Associations and dissociations between default and self-reference networks in the human brain

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ABSTRACT

Neuroimaging has revealed consistent activations in medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC) extending to precuneus both during explicit self-reference tasks and during rest, a period during which some form of self-reference is assumed to occur in the default mode of brain function. The similarity between these two patterns of midline cortical activation may reflect a common neural system for explicit and default-mode self-reference, but there is little direct evidence about the similarities and differences between the neural systems that mediate explicit self-reference versus default-mode self-reference during rest. In two experiments, we compared directly the brain regions activated by explicit self-reference during judgments about trait adjectives and by rest conditions relative to a semantic task without self-reference. Explicit self-reference preferentially engaged dorsal MPFC, rest preferentially engaged precuneus, and both self-reference and rest commonly engaged ventral MPFC and PCC. These findings indicate that there are both associations (shared components) and dissociations between the neural systems underlying explicit self-reference and the default mode of brain function.

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Introduction

Two independent lines of research have implicated anterior and posterior cortical midline regions, specifically medial prefrontal cortex (MPFC) and posterior cingulate extending to precuneus (PCC), in self-related cognition. In one line of research, tasks that permit or encourage explicit self-referential processing have consistently yielded activation in MPFC and PCC (i.e., a self-reference network) (d'Argembeau et al., 2005; Johnson et al., 2002; Kelley et al., 2002; Moran et al., 2006; Northoff and Bermpohl, 2004; Northoff et al., 2006). A second line of research has identified MPFC and PCC as brain regions in which activation is greater during rest than during engagement in a broad range of goal-directed tasks (e.g., Binder et al., 1999; Fox et al., 2005; Greicius et al., 2003; Greicius and Menon, 2004; Gusnard and Raichle, 2001; Mason et al., 2007; Mazoyer et al., 2001; McKiernan et al., 2003;2006; Raichle et al., 2001; Shulman et al., 1997). This network is thought to mediate a "default mode of brain function" that may support self-reflection about internal thoughts and feelings in the absence of external stimulus processing (Gusnard and Raichle, 2001; Raichle et al., 2001). The fact that similar regions are activated during explicit self-reference and default self-reflection has

often been taken as convergent evidence for the roles of MPFC and PCC in self-related thought, and there is evidence that a common ventral MPFC region may be activated in both sorts of self-related thoughts (d'Argembeau et al., 2005; Gusnard et al., 2001). d'Argembeau et al. (2005) used positron emission tomography (PET) to examine similarities and differences between unconstrained self-reference (participants were instructed to think about themselves) and rest. Surprisingly, however, the precise relations between the explicit self-reference and default self-reflection networks have not been delineated using fMRI because no study has compared both kinds of self-reference against a common control condition in a single group of participants. Here, in order to examine directly the relations between these two functional networks, we examined similarities and differences between explicit self-reference and rest conditions relative to a common baseline, within subjects, and in two independent cohorts so as to evaluate the reliability of any findings.

Identification of the neural network mediating self-reference has most often been examined via tasks that require participants to make explicit judgments about themselves. Self-reference studies contrast conditions in which participants judge whether trait adjectives (such as POLITE or TIMID) describe themselves versus conditions in which the same kinds of trait adjectives are judged as describing another person or judged semantically as being positive or negative in valence (Craik et al., 1999; Kelley et al., 2002; Kjaer, Nowak et al., 2002; Heatherton et al., 2006). Both MPFC and PCC regularly exhibit greater activation during self-referential judgments relative to other-referential or valence

judgments (Heatherton et al., 2006; Kelley et al., 2002; Johnson et al., 2002; Fossati et al., 2003; but see Ochsner et al., 2005; Mitchell et al., 2006). Further, MPFC is activated during passive viewing of self-relevant information (Moran et al., 2009), increases in activation linearly with the degree to which a trait is judged self-descriptive (Moran et al., 2006), and is greater at both encoding (Macrae et al., 2004) and retrieval (Fossati et al., 2004) for traits remembered versus forgotten when encoded with reference to the self. Activation in PCC is also frequently observed in self-reference tasks (Kelley et al., 2002; Kjaer et al., 2002; Lou, Luber et al., 2004; Moran et al., 2006), although it has not been consistently activated by the degree of self-relevance of items in studies that investigated this (Macrae et al., 2004; Moran et al., 2006; 2009; Phan et al., 2004). Additionally, transient disruption of PCC function by transcranial magnetic stimulation (TMS) reduces the recall of items that were previously encoded with reference to the self (Lou et al., 2004).

