Across-study and within-subject functional connectivity of a right temporo-parietal junction subregion involved in stimulus–context integration

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ABSTRACT

Bidirectional integration between sensory stimuli and contextual framing is fundamental to action control. Stimuli may entail context-dependent actions, while temporal or spatial characteristics of a stimulus train may establish a contextual framework for upcoming stimuli. Here we aimed at identifying core areas for stimulus–context integration and delineated their functional connectivity (FC) using meta-analytic connectivity modeling (MACM) and analysis of resting-state networks.

In a multi-study conjunction, consistently increased activity under higher demands on stimulus–context integration was predominantly found in the right temporo-parietal junction (TPJ), which represented the largest cluster of overlap and was thus used as the seed for the FC analyses. The conjunction between task-dependent (MACM) and task-free (resting state) FC of the right TPJ revealed a shared network comprising bilaterally inferior parietal and frontal cortices, anterior insula, premotor cortex, putamen and cerebellum, i.e., a 'ventral' action/attention network. Stronger task-dependent (vs. task-free) connectivity was observed with the pre-SMA, dorsal premotor cortex, intraparietal sulcus, basal ganglia and primary sensori motor cortex, while stronger resting-state (vs. task-dependent) connectivity was found with the dorsolateral prefrontal and medial parietal cortex.

Our data provide strong evidence that the right TPJ may represent a key region for the integration of sensory stimuli and contextual frames in action control. Task-dependent associations with regions related to stimulus processing and motor responses indicate that the right TPJ may integrate 'collaterals' of sensory processing and apply (ensuing) contextual frames, most likely via modulation of preparatory loops. Given the pattern of resting-state connectivity, internal states and goal representations may provide the substrates for the contextual integration within the TPJ in the absence of a specific task.

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Introduction

Sensorimotor control is an integral part of our daily life and the essential prerequisite to interact with one's environment, i.e. the internal and external milieu. Thus, the convergence and integration of both intero- and exteroceptive stimuli in the human brain is fundamental to allow for a comprehensive environmental picture (Berlucchi and Aglioti, 2010). In most functional neuroimaging experiments the selection of the adequate behavioral response is based on only a limited number of stimuli, i.e. the brain has to evaluate which stimuli are crucial to meet the task (Bays et al., 2010). This subset of

bottom-up (sensory) input is subsequently weighted against top-down information such as contextual rules and goals. Fundamentally, top-down signals represent feedback from 'higher' (usually multi-modal) brain regions to unimodal sensory or motor areas. Anatomically, such top-down feedback is implemented by diffuse connectivity into (primarily) dendritic terminals in cortical layers II–III, whereas bottom-up (feed-forward) connections primarily terminate in layer IV of a more circumscribed patch of the cortex. The result of this complex procedure consists of highly integrated data and constitutes the basis upon which the respective movements are planned. In the following, the term 'contextual integration' is used to denote the top-down modulation of sensorimotor processing by context-specific a-priori information. Context is here defined as any information affecting actions that is not provided by the given response stimulus itself but by the environment, ranging from explicit

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instructions about stimulus–response mappings to implicit expectations extracted from regularities in the stimulation sequence. The first aim of our study was to identify regions that are consistently (i.e. across different studies) activated by context-dependent sensorimotor control.

So far, we have only considered task-induced integration processes. However, the human brain is assumed to operate along a continuum between task-related performance and 'mental rest', i.e. 'unconstrained' cognition (Schilbach et al., 2008). This presumption is in line with several studies (Fox and Raichle, 2007; Smith et al., 2009) demonstrating that 'physiological rest' does not equate 'mental rest'. Rather, it has been hypothesized (Schilbach et al., 2008) that the absence of an externally structured task entails a re-allocation of resources toward internally oriented, i.e. 'conceptual' (Binder et al., 1999), operations resulting in 'mind-wandering' (cf. Smallwood and Schooler, 2006). Thus, the second aim of our study was to assess the functional connectivity (FC) of the above-mentioned areas in both task-dependent and task-independent mental states. The third aim was to test for commonalities and differences in the FC pattern of these two fundamental states of brain function.

To date, a large number of functional neuroimaging studies have adopted task-based experimental designs to investigate the neural correlates of stimulus–response associations in humans (Egner, 2007) and non-human primates (Connolly et al., 2009). Despite the differences in experimental designs, several studies have provided consistent evidence for an implementation of these processes in a bilateral fronto-parietal network. In line with data from single-cell recordings in non-human primates (Gottlieb and Snyder, 2010), the inferior parietal lobe (IPL) and adjacent intraparietal sulcus are conceptualized to evaluate and integrate incoming sensory input from different modalities. In this context, Spence and Driver (2004) claimed that the posterior parietal cortex plays a critical role in mediating the integration of spatial aspects of multimodal stimuli (e.g. visual, auditory or tactile) and their transformation into action-based representations. This is well in line with the presumption of IPL/IPS acting as a heteromodal integrative 'hub' committed to multisensory processing (Gottlieb, 2007; Toni et al., 2002). Such multimodal integration processes, however, may not be restricted to the posterior parietal cortex. Rather, there is evidence that multi-modal integration is also supported by regions within the (pre-)frontal and temporal cortex (Calvert et al., 2004; Driver and Noesselt, 2008). In particular, contextual information from the (pre-)frontal cortex enriches these integrative processes and permits a bidirectional coupling between stimulus and contextual framework (Koechlin and Jubault, 2006). Moreover, the function of (pre-)frontal areas in the system of sensorimotor control also comprises the exertion of 'executive control' on the (pre-)motor system (Koechlin and Summerfield, 2007). In particular, these regions were found to be involved in rule-based adjustment of motor plans, movement timing and action monitoring. Finally, the (pre-)motor areas are thought to select, initiate and execute the adequate motor program based on highly integrated information from parietal and (pre-)frontal cortex (Picard and Strick, 1996; Rizzolatti et al., 1998). Sensorimotor control thus depends on the integration of cognitive aspects with the monitoring of the internal and external milieu and the selection of appropriate responses based on these information.

