Reduced Functional Coupling in the Default-Mode Network During Self-Referential Processing

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Abstract: Activity within the default-mode network (DMN) is thought to be related to self-referential processing, such as thinking about one's preferences or personality traits. Although the DMN is generally considered to function as a network, evidence is starting to accumulate that suggests that areas of the DMN are each specialized for different subfunctions of self-referential processing. Here, we address the issue of functional specialization by investigating changes in coupling between areas of the DMN during self-referential processing. To this aim, brain activity was assessed during a task in which subjects had to indicate whether a trait adjective described their own personality (self-referential, Self condition), that of another person (other-referential, Other condition), or whether the trait was socially desirable (nonreferential, Control condition). To exclude confounding effects of cardiorespiratory processes on activity and functional coupling, we corrected the fMRI signal for these effects. Activity within areas of the DMN was found to be modulated by self-referential processing. More specifically, during the Self condition compared to the Other and Control condition, activity within the dorsal medial prefrontal cortex, ventral medial prefrontal cortex, and posterior cingulate cortex was increased. Moreover, coupling between areas of the DMN was reduced during the Self condition compared to the Other and Control condition, while coupling between regions of the DMN and regions outside the network was increased. As such, these results provide an indication for functional specialization within the DMN and support the notion that each area of the DMN is involved in different subfunctions of self-referential processing. Hum Brain Mapp 31:1117–1127, 2010. © 2010 Wiley-Liss, Inc.

Key words: fMRI; default-mode network; self-referential; social cognition; functional connectivity; respiration; heart rate

Additional Supporting Information may be found in the online version of this article.

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INTRODUCTION

During rest, a network of brain areas shows increased activation compared to when people are performing a complex task [Shulman et al., 1997]. This network is called the default-mode network (DMN) and includes the dorsal and ventral medial prefrontal cortex [dMPFC and vMPFC; Brodmann areas (BAs) 10, 9, 32, and 24], the posterior cingulate cortex/retrosplenial cortex (PCC, BA 23/31, and RSC, BA 29/30), and the lateral posterior cortex (LP, BA 39/40) [Buckner et al., 2008; Fox et al., 2005; Greicius et al., 2003; Gusnard and Raichle, 2001; Raichle et al., 2001]. Studies in humans using diffuse tensor imaging [Greicius

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et al., 2009; van den Heuvel et al., 2008] as well as studies in macaques [Kobayashi and Amaral, 2003, 2007; Ongur and Price, 2000] reported dense anatomical connections between the areas of the DMN. Furthermore, several functional connectivity studies showed strong positive correlations within the DMN both during resting-state [Damoiseaux et al., 2006; Fox et al., 2005; Greicius et al., 2003; Lowe et al., 1998; van Buuren et al., 2009] and during cognitive tasks [Greicius et al., 2003; Kjaer et al., 2002], indicating that activity within the network is highly correlated.

Several authors propose self-referential, introspective processing to underlie activity within the DMN [Amodio and Frith, 2006; Fox et al., 2005; Gusnard and Raichle, 2001; Mason et al., 2007; Uddin et al., 2008]. For example, Mason et al. [2007] reported positive correlations between DMN activity and so-called mind-wandering and negative correlations between DMN activity and task-demand. A number of studies investigated DMN activity during tasks that invoked self-referential processing such as responding to statements describing one's own personality, attitudes, or preferences. These studies show that activity within the midline areas of the DMN, the dMPFC, vMPFC, and PCC, is increased during self-referential conditions as compared to a control task [Craik et al., 1999; Fossati et al., 2003; Gusnard et al., 2001; Johnson et al., 2002, 2006; Kelley et al., 2002; Macrae et al., 2004; Mitchell et al., 2006; Ochsner et al., 2004, 2005; Schmitz et al., 2004; Schneider et al., 2008; Zysset et al., 2002]. Activity within the LP is also found to be increased during self-referential conditions [Craik et al., 1999; Fossati et al., 2003; Johnson et al., 2006; Mitchell et al., 2006; Ochsner et al., 2004; Zysset et al., 2002], although this finding is less consistent across studies.