Within the MPFC there is evidence for a functional dissociation between dorsal and ventral regions. A factor analysis of 27 imaging studies of self-reference concluded that there were three statistically independent clusters of activations across studies in ventral MPFC, dorsal MPFC, and PCC (Northoff et al., 2006). It has been proposed that dorsal MPFC is involved in the process of evaluating whether stimuli are self-referential, and ventral MPFC is involved in representing self-referential stimuli (Northoff and Bermpohl, 2004). Two studies have further elucidated the nature of the dissociation between ventral and dorsal MPFC. In one study, judgments about people who held views similar to participants yielded ventral MPFC activation, whereas judgments about people who held views dissimilar to participants yielded dorsal MPFC activation (Mitchell et al., 2006). Ventral MPFC is connected anatomically to striatal, limbic, and midbrain regions related to emotions (Northoff et al., 2006), and people may feel more emotional sympathy with a similar individual. Dorsal MPFC is connected to lateral prefrontal cortex (Northoff et al., 2006), and people may analyze dissimilar individuals in a more cognitive or analytic fashion (Mitchell et al., 2006). In a second study, dorsal MPFC was engaged when participants thought about whether trait characteristics described a person, both themselves and others, whereas ventral MPFC was engaged when participants encountered information that was particularly self-relevant (Moran et al., 2010). Thus, it appears that dorsal MPFC subserves the analysis of character in people in general, whereas the ventral MPFC subserves the analysis of personally relevant information.

The most consistent activations associated with the default mode of brain function also occur in MPFC and PCC/precuneus midline regions during rest relative to tasks, but interpretation of the psychological processes signified by these activations is difficult because participants are not performing any task at rest. Gusnard and Raichle (2001) investigated default-mode processes by comparing rest with tasks in which participants viewed scenes and made either external (non self-relevant) indoor/outdoor judgments or internal (self-relevant) pleasant/unpleasant judgments. Activation in MPFC was greater during both rest and internal judgments relative to external judgments. This suggests that MPFC activation during rest reflects self-relevant thoughts. Further evidence along these lines comes from a study that compared activation during well-practiced working memory tasks relative to novel tasks (Mason et al., 2007). This contrast revealed greater activation in both MPFC and PCC, which further linearly increased with an increasing tendency to mind-wander or daydream. This suggests that performing practice tasks allows the mind to wander towards processing information that is internal in nature and hence self-referential. In addition, the amount of self-referential thoughts reported by subjects during unrelated cognitive tasks correlated with activation in MPFC and PCC (McKiernan et al., 2003, 2006).

Although there are clear-cut similarities between the brain regions activated by explicit self-reference tasks and by the default mode of brain function during rest, it is unknown whether these activations identify a unitary self-referential neural system, or whether there are brain regions that are differentially engaged by explicit self-reference versus rest. We aimed to address this open question by comparing activations associated with explicit self-reference and rest in a single group of participants (Experiment 1), and then to assess the reliability of any findings in a second group of participants (Experiment 2). In both experiments there were three conditions: (1) explicit self-reference during a task in which participants decided whether or not trait adjectives applied to them, (2) rest, and (3) a control condition in which participants decided whether trait adjectives were positive or negative in valence. The critical question was to what extent the self-reference and rest conditions, relative to the valence condition, yielded similar and dissimilar activations.

In order to further dissociate midline brain regions, we investigated their differential resting state networks using seed-driven resting state functional connectivity analyses (rs-fcMRI). Spontaneous, very low-frequency fluctuations (<0.1 Hz) in fMRI BOLD signal reveal temporal correlations between brain regions that appear to define functional networks of the human brain (Biswal et al., 1995; Fox et al., 2005). Here we asked whether functional dissociations between self-reference and default-mode activations would be further supported by convergent rs-fcMRI dissociations.

Materials and methods

Participants

Participants were naïve, right-handed young adults (Experiment 1, N = 10, 4 women; Experiment 2, N = 25, 10 women). Participants were native English speakers, had normal or corrected-to-normal vision, and gave written informed consent in accordance with the requirements of internal review boards at MIT. They were healthy undergraduate students who self-reported that they were not contra-indicated for metal implants, prior psychiatric illness, or any neurological impairment. Participants were scanned using a 32 channel 3.0 Tesla Siemens scanner (MAGNETOM Trio, a Tim system (Siemens Healthcare, Erlangen, Germany)) in the Athinoula A. Martinos Imaging Center at the McGovern Institute for Brain Research at MIT.

Functional imaging

For Experiment 1, imaging parameters were TR = 2 s, TE = 30 ms, flip angle = 90 deg, with 30 4-mm-thick near-axial slices covering the whole brain. Most procedures were identical in Experiment 2, but a few were altered (TR = 3 s, 33 slices). Prior to each scan, four images were acquired and discarded to allow longitudinal magnetization to reach equilibrium. A high resolution, T1-weighted MPRAGE structural scan was also collected.

