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Review

Resting-state functional connectivity in major depressive disorder: A review

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ABSTRACT

Major depressive disorder (MDD) affects multiple large-scale functional networks in the brain, which has initiated a large number of studies on resting-state functional connectivity in depression. We review these recent studies using either seed-based correlation or independent component analysis and propose a model that incorporates changes in functional connectivity within current hypotheses of network-dysfunction in MDD. Although findings differ between studies, consistent findings include: (1) increased connectivity within the anterior default mode network, (2) increased connectivity between the salience network and the anterior default mode network, (3) changed connectivity between the anterior and posterior default mode network and (4) decreased connectivity between the posterior default mode network and the central executive network. These findings correspond to the current understanding of depression as a network-based disorder.

Contents

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1. Introduction

Major depressive disorder (MDD) is one of the most prevalent psychiatric disorders and is the second leading cause of disability worldwide (Ferrari et al., 2013). Despite almost 60 years of intensive neurobiological research, our current understanding of its pathophysiology is limited, which is reflected in a heterogeneous disease concept and moderate effects of treatment (Arroll et al., 2009; Mojtabai, 2013; Moncrieff et al., 2004). While earlier neuroimaging techniques have investigated focal structural and functional changes (Alcaro et al., 2010; Hamilton et al., 2013; Koenigs and Grafman, 2009; Northoff et al., 2011; Price and Drevets, 2012), depression is increasingly understood as a disorder of distributed effects of aberrant interaction in the brain (Drevets et al., 2008; Hamilton et al., 2013; Mayberg, 1997). Within this framework, brain regions are dynamically organized into functional networks of interconnected areas (or "nodes") that interact to perform specific tasks (Bressler, 1995).

With the advance of network-based research in system-level neurosciences in general, new techniques allow us to identify these large-scale brain networks, for example by looking at changes in blood-oxygen-level-dependent (BOLD) signal using functional magnetic resonance imaging (fMRI). An important methodological development in investigating these networks was the finding that they can consistently be identified during the "resting-state", i.e. when a subject is not engaged in any particular task (Biswal et al., 1995). This independence of task-based paradigms offers the important advantage of being reproducible across different populations and study settings. Following this, many recent studies have investigated how the different nodes and networks communicate by investigating synchronous spontaneous activity in different regions of the brain. This so-called "resting-state functional connectivity" (hereafter referred to as "connectivity") represents the temporal coherence of the BOLD-signal within or between regions or networks during rest and is an important addition to functional imaging techniques in unraveling the neurobiology of depression (Friston, 2011).

In MDD most findings in task-based and resting-state fMRI implicate one of three major neural networks: the default mode network (DMN), the central executive network (CEN) and the salience network (SN) (Hamilton et al., 2013; Menon, 2011; Raichle et al., 2001; Seeley et al., 2007). Two recent papers have reviewed studies on functional connectivity in depression (Smith, 2014; Wang et al., 2012), but either included only a limited number of eligible studies (Smith, 2014) or rather divergent methods which makes comparison of results problematic (Wang et al., 2012). Because of these limitations, and the large number of connectivity papers published in recent years, we aim to provide a coherent review of the resting-state functional connectivity literature in depression that takes into account the different methods used, and update the current concept of depression as a network-based disorder.

Our review will focus on changes within (1) the default mode network, (2) the central executive network, (3) the salience network and (4) the interactions between these networks. We will start by giving a short overview of these networks and their function. Then, we will provide a critical appraisal of all available studies on resting-state functional connectivity in MDD, taking into account different methods used as well as the relation to clinical characteristics and effects of treatment. Lastly, we will discuss the significance of these findings in the light of current depression hypotheses.

2. Core large-scale networks in major depressive disorder

The default mode network (DMN), the central executive network (CEN) and the salience network (SN) (Fig. 1) (Hamilton et al., 2013; Menon, 2011; Raichle et al., 2001; Seeley et al., 2007) represent the brain's function during rest, cognition and emotional processes, all of which are essential processes that are altered in depression.

2.1. Default mode network (DMN)

The default mode network (also known as the "task-negative network") was initially identified as areas that consistently showed synchronized deactivation during tasks and prominent activation during rest (Raichle et al., 2001). The fact that this network is related to processes that are mostly employed during rest such as self-generated thought has gained significant attention, especially in relation to depression (Andrews-Hanna et al., 2014; Buckner et al., 2008; Menon, 2011). The DMN is often divided into an anterior sub-network that centers on the medial prefrontal cortex (mPFC) and a posterior sub-network that centers on the posterior cingulate cortex (PCC) and the precuneus cortex (PCu) (Andrews-Hanna et al., 2010; Buckner et al., 2008). While the anterior and posterior sub-network share similar temporal dynamics, they differ in regards to their specific function (Andrews-Hanna et al., 2010, 2014). In general, both the anterior and posterior parts of the DMN are related to spontaneous or self-generated cognition. The anterior DMN is more related to self-referential processing and emotion-regulation, partly through its strong connections with limbic areas such as the amygdala. The posterior DMN has been implicated in both consciousness and memory processing through its relation to the hippocampal formation (Andrews-Hanna et al., 2014; Cavanna and Trimble, 2006; Leech and Sharp, 2014).

In addition to the core regions, associated DMN areas include the inferior parietal lobule (IPL) and the lateral temporal cortex (LTC) (Buckner et al., 2008; Greicius et al., 2003). Although not

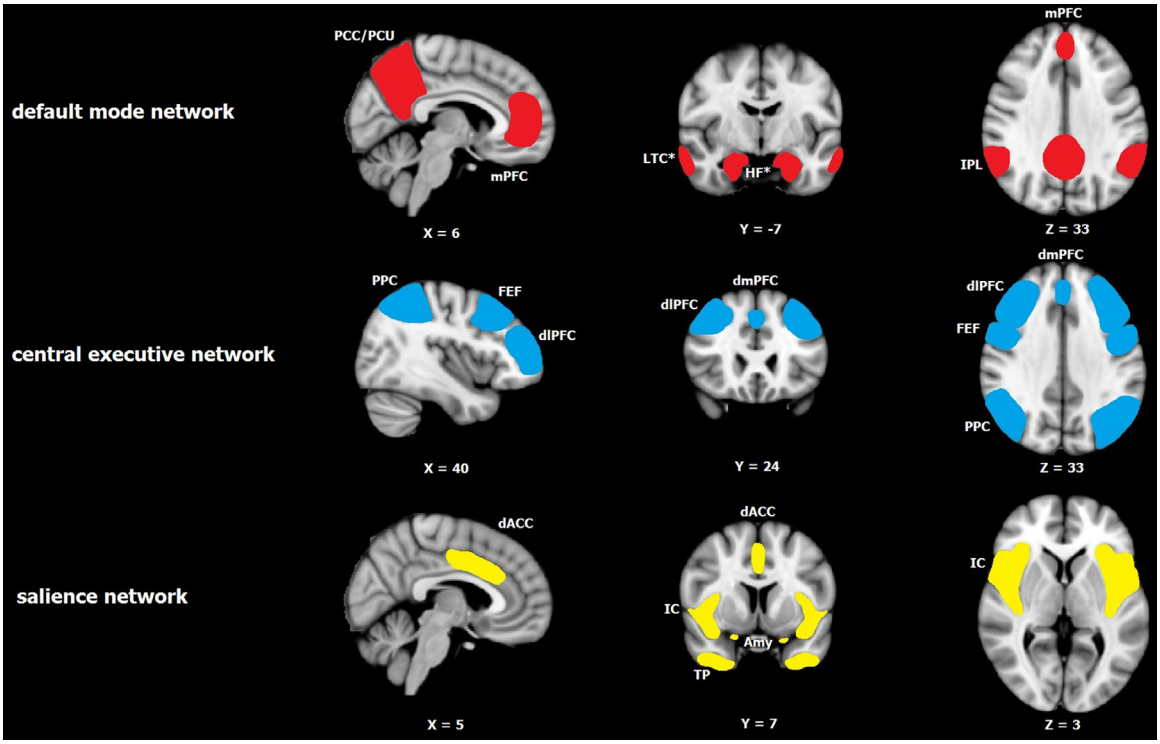

Fig. 1. *Major resting-state networks relevant in MDD.* Representation of the major resting-state networks relevant in MDD. The default mode network (DMN) consists of two core regions: the medial prefrontal cortex (mPFC) and the posterior cingulate cortex/precuneus (PCC/PCu), with the inferior parietal lobule (IPL) also being reported consistently. * The lateral temporal cortex (LTC) and the hippocampal formation (HF) are often found as being strongly related to the DMN, but likely constitute a subsystem within the DMN. The central executive network (CEN) is centered on the dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PPC), and also includes the dorsomedial prefrontal cortex (dmPFC) and frontal eye fields (FEF). The salience network consists of the insular cortex (IC), dorsal anterior cingulate cortex (dACC), temporal pole (TP) and amygdala (Amy).