In this context, the question arises as to which regions are consistently activated during the implementation of sensorimotor control, i.e. the association of a given stimulus with an arbitrary (instructed) response. Three recently published functional neuroimaging studies (Cieslik et al., 2010; Eickhoff et al., 2011; Jakobs et al., 2009) applied variations of a manual two-choice reaction-time task with graduated levels of difficulty in stimulus–response mapping. Testing for neural effects of increasing demands on stimulus–response association in each study revealed a similar bilateral, though right-hemispherically dominant, fronto-parietal network. In order to statistically validate this prima facie evidence, i.e. to detect regions featuring a significant overlap across the abovementioned studies, we applied an image-based meta-analysis (IBMA) technique to investigate the multi-study conjunction of results. In this context, regions consistently activated across studies are assumed to implement higher-order processes in the cascade of stimulus–response association.

However, even the common evidence provided by three studies might still reflect design-specific effects to a degree that precludes broad generalizations about this fundamental network. Thus, in the second part of the current study, we used meta-analytic connectivity modeling (MACM) to delineate the FC pattern of higher-order sensorimotor regions (i.e. consistently activated clusters observed in the IBMA) in the presence of an externally structured task. The basic idea behind this approach is to assess which brain regions are co-activated above chance with particular seed regions in functional neuroimaging experiments. Here, we used the BrainMap database (Laird et al., 2009; www.brainmap.org) to identify co-activations with our seed regions (i.e. the results of the above-mentioned IBMA) across all studies listed in this database and subsequently performed an ALE (activation likelihood estimation) meta-analysis on these studies (Eickhoff et al., 2009; Laird et al., 2009).

As mentioned above, regions participating in stimulus–context integration are also engaged in task-free brain states. Thus, it may be speculated that a shared procedure is based upon a subset of regions, which are activated irrespective of the current mental state. To test this hypothesis, we investigated 'resting-state' FC using functional imaging data from 100 healthy volunteers. The time-series of each seed region was cross-correlated with the time-series of all other gray-matter voxels in the brain. Consistent functional coupling across mental states (i.e. overlap of regions co-activated across studies with our seed and regions with significant intrinsic connectivity to our seed) would indicate that the seed and target regions participate in very much the same networks during task-dependent stimulus–context integration and task-free, unstructured processing. In contrast, divergent results would delineate networks that depend on the mental state and thus allow for a differentiation of internally and externally driven FC networks (Eickhoff and Grefkes, 2011).

Material and methods

Image-based meta-analysis

We performed an IBMA by multi-study conjunction over three recently published fMRI studies (Cieslik et al., 2010; Eickhoff et al., 2011; Jakobs et al., 2009). Regions consistently activated by higher demands on sensorimotor integration were identified by first computing the respective contrasts in each study, thresholded at $p < 0.05$ (cluster-level FWE-corrected; cluster-forming threshold at voxel-level $p < 0.001$; Worsley et al., 1996). In particular, the minimal number of voxels required to meet the threshold criterion ranged from 305 to 315 voxels [voxel size 1.5 mm³ isotropic; Jakobs et al., 2009: 308 voxels; Cieslik et al., 2010: 305 voxels; Eickhoff et al., 2011: 315 voxels]. Hence, the comparability across studies was ensured by enclosing similar numbers of subjects and applying the same preprocessing algorithms. Regions consistently engaged (across studies) by increasing demands for stimulus–context integration in sensorimotor control were then identified by means of conjunction analysis. Subsequently, all findings were anatomically localized using version 1.5 of the SPM Anatomy toolbox (www.fz-juelich.de/ime/spm_anatomy_toolbox, Eickhoff et al., 2005, 2006c, 2007).

Each of the three included studies applied a manual reaction-time task requiring participants to respond as fast and correctly as possible to visually presented stimuli by pressing a button with either their left or right index finger.

In the first study (Cieslik et al., 2010), 24 participants were instructed to react to lateralized stimuli (red dots) briefly presented

(200 ms) in a randomized order. Before each task block, participants were instructed to respond with either the corresponding (spatially congruent response) or the contralateral (spatially incongruent response) index finger. Activation related to increased integration demands was then assessed by contrasting incongruent with congruent trials independently of the stimulus- or response-side.

In the second study (Jakobs et al., 2009), 26 participants responded to centrally presented visual stimuli (arrows), which were either pointing uniformly to one side or in a randomized order to either side (random hands condition; 50% chance for each side) with the corresponding index finger. Increasing demands on stimulus–context integration were delineated by contrasting random hands with unilateral conditions.

In the third study (Eickhoff et al., 2011), left- or right-pointing arrows were centrally presented to 20 participants. This time, however, arrow direction was non-uniformly distributed, with 80% pointing to one side. This laterality bias was randomly varied between blocks of trials. Moreover, in some blocks this bias was covertly reversed in the middle of the block. Increased integration demands were assessed by testing for activity that was parametrically related to the acquisition and adaptation of response biases in line with the probabilistic structure of the stimuli.

The respective contrasts reflecting increased demands for stimulus–context integration in sensorimotor control were thresholded at a cluster-level FWE-corrected p<0.05. The ensuing activation maps were then subjected to a conjunction analysis, i.e. we performed the conjunction against the (conservative) conjunction null hypothesis using the minimum statistic (Nichols et al., 2005). In practice, this was implemented by first applying a voxel-level cluster-forming threshold to all three analyses. Subsequently, each of the three excursion sets was filtered for cluster extent to threshold at cluster-level FWE-corrected p<0.05 (cluster-forming threshold at voxel-level p<0.001, i.e., T>3.09). Finally, we computed the intersection between the three thresholded and filtered SPM{T}-maps. This procedure exactly conforms to the conjunction-null minimum statistic, as the intersection only becomes non-zero (and hence significant) if each of the three individual analyses was significant. This IBMA provided four regions of overlapping activation. The right TPJ showed a cluster size of 104 voxels. Additionally, we observed three smaller clusters (right IPS, bilateral dPMC) with an average cluster size just over 20 voxels. Given this dramatic difference in cluster extent, we decided to exclude these considerably smaller regions and focus our analysis on the predominant finding, which survived conservative thresholding. Hence, the only region of spatially extended overlap between significant activation in all three individual analyses (i.e. the right TPJ) represented the seed for the subsequent connectivity modeling.