Procedure

During scanning in Experiment 1, participants viewed 160 trait adjectives presented across 4 functional runs; in Experiment 2, there were 144 trait adjectives in 3 functional runs. Words were drawn from Anderson's (1968) list of trait adjectives, and lists were counterbalanced across conditions for word valence, length, and number of syllables. In Experiment 1, words were presented in a blocked design such that each word was presented for three seconds in blocks of ten words. Prior to each block onset, participants viewed a two-second cue screen describing their task for the upcoming block. Participants either judged the words in the following block for self-reference ("Does this word apply to you?") or for valence content ("Is this word positive?"). Each block was preceded and followed by a 10-second block of rest, during which a fixation cross was presented, and the order of conditions was counterbalanced within and across participants. Experiment 2 involved the same self-reference, valence, and rest conditions except that 144 trait adjectives were presented

across 3 functional runs, blocks were 21 s long, and each block had a 3 s cue followed by 6 words presented for 3 s each. In Experiment 2, there were two additional conditions involving judgments about the traits of participants' mothers and about the appearance (case) of words that were analyzed as part of a separate study and will not be described here. In both experiments, participants responded by way of a button press to indicate a yes or no response to each question.

fMRI data analysis

Data were analyzed with SPM2 and custom software. Motion correction, co-registration, normalization and smoothing were implemented in SPM2. Preprocessed data from each functional run were reviewed for artifacts (http://www.nitrc.org/projects/artifact_detect). Outliers in the image time series (Z>3) were identified and excluded in subsequent statistical analysis, which resulted in an average of nine artifactual time points per participant, or 2.45% of data. There were no significant differences in the number of artifactual time points between conditions. Functional and anatomical data were coregistered, and images were manually inspected to verify accurate

registration. In order to identify the location of functional activation in a standardized coordinate system and to facilitate inter-subject averaging, each participant's data were transformed into a standardized anatomical space provided by the SPM normalized template image. Normalized images were spatially smoothed with a 5 mm FWHM Gaussian kernel. Statistical analysis of data across participants proceeded by entering each participant's smoothed, normalized, realigned functional data into a general linear model (GLM). This first level design matrix contained factors modeling regressors for the "self" and "other" conditions as well as the instructions that were presented during the task. These factors were convolved with a canonical hemodynamic response function (Friston et al., 1995). To correct for residual motion-related variance post realignment, the six realignment parameters were included in the design matrix as regressors of no interest. Stimulus correlated motion (SCM) was calculated for each condition and motion parameter in order to verify that there were no significant between condition differences in degree of stimulus correlated motion as well as to determine whether we may be regressing out too much task related variance by including the motion parameters in the first level design matrices. A high-pass filter
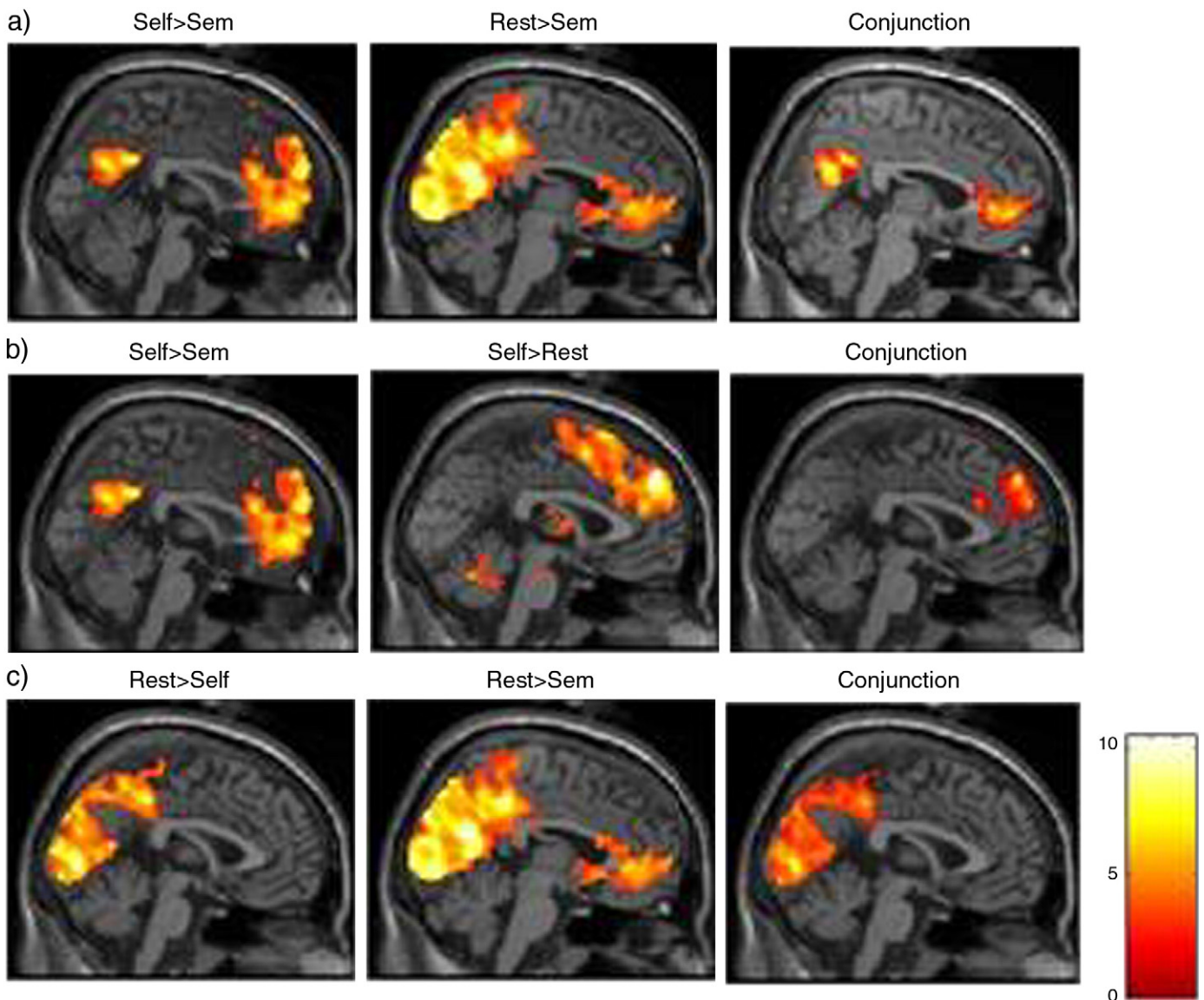