consistently reported as nodes within the DMN, the subgenual anterior cingulate cortex (sgACC) and the hippocampal formation (hippocampus and parahippocampal gyrus) also have an important functional relation to (parts of) the DMN (Andrews-Hanna et al., 2010; Buckner et al., 2008; Greicius et al., 2004; Zhou et al., 2010). These differences in the topography of the DMN are likely related to the variety of processes occurring during rest. Recent evidence points toward subsystems within the DMN that each attribute to different aspects of internal mentation, for instance a medial temporal lobe subsystem that covers the hippocampal formation and is mostly related to episodic memory activation during rest (Andrews-Hanna et al., 2010). For the purpose of this review, when considering the DMN we will limit ourselves to the "core" DMN regions that are consistently identified as part of the DMN: the mPFC, the PCC/PCu and the IPL.

2.2. Central executive network (CEN)

The central executive network (CEN, also referred to as the 'cognitive control network' or the 'cognitive-executive network') includes the lateral prefrontal cortex, the posterior parietal cortex (PPC), the frontal eye fields (FEF) and part of the dorsomedial prefrontal cortex (dmPFC) (Corbetta and Shulman, 2002; Rogers et al., 2004). Contrary to the DMN, this network is most active during cognitive tasks and is implicated in cognitive functioning including attention and working memory. The DMN and the CEN are often seen as opposing networks, and task-related interactions between these networks are changed in MDD (Hamilton et al., 2011; Sheline et al., 2009). Together with some additional areas (most notably middle temporal region, supplementary motor cortex and the fronto-insular operculum) the CEN also makes up the "task-positive network" which shows strong task-related activation (Fox et al., 2005).

2.3. Salience network (SN)

The salience network typically consists of the fronto-insular cortex, the dorsal ACC, the amygdala and temporal poles. It is activated in response to various salient stimuli including acute stress (Hermans et al., 2014; Seeley et al., 2007). It is believed to reflect paralimbic emotional processing and to play a central role in emotional control through its extensive subcortical connectivity. Moreover, it has been implicated in switching between the DMN and CEN (Goulden et al., 2014; Sridharan et al., 2008).

3. Methods

3.1. Literature search

A search in PubMed/MedLine was performed to identify papers in English reporting on resting-state functional connectivity in unipolar MDD, using "major depressive disorder", "resting state" and "functional connectivity" as search terms. Papers were selected when they (1) included patients with current MDD, (2) used fMRI, (3) made comparisons to matched healthy controls and (4) reported on measures of functional connectivity. References of the included papers were checked for citations that were not identified by our initial search. We divided papers based on the dominant network of interest, the methods used, and whether they reported on within- or between-network connectivity.

3.2. Methods selection

Given our interest in large-scale brain networks we chose to include papers using either seed-based correlation analysis (SCA) (Biswal et al., 1995) or independent component analysis (ICA) (Beckmann, 2012; Beckmann et al., 2005). We focused on these measures because they use similar data to assess connectivity (i.e. BOLD-signal over time) and are well established in the connectivity literature. A more extensive explanation of the differences between the selected methods and their limitations can be found elsewhere (Cole et al., 2010; Zuo and Xing, 2014). In short, SCA uses a predetermined region of interest or "seed", usually based on a clear hypothesis, and calculates correlations of its BOLD-signal fluctuations to those of all other voxels of the brain or to specific other seed regions. An increase in functional connectivity found using SCA therefore represents increased synchronization between two regions. By comparison, ICA does not require a prior selection of regions of interest, but instead uses all the data available within the fMRI image to decompose the entire fMRI dataset into temporally coherent, spatially independent "components", which correspond to brain networks (Beckmann et al., 2005; Smith et al., 2009).

In contrast to SCA, an increase in functional connectivity using ICA reflects the degree to which a voxel's signal over time is correlated with a specific network or component. The "model-order" of ICA represents the (calculated or selected) number of components that the data is decomposed into, where a higher model-order can be used to identify sub-networks within larger networks (Cole et al., 2010). Another frequently used measure of functional connectivity, regional homogeneity (ReHo) was excluded for the purpose of this review as it reflects local coherence within small regions and as such is less suitable to investigate large-scale brain networks (Zang et al., 2004). Papers calculating functional connectivity based on the (fractional) amplitude of low frequency fluctuations (fALFF) were also excluded because of difficulties comparing BOLD- and frequency-based changes in connectivity (Zang et al., 2007; Zuo and Xing, 2014). A recent review that included predominantly ReHo and fALFF papers found no consistent changes in functional connectivity in MDD (Smith, 2014).

4. Results

In total 8 papers using ICA (Table 1) and 28 papers applying SCA (Table 2) were included. Papers were published between 2005 and 2014, but 34 out of 36 studies were reported in the past five years. All ICA papers have investigated the DMN, while the CEN and SN were only reported in a subset of studies. Among SCA papers, the most frequently selected seed regions are the ACC, PCC and the amygdala. 25 out of the 36 studies investigated an adult population, 6 looked at an elderly group and 5 focused on adolescents. 17 out of 36 studies included patients currently on antidepressants. Most papers demonstrate state-related changes during an episode of depression, while a few also report on longitudinal changes in the context of antidepressant treatment.

4.1. Default mode network (DMN)

4.1.1. Independent component analysis (ICA)

All of the ICA studies investigating the DMN in MDD have found an increase in connectivity within several nodes of the anterior DMN compared to healthy controls (Greicius et al., 2007; Li et al., 2013; Manoliu et al., 2013; Zhu et al., 2012a). Greicius et al. (2007) were the first to investigate the role of the DMN in (medicated) depressed patients using ICA and reported increased connectivity within the subgenual ACC (sgACC), the orbitofrontal cortex (OFC) the precuneus (PCu) and the thalamus. Although a prominent node in the DMN of depressed patients, the sgACC was not part of the DMN in their healthy control subjects, implying that the DMN has a somewhat different configuration in MDD. Zhu et al. (2012b) also demonstrated increased connectivity within the anterior DMN (dorsomedial PFC (dmPFC), ventromedial PFC (vmPFC), pregenual ACC (pgACC) and medial OFC) in first-episode medication-naive MDD patients, demonstrating that this finding is not dependant on disease course or current use of medication. Interestingly, two other papers confirmed the increased connectivity within nodes of the anterior DMN. However, instead of an increased connectivity of these areas within the full DMN they found this increase to be specific within the anterior DMN (Li et al., 2013; Manoliu et al., 2013). Together these results indicate that in depression, activity within several nodes in the medial prefrontal cortex (and especially the ACC) is more synchronized with activity of the (anterior) DMN.

Similar to the anterior DMN, connectivity in the posterior parts of the DMN is predominantly found to be increased in depression. While Greicius and colleagues reported increased connectivity in the PCu with the full DMN, the two papers that subdivide the DMN into smaller sub-networks report increased connectivity of the PCC/PCu within the posterior DMN specifically (Li et al., 2013; Manoliu et al., 2013). In contrast, Zhu et al. (2012b) instead report a decrease in connectivity in the PCC, the PCu and the angular gyrus. This difference could be related to characteristics of their sample, which consisted of relatively young (mean age 20 years) and mildly depressed patients. The authors suggest that the anterior and posterior DMN show a dissociation pattern during depression, which is supported by some of the other studies.

