The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis

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ABSTRACT

Recent research has shown that intrinsic brain activity as observed by functional magnetic resonance imaging (fMRI) manifest itself as coherent signal changes in networks encompassing brain regions that span long-range neuronal pathways. One of these networks, the so called default mode network, has become the primary target in recent investigations to link intrinsic activity to cognition and how intrinsic signal changes may be altered in disease. In this study we assessed functional connectivity within the default mode network during both rest and a continuous working memory task on a region-by-region basis using partial correlation analysis, a data-driven method that provides insight into effective connectivity within neuronal networks. Prominent features of functional connectivity within the default mode network included an overall strong level of interaction between the precuneus/posterior cingulate region and the rest of the default mode network, as well as a high degree of interaction between the left and right medial temporal lobes combined with weak interactions between the medial temporal lobes and the rest of the default mode network. Additionally, we found support for strong interactions between the precuneus/posterior cingulate cortex and the left inferior parietal lobe as well as between the dorsal and ventral sections of the medial prefrontal cortex. The suggested pivotal role of the precuneus/posterior cingulate cortex in the default mode network is discussed.

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Introduction

Intrinsic functional brain connectivity as revealed by low-frequency spontaneous signal fluctuations in fMRI signal intensity time-courses has received increased attention in the neuroscience community. A first demonstration of the existence of so called resting-state networks was given by Biswal et al. (1995) by showing that brain activity in the primary sensorimotor brain areas are synchronized across the hemispheres during rest. Subsequent functional connectivity studies focusing on the detection of low-frequency fMRI signal changes using explorative, data-driven analysis methods have suggested that there exist up to 10 resting-state networks that span long-range cortico-cortical as well as well as cortical–subcortical networks in the human brain (Beckmann et al., 2005; Damoiseaux et al., 2006). Moreover, recent investigations have presented experimental data suggesting that

resting-state networks prevail during sleep (Fukunaga et al., 2006; Horovitz et al., 2008) and anaesthetic conditions (Vincent et al., 2007; Greicius et al., in press).

From a cognitive neuroscience point of view, particular attention has been paid to one of the resting-state networks, the so called default mode network (DMN, Raichle et al., 2001). There are several reasons for this interest, one being that positron emission tomography (PET) investigations have revealed that the precuneus/posterior cingulate cortex (pC/PCC) and the medial prefrontal cortex (MPFC), both previously shown to be part of the DMN, show an elevated level of metabolic activity (Raichle et al., 2001). Another reason is the recurrent observation that attention-demanding tasks cause a decrease in activity in the DMN (Shulman et al., 1997; Mazoyer et al., 2001). Finally, studies targeting the neuronal basis for self-related mental tasks have shown consistent signal increases in the DMN compared to tasks without elements of self-related mental processing (see Buckner et al., 2008 for a review). From a clinical perspective, the DMN has become a primary objective in the endeavour to characterize and localize differences in resting-state network activity as biological markers for abnormalities in brain connectivity for

a wide spectrum of psychiatric disorders. For example, previous studies using seed-based ROI correlation analyses have shown that intrinsic fMRI signal fluctuations in the precuneus/posterior cingulate cortex (pC/PCC) is altered in schizophrenia (Bluhm et al., 2007), while intrinsic functional correlation between the pC/PCC, MPFC and the right inferior parietal lobe (IPL) is altered in autism (Kennedy and Courchesne, 2008). Moreover, a recent study has shown a significant decrease in intrinsic resting-state functional correlation between the MPFC and the PCC in ADHD subjects compared to healthy controls (Castellanos et al., 2008). Using pairwise correlation measures in the healthy brain, Buckner et al. (2008) have obtained results that suggest that the pC/PCC, MPFC and the bilateral IPL together constitute a "core hub" in the DMN. The regions of this "core hub" showed strong intra-regional correlation with each other and weaker correlation with the remaining regions in the DMN such as the temporal cortex (TC) and the medial temporal lobe (MTL).