Taken together, these findings suggest that the DMN functions as a network. However, evidence is now starting to accumulate that suggest some form of functional specialization within the DMN [Buckner et al., 2008; Northoff and Bermpohl, 2004; Northoff et al., 2006]. That is, regions of the DMN are thought to be involved in different subfunctions of self-referential processing, such as monitoring, evaluating, and integrating of self-referential stimuli [Northoff and Bermpohl, 2004; Northoff et al., 2006]. In a meta-analysis of 27 PET and fMRI studies on self-referential tasks, Northoff and co-workers investigated functional specialization within the cortical midline structures. Using cluster analyses, they distinguished between three different subregions within the DMN, being the vMPFC/posterior ACC, the dMPFC, and the PCC, suggesting that the DMN consists of separate components each involved in different subfunctions of self-referential processing [Northoff et al., 2006]. Furthermore, Schmitz and Johnson [2006] investigated functional specialization within the MPFC. They reported an increase in connectivity during self-referential processing, dissociating a dorsal and a ventral MPFC network, which they interpreted as support for the notion that these regions are engaged in different subfunctions of self-referential processing.

Surprisingly, changes in connectivity between areas of the DMN during self-referential processing have not yet been reported. Such changes are to be expected if these areas are engaged in different subfunctions during self-referential processing. The failure to report changes within the DMN could be caused by influences of cardiorespiratory (CR) processes on the connectivity measures. That is, CR processes such as heart rate (HR) and respiration affect the BOLD signal independently of neuronal activity [Glover et al., 2000; Wise et al., 2004] and are found to contaminate measures of activity within as well as connectivity between brain areas [Birn et al., 2006; Shmueli et al., 2007; van Buuren et al., 2009]. Changes in connectivity due to changes in task conditions and cognitive processes could therefore be obscured by these CR effects.

Here, we address the issue of functional specialization within the DMN by investigating changes in coupling between areas of the DMN during self-referential processing. To this aim, brain activity, heart beat, and respiration are measured in 19 healthy control subjects during a selfreferential task. In this task, subjects are asked to indicate whether a trait adjective describes their own personality (self-referential, Self condition), that of another person (other-referential, Other condition), or whether the trait is socially desirable (nonreferential, Control condition). To exclude confounding effects of CR processes on connectivity and activity in the brain, the fMRI signal is corrected for CR effects [van Buuren et al., 2009].

METHODS

Participants

Nineteen right-handed (mean \pm SD Edinburgh Handedness Inventory [Oldfield, 1971] quotient, 0.82 \pm 0.15) healthy subjects (eight males; mean \pm SD years, 21.5 \pm 1.9) were included in this study. None of the participants had a history of psychiatric or neurological disorders, substance abuse, or medical disorders or had any contraindications for MRI. Participants were recruited from the University of Utrecht and received monetary compensation for participation. All gave written informed consent. The ethics committee of the University Medical Center of Utrecht approved this study.

Task

In the self-referential task [Craik et al., 1999; Kelley et al., 2002], subjects were instructed to make judgments about trait adjectives. Depending on the condition, the subjects were asked to indicate whether a trait adjective described their own personality (Self condition), the Dutch prime-minister's personality (Other condition), or whether the trait was social desirable (nonreferential, Control

Reduced Functional Coupling Within the DMN +



Figure I.

Self-reflection task. The stimulus duration and interstimulus interval (ISI) duration were dependent on the reaction time; the fixation cross appeared as soon as the subject responded for the remaining trial time.

condition) by pressing the left "yes" or the right "no" button (see Fig. 1). The words were extracted from a list with trait adjectives validated for likableness [Anderson, 1968] and translated into Dutch. Half of the adjectives were of positive valence and half were of negative valence. The task consisted of five blocks of eight trials (28 s per block) per condition alternated with rest periods of 30 s. During each trial, one trait adjective was presented for 3.5 s or until the subject responded. After each response, a fixation cross was presented for the remaining trial duration. Each task block started with an instruction trial of 2 s indicating the onset of a task condition.

Cardiorespiratory Processes

Measurements

Four electrocardiogram electrodes were affixed to the subjects' chest and a respiration band was placed at the level of the abdomen. In this way, we obtained two signals; a heartbeat signal with a trigger marking times at which an R-peak was detected and a respiratory signal measuring the expansion of the respiration band. From the heartbeat data, three signals were derived: the phase of the heartbeat (i.e. cardiac cycle), the HR, and heart rate variability (HRV). From the respiration data, the respiration cycle (i.e. respiration phase) was derived and respiration volume per time (RVT) was calculated by multiplying respiration amplitude with respiration frequency (see van Buuren et al. [2009] for a detailed description of the calculation of the CR signals). Heartbeat phase, HR, HRV, respiration phase, and RVT were used

to correct the fMRI time series data for confounding effects of CR processes.