Fig. 1. Brain regions activated in Experiment 1 for Self (trait judgment), Semantic (Sem; valence judgment), and Rest (fixation). Contrasts between conditions in first and second columns, and conjunctions of contrasts in each row in third column; (a) Self and Rest>Semantic in BA 10 and BA 31; (b) Self>Semantic and Rest in BA 9; (c) Rest>Self and Semantic in BA 7.

Table 1
Regions showing activation for Self>Semantic.

		BA	x	y	z	T score	# voxels
Superior frontal gyrus	Right	9	4	54	22	10.53	1070
Cingulate gyrus	Right	31	2	−48	30	10.23	484

Coordinates (x, y, and z) based on MNI brain (Montreal Neurologic Institute).
BA: Brodmann area.

was applied to the data with a cut-off frequency of 0.01 Hz to correct for low frequency signal drifts. The contrast images, linear combinations of beta images, from the first level analyses were then subjected to second-level random effects analyses. Group analyses for Experiments 1 and 2 were performed on (a) self-reference compared to valence task contrast, (b) rest compared to valence task contrast, (c) rest compared to self-reference contrast, and (d) self-reference compared to rest contrast.

Conjunction inferences were performed with the conjunction null method based on the minimum statistic (supremum P values over the contrasts of interest; Nichols et al., 2004). Conjunction analyses were performed using a conjunction-null test controlled at FWE-corrected cluster-level p<0.05 (combined with an uncorrected voxel-level p<0.001 height threshold). In order to identify regions associated with both self reference and default mode brain function, a conjunction analysis was performed on the (self-reference task>valence task) and (rest>valence task) contrasts. In order to identify regions preferentially related to self-reference, a conjunction analysis on the (self-reference task>valence task) and (self-reference task>rest) contrasts was performed. In order to identify regions preferentially related to rest, we examined the conjunction of the (rest>self-reference task) and (rest>valence task) contrasts. Beta values were calculated from common regions of interest (ROIs) in ventral MPFC, dorsal MPFC, PCC, and precuneus separately for all conditions. These ROIs were generated with 10 mm spheres centered around the peak coordinates of the conjunction analyses for Experiment 1. While analysis within these regions necessarily reveals greater common activation (biased estimates) across each relevant conjunction, data are displayed to characterize the pattern of activation within each area across all conditions. These same ROIs from Experiment 1 were then used to extract the independent, mean beta values from Experiment 2 (resulting in unbiased estimates and valid ROI-level statistics).

Resting-state data were analyzed from the rest blocks using a seed driven approach with in-house, custom software (http://www.nitrc.org/projects/conn/). Data were slice time corrected, realigned, coregistered, normalized, and spatially smoothed with 6-mm kernel. Physiological and other spurious sources of noise were estimated using the aCompcor method (Behzadi et al., 2007), and removed together with movement-related covariates. The residual BOLD time-series were band-pass filtered over a low-frequency window of interest (0.009 Hz<f<0.08 Hz). Correlation maps were produced by extracting the residual BOLD time course from seed regions based the conjunction ROIs, and computing Pearson's correlation coefficients between that time course and the time course of all other voxels. Correlation coefficients were converted to normally distributed scores using Fisher's transform to allow for second-level General Linear Model analyses. Second-level analyses compared the whole-brain connectivity patterns with the four seeds (conjunction ROIs). All

analyses have whole brain FDR (p<0.05) correction at the voxel level and FWE p<0.05 correction at the cluster level.

Results

Experiment 1

Self reference

There was greater activation during the self-reference task than during the valence task in regions typically associated with self reference, including MPFC extending into ACC and PCC/Precuneus (Fig. 1) (Table 1).

Default

There was greater activation during rest than during the valence task in regions typically associated with the default network, including MPFC extending into ACC as well as a large posterior region of activation, peaking in the PCC/Precuneus and extending into lateral parietal cortex, hippocampus, and parahippocampal gyrus (Fig. 1) (Table 2).

Functional associations

The conjunction analysis of self-reference and rest (each versus valence task) revealed common activations only in ventral MPFC and PCC/Precuneus (Figs. 1 and 2, Table 3).

