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Review

Default-mode brain dysfunction in mental disorders: A systematic review

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ABSTRACT

In this review we are concerned specifically with the putative role of the default-mode network (DMN) in the pathophysiology of mental disorders. First, we define the DMN concept with regard to its neuro-anatomy, its functional organisation through low frequency neuronal oscillations, its relation to other recently discovered low frequency resting state networks, and the cognitive functions it is thought to serve. Second, we introduce methodological and analytical issues and challenges. Third, we describe putative mechanisms proposed to link DMN abnormalities and mental disorders. These include interference by network activity during task performance, altered patterns of antagonism between task specific and non-specific elements, altered connectively and integrity of the DMN, and altered psychological functions served by the network DMN. Fourth, we review the empirical literature systematically. We relate DMN dysfunction to dementia, schizophrenia, epilepsy, anxiety and depression, autism and attention deficit/hyperactivity disorder drawing out common and unique elements of the disorders. Finally, we provide an integrative overview and highlight important challenges and tasks for future research.

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What does the brain do when not actively engaged in goal-directed cognitive tasks – when, for want of a better term, we might say it is at "rest"? What functions does the 'resting' brain subserve and how do these impinge on more general aspects of cognition? These intriguing questions, largely ignored in the history of cognitive psychology, have become a significant focus of research activity in cognitive neuroscience in the past few years since Marcus Raichle first coined the term 'default-mode' in relation to resting state brain function (Raichle et al., 2001). Our goal in the current paper is to explore the potential significance of the default-mode network (DMN; Greicius et al., 2003) concept for contemporary models of mental disorder. *First*, we delimit the concept of the DMN and describe its structural and functional neuroanatomy. *Second*, we explore some of the key methodological issues relating to study of DMN. *Third*, we review the empirical studies of DMN in individuals with mental disorders. *Fourth*, we draw out the potential significance of these data for theoretical models of psychopathology. A number of possibilities will be considered that focus on irregularities inherent within the patterns of coherence within the DMN, aberrant patterns of interconnections with other networks and dysfunctional patterns of transition from resting to goal-directed activity. Finally we attempt to draw out the clinical implications of altered DMN activity.

1. The default-mode network

The DMN concept although only first introduced into the published literature in 2001 has rapidly become a central theme in contemporary cognitive and clinical neuroscience. Here we identify five key elements.

1.1. Regional task-non-specific deactivations during goal-directed activity

The DMN concept comes from an emergent body of evidence demonstrating a consistent pattern of deactivation across a network of brain regions that includes precuneus/posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC) and medial, lateral and inferior parietal cortex; that occurs during the initiation of task-related activity (Raichle et al., 2001). Although deactivated during task performance, this network is active in the resting brain with a high degree of functional connectivity between regions. This resting state activity has been termed the default-mode of brain activity to denote a state in which an individual is awake and alert, but not actively involved in an attention demanding or goal-directed task (Raichle et al., 2001). A comparison of brain energy utilization during rest and active-task oriented conditions indicates that consumption is only slightly greater for the active than the resting brain (Raichle and Gusnard, 2002; Raichle and Mintun, 2006). For researchers to focus on active task-oriented conditions to the exclusion of rest may be a significant oversight. Research has concentrated on the patterns of activity within and interconnectivity between DMN brain regions during rest, and the impact that the commencement of goal-directed activity has on this. Significantly, DMN activity is *attenuated* rather than extinguished during this transition between states, and is observed, albeit at lower levels, alongside task-specific activations (Eichele et al., 2008; Fransson, 2006; Greicius et al., 2003; Greicius and Menon, 2004). The more demanding the task the stronger the deactivation appears to be (McKiernan et al., 2006; Singh and Fawcett, 2008). DMN activity persists to a substantial degree during simple sensory tasks, in which satisfactory task performance is possible with only minimal attentional resources (Greicius et al., 2003; Wilson et al., 2008), during the early stages of sleep (Horovitz et al., 2008), and to a lesser extent, under conscious sedation (Greicius et al., 2008a). It has also been shown that increased PCC activity, or reduced deactivation, systematically preceded and predicted response errors in a flanker task, up to 30 s before the error was made (Eichele et al., 2008). Momentary lapses in attention denoted by longer RTs and less accurate performance in an attentional control task have been associated with less task-induced deactivation of the DMN, and reduced activity in right inferior frontal gyrus (IFG), middle frontal gyrus (MFG) and anterior cingulate cortex (ACC; i.e. frontal control regions; Weissman et al., 2006). A notable exception to this general pattern of deactivation during goal-directed activity occurs in relation to tasks requiring self-referential thought or working memory where only specific DMN regions are specifically deactivated. For example, attenuation of the ventral MPFC occurred with tasks involving judgments that were self-referential, while activity in the dorsal MPFC increased for self-referential stimuli, suggesting the dorsal MPFC is

associated with introspective orientated thought (Gusnard et al., 2001). Working memory tasks differentially deactivate the PCC. One study observed a signal increase and spatial decrease in the PCC and a signal decrease but spatial increase in the ACC with increasing working memory load in an n-back task (Esposito et al., 2006). A similar result in the same task was also reported using a frequency-based coherence measure (Salvador et al., 2008). In contrast, earlier research reported a significant task-related decrease in PCC (Greicius et al., 2003), and although Hampson et al. (2006) did not find functional connectivity between the ventral ACC and PCC to differ between rest and a working memory task, performance was positively correlated with the degree of ventral ACC and PCC connectivity. Attenuation of DMN activity has been described as task non-specific, the extent to which goal-directed activity influences this attenuation is dependent at least in part, on cognitive load and task requirements involving functions subserved by regions within the DMN.

1.2. Coherence and functional connectivity within the DMN

The issue of how different brain regions are connected functionally, that is, how the interplay of different areas subserves cognitive function, has become a key concern in neuroscience. Empirical research has largely focussed on the functional connectivity of the DMN within the parameters of functional magnetic resonance imaging (fMRI) data and the blood oxygen level dependent (BOLD) signal; an indirect measure of neuronal activity reflecting changes in blood oxygen level contrasts within the brain (Fox and Raichle, 2007). In this context, functional connectivity simply refers to the temporal correlation between fluctuations in the BOLD signal of discrete anatomical regions (Fox and Raichle, 2007). More generally, functional connectivity between two given regions is considered in terms of the temporal coherence or correlation between the oscillatory firing rate of neuronal assemblies (Friston, 1994). Additionally, the spatial co-ordinates of the nodes within the DMN appear to substantially mirror the underlying structural connectivity between brain regions (Greicius et al., 2008b). Indeed, using a computational approach to examine spontaneous resting state fluctuations and their association with structural connectivity based on macque neocortex data, Honey et al. (2007) have demonstrated a structure–function relationship at multiple time-scales. The properties of neuronal networks indicate that low frequency oscillations are likely associated with connectivity of larger scale neuronal networks, while higher frequencies are constrained in smaller networks, and may be modulated by activity in the slower oscillating larger networks (Buzsáki and Draguhn, 2004; Fox and Raichle, 2007; Penttonen and Buzsáki, 2003). Providing the oscillatory frequencies remain similar, connectivity may be maintained across diverse brain regions despite weakened synaptic links (Buzsáki and Draguhn, 2004). In this way, very low frequencies can bind widespread neuronal assemblies each oscillating at higher frequencies (Buzsáki and Draguhn, 2004). Buzsáki and Draguhn (2004) have argued that potential functions of general neuronal connectivity include information exchange between diverse brain regions through the binding of cell assemblies and cognitive precepts, as well as the consolidation and amalgamation of learned information for long-term memory storage. The functional role of low frequency oscillations coherent across resting state networks, and particularly the DMN, remains speculative. Possible candidates include the temporal binding of information (Engel et al., 2001), particularly related to the coordination and neuronal organisation of brain activity between regions that frequently work in combination (Fox and Raichle, 2007); a record of previous patterns of connectivity mediated by task-specific activity, or even dynamic predictions about future patterns of

connectivity (Fox and Raichle, 2007; Fox et al., 2005; Raichle and Gusnard, 2005); and a binding mechanism between introspective and extrospective orienting of attention (Fransson, 2006). Developing a more comprehensive understanding of the origins and functions of such connectivity is key to understanding brain function and neuronal organisation more generally (Fox et al., 2005).

1.3. DMN characterised by low frequency BOLD signal

The DMN is characterised by very low frequency neuronal oscillations providing temporal synchrony between functionally specific and diverse brain regions (Sonuga-Barke and Castellanos, 2007). The coherence of such spontaneous oscillations accounts for significant variability in the trial-to-trial BOLD response, and as such is hypothesised to superimpose in a linear manner on task-related brain activity (Fox et al., 2006a). Biswal et al. (1995) were the first to observe the coherence between such low frequency oscillations and widely distributed neuro-anatomical networks, which have since been explored in a wide range of tasks (e.g. Gusnard et al., 2001; Kelly et al., 2008; McKiernan et al., 2006), clinical pathologies (e.g. Bluhm et al., 2007; Castellanos et al., 2008; Greicius et al., 2007, 2004; Kennedy et al., 2006; Lowe et al., 2002; Tian et al., 2006; Tinaz et al., 2008), and even in chimpanzees (Rilling et al., 2007). More limited evidence of DMN in the infant brain (Fransson et al., 2007), fragmented connectivity between DMN regions during rest in young children (7–9 years; Fair et al., 2008), and more consistent DMN connectivity in children aged 9–12 years (Thomason et al., 2008), suggests that this network of spontaneous low frequency activity undergoes developmental change and maturation.