Correction

The correction for the CR processes was performed using custom Matlab software (Aztec, http://www.niutrecht.nl/downloads/aztec). This method is described in detail in our previous study [van Buuren et al., 2009]. In short, the BOLD signal was corrected for the effects of the cardiac and respiratory cycle using RETROICOR [Glover et al., 2000]. Subsequently, the remaining BOLD signal was corrected for the effects of HR, HRV, and RVT using a multiple regression approach. To account for the variable delay between fluctuations in the BOLD signal and fluctuations in these CR processes, the time courses of these variables were shifted with multiple lags. The optimal lags for HR, HRV, and RVT were determined by calculating, for every voxel separately, the correlation between the CR time course and the BOLD signal at a range of lags. The optimal lag was then selected as the lag having the strongest absolute correlation and the lagged signal was included in the multiple regression.

The effect of the CR correction on the BOLD signal was investigated by calculating how much of the variance in BOLD signal could be explained by the CR processes. The proportion of explained variance (EV) was calculated as EV (%) = 100 × [1 - ($\sigma_{post}/\sigma_{pre}$)], where σ_{post} was the variance after correction and σ_{pre} variance before correction.



Figure 2.

Whole brain activation overlaid on the mean anatomical image. (A) Significant activation during the Self condition compared to the Control condition. (B) Significant activation during the Self condition compared to the Other condition. Cluster-defining

Functional Magnetic Resonance Imaging

Measurements

All imaging was performed on a Philips 3.0T Achieva whole-body MRI scanner (Philips Medical Systems, Best, The Netherlands). Functional images were obtained using a 2D-EPI-SENSE sequence with the following parameters: voxel size 4 mm isotropic; TR = 1,600 ms; TE = 23 ms; flip angle = 72.5°; matrix 52 × 30 × 64; field of view 208 × 120 × 256; 30-slice volume; SENSE-factor R = 2.4 (anterior–posterior). A total of 395 functional images were acquired during the self-reflection task.

After the acquisition of the functional images, an 3D Fast Field Echo (FFE) T1-weighted structural image of the whole brain was made (scan parameters: voxel size 1 mm isotropic, TR = 25 ms; TE = 2.4 ms; flip angle = 30° ; field of view $256 \times 150 \times 204$, 150 slices).

Image preprocessing

Image preprocessing and analyses were carried out with SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). After realign-

threshold of P < 0.001 with a P < 0.05 FWE-corrected cluster size of 18 voxels. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

ment, the structural scan was coregistered to the mean functional scan. Next, using unified segmentation, the structural scan was segmented and normalization parameters were estimated. Subsequently, all scans were registered to a MNI T1-standard brain using these normalization parameters and a 3D Gaussian filter (8-mm full width at half maximum) was applied to all functional images.

Whole brain analyses

The preprocessed functional images were submitted to a general linear model regression analysis after correcting for CR effects. The design matrix contained factors modeling the onsets and durations of the Self, Other, and Control 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 head motion, the six realignment parameters were included in the design matrix as regressors of no interest. A high-pass filter was applied to the data with a cut-off frequency of 0.0055 Hz to correct for drifts in the signal. Subsequently, for each subject, first

