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The triple network model of mental disorders: disease-specific characterization of cognitive large-scale brain networks via functional magnetic resonance imaging (fMRI)

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Abbreviations

AI	Anterior insula
BDI	Beck Depression Inventory
BOLD	Blood-oxygen-level-dependent
CEN	Central executive network
CPZ	Chlorpromazine-equivalent-dose
DMN	Default mode network
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion tensor imaging
ECoG	Electrocorticography
EEG	Electroencephalography
EPI	Echo planar imaging
FC	Functional connectivity
Fig.	Figure
fMRI	Functional magnetic resonance imaging
FoV	Field of view
FWE	Family-wise error
GAF	Global Assessment of Functioning
HAM-D	Hamilton Depression Scale
Hb	Hemoglobin
HC	Healthy controls
IC	Independent component
ICA	Independent component analysis
ICN	Intrinsic connectivity network
iFC	Intrinsic functional connectivity
Inter-iFC	Intrinsic functional connectivity between networks
Intra-iFC	Intrinsic functional connectivity within networks
MDD	Major depressive disorder
MNI	Montreal Neurological Institute
MPRAGE	Magnetization Prepared Rapid Gradient Echo
MRI	Magnetic resonance imaging
O2	Oxygen

PANSS	Positive and Negative Syndrome Scale
PET	Positron-emission-tomography
Rs-fMRI	Resting state fMRI
SA	Schizophrenia in state of acute psychosis
SD	Standard deviation
SM	Spatial map
SN	Salience network
SNR	Signal-to-noise-ratio
SR	Schizophrenia in state of psychotic remission
Tab.	Table
TC	Timecourse
VBM	Voxel-based morphometry
WHO	World Health Organization

Synopsis

Abstract

Context: Large-scale brain network theories provide a theoretical framework to investigate the functional architecture of the human brain and its behavioral relevance in health and disease, thus contributing to a better understanding of the underlying neurobiology of mental disorders. In particular, schizophrenia and major depressive disorder are characterized by aberrant intrinsic functional connectivity (iFC) within intrinsic connectivity networks (ICNs), including the default mode- salience- and central executive network (DMN, SN, CEN). The “triple network model of psychopathology” suggests that anterior insular (AI) dysfunction within the SN might contribute to aberrant modulation between DMN-mediated, self-related/internally-oriented and CEN-mediated, goal-directed/externally-oriented cognitive activity, giving rise to distinct disease-specific symptom dimensions such as hallucinations (“heightened salience of internal speech”) in schizophrenia and depressive ruminations (“heightened salience of self-referential thoughts”) in major depressive disorder.

Objective: The aim of this thesis was to investigate a direct association between insular dysfunction within the SN, aberrant DMN/SN/CEN interactions and severity of disease-specific symptoms in patients with schizophrenia and major depressive disorder.

Methods: Eighteen patients with schizophrenia in state of acute psychosis, 12 patients with schizophrenia in state of psychotic remission, 25 patients with major depressive disorder and three groups of age- and sex- matched healthy controls were assessed via resting-state functional magnetic resonance imaging (rs-fMRI), structural MRI and psychometric assessment. High-model-order independent component analysis (ICA) yielded 75 independent components (ICs), including subsystems of the DMN, SN and CEN. Intrinsic functional connectivity (iFC) within (intra-iFC) and between (inter-iFC) each subsystem of the DMN, SN and CEN were calculated, compared

between each patient group and the corresponding group of healthy controls and correlated with each other as well as with the severity of disease specific symptoms.

Results: All three patient groups showed aberrant intra-iFC within and aberrant inter-iFC between the DMN, SN and CEN. In particular, intra-iFC in the AI within the SN was decreased in all three groups and correlated with aberrant inter-iFC between DMN, SN and CEN and severity of disease specific symptoms.

Conclusion: Current results strongly support the “triple network theory of psychopathology” by providing first evidence for a direct association between insular dysfunction within the SN, functional DMN/SN/CEN reorganization and severity of disease-specific symptoms in patients with schizophrenia and major depressive disorder. These findings link current large-scale brain network theories with established cognitive models of psychopathology and contribute essentially to a better understanding of the functional neurobiology underlying mental disorders.

The essential findings of the current thesis were published as “Aberrant Dependence of Default Mode / Central Executive Network Interactions on Anterior Insular Salience Network Activity in Schizophrenia” in Schizophrenia Bulletin, 2013, in press and “Insular dysfunction reflects altered between-network connectivity and severity of negative symptoms in schizophrenia during psychotic remission” in Frontiers in Human Neuroscience, 2013, in press. A third manuscript entitled “Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder” is currently in review.

Zusammenfassung

Hintergrund: Large-scale Netzwerktheorien bieten ein theoretisches Konstrukt um die funktionelle Architektur des menschlichen Gehirns und deren behaviorale Relevanz bei Gesunden und Erkrankten zu untersuchen, um somit zu einem besseren Verständniss der Neurobiologie psychiatrischer Erkrankungen beizutragen. Insbesondere die Schizophrenie und die schwergradige Depression sind durch eine veränderte intrinsische Konnektivität innerhalb intrinsischer Konnektivitätsnetzwerke, wie dem Default Mode-, Salience- und Central Executive Network (DMN, SN, CEN) gekennzeichnet. Das „triple network model of psychopathology“ schlägt vor, dass eine Dysfunktion der anterioren Insel (AI) innerhalb des SN zu einer fehlerhaften Modulierung zwischen DMN-vermittelter, selbst-referenzieller/nach innen gerichteter und CEN-vermittelter, ziel-orientierter/nach außen gerichteter kognitiver Aktivität beiträgt, was zur Entstehung von krankheitsspezifischen Symptomen wie Halluzinationen („erhöhte Salienz innerer Sprache“) bei schizophrenen Patienten oder pathologisches Grübeln („erhöhte Salienz von selbst-referenziellen Gedanken“) bei depressiven Patienten beitragen könnte.

Ziel: Das Ziel der vorliegenden Arbeit war es, den direkten Zusammenhang zwischen insulärer Dysfunktion innerhalb des SN, abnormalen DMN/SN/CEN Interaktionen und dem Schweregrad von krankheitsspezifischen Symptomen bei Patienten mit Schizophrenie und schwergradiger Depression zu untersuchen.