Task-based FC: meta-analytic connectivity modeling

FC of the seed(s) during the performance of structured tasks was defined by delineating the co-activation pattern of the seed based on the activations reported in published functional imaging results. The concept behind this approach is predicated on the notion that FC is reflected in the correlation of activity in spatially distinct brain regions. That is, regions that are functionally connected should co-activate above chance in functional neuroimaging studies and vice versa. In this context, it should be noted that there are major conceptual differences between anatomical, functional and effective connectivity: (1) Anatomical connectivity denotes the presence of fiber connections linking two areas in the brain, i.e. the existence of a structural connection between their neurons. In contrast, (2) FC is correlative in nature, i.e. solely based on the likelihood of observing activation in a target region, given that activation is present within the seed area. In MACM, as performed in the current study, the unit of observation is not a specific point in an acquired time series but a

particular neuroimaging experiment. MACM thus extends the scale on which FC is evaluated beyond data points in a time series (single study) to a whole set of neuroimaging experiments (MACM across studies). Here, FC is expressed as coherent activation across experiments and should delineate networks that are conjointly recruited by a broad range of tasks. Finally, (3) effective connectivity is defined as the causal influence one area exerts over another and may be tested with approaches such as dynamic causal modeling or structural equation modeling.

Here, analysis of task-based FC was performed by MACM using the BrainMap database (Laird et al., 2009, www.brainmap.org). This database contained, at the time of analysis, the location of reported activation foci and associated meta-data of approximately 10,000 neuroimaging experiments. Of these, only fMRI studies that reported functional mapping data from healthy participants were considered. Studies investigating age, gender, disease, or drug effects were excluded. No further constraints (e.g., on acquisition or analysis details, experimental design, or stimulation procedures) were applied. Comparability with respect to the location of significant activation was ensured given the high standardization in the publication of neuroimaging data, i.e. the ubiquitous adherence to standard coordinate systems, such that all experiments contained in the database refer to activation coordinates within the same standard space. Using this broad pool of neuroimaging results, MACM can then be used to test for associations between activation probabilities of different areas. Importantly, this inference is performed independently of the paradigms used or other experimental factors but rather is solely based on the likelihood of observing activation in a target region given that activation is present within the seed area. This completely data-driven approach thus avoids selection biases that may result from adhering to current cognitive ontologies, which might not always overlap with the organizational modes of brain function.

In practice, MACM was performed in two steps: First, we identified all experiments in the BrainMap database that featured at least one focus of activation within the volume of the respective seed region (i.e. the cluster obtained from the IBMA). Second, quantitative meta-analysis (see below) was employed to test for the across-study convergence of the activity foci reported in these experiments. As all experiments entering this analysis were selected by the fact that they feature activation in the seed, highest convergence will be observed in the seed region. Significant convergence of other activity foci, however, indicates consistent co-activation, i.e., task-based FC with the seed. Thus, it has to be noted that the FC pattern as observed in the MACM analysis is not specific to a distinct task or paradigm but rather reflects regional coupling that is present across a broad range of different tasks and paradigms.

For the meta-analysis in the second step, the revised version of the activation likelihood estimation (ALE) approach was used (Eickhoff et al., 2009; Laird et al., 2009). This algorithm aims at identifying areas where the convergence of activations across different experiments is higher than expected under conditions of random spatial associations between them. The key idea behind ALE is to treat reported activation foci not as points but centers of 3-D Gaussian probability distributions reflecting the associated spatial uncertainty. For each experiment included, the probability distributions of all reported foci are combined into a modeled activation (MA) map (Turkeltaub et al., 2012). Taking the union across these MA maps for all experiments yielded voxel-wise ALE scores describing the convergence of results at each particular location of the brain. To distinguish 'true' convergence across studies from random convergence (i.e. noise), ALE scores are compared to an empirical null distribution reflecting a random spatial association between experiments (Eickhoff et al., 2011). Hereby, a random-effects inference is invoked, focusing on the above-chance convergence between studies, not the clustering of foci within a particular study. The p-value of an observed ALE score is given by the proportion of equal or higher values obtained

under the null distribution. The ALE maps, reflecting the across-study convergence of co-activations with the seed region, were thresholded at cluster level–corrected $p < 0.05$ (cluster-forming threshold: $p < 0.001$ at voxel level) and converted to Z-scores for visualization.

Task-independent connectivity: resting-state correlations

Resting-state fMRI images were acquired in 100 healthy volunteers (50 females, mean age 45.2 years) without any record of neurological or psychiatric disorders. All participants gave written informed consent to the study protocol, which had been approved by the local ethics committee of the University of Bonn. Before the imaging session, participants were instructed to keep their eyes closed and just let their mind wander without thinking of anything in particular but not to fall asleep (which was confirmed in post-scan debriefing). For each participant, 300 resting-state EPI images were acquired using blood-oxygen-level-dependent (BOLD) contrast [gradient-echo EPI pulse sequence, TR = 2.2 s, TE = 30 ms, flip angle = 90°, in-plane resolution = 3.1×3.1 mm², 36 axial slices (3.1 mm thickness) covering the entire brain].

The first four scans served as dummy images allowing for magnetic field saturation and were discarded prior to further processing using SPM8 (www.fil.ion.ucl.ac.uk/spm). The EPI images were first corrected for head movements by affine registration using a two-pass procedure in which the images were first aligned to the initial volumes and subsequently to the mean of all volumes after the first pass. The mean EPI image for each participant was then spatially normalized to the MNI single-subject template (Holmes et al., 1998) using the 'unified segmentation' approach (Ashburner and Friston, 2005), and the ensuing deformation was applied to the individual EPI volumes. Finally, images were smoothed by a 5-mm FWHM Gaussian kernel to improve signal-to-noise ratio and compensate for residual anatomical variations.

The time-series data of each voxel were processed as follows (cf. Fox et al., 2009; Weissenbacher et al., 2009): In order to reduce spurious correlations, variance that could be explained by the following nuisance variables was removed: (i) The six motion parameters derived from the image realignment; (ii) the first derivative of the realignment parameters; (iii) mean gray matter, white matter and CSF signal per time-point as obtained by averaging across voxels attributed to the respective tissue class in the SPM 8 segmentation; and (iv) coherent signal changes across the whole brain as reflected by the first five components of a principal component analysis (PCA) decomposition of the whole-brain time-series. All of these nuisance variables entered the model as first-order and – except for the PCA components – also as second-order terms. We note that the above approach, in particular the removal of variance related to the most dominant signal components, may remove some signal of interest but should increase specificity of the ensuing results (Bellec et al., 2006; Fox and Raichle, 2007). Data was then band-pass filtered preserving frequencies between 0.01 and 0.08 Hz, since meaningful resting-state correlations will predominantly be found in t frequency range, given that the BOLD response acts as a low-pass filter (Biswal et al., 1995; Fox and Raichle, 2007; Greicius et al., 2003).