1.4. Anti-correlated task-positive and task-negative resting networks

Brain activity in the resting state incorporates both task-negative and task-positive components. The DMN has been described as a task-negative network given the apparent antagonism between its activation and task performance. A second network also characterised by spontaneous low frequency activity has been identified as a task-positive network. This network includes the dorsolateral prefrontal cortex (DLPFC), inferior parietal cortex (IPC) and supplementary motor area (SMA) and appears to be associated with task-related patterns of increased alertness, and has also been related to response preparation and selection (Fox et al., 2005, 2006a; Fransson, 2005, 2006; Sonuga-Barke and Castellanos, 2007). Interestingly, the task-positive network and the DMN are temporally anti-correlated, such that task-specific activation of the task-positive network is affiliated with attenuation of the DMN. One hypothesis is that task-positive activity is thought to reflect extroceptive attentional orienting during rest, associated with preparedness for unexpected or novel environmental events. According to this account the reciprocal relationship between the task-positive component and DMN has been described as low frequency toggling between a task-independent, self-referential and introspective state and an extrospective state that ensures the individual is alert and attentive to unexpected or novel environmental events (Fox et al., 2005; Fransson, 2005, 2006). Similarly, Fransson (2006) has tentatively proposed that the desynchronicity and anti-correlation of these two networks may reflect a binding mechanism between an introspective and extrospective attentional orientation. Their high degree of temporal anti-correlation emphasises the potential degree of antagonism between the task-positive and task-negative network and the psychological functions they reflect (Sonuga-Barke and Castellanos, 2007). More recently, it has been suggested that the close temporal linkage, and strength of anti-correlation between the task-negative and task-positive network may allow them both to be considered components of a single

default network with anti-correlated components (Sonuga-Barke and Castellanos, 2007). This has led to a certain confusion with regard to terminology. Should only the task-negative network be termed the DMN and contrasted with the task-positive network? Or should both task-positive and task-negative networks be regarded as elements of the DMN? The case for including task-positive and negative components as part of the same default-mode network system is supported by a considerable amount of evidence. Fox et al. (2005) suggest that the close association between task performance and the strength of anti-correlation between the networks may reflect the underlying dynamics and organisation of the brain. This proposition allows for naturally occurring competition between the task-negative and task-positive component, such that spontaneous anti-correlated interactions between the networks will result in periodic task interference, and importantly, does not necessitate the involvement of a central executive. Indeed, it has been suggested on a number of occasions that the anti-correlation between the two networks may prove to be functionally more important, than DMN activity itself (Fox et al., 2005; Uddin et al., 2008b). For the purposes of clarity in the current review we use the DMN term to describe the task-negative network specifically. We use the term Low Frequency Resting State Networks (LFRSN) to describe both the task-positive and task-negative networks.

LFRSNs are not limited to the task-positive and task-negative networks described above. Mounting evidence attests to the more probable notion of multiple networks at rest (Beckmann et al., 2005; Damoiseaux et al., 2006; Greicius et al., 2008a; Jafri et al., 2008; Mantini et al., 2007). Indeed, coherent fluctuations in the resting state were first identified in the motor cortex (Biswal et al., 1995). In a comprehensive examination of LFRSNs in the adult human brain, Damoiseaux et al. (2006) used a form of independent component analysis (ICA) to assess coherence of BOLD signal in terms of temporal and spatial variation, as well as variations between participants. In this study, low frequency resting state fluctuations were identified in the DMN, sensory and motor networks, visual and auditory cortices, and two additional networks most likely involved in memory and executing functions. Using simultaneous electro-physiology (EEG)–fMRI recordings, Mantini et al. (2007) observed six resting state networks including the DMN, dorsal attention network, visual and auditory networks, somato-motor network and a network postulated to reflect self-referential processing. This study was based on short recordings of resting activity only; the reported relationships between EEG and BOLD require further investigation. However, it is clearly apparent that task-related activations, also reflected in low frequency spontaneous activity, are also readily identified during rest. These include both the dorsal and ventral attention systems (Fox et al., 2006b). The human brain then, is never really 'at rest', but rather an orchestra of distinct functional networks in dynamic concert. Recently, resting state networks have been examined in the infant brain, in which at least five have been identified. These include networks underpinning visual, auditory and sensorimotor activity similar to those observed in the adult brain, although there was little evidence from this for a DMN equivalent (Fransson et al., 2007). Further, investigation of the developmental trajectory of two networks, the fronto-parietal and cingulo-opercular, involved in implementing top–down task-specific control and evident during resting state fMRI, are reported to increase in integrity with age (Fair et al., 2007). Namely, short-range connections decreased and long-range connections increased with age and brain maturation (Fair et al., 2007).

1.5. What functions are subserved by the default-mode network?

What then is the functional significance of DMN activity? PCC (and adjacent precuneus) and MPFC, are the two most clearly delineated regions within the DMN in terms of their functional roles (Raichle et al., 2001). PCC appears to serve an important adaptive function and is implicated in broad-based continuous sampling of external and internal environments (Raichle et al., 2001), the attenuation of which during transition from rest facilitates focused attention during task-specific activity (Eichele et al., 2008; Raichle et al., 2001). Moreover, modulation of the PCC during working-memory tasks (Greicius et al., 2003), reduced activation at rest (Greicius et al., 2004), susceptibility to atrophy in Alzheimer's disease patients (Buckner et al., 2005), and reduced connectivity with anterior DMN regions in attention deficit/hyperactivity disorder (ADHD) participants (Castellanos et al., 2008; Uddin et al., 2008a) suggests that this region may be implicated in working memory dysfunction. Finally, PCC and retrosplenial cortex are also associated with the processing of emotionally salient stimuli, and may play a role in emotional processing related to episodic memory (Maddock, 1999). MPFC has been associated with social cognition involving the monitoring of ones own psychological states, and mentalising about the psychological states of others (Blakemore, 2008; Gusnard and Raichle, 2001; Rilling et al., 2008; Schilbach et al., 2008). In the context of DMN activity, MPFC is thought to mediate a dynamic interplay between emotional processing and cognition functions which map on to the ventral and dorsal regions, respectively (Gusnard et al., 2001; Raichle et al., 2001; Simpson et al., 2001). Ventral MPFC is heavily interconnected with other limbic structures such as amgydala, ventral striatum and hypothalamus, which Gusnard and colleagues suggest may indicate a role in relation to the mediation of visceromotor aspects of emotional information gathered from external and internal sources (Gusnard et al., 2001; Gusnard and Raichle, 2001). Both PCC/precuneus and MPFC are associated with introspective processes such as self-referential and emotional processing, and are attenuated when attention is directed toward external events (Gusnard and Raichle, 2001). Importantly, PCC activity predicts response errors in flanker tasks, which points towards the behavioural significance of the DMN (Eichele et al., 2008). The interaction of the anterior and posterior regions of the DMN may serve to organise neuronal activity (Buzsáki and Draguhn, 2004), or more simply as a state in which the mind may wander during self-referential mental processing (Fransson, 2005; Gusnard et al., 2001; Mason et al., 2007).

In summary, recent research has identified a 'default-mode' network of brain regions active in the resting brain and characterised by coherent low frequency neuronal oscillations (<0.1 Hz). During goal-directed activity the DMN is attenuated, while a second, temporally anti-correlated network, the task-positive network is activated. The high degree of temporal anti-correlation between the DMN and task-positive network, is thought to reflect a low frequency toggling between their associated psychological functions of introspective and self-referential thought and extrospective attentional orienting, respectively; allowing an individual to remain alert to unexpected environmental events. Indeed, the close temporal linkage and rivalry between associated functions is a potential argument for considering the DMN and task-positive component as part of a single network.

2. Methods and measurement models

In order to understand the findings relating DMN activity to mental disorders reviewed below and so to draw out the relevant and appropriate implications, a survey of key methodological and analytical issues is presented. Resting brain states and the DMN have been principally investigated using fMRI (e.g. Greicius et al.,

2003, 2004, 2007), although positron emission tomography (PET; e.g. Raichle et al., 2001) and electrophysiology have also been employed (e.g. Helps et al., 2008; Laufs et al., 2003b; Scheeringa et al., 2008). In this section we describe each technology and review their strengths and weaknesses with regard to the DMN. We will then highlight some key methodological challenges for the field. Finally, we review some significant analytical considerations especially in relation to measurement of low frequency brain activity.

2.1. Functional magnetic resonance imaging

The assessment of resting brain networks using the BOLD response may be achieved through a number of methods. Two of which, region-of-interest (ROI) seed-based correlation approaches and ICA, are most commonly employed in the literature. Briefly, seed-based approaches use regression or correlation analyses to examine the temporal coherence between a selected voxel or ROI and the time-series of all other voxels in the brain (Uddin et al., 2008a). Such an approach is used to examine temporal coherence between regions, and identify networks of functional connectivity (e.g. Biswal et al., 1995). In contrast, ICA is a model-free approach, which, unlike ROI seed-based analysis, is not bounded by a priori predictions. ICA decomposes data into maximally (temporally or spatially) independent components, representing the characteristic time and spatial signatures of the sources underlying the recorded mixed signals (McKeown et al., 1998). While there are theoretical advantages/disadvantages of each method – a direct comparison reveals comparable results (Bluhm et al., 2008; Greicius et al., 2004; Long et al., 2008). Other analytical approaches have also been applied. One such approach is 'network homogeneity', a voxel-wise measure that examines the correlation between any given voxel and all other voxels within brain network (Uddin et al., 2008a). Uddin et al. argue that this approach avoids a priori knowledge about potentially aberrant regions with a network. Similarly, Zang et al. (2004) have examined the correlation between a given voxel and neighbouring voxels, denoted as 'regional connectivity' or 'regional homogeneity' (Zang et al., 2007; Zhu et al., 2008). This approach is limited to the investigation of close-range connectivity. To assess local coherence in brain regions, Deshpande et al. (2007) have used a similar method, 'integrated local correlation', which unlike regional homogeneity, does not require the neighbourhood to be predefined, as it is relatively unaffected by spatial resolution. Furthermore, Zang et al. (2007) introduced an amplitude measure of low frequency fluctuation in resting state fMRI (amplitude of low frequency fluctuation; ALFF), which was further improved by Zou et al. (2008) and termed 'fractional amplitude of low frequency fluctuation'. This improved approach is thought to increase the sensitivity and specificity with which regional resting state activity may be detected (Zou et al., 2008). Finally, Greicius et al. (2004) have developed a 'goodness of fit model' to more accurately identify the functionality of ICA components. In this method, a predefined template is used to identity a network through a goodness-of-fit procedure (for further detail see Greicius et al., 2004). This method allowed comparison of the DNM in individual participants, with successful application to a clinical population (Alzheimer's disease patients), developed as an automatic ICA technique for identifying the DMN.

2.2. Electrophysiology

Although fMRI BOLD imaging is ideal for providing a representation of the spatial organisation of brain function, it is as yet unclear how these changes relate to concurrent changes in the spatial extent and magnitude of neuronal events (Debener et al., 2006). The aspect of neuronal activity which best predicts changes in BOLD contrast (i.e. combined neuronal spiking, local field potentials, changes in spontaneous rhythms, etc.) has not been established definitely (Huettel et al., 2004). Hence there may be a degree of incongruence between hemodynamic and electrophysiological signals. Moreover, despite the excellent spatial resolution of fMRI, the temporal resolution is poor. In contrast, EEG has excellent temporal resolution in which electrophysiological correlates of spontaneous, low frequency neuronal activity may be examined (Khader et al., 2008).

