi et al., 2001; Kourtzi & Kanwisher, 2001), and face selection (Yovel & Freiwald, 2013). The results of the co-activation and behavioral domain analyses imply that the cpSTS is disproportionately activated by cognitive linguistics, biological motion, and social cognition. For example, the connections between the MFG and the IPL may be involved in theory of mind, which is the ability to consider the thoughts and beliefs of other people (Hein & Knight, 2008; Otsuka et al., 2009). More interestingly, Mars, Sallet, Neubert, and Rushworth (2013) found that areas in the middle part of the superior temporal sulcus (STS) in macaques were also associated with social cognition, so it is possible that the human pSTS shares a common precursor with the macaque mid-STs. Consequently, the above results indicate that this brain area in humans plays an important role in multisensory integration processing, a finding which is consistent with previous studies (Beauchamp, 2005).

Through a more comprehensive exploration of our results, we found that the left side of the subregions' primary anatomical and

functional connections mainly supported language processing, which is consistent with a clear lateralization of the language network (Friederici & Gierhan, 2013). Contrarily, a task-based fMRI study by Saxe, Xiao, Kovacs, Perrett, and Kanwisher (2004) found that the right pSTS supported biological motion, especially when perceiving intentional action, a finding that is consistent with the results in this current study. This was further confirmed by another study that found lateralized effects in the human pSTS for dynamic faces but no consistent pattern of lateralization in monkeys (De Winter et al., 2015). These findings provide a new way of thinking about how to explore the relationships between humans and macaque monkeys, which are generally thought to have a common ancestor. What is more, the fiber tractography showed involvement of the ILF and IFOF, which previous research has showed are related to cognitive aspects of ASD (Hirose et al., 2014). Additionally, many task-based fMRI analyses identified the right pSTS as a key region in social cognition in ASD (Alaerts et al., 2014; Pantelis, Byrge, Tyszka, Adolphs, & Kennedy, 2015), a finding which is in line with our finding based on the behavioral analysis. Another study about ASD that used steady-state fMRI observed a positive relationship between the cortical thickness of the right pSTS and the social reciprocity scores of ASD but no significant relationship in the left hemisphere (Shih et al., 2011). In conclusion, these insights may further advance the quest to develop interventions for ASD, and future research should extend to the neural networks relevant to social cognition in ASD and beyond.

4.2 | Limitations

Although the subregional organization and anatomical connections of the human pSTS were revealed in detail, there are some limitations of this study that should also be considered. First, because of the inherent limitations of probabilistic tractography, the anatomical connectivity patterns may have been influenced by many factors, such as the length and the geometry of the pathways. Thus, more plausible methods need to be developed to more accurately characterize the anatomical connections of the human brain. Second, the sulcal pattern of the pSTS is a curved path, which varies between individuals and which may be obscured during normalization (Ochiai et al., 2004). To identify the subregions of the pSTS, we employed a MPM to best estimate the trajectory and location of the subregions. Last, with regard to the similarities and differences in the pSTS subregional functional and anatomical connectivity patterns, our assumption was that the anatomically connected subregions constituted a subset of the regions that were functionally connected. It is more likely that the functional connectivity reflects both direct and indirect anatomical connections between two brain regions.

5 | CONCLUSION

As far as we know, this is the first study to use DTI with probabilistic tractography to parcellate the human pSTS in vivo based on its anatomical connectivity. By mapping the whole-brain anatomical connectivity patterns, elucidating the functional connectivity patterns, and performing a functional characterization analysis for each pSTS

subregion, we found that the different subregions were involved with different functional networks. These findings may help to unravel the complex activation patterns in the pSTS from functional neuroimaging studies and improve our understanding of the pSTS from the perspective of connectivity. Furthermore, the parcellation framework and connectivity results may help to reveal the complex activation patterns in the pSTS from the perspective of functional neuroimaging studies and may provide the groundwork for more detailed studies of this brain area in its relationship with various diseases in the future.

ACKNOWLEDGMENTS

This work was partially supported by the National Natural Science Foundation of China (Grant Nos. 91432302, 31620103905, 91132301, and 81501179), the Beijing Municipal Science & Technology Commission (Grant Nos. Z161100000216139 and Z171100000117002), the Science Frontier Program of the Chinese Academy of Sciences (Grant No. QYZDJ-SSW-SMC019), the Shenzhen Peacock Plan (KQTD2015033016104926) and the Guangdong Pearl River Talents Plan Innovative and Entrepreneurial Team grant (2016ZT06S220). Data were provided by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University. Extensive editing of both the content and the language was performed by Rhoda E. and Edmund F. Perozzi. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Cheng C, Fan L, Xia X, et al. Rostro-caudal organization of the human posterior superior temporal sulcus revealed by connectivity profiles. *Hum Brain Mapp*. 2018;39:5112–5125. <https://doi.org/10.1002/hbm.24349>