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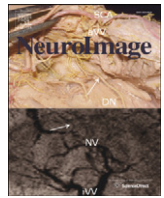
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Processing social aspects of human gaze: A combined fMRI-DTI study

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ABSTRACT

Human gaze is a critical social cue that can reveal intentions and dispositions of others. The right posterior superior temporal sulcus (pSTS) is thought to be critically involved in processing eye gaze information. We combined diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) to identify direct neural connections of right pSTS and to determine how these connections are modulated by the social significance of perceived gaze shifts. Participants saw faces with direct or averted gaze during event-related fMRI. Half of these faces remained static, and half displayed a dynamic gaze shift either towards or away from the subject. Social attention (dynamic gaze shifts towards the observer) not only increased activity in right pSTS, but also its functional connectivity with the right anterior insula (alns) and right fusiform gyrus (FG). However, direct fiber connections from pSTS were demonstrated by DTI for the right alns, but not the right FG. Moreover, the right FG responded to eye motion irrespective of direction and social significance; whereas the right alns was selectively sensitive to social significance (i.e. gaze shifts towards the observer), but not generally to eye motion. We conclude that the social aspects of mutual gaze contact are processed by direct fiber pathways between right pSTS and right alns; whereas increased connectivity with FG could reflect an enhanced perceptual analysis of changing facial features in dynamic gaze conditions and involves indirect fiber pathways with pSTS, perhaps via motion-selective regions in middle temporal (MT) gyrus that exhibited strong white-matter connections with both pSTS and FG and could thus provide inputs to these two areas.

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Introduction

Gaze direction is a critical facial cue in everyday interaction, since it can provide a wealth of socially relevant information about others and their environment even in circumstances where verbal communication is not possible. For instance, during milongas in tango argentino, men typically invite women to dance with their gaze rather than words. In many other mundane situations, a gaze straight to one's eyes represents a major signal of contact between two persons, while perceived shifts in gaze direction may signal interest and approach (if directed to the viewer) or rejection and avoidance (if averted from the viewer). Thus, decoding gaze motion plays an important role in predicting the intentions, future actions, and attitudes of other people, and can be regarded as an important source of information for "Theory of mind", the ability to understand mental states of others (Baron-Cohen, 1995), and more generally for the appraisal of self-relevance (Cristinzio et al., 2010; N'Diaye et al., 2009; Schilbach et al., 2006).

Abundant evidence suggests that the posterior superior temporal sulcus (pSTS) is critical for gaze processing, including neurophysio-

logical data in non-human primates (Campbell et al., 1990; Hasselmo et al., 1989; Perrett et al., 1992, 1985), lesion studies (Akiyama et al., 2006; Campbell et al., 1990), and neuroimaging experiments (Conty et al., 2007; Hoffman and Haxby, 2000; Pelphrey et al., 2005, 2003b; Puce et al., 1998). The right pSTS has been shown to contain overlapping representations for perception of biological movement, moral judgment and theory of mind (Bahnenmann et al., 2010) and appears to be particularly sensitive to goals and intentions conveyed by gaze in social (Bristow et al., 2007; Pelphrey et al., 2004b) and non-social (Mosconi et al., 2005; Pelphrey et al., 2004a, 2003b) paradigms.

However, still little is known about the exact neural networks mediating gaze perception, and which connections between the right pSTS and other areas are implicated in processing the social and self-relevant aspects of gaze. Recently, Nummenmaa et al. (2009) compared the functional connectivity of brain regions activated when seeing gaze shifts (from averted left to averted right position or vice versa) and opening/closing the eyes. They found that gaze shifts increased the connectivity of right pSTS with the dorsal attention network including the right intraparietal sulcus (IPS) and right frontal eye field (FEF). The dorsal attention network is thought to control endogenous attention mechanisms to enhance sensory processing of task-relevant stimuli, whereas a more ventral attention system within the fronto-insular cortex comprising the anterior insula (alns) and neighboring inferior frontal gyrus (IFG) may act as circuit-

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breaker that switch processing resources from the default mode network to the central-executive (Sridharan et al., 2008) and reorient attention toward unexpected but behaviorally significant stimuli (Corbetta et al., 2008).

Here, we investigated how the network recruited for gaze perception is modulated by the social meaning of eye motion, and examined whether changes of connectivity within this network are determined by direct structural connections between the right pSTS and other areas. Participants saw faces with or without gaze shifts during event-related fMRI. White-matter connections from the right pSTS were then defined using DTI and probabilistic fiber tracking. Based on previous results (Pelphrey et al., 2004b), we expected enhanced responses in right pSTS to gaze motion towards the observer, and a modulation of its functional coupling with the attentional systems by changes in gaze direction (Corbetta et al., 2008; Nummenmaa et al., 2009).

Materials and methods

Participants

Twenty-two volunteers (13 females, 9 males, 26.3 ± 7.7 years) took part in the study. All were right-handed, had normal or corrected to normal vision, and reported no history of neurological or psychiatric diseases. The study was approved by the Ethical Committee of the University of Geneva and conducted according to the Declaration of Helsinki.

Stimulus material and experimental design

Stimulus material included 64 movie clips (2 s duration) of eight computer generated faces (4 males and 4 females) with a neutral facial expression, created with the FACS (Facial Action Coding System)-GEN Software (Roesch et al., 2006). These stimuli were selected from a larger data base on the basis of a behavioral pilot study (6 male and 6 female subjects, mean age 25.4 ± 6.3 years) to include only stimuli in which gender was correctly identified in more than 90% of the subjects. Gaze was either direct (32 stimuli) or averted to the left or the right (16 stimuli each) at stimulus onset. Half of these faces remained static during the whole stimulus duration (static with direct gaze, SD; and static with averted gaze, SA). The other half displayed a dynamic horizontal gaze shift of 100 ms duration, either from averted to direct position (movement towards, MT) or from direct to averted position (movement away, MA), 950 ms after stimulus onset. Thus, irrespective of the starting position of gaze, the probability of gaze shifts was 50%, making it impossible for the participants to predict whether gaze movements would occur on any given trial.