Researchers have examined DMN activity in terms of traditional bands of EEG activity (Chen et al., 2008), and in terms of very slow EEG frequencies (Helps et al., 2008; Vanhatalo et al., 2004). Vanhatalo et al. (2004) reported pervasive very low frequency oscillations (0.02–0.2 Hz) across diverse scalp regions, in combination with evidence of robust phase-locking between these low frequency oscillations and traditional EEG bands of activity (Vanhatalo et al., 2004). Further, the stability of low-frequency oscillatory networks has been demonstrated over a 1-week test–retest period, both in terms of their spatial location and frequency (Helps et al., 2008). Chen et al. (2008) compared the spatial distribution and spectral power of seven bands of resting state EEG activity, in an eyes closed and eyes open condition. In the eyes closed condition, the authors report delta (0.5–3.5 Hz) activity in the prefrontal area, theta (4–7 Hz) activity at frontocentral sites, and alpha-1 (7.5–9.5 Hz) activity distributed in the anterior–posterior region. Further, alpha-2 (10–12 Hz) and beta-1 (13–23 Hz) activity were evident in posterior regions, and high frequency beta-2 (24–34 Hz) and gamma (34–45 Hz) in the prefrontal area. Comparatively, in the eyes open condition, delta activity was enhanced, and theta, alpha-1, alpha-2 and beta-1 were reduced in the respective regions. Chen et al. (2008) term this defined set of regional and frequency specific activity, the EEG default-mode network (EEG-DMN), and propose that the EEG-DMN should now be examined in the context of task-induced demands and in patient groups.

One study has investigated event-related potential (ERP) correlates of mind wandering, symptomatic of DMN interference (Smallwood et al., 2008). In this study, a positive going component elicited approximately 300 ms after stimulus onset (the P300), was reduced in amplitude on trials preceding an error, and trials preceding self-reported mind wandering (irrespective of the participant's awareness that their mind had wandered). Smallwood et al. (2008) argue that these findings reflect a reduction in the amount of attention allocated to the task environment during mind wandering, and likely indicate DMN interference of task-related processes.

The possibility of incongruence between BOLD and EEG signals, and the relative strengths and weaknesses of fMRI and EEG methodologies, highlight the advantage of combining the two modalities in simultaneously recording (Debener et al., 2005, 2006; Herrmann and Debener, 2008; Laufs, 2008). Moreover, simultaneous EEG–fMRI allows the empirical determination of the degree of overlap (or dissonance) between EEG and fMRI BOLD and may be a perfect tool to investigate the EEG correlates of DMN activity. This growing body of literature has noted correlations between the DMN and gamma (Mantini et al., 2007), beta (Laufs et al., 2003b; Mantini et al., 2007), alpha (Laufs et al., 2003a; Mantini et al., 2007), and theta (Meltzer et al., 2007; Scheeringa et al., 2008). Mid-range beta (17–23 Hz) was strongly correlated with task-independent deactivations in PCC, precuneus, temporo-parietal and dorsomedial prefrontal cortex (Laufs et al., 2003b). In view of the lack of association between alpha and resting state brain activity, Laufs et al. (2003b) hypothesise that alpha may act

as a baseline for specific brain structures associated with the attentional system, and more specifically the task-positive network (Laufs et al., 2006). In contrast, Mantini et al. (2007) reported positive correlations between beta (13–30 Hz) and alpha (8–13 Hz) with the PCC, precuneus, bilateral superior frontal gyrus and the MFG. Further regions in the DMN associated with self-referential processing such as the MPFC were positively correlated with gamma (30–50 Hz; Mantini et al., 2007). In addition, medial frontal theta power changes were negatively correlated with the BOLD response in medial frontal regions, PCC/precuneus and bilaterally in inferior frontal, inferior parietal and middle temporal cortices and the cerebellum (Scheeringa et al., 2008). Further, Meltzer et al. (2007) investigated EEG correlates of the BOLD response in separate EEG and fMRI sessions, fronto-medial theta was most strongly negatively correlated with the MPFC, although negative correlations were also found with other DMN areas such as PCC. The results of Meltzer et al. (2007) and Scheeringa et al. (2008) suggest that the DMN may operate within the theta frequency such that decreased DMN activation is associated with increased theta power during goal-directed activity. Finally, concurrent electrophysiological and fMRI recordings in rats have shown correlations between oscillatory activity in the delta range (1–4 Hz) and resting state functional connectivity (Lu et al., 2007).

2.3. Magnetoencephalography

Magnetoencephalography is a promising methodology through which electromagnetic correlates of DMN activity, including very low frequency oscillations may be examined. MEG acts as a direct neuronal activity probe with real-time resolution (in the order of ms) and can provide a high spatial resolution (in the order of mm) when coupled with structural models (this is because the homogenous conductivity of MEG is not distorted by the scalp, skull, brain and cerebrospinal fluid). This allows for accurate source analysis. Although precise MEG correlates of the DMN have not yet been investigated, there is an increasing body of research examining resting state MEG data (e.g. Bosboom et al., 2006; Osipova et al., 2006; Stam et al., 2006; Stoffers et al., 2008). Indeed, Leistner et al. (2007) have used concurrent direct current (DC) EEG and DC MEG recordings to investigate low frequency MEG oscillations (≈0.1 Hz) as participants performed very slow (0.5 Hz) and slow (1.5 Hz) finger movements. Motor-related low frequency MEG oscillations were recorded from the hemisphere contralateral to the hand used (Leistner et al., 2007). This study, in combination with the current interest in resting state MEG oscillations highlights MEG as a useful methodology in the temporal and spatial localisation of DMN activity.

2.4. Key methodological challenges

A number of key methodological challenges affect both DMN measurement and methodological models. First and foremost, it is not yet evident how oscillatory brain activity as measured by EEG/MEG relates to the DMN as identified with fMRI and PET. While MEG for instance clearly has advantages compared to EEG, it may be blind to deeper sources of the DMN such as the PCC. Whether these deeper sources express an open electromagnetic-field-oscillatory-pattern that can be observed with EEG, MEG, or both, remains to be demonstrated. The underlying problem here is how signals registered using different 'neuroimaging' modalities such as fMRI, MEG and EEG relate to each other. It is conceivable that some activity patterns picked up by EEG are not 'visible' in fMRI BOLD, and vice versa (Nunez and Silberstein, 2000), and similar examples could be constructed for the relationship between MEG and EEG. For instance, MEG and EEG reflect synchronous activity of pyramidal neurons, but both measures are differently sensitive to the orientation and distance of neural sources. Moreover, about 20% of all grey matter neurons are of non-pyramidal type and express metabolic activity that may be well reflected in the BOLD signal, but not in EEG or MEG. MEG and EEG amplitudes depend (among other biophysical properties) on the number, orientation, and of synchronisation of pyramidal neurons, but the latter effect may not be well represented in the BOLD signal. More research is needed combining different modalities, but current progress in the field of simultaneous EEG–fMRI research is promising (Debener et al., 2006; Herrmann and Debener, 2008, for review) and may help to better understand which portions of fMRI BOLD activity are reflected in EEG/MEG.

Second, low frequency electromagnetic activity is notoriously difficult to study. Interference to the low frequency fluctuations in the BOLD signal may arise from low frequency cycles in respiration and cardiac activity, and the related body and head movements may obscure EEG and MEG signals. Variations in respiration (∼0.03 Hz) correlate highly with fluctuations in the DMN (<0.1 Hz), with overlap between regions within the DMN and areas significantly affected by changes in respiration (Birn et al., 2006, 2008). When respiration per volume time changes are regressed out, the functional connectivity between regions in the DMN is improved slightly, although this improvement increases if global signal changes are regressed out (Birn et al., 2006; Fox et al., 2005). The high correlation between global signal changes and respiration volume per time changes, lead Birn et al. (2006) to argue that the global signal may more accurately reflect the temporal shape of the respiration-volume-induced fMRI signal changes and therefore lead to improved correction. Although it should be noted that such a technique may also lead to the removal of aspects of the signal one is trying to detect (Birn et al., 2006). The utility of ICA in the separation of low frequency fluctuations associated with the DMN and those associated with respiration-induced changes has been recently demonstrated (Birn et al., 2008). Nonetheless, Birn et al. (2008) emphasise that an independent measure of respiratory activity is particularly valuable to accurately identify components reflecting neuronal activity.

Much attention in the resting state fMRI literature has been directed toward the anti-correlation between the DMN and task-positive networks. Such research has commonly involved pre-processing techniques, and in particular the abovementioned regression of global mean signal fluctuations. Significantly, the possibility that such data pre-processing methods may also lead to artifactual negative correlations has been raised and should be considered in future research (Murphy et al., 2008; Smith et al., 2008). Although it is conceivable that anti-correlations between brain networks may arise as an artifact of pre-processing methodology, it is thought that previously reported anti-correlations are indeed a true representation of a physiological relationship between the DMN and task-positive networks (Fox et al., 2008). In summary, the analysis of neural activity in the low frequency range requires careful recording and artifact processing procedures (see Fox and Raichle, 2007, for a further review).

Third, the biggest challenge may be to determine the behavioural correlates of the DMN and other resting state networks. Conceptual, methodological and empirical evidence suggests that the conventional approach of analysing EEG, MEG and fMRI, which focuses on response averaging, does not provide the full picture of the brain–behaviour relationship (Makeig et al., 2004). Intrinsic activity, which may also be called brain states, may systematically contribute to behaviour, as it has been shown repeatedly, but this relationship has been determined mostly on theta or faster brain oscillations. Moreover, in the case of fMRI,

slow activity profiles in the DMN may be task-relevant but non-oscillatory in nature (e.g. Eichele et al., 2008). Recent animal research has shown that the phase of ongoing cortex activity in sensory modalities can be modulated by other modalities, and that this phase modulation relates to behavioural performance (for review, see Schroeder et al., 2008). With the development of online fMRI protocols, it might be possible to adapt a similar strategy: the adjustment of the timing of experimental stimuli with regard to the amplitude (or phase) of BOLD oscillations in the DMN may turn out to be a powerful tool and help to establish the functional relevance of the DMN.