Functional dissociations

The conjunction analysis of self-reference (versus valence judgment and rest) revealed activation only in dorsal MPFC and in the caudate nucleus bilaterally. These regions thus appeared to be engaged preferentially during the self-reference task (Fig. 1). The conjunction analysis of rest (versus both self-reference and valence
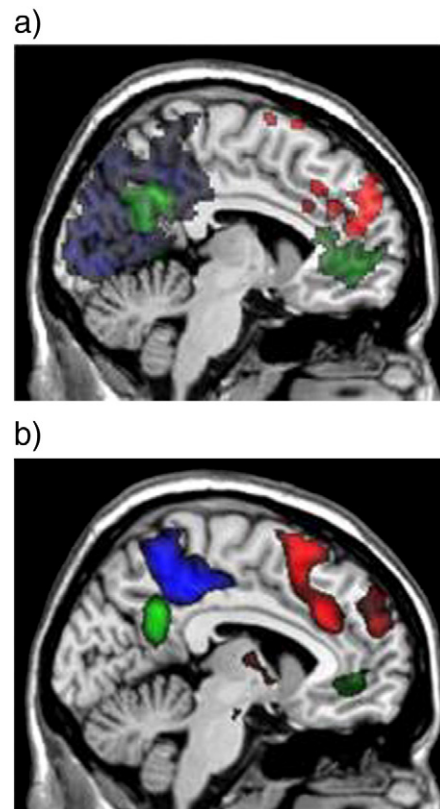
Table 2
Regions showing activation for Rest>Semantic.

	BA	x	y	z	T score	# voxels
Posterior cingulate	R	31	22	−60	20	14.31	23, 497
Superior frontal gyrus	R	10	20	58	8	9.87	2144

Coordinates (x, y, and z) based on MNI brain (Montreal Neurologic Institute).
BA: Brodmann area.

Fig. 2. Conjunction analyses of self-referential processing and default network for Experiment 1 (a) and Experiment 2 (b). GREEN: Self>Semantic and Rest>Semantic in BA 10 and BA 31; RED: Self>Semantic and Self>Rest in BA 9; BLUE: Rest>Self and Rest>Semantic in BA 7.

Table 3
Significant regions in conjunction analyses.

	BA	x	y	z	T	# voxels
a. Significant regions in conjunction of Self>Semantic and Rest>Semantic						
Experiment 1						
PCC	R	31	2	−64	28	7.31	759
Medial Frontal	R	10	2	52	0	5.85	414
Experiment 2						
PCC	R	31	9	−54	27	6.36	302
Medial Frontal Gyrus	R	10	3	45	−3	5.57	126
b. Significant regions in conjunction of Rest>Semantic and Rest>Self						
Experiment 1						
Precuneus	R	7	4	−40	44	13.06	8005
Experiment 2						
Precuneus	R	7	12	−39	45	10.81	1198
c. Significant regions in conjunction of Self>Semantic and Self>Rest						
Experiment 1						
MFG	M	9	0	52	42	7.37	374
Experiment 2						
MFG	M	9	3	30	33	7.75	1131

Coordinates (x, y, and z) are based on MNI brain (Montreal Neurologic Institute).
BA: Brodmann area. p<0.05 FWE cluster corrected.

task) revealed activation in precuneus, which extended posteriorly. This region thus appeared to be engaged preferentially during rest (Figs. 1 and 2). The extent of the activation was unexpectedly and atypically broad, and was not replicated in Experiment 2.

Parameter estimates

Parameter estimates were extracted from 10 mm spheres around the peaks of the conjunction ROIs for comparison with Experiment 2 (Fig. 3.).

Experiment 2

Behavioral data

Participants were significantly slower to respond on self trials relative to semantic trials (self mean ± s.e.m. (msec), 1362 ± 54; semantic, 1209 ± 42, two-tailed paired t-test: t(24) = 5.68, p<0.001).

Functional associations and dissociations

We applied the same voxel-level conjunction analyses to data from Experiment 2. There was a similar pattern of shared and differential activations across both experiments (Fig. 2, Table 3).

Parameter estimates

ROI analyses interrogating the regions defined by Experiment 1 conjunctions revealed the same pattern of activations in Experiment 2 data: 1) preferential activation for rest in precuneus (BA 7: rest-semantic, t(24) = 9.42, p<0.001; rest>self, t(24) = 7.32, p<0.001); 2) preferential activation for self in dorsal MPFC (BA 9: self>semantic, t(24) = 6.22, p<0.001; self>rest, t(24) = 5.73, p<0.001); and activation for both rest and self in ventral MPFC (BA 10: rest>semantic, t(24) = 4.29, p<0.001; self>semantic, t(24) = 6.15, p<0.001) and PCC (BA 31: rest>semantic, t(24) = 4.40, p<0.001; self>semantic, t(24) = 5.87, p<0.001) (Fig. 3c).

Rs-fcMRI analyses

During rest, the "self" ROI (dorsal MPFC) had higher connectivity (p<0.001) with bilateral inferior frontal gyrus (BA 47) than the "self and rest" ROI (ventral MPFC and PCC) (Fig. 4a, Table 4). The "rest" ROI (precuneus) had higher connectivity (p<0.001) with bilateral parietal (BA 40) and bilateral dorsal lateral prefrontal cortex (BA 9, BA 46) than the "self and rest" (PCC and ventral MPFC) (Fig. 4b and c, Table 4).