Stimuli were presented in fully randomized order using an event-related design. Although blocked designs may yield stronger signal for analysis of effective connectivity (Gitelman et al., 2003), we preferred an event-related design to rule out any systematic anticipation of the subjects for the occurrence and/or direction of gaze shifts, and thus increase the recruitment of brain structures involved in detecting unexpected behaviorally significant stimuli. Furthermore, blocked presentations of dynamic eye movements might induce a perception of gaze shifts in the opposite direction due to the changing eye position between offset of one stimulus and onset of the next. Trial onsets were jittered relative to scan onset in steps of 850 ms, and the inter-trial interval ranged from 6.8 to 10.2 s. A fixation cross was shown between stimulus presentations. Subjects were instructed to classify the gender of the faces as accurately and quickly as possible, by pressing on one of two MRI-compatible response pads.

Image acquisition

Structural and functional imaging data were acquired using a 3 T scanner (Siemens TRIO, Erlangen, Germany). A magnetization

prepared rapid acquisition gradient echo sequence was employed to acquire high-resolution ($0.9 \times 0.9 \times 0.9$ mm³) T_1 -weighted structural images (repetition time (TR)=1.9 s, echo time (TE)=2.32 ms, inversion time (TI)=900 ms). 330 functional images were obtained using a multislice echo planar imaging (EPI) sequence (32 axial slices acquired in descending order, slice thickness 4 mm + 1 mm gap, TR=1.7 s, TE=30 ms, field of view (FOV)= 192×192 mm², 64×64 matrix, flip angle=90°, bandwidth 1562 Hz/Px). For offline correction of EPI image distortions, a static fieldmap (36 slices acquired in descending order, slice thickness=3 mm + 1 mm gap, TR=400 ms, TE (1)=5.19 ms, TE (2)=7.65 ms, FOV= 192×192 mm², 64×64 matrix) was acquired prior to the functional measurements.

Diffusion-weighted images were obtained using a “Skejskal–Tanner” sequence (TR=8.3 s, TE=82 ms, flip angle=90°, 64 axial slices, 2 acquisitions) with a spatial resolution of $2 \times 2 \times 2$ mm³. Diffusion-weighted imaging was performed along 30 independent directions with a b-value of 1000 s/mm². Furthermore, a reference image with a b-value of 0 s/mm² was acquired.

Conventional fMRI data analysis

The first five fMRI volumes were discarded from further analysis to exclude measurements that preceded T_1 equilibrium. Functional images were analyzed using statistical parametric mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London, UK, www.fil.ion.ucl.ac.uk/spm/). Preprocessing steps comprised realignment to the first volume of the time series, unwarping by use of a static field map (Andersson et al., 2001), correction for differences in slice acquisition time, and normalization into MNI space (Montreal Neurological Institute, (Collins et al., 1994), resampled voxel size: $3 \times 3 \times 3$ mm³). Images were additionally smoothed with an isotropic Gaussian filter (8 mm full width at half maximum). Statistical analysis relied on a general linear model (GLM, Friston et al., 1994).

Separate regressors were defined for each of the four stimulus conditions (SD, SA, MT, and MA) using a stick function convolved with the hemodynamic response function. Events were time-locked to the onset of possible gaze shifts (one second after stimulus onset). To remove low frequency components, a high-pass filter with a cutoff-frequency of 1/128 Hz was used. Serial autocorrelations were accounted for by modelling the error term as a first-order autoregressive process with a coefficient of 0.2 (Friston et al., 2002) plus a white noise component (Purdon and Weisskoff, 1998).

Note that because only one experimental factor (gaze shift versus no gaze shift) was fixed while the other factor (direct gaze versus averted gaze) changed during presentation of the stimuli (at the time of eye motion, see Fig. 1), our experiment cannot be considered as a classical 2×2 factorial design. Due to their dynamic nature, all stimuli with a gaze shift contained periods with eye contact (or straight gaze), either in their initial or in their final phase (950 ms duration each), which could therefore not be modeled separately due to the temporal resolution limits of fMRI. Instead, our experiment was designed to first identify brain areas that react to eye motion and then determine those that show differential responses as a function of perceived gaze contact versus gaze aversion. To this end, we first contrasted all stimuli with gaze motion and static stimuli (MT + MA > SD + SA) to localize motion-responsive regions. We then submitted beta estimates of these areas to paired t-tests to probe their sensitivity to social information conveyed by the different gaze shift directions in the dynamic condition (MT > MA and vice versa). Similarly, clusters showing a differential response to the two types of gaze shifts (MT > MA and MA > MT) were tested to determine whether they also exhibited any general response to gaze motion (MT + MA > SD + SA). For completeness, effects of eye gaze direction were also examined in static conditions (SD vs SA). All results are reported at a statistical height threshold of $p < 0.001$ (uncorrected). Significance was assessed at cluster level $k > 50$ voxels ($p < 0.05$, corrected for multiple

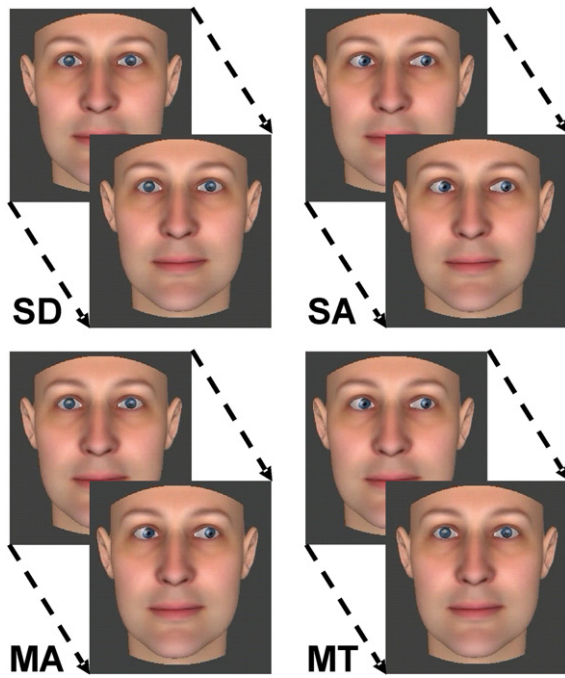


Fig. 1. Experimental design. Each stimulus (total $n = 64$) had a duration of 2 s. Gaze position at onset (upper left face) and offset (lower right face) are shown for each of the four experimental conditions (SD = static with direct gaze, SA = static with averted gaze, MA = eye movement away, MT = eye movement towards the viewer).

comparisons across the whole brain). For brain regions demonstrating consistent long-range fiber connections (i.e. outside the occipital and temporal lobe or neighboring supramarginal and angular gyrus) with right pSTS across subjects, a small volume correction (SVC, $p < 0.05$, Worsley et al., 1996) was carried out based on the automatic anatomic labeling toolbox (AAL, Tzourio-Mazoyer et al., 2002).