2.5. Key analytical challenges

2.5.1. Analysing very low frequency oscillations measured using multi-channel MEG and EEG recordings

The analysis of slow waves in the range of $0.01 < f < 0.1$ Hz (which have previously been discarded as noise) in a MEG system with a dense array of sensors has several implications. Longer time recordings (in the order of tens of minutes) are required to be able to extract these very low frequency components accurately. This may compromise the compliance of the participants when given a repetitive task in an experiment. Technically, it also leads to loss of stationarity and to drifts in the recordings – although these can be mediated by careful recording of the data. The sampling rate chosen needs to be high enough to ensure that there are enough data points available for accurate calculation of fast Fourier transforms (FFT) within the desired frequency range. Moreover, electromagnetic brain signals exhibit power spectra with high power at low frequencies, normalisation of this $1/f$ trend is required to render a flat base spectrum when no extra low frequency activity is present and to reveal distinct peaks related to specific cognitive tasks or mental conditions (such as resting states). This is particularly important in the analysis of such infra-slow oscillations (Demanuele et al., 2007).

MEG data is obtained from an inherently 'noisy' recording process and typically contains a mixture of artifacts and brain signals from a variety of sources such as muscle and ocular components, along with various active, if not all superficial brain regions. This implies that denoising techniques such as ICA need to be used for proper network analysis.

Large sensor arrays result in a data deluge problem, which has practical considerations such as long computational times and large memory requirements for the application of signal processing techniques. However, the large multi-dimensional datasets also bring with them issues related to the appropriate choice of the analysis technique.

2.5.2. Denoising and dimensionality reduction

The data-deluge problem, coupled with the artifactual and multi-source data recordings, make these ideal candidates for the use of blind source separation (BSS) strategies in order to remove artifacts, reduce dimensionality and single out useful brain sources. ICA is a specific form of BSS which is used in the identification and separation of sources with little prior information. The components are assumed to be mixed, either linearly or nonlinearly, and the components themselves, together with the mixing system, are assumed to be unknown. ICA has been extensively used for the analysis of electromagnetic brain signals (James and Hesse, 2005; Vigario et al., 2000). Depending on the algorithm used, ICA provides *estimates* of brain sources, some-where between the *actual* brain sources and the scalp signals, such that the recovered components are *maximally independent*. Generally, separate independent components are grouped together to form a subspace which represents the brain sources

of interest. Thus ICA provides a useful tool for denoising the electrophysiological data by distinguishing artifacts and useful brain sources (Jung et al., 2000; Makeig et al., 2002; Vigario et al., 1998).

Single channel ICA (SCICA) is a special form of ICA that isolates underlying components using only temporal information inherent in *single channel* recordings (Davies and James, 2007). A multi-channel MEG system is highly dense and channels that are close to each other tend to be influenced by activity from similar brain areas. By analysing fewer channels in specific brain regions one would still be able to extract underlying temporal generators contributing to the measured signals. This automatically achieves dimensional reduction since a number of spatially distinct brain channels can be chosen out of the dense multi-channel recordings and underlying independent brain sources can still be extracted.

2.5.3. Extraction of spatial, temporal and spectral information from data

Many signal processing techniques exist to enable maximal extraction of spatial, temporal and spectral information from electromagnetic brain signals, an area of constant research and development. Spectral analyses involving FFTs have been widely used for the analysis of neurophysiological signals (Bruns, 2004). However the FFT, which is a time-frequency transformation of the measured signal, does not cater for variations in the statistical properties of the data with time, making it unsuitable for non-stationary signals. For this reason this analysis is often carried out repeatedly with a sliding time window to provide a continuous evaluation of spectral parameters with time. This method, known as the short time Fourier transform (STFT), is very useful in the study of brain dynamics (Bruns, 2004). An alternative to the STFT is the wavelet transform (WT), which can represent finite, non-periodic and/or non-stationary signals. The idea of the WT is to convolve the measured signal with a number of oscillatory filter kernels, each representing different frequency bands. In this way the temporal characteristics of a signal are represented by its spectral components in the frequency domain. WTs provide a higher time-frequency resolution than the STFT but they take much longer to compute (Gramatikov and Georgiev, 1995). These analyses provide spectral parameters such as amplitude and phase, from which a variety of important coupling measures, such as coherence and phase synchrony, can be derived.

Coherence, however, does not separate the effects of amplitude and phase in the interrelation between two signals. Lachaux et al. (1999) discuss the limitations of coherence as a tool to indicate brain interactions, namely that coherence can be applied only to stationary signals and that it does not specifically quantify phase relationships. Coherence increases with amplitude covariance, although the relative contribution of amplitude and phase correlations in the coherence value is not clear. As coherence mixes the amplitude information with that of phase, it is not considered suitable for the detection of phase locking of brain oscillators. For these reasons, phase synchrony – a measure that indicates whether the phase shift between two channels is close to a constant over the specified time interval – is used as a separate measure. Here, the phase component is obtained separately from the amplitude component for a given frequency (Tcheslavski and Beex, 2006). Phase locking is in fact sufficient to conclude that two brain signals interact.

Finally, it is argued that measuring coherence and phase synchrony directly from scalp recordings, which are only a diffused representation of the actual brain sources, leads to cohesive/synchronous results that may be spurious due to volume conduction effects (Delorme et al., 2002). This can be avoided by applying these measures to sources derived from BSS

techniques since these sources are said to be maximally independent. ICA removes the background coherence by eliminating the "crosstalk" caused by volume conduction, and by separating unrelated noise sources while maintaining the same time resolution as the recorded EEG/MEG.

3. Putative mechanisms for default-mode-related dysfunction in mental disorder

DMN abnormalities may take a number of different forms and be implicated in a number of different ways in the pathophysiology of mental disorder. Here we outline some putative mechanisms of potential significance for the study of the causal pathways to mental disorder. All empirical research described in the following section refers to resting state fMRI data unless otherwise stated.

3.1. Default-mode interference during task performance

The ability to maintain attentional focus and resist distraction or lapses of attention is conventionally considered to underlie higher order top–down control. To date, research examining focused and sustained attention has concentrated on goal-directed and task-specific information processing (Kingstone et al., 2003; Smilek et al., 2006). Deficits in attentional control are most commonly interpreted in terms of fluctuations in attention due to limited resources for effortful control arising from either state or trait factors, and/or their interaction (Sonuga-Barke and Castellanos, 2007). Recently, two groups have suggested that the DMN may represent a mechanism underlying deficient top–down attentional control (Mason et al., 2007; Sonuga-Barke and Castellanos, 2007). Both perspectives predict that attentional lapses during goal-directed action may be a result of interference arising from spontaneous, and most likely self-referential, thought.

In accord with Fox et al. (2005) who suggest that spontaneous low frequency activity of the DMN may interfere with task-specific attention and contribute to impaired task performance, Sonuga-Barke and Castellanos have proposed the default-mode interference hypothesis (2007) which states:

> Spontaneous low frequency activity in the task-negative component of the default-mode network which is routinely attenuated during goal directed tasks, can under certain circumstances (e.g. suboptimal motivational states or in individuals with attention disorders) persist into or remerge during periods of task-related active processing to such an extent that it competes with task-specific neural processing and creates the context for periodic attentional intrusions/lapses and cyclical deficits in performance; the temporal signatures of task-negative fluctuations being mirrored in patterns of attention and performance (Sonuga-Barke and Castellanos, 2007, p. 981)

The default-mode interference hypothesis argues that in the context of a normally functioning system, the task-negative DMN component will be attenuated during goal-directed action, and that this attenuation should be independent of task content with the exception of modulations in cognitive load, under sustained or focused attention requirements, and during tasks that involve functions subserved by the DMN. Sonuga-Barke and Castellanos suggest that the degree and maintenance of attenuation will relate specifically to both state factors such as motivation, and trait factors, such as disorder. Further, it is postulated that a threshold may exist under which the task-negative component of the DMN may persist during task-specific activity without impinging on task performance, but over which cyclical attentional lapses will transpire. Expressly, where the magnitude of the low-frequency task-negative oscillations exceed the threshold, lapses in attention will be caused by intrusions of introspective thought which produce increased variability in task performance. Importantly, due to the synchronisation between the fluctuations in the task-negative component of the DMN and associated increases in introspective thought, attentional lapses and performance variability will have the temporal signature of $0.01 < Hz < 0.1$. The default-mode interference hypothesis also highlights the importance of efficacious *transition* from rest to task. Four influential components which moderate such a transition are described: affinity to the default-mode, affinity to the goal-directed state or intrinsic motivation, extrinsic motivation and the accessibility and degree of cognitive effort (see Sonuga-Barke and Castellanos, 2007, p. 983).

Similarly, the notion of wandering minds (Mason et al., 2007) postulates that 'mind wandering' denotes a psychological baseline when the brain is otherwise disengaged, and from which individuals will transfer during a goal-directed action. Mason and colleagues report an association between DMN activity and an increased incidence of task-unrelated thought that persists during tasks with low cognitive demands, and may present as a source of interference during more engaging goal-directed activity. Importantly, Mason et al. (2007) do not suggest that the content or purpose of mind wandering represents an adaptive mechanism, but rather that the brain's ability to effectively and concurrently manage multiple tasks has evolved, and minds wandered simply because they can. In a comment on the 'wandering minds' hypothesis, Gilbert et al. (2007) refer to their previous findings of increased MPFC activity on trials with faster RTs, which they argue implicates the DMN in terms of a perceptual function, and highlight the importance of considering DMN activity in terms of stimulus-orientated rather than exclusively task-unrelated thought. The notion of wandering minds provides another possible theory of attentional lapses during task performance, and it is conceivable that generalised deficits in attention and cognitive control may well coincide with an increased incidence of stimulus-independent thought or mind wandering and the intrusion of increased activity in the DMN.

In psychopathology, atypical patterns of anti-correlations between the DMN and task-positive network, decreased connectivity between DMN regions and altered patterns of DMN function are all implicated in the symptomatic intrusion of the DMN in task-specific neural processing, resulting lapses in attention and effects of performance variability. The precise clinical manifestations of each of these notions will be demarcated in the following section.

3.2. Altered patterns of antagonism between the task-positive network and DMN

Perhaps one of the most important themes developing in DMN research is the significance of the antagonistic relationship between the DMN and task-positive network in normal functioning systems. Indeed, a number of authors have suggested that it is this reciprocal relationship that may be of more scientific interest than default-mode activity per se (Fox et al., 2005). If the efficacy of such anti-correlations is important for overall functioning in a normal population, it is likely that altered patterns of antagonism will be manifest in mental disorder. There is developing evidence that this might be so.

