

Lateralization in intrinsic functional connectivity of the temporoparietal junction with salience- and attention-related brain networks

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Kucyi A, Hodaie M, Davis KD. Lateralization in intrinsic functional connectivity of the temporoparietal junction with salience- and attention-related brain networks. *J Neurophysiol* 108: 3382–3392, 2012. First published September 26, 2012; doi:10.1152/jn.00674.2012.—Neuroimaging studies have demonstrated that the right temporoparietal junction (TPJ) is activated during detection of salient stimuli, including pain, in the sensory environment. Right TPJ damage more often produces spatial neglect than left TPJ damage. We recently reported a right lateralized system of white matter connectivity of the TPJ. However, lateralization in intrinsic TPJ functional connectivity during a task/stimuli-independent state has not been fully characterized. Here we used resting-state functional MRI in healthy humans to compare the functional connectivity of right and left TPJ with salience- and attention-related brain networks. Independent components analysis revealed that both right and left TPJ were functionally connected with a network that included the anterior insula, dorsolateral prefrontal cortex (PFC), and mid-cingulate cortex, considered to be the salience/ventral attention network. Dual regression revealed this network was more strongly connected with right TPJ than left TPJ. Seed-based functional connectivity analysis showed 1) negative connectivity the TPJ bilaterally with the “default mode network”; 2) positive connectivity of TPJ bilaterally with the salience/ventral attention network; 3) stronger connectivity between right TPJ compared with left TPJ with regions within the salience/ventral attention network and mid-insula, S2, and temporal/parietal opercula (implicated in pain); and 4) stronger connectivity of left TPJ compared with right TPJ with the “executive control network,” including the dorsomedial/medial PFC, inferior frontal gyrus, and cerebellum (crus I/II). Our findings build on classic lesion and neuroimaging studies, demonstrating a complex spatial network organization of lateralization in TPJ functional connectivity in the absence of an overt stimulus.

attention; functional connectivity; pain; salience; temporoparietal junction

THE RIGHT TEMPOROPARIETAL JUNCTION (TPJ) responds robustly and consistently to sensory inputs that are novel and salient, regardless of sensory modality (Downar et al. 2000, 2001, 2002, 2003). Stimulus-driven activations of the right TPJ are typically reported together with responses in other ventral regions in the right hemisphere, most commonly the anterior insula (aINS) and inferior frontal gyrus (IFG), suggesting that these regions encompass a right-lateralized “ventral attention network” (Corbetta et al. 2008). Regions within the ventral

attention network also encode the prolonged salience of pain (Downar et al. 2003) and show remarkable overlap with the primary regions that are damaged in stroke-induced spatial neglect (Corbetta and Shulman 2011).

The left TPJ is not generally classified as being part of the ventral attention network. Some studies have found that it can respond in tandem with the right TPJ during stimulus-driven attention (Asplund et al. 2010; Downar et al. 2000, 2001), albeit less frequently than right TPJ (Corbetta and Shulman 2011). DiQuattro and Geng (2011) recently provided evidence for a “left hemisphere homolog” of the right-lateralized ventral attention network, involving the left TPJ and IFG, which may be sensitive to contextual relevance of sensory stimuli rather than salience, per se. However, the function of the left TPJ remains poorly investigated and understood.

The coactivation of the right and left TPJ with other regions suggests that each TPJ functions as part of an integrated network rather than in isolation. Such TPJ networks can be delineated with MRI-based structural and functional connectivity. One approach to uncovering the basis of lateralization in TPJ function is to study structural connectivity between the TPJ and regions involved in stimulus-driven attention. We recently used diffusion MRI and probabilistic tractography to demonstrate that there is stronger TPJ-insula connectivity in the right compared with left hemisphere (Kucyi et al. 2012). Another tractography study reported that subcomponent III of the superior longitudinal fasciculus, an association fiber pathway that putatively connects frontal with parietal regions of the ventral attention network, is larger in the right compared with left hemisphere (Thiebaut de Schotten et al. 2011). These findings provide an anatomical framework for a right-lateralized ventral attention network involved in salience detection. However, the implications for functional brain network organization remain unknown.

Resting-state functional MRI (rs-fMRI) and functional connectivity analysis is an emerging experimental approach that provides complementary information to diffusion MRI and task fMRI studies. In rs-fMRI, data are acquired while subjects are not engaged in any particular task. Despite the unconstrained nature of this paradigm, a highly consistent finding is that specific sets of brain regions, comprising “intrinsic connectivity networks” (ICNs), exhibit correlated temporal fluctuations in activity predominantly in the infra-slow frequency range (0.01–0.1 Hz) (Beckmann et al. 2005; Damoiseaux et al. 2006). Regions exhibiting this functional connectivity are thought to be working together as a functional unit and may be

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anatomically connected (although not necessarily through monosynaptic connections) (Honey et al. 2009). Additionally, ICNs resemble patterns of brain regions that commonly coactivate with one another, suggesting that these networks are behaviorally relevant (Laird et al. 2011; Smith et al. 2009). Notably, rs-fMRI studies have provided important insights into hemispheric asymmetry in brain organization (Cauda et al. 2011; Liu et al. 2009).

The complementary approaches of seed-based connectivity analysis and independent components analysis (ICA) have previously been used to identify and investigate the intrinsic functional connectivity of the TPJ with the rest of the brain. Using the time courses of the right TPJ and ventral frontal cortex for seed-based correlation analysis, Fox et al. (2006) showed that the ventral attention network exhibits functional connectivity at rest in a predominantly (but not exclusively) right-lateralized fashion. Other reports, using ICA, have shown that bilateral regions within the vicinity of the TPJ are part of the “salience network,” which includes the aINS, ventral frontal cortex, mid-cingulate cortex (MCC), and dorsolateral prefrontal cortex (dlPFC) (Seeley et al. 2007; Weissman-Fogel et al. 2010). The connectivity of the TPJ with these bilateral regions was confirmed in an rs-fMRI study using a clustering approach in a very large subject sample ($N = 1,000$) (Yeo et al. 2011). The authors referred to the network as the “ventral attention network” (Yeo et al. 2011), so the distinction between salience and ventral attention networks remains unclear. Lateralization in intrinsic functional connectivity of the TPJ with the salience/ventral attention network has not been fully characterized.

Here we aimed to compare and contrast the resting functional connectivity of the right and left TPJ with salience- and attention-related brain networks using ICA, dual regression, and seed-based connectivity analysis. On the basis of our previous task fMRI and structural MRI studies, we hypothesized that the right TPJ would be more strongly connected with the salience/ventral attention network as well as regions involved in stimulus-driven attention and pain. Given previous findings that the left TPJ responds less frequently to salient stimuli than the right TPJ and that the left TPJ activity may be sensitive to contextual integration of sensory input, we hypothesized that the left TPJ would be more strongly connected with regions involved in top-down attention.

METHODS

Subjects and image acquisition. Subjects were 28 right-handed adults (13 females, 15 males; age 28.8 ± 4.3 , mean $\pm$ SD) with no history of neurological or psychiatric illness. Informed written consent was obtained from all study participants for procedures approved by the University Health Network Research Ethics Board.