Methoden: Achtzehn Patienten mit Schizophrenie im Status der akuten Psychose, 12 Patienten mit Schizophrenie im Status der Remission, 25 Patienten mit schwergradiger Depression und 3 Gruppen mit alters- und geschlechtskontrollierten gesunden Kontrollprobanden wurden mittels funktioneller Magnetresonanztomographie unter Ruhebedingungen (rs-fMRT), struktureller MRT und psychometrischer Erhebung untersucht. Eine hochauflösende Independent Component Analysis (ICA) ergab 75 unabhängige Komponenten (ICs), unter anderem Subsysteme des DMN, SN und CEN. Intrinsische funktionelle Konnektivität (iFC)

innerhalb (intra-iFC) und zwischen (inter-iFC) den Subsystemen des DMN, SN and CEN wurden berechnet, zwischen den Patientengruppen und den korrespondierenden Gruppen von gesunden Kontrollprobanden verglichen und sowohl miteinander, als auch mit dem Schweregrad von krankheitsspezifischen Symptomen korreliert.

Ergebnisse: Alle 3 Patientengruppen zeigten veränderte intrinsische funktionelle Konnektivität innerhalb und zwischen den Subsystemen des DMN, SN und CEN. Insbesondere war in allen 3 Gruppen die Konnektivität in der anterioren Insel innerhalb des SN verringert und korrelierte mit der abnormen Konnektivität zwischen DMN, SN und CEN und dem Schweregrad der krankheitsspezifischen Symptomatik.

Schlussfolgerung: Die Resultate der vorliegenden Arbeit stützen die "triple network theory of psychopathology", indem sie erste Evidenz für einen direkten Zusammenhang zwischen insulärer Dysfunktion innerhalb des SN, einer funktionellen Reorganisation des DMN, SN und CEN sowie dem Schweregrad von krankheitsspezifischen Symptomen bei Patienten mit Schizophrenie und schwergradiger Depression liefern. Diese Befunde stellen einen Zusammenhang zwischen modernen large-scale Netzwerktheorien und traditionellen kognitiven Modellen her und leisten einen wesentlichen Beitrag zum besseren Verständnis der funktionellen Neurobiologie von psychiatrischen Erkrankungen.

Die wesentlichen Befunde der vorliegenden Arbeit wurden unter dem Titel "Aberrant Dependence of Default Mode / Central Executive Network Interactions on Anterior Insular Salience Network Activity in Schizophrenia" in Schizophrenia Bulletin, 2013, in press, sowie unter dem Titel "Insular dysfunction reflects altered between-network connectivity and severity of negative symptoms in schizophrenia during psychotic remission" in Frontiers in Human Neuroscience, 2013, in press, veröffentlicht. Ein drittes Manuskript mit dem Titel "Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder" befindet sich gegenwärtig im Review.