While using a high model order for ICA can reliably identify sub-networks within the DMN (Abbott et al., 2013; Manoliu et al., 2013), Li and colleagues found this split even using a low model-order ICA (20 components). They identified an anterior and posterior sub-network that were spatially independent and showed asynchronous activity patterns (Li et al., 2013). This distinction was further supported by the effects of antidepressant treatment that normalized the increased connectivity in the posterior DMN, but not in the anterior DMN. The hypothesis of a dissociation within the DMN is also supported by findings of Guo et al. (2014), who used ICA to identify the DMN and found that network homogeneity (defined as the mean correlation of a voxel with all other voxel's within a network) within the DMN was increased in the anterior DMN (dmPFC), but decreased in the posterior part (inferior temporal gyrus). The final two papers exploring connectivity within the DMN using ICA found no changes in connectivity (Sexton et al., 2014; Veer et al., 2010). However, since both studies investigated a mixed group of mild and remitted MDD this limits a direct comparison with the above findings.

4.1.2. Seed-based correlation analysis (SCA)

Based on earlier work defining the DMN and results from resting-state and activation studies, the most commonly used seed regions in SCA studies investigating the DMN are either the sgACC or the PCC (Greicius et al., 2007, 2003). Importantly though, the sgACC is not always considered part of the DMN (Sheline et al., 2010) although several authors point toward its inclusion in the DMN in depressed samples (Greicius et al., 2007; Zhou et al., 2010). A study by Zhou et al. (2010) on this issue found that the recruitment of the sgACC within the DMN is specific for MDD and not present in healthy controls. This is an important finding which limits the use of this area as a seed region to study the DMN as a whole when comparing different subject groups. Therefore we will focus on studies using DMN seeds in the mPFC (dorsal to the ACC) and the PCC/PCu and address the sgACC separately.

For the anterior DMN, only two papers selected seeds in the medial prefrontal cortex dorsal to the ACC (Sheline et al., 2010; Van Tol et al., 2013). Consistent with the hypothesis of a

Table 1
Summary of studies using independent component analysis.

Paper	No. patients (mean age) Population	Med	No. IC	Design	Within-network connectivity[a]			Between-network connectivity	Longitudinal effects
					Default mode network	Central executive network	Salience network		
Greicius 2007	28 (38.5 yr) Severe	Y	25	Cross-sectional	↑ sgACC ↑ thalamus ↑ OFC ↑ PCu	N/A	N/A	N/A	N/A
Zhu 2012	35 (20.5 yr) First episode Mild	N	30	Cross-sectional	↑ dmPFC ↑ pgACC ↑ vmPFC ↑ mOFC ↓ PCC ↓ PCu ↓ angular gyrus	N/A	N/A	N/A	N/A
Li 2013	24 (31.8 yr) Severe	N	20	Longitudinal	Within anterior DMN ↑ mPFC (L) Within posterior DMN ↓ PCu (B)	N/A	N/A	Split of DMN into anterior and posterior DMN.	Antidepressants normalized connectivity in posterior DMN
Guo 2014[b]	24 (25.6 yr) First episode Severe	N	N/A	Cross-sectional	↑ dmPFC ↓ inferior temporal gyrus	N/A	N/A	N/A	N/A
Sexton 2012	36 (71.8 yr) Geriatric mild/remitted	Y	25 and 70	Cross-sectional	No significant findings	No significant findings	No significant findings	N/A	N/A
Veer 2010[c]	19 (36.1 yr) Mild/remitted	N	20	Cross-sectional	No significant findings	↓ Frontal pole	↑ inferior frontal gyrus (R) ↓ amygdala (B) ↓ anterior insula (L)	N/A	N/A
Abbott 2013	12 (66.4 yr) Geriatric Recurrent Severe	Y	70	Longitudinal	N/A	N/A	N/A	↓ pDMN—dmPFC ↓ pDMN—left dlPFC	ECT normalized pDMN-dmPFC and pDMN-dlPFC connectivity
Manoliu 2014	25 (48.8 yr) Recurrent Severe	Y	75	Cross-sectional	Within anterior DMN ↑ ACC (B) Within inferior–posterior DMN ↑ PCu (B) Within superior–posterior DMN ↑/↓ PCu (B)	Within right ventral CEN No significant findings Within left ventral CEN ↑ angular gyrus (R) ↓ PCu (L) ↓ middle temporal gyrus (L) Within dorsal CEN ↑ postcentral gyrus (R)	↑ ACC (B) ↓ insula (B)	↑ ipDMN-SN ↓ ipDMN—dCEN ↓ spDMN-dCEN	N/A

Abbreviations: ↑: increased functional connectivity; ↓: decreased functional connectivity; (L) left; (R): right; (B): bilateral; Med.: medication; IC: independent components; ICA: independent component analysis; MDD: major depressive disorder; sgACC: subgenual anterior cingulate cortex; OFC: orbitofrontal cortex; PCu: precuneus; dmPFC: dorsomedial prefrontal cortex; pgACC: pregenual anterior cingulate cortex, vmPFC: ventromedial prefrontal cortex, mOFC: medial orbitofrontal cortex; PCC: posterior cingulate cortex; DMN: default mode network; mPFC: medial prefrontal cortex; pDMN: posterior default mode network; dlPFC: dorsolateral prefrontal cortex; ECT: electroconvulsive therapy; ACC: anterior cingulate cortex; CEN: central executive network; ipDMN: inferior–posterior default mode network; SN: salience network; dCEN: dorsal central executive network; spDMN: superior–posterior default mode network.

[a] Within-network connectivity reflects changed connectivity to the network under investigation as a whole.

[b] Guo and colleagues report on network homogeneity, with the DMN derived from ICA on the control subjects.

[c] Veer and colleagues report changes in networks that only partly overlap with the typical network configurations.

Table 2
Summary of studies using seed-based correlation analysis[a].

Paper	No. patients (mean age), population	Med	Seed regions	Design	Default mode network	Central executive network	Salience network	Other	Longitudinal effects
Andreescu 2009	47 (68.7 yr) Late-life Moderate-severe	N	PCC	Longitudinal	↑ PCC—PCu ↓ PCC—medFG	N/A	N/A	N/A	Antidepressant treatment: ↑ PCC—medFG, dACC (not significant)
Berman 2011	15 (25.7 yr) Moderate-severe	Y	PCC, mPFC	Cross-sectional	↑ PCC—sgACC	N/A	N/A	N/A	N/A
Bluhm 2009	14 (21.9 yr) Moderate	Y	PCC/PCu	Cross-sectional	↑ PCC/PCu—caudate nucleus (B)	N/A	N/A	N/A	N/A
Wu 2011	12 (70.5 yr) Late-life Moderate-severe	N	PCC	Longitudinal	↑ PCC—dmPFC, OFC ↓ PCC—sgACC	N/A	N/A	N/A	Antidepressant treatment: ↓ PCC -dmPFC, OFC
Zhou 2010	18 (38.9 yr) First episode Moderate	N	PCC/PCu, dlPFC (R)	Cross-sectional	sgACC and PHC (R) specific for DMN in MDD ↑ PCC/PCu, mPFC/mOFC	Mid-PCC (L) specific for CEN in MDD ↑ lateral PFC and IPL (B) ↓ PCC/PCu, mPFC/OFC, LPC and anterior temporal regions	N/A	N/A	N/A
van Tol 2013	20 (38.3 yr) Mild-moderate	Y	dmPFC, dlPFC, rostral STG, pMCC	Cross-sectional	↑ dmPFC—FIC (L) ↓ dmPFC—PCu, AG, MTG, FIO	No significant findings	N/A	↓ rostral STG—pgACC, medFG, OFC (B)	N/A
Pannekoek 2014	26 (15.4 yr) Adolescent Treatment-naive Mild-moderate	N	PCC/PCu, amygdala, dACC	Cross-sectional	No significant findings	N/A	↑ Amygdala—TP (R), precentral gyrus, postcentral gyrus ↓ amygdala—FP (L), pgACC (R), paracingulate cortex (R), LPC (L)	N/A	N/A
Alexopoulos 2012	16 (69 yr) Late-life Moderate	Y	PCC, dACC, dlPFC	Prospective	↑ Within the DMN	↓ within the CEN	N/A	N/A	Antidepressant treatment (escitalopram): ↓ within the CEN predicts low remission rate
Liston 2014	17 (42.3 yr) Treatment-resistant MDD and bipolar II depression Mild-severe	Y	sgACC, dlPFC (L)	Longitudinal	↑ sgACC—DMN	↓ within the CEN	N/A	N/A	rTMS treatment: ↓ vmPFC, pgACC, PCu. Induced anticorrelation DMN—dlPFC Predictive: ↑ sgACC at baseline predicts good response
Sheline 2010	18 (35.9 yr) Moderate-severe	N	sgACC, dlPFC, PCC, 'dorsal nexus'	Cross-sectional	↑ From sgACC, dlPFC and PCC with 'dorsal nexus' (part of dmPFC)	↑ 'dorsal nexus' (dmPFC)	N/A	↑ sgACC—'dorsal nexus' (dmPFC) ↑ 'dorsal nexus'—ACC, vmPFC, dlPFC, PCC, PCu	N/A
Ye 2012	22 (46.7 yr) First episode Moderate	Y	dlPFC	Cross-sectional	N/A	↑ dlPFC—ACC (L), PHC (L), thalamus, precentral gyrus ↓ dlPFC—parietal cortex (R)	N/A	N/A	N/A