Effective connectivity analysis of fMRI data

A psychophysiological interaction (PPI, Friston et al., 1997) analysis was conducted to identify brain areas showing a contextual modulation of their functional coupling with right pSTS as a function of the social significance perceived from gaze motion (MT > MA). To this end, subject-wise PPI models were run which contained three regressors for the physiological variable, the psychological variable, and the psychophysiological interaction. The physiological variable was defined as the time course of activity in the right pSTS cluster as obtained by the GLM contrast MT + MA > SD + SA. To allow for intersubject variability of the STS (Kreifelts et al., 2009; Ochiai et al., 2004) not accounted for by 3D normalization procedures, subject-wise time courses were extracted from a sphere with 6 mm radius centered on the individual maxima for motion-sensitivity within the group cluster. The psychological variable was defined by the contrast MT > MA. The psychophysiological interaction was obtained by deconvolving the hemodynamic time course of the physiological variable, multiplying it with the psychological variable and reconvolving it with the hemodynamic response function. This deconvolution-reconvolution procedure was specifically developed for measures of effective connectivity using PPI analyses in event-related designs (Gitelman et al., 2003). PPI results are reported at a statistical height threshold of $p < 0.001$ (uncorrected) and significance was assessed at cluster level $k > 50$ voxels ($p < 0.05$, corrected for multiple comparisons across the whole brain). Given the lower sensitivity of PPI analyses in event-related designs, we additionally performed region of interest analyses for all brain areas that showed either a general effect for gaze motion or social information in gaze as determined by the conventional GLM contrasts (see previous discussion) using a more

liberal height threshold of $p < 0.01$ (uncorrected). Correction for multiple comparisons was carried out using a small volume correction for these ROIs ($p < 0.05$, SVC corrected).

Structural connectivity analysis of DTI data

Diffusion-weighted data were analyzed using the FSL 4.04 (FMRIB Software Library, Oxford University, www.fmrib.ox.ac.uk/fsl). Pre-processing of diffusion-weighted images included eddy current correction and averaging across the two acquisitions. The Bayesian estimation method of the FMRIB's Diffusion Toolbox (Behrens et al., 2007, 2003) was used to determine the two most probable fiber directions within each voxel. Clusters identified by fMRI that showed significant effects for gaze shifts at the group level (i.e. pSTS and posterior middle temporal gyrus, pMTG) were transferred to the individual anatomical space, and served as seed regions to perform probabilistic fiber tracking through the native whole brain volume. Probabilistic fiber tracking maps were thresholded at 5% of the maximum value to reduce false-positive fiber tracks. These thresholded probabilistic fiber tracking maps were then back-transformed to MNI space, and binary connectivity maps (containing ones in voxels where connections were found and zeros elsewhere) were generated for each subject. These individual binary connectivity maps were added across subjects and fibers present in more than 50% of the subjects were displayed on a mean normalized T1-weighted image of the subjects. The individual brain atlas toolbox in SPM (IBASPM) was used to generate individual grey matter masks of 80 cortical areas. These masks were used to investigate which of the distant cortical areas are consistently (>50% of the subjects) connected with the seed region (e.g. pSTS). To ensure specificity of the connections of right pSTS, we statistically compared its probabilistic connectivity values with those obtained for the neighboring motion-sensitive pMTG using pair-wise T-tests (height threshold: $p < 0.001$).

Results

Behavioral data

The performance on the face gender classification task was practically flawless for all four stimulus conditions (96–98%) indicating that the participants attended to all stimuli. Reaction times (all values = mean $\pm$ standard error) for faces with gaze shifts (724 ms $\pm$ 36 ms) and static gaze (723 ms $\pm$ 37 ms) were not statistically different ($t(21) = 0.20$, two-tailed $p = 0.85$). Similarly, gaze shift toward (728 ms $\pm$ 38 ms) and away from the viewer (717 ms $\pm$ 38 ms) did not result in significantly different reaction times ($t(21) = 0.67$, two-tailed $p = 0.51$).

Conventional fMRI analysis

Stimuli with gaze shifts elicited significantly stronger responses ($p < 0.05$, corrected) in bilateral pSTS and posterior middle temporal gyrus (pMTG), as compared with those with static gaze (see Fig. 2a). In the right hemisphere, the activation clusters in pSTS and pMTG extended from $y = -36$ to $y = -72$, whereas in the left hemisphere they were generally located one centimeter more posterior between $y = -45$ and $y = -82$. Other brain regions that reacted stronger to stimuli with eye movements than to static gaze ($p < 0.001$, uncorrected) were found in the right fusiform gyrus (FG) and left IFG (see Table 1). Among these areas, only the right pSTS was sensitive to the social meaning of different gaze directions, with enhanced responses when the eyes shifted toward rather than away from the viewer (MT > MA, $p < 0.05$, see Figs. 2b–g).

A whole brain analysis directly contrasting gaze shifts toward versus away from the viewer also revealed significant activation within the right anterior insula (alns), partly extending into the