All subjects underwent MRI in a 3T GE MRI system fitted with an 8-channel phased-array head coil. Resting-state blood oxygen level-dependent (BOLD) fMRI was acquired during a 5-min 8-s period using T2*-weighted echo-planar imaging with the following parameters: TR = 2,000 ms, TE = 40 ms, flip angle = 45° , 28 axial slices per volume, 64×64 matrix, $3.125 \times 3.125 \times 4$ -mm³ voxels. During this scan, subjects were instructed to close their eyes and not to think of anything in particular but not to fall asleep. High-resolution whole brain T1-weighted anatomical scans were also acquired using a three-dimensional inversion recovery-prepared fast spoiled gradient recalled (IR-FSPGR) sequence with the following parameters: 160 axial slices, $0.94 \times 0.94 \times 1.0$ -mm³ voxels, 256×256 matrix, field

of view = 24×24 cm, flip angle = 20° , TE = 5 ms, TR = 12 ms, TI = 300 ms. All analyses were conducted using FSL (FMRIB's Software Library v.4.1, <http://www.fmrib.ox.ac.uk/fsl/>) (Smith et al. 2004). Data were visualized using Caret (<http://brainvis.wustl.edu/wiki/index.php/Caret>About>) and FSLview.

Independent components analysis: identification of the salience/ventral attention network. We first conducted spatial group ICA to identify the TPJ as part of the salience/ventral attention network, using the Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC v3.10) toolbox implemented in FSL (Beckmann and Smith 2004). Preprocessing of each subject's raw resting-state data involved the following elements: deletion of the first 6 volumes, high-pass filtering (0.01-Hz cutoff), motion correction with FMRIB's Linear Image Registration Tool (FLIRT) (Jenkinson et al. 2002), non-brain substance removal using the brain extraction tool (Smith 2002), spatial smoothing with a 5-mm full-width at half-maximum kernel, and linear registration between T2*-weighted and T1-weighted space (7 degrees of freedom) as well as between T1-weighted space and 2-mm³ standard MNI152 stereotaxic space (12 degrees of freedom). Mean head motion across subjects, as indicated by the absolute mean displacement of each brain volume relative to the previous volume reported by FLIRT, was 0.15 ± 0.13 mm.

The time courses from all subjects were then variance-normalized to improve component estimation (Beckmann and Smith 2004) and temporally concatenated across subjects. We then interrogated 25 components to identify the salience/ventral attention network. We limited the number of output components to 25 because previous studies suggest that this number of components should be suitable for identifying the salience network (Habas et al. 2009; Shirer et al. 2012; Uddin et al. 2011). The components were visually inspected to identify the salience/ventral attention network as a component that included the aINS, MCC, and dlPFC after stringent thresholding at $Z > 4.6$.

Dual regression: comparison of left and right TPJ connectivity with the salience/ventral attention network. We next used a previously described and validated dual-regression procedure (Filippini et al. 2009; Zuo et al. 2010) that provides a method to compare functional connectivity strength of the right vs. left TPJ with the salience network. Dual regression is a statistical approach that can be applied after group ICA and involves a first regression that uses group-level spatial components to find time courses associated with each component in each individual, followed by a second regression that uses the individual time courses to find subject-specific functional connectivity maps for each component. To perform the first regression, we used unthresholded group-level spatial components as regressors for each individual's preprocessed fMRI data. This produced a time series for each component in each subject. These time series were then used as temporal regressors for each individual's preprocessed fMRI data, resulting in statistical parametric maps representing functional connectivity strength of each voxel with each component. We then transformed these maps to standard space and defined regions of interest as 6-mm-diameter spheres surrounding center-of-gravity coordinates of the clusters for the right TPJ ($x = 62$, $y = -36$, $z = 28$), left TPJ ($x = -64$, $y = -44$, $z = 28$), right aINS ($x = 38$, $y = 14$, $z = 0$), left aINS ($x = -38$, $y = 12$; $z = -2$), right dlPFC ($x = 32$, $y = 50$, $z = 20$), and left dlPFC ($x = -32$, $y = 50$, $z = 20$) in the group-ICA salience/ventral attention network. We similarly defined regions of interest for the left MCC ($x = -6$, $y = 28$, $z = 24$) and right MCC ($x = 6$, $y = 26$, $z = 24$) but used peak rather than center-of-gravity coordinates in the group-ICA salience/ventral attention network so that these regions of interest did not cross the midline. All of the bilateral region pairs are close to being mirror images, except the right TPJ is more anterior than the left TPJ, which is consistent with previous studies (Downar et al. 2000, 2001; Kucyi et al. 2012). These regions of interest were then transformed back to individual functional space, and the mean functional connectivity scores (Z values) were extracted. Two-tailed paired t -tests were used to compare mean Z

values of the right vs. left TPJ across the 28 subjects. Furthermore, to examine the specificity of lateralization in TPJ connectivity, we computed a lateralization index (Kucyi et al. 2012) for each major node in salience/ventral attention network (aINS, MCC, dlPFC, TPJ) as follows:

Lateralization Index

$$= \frac{(\text{Right} - \text{Left functional connectivity } z \text{ score})}{(\text{Right} + \text{Left functional connectivity } z \text{ score})}$$

One-sample *t*-tests were conducted on these lateralization index values for each node with significance level set at $P < 0.05$ (Bonferroni corrected).

Whole brain seed-based connectivity analysis: lateralized wide-spread connectivity with the right and left TPJ. We conducted a seed-based connectivity analysis to identify brain regions that have either similar or different connectivity with the right vs. left TPJ. For this analysis, we first used FLIRT to perform motion correction and registration on the raw fMRI data. To minimize the contributions of nonneuronal noise in the data (e.g., heart rate/respiration, scanner-related drift), we implemented the aCompCor method (Behzadi et al. 2007) following the general procedures of Chai et al. (2012). We used the aCompCor method instead of global signal regression (GSR) because GSR does not account for the complex spatiotemporal patterns of noise in rs-fMRI data and introduces spurious negative functional connectivity in seed-based analyses (Murphy et al. 2009). White matter (WM) and cerebrospinal fluid (CSF) masks were obtained using FMRIB's Automated Segmentation Tool (FAST) (Zhang et al. 2001) on the T1-weighted images. The segments were thresholded at a partial volume fraction of 0.99, binarized, and then registered to functional space. To further reduce the effects of partial voluming, we thresholded these transformed images at intensities of 0.55 for CSF and 0.85 for WM. We then applied a three-dimensional nearest neighbor criteria to erode the WM further (this was not done for the CSF mask, which was already too small to be eroded further). Using the time series within these conservative WM and CSF masks, we performed principal components analysis in MATLAB (v7.12.0, <http://www.mathworks.com/products/matlab/>) and regressed out the first five components of each mask from the motion-corrected whole brain images. Subsequently, we regressed out the six motion parameters estimated with FLIRT. Brain extraction (Smith 2002), bandpass temporal filtering (0.01–0.1 Hz), and spatial smoothing (6-mm full-

width at half-maximum kernel) were then performed. The resulting preprocessed images were used for seed-based connectivity analysis.