Table 2 (*Continued*)

Paper	No. patients (mean age), population	Med	Seed regions	Design	Default mode network	Central executive network	Salience network	Other	Longitudinal effects
Lui 2011	28/32 (33/32 yr) Responders (28)/ Non-responders (32) Severe	N	13 seeds (B)	Prospective	N/A	↓ within prefrontal-limbic-thalamic circuit	Responders vs. non-responders (at baseline): ↓ amygdala (L) —ACC ↓ insula (R) —ACC, PCu	↓ Within prefrontal-limbic-thalamic circuit	N/A
Avery 2013	20 (26 yr) Mild-severe	N	dmIC	Cross-sectional	N/A	N/A	↑ dmIC—amygdala, mOFC, MTG (R), MOG (R) ↓ dmIC—cerebellum	N/A	N/A
Cullen 2014	41 (15.7 yr) Adolescent Moderate-severe	N	Amygdala	Cross-sectional	N/A	N/A	↑ Amygdala—PCu ↓ amygdala—PHC (L), hippocampus (L), TP, brainstem	N/A	N/A
Ramasubbu 2014	55 (36.5 yr) Moderate-severe	N	Amygdala	Cross-sectional	N/A	N/A	↓ Amygdala—ventral neural system (vlPFC, insula, PCu)	N/A	N/A
Tang 2013	28 (29.3 yr) Treatment-naive Severe	N	Amygdala	Cross-sectional	N/A	N/A	↓ Amygdala—vlPFC (L)	N/A	N/A
Yue 2013	22 (67.6 yr) Late-onset Severe	N	Amygdala	Cross-sectional	N/A	N/A	↓ Amygdala (L) —MFG (R), SFG (L), postcentral gyrus (R) ↓ amygdala (R) MOG (R)	N/A	N/A
Tahmasian 2013	21 (51 yr) Recurrent Severe	Y	Amygdala, hippocampus	Cross-sectional	N/A	N/A	Reduced negative connectivity amygdala/hippocampus—dmPFC/FIO	N/A	N/A
Horn 2010	28 (39.2 yr) Moderate	Y	pgACC, AI (L)[b]	Cross-sectional	N/A	N/A	N/A	↑ pgACC—AI (L)	N/A
Anand 2005	15 (29 yr) Moderate-severe	N	pgACC, amygdala, PST and medial thalamus[b]	Cross-sectional	N/A	N/A	N/A	↓ pgACC—PST, medial thalamus ↓ pgACC—amygdala (not significant)	N/A
Cao 2012	42 (29.2 yr) First episode Severe	N	Hippocampus	Cross-sectional	N/A	N/A	N/A	Reduced negative connectivity hippocampus—MFG (B), —right IPL (R), cerebellum (R)	N/A
Connolly 2013	23 (16 yr) Adolescent First episode Moderate	N	sgACC	Cross-sectional	N/A	N/A	N/A	↑ sgACC—insula, amygdala	N/A
Cullen 2009	12 (16.5 yr) Adolescent Moderate	Y	sgACC, pgACC, spACC, amygdala	Cross-sectional	N/A	N/A	N/A	↓ sgACC—spACC, lateral frontal cortex, STG and insula	N/A
Davey 2012	18 (18.9 yr) Adolescent Severe	Y	sgACC, pgACC, aMCC, pMCC	Cross-sectional	N/A	N/A	N/A	↑ sgACC—dmPFC ↑ pgACC—dlPFC ↓ pgACC—caudate nucleus	N/A
de Kwaasteniet 2013	18 (44.6 yr) Severe	Y	sgACC	Cross-sectional	N/A	N/A	N/A	↑ sgACC—amygdala, hippocampus, OFC, thalamus	N/A
Gabbay 2013	21 (17.1 yr) Adolescent Moderate	N	6 striatal seeds (B)	Cross-sectional	N/A	N/A	N/A	↑ In frontostriatal circuitry	N/A

Furman 2011	21 (39.2 yr) Female subjects Severe	Y	4 striatal seeds (B)	Cross-sectional	N/A	N/A	N/A	↑ Dorsal caudate—dorsal PFC ↓ ventral striatum—vmPFC, sgACC	N/A
Ma 2012	18/17 (27.4/26.7 yr) Treatment-resistant (18)/First episode (17) Severe	Y/N	MTG (R) and caudate nucleus (B)	Cross-sectional	N/A	N/A	N/A	↑ MTG (R) –SMG (L) ↓ MTG (R) –AG (R), PCu (L), PHC ↑/↓ caudate nucleus—MFG/IFG	N/A

Abbreviations: ↑: increased function connectivity; ↓: decreased functional connectivity; (L) left; (R): right; (B): bilateral; Med: medication; MDD: major depressive disorder; PCC: posterior cingulate cortex; PCu: precuneus; medFG: medial frontal gyrus; dACC: dorsal anterior cingulate cortex; mPFC: medial prefrontal cortex; sgACC: subgenual anterior cingulate cortex; dmPFC: dorsomedial prefrontal cortex; OFC: orbitofrontal cortex; dlPFC: dorsolateral prefrontal cortex; PHC: parahippocampal cortex; DMN: default mode network; mOFC: medial orbitofrontal cortex; CEN: central executive network; PFC: prefrontal cortex; IPL: inferior parietal lobule; LPC: lateral parietal cortex; STG: superior temporal gyrus; pMCC: posterior midcingulate cortex; MCC: midcingulate cortex; FIC: fronto-insular cortex; AG: angular gyrus; MTG: middle temporal gyrus; FIO: fronto-insular operculum; TP: temporal pole; FP: frontal pole; pgACC: pregenual anterior cingulate cortex; rTMS: repetitive transcranial magnetic stimulation; vmPFC: ventromedial prefrontal cortex; ACC: anterior cingulate cortex; dmIC: dorsomedial insular cortex; MOG: middle occipital gyrus; vlPFC: ventrolateral prefrontal cortex; MFG: middle frontal gyrus; SFG: superior frontal gyrus; AI: anterior insula; PST: pallidostriatum; spACC: supragenual anterior cingulate cortex; aMCC: anterior midcingulate cortex; SMG: supramarginal gyrus; IFG: inferior frontal gyrus.

[a] Table shows changed connectivity between different nodes in the networks, organized by which network is investigated by the seed region.