Graphical abstract

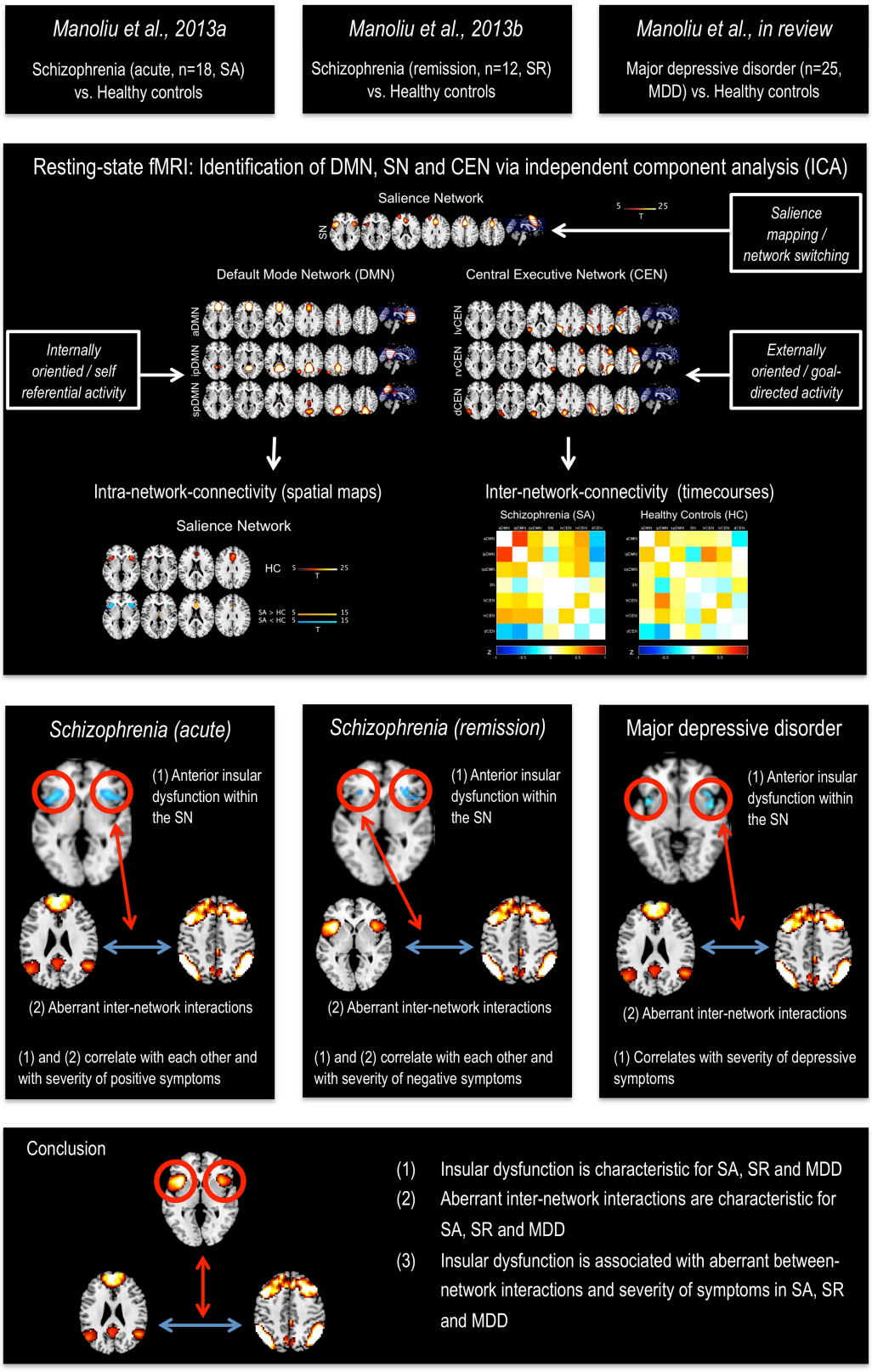

Figure 1. Synopsis of the three studies, which are part of the current thesis (Manoliu et al., 2013a); (Manoliu et al., 2013b); (Manoliu et al., in review).

1. Introduction

1.1. Motivation of the current thesis

Mental disorders are characterized by aberrant thinking, volition, feeling and acting and can reach such a severity that the patient´s social, occupational, and psychological functioning is severely compromised (American Psychiatric Association, 2000). According to the World Health Organization´s “global burden of disease study 2010” , mental disorders are becoming more and more frequent, currently accounting for 22,7% of years lived with disease, regardless of age, gender, social status or georgraphical origin (YLD, (Vos et al., 2012)). Due to their remarkable severity, disabling nature and high incidence and, as a consequence, high socioeconomic relevance (Murray et al., 2012), two distinct mental disorders are of particular interest: schizophrenia (van Os and Kapur, 2009) and major depressive disorder (MDD) (Donohue and Pincus, 2007). However, the neurobiological mechanisms mediating deficits in processing of emotions and cognition and therefore possibly underlying mental disorders are still unknown.

With the rise of modern neuroimaging, it has become possible for the first time to investigate the neuronal correlates of mental disorders in patients in a mostly non-invasive way in-vivo (Bandettini, 2012a). Several techniques, including electroencephalography (EEG), electrocorticography (ECoG), magnetoencephalography (MEG) and positron emission tomography (PET) contributed significantly to our understanding of the functional architecture of the human brain and how brain activity mediates cognitive states and processes (Raichle, 2009). However, a major breakthrough occurred in the early nineties, when two research groups obtained first successful results applying a newly discovered method called “functional magnetic resonance imaging” (fMRI) – a novel and promising approach, which measures the endogenous blood oxygenation level dependent (BOLD) signal to indirectly estimate neuronal activity in a fast, non-invasive and

surprisingly robust way (Bandettini, 2012a). During the first 10 to 15 years of fMRI research, studies have been focusing mainly on measuring brain activity during various tasks – from simple visual stimuli to intricate cognitive tasks (Raichle and Snyder, 2007). By contrasting the brain´s activity patterns during task with its activity patterns during task-related control conditions including rest, which is a condition with no imposed stimuli or other psychologically salient events (Snyder and Raichle, 2012), an increasing number of research groups aimed to map distinct activity patterns representing functional subdivisions of the human brain, each supporting specific neurocognitive functions (“neurocognitive subtraction”) (Raichle, 2009).

Over the last couple of years, however, attention has shifted from investigating the brain´s activity during cognitive tasks towards explicitly exploring the brains activity during the resting state (Beckmann, 2012). This paradigm shift occurred due to 2 particular reasons: (1) Since the brain is consuming over 80% of it´s energy during rest (Shulman et al., 2004), it has been suggested that even during rest, the brain is highly active (Gusnard et al., 2001). (2) As early as in 1995, it has been demonstrated that the brain displays specific patterns of activity representing it´s basic functional architecture (Biswal et al., 1995) during rest. In more detail, it has been shown that the brain is organized in functional intrinsic connectivity networks (ICNs), which are characterized by synchronous fluctuations of activity across different brain regions and subserve the processing and maintenance of sensory, motoric and cognitive functions (Biswal et al., 2010). Since these brain regions are frequently divided by relatively long distances and represent the brains activity on a larger system scale, they have been also referred to as “large-scale brain networks” (Bressler and Menon, 2010).

Three distinct ICNs have been suggested to play a crucial role in the processing and evaluation of internal and external stimuli and have therefore been defined as “core cognitive networks” (Uddin et al., 2011): the default mode network (DMN), the salience network (SN) and the

central executive network (CEN). The DMN, which comprises the ventromedial prefrontal cortex, the posterior cingulate cortex, bilateral inferior parietal cortex and the middle temporal lobe, is involved in self-related / internally oriented processes (Buckner et al., 2008). The CEN, which comprises primarily the dorsolateral prefrontal cortex and posterior parietal cortex, is involved in goal-directed / externally oriented tasks (Fox and Raichle, 2007). The SN includes the anterior insular cortex (AI) and dorsal anterior cingulate cortex and is involved in the initiation and maintenance of salience mapping, thus contributing to the evaluation of the importance of incoming stimuli (Seeley et al., 2007). Furthermore, the SN modulates the interaction between the internally oriented DMN and the externally oriented CEN, thus allowing a situation- and context-sensitive engagement and disengagement of appropriate ICNs (Sridharan et al., 2008); (Menon and Uddin, 2010).