While substantial information has been gained in terms of the spatial location of brain regions that participate in resting-state networks and how these networks are altered during cognitive work and disease (e.g. see Fox and Raichle, 2007; Buckner et al., 2008), less is known of the functional connectivity within the DMN. Investigations that previously have studied default mode activity have typically relied on voxel-based differences in correlation strength calculated on the basis of reference signal intensity time-courses extracted from seed regions of interest (ROIs) positioned in one or several default mode brain areas. Although this approach has been successfully applied to investigate the putative role of the DMN in both health and disease, it provides little information regarding differences in functional interactions at the level of individual brain areas (or equivalently network nodes) in the DMN. In other words, a pairwise correlation analysis of DMN activity does not take into account the covariance structure of the entire DMN and potentially interesting information is lost. Moreover, all seed-based ROI analysis approaches to connectivity investigations are to some extent vulnerable to user-introduced bias in terms of the choices of seed regions made by the investigator.

The goal of the present work was to investigate functional connectivity within the DMN and at the same time addressing the methodological limitations described above. Functional connectivity within the DMN during both rest and a working memory task was assessed in a two-step procedure. First, estimates of regional fMRI signal intensity time-courses in the DMN were extracted based on information contained in statistical maps created by an independent component analysis. Second, functional connectivity within the DMN was assessed using a partial correlation technique that estimates the level of interaction between any two network nodes after removal of the common influences from all other nodes. The partial correlation analysis showed that the pC/PCC was the only node that exhibited interactions with virtually all other network nodes. The cognitive implications and uses of the observed patterns of interactions within the DMN are discussed.

Materials and methods

The results presented in this study constitute a re-analysis of dataset that has been described previously (Fransson, 2006) using new analytical tools. We here provide basic information regarding the participants, task and scanning procedures. For a more detailed account, we refer the reader to Fransson (2006).

Subjects and tasks

Seventeen subjects (5 males, age span 22–41 years) participated in this study. No subject had any history of neurological or psychiatric illness. All MR examinations were carried out according to the ethical guidelines and declarations of the Declaration of Helsinki (1975) and the current study was approved by the local ethics committee at the Karolinska University Hospital. All subjects participated in two 10 min echo-planar imaging (EPI), blood oxygenation level dependent (BOLD) scanning sessions during which they either performed a resting-state task with their eyes fixating on a hair-cross centred on a white black screen or engaged in a continuous verbal 2-back working memory task.

MR image acquisition

All MRI data was acquired on a General Electric Twin-Speed Signa Horizon 1.5 T MRI scanner. Echo-planar imaging (TR/TE=2000/40 ms, flip=80°, 64×64 matrix size, FOV=220×220 mm, 29 slices) was used to detect BOLD fMRI signal changes during rest and the working memory task. 300 echo-planar image volumes were acquired for each task.

Image pre-processing

All image processing was performed using the SPM2 software package (Wellcome Department of Imaging Neuroscience, London, UK, Friston et al., 1995). As a first step, functional image time-series were corrected for head motion by realigning all images to the first image volume. Second, the mean EPI image for each subject was co-registered to a corresponding T1-weighted high-resolution image volume and subsequently spatially normalized and re-sampled ($3 \times 3 \times 3$ mm^3 voxels) to the approximate Talairach space (Talairach and Tournoux, 1988) as defined by the MNI (Montreal Neurological Institute) EPI template in SPM2. As a last step, the normalized echo-planar image volumes were spatially filtered using an isotropic Gaussian filter (6 mm FWHM).

Selection of regions of interest

Previous studies have consistently shown that the dorsal and ventral parts of the medial prefrontal cortex, precuneus/posterior cingulate cortex, lateral parietal cortex, temporal cortex as well as the medial temporal lobe are involved in the default mode network (Buckner et al., 2008). Hence, for our network analysis of DMN activity we chose to extract fMRI signal intensity time-courses from nine brain regions (network nodes): precuneus/posterior cingulate cortex (pC/pCC), left and right inferior parietal lobe (lIPL, rIPL), dorsal and ventral medial prefrontal cortex (dmPFC, vmPFC), left and right temporal cortex (lTC, rTC) and left and right medial temporal lobes (lMTL, rMTL). A selection of regional DMN activity was accomplished in a three-step procedure. First, an independent component analysis (ICA) of the resting-state data was performed and 60 spatio-temporal independent components were extracted from each individual dataset