As for the MACM analysis, seed regions of interest were provided by the clusters obtained from the IBMA. Time-courses were extracted for all voxels within the particular cluster that were located in the gray matter of the individual participant as indicated by a segmentation of the individual EPI image (Ashburner and Friston, 2005). Of the 104 voxels in the right TPJ cluster, the number of voxels more likely representing gray matter than any other tissue class was on average (across subjects) 90.7 (SD = 10.6; range: 71–104). The time course of the seed region was then expressed as the first eigenvariate of the individual voxels. Linear (Pearson) correlation coefficients between the time series of the seed regions (clusters obtained from the IBMA) and all other gray-matter voxels in the brain were

computed to quantify resting-state FC. These voxel-wise correlation coefficients were then transformed into Fisher's Z-scores and tested for consistency by a one-sample T-test across subjects. The results of this random-effects analysis were then thresholded at a cluster level–corrected threshold of $p < 0.05$ (cluster–forming threshold: $p < 0.001$ at voxel-level).

Conjunction and differences between MACM and resting-state FC

In order to delineate areas showing task-dependent and task-independent FC with the seed region(s) obtained from the IBMA, we performed a conjunction analysis between the MACM and resting-state analyses using the strict minimum statistic (Nichols et al., 2005). That is, for each seed region, we identified those voxels that showed significant FC with this seed in the analysis of interactions in the task-dependent as well as in the analysis of interactions in the task-independent state. In practice such consistent connectivity was delineated by computing the intersection of the (cluster-level FWE-corrected) connectivity maps from the two analyses detailed above.

Comparison between task-dependent and task-independent FC was performed by computing the voxel-wise contrast between the Z-scores obtained from the MACM and resting-state analyses. Difference Z-scores were deemed significant if they corresponded to $p < 0.001$. Finally, results from the difference analysis were masked with the respective main effect, that is, voxels showing stronger connectivity in MACM vs. resting-state analyses were only retained if they indeed showed a significant task-driven connectivity with the seed (as revealed by the MACM analysis).

Results

Image-based meta-analysis

In each of the three included studies, increased demands on sensorimotor control recruited a widespread bilateral though right-dominant fronto-parietal network (Figs. 1A–C). The IBMA then indicated four regions of overlapping activation. Among these, a cluster in the right TPJ represented the most extensive region of overlap with a cluster size of 104 voxels. Additionally, we observed three considerably smaller clusters (right IPS, bilateral dPMC) with an average cluster size just over 20 voxels. Given this clear difference in cluster extent, we decided to focus the subsequent connectivity analyses on the predominant cluster found in the right TPJ (Fig. 1D). Thus, the right TPJ (area PFm, Caspers et al., 2006, 2008; MNI peak coordinates: 58/− 46/27 [cluster-size: 104 voxels/351 mm³], see Supplementary Fig. S1) was used as the sole seed region for the analysis of task-depended and task-independent FC via MACM and resting-state correlations.

FC analysis by coordinate-based meta-analysis (MACM)

In addition to the 'shared' network as described below, task-dependent FC (Fig. 2B1), as revealed by MACM, involved the bilateral pre-supplementary motor area (pre-SMA, area 6, Geyer, 2004), ventral and dorsal premotor cortex (vPMC/dMPC, area 6, Geyer, 2004), and the thalamus. Furthermore, left-hemispheric putamen, (vPMC), M1 (area 4p; Geyer et al., 1996), and S1 (areas 3b, 3a, 2; Geyer et al., 1999, 2000; Grefkes et al., 2001) as well as right-hemispheric pallidum and caudate nucleus revealed significant co-activation. Co-activations were also found in the region of the right areas 44/45 (Amunts et al., 1999) and bilateral anterior intraparietal sulcus (hIP2; Choi et al., 2006) extending into the superior (area 7PC, Scheperjans et al., 2008a,b) and inferior (area PFcm, Caspers et al., 2006, 2008) parietal lobe. When assessing the paradigm classes of
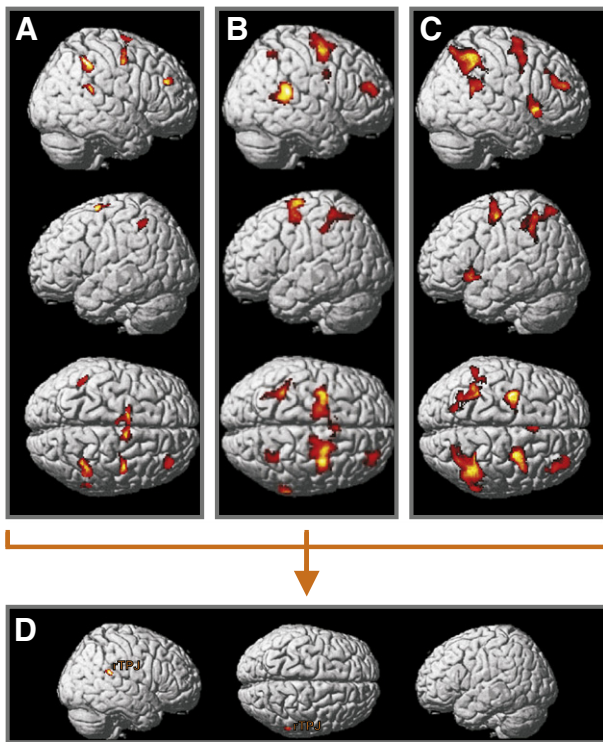
Fig. 1. In three recently published neuroimaging studies (A: Eickhoff et al., 2011, B: Jakobs et al., 2009, C: Cieslik et al., 2010), we applied variations of a manual two-choice reaction time task to investigate neural correlates of increasing demands on sensorimotor top-down control. In each of these studies, we observed activation of a similar bilateral, though right-hemispheric dominant fronto-parietal network. Significant activations are projected onto rendered surfaces of the MNI single-subject template brain. The subsequent image-based meta-analysis revealed a single focus of convergent activation in the right temporo-parietal junction (D) which was thus used as the seed region for the analysis of functional connectivity.

those experiments that featured activation in the right TPJ seed and hence contributed to the MACM analysis, we observed that several different kinds of paradigms/tasks were associated with right TPJ activation (see Supplementary Fig. S2). A strong predominance of any particular kind of task, however, was not found, with strong contributions of somatosensory, visual, cognitive, and motor tasks.