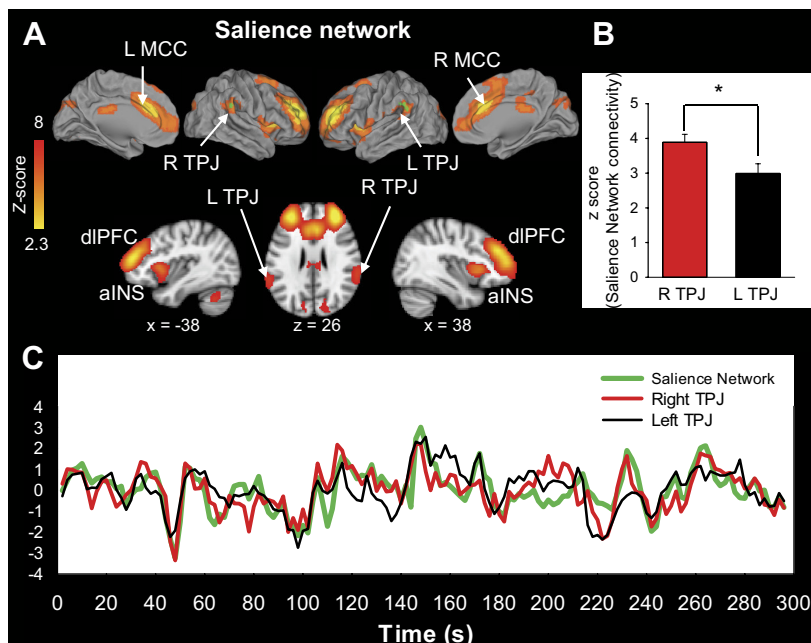
The seed regions in the right and left TPJ were defined in standard space using 6-mm-diameter spheres surrounding the center-of-gravity coordinates of the right and left TPJ clusters in the salience network obtained with ICA (see above). These TPJ seeds overlapped with spatial clusters previously reported to be part of the salience network (Seeley et al. 2007; Weissman-Fogel et al. 2010; Yeo et al. 2011). The seeds were converted to each individual's functional scan space using the affine transformation matrices obtained with FLIRT. The mean time series for each seeds' voxels were then extracted from the preprocessed images.

The preprocessed images were used for first-level analyses with the FMRIB Expert Analysis Tool (FEAT). We first identified the overall connectivity of the right and left TPJ and the regions where the seeds' connectivities overlap. To do this, we used a model for the right TPJ and another model for the left TPJ, each with regressors constructed from the seed time series. We then identified differences in connectivity of the two seeds using a third model that included the time series of both the right and left TPJ. Second-level analyses were conducted using FMRIB's Local Analysis of Mixed Effects (FLAME) with contrasts designed to identify right TPJ connectivity, left TPJ connectivity, right TPJ > left TPJ connectivity, and left TPJ > right TPJ connectivity. The significance level was set at a family-wise error-corrected threshold of $Z > 2.3$ and a cluster-based threshold of $P < 0.05$. For the purpose of visualizing regions where the right and left TPJ have common connectivity, the significant voxels from the second-level right TPJ only and left TPJ only models were overlaid.

RESULTS

Identification of the salience/ventral attention. The ICA component reflecting the salience/ventral attention network was identified from the group ICA results based on visual inspection (Fig. 1A). Consistent with previous reports (Habas et al. 2009; Seeley et al. 2007; Weissman-Fogel et al. 2010) and meeting our definition criteria, this component included the bilateral aINS, dlPFC (BA 46), and MCC (BA 24). In addition, this component included the TPJ (BA 40/22/39), posterior cingulate cortex (PCC; BA 23), cuneus (BA 17), right putamen, and right cerebellum (predominantly lobule VI/crus I).

Fig. 1. A: the salience network, derived from group independent components analysis (ICA) of 28 healthy human subjects, with the temporoparietal junction (TPJ) seed regions used in subsequent analyses shown. L, left; R, right; aINS, anterior insula; dlPFC, dorsolateral prefrontal cortex; MCC, mid-cingulate cortex. B: dual-regression results revealing stronger connectivity of right TPJ than left TPJ with the salience network ($*P = 0.0043$). C: example plot from a single subject who exhibited stronger functional connectivity of the salience network with the right TPJ than with the left TPJ. The salience network signal time course was extracted by using the group-level ICA spatial component as a regressor for the subject's preprocessed functional MRI data (part of the dual-regression approach, described in METHODS), and the TPJ time series were extracted from preprocessed data.



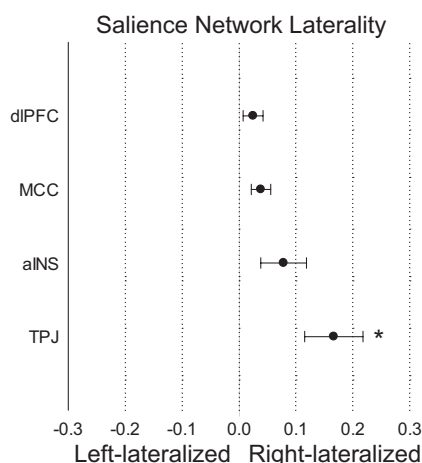


Fig. 2. Plot of lateralization index values (means $\pm$ SE) across 28 subjects for functional connectivity of the dlPFC, MCC, aINS, and TPJ with the salience/ventral attention network (* $P < 0.05$, Bonferroni-corrected 1-sample t -test).

Lateralization in connectivity of the TPJ with the salience/ventral attention network. Connectivity with the salience/ventral attention network was greater for the right TPJ than for the left TPJ ($P = 0.0043$) based on extracting the functional connectivity (Z) values for TPJ regions of interest obtained from dual regression of the group ICA (Fig. 1B). Example data from a single subject who exhibited stronger connectivity of

the salience/ventral attention network with the right TPJ than with the left TPJ are shown in Fig. 1C. For this subject, the frequency of salience/ventral attention network activity fluctuations was ~ 0.05 Hz. One-sample t -tests of lateralization index values confirmed significant right-lateralized connectivity of the TPJ ($P = 0.003$) and indicated trends (at the uncorrected level) toward right-lateralized connectivity of the aINS ($P = 0.06$), MCC ($P = 0.03$), and dlPFC ($P = 0.17$) with the salience/ventral attention network (Fig. 2).

Lateralized functional connectivity of the TPJ with the whole brain. Seed-based analysis of the right TPJ revealed significant positive functional connectivity with bilateral TPJ, insula, MCC, dlPFC, and PCC, as well as frontal, temporal, and parietal regions (Fig. 3A; see Table 1 for full list). Seed-based analysis of the left TPJ revealed significant positive functional connectivity with the bilateral TPJ, insula, MCC, and dlPFC, as well as frontal and temporal regions (Fig. 3A; see Table 1 for full list). The conjunction analysis revealed large clusters of overlap in positive functional connectivity of the right and left TPJ with the bilateral TPJ (BA 40/22/39), anterior/mid insula, ventrolateral PFC (BA 44/47/12), MCC (BA 24), PCC (BA 23/31), dlPFC (BA 46), and middle temporal gyrus (BA 37) (Fig. 3B).