using the MELODIC FSL software (MELODIC v4.0; FMRIB Oxford University, UK, Beckmann and Smith, 2004). Second, by matching each independent component with a spatial template of the default mode network based on an independent dataset (Fransson, 2005), the spatially best-fitting independent component was extracted for each subject as previously described (Greicius et al., 2004, 2007). Third, local estimates of default mode activity in each network region were identified in terms of voxels exhibiting local Z-score maximum in the best-fitting independent component. To ensure that only the relevant anatomical structures were included, the search for each local maxima was constrained by using the WFU (Wake Forest University) Pickatlas toolbox (Maldjian et al., 2003) together with the AAL (Automatic Anatomical Labelling) atlas (Tzourio-Mazoyer et al., 2002) within SPM. A table of the AAL atlas structures included in the search for each local maximum is given in Supplementary Table 1. Consequently, the exact spatial location for the ROIs was allowed to vary between individuals, although only within the anatomical boundaries detailed in Supplementary Table 1. Although the anatomical constraints were set to be rather liberal, the possibility that they impose a user-introduced bias in the ROI selection process cannot be fully ruled out. An additional constraint was that the individual regions had to be located at least 15 mm apart. Since the distance between the dorsal and ventral medial prefrontal cortex was less than 15 mm in three subjects, the data from these three subjects were discarded and the subsequent partial and marginal correlation analysis was based on the remaining fourteen subjects. A representation of DMN activity during rest in the extracted independent components is shown in Fig. 1. Finally, signal intensity time-courses during both rest and the working memory task were extracted using spherical ROIs with a radius of 6 mm. All signal intensity time-courses were bandpass filtered (passband 0.012–0.1 Hz) and orthogonalized with respect to the global mean brain signal. Thus, in each individual, 9 (network regions/nodes)×2 (conditions: rest and working memory) BOLD signal intensity time-courses were extracted, resulting in two datasets per subject pertaining to default mode network activity in the nine network regions. The spatial variability between subjects in the exact anatomical location of ROIs for the ICA-based ROI selection method is shown in the MNI space in Supplementary Figure 1. A quantitative account of the spatial variability between subjects for the ICA-based ROI locations is given in Supplementary Table 2.

Partial correlation analysis

The aim of the present analysis was to address the structure of functional connectivity on a node-by-node basis within the DMN. Typically, investigations regarding effective connectivity for a given functional network in the brain would be approached by using hypothesis-driven data modelling tools such as structural equation modelling (SEM) or dynamic causal modelling (DCM). Both methods are able to provide estimates of effective connectivity provided that detailed knowledge regarding both the structural and functional characteristics of the network exist and can be incorporated into the model. However, hypothesis-driven modelling methods are not easily applicable in this case since information regarding the functional architecture of resting-state networks driven by intrinsic activity is very scarce. Therefore, we have here chosen to use partial correlation analysis, a purely data-driven analysis approach that requires no a priori information and thereby avoiding potential modelling pitfalls in terms of biasing our model of default mode activity by constraints that have weak experimental and/or theoretical support.

In brief, partial correlation analysis of a network composed of R regions consists of computing the conditional correlation between any pair of two regions with respect to the remaining R-2 regions. Hence, partial correlation analysis allows for the removal of mutual dependencies originating from other brain region's common influences (Marrelec et al., 2006; 2007; Salvador et al., 2005; Liu et al., 2008). In other words, a partial correlation coefficient reflects the level of interaction between two regions once the signals of these two regions have been projected onto the subspace orthogonal to the space spanned by the time-courses of all the other regions in the network. As such, this data-driven approach provides access to a measure of interactivity between any two brain regions in a network of arbitrary size that is closer to effective connectivity than marginal correlations (Marrelec et al., 2006, 2007, 2008).

Partial and marginal correlation coefficients between all nine network nodes in the DMN during rest as well as during the working memory task were computed at a group level using a hierarchical model that takes intra- as well as inter-subject variability into account. Statistical inference of inter-action between any two network nodes was done in a Bayesian framework where a Gibbs sampling scheme was used to estimate the posterior distribution of the group partial correlation matrix. Both marginal and partial correlation coefficients were thresholded at $p < 0.05$ under the null
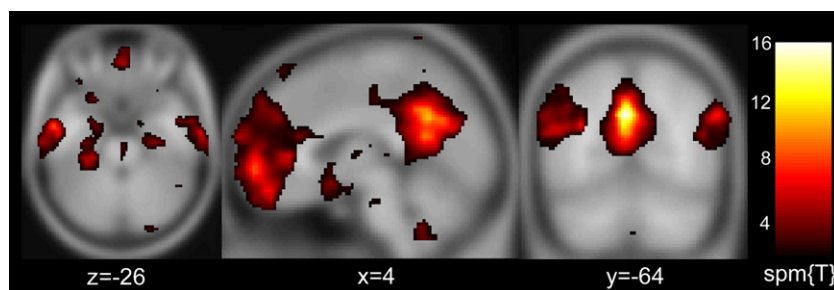