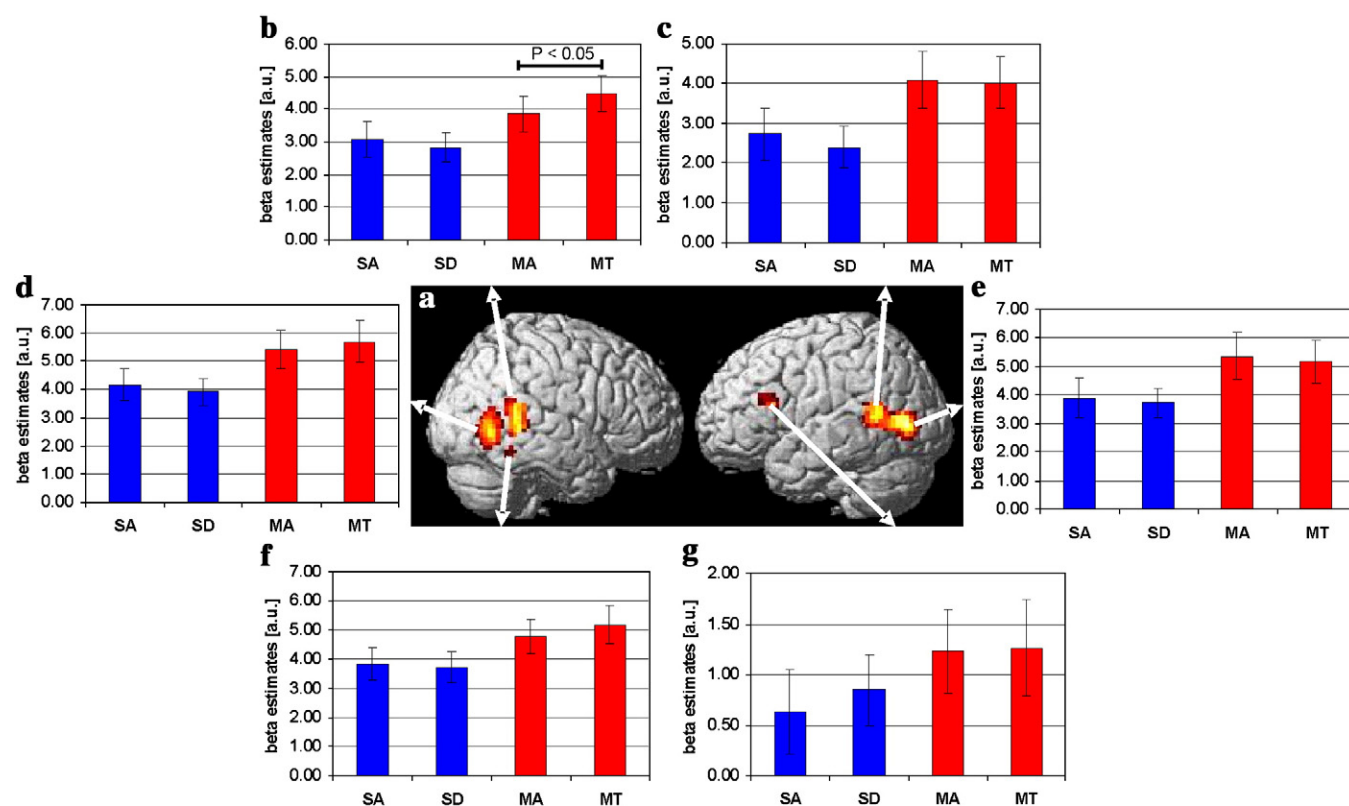


Fig. 2. Brain areas (a) responding stronger ($p < 0.001$, uncorrected) to stimuli with an eye gaze shift (MA = movement away, MT movement toward the viewer) than to static stimuli (SD = static averted, SA = static direct). Average parameter estimates of activity (beta values, arbitrary units, mean $\pm$ standard error) are illustrated (b–g) for stimuli with (red bars) and without (blue bars) eye movements in right pSTS (b), left pSTS (c), right pMTG (d), left pMTG (e), right FG (f) and left IFG (g).

triangular part of the IFG (MNI coordinates: $x = 39$, $y = 21$, $z = 3$; $Z = 3.71$; $k = 31$ (23 voxels within alns, 8 voxels within IFG); $p < 0.05$, SVC corrected for the insula as defined by AAL; see Figs. 3a–c). Interestingly, the right alns did not generally react stronger to stimuli with eye movement compared to static stimuli, as shown by its response to gaze aversion (MA) that was similar to, or even smaller than, its response to static faces ($t(21) = -0.15$; $p = 0.88$; see Fig. 3d). Conversely, no region showed significantly greater activation to gaze shifts away from the viewer versus shifts toward the viewer. Comparing averted and straight gaze in static faces did not reveal any significant activation.

At a lower height threshold ($p < 0.05$, uncorrected) stronger responses to stimuli with gaze motion than to static faces was found in the right amygdala (MNI coordinates: $x = 15$, $y = -6$, $z = -15$; $Z = 2.26$; $k = 32$). Even at this low threshold, no significant influence of gaze direction on amygdala responses was found for the static or the dynamic conditions.

Effective connectivity analysis as a function of social significance of gaze

The PPI analysis across the whole brain revealed a significant increase in functional coupling of the right pSTS with several visual

areas including the right FG (MNI coordinates: $x = 33$, $y = -69$, $z = -12$; $Z = 3.75$; $k = 85$ voxels; $p < 0.05$, corrected at cluster level) when eye gaze shifted toward as compared to away from the viewer. In addition, the ROI analyses (see Materials and methods) also revealed significantly increased effective connectivity for the contralateral pSTS, bilateral pMTG, and most importantly right alns (all $p < 0.05$, SVC corrected). Other brain areas that showed enhanced coupling with the right pSTS at the more liberal threshold ($p < 0.01$,

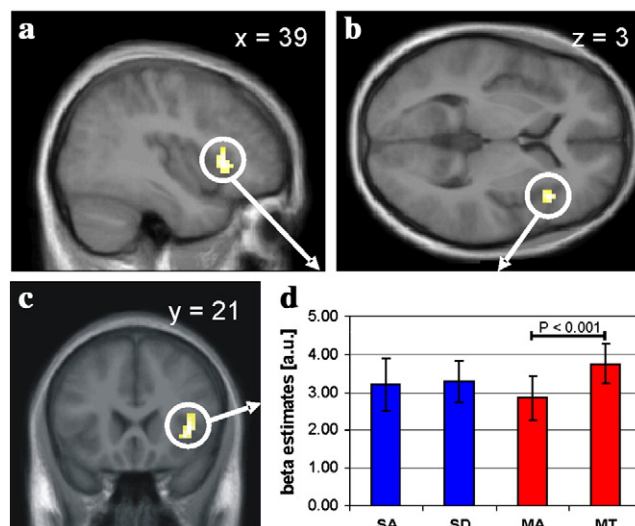


Fig. 3. Stronger activation ($p < 0.001$, uncorrected) to gaze shifts towards (MT) rather than away (MA) from the viewer were observed in the right anterior insula (mean $\pm$ standard error), shown here on sagittal (a), horizontal (b) and coronal (c) slices. Average parameter estimates of activity (betas) are plotted (d) for stimuli with (red bars) and without (blue bars) gaze motion. SD = static direct, SA = static avert.

Table 1

Brain regions activated stronger by faces with than without gaze shift.

Anatomical definition	MNI coordinates	Z score	Cluster size
Left pSTS	−51 −54 15	4.52	168*
Left pMTG	−48 −72 6	4.31	175*
Right pSTS	60 −45 0	4.29	183*
Right pMTG	45 −66 6	4.18	188*
Left IFG	−48 18 18	3.60	35
Right FG	45 −45 −18	3.57	23

* $p < 0.05$, corrected at cluster level ($k > 50$ voxels) across the whole brain.

uncorrected) included bilateral IPS and bilateral prefrontal cortex (including a region at the junction of the precentral and superior frontal sulcus likely to correspond to the FEF, see Fig. 4, Table 2). There was no significant increase in connectivity for the reverse comparison of MA>MT.