Discussion

This study aimed to identify associations and dissociations in midline cortical structures between the self-reference network and the default network. The two networks were associated by their common inclusion of ventral MPFC (BA 10) and PCC (BA 31). The two networks were doubly dissociated by preferential engagement of dorsal MPFC (BA 9) for self-reference and of precuneus (BA 7) for rest. The general patterns of functional associations and dissociations of the three conjunctions were similar in the two experiments. In addition, the parameter estimates in Experiment 2, which were extracted from the ROIs defined in Experiment 1, were strikingly similar to the parameter estimates extracted in Experiment 1. Thus, the self-reference and default networks shared some components, but were also distinctive by their unshared components (Table 5).

Ventral MPFC and PCC appear to be engaged during both self-referential processing and rest. Both regions are frequently identified as being activated during self-reference tasks (e.g., Kelley et al., 2002; Kjaer et al., 2002; Lou et al., 2004; Moran et al., 2006), and during rest relative to task (e.g., Binder et al., 1999; Fox et al., 2005; Greicius et al., 2003; Greicius and Menon, 2004; Gusnard and Raichle, 2001; Mason et al., 2007; Mazoyer et al., 2001; McKiernan et al., 2003, 2006; Raichle et al., 2001; Shulman et al., 1997). The overlap between default and self-reference functions in these regions is further supported by
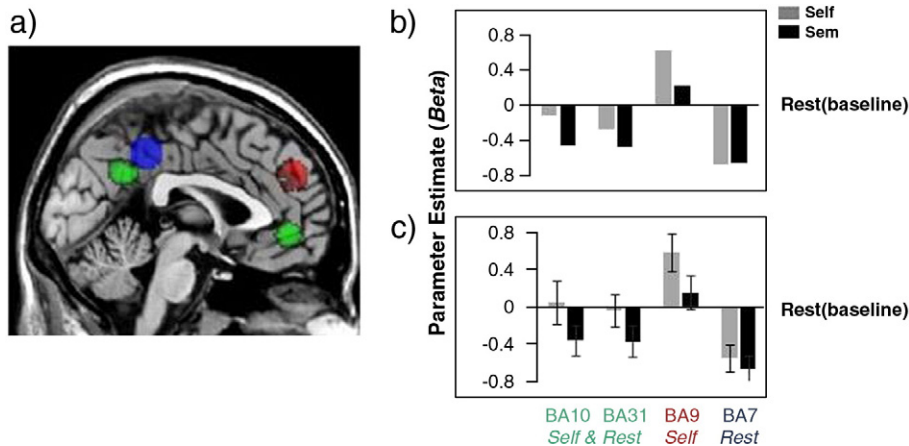

Fig. 3. Conjunction spheres and mean parameter estimates: a) 10 mm conjunction spheres around peak activations for Experiment 1: GREEN: (Self>Semantic and Rest>Semantic); RED: (Self>Semantic and Self>Rest); BLUE: (Rest>Self and Rest > Semantic). b) Mean parameter estimates for regions of interest: Mean beta values, representing percentage BOLD signal differences between the self-referential and semantic conditions vs. resting baseline for the 10 mm conjunction spheres for Experiment 1 (b) and for Experiment 2 (c). Error bars represent 95% confidence intervals (Experiment 2 only, where ROI definitions and beta estimates were independently obtained).
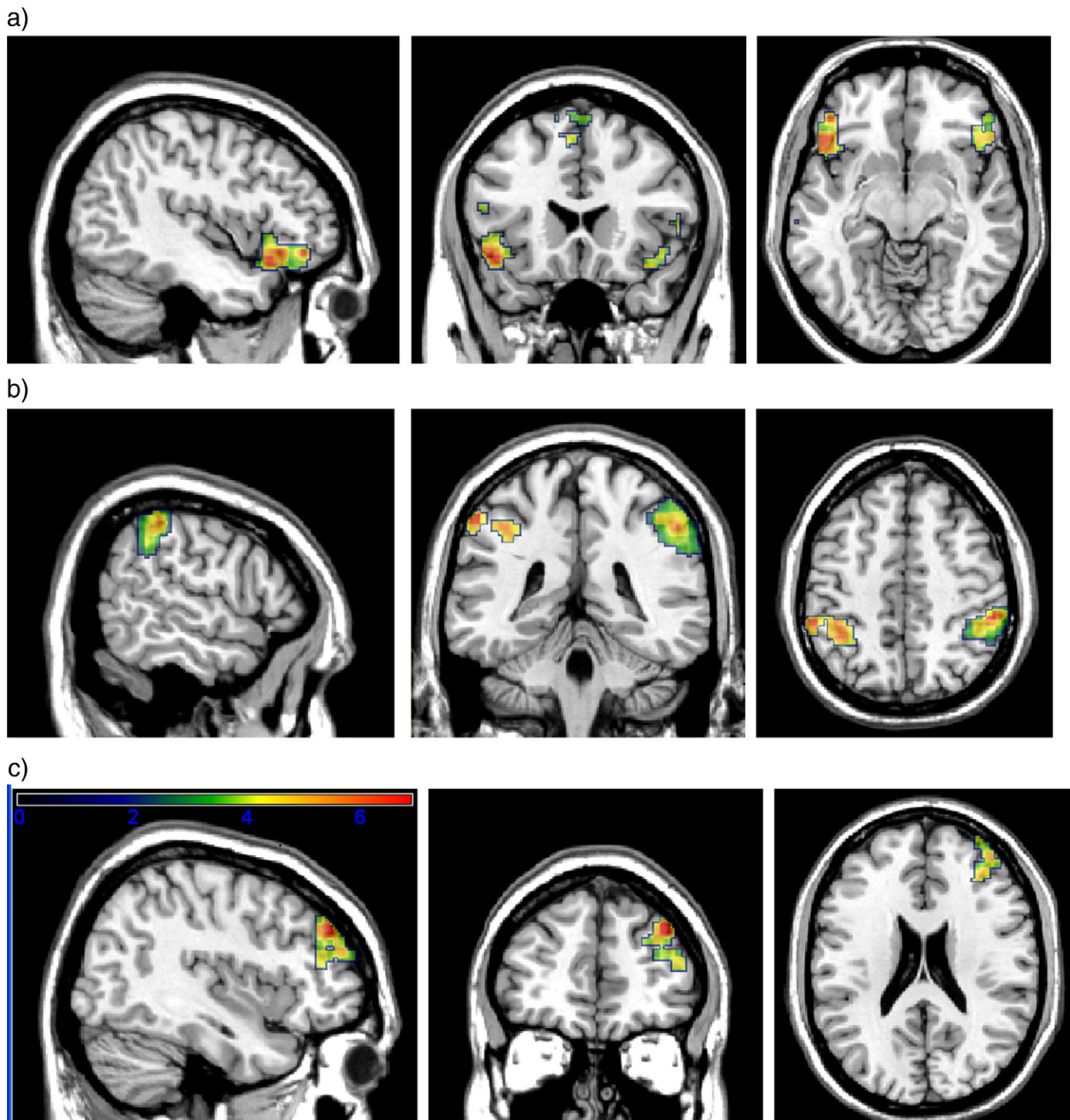
a)