Fig. 1. A group-level analysis of default mode activity based on an ICA analysis of resting-state fMRI data from fourteen subjects. Individual independent components were extracted from each subject and analyzed at a group level using a one-sampled *t*-test thresholded at $p < 0.05$ (corrected, FDR). Activation maps shown in an axial, sagittal and coronal slice orientation show consistent activity in the precuneus/posterior cingulate cortex, medial prefrontal cortex, bilateral inferior parietal lobe, medial temporal lobe as well as in the lateral temporal cortex.

hypothesis that no interaction between pairs of network nodes exists. A detailed mathematical description of the algorithm and its implementation as outlined here is given in Marrelec et al. (2006).

Results

At a group level, intrinsic activity during rest in the DMN was faithfully represented by the extracted independent component analysis as shown in Fig. 1. Pertinent to our network analysis, consistent activity was found in the pC/PCC, bilateral lateral temporal cortex, MTL, inferior parietal cortex and the dorsal as well as the ventral aspects of the MPFC. Our network modelling results are presented in Fig. 2. Connectivity within the DMN during rest and the continuous verbal 2-back task is shown using either marginal or partial correlation as a measure of functional connectivity. A detailed account of the magnitudes for the corresponding correlation coefficients for each individual link is shown in Fig. 3.

As expected, marginal correlation coefficients were significantly larger than zero for links between all pairs of network nodes in our model of the default mode. That is, every network node was positively correlated with all the other nodes in the DMN during rest (Fig. 2, upper left panel). However, when correlation between any two nodes was conditioned on all other nodes in the DMN, the partial correlation analysis showed that the pC/PCC region is presumably a central node in the DMN since it was the only region to interact directly with all other regions, with the exception of the right MTL which in turn interacted only with the left MTL (Fig. 2, lower left panel). We also noted the strong degree of interactivity between the pC/pCC and the left inferior parietal cortex as well as the dorsal part of the medial prefrontal cortex (Fig. 2, lower left; Fig. 3, bottom graph). Moreover, it is also of interest to note that while the left and right MTL strongly interacted during rest, their degree of interactivity with the rest of the network nodes was weak. Specifically, the only significant interactions between the medial temporal lobes and the rest of the default mode

network were between the left MTL and the pC/pCC and the left temporal cortex, respectively. In addition, there seems to exist a strong interaction between the dorsal and ventral parts of the medial prefrontal cortex (MPFC) that survives a conditioning with respect to the remaining regions of the default mode network. Finally, the continuous verbal 2-back task seemed to cause a global reduction in functional interactivity within the DMN, although the overall functional structure within the DMN was to a large extent preserved (Fig. 2, lower and upper right panel).