		MNI coordinates					
Brain region	BA	x	у	Z	Voxels	Z score	
		Self > Co	ontrol				
Dorsal medial prefrontal cortex	10	-4	48	16	1625	6.06	
Retrosplenial cortex	30	-8	-60	8	228	5.15	
Inferior frontal gyrus	47	-32	16	-24	119	4.64	
Inferior temporal pole	20	44	-16	-20	127	4.42	
· ·		Other > C	Control				
Middle temporal gyrus	21	-60	-12	-16	58	5.73	
Posterior cingulate cortex	23	0	-56	16	108	5.27	
Middle temporal pole	38	48	12	-28	121	5.09	
Dorsal medial prefrontal cortex	9	-4	52	32	244	4.88	
Inferior temporal gyrus	21	-44	8	-36	79	4.67	
Orbital frontal cortex	11	0	48	-16	42	4.01	
		Self > C	Other				
Retrosplenial cortex	30	-8	-64	4	133	5.52	
Dorsal medial prefrontal cortex	9	0	52	20	516	5.04	
Middle temporal lobe	21	-64	-52	8	148	5.03	
Caudate		-8	0	8	248	4.68	
Middle occipital lobe	19	40	-80	0	83	4.64	
Hippocampus		24	-24	-16	39	4.54	
Superior frontal cortex	9	-20	40	40	37	4.32	
Precuneus	7	-4	-48	44	22	4.12	
Middle occipital lobe	19	-32	-84	4	55	4.10	
Inferior parietal lobe	40	64	-48	28	40	4.07	
Insula	13	44	8	16	21	4.03	
Middle cingulate	24	-36	-16	36	20	3.95	
Middle frontal cortex	10	32	52	24	31	3.77	
Supplementary motor area	6	12	12	64	41	3.73	

TABLE I. Whole-brain activation levels

BA = Brodmann area.

Clusters showing significant activation during the Self condition compared to the Control condition (upper part), during the Other condition compared to the Control condition (middle part), or during the Self condition compared to the Other condition (lower part). MNI coordinates represent the location of the peak voxels.

Cluster-defining threshold of P < 0.001 with a P < 0.05 FWE-corrected cluster size of 18 voxels.

level contrast images were created for each condition compared to baseline and compared to all other conditions.

Next, group activation maps were calculated for each contrast using a random effects analysis approach. All group activation maps were tested for significance at a cluster-defining threshold of P < 0.001 with a P < 0.05 familywise error-corrected (FWE-corrected) cluster size of 18 voxels.

To provide more insight in the underlying pattern of activity, exploratory regions of interest (ROI) analyses were conducted [Poldrack, 2007] using a 4-mm-radius sphere around the peaks of activation within the midline areas of the DMN, dMPFC, vMPFC, and PCC, in the contrast [Self > Control]. These ROI analyses were not used for inference and are depicted in Supporting Information Figure 1.

Psychophysiological interaction analyses

To investigate changes in coupling within the DMN during self-referential processing, psychophysiological interaction (PPI) analyses [Friston et al., 1997] were conducted using SPM5. A PPI shows changes in functional coupling between a seed region and other regions in relation to a psychological factor (i.e. the various task conditions). For each seed region, two PPI analyses were conducted to investigate changes in functional coupling during, respectively, the Self versus Control condition and Self versus Other condition (i.e. psychological factor). A 4-mm-radius sphere around the peaks of activation within the midline areas of the DMN, dMPFC, vMPFC, and PCC, in the contrast (Self > Control) were taken as seed regions for the PPI analyses as follows. For each subject, the first eigenvariate of the BOLD signal within each seed region (i.e. volume of interest) was calculated and adjusted for average activation during the task (i.e. F-contrast showing effects of task) and head motion. The interaction between activity within the seed regions and each psychological factor (i.e. PPI regressor) was then calculated and activity positively related to each interaction as well as negatively related activity was investigated. Subsequently, these





Areas showing significant psychophysiological interactions overlaid on the mean anatomical image. Areas showing decreased (blue) or increased (red) coupling with (**A**) the dMPFC, (**B**) the vMPFC, (**C**) the PCC during the Self condition compared to the Control condition, and with (**D**) the PCC during the Self condi-

individual contrast images of the PPI analyses were entered in second level analyses to test for groupwise effects. To test in which areas activity was significantly explained (positively or negatively) by the PPI regressor (i.e. interaction between the presence of self-referential processing and activity in one of the seed regions), *t*-tests were performed. Significance of the group *t*-maps was assessed at a cluster-defining threshold of P < 0.001 and a P < 0.05 FWE-corrected cluster size of 23 voxels.