Structural connectivity analysis

We next conducted a probabilistic fiber tracking analysis with pSTS and pMTG in both hemispheres as seed regions. Tables 3 and 4 summarize all brain areas (as defined in the standardized anatomical atlas IBASPM) showing direct white-matter connections with at least one of these seed regions in more than half of the subjects. Both left and right pSTS (Table 3) were consistently connected to neighboring structures in superior, middle and inferior temporal gyrus as well as to the angular, supramarginal, and middle occipital gyrus. Fiber connections with the inferior occipital gyrus (IOG) were found for all subjects in the left, but only for three subjects in the right hemisphere (see Figs. 5a and b). This asymmetry in connection frequency was highly significant (chi-square = 30.01, $p < 0.001$) and cannot be explained by poor DTI signal for these regions because, in sharp contrast, the white-matter connections from pMTG were found to be very symmetrical (see later discussion).

The most consistent long-range fiber connection (20 of 22 subjects) of the right pSTS projected via the superior longitudinal fasciculus (SLF) to a region in right alns (Table 3). Remarkably, the latter overlapped with the region found to be sensitive to social significance of direct gaze in our fMRI analysis (see Figs. 5c and e) and showing increased functional coupling with right pSTS in this condition (see Table 2). By contrast, fibers originating from the left pSTS terminated more dorsally in left prefrontal cortex, near a cluster in the left IFG found to be more generally motion-sensitive in our fMRI analysis (Table 1). Only infrequent connections (9/22) were found between pSTS and alns on the left side. This hemispheric asymmetry in frequency of white-matter fibers between pSTS and alns was highly significant (chi-square = 10.12, $p = 0.0015$). In addition, areas in the inferior frontal gyrus (IFG), particularly its triangular and orbital parts, were also more consistently connected with the pSTS in the right than the left hemisphere. Finally, connections to the posterior part of the inferior parietal lobe (IPL) were found in both hemispheres for most subjects (see Figs. 5a and b).

The pMTG (Table 4) showed a very symmetric short-range connectivity pattern in both hemispheres, with direct fibers to fusiform cortex, angular gyrus, and several visual areas in most subjects (Table 3). For long-range connections, we also found a similar connectivity pattern in both hemispheres, with the most consistent fibers projecting toward the posterior insula and amygdala, but also to a lesser degree to the parahippocampal regions, temporal poles, and inferior frontal regions. The finding of consistent connections of the amygdala with pMTG might be related to the fact that motion (particularly when it is unexpected or related to approaching stimuli) may also often constitute a behaviorally relevant event, necessitating a short pathway between motion-sensors in pMTG and the amygdala, allowing fast detection and appropriate reactions. By contrast, the

Table 2

Brain regions showing increased functional connectivity with right pSTS as a function of social significance of gaze shifts (PPI).

Anatomical definition	MNI coordinates	Z score	Cluster size
Right visual cortex			1088*
Fusiform gyrus	−51 −54 15	3.75**	
Inferior temporal gyrus	−45 −57 −12	3.69	
Posterior middle temporal gyrus	45 −69 9	3.37**	
Calcarine fissure	18 −93 −3	3.27	
Left visual cortex			759*
Middle occipital gyrus	−39 −81 −3	3.69	
Lingual gyrus	−12 −48 −9	3.44	
Calcarine fissure	−9 −96 0	2.78	
Left posterior temporal cortex			178
Posterior middle temporal gyrus	−51 −48 9	3.41**	
Superior temporal sulcus	−63 −33 9	3.22**	
Mediodorsal Thalamus	−3 −30 0	3.33	53
Left posterior middle frontal gyrus	−42 0 −42	3.14	70
Right frontal eye field	21 −3 51	3.08	34
Right superior temporal sulcus	60 −36 6	3.00	48
Right posterior middle frontal gyrus	45 3 36	2.98	145
Left caudate nucleus	−9 6 15	2.96	58
Right supplementary motor area	9 15 57	2.78	42
Right medial superior frontal gyrus	0 42 36	2.71	26
Right intraparietal sulcus	54 −42 45	2.68	22
Right anterior insula	39 18 6	2.67**	25
Left frontal eye field	−30 18 36	2.60	26
Right caudate nucleus	6 6 12	2.54	26
Left middle cingulum	−3 18 36	2.53	30

* $p < 0.05$, corrected at cluster level across the whole brain.

** $p < 0.05$, small volume corrected for region of interest.

extraction of socially relevant information is likely to require more specialized processing in other areas within prefrontal and insular cortex, possibly explaining why no direct connections with the amygdala were found for pSTS.

The most prominent interhemispheric differences were found for connections to the IPL and the superior frontal gyrus, which were observed in most subjects in the left (16 and 15/22, respectively), but not in the right hemisphere (5 and 2/22, respectively). This asymmetry was significant for both target regions (chi-square > 9.11, $p < 0.0025$).

To formally test for the specificity of fiber connections from right pSTS to other distant brain regions, we statistically compared the probabilistic fiber tracking maps obtained with a seed in this region, relative to the maps obtained for the neighboring right pMTG (using a second-level pair-wise group analysis across the whole brain). Results indicated that the right pSTS was significantly more connected to the right IPL and the anterior superior part of the right insula (see Fig. 6, red fibers) overlapping with the region found to be sensitive to social information in eye gaze in the conventional fMRI analysis (contrast MT>MA) and increased its functional coupling with right pSTS during gaze shifts towards the observer. Conversely, the right pMTG was more strongly connected to several areas in the visual cortex plus inferior and medial temporal lobe (see Fig. 6, blue fibers), including the region in FG that reacted more strongly to stimuli with eye motion than to static faces. In addition, fiber connections from pMTG

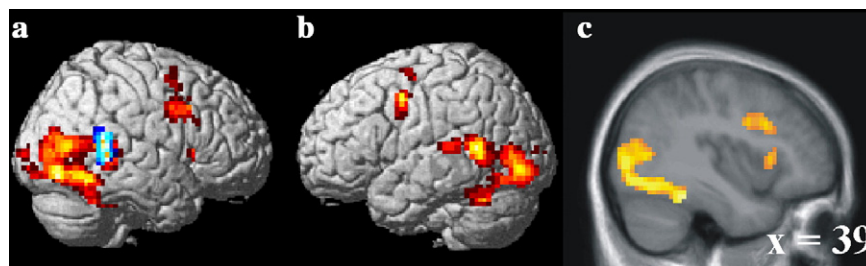


Fig. 4. Brain regions showing an increase of functional connectivity ($p < 0.01$, uncorrected) with the right pSTS (cluster in blue/cyan) in the right (a) and left (b) hemisphere. Sagittal slice (c) at $x = 39$ showing modulation of functional connectivity with the right fusiform gyrus, in addition to middle frontal gyrus and anterior insula.