Discussion

In this study, we have presented an investigation to gain insights on how intrinsic activity is routed at the level of individual brain regions in the default mode network. The usage of a data-driven analysis approach allowed us to estimate functional connectivity without making any prior assumptions on how intrinsic activity is implemented within the DMN. Importantly, compared to calculating the pairwise (marginal) correlation coefficients for all brain regions in the DMN, the partial correlation approach provided the means to characterize interactions between any two network nodes in terms that are close to effective connectivity, i.e. the degree to which activity in one brain area modulates activity in another area. In this context, the pC/PCC node is particularly noteworthy, since after conditioning it was the only node in the default mode network that directly interacted with virtually all other nodes. We interpret this observation that the pC/PCC may play a pivotal role in how intrinsic activity is mediated throughout the DMN. This interpretation is in harmony with the notion that the pC/PCC is a key region in the neuronal network that sustains a sense of self-consciousness that is engaged in self-referential mental thoughts during rest. The strong interactivity of the pC/PCC as demonstrated here is also in line with previous neuroimaging studies that have implicated the pC/PCC in a range of cognitive tasks that touches upon various aspects of self-processing (for recent reviews see Cavanna and Trimble,
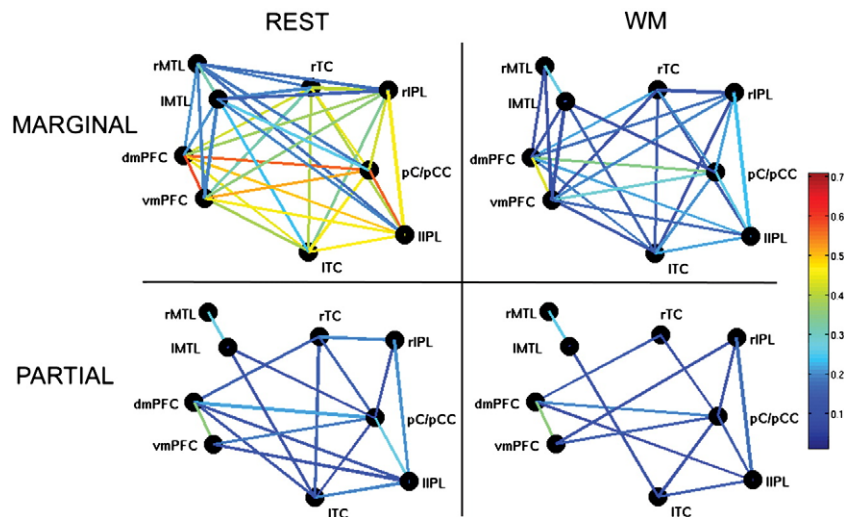

Fig. 2. The upper two panels show in a network graph format the marginal, i.e. pairwise correlation coefficients computed for the nine brain regions (network nodes) in the default mode network during rest (upper left panel) and the continuous working memory task (upper right panel). The correlation strength between any two nodes is colour-coded according to the colour-bar on the right side of the figure. The lower two panels show the degree of functional interactivity, i.e. the partial correlation coefficients for the nine nodes during both rest (lower left panel) and the working memory task (lower right panel). Only network links that were significantly larger than zero ($p < 0.05$) are shown. All network connectivity shown here is based on an independent component analysis approach to extract local changes in intrinsic activity in each network node and subject.
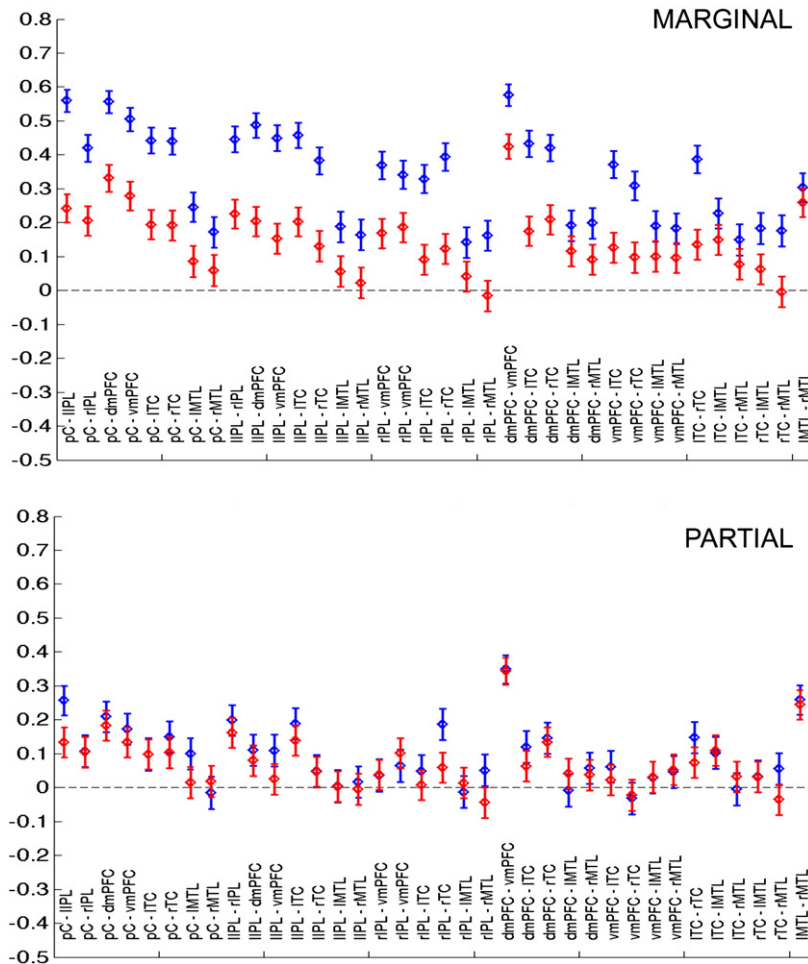
Fig. 3. The upper graph shows the magnitude of the marginal correlation coefficients for all 36 links in the nine node model of intrinsic activity in the default mode network. The lower plot shows the magnitude of the corresponding partial correlation coefficients within the default mode network. The coefficients obtained for rest are marked in blue while the corresponding coefficients for the continuous working memory task are marked in red. Similar to the data presented in Fig. 2, all coefficients shown here are computed on signal intensity time-courses extracted by an independent component analysis approach to find subject specific local maxima of intrinsic activity in each network node.