RESULTS

Behavioral Results

During the Control condition, more than 90% of the responses matched those of the validated ratings on lik-

tion compared to the Other condition. Seed regions are depicted in green. Cluster-defining threshold of P < 0.001 with a P < 0.05 FWE-corrected cluster size of 23 voxels. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

ableness (mean \pm SD, 92.8 \pm 3.1%), indicating that the subjects paid attention to the task. Reaction times differed significantly between the task conditions [*F*(2,36) = 17.35, *P* < 0.0005]. Subsequent paired-sample *t*-tests showed that the subjects responded faster during the Control condition (mean \pm SD, 1299 \pm 182 ms) compared to the Self condition [mean \pm SD, 1403 \pm 162 ms; *t*(18) = -4.62, *P* < 0.0005] and the Other condition [mean \pm SD, 1434 \pm 188 ms; *t*(18) = -5.06, *P* < 0.0005]. Reaction times during the Self and Other condition did not differ (*P* = 0.19).

Effects of CR Correction

To investigate the impact of the correction for CR processes on the BOLD signal, the variance explained by the CR processes was calculated. On average, 22.2% (±SD

		MNI coordinates				
Brain region	BA	x	y	Z	Voxels	Z score
		dMPFC:	Positive			
Inferior frontal gyrus	44	-48	12	16	682	5.01
Middle temporal gyrus	21	-48	-44	-4	28	4.31
Anterior cingulate cortex	32	12	24	36	38	3.93
Precuneus	7	-24	-64	40	47	3.87
		dMPFC:	Negative			
Posterior cingulate cortex	23	4	-64	24	137	4.52
5		vMPFC:	Positive			
Postcentral gyrus	3	-56	-12	44	216	4.43
Inferior frontal gyrus	45	-40	24	0	41	4.20
Supplementary motor area	6	-4	-8	60	46	3.88
		vMPFC:	Negative			
Angular gyrus	39	-48	-76	28	72	4.58
Posterior cingulate cortex	31	4	-64	28	168	4.40
Angular gyrus	39	44	-64	28	29	3.63
0 00		PCC: F	ositive			
Precentral gyrus	4	-48	-12	44	32	3.58
		PCC: N	legative			
Angular gyrus	39	48	56	36	32	3.50

TABLE II. PPI results Self versus Control

BA = Brodmann area.

Clusters showing positive or negative PPI with the dMPFC, vMPFC, and PCC during the Self condition compared to the Control condition.

MNI coordinates represent the location of the peak voxels.

Cluster-defining threshold of P < 0.001 with a P < 0.05 FWE-corrected cluster size of 23 voxels.

3.8%) of the variance in the whole brain could be explained by the CR correction, indicating that the CR correction removed a considerable proportion of the variance within the BOLD signal. This is consistent with results from our previous study [van Buuren et al., 2009].

Whole Brain Analyses

Results of the whole brain analyses are presented in Figure 2 and Table I.

The dMPFC, extending into the vMPFC, and the retrosplenial cortex (RSC) were more active during the Self condition compared to the Control condition. When comparing the Self condition to the Other condition, the dMPFC, extending into the vMPFC, and the RSC as well as the inferior parietal gyrus (i.e. lateral posterior cortex, LP) showed increased activity (see Table I). These findings of increased activity within areas of the DMN even after correcting for CR effects indicate that these areas are engaged in some form of self-referential processing. In addition, when comparing the Other condition to the Control condition, increased activity was found within a more superior region of the dMPFC and the PCC.

Psychophysiological Interaction Analyses

Psychophysiological interaction (PPI) analyses were performed to investigate changes in functional coupling during self-referential processing. Peaks of activation within the three midline areas of the DMN in the contrast (Self > Control) were taken as seed regions: a seed region located in the dMPFC (x,y,z = -4, 48, 16), the vMPFC (x,y,z = 0, 64, 4), and the PCC (x,y,z = -4, -52, 28). Two PPI analyses were performed for each seed region, showing changes in functional coupling between each seed region and other areas during the Self versus Control condition and the Self versus Other condition, respectively. Results of the PPI analyses are presented in Figure 3 and Tables II and III.

Self versus Control condition—dMPFC

There was an increase in coupling between activity within the inferior frontal gyrus (IFG) extending into the supplementary motor area (SMA), middle temporal gyrus, precuneus and dorsal anterior cingulate cortex (dorsal ACC), and activity in the dMPFC during the Self condition compared to the Control condition. Results of the negative interaction contrast showed that there was a decrease in coupling between activity within the PCC and activity within the dMPFC during the Self condition compared to the Control condition.