In a group of schizophrenic patients, Zhou et al. (2007) reported significantly increased resting state connectivity in the task-positive network and DMN in the patient group, alongside significantly increased anti-correlations between the networks. These results were more specifically associated with bilateral

dorsal MPFC, inferior temporal gyrus, and lateral parietal region in the DMN; and right dorsal lateral PFC and bilateral insula and orbital frontal gyrus in the task-positive network. The authors argue that the increased anti-correlations reflect increased antagonism and excessive competition between the networks, and most likely contribute to the over-mentalising and deficit in attentional control symptomatic of schizophrenia. More interestingly, reduced anti-correlations were evident between the right dorsal premotor cortex and the PCC and bilateral parietal region of the DMN and suggest that the right dorsal premotor cortex may be instructive in mediating the anti-correlation between the DMN and task-positive networks (Zhou et al., 2007).

In contrast to an increased anti-correlation between networks in a schizophrenic patient group, Kennedy and Courchesne (2008) report no significant anti-correlations in a sample of individuals with autism spectrum disorder (ASD). This patient group did not show any abnormal patterns of connectivity in the task-positive network, but did show reduced connectivity in the DMN mainly associated with the MPFC. Notably, these findings were unaffected by IQ and medication. Kennedy and Courchesne (2008) interpret these results as an imbalance between the task-positive and DMN networks, and suggest that this may bias an individual with ASD toward non-social and emotional processing styles. Moreover, it is suggested that such a neural bias may exist from a young age, affecting the developmental trajectory of social and emotional processing (Kennedy and Courchesne, 2008).

Similarly, resting state BOLD fMRI scans revealed a reduced anti-correlation in an ADHD population relative to controls, thought to relate to attentional lapses and performance variability symptomatic of this disorder (Castellanos et al., 2008). Indeed, in a normal population, intra-individual variation in the strength of the anti-correlation between the DMN and task-positive components is related to behavioural variability in a flanker task, particularly for more cognitively demanding stimuli (Kelly et al., 2008). Specifically, stronger anti-correlations between the networks were related to more consistent behavioural performance, highlighting the behavioural significance of the anti-correlation between DMN and task-related activation of the task-positive component. That previous research has emphasised the clinical significance of intra-individual variability in (flanker) task performance (e.g. Castellanos et al., 2005; Klein et al., 2006), provides impetus for future research investigating the temporal and oscillatory anti-correlations between the DMN and task-positive brain activity, and association with intra-individual variability in task performance. Although an aside, and in consideration of possible ameliorating effects on attention, Hahn et al. (2007) reported nicotine to increase deactivation within the DMN for task-specific cues, indicating increased preparation and improvements in attentional control (Hahn et al., 2007). This provides very preliminary evidence that the DMN may be mediated, and attention improved with psychopharmacological intervention.

These results are demonstrative of the importance of regulated competition between the task-positive and DMN networks, and provide initial support for the conjectured significance of altered patterns of antagonism between the networks. In this sense, excessive rivalry between the functions subserved by the networks and associated neural processing, will be accompanied by cyclical fluctuations in attention and deficits in goal-directed action. Generally, this will manifest as an attentional deficit. Comparatively, reduced anti-correlations reflect disparity between the networks, and may arise from dysfunction in one or both of the networks, most likely indicating aberrant DMN activity. Finally, the default-mode interference hypothesis (Sonuga-Barke and Castellanos, 2007) and the notion of wandering minds (Mason et al., 2007) provide a context in which such findings can be further investigated through a programme of systematic research.

3.3. Altered connectivity suggesting altered integrity of the default-mode functional network

Altered connectivity is a conspicuous characteristic of the altered integrity of the DMN and affiliated functions in mental disorder and also aging in the resting state (Damoiseaux et al., 2008) and during semantic classification task performance (Andrews-Hanna et al., 2007). In Alzheimer's disease, connectivity between the right hippocampus and many component regions of the DMN, including the dorsal MPFC, ventral ACC, middle temporal gyrus (MTG) and the right PCC is reduced (Wang et al., 2006), and likely relates to a dysfunction of working memory and attentional processes. Similarly, although one study has reported increased resting state functional connectivity within the DMN in adolescents with ADHD (Tian et al., 2006), more commonly, aberrant functional connectivity between the anterior (e.g. MFPC and superior frontal gyrus) and posterior (e.g. PCC/precuneus) components of the DMN is observed (Castellanos et al., 2008; Uddin et al., 2008a). Castellanos et al. (2008) speculate that this atypical pattern of connectivity may reflect neural underpinnings of an altered relationship between working memory and attentional control.

In autism, connectivity is reduced within the DMN, particularly between the ACC and PCC, reflecting disturbance of self-referential and emotional processing (Cherkassky et al., 2006; Kennedy and Courchesne, 2008; Kennedy et al., 2006). Significantly, such an interpretation is congruous with normal levels of connectivity in the task-positive network of this clinical group (Kennedy and Courchesne, 2008).

Finally, in schizophrenia, increased connectivity between the DMN and other resting state networks suggests greater dependence on other resting state networks, most likely associated with increased distraction due to hallucinations and delusional experiences (Jafri et al., 2008). Moreover, increased connectivity within the DMN and task-positive network in schizophrenic patients at rest implies that these individuals are susceptible to over-mentalising and excessive alertness to the external environment, respectively (Zhou et al., 2007). In contrast, some research has reported widespread decreased regional homogeneity in the DMN in schizophrenic patient groups (Liu et al., 2006).

Altered patterns of functional connectivity within the DMN and the task-positive network, may lead to dysfunctional associations between the affiliated psychological processes. Decreased connectivity between the anterior and posterior components of the DMN may well underlie deficits in self-referential processing, attentional control and working memory. In contrast, over zealous connectivity within the DMN and task-positive network, in addition to other resting state networks, instigates excessive introspective and extrospective processing. Indeed, aberrant increases in connectivity will likely manifest in delusional experience, over ardent mentalising, and attentional lapses due to the disproportionate involvement and interaction between the DMN and associated networks.

3.4. Altered patterns of DMN activity

Atypical patterns of DMN activity are apparent in a number of mental disorders, and are typically characterised by dysfunction of introspective mental processes. In schizophrenia, positive symptom severity was correlated with increased deactivation in the MFG, precuneus, and the left MTG in an oddball task (Garrity et al., 2007), while impaired self-monitoring processes and stimulus-independent thought have been associated with abnormal low frequency resting state connectivity (Bluhm et al., 2007; Liang et al., 2006). In autism however, atypical or reduced self-referential, affective and introspective thought is associated with

low activation of the DMN in the resting state. Additionally, atypical emotional processing in autism is notable by the absence of any functional activation of the medial orbital frontal component of the DMN during the processing of emotional compared with neutral words in a Stroop task (Kennedy et al., 2006). Indeed, reduced task-induced deactivation of the DMN during a number-word Stroop task has been associated with greater social impairment in participants with autism (Kennedy et al., 2006). More specifically, reduced DMN connectivity in autism is associated with the MPFC. It has been suggested that this altered pattern of DMN activity may influence the social, emotional and introspective deficits commonly associated with autism (Kennedy and Courchesne, 2008). In contrast, concrete, extrospective processing related to the task-positive network is seemingly unaffected in high-functioning autistic individuals (Kennedy and Courchesne, 2008). Kennedy and Courchesne (2008) postulate that the DMN may provide a neurocognitive framework in which the marked differences in social and emotional processing of individuals with autism may be understood.

In depressed patients, the subgenal cingulate is a prominent region within the DMN and related to the length of depressive episode, while noticeably absent in the DMN of control participants (Greicius et al., 2007). Further, in this patient group increased connectivity between the DMN and the thalamus is argued to reflect increased interaction between the thalamus and subgenal cingulate due to increased emotional processing, at the expensive of executive functions (Greicius et al., 2007). In patients with anxiety disorders, reduced deactivation of MPFC and increased deactivation of the PCC is thought to be indicative of increased levels of anxiety (MPFC) and emotional processing (PCC) of task-specific threat words.

Importantly, differential task-specific deactivation of the DMN provides a point of comparison between the severity and type of mental disorder. The magnitude, timing and spatial characteristics of deactivation during a working memory task distinguished Alzheimer's from mildly cognitively impaired and control groups (Rombouts et al., 2005). Bai et al. (2008) have also reported decreased regional homogeneity in the PCC/precuneus in amnestic type mild cognitive impaired participants, while He et al. (2007) report similar findings in Alzheimer's patients. Notably, this effect correlated positively with disease progression as measured by the mini-mental state exam scores (He et al., 2007). Interestingly, altered deactivation is also evident in participants at genetic risk for developing Alzheimer's disease (Persson et al., 2008).

4. A systematic review of empirical studies of default-mode abnormalities and mental disorders

For this review, computerised searches were conducted using the Nature journals online, PubMed, Proquest 5000, Psycinfo and ScienceDirect databases. The following terms default-mode, resting state, low frequency oscillations, functional connectivity and task-positive network were entered into the databases. Further, the table of contents of journals that often publish articles relevant to this topic were also reviewed including *Biological Psychiatry*, *Human Brain Mapping*, *Journal of Cognitive Neuroscience*, *Nature Neuroscience*, *NeuroImage* and *Proceedings of the National Academy of Sciences of the United States of America*. Finally, the reference lists of pertinent articles were also scanned for related studies. Given the focus on mental disorders, empirical research examining atypical DMN activity in the context of multiple sclerosis (Lowe et al., 2002), Parkinson's disease (Tinaz et al., 2008), fragile X syndrome (Menon et al., 2004), hepatic cirrhosis (Zhang et al., 2007), and chronic pain (Baliki et al., 2008) was not

considered. The following sections aim to provide a comprehensive and systematic review of empirical research of DMN abnormalities and mental disorder. The studies and their findings are summarized in Table 1, and interpreted in terms of the putative mechanisms described above.