FC analysis of resting-state imaging data

In the resting state (Fig. 2B2), reflecting rTPJ connectivity in the absence of a structured task, we observed, in addition to the shared network described below, significant correlations with the dorsolateral prefrontal cortex (DLPFC), insula (Id1, Kurth et al., 2010b), middle cingulate cortex (Palomero-Gallagher et al., 2008, 2009) and inferior/superior parietal lobe. Additional left-hemispheric correlation was found with the operculum (OP1, OP4; Eickhoff et al., 2006a,b), cerebellum (lobule VII, crus I & II; Diedrichsen et al., 2009), dPMC, precuneus, and temporal pole, whereas additional right-hemispheric correlation occurred with area 45 (Amunts et al., 1999) and inferior temporal gyrus.

Conjunction across MACM and resting-state FC analyses

The conjunction (Fig. 2C) across both individual FC analyses (Figs. 2B1 & 2B2) revealed a shared network comprising bilaterally the inferior parietal cortex (areas PF, PFm) extending into the TPJ, inferior frontal area 44, the anterior dorsal insula and the SMA (area 6, Geyer, 2004). Right-hemispheric activation was observed in the dPMC and middle cingulate cortex, the posterior DLPFC (cf. Rottschy et al., 2012), the middle temporal gyrus, putamen and OP 4.

Activation restricted to the left hemisphere was only found in the cerebellum (lobule VI). In summary, in both task-dependent and task-free states, the right TPJ entertains close FC with a bilateral, though right-dominant network resembling the 'ventral action-control/attention network' as described by Corbetta and Shulman (2002).

Difference between MACM and resting-state FC analyses

Fig. 2A1 illustrates the pattern of FC that was specific for the task-dependent state as revealed by the contrast of 'MACM > resting state connectivity' (see also Supplementary Table S1). We observed significantly stronger task-dependent FC of the right TPJ with the medial premotor cortex (SMA/pre-SMA), bilateral area 44, dPMC, intraparietal sulcus/superior parietal lobe (7A, 7PC, hIP3), and thalamus as well as left-hemispheric regions of more pronounced connectivity with vPMC, putamen, insula lobe, and cerebellum (lobule VI). In the right hemisphere, V5 (hOC5, Malikovic et al., 2007) featured stronger task-dependent than task-independent FC with the right TPJ.

The reversed contrast ('resting state > MACM connectivity', Fig. 2A2) revealed areas featuring stronger FC with the seed in the task-free resting state (see also Supplementary Table S1). Such a pattern was significantly seen bilaterally in the medial superior parietal lobe (5 Ci, 7A, 5 M, Scheperjans et al., 2005), dorsolateral prefrontal cortex, and anterior/middle cingulate cortex.

Discussion

We demonstrated that across three studies, increased demand on stimulus–context integration in sensorimotor control was consistently associated with increased activation of the right TPJ (Fig. 1D, see also Fig. S1). Subsequently, whole-brain functional connectivity of this region was delineated via meta-analytic connectivity modeling (task-dependent FC) and analysis of resting-state images from 100 healthy volunteers (task-independent FC).

Convergent functional coupling across approaches, i.e. independent of the presence or absence of an externally structured task, was observed in a shared network with right-hemispheric dominance. Herein, the inferior parietal cortex, area 44, anterior dorsal insula, and SMA (Fig. 2C) were found bilaterally. Dorsal premotor cortex, middle temporal gyrus, middle cingulate cortex, putamen, and parietal opercular area OP4 of the right hemisphere as well as the left-hemispheric cerebellum featured unilateral convergent functional coupling with the right TPJ.

Stronger task-independent FC with the seed ('resting state >-MACM connectivity', Fig. 2A2, Table S1) was observed bilaterally in the medial superior parietal lobe (precuneus) and adjacent posterior cingulate cortex, dorsolateral prefrontal cortex, and anterior/middle cingulate cortex.

The reversed contrast, i.e. FC specific for the task-dependent state ('MACM connectivity > resting state', Fig. 2A1, Table S1), revealed significantly stronger coupling of the right TPJ with bilateral premotor regions (SMA/pre-SMA, dPMC), area 44, superior parietal cortex, and thalamus. In addition, we observed differential co-activation with left-hemispheric vPMC, insula, putamen, and cerebellum (lobule VI) as well as with V5 (hOC5) in the right hemisphere.