Recently, it has been proposed that a reorganization of these large-scale networks might be a common feature of several psychiatric disorders, including schizophrenia and MDD (Menon, 2011). In particular, structural and functional anomalies within the AI have frequently been reported in patients with schizophrenia (Murray et al., 2008); (Ellison-Wright et al., 2008); (Ellison-Wright and Bullmore, 2009); (Palaniyappan and Liddle, 2012) and MDD (Strigo et al., 2008); (Horn et al., 2010); (Sliz and Hayley, 2012); (Diener et al., 2012); (Hamilton et al., 2013). The AI is a crucial node of the SN (Seeley et al., 2007) and has been demonstrated to be the main driving instance for the modulation of DMN/CEN interactions in healthy individuals (Sridharan et al., 2008). Therefore, AI dysfunction might lead to an aberrant modulation of DMN-mediated, internally oriented cognitive processes and CEN-oriented, externally-oriented cognitive processes, possibly underlying distinct psychopathological symptom dimensions, including patients´ difficulties to distinguish whether perceived stimuli are externally or internally generated (e.g. in schizophrenia (Palaniyappan and Liddle, 2012)), or to disengage persistent, negative-biased self-related cognitive processes (e.g. in MDD (Hamilton et al., 2013)). Consequently, Vinod Menon

postulated a unified large-scale brain network model possibly explaining cognitive and affective symptoms in mental disorders in terms of modern intrinsic network theories: the “triple network model of psychopathology” (Menon, 2011). According to this model, insular dysfunction within the SN leads to abnormal salience mapping and disrupted DMN/CEN interactions, causing aberrant recruitment of self-referential DMN- and goal-directed CEN-activity and thus explaining typical symptom dimensions in severe mental disorders, such as schizophrenia and MDD (Menon, 2011).

The aim of this thesis was to investigate, whether insular dysfunction within the SN was present in patients with schizophrenia and MDD and whether potential insular dysfunction was associated with a functional reorganization within and between the DMN, SN and CEN and severity of disease-specific symptoms. The evidence of a potential reorganization of large-scale ICNs might contribute to our better understanding of the neurobiology of schizophrenia and MDD, especially regarding potential similarities and differences in their etiopathology, and even represent a first step towards a neuroimaging-based biomarker for mental disorders.

In order to better understand the hypothesis of the current thesis, the methodological background of the applied methods as well as the neurobiology of schizophrenia and MDD will be presented in more detail in the next section. The first three subsections will present a short history of the emergence of modern fMRI research from the first description of the BOLD signal over the serendipitous discovery of resting-state functional connectivity networks to the formulation of modern large-scale network models of psychopathology. The following two sections will depict the neurobiology of schizophrenia and MDD, particularly in the context of modern neuroimaging.

1.2. Theoretical and methodological background

1.2.1. From BOLD-signal to resting-state functional connectivity

Neuronal activity requires energy, which is provided by the transport of glucose and hemoglobin-bound oxygen in the blood (Shulman et al., 2004). Since hemoglobin (Hb) is diamagnetic in its oxygenated state but paramagnetic in its deoxygenated state (Pauling and Coryell, 1936), Ogawa and colleagues could demonstrate in the early 1990s that, by applying distinct MRI sequences, the level of blood oxygenation could be depicted in image contrasts (Ogawa et al., 1990b) and, most importantly, is related to neuronal activity and change of functional brain states in vivo (Ogawa et al., 1992). In more detail, neuronal activity induces several physiological responses in the adjacent blood vessels ("neurovascular coupling" (Buxton et al., 2004)), leading to an increased cerebral blood flow and therefore to an increased amount of oxygenated Hb compared to deoxygenated Hb ("haemodynamic response" (Buxton, 2012)). Since the measured signal depended on the paramagnetic properties of deoxygenated Hb, Ogawa named the resulting differences in signal on T2*-weighted images "blood oxygenation level dependent" (BOLD) contrast (Ogawa et al., 1990a).

The first 10 to 15 years, studies assessed the BOLD-signal in healthy participants and patients with various disorders to investigate possible aberrant neuronal responses to a broad range of stimuli and/or during numerous tasks, ranging from simple sensorimotor- to elaborate cognitive tasks (Bandettini, 2012a). However, 2 central findings lead to the insight that the human brain might display functional meaningful activity even during rest. (1) Although the human brain represents only 2% of our body mass, it consumes about 20% of the body´s oxygen (Shulman et al., 2004). Over 80% of the used energy supports cycling of neurotransmitters (predominately glutamate and GABA) and is therefore linked to ongoing neuronal firing during the resting state (Shulman et al., 2004). Furthermoe, oxygen consumption increases only by

approximately 5% when subjects performed cognitive tasks (Fox et al., 1988), strongly suggesting that the human brain exhibits ongoing activity regardless of any observable behaviour (Snyder and Raichle, 2012). (2) In 1995, a young graduate student named Bharat Biswal published first results of his thesis, demonstrating for the first time, that a fMRI signal measured while participants were not engaging any cognitive task yielded significant correlations between brain regions, which are functionally related to each other (i.e. the left and right sensorimotor cortices), suggesting that the brain, even during rest, yielded some meaningful activity patterns (Biswal et al., 1995). Since the term "functional connectivity" already was introduced in the field of fMRI research by Karl Friston, Biswal and colleagues decided to name this newly discovered phenomenon "resting state functional connectivity" (Biswal, 2012).

1.2.2. From resting-state functional connectivity to intrinsic connectivity networks

Initially, the discovery of Biswal received mixed reactions, including advise from senior graduate students in his lab to abandon this unpromising field of resarch and the statement of a senior research fellow that "this is what was to be expected if graduate students were left to run their own experiments" (Biswal, 2012). However, after several studies ruled out the possibility that the resting-state BOLD signal is caused by non neuronal artefacts, such as motion and cardiac pulsation (Snyder and Raichle, 2012), Greicius and colleagues demonstrated in 2003 the great potential of resting state fMRI by presenting the first analysis of the default mode network, an intrinsic connectivity network maintaining self-referential cognitive activity (Buckner et al., 2008) by extracting the BOLD-signal out of one region of the posterior cingulate cortex and correlating it with the BOLD-signal time series in all other brain regions (Greicius et al., 2003). Today, numerous similar patterns of coherent BOLD-signal fluctuation between remote brain regions have been described in the human brain and are referred to as "resting state

networks" or, more correctly, as "intrinsic connectivity networks" (Laird et al., 2011).