2006; Buckner and Carroll, 2007). Additionally, a pivotal status of the pC/PCC node is also justified from a metabolic and mechanistic perspective in that previous PET studies have shown that the metabolic activity is higher in the pC/PCC than all other regions during rest (Gusnard and Raichle, 2001). Moreover, a previous resting-state fMRI study that employed a model including a cosine basis set spanning the frequency interval of interest together with an *F*-test that tested for the presence of low-frequency signal fluctuations showed a particular strong presence of spontaneous signal changes in pC/PCC and to a somewhat lesser degree in the MPFC and left lateral parietal cortex than in any other region in the DMN (see Fransson, 2005, Fig 3. p. 20). Pertinent to this finding is also the fact that previous PET studies have shown a reduction in brain metabolism in the pC/PCC in the earliest clinical and pre-clinical phases of Alzheimer's disease (Minoshima et al., 1997). Moreover, recent resting-state fMRI studies of DMN activity in patients diagnosed to be in the early stages of Alzheimer's disease have revealed regionally specific reductions in coherence of low-frequency signal fluctuations in the precuneus (He et al., 2007). Additionally, a recent fMRI study has demonstrated reduced functional connectivity between the precuneus/PCC and the MTL in patients with amnesic mild cognitive impairment, a

syndrome of high risk of developing Alzheimer's disease (Sorg et al., 2007).

The strong interaction between the dorsal and ventral parts of the MPFC during both rest and working memory was preserved in the partial correlation analysis. This finding is perhaps not overly surprising since the functional border between the two is not clear-cut from an intrinsic activity perspective. Although local maxima of intrinsic activity located specifically in either part have been reported (Greicius et al., 2003; Fransson, 2005; Fox et al., 2005), intrinsic activity in the MPFC is often observed as a contiguous cluster of activity that spans the MPFC along its entire dorsal–ventral extension (Fransson, 2005; Fox et al., 2005). This observation is also reflected by the fact that the data from 3 subjects were discarded from the network analysis due to a close proximity (less than 15 mm) of local maxima in resting-state activity in the dorsal and ventral MPFC. Similarly, the strong interaction across hemispheres for the MTLs during both rest and the working memory task is noteworthy. This finding together with the observation that the interaction between the bilateral MTLs and the remaining DMN were rather weak suggests that intrinsic activity in the medial temporal lobes operates, at least in part, independently from the rest of the DMN. It should also be mentioned that this view on the role of

the MTL in the default mode network is not in conflict with a previously published study on the MTL and intrinsic activity since pairwise marginal correlation was used as a measure of functional connectivity in that study (Vincent et al., 2006). Additionally, the partial correlation analysis suggests a tendency for slightly stronger interactions in the left compared to the right hemisphere. For example, the left temporal cortex was the only region to interact with the MTL and the left inferior parietal lobe region was significantly interactive with both the dorsal and ventral parts of the MPFC.