Table 3
Short-range and long-range fiber connections from pSTS in each hemisphere.

Target region	Seed region	Seed region
	Right pSTS	Left pSTS
<i>Short-range fiber connections</i>		
Superior temporal gyrus	22/22	22/22
Middle temporal gyrus	22/22	22/22
Inferior temporal gyrus	22/22	22/22
Angular gyrus	22/22	22/22
Supramarginal gyrus	22/22	21/22
Middle occipital gyrus	21/22	22/22
Inferior occipital gyrus	3/22	22/22
<i>Long-range fiber connections</i>		
Insula	20/22	9/22
Inferior parietal lobe	17/22	17/22
Inferior frontal gyrus, triangular part	16/22	9/22
Inferior frontal gyrus, opercular part	14/22	12/22
Inferior frontal gyrus, orbital part	12/22	3/22
Rolandic operculum	14/22	8/22
Postcentral gyrus	7/22	13/22

All values correspond to the number of subjects who exhibited a structural connection between the seed and the target areas, among all 22 volunteers who were scanned.

terminated more posterior and inferior within the insular cortex than those from pSTS confirming a distinctive pattern of white-matter connections for right pSTS and pMTG.

Discussion

Our study combined structural and effective connectivity analyses to investigate the neural networks involved in gaze processing. Structural connectivity methods reveal the anatomical connection profile of brain areas, but cannot clarify which of these connections are relevant for specific cognitive processes. On the other hand, effective connectivity analyses disclose networks with increased coupling during a cognitive task, but are blind as to whether such coupling occurs by direct connections or via one or several relays (Friston et al., 1997). Here we combined both approaches to overcome these limitations, and to determine the role of the pSTS in gaze processing.

Table 4
Short-range and long-range fiber connections from pMTG in each hemisphere.

Target region	Seed region	Seed region
	Right pMTG	Left pMTG
<i>Short-range fiber connections</i>		
Middle temporal gyrus	22/22	22/22
Inferior temporal gyrus	22/22	22/22
Middle occipital gyrus	22/22	22/22
Inferior occipital gyrus	22/22	22/22
Fusiform gyrus	22/22	22/22
Angular gyrus	21/22	18/21
Superior occipital gyrus	19/22	19/22
Superior temporal gyrus	18/22	14/22
Cuneus	16/22	11/22
Lingual gyrus	12/22	9/22
<i>Long-range fiber connections</i>		
Insula	19/22	20/22
Amygdala	17/22	19/22
Inferior parietal lobe	5/22	16/22
Hippocampus	13/22	15/22
Superior frontal gyrus	2/22	15/22
Medial orbitofrontal gyrus	11/22	15/22
Temporal pole, middle temporal part	14/22	13/22
Inferior frontal gyrus, orbital part	13/22	13/22
Parahippocampal gyrus	10/22	13/22
Temporal pole, superior temporal part	12/22	11/22

All values correspond to the number of subjects who exhibited a structural connection between the seed and the target areas, among all 22 volunteers who were scanned.

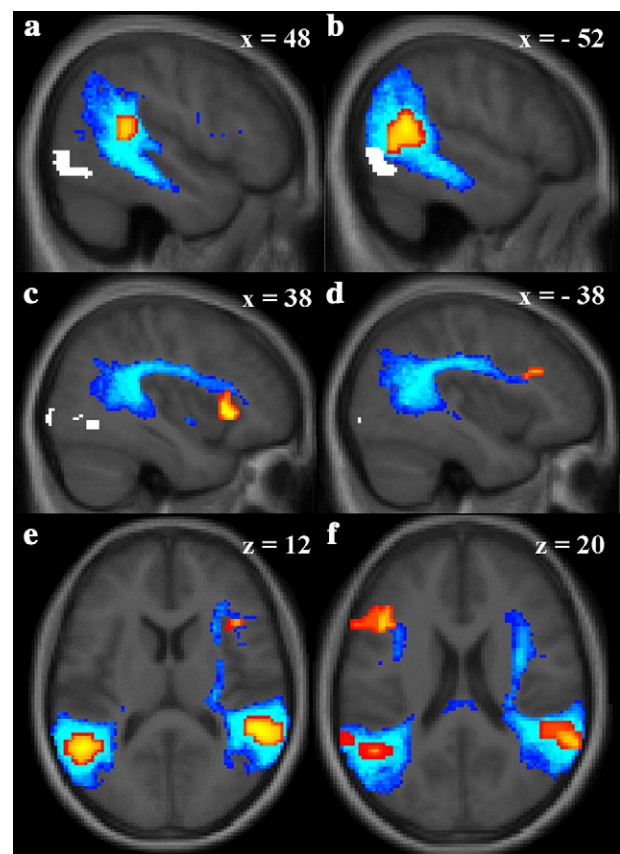


Fig. 5. Fiber tract connections (in blue/cyan) from the right pSTS (activation cluster shown in red/yellow) did not reach the right inferior occipital gyrus (IOG, white area in a), while all subjects had fiber connections between the left pSTS and the left IOG (white area in b). Fiber tracts from the right pSTS projected via the superior longitudinal fasciculus (SLF) to an area in the anterior insula that overlapped with an activation cluster found to be sensitive to social information in gaze (c and e), while projections from the left pSTS terminated more dorsally in the left inferior frontal gyrus, near an activation cluster with global motion-sensitive responses (d and f).

As expected, comparing stimuli with and without gaze shifts revealed bilateral activation in pSTS, a region known to respond to biological motion (Bahnmann et al., 2010; Pelphrey et al., 2003a; Puce et al., 1998), and in pMTG, corresponding to the motion-sensitive MT/V5 complex (Watson et al., 1993). We also found enhanced responses to stimuli with eye motion in the right FG, replicating previous fMRI results (Pelphrey et al., 2004b) and supporting the view that processing of some changeable facial features may recruit the fusiform cortex (Calder and Young, 2005; Fairhall and Ishai, 2007; Nummenmaa and Calder, 2009; Tsuchiya et al., 2008). However, the FG did not differentiate between the two types of gaze shifts. This finding converges with previous fMRI results suggesting that this area is sensitive to an eye motion in general, but not specialized in extracting directional information (Hooker et al., 2003).