b)

c)

Fig. 4. Resting-state functional connectivity differences between regions of interest from sagittal (first column), coronal (second column), and axial (third column) views: a) greater connectivity in bilateral VLPFC (BA 47) with BA 9 (self ROI) than with BA10/BA 31 (self and rest ROI); b) greater connectivity in bilateral parietal cortex (BA 40) with BA 7 (rest ROI) than with BA10/BA 31 (self and rest ROI); and c) greater connectivity in bilateral DLPFC (BA 9 and BA 46) with BA 7 (rest ROI) than with BA 10/BA 31 (self and rest ROI).

evidence that the incidence of self-referential thoughts is much higher during rest than during goal-directed tasks (d'Argembeau et al., 2005; Mason et al., 2007), and that activations in these regions correlate with the incidence of self-referential thoughts during unrelated tasks (ventral MPFC: d'Argembeau et al., 2005; ventral MPFC and PCC: McKiernan et al., 2006). These findings raise the possibility that activation during rest in ventral MPFC and PCC is essentially a product of self-referential thought in the absence of attention to external stimuli.

Dorsal MPFC was selectively engaged during explicit self-reference, and not differentially engaged by rest relative to semantic judgments about valence. There is evidence, however, that this region is not primarily focused on one's own thoughts and feelings, but rather widely engaged in consideration of psychological traits in people, both other people and oneself. Dorsal MPFC is more engaged when people think about themselves in relation to a dissimilar other person than a similar other person (Mitchell et al., 2006), or when people think about other people than animals (Mason et al., 2004). Dorsal MPFC was more engaged when people thought about character (traits) than appearance of people, but this was similar for thinking about oneself, one's mother, or former President Bush (i.e., it was not specific to self-reflection) (Moran et al., 2010). Further, in the present

Table 4
Resting-state functional connectivity differences.

	k	x	y	z	FWE-p	T	delta(Z)
a. Resting-state functional connectivity greater for Self than Self and Rest							
L BA47	342	−48	20	12	<.001	6.95	.32
R BA47	124	54	26	−10	.001	6.27	.26
b. Resting-state functional connectivity greater for Rest than Self and Rest							
R BA40	1043	54	−36	48	<.001	8.83	.31
R BA9/46	650	36	44	36	<.001	7.27	.25
L BA40	565	−38	−42	44	.026	7.34	.26
L BA9/46	243	−38	50	8	<.001	7.07	.24

study, dorsal MPFC was more functionally connected with VLPFC (BA 47) than the ventral MPFC/PCC system that was activated for both self-reference and rest. VLPFC regions are typically conceptualized as supporting external task-related working-memory and reasoning operations rather than internal reflection. Thus, dorsal MPFC appears to be engaged when people explicitly consider character or traits in people.