4.1. Alzheimer's disease and mild cognitive impairment

In the context of the DMN, Alzheimer's disease is one of the most widely investigated pathologies, particularly in view of the putative association between the DMN and working memory (Buckner et al., 2005; Firbank et al., 2007; Greicius et al., 2004; He et al., 2007; Rombouts et al., 2005; Sorg et al., 2007; Wang et al., 2006). The impact of normal aging on the functional connectivity of DMN and related cognitive functions has also received recent research attention (e.g. Andrews-Hanna et al., 2007; Damoiseaux et al., 2008). Specifically, in a semantic classification task, low frequency functional connectivity between anterior (MPFC) and posterior (PCC/retrosplenial cortex) regions of the DMN was negatively associated with age, as were the magnitude of task-related deactivations (Andrews-Hanna et al., 2007). Moreover, there was a positive relationship between the strength of functional connectivity in the DMN and the magnitude of task-related deactivations. Investigation of the functional correlations within the dorsal anterior attention system revealed similar interactions with age (Andrews-Hanna et al., 2007). In a resting state study, Damoiseaux et al. (2008) report decreased BOLD signal in the anterior (including MFG) and posterior (including the PCC) regions of the DMN in older participants. The anterior aspect of the DMN was negatively correlated with age and related to cognitive decline in the older group (Damoiseaux et al., 2008). In earlier research employing a simple sensory-motor processing task, activity in the DMN was reduced in patients with Alzheimer's disease relative to controls, particularly in the PCC and medial temporal lobe (Greicius et al., 2004). In this study, ICA of resting state data revealed a significant role of the hippocampus in DMN activity, while goodness of fit analyses using a DMN template were able to delineate Alzheimer's participants from healthy elderly controls with a sensitivity of 85% and specificity of 77% (Greicius et al., 2004). A resting state study also intimating a prominent role of the hippocampus in the DMN activity of Alzheimer's disease patients revealed reduced functional connectivity between right hippocampus and MPFC, ventral ACC, inferotemporal cortex, right cuneus, right superior and MTG and PCC in the patient group, although a concurrent increase in connectivity between the left hippocampus and the right DLPFC was also observed (Wang et al., 2006). This has been interpreted as reflecting compensatory processes as patients attempt to overcome cognitive and performance deficits (Wang et al., 2006).

Moreover, mildly cognitively impaired participants could be differentiated from healthy controls, and from Alzheimer's participants by the extent of deactivation of DMN regions including MFG, anterior cingulate gyrus and PCC/precuneus during a working memory task (Rombouts et al., 2005). Deactivation of frontal DMN regions was restricted (to medial frontal regions) in participants with mild cognitive impairment compared with controls, and even more significantly restricted (to ACC) in Alzheimer's patients, significantly differentiating them from the mildly cognitively impaired group (Rombouts et al., 2005). The phase of deactivation also distinguished control and patient groups, with an initial increase, followed by a decrease, in ACC and MFG in controls, with less early deactivation in the mildly cognitively impaired and Alzheimer's patients (Rombouts et al., 2005). Further, reduced resting state DMN connectivity (Sorg et al., 2007) and reductions in regional homogeneity over PCC/precuneus

Table 1
A summary of empirical findings of altered DMN activity in individuals with mental disorders

Mental disorder	Measure	Task	DMN deactivation		Connectivity		Anti-correlation	DMN function
			Anterior	Posterior	DMN	TPN		
Alzheimer's disease								
Greicius et al. (2004)	fMRI-ICA	SM	–	–	↓	–	–	–
Rombouts et al. (2005)	fMRI-ICA	WM	↓ MCI & C	MCI < C	–	–	–	–
Buckner et al. (2005)	See text	WM	–	–	–	–	–	PCC at risk of atrophy
Wang et al. (2006)	fMRI-ROI	RS	–	–	↓	–	–	–
Firbank et al. (2007)	MRI-FA	RS	–	–	↓	–	–	Effect of global atrophy
He et al. (2007)	fMRI-ReHo	RS	–	–	↓ PCC	–	–	PCC related to MMSE
At risk of Alzheimer's								
Sorg et al. (2007) (MCI)	fMRI-ICA, ROI	RS	↓	↓	↓	–	–	–
Bai et al. (2008) (MCI)	fMRI-ReHo	RS	–	–	↓*	–	–	*Controlled for atrophy, age
Persson et al. (2008) (APOE4)	fMRI-ROI	Semantic	↓	↓	–	–	–	–
Schizophrenia								
Liang et al. (2006)	fMRI-parcellation	RS	–	–	↓	–	–	–
Bluhm et al. (2007)	fMRI-ROI	RS	–	–	↓*	–	–	*Related to +ve symptoms
Garrity et al. (2007)	fMRI-ICA	Oddball	↑*	–	–	–	–	*Related to +ve symptoms
Zhou et al. (2007)	fMRI-ROI	RS	–	–	↑	↑	↑	–
Pomarol-Clotet et al. (2008)	fMRI-ICA	WM	↓MPFC*	–	–	–	–	*Unrelated to performance
Depression								
Greicius et al. (2007)	fMRI-ICA	RS	–	–	↑*	–	–	*Related to refractoriness
Anxiety								
Zhao et al. (2007)	fMRI-ROI	EPT	↓	↑	–	–	–	MPFC related to anxiety
Epilepsy								
Laufs et al. (2007) (no control)	EEG & fMRI	RS	↓*	↓*	–	–	–	*Related to IED in TLE
Lui et al. (2008) (GS, PS, C)	fMRI-GLM	RS	–	–	↓ PCC*	–	–	*GS patients only
ASD								
Cherkassky et al. (2006)	fMRI-ROI	RS	Non-sig	Non-sig	↓	–	–	–
Kennedy et al. (2006)	fMRI-ROI	Stroop	↓	↓	–	–	–	–
Kennedy and Courchesne (2008)	fMRI-ROI	RS	–	–	↓*	Non-sig	↓	*Specifically MPFC
ADHD								
Tian et al. (2006)	fMRI-ROI	RS	–	–	↑	–	–	–
Cao et al. (2006)	fMRI-ReHo	RS	–	–	↓	–	–	–
Castellanos et al. (2008)	fMRI-ROI	RS	–	–	↓	–	↓	–
Uddin et al. (2008a)	fMRI-NeHo	RS	–	–	↓*	–	–	*Specifically PCC
Helps et al. (2008)	DC-EEG	RS	–	–	↓	–	–	–

Abbreviations and symbols used in this table: DMN, default-mode network; TPN, task-positive network; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging; EEG, electroencephalogram; ICA, independent component analysis; ROI, region-of-interest; ReHo, regional homogeneity; NeHo, network homogeneity; FA, fractional anisotropy; RS, resting-state; SM, sensory motor task; EPT, emotional processing task; WM, working memory task; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; MCI, mild cognitive impairment; GS, generalised seizure patients; PS, partial seizure patients; C, controls; MMSE, mini mental state exam; (–) indicates that this was not tested; (↑) reflects an increase, for DMN deactivation it refers to increased deactivation; (↓) reflects a decrease, for DMN deactivation it refers to reduced deactivation; 'non-sig' indicates the groups did not differ significantly; (*) indicates association between DMN function and particular result. All results are considered in comparison to a normal control group unless otherwise specified.

have been observed in patients with mild amnesic cognitive impairment who are at risk of developing Alzheimer's disease (Bai et al., 2008) and patients with Alzheimer's disease (He et al., 2007).

A large study (n = 764) investigating atrophy in Alzheimer's disease compared data across two forms of PET, structural MRI and fMRI data in a group of Alzheimer's patients and young adults at rest and during a working memory task (Buckner et al., 2005). The DMN activity at rest in young adults was positively correlated with the pattern of amyloid deposits in elderly Alzheimer's patients, suggesting an association with brain metabolism (Buckner et al., 2005). Indeed, precuneus, PCC and retrosplenial cortex were thought to be preferentially vulnerable to atrophy (Buckner et al., 2005). In the resting state, global atrophy has also been associated with dementia disease progression and the disruption of white matter (as measured by fractional anisotropy) connecting the PCC and lateral parietal regions (Firbank et al., 2007). In addition, He et al. (2007) observed statistically significant decreases in resting state regional coherence of the low frequency bold fluctuations in the PCC/precuneus in Alzheimer's disease patients, even after PCC/precuneus atrophy had been statistically controlled for. Although

the results remained significant, they did decrease in statistical power, indicating that decreased regional coherence of the low frequency bold fluctuations in the PCC/precuenus may in part be explained by atrophy in Alzheimer's patients (He et al., 2007).

In light of altered deactivation of the DMN in Alzheimer's disease patients, and to a lesser extent, healthy older adults; Persson et al. (2008) investigated DMN activity during a semantic categorisation task in non-demented carriers of the apolipoprotein E4 (APOE4) allele. Genetic studies have shown an association between a functionally active APOE4 allele and Alzheimer's disease, and there is some evidence of reduced functional connectivity in APOE4 carriers (e.g. Lind et al., 2006). Persson et al. (2008) observed reduced task-induced deactivation of the MPFC, middle temporal cortex, medial parietal region, and right parietal lateral cortex in APOE4 carriers. The authors suggest that genetic susceptibility to AD may affect the magnitude of DMN deactivations. In addition, Persson et al. argue that individuals with a genetic risk for Alzheimer's disease may have a reduced ability to suspend DMN activity during an active task, or alternatively genetic risk may be related to reduced resting state metabolism

and/or structural changes. Furthermore, increased positive correlations were observed for the APOE4 group between right inferior PFC and MPFC and left middle temporal cortex. This was thought to reflect compensatory processes in the APOE4 group in line with the lack of performance differences. This may open up the possibility of early classification of pre-clinical Alzheimer's disease.

In a review of resting state fMRI research in Alzheimer's disease, Liu et al. (2008), suggest that altered patterns of functional connectivity in Alzhemier's patients may indicate a disconnection syndrome. In light of the mounting evidence, Wermke et al. (2008) propose a model to incorporate current findings of atypical default-mode activity in patients with Alzheimer's disease. In their model the brain operates from a given baseline to activate task-important regions, and deactivate regions unrelated to the particular task. This system begins to malfunction with advancing neuro-degeneration, and fails to respond appropriately both in terms of task-specific activation and deactivation of the pertinent brain regions. The model is described in terms of a clock, in which the main hand of the clock reflects task performance and influenced by the strength of the task-specific activation response (Wermke et al., 2008). The efficacy of activation is governed by the baseline—a damaged baseline, in the case of mild cognitive impairment, will require greater cognitive effort to reach the relative activation signal strength of a 'healthy' baseline. More severely affected baselines in Alzheimer's disease patients, may not reach adequate activation signal strength, leading to a decline in cognitive performance. Task performance is also thought to be dependent on healthy deactivation of task-irrelevant brain regions to facilitate focused, task-related processes. It is argued, that effective task or cognitive performance relies on the coordination and collaboration of the activation and deactivation response, and if one component 'fails', the whole system is jeopardised (see Wermke et al., 2008).