Concepts of functional connectivity

FC is defined as the 'temporal coincidence of spatially distant neuro-physiological events' and may be assessed with cross-correlation of, e.g., spiking patterns or field potentials in neurophysiological experiments (Schlögl and Supp, 2006). Currently, however, most FC analyses are based on (resting-state) fMRI. In their seminal study, Biswal et al. (1995) cross-correlated the time courses of resting-state fMRI signals from different brain regions, noting that FC may be inferred from significant correlation in the signal fluctuations
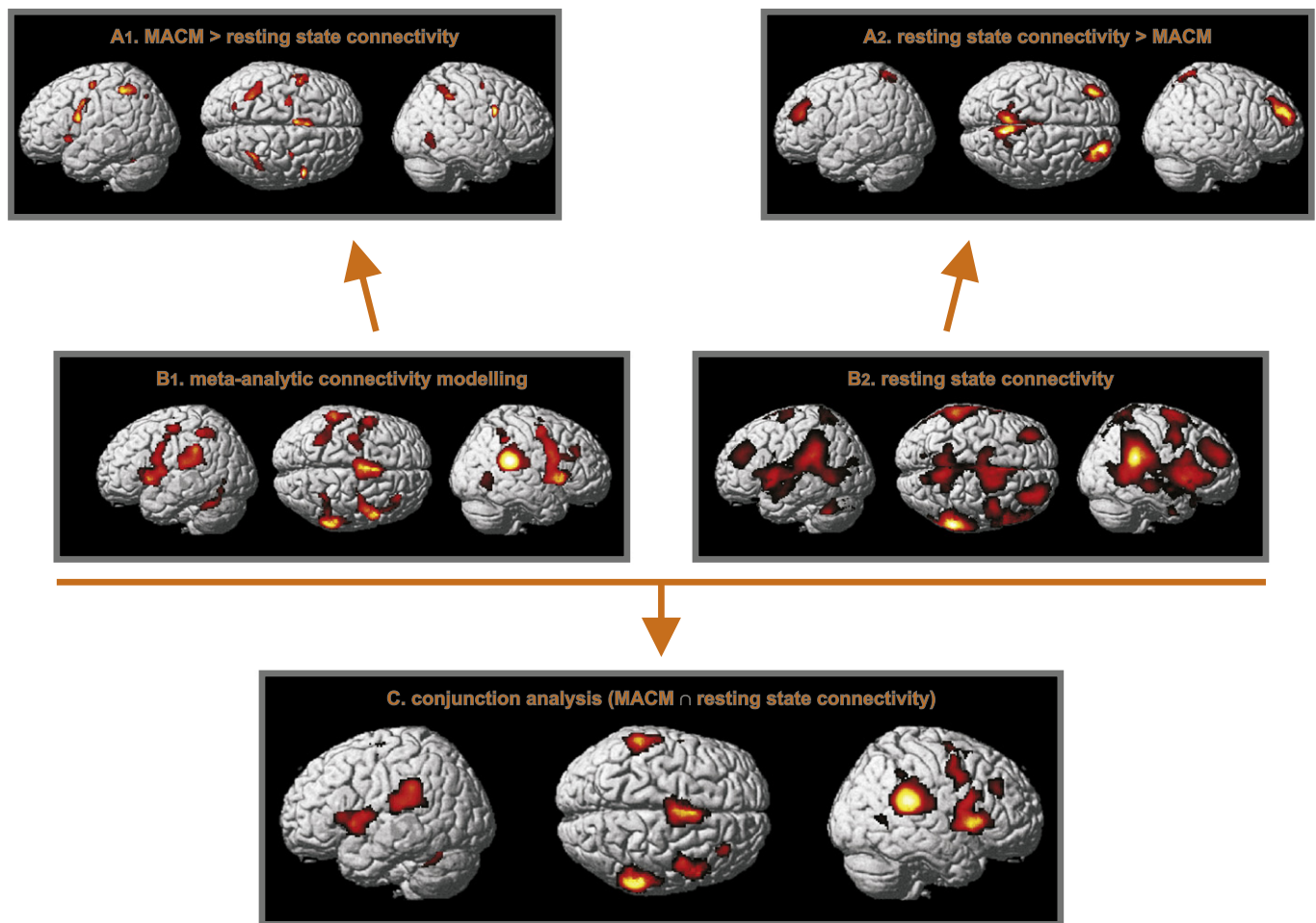
Fig. 2. The conjunction analysis (C) across task-dependent connectivity (MACM, B1) and that obtained for the task-free state (B2) revealed a shared network comprising bilateral inferior parietal cortex, area 44, insula, and supplementary motor area (SMA), right premotor and middle cingulate cortex, middle temporal gyrus, putamen, and OP4 as well as the left cerebellum. In both task-driven and task-free states, the right TPJ thus entertains close functional connectivity with a bilateral though right-dominant 'ventral' action-control/attention network (Corbetta and Shulman, 2002). Functional connectivity specific for the task-dependent mental state (A1) additionally involved bilateral (pre-)SMA, dorsal premotor cortex, area 44, intraparietal sulcus, and thalamus, left basal ganglia and vPMC as well as right V5. Conversely, in the resting-state analysis (A2), reflecting TPJ connectivity in the absence of a structured task, we observed selectively increased connectivity with bilateral dorsolateral prefrontal cortex, medial superior parietal cortex (precuneus), and anterior/middle cingulate cortex.

across distant brain regions. Here, we assessed correlation (across scans, i.e., time) between the BOLD-signal time course of the right TPJ and time courses of all other locations in the brain. Using this approach, we aimed at identifying regions that are significantly (functionally) coupled with the seed region in the task-independent state.

Large-scale databases such as BrainMap (Laird et al., 2009, www. brainmap.org) and algorithms for meta-analytic connectivity modeling (MACM; Laird et al., 2009; Eickhoff et al., 2009) constitute the basis for comprehensive task-based FC analyses: MACM is based on the idea of assessing which brain regions co-activate above chance with the seed across a large range of functional tasks. In contrast to the more traditional definition of FC as coherent fluctuations across time, in MACM, the unit of observation is the neuroimaging experiment. The strength of MACM is the delineation of networks that are conjointly recruited across a broad range of tasks, reflecting robust patterns of coordinated activity in response to an externally structured task.

These two approaches hence provide complementary methods of investigating FC: Task-independent FC was assessed by correlating resting-state fMRI time-series, while task-dependent FC was revealed by investigating significant co-activations of the seed region across different neuroimaging experiments (Eickhoff and Grefkes, 2011). Together, these allow a comprehensive assessment of the FC of the right TPJ across fundamentally different mental states.

Right TPJ in and beyond stimulus–context integration

In the present study, we defined the location of a seed region in the right TPJ based on a multi-study conjunction of experiments on stimulus–context integration and then assessed its co-activation patterns across a wide range of tasks as well as resting-state BOLD signal correlations. Therefore, the FC analyses did not pertain specifically to stimulus–context integration but rather provided an across-task and a no-task assessment of the interactions of the seed (Eickhoff and Grefkes, 2011). That is, our results reflect general interactions of the seed region, not those specific to stimulus–context integration. Nevertheless, the approach taken to identify the seed has important implications for the interpretation of our connectivity data, as a rather broadly defined macroanatomical region like the TPJ may contain several different functional modules. That is, different areas within a region like the TPJ may hold different functions and hence potentially also connectivity patterns. In fact, when considering the current literature on the TPJ, it may be noted that this region is not only implicated in action control and stimulus–context integration but also in several other tasks, some of which seem to hold psychological similarities (e.g. stimulus-driven attention, visual search; Corbetta and Shulman, 2002; Mavritsaki et al., 2010; Menon et al., 2001), while others appear completely unrelated (e.g. social cognition, mentalizing, perspective taking; Decety and Lamm, 2007; David et al., 2008;

Vogeley et al., 2001). There is thus good evidence for a functional heterogeneity within the TPJ. Given this very likely differentiation, we would argue that the tasks used to define a seed should have an important influence on the subsequent connectivity analyses even though these consider across-task and no-task interactions. To illustrate this point, it may be assumed that a seed in the right TPJ defined by a conjunction across social-cognition tasks would have had a different location within this region and most likely also a different pattern of MACM and resting-state connectivity. While our approach hence does not definitively associate a brain region and its connectivity to a particular cognitive function such as stimulus–context integration, the functional context established by the definition of the seed nevertheless provides its precise allocation to a (functional) module and hence an important constraint to the interpretation of the observed connectivity patterns. This holds in particular for regions that are as broadly defined and functionally heterogeneous as the TPJ.