In general, intrinsic connectivity networks (ICNs) represent spontaneous BOLD-signal fluctuations within a slow frequency range of < 0.01 Hz (Niazy et al., 2011). It is important to note that ICNs identified during rest display close correspondance to activity patterns identified during tasks (Smith et al., 2009), indicating that intrinsically coherent functional networks are also engaged during cognition (Menon, 2011). Furthermore, functional connectivity patters during rest resemble structural connectivity maps, suggesting that ICNs might represent a framework for neuronal activity (Keller et al., 2011). Indeed, it has been recently demonstrated that low-frequency fluctuations of BOLD-signal are correlated with the pattern and magnitude of corticocortical evoked potentials, strongly supporting the notion that ICNs represent the basic functional architecture of the brain and are involved in maintaining and updating the brain´s repertoire of functional responses (Keller et al., 2011). Finally, ICNs are consistent over individual subjects (Damoiseaux et al., 2006), species (Vincent et al., 2007) and states, including sleep (Liu et al., 2008) and anaesthesia (Greicius et al., 2008), and are detectable in infants (Fransson et al., 2011), newborn (Fransson et al., 2009) and, since recently, even in fetuses in utero (Schopf et al., 2012a); (Schopf et al., 2012b). However, ICNs are selectively altered in mental disorders (Sorg et al., 2007); (Northoff et al., 2011); (Williamson and Allman, 2012), suggesting that investigation of ICNs in patients with psychiatric disorders might represent a promising approach to explore the neurobiology of the underlying disease (Menon, 2011).

Currently, two complementary methods are available to investigate resting state functional connectivity: seed based correlation analysis (SCA) and independent component analysis (ICA) (Cole et al., 2010). In SCA, the timecourse of the BOLD-signal within distinct a-priori selected voxels is extracted and correlated with the time course in all other voxels in the brain, providing the possibility to obtain straight-forward answers

to a-priori formulated hypotheses (Biswal et al., 1995); (Greicius et al., 2003); (Fox et al., 2005). Although SCA has become very popular due to its simplicity, several limitations have to be taken into consideration, including the requirement of extensive preprocessing since the raw BOLD timecourse contains also non-neuronal sources (Snyder and Raichle, 2012) and the extreme variability of results dependent on the a-priori selection of the seed region (Cole et al., 2010). ICA on the other hand is a data driven method which is able to identify statistical independent sources from multivariate data (Beckmann, 2012). In particular, ICA decomposes the resting state fMRI data into spatial independent components (ICNs) reflecting patterns of synchrounous activity, each characterized by a specific timecourse (TC) and a specific spatial map (SM) reflecting all voxels associated with the TC (Calhoun et al., 2001). Since ICA works completely data-driven, the aforesaid disadvantages of SCA do not apply: signals from various non-neuronal sources are identified as seperate components, and no a-prior selection of regions of interest is required, making ICA free of the subjective bias of manual region selection (Beckmann et al., 2005); (Cole et al., 2010). Presently, the number of described ICNs identified via ICA is rapidly increasing: while in 2005, first ICA studies reported only few cortical ICNs, including the default mode network, attention networks as well as motor- and somatosensory networks (Beckmann et al., 2005); (De Luca et al., 2006); (Damoiseaux et al., 2006), recent studies described 28 ICNs (Allen et al., 2011), including subcortical ICNs (Robinson et al., 2009); (Ystad et al., 2010); (Sorg et al., 2013) and functional subsystems of known ICNs (Abou-Elseoud et al., 2010). In general, described ICNs cover all cortical parts of the human brain, the cerebellum and subcortical structures, such as the striatum, hippocampus, amygdala and thalamus and match well-known patterns of cortical activity during tasks (Laird et al., 2011). Currently, ICNs are classified into ICNs similar to primary systems, such as the visual, auditory or sensorimotor systems, and ICNs resembling activity patterns associated with higher cognitive functions, including emotion processing and -regulation, mediation of attention and self-related / externally

oriented cognitive processing (Allen et al., 2011). Especially those ICNs potentially representing cognitive subsystems are of particular interest regarding the investigation of cognitive dysfunction in mental disorders.

1.2.3. From intrinsic connectivity networks to large-scale brain network models of psychopathology

The knowledge about ICNs offers a promising paradigm to investigate the neurobiology underlying mental disorders (Menon, 2011). Most notably, three ICNs are of particular interest regarding the understanding of cognitive dysfunction and are therefore subsumed under the expression “core cognitive networks” (Uddin et al., 2011): the default mode network (DMN), salience network (SN) and central executive network (CEN). The DMN comprises mainly the ventromedial prefrontal cortex and posterior cingulate cortex as well as the angular gyrus and medial temporal lobe and is involved in self-referential cognitive activity, autobiographcal memory and social-oriented cognitive processes (Buckner et al., 2008). The CEN comprises primarily the dorsolateral prefrontalcortex and the posterior parietal cortex and shows activation during goal-directed, cognitively demanding tasks, including decision making and working memory processing (Fox and Raichle, 2007). The SN comprises mainly the anterior insular cortex and dorsal anterior cingulate cortex and mediates the evaluation of external and/or internal salient stimuli and events, such as emotions, pain and interoception (Seeley et al., 2007). Together, these three core cognitive networks form a system of stimulus-dependent agonism and antagonism: while DMN activity increases during self-referential tasks and decreases during goal-directed activity, the CEN displays opposite activity, with activation during externally-directed processing and deactivation during internally-related evaluation (Raichle et al., 2001); (Greicius et al., 2003); (Greicius and Menon, 2004); (Raichle, 2011).

Recently, it has been demonstrated that the SN, more specifically the anterior insular cortex (AI) within the SN, plays a pivot role in modulating

the interactions between the DMN and CEN and therefore between the processing and maintenance of internally-oriented and externally-oriented cognitive processes (Sridharan et al., 2008). In particular, the AI is involved in evaluating the salience of incoming stimuli and initiating the adequate behavioral response via engagement of appropriate networks (Menon and Uddin, 2010). However, AI dysfunction within the SN might induce deviant salience mapping and cause aberrant engagement and disengagement of appropriate networks, giving rise to cognitive deficits and inadequate behavioral responses (Menon, 2011). Based on this notion, the "triple network model of psychopathology", a large-scale network model of mental dysfunction, suggests that aberrant interactions between DMN, SN and CEN, possibly explained by insular dysfunction with the SN, might underlie several mental disorders (Menon, 2011), especially schizophrenia (Palaniyappan and Liddle, 2012) and MDD (Hamilton et al., 2013). The aim of the current thesis was to investigate the interactions within and between the DMN, SN and CEN in patients with schizophrenia and MDD to find evidence for an association between insular dysfunction, DMN/SN/CEN reorganization and disease-specific symptom dimensions in mental disorders according to the postulated "triple network model of psychopathology".