Self versus Control condition—vMPFC

An increase in coupling was found between the vMPFC and postcentral gyrus, SMA, and IFG during the Self condition compared to the Control condition. A decrease in

		MNI coordinates						
Brain region	BA	x	у	Z	Voxels	Z score		
			Desiliar					
Insula	13	-40	0	16	188	4.77		
Superior temporal gyrus	38	-40	12	-32	55	4.63		
Postcentral gyrus	3	-48	-24	56	195	4.52		
Supplementary motor area	6	-4	12	56	172	4.39		
Superior frontal gyrus	8	-8	44	40	25	4.13		
1 0,5		dMPFC:	Negative					
ns			0					
		vMPFC	: Positive					
Inferior frontal gyrus	45	-44	28	-4	335	5.20		
Supplementary motor area	6	-8	36	60	355	4.89		
Postcentral gyrus	3	-40	-16	60	67	3.82		
Hippocampus		-28	-20	-12	33	3.76		
		vMPFC:	Negative					
ns								
		PCC: 1	Positive					
ns								
		PCC: N	Vegative					
Inferior parietal lobe	40	56	-56	44	39	4.31		

TABLE III. PPI results Self versus Other

BA = Brodmann area; ns = nonsignificant.

Clusters showing positive or negative PPI with the dMPFC, vMPFC, and PCC during the Self condition compared to the Other condition.

MNI coordinates represent the location of the peak voxels.

Cluster-defining threshold of P < 0.001 with a P < 0.05 FWE-corrected cluster size of 23 voxels.

coupling with activity within the vMPFC was found within the PCC, left and right angular gyrus (i.e. lateral posterior cortices, LP) during the Self condition compared to the Control condition.

Self versus Control condition—PCC

There was an increase in coupling between activity within the PCC and activity within the precentral gyrus during the Self condition compared to the Control condition. Coupling between activity within the PCC and activity within the right angular gyrus (i.e. LP) was found to be decreased when comparing the Self to the Control condition.

Self versus Other condition—dMPFC

An increase in coupling between activity within the dMPFC and insula, extending into the IFG, the superior temporal gyrus, postcentral gyrus, SMA, and superior frontal gyrus was found during the Self condition compared to the Other condition (Table III). Results of the negative interaction contrast did not reach significance, indicating that functional coupling between the dMPFC and other areas of the DMN did not decrease during the Self condition as compared to the Other condition.

Self versus Other condition—vMPFC

When comparing the Self condition to the Other condition, an increase in coupling was found between activity within the vMPFC and activity within the IFG, extending into the insula, the superior frontal gyrus, postcentral gyrus as well as the left hippocampus. No decreases in coupling with activity within the vMPFC were observed.

Self versus Other condition—PCC

Results of the positive interaction contrast did not reach significance; however, a decrease in coupling between activity within the PCC and right inferior parietal lobule was found during the Self condition compared to the Other condition.

DISCUSSION

In this study, we addressed functional specialization in the DMN by investigating functional coupling during selfreferential processing. We used an extensive correction method to remove confounding effects of CR processes, namely heartbeat and respiration. Consistent with previous reports, activation within the midline areas of the DMN was increased during self-referential processing [Craik et al., 1999; D'Argembeau et al., 2005; Fossati et al., 2003; Johnson et al., 2002; Kelley et al., 2002; Kjaer et al., 2002; Macrae et al., 2004; Mitchell et al., 2006; Moran et al., 2006; Schmitz et al., 2004; Zysset et al., 2002]. More specifically, activity within the dorsal medial prefrontal cortex (dMPFC), ventral MPFC (vMPFC), and posterior cingulate cortex/retrosplenial cortex (PCC/RSC) was increased when judging personality traits with respect to oneself (i.e. self-referential processing) as compared to making judgements about another person (i.e other-referential) or the social desirability of the traits (i.e. nonreferential). In addition, we found increased activation within the lateral posterior cortices (LP) when making judgments about personality traits with respect to oneself compared to making judgments with respect to another person. Furthermore, when engaged in self-referential processing, functional coupling between areas of the DMN was decreased, while coupling with areas outside the network was increased, providing an indication for functional specialization within the DMN.