Significant negative functional connectivity of the right TPJ was found with the medial prefrontal cortex (mPFC), PCC/precuneus, lateral parietal cortex (LPC), an area within the

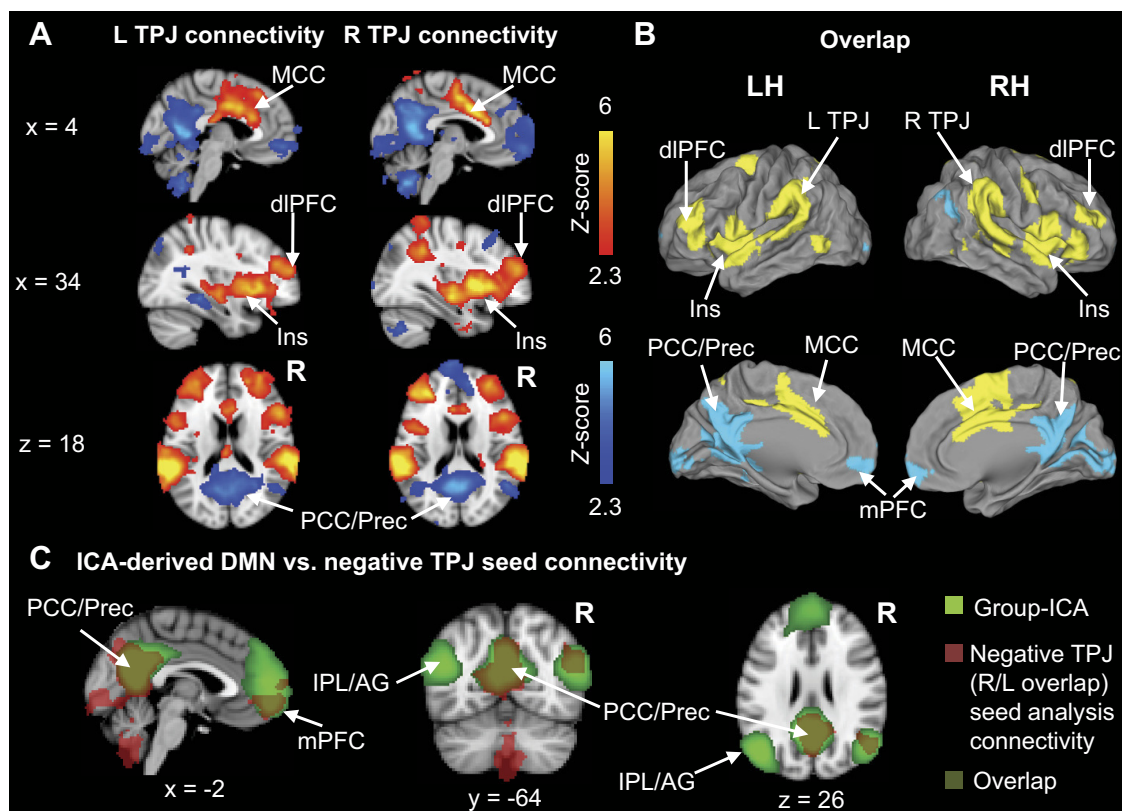


Fig. 3. A: results for seed-based connectivity analysis of the left TPJ and right TPJ, displaying regions that exhibit significant positive (red/yellow) and negative (blue) functional connectivity with each seed region (family-wise error corrected at $Z > 2.3$, cluster-based threshold of $P < 0.05$). Ins, insula; PCC, posterior cingulate cortex; Prec, precuneus. B: overlap of regions that exhibit significant positive (yellow) and negative (blue) connectivity with both the right and left TPJ. LH, left hemisphere; RH, right hemisphere. C: results from the negative TPJ seed connectivity contrast (right/left overlap) overlaid on the group ICA-derived component representing the default mode network. Red indicates overlap of right/left TPJ seed negative connectivity contrast; green indicates group ICA-derived default mode network (DMN); and olive indicates overlap of red and green areas. Both maps are thresholded at $Z > 2.3$. AG, angular gyrus; IPL, inferior parietal lobule.

Table 1. Peak MNI coordinates for regions exhibiting positive functional connectivity with the right and left TPJ

L TPJ Positive Connectivity					R TPJ Positive Connectivity				
Region	$Z_{\max}$	Peak voxel (MNI coordinates)			Region	$Z_{\max}$	Peak voxel (MNI coordinates)		
		x	y	z			x	y	z
TPJ					TPJ				
L TPJ	9.7	-66	-44	28	R TPJ	10.6	64	-36	30
R TPJ	7.4	66	-36	26	L TPJ	7.7	-62	-40	32
R TPJ	7.4	68	-30	28	Insular Cortex				
Insular Cortex					R mINS	7.3	36	6	4
L pINS	6.6	-40	-12	-8	L pINS	7.0	-36	-16	-8
L aINS	5.8	-38	8	-6	Cingulate Cortex				
L pINS	5.8	-38	-10	-14	L MCC	6.3	-6	6	34
Cingulate cortex					L PCC	5.6	-14	-26	32
R MCC	5.7	4	10	32	Temporal lobe				
Temporal lobe					L operculum	7.1	-46	4	-6
R temporal pole	6.6	56	12	-8	R MTG	4.6	50	-56	-2
L MTG	4.5	-50	-60	-2	L MTG	4.2	-56	-62	-4
Frontal lobe					Parietal lobe				
L IFG	6.3	-36	24	6	R SMG	4.8	36	-46	38
L IFG	6.1	-56	10	10	R precuneus	4.7	12	-60	56
R IFG	6.9	56	18	12	Frontal lobe				
R M1	6.9	48	2	36	L dlPFC	6.0	-32	42	18
R IFG	6.0	44	30	-8	R dlPFC	4.9	32	50	18
L dlPFC	5.4	-36	40	26	R M1	5.0	52	2	36
R SMA	5.23	6	4	56					
R dlPFC	4.62	34	42	24					

Peak MNI (Montreal Neurological Institute) coordinates for regions exhibiting positive functional connectivity ($Z_{\max}$) with the right (R) and left (L) temporoparietal junction (TPJ; family-wise error corrected at $Z > 2.3$, cluster-based threshold of $P < 0.05$). Large clusters that extended across multiple brain regions are partitioned according to the Harvard-Oxford cortical structural atlas. aINS, anterior insula; dlPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; MCC, mid-cingulate cortex; M1, primary motor cortex; mINS, middle insula; MTG, middle temporal gyrus; PCC, posterior cingulate cortex; pINS, posterior insula; SMA, supplementary motor area; SMG, supramarginal gyrus.

dlPFC and the cerebellum (IX) (Fig. 3A; see Table 2 for full list). Significant negative functional connectivity of the left TPJ was found with the mPFC, PCC/precuneus, LPC, and cerebellum (IX) (Fig. 3A; see Table 2 for full list). The overlay of right and left TPJ negative functional connectivity maps revealed large clusters of overlap in the mPFC (BA 32/9/10),