In summary, reduced connectivity between MPFC and PCC regions of the DMN is associated with aging, and the anterior region of the DMN is correlated with cognitive decline. In Alzheimer's patients, the hippocampus features as a prominent node within the DMN and shows reduced connectivity with other DMN regions. Indeed, there is increasing evidence that the DMN, particularly the anterior components, might provide a clinically instructive instrument in the differential diagnosis of Alzheimer's patients, patients with mild cognitive impairment, and those with a genetic risk of developing Alzheimer's disease, from controls. Finally, due to the high metabolism of DMN regions, and particularly the PCC/precuneus, these regions are particularly vulnerable to atrophy in Alzheimer's patients, although reduced functional connectivity in the DMN of patients cannot be completely explained by atrophy.

4.2. Schizophrenia

Atypical functional connectivity in resting state networks, particularly the DMN, has also been observed in schizophrenic patients (Bluhm et al., 2007; Calhoun et al., 2008; Garrity et al., 2007; Jafri et al., 2008; Liang et al., 2006; Pomarol-Clotet et al., 2008; Williamson, 2007; Zhou et al., 2007). Initial research reported widespread and non-specific disconnectivity in schizophrenic patients in an eyes closed resting condition (Liang et al., 2006). Despite quite a substantial overlap in their sample, the same group subsequently reported increased resting state functional connectivity within the DMN and task-positive network, consistent with increased anti-correlations between these networks in paranoid schizophrenic participants (Zhou et al., 2007). Such disparity is likely the result of the different analytical techniques used to measure functional connectivity, and the heterogeneity of

this disorder (Zhou et al., 2007). Increased connectivity within the DMN and task-positive network suggests paranoid schizophrenics demonstrate increased sensitivity to both the external environment and self-referential or introspective thought. The strength of the anti-correlation between these two networks also indicates that these processes are in excessive competition for this patient group (Zhou et al., 2007).

In an n-back working memory task, Pomarol-Clotet et al. (2008) report reduced activation of the DLPFC in patients with schizophrenia to be a function of impaired task performance. In contrast, a reduced deactivation of the DMN in the medial frontal area was not found to be dependent on task performance (Pomarol-Clotet et al., 2008). ICA analysis has also revealed differences in both spatial and temporal connectivity of the DMN during an auditory oddball task (Garrity et al., 2007). In this study, and in contrast to Pomarol-Clotet et al. (2008), schizophrenic patients showed greater deactivation of the DMN in the frontal gyrus, and decreased activation of the ACC relative to controls, potentially related to attentional deficits observed in schizophrenia (Garrity et al., 2007). Moreover, a greater section of parahippocampal gyrus was included in the DMN for patients, and while low-frequency oscillations (0.03 Hz) in the DMN were evident for controls, patients showed significantly higher frequency oscillations (0.08–0.24 Hz). Finally, greater deactivation in the MFG, precuneus, and the left MTG were correlated with positive symptoms of schizophrenia (Garrity et al., 2007).

Consistent with the task-related findings of Garrity et al. (2007), disconnectivity of the low-frequency oscillatory (<0.1 Hz) activity in the PCC, medial prefrontal, lateral parietal and cerebellar regions during rest has also been observed in another two studies examining this clinical group during rest (Bluhm et al., 2007) and during a similar auditory oddball task (Calhoun et al., 2008). Although in contrast, a recent finding of increased connectivity between the DMN and other resting state networks using spatial ICA, has been hypothesised to reflect distraction and hallucinatory experiences of schizophrenic patients (Jafri et al., 2008). The relationship between the apparent self-monitoring function of regions within the DMN and schizophrenia provide impetus for future research. However, the disparity in methodologies and findings highlight the need for methodological consistency if we are to properly understand the association between functional connectivity in the DMN and underlying mechanisms that give rise to the symptomology of schizophrenia (Williamson, 2007).

In summary, greater connectivity in the DMN and task-positive network in schizophrenic patients may reflect 'over-zealous' attentional orientation to introspective and extrospective thought, while the increased anti-correlation between these two networks suggests excessive rivalry or antagonism between the neural processing and associated psychological functions of these networks. Increased deactivation of specific DMN regions including MFG and precuneus was associated with the positive symptoms of schizophrenia, while reduced deactivation of ACC was suggested to be associated with reduced attentional control.

4.3. Depression and anxiety

The ruminative, self-referential focus of depressed patients has led to predictions of differences between this clinical group and controls in terms of DMN connectivity (Greicius et al., 2007). Following ICA analysis of resting state fMRI data, subgenual cingulate was found to contribute disproportionally to the connectivity of the DMN in this patient group, with increases in connectivity associated with depression refractoriness, or the length of the current depressive episode (Greicius et al., 2007). There was also increased functional connectivity in the thalamus

during rest. Greicius et al. (2007) suggest that increased connectivity in 'affective' regions may detrimentally affect connectivity in regions associated with cognitive processing such as the dorsal anterior cingulate (Greicius et al., 2007).

Interestingly, in an investigation of DMN connectivity during an emotional processing task, no difference in the deactivation of the DMN was evident between a group of anxiety patients or controls when emotionally neutral words were alternated with rest. In contrast, when threat words were alternated with emotionally neutral words, anxiety patients demonstrated reduced deactivation of the MPFC and increased deactivation of the PCC relative to controls (Zhao et al., 2007). These results may reflect increased anxiety levels and more extensive memory processing of threat words, respectively (Zhao et al., 2007).

In summary, the subgenual cingulate was specific to the DMN of depressed patients, and is associated with the length of depressive episode. Anxiety was associated with reduced deactivation of the MPFC, although whether this relates to a specific dysfunction of the DMN is questionable.

4.4. Epilepsy

In an interesting combination of EEG and fMRI methodology, deactivation of the DMN, particularly in PCC/precuneus, and left and right parietal lobes was evident during interictal epileptic discharges in a group of awake but relaxed, temporal lobe epileptics (Laufs et al., 2007). Similar deactivation was not observed for extra-temporal lobe epileptic patients, thought to be either a result of reduced EEG sensitivity to interictal epileptic discharges in this group, or differences in the primary pathology (Laufs et al., 2007). Laufs et al. (2007) suggest that their findings may not be specific to epilepsy, but instead reflect altered mental states in general. Conversely, they argue that the transient cognitive impairments and performance deficits associated with temporal lobe epilepsy may be associated with dysfunction of the DMN. In accord with the latter proposition, Lui et al. (2008) report a lack of resting state low frequency activation of PCC/precuneus in patients with generalised seizures compared to controls, but no difference between controls and patients with partial seizures. The authors acknowledge that although it is difficult to determine whether aberrant DMN activation is a consequence or antecedent of the spike and slow-wave discharges symptomatic of generalised seizure patients, it may explain at least in part, why generalised seizure patients demonstrate greater cognitive impairment (Lui et al., 2008).

4.5. Autism spectrum disorder

Altered patterns of introspective thought, social and emotional processing characteristic of this disorder are reflected in aberrant deactivation of the DMN of ASD patients (Cherkassky et al., 2006; Kennedy and Courchesne, 2008; Kennedy et al., 2006). In three versions of the Stroop task, adult autistic participants failed to show evidence of deactivation of the DMN, although there was little evidence of a difference in task performance between the groups (Kennedy et al., 2006). It is hypothesised that midline DMN activity is actually low at rest in autistic patients, and that abnormal preoccupations that are symptomatic of this spectrum of disorders and occur during the resting state, are concrete rather than affective in nature (Kennedy et al., 2006). Nonetheless, Cherkassky et al. (2006) did not report any differences between an autistic and control group in DMN activation during rest. However, they did observe decreased resting state functional connectivity between ACC and PCC, and in line with Kennedy et al. (2006), propose that there is an absence of self-referential thought in autism. A more recent resting state study reported reduced

functional connectivity in DMN but not the task-positive network in an adult autistic sample (Kennedy and Courchesne, 2008). Specifically, reduced connectivity was localised to MPFC and left angular gyrus, and while the DMN and task-positive networks were significantly anti-correlated in controls, no such anti-correlation was observed in the ASD group.

Intriguingly, activity within the task-positive network did not differentiate autism, while abnormalities in the DMN were observed and related specifically to reduced connectivity in MPFC, which is associated with social and emotional processing. Moreover, the lack of anti-correlation between the networks in autism may indicate an imbalance in the toggling of these networks (Kennedy and Courchesne, 2008). Finally, it has been postulated that a deficit in the mirror neuron network is associated with DMN dysregulation in autism, suggesting that this disorder may arise from an atypical processing of self and relationship with others (Iacoboni, 2006).

In summary, DMN activity in autistic patients is thought to be low at rest, with reduced connectivity between anterior and posterior DMN regions probably reflecting a disturbance of self-referential thought. In contrast to altered connectivity in the DMN, connectivity in the task-positive network appears normal in autism. Moreover, the absence of an anti-correlation between the DMN and task-positive networks, suggests an imbalance in the toggling between these networks, driven by a paucity of introspective thought.

4.6. Attention deficit/hyperactivity disorder

Attentional lapses, commonly observed in the task performance of individuals with ADHD, may point to a role for DMN interference in ADHD. Tian et al. (2006) was the first to examine functional connectivity within the DMN at rest for adolescents with ADHD, using ACC as the seed region. In this study, increased functional connectivity with dorsal ACC was observed for bilateral dorsal ACC, bilateral thalamus, bilatertal cerebellum, bilateral insula and bilateral brain stem in the ADHD compared to control group. Tian et al. suggest that this increased connectivity in the ADHD group may reflect abnormalities in the autonomic control functions associated with these regions (Tian et al., 2006), although alternative interpretations include an increased affinity with the DMN (Sonuga-Barke and Castellanos, 2007). In contrast to Tian et al. (2006); Castellanos et al. (2008) have reported reductions in the resting state anti-correlation between dorsal ACC and PCC/precuneus in an adult ADHD group. In controls, PCC/precuneus activity correlated positively with other regions in the DMN. In the ADHD group, the anterior component of the DMN was markedly absent, with significant group differences in medial PFC, superior frontal gyrus and also in PCC/precuneus. Specifically, the ADHD group showed less negatively correlated functional activity in the ACC, MFG and superior temporal gyrus. Given this reduced resting state functional connectivity between the anterior and posterior regions of the DMN may indicate a relationship between working memory deficits and attentional lapses in ADHD (Castellanos et al., 2008). In a similar resting state study using a network homogeneity measure of functional connectivity, adult ADHD and control groups did not differ on global measures of DMN homogeneity, although significantly reduced network homogeneity in the posterior regions of the DMN, particularly the precuneus was observed in the ADHD group (Uddin et al., 2008a). Despite differences in methodology, these findings substantiate those of Castellanos et al. (2008), and suggest that decreased functional interactions between the anterior and posterior regions of the DMN may underlie some of the executive function deficits observed in the ADHD population (Uddin et al., 2008a).