[b] Direct correlation of seed-regions (not whole-brain correlation).

dissociation between the anterior and posterior DMN in depression, Van Tol et al. (2013) found a decrease in connectivity of the dmPFC with the posterior DMN. Furthermore, connectivity of the dmPFC to the left anterior insula was increased, indicative of increased connectivity between the anterior DMN and the SN. Sheline et al. (2010) selected their dmPFC seed based on an overlapping increase in connectivity from three different seeds (sgACC, PCu and dlPFC). They hypothesized that this region, which they termed the 'dorsal nexus', is a converging point of increased connectivity and could give rise to the complex dysfunctions seen in depression. Using this area as a seed revealed a pattern of increased connectivity with medial prefrontal (ACC, ventromedial prefrontal cortex (vmPFC)), medial posterior (PCC, PCu) and lateral prefrontal (dlPFC) areas. The different findings between these two studies could be related to differences in medication status and differences in seed-selection; while van Tol and colleagues based their seed on an area of reduced cortical thickness, Sheline and colleagues defined their seed by its hyperconnectivity with other seed regions.

In addition to the papers using seeds in the anterior DMN, eight papers investigating the DMN used seed regions located in the posterior DMN (PCC or PCu) (Alexopoulos et al., 2012; Andreescu et al., 2013; Berman et al., 2011; Bluhm et al., 2009; Davey et al., 2012; Pannekoek et al., 2014; Sheline et al., 2010; Wu et al., 2011a). In general, these studies show inconsistent changes in connectivity between anterior and posterior nodes of the DMN.

In line with some of the ICA-papers, Alexopoulos et al. (2012) found connectivity of the PCC to be increased with both anterior (sgACC, vmPFC) and posterior (PCu) nodes of the DMN in a medicated group of late-onset depression. Berman et al. (2011) also found increased connectivity of the posterior DMN with the sgACC in a much younger (mean age 25.7 years) medicated patient group. Similarly, Zhou et al. (2010) reported increased connectivity of the PCC with other posterior DMN nodes and the mPFC and OFC. Interestingly, another study in a smaller unmedicated group of elderly depressed patients also reported increased connectivity of the PCC with the dmPFC and OFC, but connectivity of the PCC with the sgACC was decreased (Wu et al., 2011a). This decrease in connectivity was partly restored after 12 weeks of treatment with paroxetine, which suggests that antidepressant treatment influences connectivity between anterior and posterior DMN regions. Further evidence for this hypothesis was reported by Andreescu et al. (2013) in a larger group of unmedicated elderly. At baseline, they found increased connectivity of the PCC with other nodes in the posterior DMN, but decreased connectivity with the medial frontal gyrus. After 12 weeks of antidepressant treatment connectivity in both the bilateral medial frontal gyrus and the dorsal ACC (dACC, part of the SN) was increased, although these effects did not survive correction for white matter hyperintensities. The other papers investigated connectivity from the posterior DMN in young adults and adolescents and reported a decrease in connectivity with the caudate nucleus (Bluhm et al., 2009) or no changes (Pannekoek et al., 2014).

In summary, SCA studies from the posterior DMN mainly report increased connectivity with different medial prefrontal regions, which might be related to medication status. Longitudinal studies also point toward an effect of antidepressant treatment on connectivity between the anterior and posterior DMN.

4.2. Central executive network (CEN)

4.2.1. Independent component analysis (ICA)

A limited number of papers thus far has used ICA to investigate connectivity within the CEN in depression (Manoliu et al., 2013; Sexton et al., 2014). Manoliu and colleagues used a high model-order ICA (75) to define three sub-networks within the CEN. They report increased connectivity of the right angular gyrus within the

left ventral CEN and of the right postcentral gyrus within the dorsal CEN. Veer et al. (2010) did report decreased connectivity of the frontal pole, but within an attentional network that only partly overlapped with the typical CEN-configuration. A study investigating the CEN in a group of mostly remitted patients found no differences in connectivity (Sexton et al., 2014).

4.2.2. Seed-based correlation analysis (SCA)

SCA studies on connectivity of the CEN are consistent in using the dlPFC as a seed region (Alexopoulos et al., 2012; Liston et al., 2014; Lui et al., 2011; Sheline et al., 2010; Van Tol et al., 2013; Ye et al., 2012) and most show decreased connectivity of the dlPFC with other regions of the CEN. This hypoconnectivity within the CEN was found in medicated patients with a first depressive episode (Ye et al., 2012), late-life depression (Alexopoulos et al., 2012) and treatment-resistant depression (Liston et al., 2014). A longitudinal study by Lui et al. (2011) investigated a group of medication-naive depressed patients before starting antidepressant treatment. Interestingly, they report decreased connectivity of the dlPFC with the parietal cortex and PCu specifically in those patients who would later respond to antidepressant treatment, while those that failed to respond instead showed decreased connectivity of the dlPFC with several regions of the SN (insula, dACC).

Two studies also report areas of increased connectivity with the dlPFC, while one found no changes (Van Tol et al., 2013). Ye et al. (2012) found that in a first episode of depression connectivity of the dlPFC was increased with the left dACC, left parahippocampus, thalamus and precentral gyrus, while Sheline et al. (2010) report increased connectivity with the 'dorsal nexus', an area in the dmPFC with overlapping increased connectivity from different seeds.

4.3. Salience network (SN)

4.3.1. Independent component analysis (ICA)

Networks related to emotion regulation were investigated in three papers using ICA (Sexton et al., 2014; Manoliu et al., 2013; Veer et al., 2010). Manoliu and colleagues identified the SN and found increased connectivity within the bilateral ACC and decreased connectivity within the bilateral anterior insula. Notably, the decreased connectivity in the right anterior insula was inversely correlated with depression severity and positively correlated with decreased connectivity between the DMN and the CEN (Manoliu et al., 2013), which is in line with the insula's involvement in switching between the DMN and the CEN (Goulden et al., 2014; Hamilton et al., 2013; Sridharan et al., 2008). Consistent with a decreased connectivity within the SN, Veer et al. (2010) report a decoupling of both the insula and amygdala within a network involved in emotional processing, although this network is different from the typical SN. Sexton et al. (2014) found no difference within an "affective network" that was centered on the sgACC and ventral mPFC in mostly remitted patients.

4.3.2. Seed-based correlation analysis (SCA)

The most investigated seed regions involved in the SN are the insular cortex (Avery et al., 2013; Horn et al., 2010; Lui et al., 2011) and the amygdala (Anand et al., 2005a; Lui et al., 2011; Pannekoek et al., 2014; Ramasubbu et al., 2014; Tahmasian et al., 2013; Tang et al., 2013; Yue et al., 2013). Compared to the DMN and the CEN, the SN is less well-defined during the resting-state, although many authors report changes in networks related to emotional processing. Possibly related to this, changes in the SN appear less consistent and more node-dependant in comparison to the DMN and CEN.

Consistent with the ICA-based finding of increased connectivity of the SN with the ACC (Manoliu et al., 2013), SCA investigating the insula found that its connectivity was increased with the pregenual ACC (Horn et al., 2010) and the medial OFC (Avery et al., 2013). This increased connectivity to nodes of the anterior DMN is in line with hyperconnectivity of the anterior DMN and the insula's hypothesized role in orchestrating network interactions (Goulden et al., 2014; Hamilton et al., 2013; Sridharan et al., 2008). Another important node in the SN and highly relevant for MDD (Phillips et al., 2003; Price and Drevets, 2010), the amygdala is typically found to have decreased connectivity with various brain regions (Cullen et al., 2014; Yue et al., 2013). In line with the uncoupling of the amygdala and insula from the SN as found using ICA (Manoliu et al., 2013; Veer et al., 2010), two other papers also reported decreased connectivity between the amygdala and the insula (Ramasubbu et al., 2014; Tahmasian et al., 2013). In further support of a dissociation within the SN, another study found decreased connectivity of the insula with the dACC in adolescent depression (Pannekoek et al., 2014).