The precuneus was selectively engaged by rest relative to both self-reflection and semantic judgments. Many studies have reported activation for rest relative to tasks in a broad swath of cortex that includes adjacent precuneus and PCC regions. Unlike the contrasts that have been noted between dorsal and ventral MPFC (e.g., meta-analysis from Northoff and Bermpohl, 2004; Mitchell et al., 2006; Moran et al., 2010.), there have been fewer studies differentiating these two posterior regions associated with the default mode. One study, however, directly contrasted activations associated with self-reference versus episodic memory retrieval (Sajonz et al., 2010). There were both common and dissociable networks associated with the two kinds of tasks, and notably self-referential processing was more associated with PCC (as found also in the present study) and episodic retrieval more associated with precuneus. This finding is consistent with a number of studies reporting precuneus activation for episodic memory retrieval (reviewed in Cavanna and Trimble, 2006). Thus, it is possible that the greater activation of precuneus during rest in the present study reflects episodic, autobiographical memory retrieval that is more likely to occur during rest than either semantic or self-reference conditions. Consistent with this interpretation is our finding of greater resting functional connectivity between the preuneus and bilateral parietal (BA 40) and bilateral dorsal lateral prefrontal (BA 9–46) cortices, which are brain regions implicated in episodic memory retrieval (reviewed in Spaniol et al., 2009).

These fMRI findings converge well with PET findings about specialization within medial cortical regions (d'Argembeau et al., 2005). In that study, participants either reflected on specified topics (themselves, another person, or social issues) and or were at rest. Consistent with the present findings, there was greater activation in dorsal MPFC for self-reflection than rest, in precuneus (BA 7) for rest than self-reflection, and common activation for self-reflection and rest in ventral MPFC (the only difference being the common activation for rest and self-reflection reported here in PCC). The two studies operationalized "self-reflection" in complementary ways. The PET study involved reflection in all conditions, which makes the conditions more directly comparable, but results in less control over the

self-reflection condition. The fMRI study has stronger control over self-reflected cognition through task performance, but introduces perceptual and motor differences among conditions. The similarity of findings, therefore, supports the stronger relation of ventral MPFC to both self-reflection and rest, and the preferential relations of dorsal PFC and precuneus to self-reflection and rest, respectively.

We did not find activation of dorsal MPFC during rest relative to either self-reference or semantic judgments. The neuroimaging study most similar to our own also did not report dorsal MPFC activation during rest relative to tasks (d'Argembeau et al., 2005), but other studies have reported dorsal MPFC activation during rest (e.g., Shulman et al., 1997; Buckner et al., 2008). This suggests that variable activation of dorsal mPFC during rest depends either on the specific task contrast or may be variable depending on what thoughts occur during rest.

Other investigators have reported functional dissociations of the cortical midline regions, especially ventral MPFC and dorsal MPFC. Some studies have investigated task-dependent changes in functional connectivity (without rest) via psychophysiological interaction (PPI) analyses. Self-reference tasks, relative to other tasks, reduce functional connectivity within cortical midline regions (van Buuren et al., 2010), and increase functional connectivity between cortical midline regions and areas outside these regions (Schmitz and Johnson, 2006; van Buuren et al., 2010). Further, there is dissociation in task-dependent connectivity between dorsal and ventral MPC regions (Schmitz and Johnson, 2006) that parallels the connectivity difference during rest reported in the present study. Other analyses have identified cortical hubs, regions of high functional connectivity, and also reported dissociations among cortical midline regions (Buckner et al., 2008, 2009). Ventral MPFC and PCC appear to be linked in a common network, as they were in the present study. In contrast, dorsal MPFC was linked in a common network with dorsolateral prefrontal cortex, as found in the present study during rest. Thus, there are multiple criteria by which cortical midline regions can be functionally associated or dissociated. Our study is consistent with these findings in general, but specifically delineates that associations and dissociations between explicit self-reference and rest.

A limitation of these findings is the inherent difference between self-reference and default (rest) task conditions. The self-reference and semantic (valence) conditions were equated in multiple perceptual, cognitive, and motor dimensions, including stimuli (trait adjectives), two-alternative judgments, and button-press responses. Rest conditions that reveal the default network involve different perceptual (fixation cross), cognitive (uncontrolled thinking), and motor (no response) dimensions. Thus, direct comparisons between rest and active task conditions are confounded in this study as they are in all contrasts of rest and active tasks.

Conclusion

In sum, the present findings reveal that there are both associations and dissociations between the brain regions invoked by explicit self-reference and by the default mode of brain function. The ventral MPFC and the PCC were associated with both self-reference and default mode brain functions. The dorsal MPFC was associated with self-reference only, although this region appears to subserve trait judgments about people in general, including, but not selective for, oneself. The precuneus was associated only with default-mode function, perhaps subserving autobiographical memory retrieval that occurs spontaneously during rest but that is not invoked for self-reference as measured by trait judgments.

Conflict of interest

The authors of the study have no conflict of interest to declare.

Table 5
Correlation coefficients between conjunction ROIs.

	Self	Rest	Self and Rest
Self	1	0.09	0.45
Rest		1	0.47
Self and Rest			1

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