Right TPJ and the concept of predictive coding

The performed multi-study conjunction indicated that the right TPJ (area PFm) as the most extensive region of overlap between three neuroimaging contrasts probing increased demands for sensorimotor control and stimulus–response integration. Previous studies point to a key role of this region also in other 'higher cognitive functions', such as attention (Corbetta and Shulman, 2002) or visuomotor integration (Mooshagian et al., 2008). This raises the question as to how these operations can be integrated in a comprehensive theoretical construct.

Predictive coding (Rao and Ballard, 1999; Summerfield and Mangels, 2006; Kilner et al., 2007a) is a hypothesis on the fundamental nature of neuronal information processing. Within this model the brain is conceptualized as a Bayesian machine, i.e. perception is based upon generative models enabling probabilistic inference on sensory inputs and the underlying causes. This is enabled by a hierarchical organization of brain regions with reciprocal connections between them. The prediction error, i.e. the difference between sensory input and internal prediction, is computed at each level and passed to higher levels via forward connections. Its size reflects the accuracy of the predictions and potential necessity for adjustment. Feedback connections pass predictions back to the lower level. The objective of these computations is the (unconscious and highly automated) minimization of the environmental entropy (i.e. average uncertainty) to optimize predictions about incoming information. So far, evidence for predictive coding has mainly been discussed in the context of sensory paradigms (Behrens et al., 2007; Summerfield and Mangels, 2006). However, observations of faster reaction times and reduced error rates for predominant relative to deviant cues have raised the notion of predictive motor coding. Mechanistically, predictions about prospective sensory input should entail the a priori preparation of an adequate motor program. If an upcoming stimulus matches the prediction, the prepared motor program simply has to be released, instead of being chosen de novo from the motor repertoire, resulting in more efficient reactions.

As each of the three studies used to define the seed region presented lateralized visual stimuli and required lateralized responses, it may be argued that the observed effects may be attributable to increased attention and spatial (re-)orientation (Corbetta and Shulman, 2002; Thiel et al., 2004). In particular, stimuli appeared more frequently in the unexpected (and hence unattended; Shulman et al., 2009) location in 'high-demand' conditions. This is well in line with a study of Downar et al. (2000) observing an involvement of (predominantly) the right TPJ in multimodal change detection, i.e. detection of 'salient' stimuli. We would argue that these interpretations (re-orientation or attentional demands) may be reconciled with predictive coding concepts. Under this theoretical framework, stimulus-

driven re-orienting may be understood as the upstream effects of high prediction errors, which trigger a reactive orientation toward the site of the unpredicted stimulus. In a Bayesian system of sensory inference, attention may thus be conceptualized as inference on the precision of predictions (Feldman and Friston, 2010). If a prediction error is high, attentional re-orientation is instantiated.

Lesions of (especially) the right (Vallar et al., 1993) TPJ have been conjectured to clinically manifest themselves as a lack of awareness of space on the contralesional side of the body, i.e., neglect (Mavritsaki et al., 2010). In accordance with the theoretical framework outlined above, a unilateral deficit in evaluating upstreaming stimuli may result in persistent 'attention' to only one (i.e. the ipsilesional) side of the environment. However, Karnath et al. (2001) emphasized that 'the superior temporal cortex rather than the IPL or TPO junction is the substrate of spatial neglect in both monkeys and humans' (p. 952). Thus, the putative involvement of (r)TPJ lesions in neglect is still a matter of debate.

In summary, based on the assumption that probabilistic inference is an integral part of sensory processing and motor preparation, the concept of predictive coding may provide a theoretical framework for the computational processes underlying stimulus–response integration for sensorimotor control. Based on the current multi-study conjunction we would argue that the right TPJ might be a key structure for implementing attentional (re-)orientation by inference on prediction errors within this framework.

Core network of consistent functional connectivity

The term 'core network' denotes regions featuring convergent functional coupling with the right TPJ in the task-driven and endogenously controlled state (Fig. 2C). Its nodes are thus part of very much the same networks as the seed irrespective of the current mental state. In this context, it has to be noted that close resemblance between 'resting-state networks' and those jointly engaged in task-based studies has been reported and hence the notion of 'rest' in the absence of a specific task has evolved into a concept of an unconstrained sampling of different brain networks with preponderance for introspective aspects (Raichle et al., 2001; Schilbach et al., 2008; Smith et al., 2009).

The human insula (most notably the anterior dorsal portion) activates in a broad range of tasks across diverse functional domains, such as emotion processing, interoception, (working) memory and attention (Craig, 2009; Kurth et al., 2010a). Thus, the insula is regarded as integration area, mediating dynamic information flow between large-scale brain networks (Dosenbach et al., 2006; Menon and Uddin, 2010) as well as providing a link between the processing of external information and monitoring the internal milieu (Craig, 2009). In the current study, consistent co-activation of the anterior dorsal insula may therefore originate from its function as an integrative hub controlling the flow of information and implementing task-sets, i.e., high-level priors.

Several neuroimaging studies provide evidence for a role of the inferior parietal cortex (IPL) in the multi-modal integration of stimuli (Renier et al., 2009) as well as movement planning and execution (Iacoboni, 2006). The FC with the (right) TPJ reflects the dense anatomical connectivity between these (Lewis and Van Essen, 2000). Most likely, the IPL might implement the planning, selection and preparation of movement routines that is controlled by the predictions (and associated errors) provided by the right TPJ.