Activity within the midline areas of the DMN was increased not only during self-referential processing but also when subjects were involved in making judgments about personality traits with respect to another person. This is in line with previous studies, which suggest that when making judgments about another person, people are engaged in some form of self-referential processing [Amodio and Frith, 2006; D'Argembeau et al., 2007; Johnson et al., 2006; Northoff et al., 2006; Schmitz et al., 2004; Vogeley and Fink, 2003]. That is, when judging another person's personality or feelings, people tend to reflect on their own feelings, personality, and experiences. However, the extent of self-referential processing is thought to be greater when thinking of one's own personality as compared to another person's personality. Indeed, activity was increased within the DMN during self-referential processing when compared to other-referential processing. It is important to note that these increases in activity represent relative increases. That is, although the dMPFC and vMPFC show increased activation during self-referential processing, these areas as well as the PCC show less deactivation instead of increased activation during other-referential processing compared to nonreferential processing.

In addition to these activation changes, we found that during self-referential processing functional coupling between the dMPFC and PCC, between the vMPFC and PCC and LP as well as between the PCC and right LP was decreased when compared to nonreferential control processing. When comparing self-referential processing to other-referential processing, a decrease in coupling was observed between the PCC and right LP. In contrast, functional coupling between the vMPFC, dMPFC and PCC and areas outside the DMN, including the inferior frontal gyrus, superior frontal gyrus, insula, middle temporal gyrus, somatosensory cortex and hippocampus, was increased during self-referential processing. This increased coupling with regions outside the DMN suggests that the areas of the DMN are also part of other networks.

To our knowledge, this is the first study to report a decrease in functional coupling within the DMN during

self-referential processing. A previous study by Schmitz and Johnson [2006] did report an increase in coupling between activity in areas of the DMN and activity in areas outside the network during self-referential processing, but did not find changes in coupling between areas of the DMN. The differences between the results of the current study and the study of Schmitz and Johnson could be due to confounding effects of CR processes, but may also be caused by differences in seed regions, which were located closer to the midline of the brain in the current study. Also, the task of the current study differed from the task used by Schmitz and Johnson in that an other-referential condition as well as periods of rest were included in addition to the self-referential and control condition.

Although the results from the current study provide support for the notion that areas of the DMN are engaged in different subfunctions of self-referential processing, these findings do not necessarily imply that self-referential processing solely drives activity within the DMN during resting-state. In addition, the task used in this study did not allow us to specify the possible subfunctions of selfreferential processing. However, results of previous studies do provide some indication of the nature of the subfunctions. That is, the ventral part of the MPFC is thought to play a role predominantly in identifying stimuli as selfrelevant by integrating cognitive and emotional processing [Gusnard et al., 2001; Northoff and Bermpohl, 2004; Northoff et al., 2006; Schmitz and Johnson, 2007], whereas the dorsal part of the MPFC has been associated with introspective self-referential processing such as the appraisal and evaluation of the self-relevant stimuli [Gallagher and Frith, 2003; Gusnard et al., 2001; Lane et al., 1997]. The PCC and the LP are, given their dense connections with the hippocampal formation [Kobayashi and Amaral, 2003, 2007], thought to be involved in integrating new self-referential stimuli in a context of autobiographic memories and past self-referential stimuli. To further investigate functional specialization within the DMN, it would be useful to investigate changes in functional coupling during a more elaborate task that encompasses the various components of self-referential processing such as identifying, monitoring, evaluating, and integrating of self-referential stimuli.

Future studies investigating functional specialization may also benefit from the use of different effective connectivity techniques such as dynamic causal modelling [Friston et al., 2003] or structural equation modelling [McIntosh and Gonzalez-Lima, 1994]. In the current study, psychophysiological interaction (PPI) analyses were used to investigate changes in functional coupling. By using PPI, we were only able to model contributions from a single area at a time (i.e. modulation by the dMPFC, vMPFC, and PCC), as a PPI only gives an indication in which area activity covariates with one other region (i.e. the seed region) as a function of the psychological variable. In contrast, dynamic causal modelling and structural equation modelling allow inference of causal interactions between multiple areas.

The current study confirms that, even after correcting for confounding effects of CR processing, activity within areas of the DMN is related to self-referential processing. More specifically, we found increased activity within the dMPFC, vMPFC, PCC as well as the LP during self-referential processing. In addition, functional coupling between these regions was reduced during such processing, while coupling with areas outside the DMN was increased, suggesting that subregions of the DMN are also part of different networks. As such, these results provide an indication for functional specialization within the DMN, suggesting that each area of the DMN is involved in different subfunctions of self-referential processing.

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