Other areas that were repeatedly found to have decreased connectivity with the amygdala include the left ventrolateral PFC (vlPFC) (Ramasubbu et al., 2014; Tang et al., 2013) and the ACC (Lui et al., 2011; Pannekoek et al., 2014). Despite the majority of papers reporting decreased connectivity of the amygdala, two studies instead reported an increase in connectivity of the amygdala with the temporal pole, which was found to correlate with depression severity (Pannekoek et al., 2014; Ramasubbu et al., 2014). Together, studies on amygdala connectivity mainly show a pattern of dissociation from the rest of the brain, and more specifically the SN, with a possible exception for the temporal pole.

4.4. Other seed-based correlation analysis

4.4.1. Anterior cingulate cortex (ACC)

The anterior cingulate cortex has several anatomically defined subregions that have been investigated in the context of MDD. SCA studies on the ACC mainly report increased connectivity with regions in the anterior DMN, and some show evidence for increased connectivity with regions of the SN. As discussed earlier, the sgACC is sometimes included within the DMN, although this inclusion could be specific during the depressed state (Greicius et al., 2007; Zhou et al., 2010).

Sheline et al. (2010) used the sgACC as a seed region and reported increased connectivity with the 'dorsal nexus', an area in the dmPFC. Consistent with these findings, Davey et al. (2012) also report increased connectivity from the ACC to both dorsomedial and dorsolateral prefrontal cortex. Further elaborating on these regions, Liston et al. (2014) investigated patients during the course of repetitive transcranial magnetic stimulation (rTMS), and found that at baseline connectivity of the sgACC with the DMN was increased, while connectivity of the sgACC with the CEN was decreased. Not only did rTMS reduce the connectivity of the sgACC with the DMN, but higher pretreatment connectivity also predicted a good response to treatment, an important finding replicated in another rTMS study (Salomons et al., 2014). De Kwaasteniet et al. (2013) also used the sgACC as a seed region and found a pattern of increased connectivity which is remarkably similar to the ICA-based findings of Greicius et al. (2007), including increased connectivity with the OFC and the thalamus, in addition to increased connectivity with the hippocampus and amygdala.

Three studies used the sgACC as a seed region to investigate changes in connectivity specifically in adolescent depression (Connolly et al., 2013; Cullen et al., 2009; Davey et al., 2012). Davey et al. (2012) found connectivity increased with the dmPFC, which is in line with increased connectivity of the sgACC with the DMN in depression (Greicius et al., 2007; Zhou et al., 2010). Connolly et al. (2013) showed that depressed adolescents exhibit greater connectivity of the sgACC with the amygdala and the insula, but decreased connectivity with the PCu. They interpreted their findings

as aberrant connectivity between the DMN and the SN, with the insula possibly driving the difficulties in network transition as proposed by others (Manoliu et al., 2013). In addition, the decrease in connectivity between the sgACC and the PCu is consistent with the studies reporting decreased connectivity between the anterior and posterior DMN (Li et al., 2013; Zhu et al., 2012b). Although not discussed, the four different seeds in the sgACC did show significantly different patterns of changed connectivity, which underlines the effect of small variances in seed selection. In contrast to the majority of papers on sgACC connectivity, Cullen et al. (2009) found decreased connectivity of the sgACC within an ACC-network including the insula, although their conflicting findings can probably be attributed to the fact that subjects were listening to their own choice of music, which has been shown to influence emotional network connectivity (Koelsch and Skouras, 2014). In summary, SCA studies confirm increased connectivity of the sgACC with the anterior DMN and nodes of the SN (amygdala and insula).

Two papers opting for direct correlations (as opposed to whole-brain SCA) used seeds placed in the pgACC (Anand et al., 2005a; Horn et al., 2010). Employing direct correlation over whole-brain SCA has a trade-off in being more sensitive to node-specific effects while being less informative about large-scale networks. Anand et al. (2005a) found that direct correlations between the pgACC and limbic structures (amygdala, pallidostriatum and thalamus) were decreased, explaining it as a potential decrease in ACC-mediated regulation of limbic areas. Another study by Horn et al. (2010) showed increased connectivity between pgACC and the left anterior insula. With the insula being implicated in switching between different states or networks, they too proposed that the increased assignment of the insula to the anterior DMN leads to a decrease in the ability to direct attention away from inward/self-related processing.

4.4.2. Hippocampus and subcortical areas

In addition to the amygdala, changes in connectivity of several other subcortical structures have been investigated in depression. Two studies report decreased connectivity of the hippocampus with the insular cortex (Lui et al., 2011; Tahmasian et al., 2013). As the hippocampus (together with the parahippocampal gyrus) is strongly related to the posterior DMN, this could reflect a decrease in connectivity between the insula and the posterior DMN. Only one study focused on connectivity of the hippocampus specifically (Cao et al., 2012). Although they did not confirm any changes in connectivity with the insula, they did find impaired negative connectivity (reduced negative correlation) of the hippocampus with bilateral middle frontal gyrus, the right inferior parietal cortex and the right cerebellum. They interpreted this reduction in negative correlation as a failure of the hippocampus to segregate its function in the depressed state, which could be related to the emotional and cognitive dysfunction in MDD.

A study focusing on the connectivity of subcortical structures (Gabbay et al., 2013) used seeds placed in the nucleus accumbens (NAc), caudate nucleus, and putamen. They found an increase in connectivity with the dmPFC in adolescent depression for these nodes. Another paper using a seed in the striatum instead found decreased connectivity with vmPFC and sgACC and increased connectivity with the medial frontal gyrus (Furman et al., 2011). A paper by Lui et al. (2011) also included seeds in the putamen and thalamus that showed decreased connectivity to regions in the lateral prefontal cortex. In addition, the thalamus also showed decreased connectivity with the insula. Overall, their study on 13 different regions of interest concluded that there is a pattern of significantly reduced connectivity within prefrontal–limbic–thalamic areas bilaterally, which they consider to represent the loss of top-down regulation of prefrontal cortex over limbic regions in MDD. Finally, Ma et al. (2012) used seeds in the right middle temporal gyrus (MTG) and caudate nucleus based on reduction in gray matter density and found abnormal connectivity with the DMN for the MTG, but not for the caudate nucleus. Unfortunately, since they found both increased and decreased connectivity in various regions, these findings are difficult to interpret.

4.5. Between-network connectivity

Changed connectivity between two nodes of different networks can reflect an alteration in the interaction between these networks. However, several authors also specifically addressed how connectivity between the larger networks changes in depression using ICA. The study by Manoliu et al. (2013), in addition to the above mentioned within-network connectivity, also investigated between-network connectivity for three sub-networks of the DMN (anterior, inferior–posterior, superior–posterior), three sub-networks of the CEN (left ventral, right ventral, dorsal) and the SN. They found increased connectivity between the inferior–posterior DMN and the SN, and decreased connectivity between both of the posterior DMN sub-networks and the dorsal CEN, which was related to the decreased connectivity of the right anterior insula within the SN. Consistent with these findings, Abbott and colleagues investigated between-network connectivity in a group of treatment-resistant depressed patients prior to electroconvulsive therapy and also found decreased connectivity between posterior DMN and the CEN (dlPFC) at baseline. In line with the hypothesis of dissociation within the DMN, they also found decreased connectivity between the posterior DMN and the dmPFC (Abbott et al., 2013). The between-network connectivity changed from negative to positive following electroconvulsive therapy, which is consistent with the SCA findings of antidepressant treatment affecting connectivity within the DMN. These findings also highlight the importance of between-network interactions in addition to the within-network findings.

5. Discussion

Due to the relative ease of collecting resting-state fMRI scans and the availability of new techniques such as ICA to accommodate the large amount of information involved, a large body of investigations into resting-state functional connectivity in depression is available now. Our review of the currently available data has yielded several findings that were consistent across different methods:

(1) increased connectivity within the anterior DMN,
(2) increased connectivity between the anterior DMN and the SN,
(3) changed connectivity between the anterior and the posterior DMN, and
(4) decreased connectivity between the posterior DMN and the CEN.

A summary of these findings is represented in Fig. 2. We will discuss the support for these findings and their implications for our current understanding of MDD and its treatment.