We note that we found no significant modulation of the amygdala by social content of gaze. However, previous studies have reported various effects of gaze processing in the human amygdala, including enhanced activity to either direct gaze (Kawashima et al., 1999) or averted gaze (Hadjikhani et al., 2008; Staube et al., 2010) or, as in our study, no differential activity for the two gaze directions with static (Wicker et al., 1998) or dynamic stimuli (Pelphrey et al., 2003b; Pelphrey et al., 2004b). Possible explanations for this inconsistency include a low signal-to-noise ratio, since fMRI of subnuclei of the amygdala in monkeys has shown that gaze specific responses are restricted to the central nucleus and the bed nucleus of the stria terminalis (Hoffman et al., 2007); or alternatively, interactions with other experimental factors such as head direction, task instructions, or

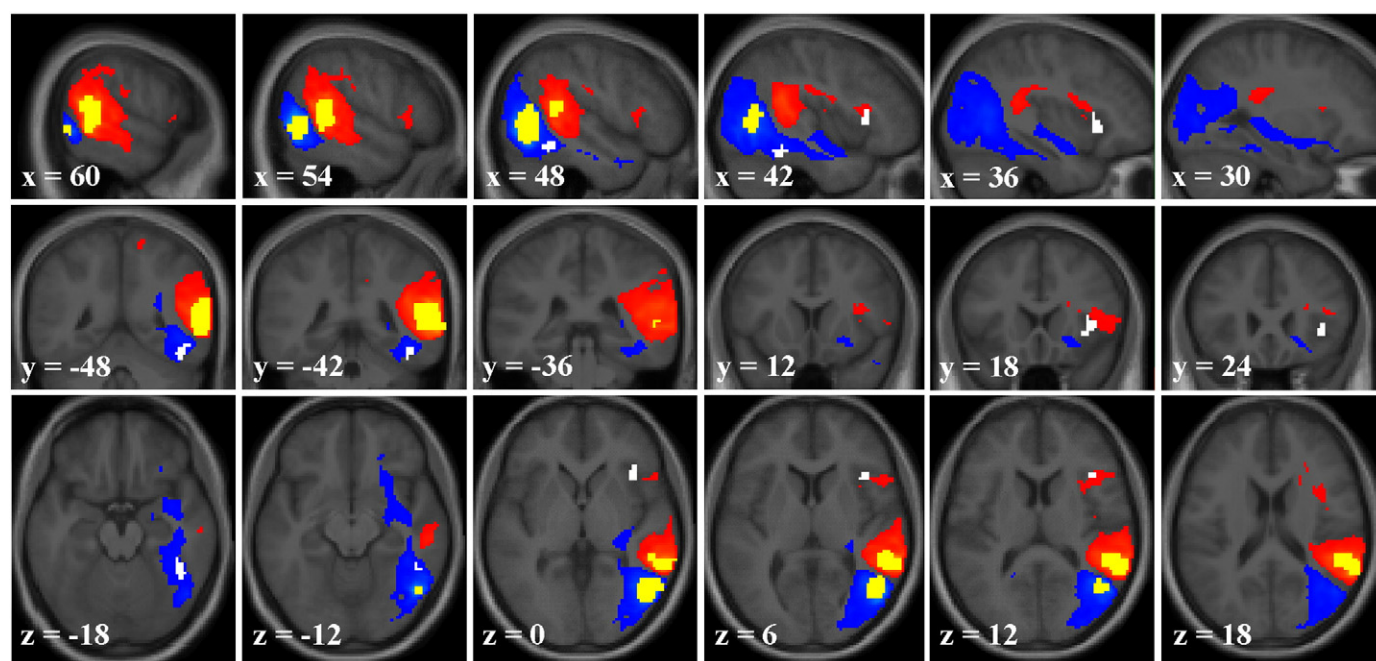


Fig. 6. Statistical comparison ($p < 0.001$, uncorrected) of connections originating from right pSTS and right pMTG (seed areas in yellow). Significantly stronger fiber connections from right pSTS (red tracts) terminated in the cluster in the right anterior insula sensitive to eye gaze direction (white area). Fiber connections from the right pMTG (blue tracts) terminated in and around the motion-sensitive cluster in the fusiform gyrus (white area).

facial expressions may also modulate the type and magnitude of amygdala responses (Adams et al., 2003; N'Diaye et al., 2009).

Recent studies using interactive eye tracking paradigms (Wilms et al., 2010) in which study participants could actively draw the attention of a virtual partner to a certain object in space (Schilbach et al., 2010b) demonstrated increased responses within the medial prefrontal cortex during joint attention. Furthermore, a linear dependency of MPFC activity and gaze duration has been found (Kuzmanovic et al., 2009). In our study, activity within the MPFC was neither influenced by gaze motion or direction of gaze shifts. This negative finding is probably due to the fact that our paradigm did not involve instructions to interact with the presented faces and is in agreement with previous studies investigating gaze processing on a purely perceptual level (Hoffman and Haxby, 2000; Kawashima et al., 1999; Nummenmaa et al., 2009; Pelphrey et al., 2003b, 2004b; Wicker et al., 1998).

Location and functional properties of pSTS

The pSTS area responding to gaze shifts was slightly more posterior in the left than right hemisphere, consistent with other neuroimaging experiments (Pelphrey et al., 2005, 2003b, 2004b; Puce et al., 1998). This asymmetry accords with a posterior displacement of the whole left STS (Ochiai et al., 2004), reflecting the increased size of the planum temporale in the language-dominant hemisphere (Geschwind and Levitsky, 1968). A similar shift was observed for STS regions integrating emotional signals from voice and face (Ethofer et al., 2006; Kreifelts et al., 2007).

We found that the pSTS region discriminated between gaze shifts with different social meaning, and preferentially responded to eye motion toward the viewer. This accords with the findings that this area may distinguish between gaze signaling approach and avoidance (Pelphrey et al., 2004b). No modulation by the social meaning of gaze shifts was found in left pSTS (or pMTG on either side). Accordingly, recent studies suggested that the left pSTS may process the causality of biological motion (Morris et al., 2008) and integrates biological motion with language (Holle et al., 2010; Willems et al., 2009), whereas the right pSTS is more specifically engaged by emotional and social information (Blakemore et al., 2004).