PCC/precuneus (BA 23/31/7), right LPC (BA 39), and cerebellum (IX) (Fig. 3B). Since these negative connectivity maps largely resembled the “default mode network” (DMN), we sought to confirm these findings using a group ICA-derived component resembling the DMN and the dual-regression approach described above. We used previously reported criteria

Table 2. Peak MNI coordinates for regions exhibiting negative functional connectivity with the right and left TPJ

L TPJ Negative Connectivity					R TPJ Negative Connectivity				
Region	$Z_{\max}$	Peak voxel (MNI coordinates)			Region	$Z_{\max}$	Peak voxel (MNI coordinates)		
		x	y	z			x	y	z
Cingulate cortex					Parietal lobe				
R PCC	5.8	6	-54	4	L precuneus	5.6	-8	-58	14
L PCC	5.2	-4	-52	4	R precuneus	5.5	6	-56	12
Parietal lobe					Precuneus	5.1	0	-74	38
R precuneus	5.6	6	-60	12	L LPC	5.0	-38	-80	36
L precuneus	5.3	-6	-62	12	R LPC	5.6	52	-60	26
L precuneus	5.2	-6	-60	6	R LPC	4.9	60	-68	24
L precuneus	5.2	-4	-56	6	R LPC	3.9	48	-74	38
R LPC	4.0	56	-64	28	Frontal lobe				
Frontal lobe					L dlPFC	5.4	-26	22	46
R mPFC	4.4	6	58	-10	L mPFC	4.7	-10	74	10
L mPFC	4.3	-8	54	-10	L dlPFC	4.5	-20	34	34
mPFC	3.4	0	68	-12	R mPFC	4.5	2	68	-12
R mPFC	2.9	2	70	4	R mPFC	4.4	8	68	-8
R frontal pole	2.9	22	70	-2	R dlPFC	4.4	20	44	42
L mPFC	2.9	-6	72	10	Cerebellum				
Cerebellum					IX	5.9	2	-64	-50
IX	5.0	-10	-56	-52	IX	5.7	6	-58	-48

Peak MNI coordinates for regions exhibiting negative functional connectivity with the right and left TPJ (family-wise error corrected at $Z > 2.3$, cluster-based threshold of $P < 0.05$). Large clusters that extended across multiple brain regions are partitioned according to the Harvard-Oxford cortical structural atlas and FSL's cerebellar atlas. LPC, lateral parietal cortex; mPFC, medial prefrontal cortex.

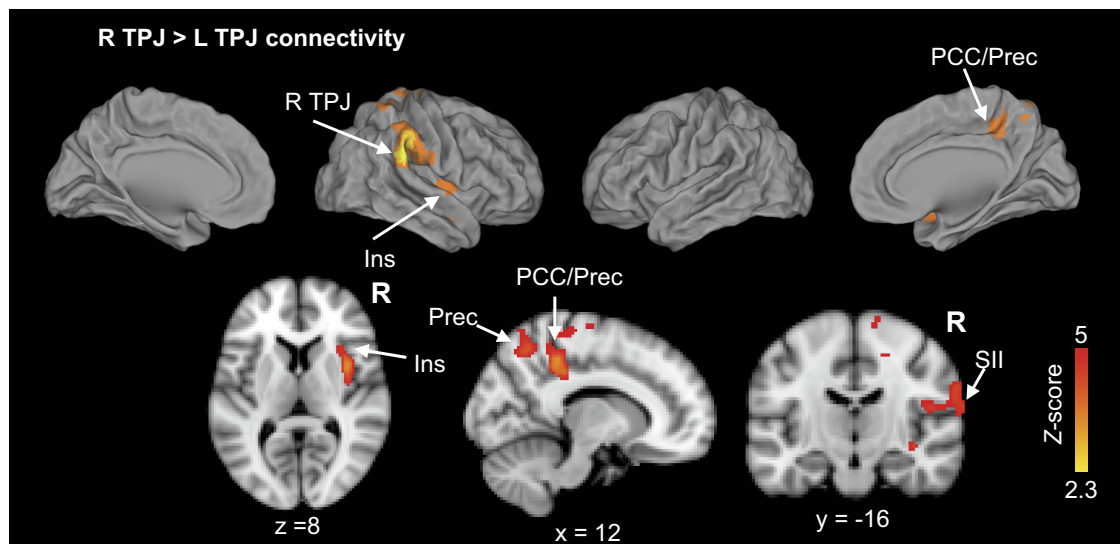


Fig. 4. Results for the contrast right TPJ > left TPJ functional connectivity from seed-based connectivity analysis (family-wise error corrected at $Z > 2.3$, cluster-based threshold of $P < 0.05$). SII, secondary somatosensory cortex.

to identify the DMN as a component including the mPFC (BA 9, 10 and 32), LPC/angular gyrus (BA 39), and PCC/precuneus (BA 23/31) (Habas et al. 2009) with a stringent threshold of $Z > 4.6$. For visual comparison, we overlaid the TPJ negative connectivity map (overlap of right and left TPJ contrasts) on the ICA-derived DMN thresholded at $Z > 2.3$ (Fig. 3C). Dual regression for this component, using the right and left TPJ as regions of interest, confirmed negative connectivity of right TPJ (Z score = -1.01 ± 0.33 , mean $\pm$ SE) and left TPJ (Z score = -1.45 ± 0.24 , mean $\pm$ SE) with the DMN.

The lateralization of right TPJ connectivity is shown in Fig. 4. The right TPJ lateralized map (derived from the contrast right TPJ > left TPJ connectivity) revealed differences in functional connectivity with the right anterior/mid insula, right temporal and parietal operculum/SII, right PCC/precuneus, and additional temporal and parietal regions (Fig. 4; see Table 3 for full

list). This is in stark contrast to the left TPJ lateralized map (Fig. 5A) (derived from the contrast left TPJ > right TPJ connectivity) that revealed differences in functional connectivity with a large bilateral cluster extending from ventromedial mPFC to the dorsomedial PFC/supplementary eye fields, left lateral frontal regions including IFG, left middle temporal gyrus, and right cerebellar regions (crus I/II) (Fig. 5A; see Table 4 for full list). Since this left-lateralized TPJ seed connectivity map resembled the executive control network identified by Seeley et al. (2007), we sought to confirm and visualize that this map was consistent with the executive control network within our data set. We therefore overlaid the left TPJ > right TPJ connectivity results on a component derived from our group-ICA results (both thresholded at $Z > 2.3$) that was identified as the left executive control network (Fig. 5B). We used previously reported criteria to identify this

Table 3. Peak MNI coordinates and parameter estimate values for the contrast right TPJ > left TPJ functional connectivity