The overall preserved structure of functional interactivity during the working memory task (Fig. 2 upper and lower right panels) is in agreement with previous seed-based ROI marginal correlation analyses (Fransson, 2006). The persistence of intrinsic activity in the DMN during a continuous verbal 2-back working memory task, a task that provides very little time to conscious, non-task related self-referential thinking, further supports the idea that intrinsic activity in the DMN is not caused exclusively by spontaneous changes in conscious thought. This line of reasoning is further reinforced by recent studies that have shown that DMN activity is preserved during early stages of sleep (Fukunaga et al., 2006; Horovitz et al., 2008) as well as during anaesthesia (Vincent et al., 2007). Pertinent to our results, it is interesting to note that a recent study observed a specific effect in terms of reduced intrinsic activity in the pC/PCC region during conscious sedation by means of administration of midazolam (Greicius et al., in press). The hypothesis that behaviour contributes to spontaneous activity in resting-state networks was recently addressed in a recent study by Fox et al. that observed a correlation between button press force and spontaneous trial-to-trial variability in the left somatomotor cortex (Fox et al., 2007). Although the neuronal mechanism that causes spontaneous low-frequency signal changes is currently unknown, we interpret the experimental data and results presented so far that conscious as well as unconscious neuronal processes may contribute to intrinsic brain activity (see also Fransson, 2006).

One of the previously proposed functional roles of the DMN is that it supports an ability to perform internal mentation in the sense that the DMN provides a platform for putting together dynamic mental scenarios that are largely detached from the external world (Buckner and Carroll, 2007). Typically, these scenarios would contain elements of auto-biographical episodic memory, self-related prospective thoughts, moral judgments as well as evaluations of other persons' intentions (theory-of-mind). Further, it has been suggested that the purpose for a continuously on-going internal mentation process is to act as a simulator and predictor of future events that builds upon previous experiences. With this hypothesis in mind, it has been noted that previous task-driven neuroimaging studies support the idea that the default mode network can be divided into two subsystems (Buckner et al., 2008). On one hand, previous studies have shown that the posterior part of the DMN including the pC/PCC, bilateral IPL and the MTL region are activated in episodic memory retrieval (e.g. Wagner et al., 2005). Moreover, it has recently been shown that this subsystem is synchronized through spontaneous signal changes (Vincent et al., 2006). On the other hand, tasks that involve self-referential mental thoughts typically activate the anterior part of the DMN and the pC/PCC (Gusnard et al., 2001). Since the process of simulating future events to a large extent engages the same neuronal circuits as remembering past events (e.g. see recent review by Schacter et al., 2008), it is plausible to assume that a neuronal platform for internal mentation as described above would require an interaction between the two subsystems (Buckner et al., 2008). Then, the strong interconnectivity between the pC/PCC node and the rest of the DMN as revealed by the partial correlation network analysis adds further support for the hypothesis that the pC/PCC node in the DMN acts as a convergence node where information processing in the two subsystems is integrated.

It could be argued that a more fine-grained model of DMN activity is warranted and that the nine network nodes selected here are unnecessarily limited in scope. For example, it is plausible that the parahippocampal gyrus and the hippocampus may serve different functions within the DMN and thus should be represented as separate network nodes. To address this concern, we initially tried to locate separate maxima of intrinsic activity by performing individual searches in the hippocampus and parahippocampal gyrus as anatomically delineated in the AAL atlas. However, in the majority of subjects, the distance between local maxima in the hippocampus and parahippocampal gyrus was less than 12 mm, which would make an interpretation of separate contributions for these regions in relation to functional interactivity dubious. Since our results suggests the ICA-based approach is less biased while at the same time providing good sensitivity to local changes in intrinsic activity, we here refrained from further refinements of our network model. A separation of parahippocampal versus hippocampus intrinsic activity would most likely require a considerably higher spatial resolution in the raw functional MR images than used here. It should also be stressed that while partial correlation analysis provides estimates of functional interactions it does not give information regarding causality (Marrelec et al., 2006).

In sum, using a novel approach to extract local changes in intrinsic activity combined with a data-driven analysis approach, we have presented a first assessment of functional connectivity on a node-by-node basis within the DMN. A prominent finding included a putative pivotal role for the pC/PCC in the default mode network. In this context, changes in intrinsic brain activity specific to developmental (Fransson et al., 2007; Fair et al., 2008), aging (Andrews-Hanna et al., 2007; Damoiseaux et al., 2007) as well as disease-related mechanisms (e.g. Garrity et al., 2007; Castellanos et al., 2008) have recently been reported (for recent reviews see Buckner et al., 2008 and Fox and Raichle, 2007). We suggest that the results presented here can serve as a template for informed modelling approaches in a network framework to map and characterize changes in DMN intrinsic activity in both health and disease.

Acknowledgment

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2008.05.059.

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