5.1. Increased connectivity within the anterior DMN

The most consistent finding across all studies is increased connectivity in the anterior DMN, both within the DMN as a whole and between the different anterior nodes. In depression, gray matter volume in this area is typically decreased, while activity is increased both during rest (Drevets et al., 2008; Hamani et al., 2011; Mayberg et al., 2005; Rodríguez-Cano et al., 2014) and in response to emotionally salient stimuli (Gotlib et al., 2005; Sheline et al., 2009). Adding to this, the attenuation of anterior DMN activity during cognitive tasks (Gusnard et al., 2001) is impaired in the depressed state

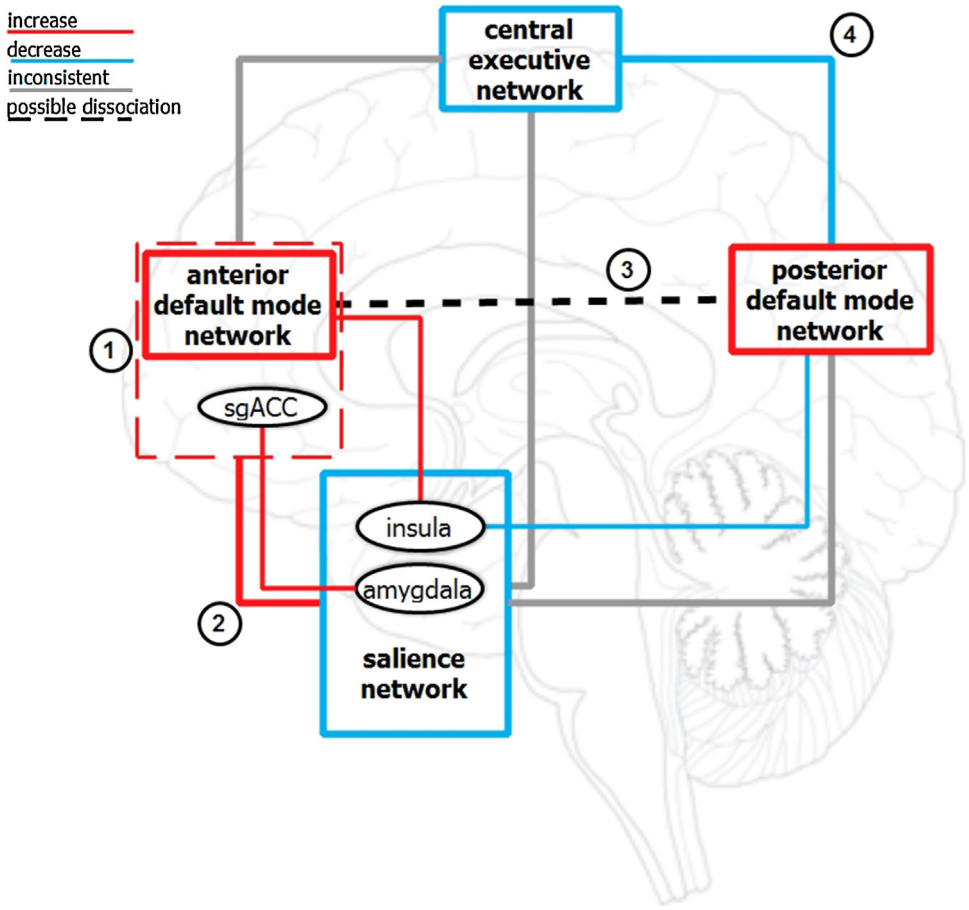

Fig. 2. *Within- and between-network connectivity changes in major depressive disorder.* Red/blue outlines represent a within-network increase/decrease in connectivity; red/blue lines between networks represent a between-network increase/decrease in connectivity. Black ellipses represent key nodes related to connectivity. Numbers represent main findings: (1): increase in anterior DMN connectivity and inclusion of sgACC within the anterior DMN, (2): increased connectivity between anterior DMN and SN, (3): changed connectivity between anterior and posterior DMN, (4): decreased connectivity between posterior DMN and CEN. Abbreviations: sgACC: subgenual ACC. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(Rodríguez-Cano et al., 2014; Sheline et al., 2009). Hyperactivity in the sgACC has been a consistent finding (Hamani et al., 2011), and activity within this node serves also as a marker of treatment response (Pizzagalli, 2011). Because of this, the change in DMN configuration to incorporate the sgACC in depression is intriguing (Greicius et al., 2007; Zhou et al., 2010), especially considering its extensive structural connectivity to both the DMN and the SN.

5.2. Increased connectivity between the anterior DMN and the SN

Although not as often reported as the increase in anterior DMN connectivity, several papers indicate an increase in functional connectivity between the anterior DMN and the SN, which is consistent with reports of increased structural connectivity (Fang et al., 2012). Hyperactivity of the amygdala, especially in response to negative stimuli, is common in depressed patients and has been hypothesized to interact with the mPFC to underlie the negativity bias in MDD (Murray et al., 2011; Price and Drevets, 2012). The repeat finding of increased connectivity between the amygdala and sgACC, in addition to a recent report on its relation to disease onset (Davey et al., 2014), therefore further highlights the relevance of this connection in MDD. However, whether these changes in connectivity constitute an increase in top-down modulation of limbic hyperactivity, bottom-up interference of self-processing regions, or both, is unclear. Surprisingly, connectivity of the amygdala with other brain regions implicated in emotional control is decreased in MDD, which could indicate an inability to control amygdala hyperactivity by regions other than the sgACC. This is in line with a recent review by Rive et al. (2013), who showed both differential functioning of ACC regions and an inability to recruit additional prefrontal resources in emotional control in depressed patients. The decreased connectivity of the amygdala with more lateral brain regions (insula and lateral PFC) is also consistent with limbic hyperactivity and lateral hypoactivity as found in resting-state activation studies in depression (Northoff et al., 2011). It is also remarkably similar to the limbic–cortical dysregulation model initially hypothesized by Mayberg (1997) that explains MDD as an inability to regulate hyperactive "ventral limbic" areas (including the ventral insula, amygdala, hypothalamus, hippocampus, vmPFC and sgACC) by hypoactive "dorsal limbic" areas (including dACC, PCC, inferior parietal, dorsal frontal areas). This model also implicates the rostral ACC as a key area in both MDD and treatment response.

5.3. Changed connectivity between the anterior DMN and the posterior DMN

Connectivity between anterior and posterior nodes of the DMN has repeatedly been found to be changed in MDD. Studies using ICA and SCA with anterior DMN seeds mainly report evidence of a dissociation of the DMN, while in the SCA investigations using seeds in the posterior DMN the majority reports increased connectivity between anterior and posterior nodes. As described earlier, an anterior and posterior sub-network within the DMN has been identified in healthy subjects (Andrews-Hanna et al., 2010; Buckner

et al., 2008) and they were shown to contribute to different aspects of self-generated thought. However, the implications of changes in functional connectivity between the anterior and posterior sub-networks are not well understood, although a paper by Leech and Sharp (2014) hypothesized that an increase in PCC connectivity with anterior DMN regions would relate to an increase in internally directed attention, which is in line with its correlation to rumination scores in depression (Berman et al., 2011). In depressed patients findings of decreased connectivity between the anterior and posterior DMN are supported by a decrease in structural connectivity in a sgACC-posterior DMN based network (Korgaonkar et al., 2014). Considering that using a higher model-order in ICA reliably splits the DMN into its sub-networks (Abbott et al., 2013; Manoliu et al., 2013), a possible explanation for the inconsistent findings is that MDD merely accentuates a normal functional distinction already present within the DMN in healthy subjects. Regardless, it is worth noting that while findings are inconsistent, several authors have reported treatment for depression to selectively affect parts of the DMN, which underlines the relevance of the distinction between anterior and posterior sub-networks.