Region	$Z_{\max}$	R TPJ > L TPJ Connectivity			L TPJ connectivity PE		R TPJ connectivity PE	
		Peak voxel (MNI coordinates)			Mean	SE	Mean	SE
		x	y	z				
TPJ								
R TPJ	8.0	64	-34	28	-0.05	0.05	1.25	0.05
R TPJ	4.2	70	-20	18	-0.11	0.1	0.6	0.09
Insular cortex								
R mINS	4.1	38	2	6	-0.05	0.06	0.37	0.04
Cingulate cortex								
R PCC/precuneus	4.0	10	-40	46	-0.2	0.08	0.45	0.09
Temporal lobe								
R temporal pole	4.0	44	0	-20	-0.38	0.14	0.6	0.12
R temporal pole	4.0	42	4	-20	-0.36	0.12	0.53	0.11
R operculum	3.4	54	0	0	-0.08	0.09	0.52	0.08
R operculum	3.3	50	-4	-4	-0.07	0.08	0.42	0.07
R temporal pole	3.3	42	-6	-24	-0.06	0.06	0.29	0.05
Parietal lobe								
R operculum/SII	3.8	50	-12	16	-0.15	0.04	0.14	0.03
R SPL	3.8	34	-48	68	-0.32	0.13	0.74	0.15

Peak MNI coordinates and parameter estimate (PE) values for the contrast R TPJ > L TPJ functional connectivity (family-wise error corrected at $Z > 2.3$, cluster-based threshold of $P < 0.05$). Large clusters that extended across multiple brain regions are partitioned according to the Harvard-Oxford cortical/subcortical structural atlases. SPL, superior parietal lobule.

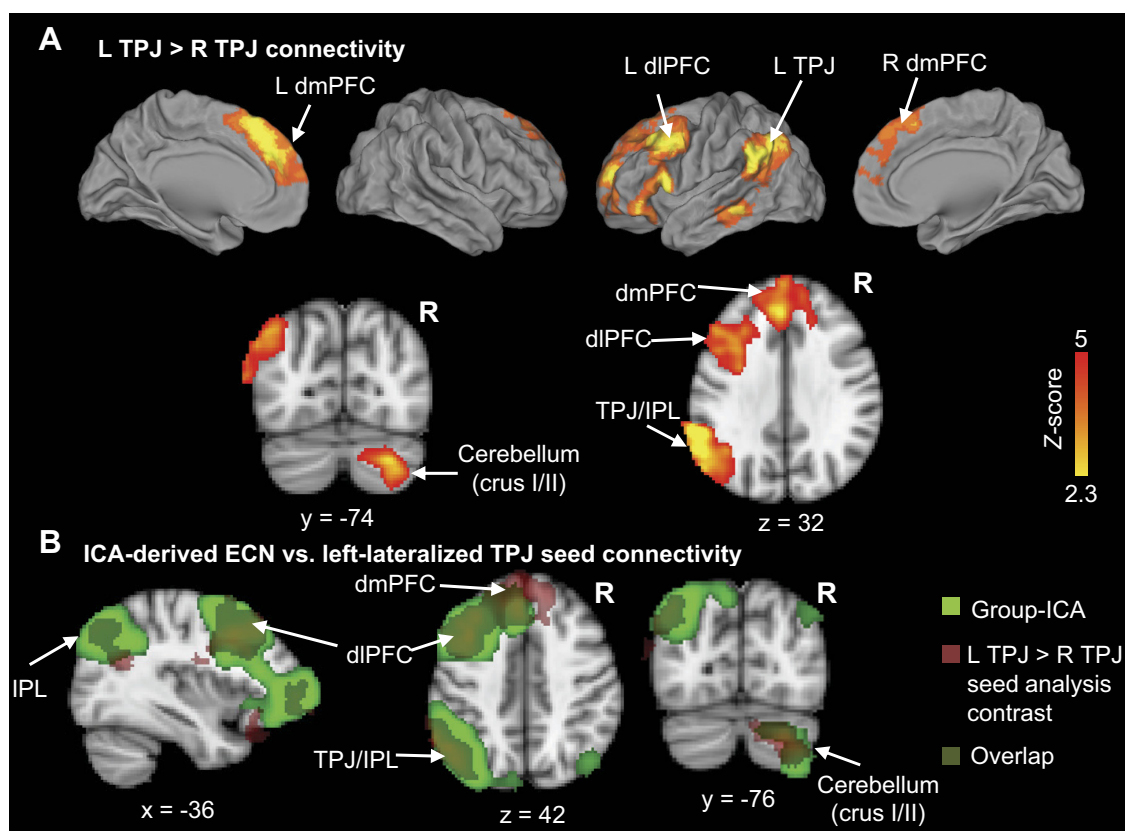


Fig. 5. *A*: results for the contrast left TPJ > right TPJ functional connectivity from seed-based connectivity analysis (family-wise error corrected at $Z > 2.3$, cluster-based threshold of $P < 0.05$). dmPFC, dorsomedial prefrontal cortex. *B*: results from the left TPJ > right TPJ seed connectivity contrast overlaid on the group ICA-derived component representing the left executive control network. Red indicates left TPJ > right TPJ contrast; green indicates group ICA-derived executive control network; and olive indicates overlap of red and green areas. Both maps are thresholded at $Z > 2.3$. ECN, executive control network.

network as a component including the dorsolateral, mid-dorsolateral, and dorsomedial PFC (BA 8, 9, and 45/46), orbito-frontal cortex (BA 47), superior parietal cortex (BA7), angular gyrus (BA 39), and crus I/II of the cerebellum (Habas et al. 2009; Seeley et al. 2007) at a stringent threshold of $Z > 4.6$. As shown in Fig. 5*B*, the main clusters identified from the left TPJ > right TPJ contrast overlap with the ICA-derived left executive control network (except for the right dorsomedial PFC, which is part of the right executive control network).

As shown in Table 3, the majority of the average parameter estimate values (i.e., β -values) for regions with significantly different connectivity for the right TPJ > left TPJ contrast were positive for right TPJ and close to zero or negative for left TPJ, suggesting that differences were mainly driven by stronger positive connectivity of right than left TPJ. As shown in Table 4, the majority of average parameter estimate values for regions with significantly different connectivity for the left TPJ > right TPJ contrast were positive for left TPJ and negative for right TPJ, suggesting that differences were driven by opposing patterns of functional coupling.

DISCUSSION

Classic lesion studies implicate the right TPJ in attentional functions, and task fMRI more specifically implicates the right TPJ in salience detection, pain, and stimulus-driven attention. Here we show that lateralization in TPJ functional connectivity with salience- and attention-related brain networks is also

present when human subjects are at rest. Our main findings were that 1) the right TPJ, compared with the left TPJ, is more strongly connected with the salience/ventral attention network and other regions implicated in salience/pain-related processing (e.g., insula, SII/operculum); 2) the left TPJ, compared with the right TPJ, is more strongly connected with regions implicated in executive control (e.g., dorsomedial PFC, supplementary eye fields, dIPFC cerebellar regions); and 3) the right and left TPJ both exhibit negative functional connectivity with the DMN (e.g., mPFC, PCC/precuneus, LPC).