1.2.4. Neurobiology of Schizophrenia

Schizophrenia is a severe mental disorder affecting numerous facets of behaviour, thinking and emotion and presents with characteristic symptoms, such as delusions, hallucinations, disorganization and negative symptoms (e.g. blunted affect and emotional withdrawal) (Bäuml, 2008). The lifetime prevalence of schizophrenia is 1% and rises to 2.3%, if other psychotic disorders, such as delusional disorder and brief psychotic disorder, are also taken into account (Perala et al., 2007). Furthermore, men show a slightly higher risk to develop schizophrenia compared to women with a incidence risk ratio of 1.42:1 (Aleman et al., 2003). Although several risk factors for developing schizophrenia have been identified, including various genetic and

environmental aspects, such as urbanicity (Pedersen and Mortensen, 2001), migration (Cantor-Graae and Selten, 2005) as well as obstetric and perinatal complications (Geddes and Lawrie, 1995); (Verdoux et al., 1997); (Geddes et al., 1999), the etiology of schizophrenia is still unclear (Tandon et al., 2008). According to the vulnerability-stress-model, it is currently assumed that these “vulnerability factors” might increase the probability of the manifestation of schizophrenia, which is triggered by internal/external stressors (Jones and Fernyhough, 2007); (Nuechterlein et al., 1994); (Yank et al., 1993).

With the rise of modern neuroimaging, a fast increasing number of studies explored the brain´s structural, neurochemical and functional properties in patients with schizophrenia (van Os and Kapur, 2009). Regarding neurochemical anomalies, several studies demonstrated that patients with schizophrenia show increased dopaminergic neurotransmission (Keshavan et al., 2008) within the striatum. In particular, this increase is located primarily presynaptic, affecting the synthesis capacity, the release, and the baseline levels of striatal synaptic dopamine (Howes et al., 2012); (Fusar-Poli and Meyer-Lindenberg, 2013a); (Fusar-Poli and Meyer-Lindenberg, 2013b). Furthermore, the increased levels of dopamine within the striatum are associated with the severity of psychosis and even present in individuals with prodromal psychotic symptoms (Howes et al., 2009), presumably explaining the improvement of psychotic symptoms when treated with antipsychotics, which block dopamine D2/3 receptors (Kapur et al., 2006). Taken together, these findings support the dopamine-hypothesis of schizophrenia, a model linking disease-specific symptom dimensions to aberrant dopaminergic neurotransmission (Carlsson, 1977); (Carlsson and Carlsson, 1990); (Carlsson, 2006). Regarding the structure of the brain, several studies demonstrated widely-distributed decreased gray matter (GM) along with enlarged ventricles and aberrant architecture of white matter tracts between distinct brain regions as measured via diffusion-tensor imaging (DTI) (Ellison-Wright et al., 2008); (Glahn et al., 2008); (Ellison-Wright and Bullmore, 2009); (Palaniyappan et al., 2011).

Naturally, aberrant structural and neurochemical properties in patients with schizophrenia lead to abnormal functional patterns within and between several brain regions forming functional networks mediating important cognitive processes (van Os and Kapur, 2009). Indeed, the idea that aberrant connectivity between widely-distributed brain regions in contrast to locally isolated lesions might underlie schizophrenia was proposed already over one century ago by Carl Wernicke (Wernicke, 1906), finding expression in the commonly used term “schizophrenia”, introduced by Eugen Bleuler (Bleuler, 1911) to emphasize the “splitting” of different cognitive subsystems in patients with schizophrenia (Stephan et al., 2006). However, the investigation of this notion was not possible until the introduction of electrophysiological techniques and, most notably, the advent of fMRI in the early 1990s (van Os and Kapur, 2009). Since then, numerous fMRI studies demonstrated aberrant functional connectivity during both task (Garrity et al., 2007) and rest (Whitfield-Gabrieli and Ford, 2012) within and between distinct brain regions forming ICNs in patients with schizophrenia. However, it is to note that the presented findings were seldom unidirectional; instead, findings were remarkably heterogeneous, showing both increased and decreased connectivity within ICNs, therefore leading to the insight that schizophrenia might be rather a “dysconnectivity syndrome” than a “disconnectivity syndrome” (the greek prefix “δυσ-“ / “dys”- means bad or ill, while the latin prefix “dis-” means apart (Stephan et al., 2009)). In particular, functional anomalies have been reported within and between the internally oriented DMN and the externally oriented CEN during both task and rest (Garrity et al., 2007); (Whitfield-Gabrieli et al., 2009); (Minzenberg et al., 2009); (Rotarska-Jagiela et al., 2010); (Skudlarski et al., 2010); (Hasenkamp et al., 2011), indicating that impaired coordination of self-related and goal-directed cognitive processes might underlie schizophrenia (Williamson, 2007). As already described in the previous section, DMN/CEN interactions are mainly modulated by the anterior insular cortex (AI) within the SN in healthy subjects (Sridharan et al., 2008). Since several studies reported structural and functional anomalies within the AI in patients with schizophrenia (Ellison-Wright et

al., 2008); (Murray et al., 2008); (Ellison-Wright and Bullmore, 2009); (White et al., 2010); (Palaniyappan et al., 2012), it has been suggested that AI dysfunction might cause disrupted DMN/CEN interactions and aberrant salience mapping within the SN, underlying disease-specific symptoms in schizophrenia (Palaniyappan and Liddle, 2012). However, evidence is still missing whether and how insular dysfunction within the SN is associated with aberrant DMN/CEN interactions and severity of symptoms in patients with schizophrenia.