5.4. Decreased connectivity between the posterior DMN and the CEN

Another interesting finding concerning the posterior DMN specifically is its decreased connectivity with the CEN. In line with the role the posterior DMN has in awareness and directed attention (Leech and Sharp, 2014) and the role of the CEN in higher cognitive functioning (Corbetta and Shulman, 2002), the change in their interaction could underlie difficulty in switching from a "default-state" in which the DMN is dominant and which is directed internally, to an "executive state" in which the CEN is dominant and attention is directed toward outward stimuli (Hamilton et al., 2013). Several authors have implicated that the insular cortex might be crucial for this shift in network-dominance (Goulden et al., 2014; Hamilton et al., 2011; Manoliu et al., 2013; Sridharan et al., 2008), which is supported by the increased connectivity of the insula with the anterior DMN and decreased connectivity with other networks.

5.5. Clinical correlates and treatment effects

Many authors have attempted to correlate clinical measures to changes in connectivity in MDD. In agreement with the most consistent regions of changed connectivity, nearly all findings of significant correlation between connectivity and clinical scores are either within the DMN or the interaction between the DMN and the SN. In short, severity of disease was related to connectivity of the sgACC (Connolly et al., 2013; Davey et al., 2012; De Kwaasteniet et al., 2013; Salomons et al., 2014), the dmPFC (Sheline et al., 2010), the dACC (Pannekoek et al., 2014), the dorsal caudate (Furman et al., 2011) and the insula (Avery et al., 2013; Manoliu et al., 2013). Connectivity of the sgACC was further related to disease duration (Greicius et al., 2007) and rumination (Berman et al., 2011; Connolly et al., 2013; Zhu et al., 2012b), while connectivity within the posterior DMN was related to overgeneralized memory (Zhu et al., 2012b).

Adding to this, numerous authors have reported changes in connectivity through various treatment modalities. Longitudinal studies found antidepressant medication to affect the anterior and posterior DMN differently, but whether the effect is specific for the sgACC (Kozel et al., 2011), the anterior DMN (Wu et al., 2011b), posterior DMN (Li et al., 2013), their interaction (Andreescu et al., 2013) or the interaction between parts of the DMN and the SN (Anand et al., 2005b; McCabe et al., 2011) is unclear. However, as most of these changes were in subjects with a baseline difference in connectivity within the DMN this signifies that effective antidepressant treatment restores aberrant network configuration within the DMN. Consistent with this, other treatment modalities find similar effects with TMS normalizing an increase in sgACC-DMN connectivity (Baeken et al., 2014; Liston et al., 2014; Salomons et al., 2014) and ECT also targeting disrupted connectivity between the anterior and posterior DMN (Abbott et al., 2013; Beall et al., 2012) and between the DMN and the CEN (Abbott et al., 2013; Beall et al., 2012; Perrin et al., 2012). Studies looking at differences between treatment-sensitive and treatment-unresponsive patients in a longitudinal setting also found that responders showed lower baseline connectivity of the PCC with the striatum (Andreescu et al., 2013) and higher connectivity of the insula with DMN nodes (Lui et al., 2011). Extending the clinical relevance of connectivity measures, a number of authors have been able to predict treatment response using functional connectivity. A positive response to rTMS was predicted by high baseline connectivity of the sgACC with the DMN (Liston et al., 2014; Salomons et al., 2014) or strong anticorrelation of the sgACC with the stimulation site in the dlPFC (Fox et al., 2012). More recently, a paper by Van Waarde et al. (2014) showed that connectivity patterns in two networks centered on the dmPFC and ACC could identify responders to ECT with high reliability, which corresponds with our findings that the majority of consistent changes in connectivity center on networks related to the anterior DMN.

Importantly, due to the differences in methods and results there is as of yet no compelling evidence for differentiating different subtypes of depression based on connectivity measures. As subtypes of depression respond differently to treatment strategies, this is a line of research that could prove promising in the future (Bühler et al., 2014; Gili et al., 2012; Rush, 2007).

5.6. Methodological considerations and limitations

Although the primary findings as presented above expand our current understanding of MDD, it is important to also address the shortcomings of current connectivity investigations. Especially for seed-based approaches even the most consistent findings are often not reproduced or connectivity changes are only found using one of the regions as a seed. For instance, a number of studies find increased connectivity for the sgACC with the amygdala when using the sgACC as a seed region, while none of the papers using the amygdala as a seed regions report increased connectivity with the sgACC. This heterogeneity in findings could reflect heterogeneity within the disorder itself, which is inherent to the symptom-based classification used to diagnose depression. However, it could also reflect the methodological difficulty in correct seed-selection and the problems introduced when correlating one or a few seeds to all other brain voxels. This is illustrated when papers use several similar seed voxels close to one another and find large differences in the emerging connectivity pattern (Cole et al., 2010; Connolly et al., 2013), which shows that small variation in seed selection can significantly impact the final results. In short, while seed-based approaches are very sensitive to changes in connectivity of the seed-region under investigation, this high sensitivity could also induce spurious findings with no biological meaning, for instance by merely reflecting similarity in noise within the two regions. This also limits the conclusions that we can draw from singular findings in papers using SCA. Another important methodological concern is the use of global signal regression in a number of the SCA papers, as this has repeatedly been shown to induce anti-correlations in the data (Murphy et al., 2009; Saad et al., 2012).

In contrast to the SCA-based papers, studies using ICA to identify networks appear much more consistent in their findings, as in fact all studies using a depressed group found increased connectivity within the anterior DMN, and nearly all report changes in the

connectivity of anterior and posterior DMN regions. A limitation of ICA however is that there is no clear consensus on a "correct" number of components to identify, and this directly influences the possible outcomes. However, different model-orders could also be used to further our understanding of sub-networks within networks. For example, a limited number of components could be used to look at large-scale networks (e.g. the DMN as a whole), while a high number of components in the same data would allow us to look at decompositions into sub-networks and investigate the underlying changes in network configuration (e.g. interaction between anterior and posterior DMN). A limitation of investigating neural networks in general is that there is no consensus on the boundaries of these networks. Additionally, while key nodes are identified consistently, associated regions may vary in their connectivity to any given network. Finally, a limitation of both ICA and SCA is that there is no clear consensus on what statistical thresholds should be used to either identify networks or make claims about the reliability of certain findings. For example, papers vary between what cluster size represents a significant finding. As these statistics are also influenced by the data used and the choices made during preprocessing, one common threshold will not be suitable for all study designs. Instead, researchers should provide clear information about their methodological considerations.

5.7. Future directions

Based on the current findings and methodological properties of the different techniques, there are several recommendations for future researchers. The decreased bias and increased consistency of findings using ICA over SCA leads us to propose that ICA should be used to give a model free estimation of regions of change in depression. Consequently, SCA should be used to further expand upon these significant findings by being more sensitive to specific changes less related to within network connectivity. As mentioned above, the number of components used in ICA analysis could help to delineate within-network configurations and sub-networks. Furthermore, large-scale networks are not static, but instead change over time even during rest (Gonzalez-Castillo et al., 2014; Zalesky et al., 2014). More insight into these network dynamics, for instance by looking at causal interactions and directionality of influence between the different nodes or networks, could inform us how the activation of networks is coordinated and possibly how network control is changed under various conditions such as the depressed state. Finally, relating changes in connectivity to distinct symptom profiles and neurocognitive domains would help us tackle the issue of large heterogeneity within MDD and improve treatment strategies for specific depression subtypes.

6. Conclusion

Connectivity studies in MDD expand upon activation studies by reporting increased connectivity within nodes of the anterior DMN and between the anterior DMN and the SN, changed connectivity between the anterior and posterior DMN and decreased connectivity between the posterior DMN and the CEN. We propose that this reflects a state of increased interaction between self-referential and emotional networks, and the dominance of negative self-referential over cognitive processing which corresponds to the clinical symptoms of depression. The consistent differences found in the interaction between nodes and networks, as well as its clinical potential in predicting treatment response, highlights the importance of functional connectivity in furthering our understanding and treatment of depression. Future studies should focus more on model-free investigations to elucidate true underlying biology, for example using ICA, while methods with high sensitivity such as SCA could be used to confirm and expand upon the found changes. Furthermore, investigations into how large-scale networks consist of sub-networks and the interactions between different networks are important challenges for current researchers in the field.

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