Overall, these findings are concordant with the notion that the right TPJ has a dominant role in general salience detection (Corbetta et al. 2008), whereas the left TPJ may integrate salient sensory information with contextual knowledge to control attention (DiQuattro and Geng 2011). The application of resting-state fMRI in this study builds on our understanding of lateralization in TPJ function and anatomy based on task fMRI, lesion, and stimulation studies (Corbetta et al. 2008) as well as white matter connectivity studies (Kucyi et al. 2012; Thiebaut de Schotten et al. 2011).

TPJ as part of the salience/ventral attention network. The salience network was initially defined by Seeley et al. (2007) as a set of regions that encode emotional and cognitive processes that are personally relevant, whereas the ventral attention network is implicated in bottom-up/stimulus-driven attention (Corbetta et al. 2008). Although these proposed roles of salience vs. ventral attention networks are not identical, the high degree of spatial overlap between the two putative networks, as

Table 4. Peak MNI coordinates and parameter estimate values for the contrast left TPJ > right TPJ functional connectivity

Region	$Z_{\max}$	L TPJ > R TPJ Connectivity						
		Peak voxel (MNI coordinates)			L TPJ Connectivity PE		R TPJ Connectivity PE	
		x	y	z	Mean	SE	Mean	SE
TPJ								
L TPJ	8.3	-66	-44	28	1.32	0.05	-0.08	0.05
L TPJ	5.0	-52	-62	42	0.64	0.12	-0.74	0.15
L TPJ	4.7	-48	-68	42	0.57	0.15	-0.82	0.15
L TPJ	4.7	-56	-70	34	0.34	0.09	-0.47	0.06
L TPJ	4.7	-62	-56	20	0.87	0.13	-0.44	0.12
Temporal lobe								
L MTG	4.2	-64	-40	-12	0.46	0.1	-0.47	0.11
Frontal lobe								
L dmPFC	5.4	-2	28	50	0.75	0.1	-0.38	0.08
L dmPFC	5.3	-4	40	30	0.45	0.1	-0.48	0.07
L IFG	5.2	-52	16	6	0.66	0.1	-0.31	0.08
L dlPFC	5.1	-38	14	40	0.36	0.09	-0.43	0.06
L dmPFC	5.1	-6	34	44	0.5	0.08	-0.31	0.07
L frontal pole	4.8	-22	56	16	0.53	0.08	-0.32	0.08
Cerebellum								
R crus I/II	5.1	28	-76	-36	0.24	0.06	-0.23	0.05
R crus II	4.9	22	-82	-40	0.34	0.07	-0.27	0.06
R crus II	4.5	32	-76	-42	0.25	0.05	-0.25	0.06

Peak MNI coordinates and PE values for the contrast L TPJ > R TPJ functional connectivity (family-wise error corrected at $Z > 2.3$, cluster-based threshold of $P < 0.05$). Large clusters that extended across multiple brain regions are partitioned according to the Harvard-Oxford cortical/subcortical structural atlases and FSL's cerebellar atlas. dmPFC, dorsomedial prefrontal cortex.

well the observation that regions within the salience network, such as the MCC, respond robustly during salient sensory stimulation (Downar et al. 2000, 2001, 2002), suggests that the salience and ventral attention networks are highly functionally inter-related and/or can be considered as a single bilateral network.

The aINS and MCC are considered to be the core of the salience network (Menon and Uddin 2010) and are also among the regions that are mostly commonly activated in many types of task fMRI, including pain studies (Davis 2011; Menon and Uddin 2010; Yarkoni et al. 2011). One reason these regions are so commonly activated in imaging studies is that many tasks involve stimuli that engage bottom-up attention/salience detection (Menon and Uddin 2010), a function that has previously been associated with aINS, MCC, and (especially right) TPJ activation (Downar et al. 2000, 2001, 2002). Support for this notion comes from a pharmacological fMRI study in which activation of and interconnectivity within the salience network, including the bilateral TPJ, was linked to activity of the noradrenergic system (Hermans et al. 2011). The noradrenergic system, originating in the locus coeruleus of the brain stem, has a phylogenetically preserved role across multiple organisms in acute stress and in responding broadly to multimodal sensory input (Corbetta et al. 2008). Therefore, as a neocortical extension of a primitive alerting/vigilance system, the salience network may function in bringing behaviorally relevant events in the sensory environment to conscious awareness.

In lower vertebrates there is evidence that the right hemisphere is specialized for maintaining a state of alertness, a function that is mediated by the locus coeruleus noradrenergic system (Corbetta and Shulman 2011; Posner and Petersen 1990). The human right hemispheric bias in stimulus-driven attention (especially in the right TPJ) may represent a sort of "vestige" of this system. Right-lateralized functional connectivity of the TPJ with the salience network during a task-free,

stimulus-independent state is in line with this notion, and temporal variability in the degree of this connectivity may be related to the current state of salience monitoring.

The right TPJ and pain. Pain is intrinsically a highly salient perception that serves to alert organisms of danger (Eccleston and Crombez 1999) and therefore provides an ideal tool to investigate neural activity associated with salience detection (Davis 2011; Legrain et al. 2011). We have previously found that activity in right-lateralized regions within the salience/ventral attention network, including the right TPJ, encodes the prolonged salience of pain (Downar et al. 2003). There is also a high degree of overlap between regions within the salience network and regions that are activated during pain (Mouraux et al. 2011), and a recent meta-analysis suggests that there is a right hemisphere dominance in insula and cingulate cortex activations during painful stimulation (Duerden and Albanese 2011).

In addition to our present finding of stronger right TPJ than left TPJ functional connectivity with the salience network, our seed-based analysis revealed stronger coupling between right TPJ than left TPJ with regions that are well-known to be involved in the sensory-discriminative and affective-motivational aspects of pain (right aINS, SII) (Apkarian et al. 2005; Duerden and Albanese 2011). Notably, when we did not apply a cluster significance threshold for the right TPJ > left TPJ functional connectivity contrast at the level of $Z > 2.3$, the aINS and SII findings were bilateral and there was an additional cluster in the MCC (data not shown). It is therefore possible that a network involved in encoding highly salient nociceptive information has more fluid communication with right TPJ than with left TPJ. Our previous finding of stronger white matter connectivity between the TPJ and anterior/mid insula in the right compared with the left hemisphere also supports this notion (Kucyi et al. 2012).

The present results may have implications for the understanding of chronic pain disorders. Structural abnormalities in multiple chronic pain disorders often involve the insula and MCC (Blankstein et al. 2010; Davis et al. 2008; Moayed et al. 2011). On the basis of our findings, damage to these regions would affect functional connectivity with the right TPJ differently than with the left TPJ. A recent report found increased connectivity in patients with migraine between the bilateral TPJ (labeled as supramarginal gyrus) and the periaqueductal gray, an important midbrain node in the descending pain modulatory system (Mainiero et al. 2011). Future investigations of chronic pain could address the question of TPJ laterality through direct voxelwise comparisons of right vs. left TPJ functional connectivity.