Modulation of connectivity with right pSTS during gaze processing

The PPI analysis demonstrated that the social significance of gaze shifts modulated the effective connectivity of right pSTS with other core regions of the gaze processing network (Puce et al., 1998), including the contralateral (left) pSTS and bilateral motion-sensitive regions in pMTG. Most critically, gaze shifts toward the viewer increased connectivity with the right alns, overlapping with the site receiving direct fiber connections from ipsilateral pSTS, but also enhanced the coupling with bilateral IPS and FEF, which belong to the dorsal attention system, and with the bilateral MFG, which is thought to constitute an interface between the ventral and dorsal attention systems (Corbetta et al., 2008). Changes in effective connectivity within these attention-related areas might be induced through direct pathways from pSTS to right alns and subsequent projections to MFG. These fMRI results provide novel insights concerning the influence of eye gaze on networks mediating attention and cognitive control.

In keeping with our findings, Nummenmaa et al. (2009) also observed connectivity changes between right pSTS and parts of the attentional system during perceived gaze shifts. However, eye motion in their study did not imply social attention toward the viewer (i.e. gaze shifted from one averted position to the other), and stimuli were presented in a block-design making the occurrence of such shifts predictable for the participants. This might explain why their study did not observe increased coupling with the right alns, which appears primarily involved in stimulus-triggered reorienting of attention (to unexpected behaviorally relevant stimuli, Corbetta et al., 2008).

In addition, we found significant changes in pSTS connectivity with early visual cortices and right FG during direct gaze shifts, suggesting that visual processing is up-regulated by socially relevant information in this condition. Notably, these effects also affected the right FG which is typically recruited during processing of invariant facial features, such as identity (Haxby et al., 2000; Hoffman and Haxby, 2000). This result adds to increasing evidence that these ventral extrastriate visual areas are also involved in encoding changeable features of faces in some conditions (Calder and Young, 2005), and suggests that gaze motion toward the viewer could trigger face recognition mechanisms in order to identify the person who is

interested in social contact. However, because DTI showed no direct fiber connections between pSTS and early visual areas or FG, we propose that these changes in effective connectivity occurred via other brain regions, possibly involving projections from pMTG which exhibited strong structural connectivity with pSTS as well as FG and lateral occipital areas. The pMTG region is indeed well placed to send visual motion information to both pSTS and FG. Moreover, the right FG was found to be sensitive to eye motion, but not to the social significance of gaze direction (unlike right aIns), consistent with more direct links with motion-sensitive processing in pMTG, rather than higher-level social functions mediated by pSTS.

Anatomical fiber connections of pSTS

To our knowledge, this is the first study investigating the structural connectivity of the gaze network. We show that, in both hemispheres, pSTS is densely connected with neighboring structures including motion-sensitive areas within pMTG. However, we found no direct fiber connections from pSTS to lower-order visual cortices, suggesting a hierarchy of information processing in which modules specialized for biological motion in pSTS receive their inputs from motion-sensitive areas in pMTG.

A striking difference between the short-distance connections of right and left pSTS concerned the frequency of direct fibers to IOG, which were present in all participants in the left, but only three participants in the right hemisphere. These findings converge with an fMRI study reporting that the left, but not the right IOG responds stronger to dynamic than to static faces (Schultz and Pilz, 2009), and suggest a direct interaction between left pSTS and IOG that may contribute to the perception of dynamic facial features. However, the exact role of this pathway, and its specificity for facial movements with linguistic or communicative functions (e.g. lip reading), need further investigation.

Another striking asymmetry was found in favor of the right pSTS. The most consistent long-range connections from this region ran through the SLF and terminated in the right aIns, overlapping with a region modulated by the social meaning of gaze shifts. These connections were much weaker in the left hemisphere, where the aIns is thought to be part of the language network (Dronkers, 1996). The right aIns, abutting the lower IFG, plays a crucial role in the ventral attention system that is recruited by unexpected but behaviorally relevant stimuli (Corbetta et al., 2008). It is a core region of networks mediating cognitive control and goal-oriented behavior (Dosenbach et al., 2006), particularly for implementing current task sets and monitoring performance (Taylor et al., 2007) and is also generally implicated in the appraisal of affective or motivational self-relevance (Schmitz and Johnson, 2007). Its structural and functional connectivity with right pSTS, as revealed here, suggests that aIns may provide a central hub between gaze processing and cognitive control systems, serving to reorient attention and switch current mental set in response to perceived eye contact.

In contrast, fibers from the left pSTS projected to a motion-sensitive cluster in dorsal left IFG that was insensitive to social aspects of eye gaze in our study, but has been shown to exhibit pronounced activation during execution of motor responses that are incongruent to observed gaze shifts (Schilbach et al., 2010a). Thus, these direct connections might underlie inhibitory control during perception of eye motion. Furthermore, these direct connections with left IFG nicely dovetail with fMRI findings demonstrating coactivations (Holle et al., 2010) and effective connectivity (Willems et al., 2009) of left pSTS and IFG during integration of speech and gestures. Finally, both left and right pSTS were connected with posterior parts of the ipsilateral IPL. This accords with tracer studies in monkeys (Cusick et al., 1995) and the notion that the posterior parietal cortex is involved in visuospatial processing (Orban et al., 2006). Future studies should address the question whether these connections might subserve interactions

between pSTS and parietal systems that mediate non-social effects of biological motion on visual attention (Hoffman and Haxby, 2000; Nummenmaa et al., 2009; Vuilleumier, 2002).

Conclusion

By combining structural and effective connectivity analyses, our study provides new insights on network underlying gaze perception. Our findings confirm the role of right pSTS in processing of socially relevant biological motion such as eye gaze (Pelphrey et al., 2004b). We show that direct long-range fiber connections of right pSTS project via the SLF to the right aIns, and that social significance of gaze shifts modulates neural coupling between these two areas. Increased functional connectivity during gaze shifts toward the viewer was also found between right pSTS and visual areas, including FG, but the lack of direct fibers between these two regions indicate that such modulations may occur via other areas, such as pMTG. Right FG was sensitive to eye motion, but not social meaning, whereas right aIns specifically reacted to the social significance of direct gaze shifts. Based on these anatomical and functional properties, we propose that social information expressed by gaze is processed by projections from pSTS to aIns to control attention and goal-oriented behavior, while interactions with pMTG and FG influence the perceptual analysis of facial features (e.g. identity).

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