Cao et al. (2006) investigated spontaneous, low frequency resting state fMRI data in children with ADHD using the regional homogeneity method described by Zang et al. (2004). This study reported decreased regional homogeneity in fronto-striatal-cerebellar circuits in the ADHD group, specifically in regions that included bilateral inferior frontal gyrus, right inferior ACC, left caudate, bilateral pyramis and left precuneus (Cao et al., 2006). Based on this work and others from the same group (e.g. Tian et al., 2006), Zhu et al. (2008) employed Fisher discriminative analysis on regional homogeneity measures of resting state brain activity in children with ADHD, and reported a correct classification rate of 85% using leave-one-out cross validation, and a sensitivity and specificity of 78% and 91%, respectively. In another alternative method of measuring low frequency fluctuations in the BOLD signal, Zang et al. (2007) measure the amplitude of the fluctuations in resting state fMRI data, and observed reduced amplitudes in children with ADHD in the right inferior frontal cortex, bilateral cerebellum and vermis. Children with ADHD also showed increased amplitudes in the right ACC, left lateral cerebellum, left fusiform gyrus, right inferior temporal gyrus, left sensorimotor cortex and bilateral brain stem (Zang et al., 2007). Recent research has reported reduced power in low frequency resting state networks (0.06–0.2 Hz) as measured by DC EEG in a non-clinical sample of hyperactive participants who rated themselves as inattentive (Helps et al., 2008). This result differentiated the aforementioned group from hyperactive participants who did not rate themselves as inattentive and normal controls, and highlights the association between attentional control and the DMN, and the importance of future research in clinical populations such as ADHD (Helps et al., 2008).

In summary, ADHD appears to be associated with altered patterns of connectivity within the DMN, likely related to abnormal fronto-striatal-cerebellar circuits, this as well as atypical antagonism between the DMN and task-positive networks may underpin the pathophysiology of this clinical group. In particular, altered DMN connectivity is mostly likely related to the attentional lapses, working memory deficits and task performance variability symptomatic of ADHD.

5. Integration and future directions

In the current paper we have considered the relevance of the DMN in relation to mental disorders. There are a number of important observations that may be drawn from the preceding sections, which have significance for theoretical models of psychopathology and provide directions for future research.

5.1. Putative mechanisms

Table 1 shows the coverage of research into the different mechanisms discussed in Section 3. There are obvious important observations. First, although only a few studies considered the anti-correlation between the DMN and task-positive network, the significance of altered patterns of activity in mental disorder are highlighted in ASD, ADHD and schizophrenia. These findings emphasise the importance of regulated competition between these networks in a normally functioning system. In mental disorder, the absence of, or reductions in, the anti-correlation between the DMN and task-positive network manifest as reduced introspective thought (ASD) and attentional lapses (ADHD); while excessive antagonism will likely result in zealous toggling between extrospective and introspective processes (schizophrenia). Second, the integrity of the DMN is affected by reductions in connectivity, and is associated with deficits in attention and working memory (Alzheimer's disease, ADHD, schizophrenia), as well as problems with self-referential and introspective mental processing (ASD). In contrast, increased connectivity has been associated with maladaptive emotional and introspective processing (depression, schizophrenia). Third, altered patterns of DMN functional connectivity commonly characterise dysfunctional introspective processing – connectivity in the DMN is negatively related to the positive symptoms of schizophrenia, while enhanced connectivity in the subgenual cingulate is associated with the length of depressive episode. Finally, altered patterns of connectivity, atypical anti-correlations between the DMN and task-positive network, and reduced integrity of DMN functions, observed in a range of mental disorders, are all potential and pervasive sources of interference during goal-directed activity.

5.2. Aetiology

The aetiology of the altered DMN in mental disorder remains unclear. Indeed, the underlying neurochemistry, and potential genetic and environmental effects on DMN function have been rarely examined in the context of normal functioning systems or mental disorder. One study investigated resting state concentrations of GABA in the ACC, and observed an association between GABA concentrations and the strength of the negative BOLD response in the ACC during an emotional processing task (Northoff et al., 2007). Dopamine, a second potential neurochemical modulator of DMN activity, has been reported to mediate low frequency oscillations of the BOLD response (Achard and Bullmore, 2007; Honey et al., 2003). Following attenuated dopamine transmission, Achard and Bullmore (2007) observed detrimental effects on connectivity in global and local networks. In view of the role of dopamine in the mediation of goal-directed activity in ADHD (Tripp and Wickens, 2008), and previous reports of dopaminergic drugs and the modulation of low frequency fluctuations in the BOLD response, future research in the context of the DMN is warranted.

There is also preliminary evidence for a role of genetics in altered patterns of DMN connectivity in individuals at genetic risk of developing Alzheimer's disease (Persson et al., 2008). Notably, mental disorders which show atypical patterns of DMN activity such as schizophrenia, ASD and ADHD, are also thought to have strong genetic components. The role of genetics in altered patterns of DMN activity should be explored further within the context of current perspectives on psychopathology. Moreover, the association between altered DMN activity in mental disorder and the potential role of environmental influences also requires consideration. Future research could explore the potential influence of environmental factors, such as social and emotional relationships with peers and family and parental style particularly in relation to disorders such as ASD and ADHD development, on the normal functioning of the DMN. A systematic approach is required to explore the aetiology of altered DMN activity in mental disorder.

5.3. Methodology

The DMN literature to date has explored this concept using PET, fMRI and EEG methodologies. Functional connectivity and the deactivation of the DMN during goal-directed activity have been most commonly explored in terms of low frequency fluctuations in the BOLD signal. In Section 2 we explored the strength and weakness of each technology, and we introduced MEG, highlighting the high temporal and spatial resolution of MEG as an important tool for future research in the DMN. Alternatively, simultaneous fMRI and EEG recordings permit the profitable association of the high temporal resolution of EEG with the high spatial resolution of fMRI data. Such research has reported

intriguing correlations between a range of EEG frequency bands and DMN activity. Finally, DC EEG provides another promising avenue for future DMN research, allowing assessment of very low frequency EEG oscillations in relation to the DMN. One study has provided preliminary evidence of the utility of such a measure in non-clinical hyperactive participants (Helps et al., 2008), however further research is necessary. A well-defined methodological protocol within each of these technologies will facilitate the efficacious comparison of research findings and aid explication of DMN differences in clinical populations.

5.4. Analysis

Section 2 also highlighted a number of key analytical issues within each of the previously described methodologies. The issues inherent with performing temporal, spatial and spectral analysis on high density neurophysiological recordings are not trivial, and are compounded due to the presence of artifact and multiple underlying brain sources coupled with volume conduction effects. ICA as a specific BSS method has been identified as a technique that can handle the high-density recordings, and the presence of artifacts to discriminate between multiple underlying brain sources. Within fMRI, functional connectivity within the DMN and task-positive network has been examined using ICA, ROI (seed region) approaches, an amplitude measure of low frequency fluctuations, regional homogeneity and network homogeneity which examine the correlation between a given voxel and all other voxels within a predefined region or network, respectively. While region of interest approaches require a priori selection of the seed region, approaches such as ICA are not constrained by a priori hypotheses. ICA is also useful in the delineation and effective removal of non-neuronal noise (and other artifacts), although caveats of ICA include the difficulty of data interpretation for functional comparisons across subjects and between groups (see Fox and Raichle, 2007, for a review).

5.5. Clinical relevance

The wealth of empirical research into altered patterns of DMN activity in mental disorder has highlighted the potential clinical relevance of the DMN for contemporary models of psychopathology. There are a number of specific findings that demonstrate the utility of the DMN in clinical research for purposes of differential diagnosis. Firstly, the efficacious transition between rest to task and deactivation of the DMN during goal-directed activity is particularly susceptible to dysfunction in mental disorders characterised by attentional deficits (e.g. ADHD and schizophrenia). Secondly, functional connectivity in the DMN and task-positive networks may highlight problems of reduced connectivity in the DMN (e.g. ASD) and/or task-positive networks, or excess connectivity in one or both of these networks (e.g. schizophrenia). Third, the reciprocal relationship and strength of the anti-correlation between the task-positive and DMN components also appears to be a useful instrument in discerning clinically specific vulnerabilities in introspective and extrospective orienting in a number of mental disorders (e.g. ADHD: Castellanos et al., 2008; ASD: Kennedy and Courchesne, 2008; schizophrenia: Zhou et al., 2008). Finally, the functional heterogeneity of regions within the DMN and task-positive network should also be noted, alongside the congruence between the functional role associated with these regions and their relationship with particular clinical pathologies (e.g. anxiety and MPFC: Zhao et al., 2007; depression and subgenal cingulate: Greicius et al., 2007). The extent to which the DMN may be a potentially significant clinical tool warrants further research, although current evidence suggests the DMN is relevant to models

of mental disorder. Prospectively, the DMN may prove valuable in differential diagnosis, and provide an opportunity through which new and existing treatments may be explored.

6. In conclusion

In recent years there has been a surge of scientific interest in resting state brain function and the DMN. This interest has extended to the altered patterns of DMN activity in individuals with mental disorder. In the current paper we have described some putative mechanisms for default-mode related dysfunction in mental disorder and have attempted to draw out the potential significance of these for theoretical models of psychopathology. Future research should now focus on a systematic exploration of the DMN in the context of contemporary models of psychopathology. Empirical research should examine current predictions of the role of DMN in mental disorder, such as the default-mode interference hypothesis (Sonuga-Barke and Castellanos, 2007). In particular, the anti-correlation and toggling between task positive and DMN components and the transition from rest to task warrants further exploration, and particularly with regard to comparisons of normal and aberrant transitioning between these states (Sonuga-Barke and Castellanos, 2007). Moreover explication of the maintenance of goal-directed attention and the attenuation of interference from the DMN should be examined in future work with reference to trial-to-trial variability in task performance so often observed in clinical populations (Kelly et al., 2008). Evidently, variations in the cognitive requirements of the experimental tasks will necessarily delineate particular vulnerabilities in clinical populations, and the resultant effects on efficacious task performance, including DMN attenuation and toggling with task-positive network. Finally, as some mental disorders are known to develop in early childhood, future research should systematically explore the developmental trajectory of the DMN in a normal population and compare this with the maturation of the DMN in clinical populations, such as in children with ADHD and ASD.

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