The left TPJ and executive control. Our results indicate that the strongest functional connectivity of the left TPJ is predominantly with regions in the salience network, but the left TPJ exhibits stronger functional connectivity compared with the right TPJ with a set of regions outside the salience network, including the bilateral dorsomedial PFC, left IFG, left inferior parietal lobule, and right cerebellar regions (crus I/II). When we did not apply a cluster significance threshold for the left TPJ > right TPJ functional connectivity contrast at the level of $Z > 2.3$, there were additional clusters in the left caudate nucleus and additional right hemisphere regions (besides the right dorsomedial PFC, which survived cluster significance) that mirrored those that were found in the left hemisphere, including the right dlPFC, orbitofrontal cortex, middle temporal gyrus, and angular gyrus (data not shown). Interestingly, these cortical and subcortical as well as cerebellar regions show remarkable overlap with the previously identified left and right executive control networks (Habas et al. 2009; Seeley et al. 2007), which are involved in top-down control of attention. A left hemisphere-dominant role of the TPJ in executive control is somewhat consistent with the notion that the left TPJ integrates contextual knowledge with incoming sensory information (DiQuattro and Geng 2011). In other words, the function of the left TPJ may lie at the interface of top-down and bottom-up attention through interactions with the salience and executive control networks, respectively. These interactions may be mediated by the dlPFC, which is part of both the salience and executive control networks (Seeley et al. 2007).

Interestingly, we found that the right TPJ is negatively connected with regions in the executive control network, an opposite pattern compared with the left TPJ. This type of organization may allow the right TPJ to filter out influences of top-down information, thereby enhancing salience detection.

Negative functional connectivity with the DMN. Our findings of negative functional connectivity of the TPJ with the DMN (mPFC, PCC/precuneus, LPC) are in line with other studies that have identified anticorrelated activity between task-positive networks (salience and executive control) and the DMN (Fox et al. 2005; Fransson 2005). Notably, previous rs-fMRI studies with this finding have been criticized for their methodology that included GSR, a data preprocessing step that may introduce artifactual negative functional connectivity (Chai et al. 2012; Murphy et al. 2009). Therefore, in our seed-based connectivity analysis, we chose to implement the aCompCor method (Behzadi et al. 2007; Chai et al. 2012) for noise removal instead of GSR. The spectral distribution of nonneuronal signals that are removed with aCompCor is similar to that

obtained with methods that involve on-line cardiac and respiratory measurements to remove physiological noise (Behzadi et al. 2007). We therefore suggest that the negative functional connectivity that we identified between the TPJ and DMN is based on neural activity.

Because of the role of the DMN in internally oriented attention (Andrews-Hanna 2012; Christoff et al. 2009) and the role of the TPJ in detection of sensory events in the external environment (Corbetta et al. 2008), negative functional connectivity between the DMN and TPJ may highlight their opposing roles. Notably, although we identified stronger right than left TPJ connectivity with the PCC/precuneus, this specific cluster did not overlap with PCC/precuneus areas that were negatively connected with the TPJ. Instead, the cluster overlapped with a more anterior area within the PCC that was also identified as being part of the salience/ventral attention network with ICA. This is in line with our finding from ICA/dual regression that the right TPJ is more strongly connected than the left TPJ with the salience/ventral attention network.

Anatomical specificity of the TPJ and other proposed roles. The functional connectivity spatial patterns reported here are broadly consistent with previous studies that have used ICA (Habas et al. 2009; Seeley et al. 2007; Shirer et al. 2012; Weissman-Fogel et al. 2010) as well seed-based connectivity of the insula (Cauda et al. 2011; Taylor et al. 2009), cingulate cortex (Margulies et al. 2007), and right TPJ (Jakobs et al. 2012; Mars et al. 2012). However, not all previous studies using ICA have reported that the TPJ is part of the salience network (Habas et al. 2009; Uddin et al. 2011). Discrepancies may be due to many factors, including differences in number of subjects, preprocessing parameters, and number of components chosen/outputted by ICA. Resting-state fMRI studies of the salience network have also found clusters within the vicinity of the TPJ but reported these with different nomenclature (e.g., the gyrus/sulcus of the peak coordinates). For example, in the original report of the salience network defined with ICA (Seeley et al. 2007), the right “parietal operculum” coordinates are within the vicinity of the right TPJ reported here. In this study we chose to classify the region as “TPJ” due to concordance with previous definitions describing this region as encompassing portions of the inferior parietal lobule, supramarginal gyrus, and posterior superior temporal gyrus/sulcus (Brodmann areas 40 and 22) (Corbetta et al. 2008; Decety and Lamm 2007; Downar et al. 2000; Mars et al. 2012). The high degree of concordance between our ICA results and the conjunction analysis of right and left TPJ seed-based connectivity confirms that the bilateral TPJ is part of the salience network. A recent large-scale clustering analysis of rs-fMRI data from 1,000 healthy subjects also showed that the bilateral anterior TPJ is part of the salience/ventral attention network (Yeo et al. 2011).

Brain regions termed “TPJ” in previous studies have been implicated in a number of functions that cannot necessarily be reconciled with a specialization for stimulus-driven attention/salience detection discussed here (Decety and Lamm 2007). For example, the TPJ has been implicated in social cognition/theory of mind (Andrews-Hanna 2012), out-of-body experiences (Ionta et al. 2011), and temporal order judgment (Spierer et al. 2009). It remains unclear whether the same or different neuronal populations within the TPJ are involved in this

diverse range of functions, but recent evidence suggests that anatomically and functionally distinct TPJ subregions exist. Mars et al. (2012) parcellated the right TPJ into anterior and posterior subregions on the basis of structural connectivity profiles obtained with probabilistic tractography. The anterior subregion displayed stronger resting functional connectivity with the ventral PFC/aINS than the posterior subregion (Mars et al. 2012) and appears to be consistent with the region that we investigated presently as part of the salience network. In contrast, the posterior subregion was more strongly coupled with the anterior mPFC (Mars et al. 2012). We therefore suggest that the anterior TPJ displays right-lateralized anatomical and functional characteristics related to salience detection.

Conclusions. We have provided resting-state fMRI evidence that right and left TPJ exhibit differences in functional connectivity with salience- and attention-related brain networks. Our findings support the notion that the right TPJ is functionally associated with regions that have a dominant, generalized role in salience detection, whereas the left TPJ is functionally associated with regions involved in integrating sensory salience with top-down attentional control. Given the intricate links among resting-state functional connectivity, structural connectivity, and task-/stimulus-evoked coactivation patterns, our findings inform and build on previous studies using other modalities to investigate asymmetry in TPJ anatomy and function. The lateralization of TPJ connectivity reported in this article involves brain networks that are disrupted in spatial neglect (Corbetta and Shulman 2011) and regions with structural abnormalities in multiple chronic pain disorders (May 2011), and therefore our findings may help improve the understanding of these conditions.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.K., M.H., and K.D.D. conception and design of research; A.K. analyzed data; A.K., M.H., and K.D.D. interpreted results of experiments; A.K. prepared figures; A.K. drafted manuscript; A.K., M.H., and K.D.D. edited and revised manuscript; A.K., M.H., and K.D.D. approved final version of manuscript.

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