1.2.5. Neurobiology of major depressive disorder

Major depressive disorder (MDD) is a disabling mental disorder associated with a intense negative interpretation of the environment, oneself and one´s own future (Beck, 1967). It is characterized by at least one major depressive episode (MDE), which presents frequently with depressed mood, loss of interest or pleasure, feelings of worthlessness and guilt, including frequent ruminations, cognitive symptoms and recurrent thoughts of death (American Psychiatric Association, 2000). With a lifetime prevalence of 16.2%, MDD is a common and widely distributed mental disorder (Kessler et al., 2003). Although MDD represents a major public health problem due to increased functional disability and mortality in patients (Donohue and Pincus, 2007), the etiopathology is yet unclear. According to the diathesis-stress-model of MDD (Monroe and Simons, 1991), it is assumed that distinct internal and/or external stressors might trigger the onset of MDD against the background of an individual level of vulnerability, which results from various factors, including genetic factors (Kendler et al., 2002); (Kendler et al., 2006) and early life experiences (Slavich et al., 2011); (Willner et al., 2012).

Over the last decades, numerous imaging studies investigated possible neurochemical, structural and functional alterations possibly underlying MDD. One of the most prominent neurobiological model of MDD is the monoamine hypothesis, suggesting that MDD is associated with a

relative and/or absolute deficit of monoamines particularly Noradrenaline (NA) and serotonin (5-HT) in functional relevant brain areas (Hirschfeld, 2000). This model is further supported by the fact, that most antidepressant drugs prevent the reuptake of monoamines, therefore increasing the synaptic concentration of 5-HT and/or NA and leading to an improvement of symptoms (Willner et al., 2012). However, it is to note that the actual antidepressant effect of these drugs might be associated with the the proneurogenic effect induced by inhibition of the reuptake of 5-HT and NA, which, in turn, increases the levels of the neurotrophin BDNF (Brain-derived neurotrophic factor) via activation of intracellular second messangers (Tardito et al., 2006), therefore inducing neurogenesis (Boldrini et al., 2009); (Boldrini et al., 2012). Indeed, several MRI studies reported consistently widely-distributed decreased gray matter in patients with MDD (Bora et al., 2012), which was associated with severity of symptoms particularly within the hippocampus (Cheng et al., 2010).

Considering these structural and neurochemical anomalies, it seems hardly surprising that patients with MDD display aberrant functional connectivity during both task (Fitzgerald et al., 2008b); (Diener et al., 2012) and rest (Fitzgerald et al., 2008a); (Hamilton et al., 2013). Due to its relevance regarding the maintenance of self-referential cognitive processes, several studies investigated the DMN in patients with MDD, reporting aberrant de-activation during task (Sheline et al., 2009) and increased connectivity during rest (Greicius et al., 2007); (Broyd et al., 2009); (Posner et al., 2013), indicating that DMN mediated, internally related cognitive activity might be more sensitive to internal events than to external stimuli in patients with MDD (Hamilton et al., 2011b). Furthermore, DMN/CEN coordination has been shown to be altered in patients with MDD (Hamilton et al., 2011b) and to be linked with aberrant activation patterns of the anterior insular cortex within the SN, which, in turn, displays aberrant structural and functional connectivity in patients with MDD (Diener et al., 2012); (Sliz and Hayley, 2012). Therefore, it has been proposed that insular dysfunction within the SN

might explain deviant DMN/CEN interactions, possibly being associated with the lack of ability to disengage DMN-mediated processes, hence leading to the rise of disease-specific depressive symptoms. However, it is still unclear whether and how aberrant connectivity within the SN is associated with severity of symptoms and aberrant DMN/CEN interactions in patients with MDD.

1.3. Scientific Questions

According to the “triple network model of psychopathology” (Menon, 2011) and its implications for patients with schizophrenia (Palaniyappan and Liddle, 2012) and patients with MDD (Hamilton et al., 2013), following questions were formulated:

(1) Is insular dysfunction within the SN present in patients with schizophrenia and MDD?
(2) Are DMN/SN/CEN interactions altered in patients with schizophrenia and MDD?
(3) Are these potential findings related to each other and to the severity of disease-specific symptoms in patients with schizophrenia and MDD?

To investigate these questions, three different studies were performed in scope of this thesis, each assessing rs-fMRI, structural fMRI and psychometric characteristics in different patient populations and age- and sex-matched healthy controls (HC) applying a standardized methodological approach: The first study investigated ICNs in 18 patients with schizophrenia during state of acute psychosis (SA) and 20 HC (Manoliu et al., 2013a). The second study investigated ICNs in 12 patients with schizophrenia during state of remission, i.e. in absence of psychosis (SR), and 12 HC (Manoliu et al., 2013b). The third study investigated ICNs in 25 patients with MDD and 25 HC (Manoliu et al., in review). For graphical summary of all three studies, please see Fig. 1.

2. Methods

In general, this thesis consists of three studies investigating a potential relationship between insular dysfunction and aberrant between-network interactions in psychiatric disorders, including patients with schizophrenia during acute psychosis (Manoliu et al., 2013a), patients with schizophrenia during remission (Manoliu et al., 2013b) and patients with major depressive disorder (Manoliu et al., in review). Since all three studies were carried out within the framework of this thesis, identical methodological approaches developed specifically to investigate the potential reorganization within and between the DMN, SN and CEN have been applied in each study to ensure an adequate comparability between the studies, thus contributing to a better understanding of possible associations between insular dysfunction and aberrant inter-network connectivity in psychiatric disorders in general (Menon, 2011). In the following sections, the individual groups of participants will be presented separately for each study carried out in scope of this thesis. Subsequently, the methods used for data acquisition, data analysis and statistical analysis of the data will be presented in joint sections.