It should be noted that this 'core network' (right TPJ, anterior insula, IPL) resembles the so-called 'ventral attention network' (Corbetta and Shulman, 2002), typically activated during the detection of salient and behaviorally relevant stimuli, i.e. stimulus-driven reorienting, and acting as a 'circuit breaker' for ongoing processes in the dorsal attention network (Corbetta et al., 2008). The close similarity between the 'core network' and the 'ventral attention network'

thus fits well with the Bayesian framework of stimulus-driven reorienting as outlined above. In line with the FC data provided by Fox et al. (2006) we would thus argue for an important role of the TPJ within the ventral attention network, potentially reflecting a computational core in a predictive coding system.

Stronger couplings in the task-dependent state

In a system of Bayesian inference, minimization of prediction errors requires the supply with bottom-up (sensory) information. In this context, bilateral activation of the thalamus may be reconciled with its putative function as 'input gate' routing upstreaming information to sensorimotor and association cortices (Johansen-Berg et al., 2005) with collaterals to the TPJ as a predictive integrator. This interpretation may particularly hold for the right hemisphere where activation in the thalamus was observed in those parts that were shown to connect to the temporal cortex (including the TPJ) (Behrens et al., 2003). On the left hemisphere, in contrast, predominant activation in regions projecting to the prefrontal cortex (probably mediodorsal nucleus) may reflect the role of the thalamus as a cortico-cortical integration hub (Cappe et al., 2009), such as the possible involvement of the mediodorsal thalamus in sending prospective motor information to the DLPFC (Watanabe and Funahashi, 2012).

Regions of the posterior parietal cortex, in particular the superior parietal lobe and intraparietal sulcus (SPL/IPS), are involved in stimulus–context integration and stimulus–response matching (Wolfensteller and von Cramon, 2010). Thus, functional coupling with these regions may indicate pre-processing of incoming information by these, i.e. 'outsourcing' of lower-level integration processes. In other words, there may be parallel processing of the stimuli themselves (in the SPL/IPS) and their match with current predictive codes (in the right TPJ), allowing inference on both stimuli and predictions. Formally, this would entail a functional hierarchy between the SPL/IPS and the higher-level right TPJ.

Subsequently, the frontal areas may utilize this prediction to adjust behavioral plans and goals (Koechlin and Summerfield, 2007), linking predictive coding on sensory information with predictive motor coding. In the current study, bilateral co-activation of area 44 may indicate this region as an important node for the 'action' stream, which is consistent with previous evidence implicating this region in behavioral planning and executive top-down influences on premotor areas (Koechlin and Jubault, 2006). The coupling between the right TPJ and area 44 may hence correspond to an alignment between predictions and the preparation of adequate behavioral responses. Such response patterns may be pre-selected and hence prepared in the likewise co-activated premotor areas, i.e., the dPMC and the pre-SMA. While FC analyses may not reveal the directionality of interactions, based on previous evidence we would propose the following relationship between these regions: Whereas area 44 provides the link between the sensory and motor domain, the pre-SMA may subsequently control the implementation of motor preparation in the dPMC. This view would be in line with observations that the pre-SMA is involved in executive motor control, e.g., modifications of movement plans by inhibition or switching of responses (Picard and Strick, 1996). In contrast, the dPMC features close interactions with the motor output system (Chouinard and Paus, 2006; Dum and Strick, 2005) and therefore is a putative recipient of the generated motor plans. In the proposed model, the dPMC would thus constitute the lowest stage of the motor stream, implementing the actual preparation of motor responses.

In summary, we thus propose that the task-based FC data, in synopsis with previous evidence from humans and non-human primates, may indicate interaction of the right TPJ with a 'sensory stream' of predictive coding consisting of the thalamus as the sensory gateway and the SPL/IPS for stimulus processing on one hand as well as with a 'motor stream' comprising area 44, pre-SMA and dPMC, itself potentially organized in a hierarchical fashion reflecting a progression from more abstract motor plans to the preparation of a particular action (i.e. the specification of free parameters in motor commands, such as direction, extent and force of a given movement).

Stronger couplings in the task-independent state

Patterns of neural activation in the absence of an externally structured task reflect the brain's 'physiological baseline' (Gusnard and Raichle, 2001) but may not be equated with 'mental rest' due to the high spatio-temporal structuring of ongoing activity that seems to reflect task-relevant networks (cf. Fox and Raichle, 2007; Smith et al., 2009). Rather than being at rest, the brain should thus be in a state of unconstrained cognition (Schilbach et al., 2008), i.e. implementing a broad variety of (predominantly internally oriented) operations. In the current study, we observed increased connectivity of the right TPJ in this task-independent (compared to stimulus-driven) brain state with a bilateral network comprising the anterior cingulate and dorsolateral prefrontal cortices as well as the precuneus and adjacent posterior cingulate cortex (PrC/PPC).

Interestingly, medial parietal and cingulate cortices were reported to show highest levels of glucose consumption in the endogenously controlled state (Gusnard and Raichle, 2001) and de-activate upon commencement of structured tasks (Schilbach et al., 2008), supporting the notion of a 'default-mode network'. Nevertheless, activity within these regions is not restricted to the 'physiological baseline'. Rather, they have been observed in a broad range of internally directed cognitive tasks including episodic memory and first-person perspective taking (Vogeley et al., 2001) as well as the processing of self-relevant information and intentions, including intentions to act (cf. Cavanna and Trimble, 2006). It may hence be assumed that in the mode of unconstrained cognition these midline regions may gather and integrate information about past self-referential events. Hereby, they could provide personal experience as an important backdrop for mental operations in the absence of externally structured tasks or sensory information. In contrast, the (anterior) dorsolateral prefrontal cortex has been conceptualized as a key node for the generation and representation of internal goal and task-set representation, i.e., overarching plans (Koechlin and Summerfield, 2007). Though speculative, we would thus propose that the right TPJ may provide the computational link between autobiographic memories (past; PrC/PPC), self-reference (present; anterior cingulate cortex and goal-representations (future; DLPFC) by evaluating predictive codes. In a Bayesian framework, this would thus represent the basis of forming predictions about future long-term goals based on previous experience. How does this relate to the apparent role of the right TPJ during stimulus-driven tasks, namely optimizing short-term representations of the sensory environment for motor preparation? We would conclude that by interaction with domain-specific brain regions, the right TPJ and anterior insula forming the 'core network' may implement the governance of predictive coding across a wide range of mental states, irrespective of the domain (perceptual, motor or cognitive) and time course (short-term or long-term).

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Acknowledgments

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