2.1. Participants

In general, all patients and all healthy controls provided informed consent according to the Human Research Committee guidelines of the Klinikum rechts der Isar, Technische Universitat München. Patients were recruited from the Department of Psychiatry, Klinikum Rechts der Isar, Technische Universität München. Controls were recruited by word-of-mouth advertising. All patients met criteria for their respective diagnosis according to DSM IV (American Psychiatric Association, 2000). The psychiatric interview was conducted according to the Structured Clinical Interview for DSM-IV (SCID-I (Spitzer et al., 1992)). The severity of disease-specific symptoms was assessed on the day of scanning via disease-specific psychometric assessment (Kay et al., 1987); (Spitzer et al., 1992); (Hamilton, 1960); (Beck et al., 1961) (see

below for detailed presentation of used psychometric tests and subjects´ clinical characterization). Furthermore, each participant´s complete medical history was assessed, including current and past internal and neurological diseases as well as intake of psychotropic medication or substance abuse. All participants underwent 10 min of rs-fMRI with the instruction to keep their eyes closed and not to fall asleep. It was verified that subjects stayed awake by interrogating via intercom immediately after the rs-fMRI scan. No patient had to withdraw during the scanning session. A subgroup of participants assessed in scope of this thesis was re-analyzed regarding independent scientific questions in scope of other studies and resulting dissertations (Sorg et al., 2013).

2.1.1. Patients with schizophrenia during psychosis and corresponding group of healthy controls

Eighteen patients with schizophrenia during state of acute psychosis and 20 age- and sex-matched healthy controls participated in the study. Patients met criteria for schizohrenia during state of acute psychosis in accordance to DSM-IV (American Psychiatric Association, 2000). Only patients between 18 and 60 years of age were included. Patients with schizoaffective disorder, bipolar disorder or major depressive disorder with psychotic symptoms were excluded. Further exclusion criteria were current or past neurological disorders, current or past systemic internal disorders, substance abuse and structural cerebral pathologies as revealed by structural MRI. All healthy controls were free of any current or past psychiatric, neurological or systemic disorder or psychotropic medication. On the day of scanning, severity of clinical symptoms was assessed with the Positive and Negative Syndrome Scale (PANSS, (Kay et al., 1987)). The global level of social, occupational and psychological functioning was assessed with the Global Assessment of Functioning Scale (Spitzer et al., 1992). Two out of 18 patients with schizophrenia during state of acute psychosis received no psychotropic medication at the timepoint of fMRI assessment. All other patients received psychotropic medication as presented in Tab. S1 in the

supplement (see also Tab. 1 for patients´ mean chlorpromazine-equivalent dose). Healthy controls received no medication at the timepoint of scanning.

Table 1. Demographic and clinical characteristics for patients with schizophrenia during acute psychosis and corresponding healthy controls.

	SA (n=18)	**HC** (n=20)	**SA vs. HC**[1]	
Measure	**Mean (SD)**	**Mean (SD)**	**T-score**	**p-value**
Age	35.33 (12.49)	34.00 (13.35)	0.317	0.753
Sex (m/f)	9 / 9	9 / 11		
PANSS				
Total	76.44 (18.45)	30.15 (0.67)	11.231	<0.001*
Positive	18.06 (5.74)	7.05 (0.22)	8.574	<0.001*
Negative	19.94 (8.11)	7.10 (0.45)	7.08	<0.001*
General	37.67 (9.93)	16.05 (0.23)	9.743	<0.001*
GAF	41.50 (11.55)	99.75 (1.12)	-22.478	<0.001*
CPZ	466.72 (440.49)			
Duration of illness [years]	7.00 (6.84)			

[1]two-sample t-test; *significant for p<0.05, Bonferroni-corrected for multiple comparisons. Abbreviations: SA, patients with schizophrenia during acute state of psychosis; HC, healthy control group; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning Scale; CPZ, chlorpromazine equivalent dose. Adapted table and legend taken from (Manoliu et al., 2013a).

2.1.2. Patients with schizophrenia during remission and corresponding group of healthy controls

Twelve patients with schizophrenia during state of remission and 12 age- and sex-matched healthy controls participated in this study. Out of 18 patients with schizophrenia during state of acute psychosis, 12 patients agreed to participate in a second assessment of resting-state fMRI during state of remission. All of them met criteria for schizophrenia during state of remission in accordance to DSM-IV (American Psychiatric Association, 2000). Further inclusion- and exclusion criteria as well as clinical characterization for the second scan follow exactly the description for patients with schizphrenia during state of acute psychosis. Four out of 12 patients with schizophrenia during state of remission received no psychotropic medication at the timepoint of fMRI

assessment. All other patients received psychotropic medication as presented in Tab. S2 in the supplement (see also Tab. 2 for patients´ mean chlorpromazine-equivalent dose). Healthy controls received no medication at the timepoint of scanning.

Table 2. Demographic and clinical characteristics for patients with schizophrenia during remission and corresponding healthy controls.

	SR (n=12)	**HC** (n=12)	**SR vs. HC**[1]	
Measure	**Mean (SD)**	**Mean (SD)**	**T-score**	**p-value**
Age	32.50 (10.04)	34,67 (12,25)	-0.474	0.640
Sex (m/f)	4 / 8	4 / 8		
PANSS				
Total	53.09 (14.56)	30.41 (1.44)	5.379	<0.001*
Positive	12.09 (3.75)	7.08 (0.29)	4.824	<0.001*
Negative	13.08 (5.95)	7.17 (0.58)	3.431	0.002*
General	27.36 (8.69)	16.17 (0.58)	4.458	<0.001*
GAF	59.09 (15.14)	99.17 (2.89)	-9.013	<0.001*
CPZ	207.42 (198.12)			
Duration of illness [years]	4.11 (3.29)			

[1]two-sample t-test; *significant for p<0.05, Bonferroni-corrected for multiple comparisons. Abbreviations: SR, patients with schizophrenia during state of remission; HC, healthy control group; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning Scale; CPZ, chlorpromazine equivalent dose. Table and legend taken from (Manoliu et al., 2013b).

2.1.3. Patients with major depressive disorder and corresponding group of healthy controls

Twenty-five patients with major depressive disorder and 25 age- and sex-matched healthy controls participated in this study. Patients met criteria for major depressive disorder in accordance to DSM-IV (American Psychiatric Association, 2000). It is to note that 14 out of 25 patients had a psychiatric co-morbidity, including generalized anxiety disorder (n=6), somatization disorder (n=3) and avoidant or dependent personality disorder (n=5). Patients with schizoaffective disorder, bipolar disoder or schizophrenia were excluded. Further exclusion criteria were current or past neurological disorders, current or past systemic internal disorders, substance abuse and structural cerebral pathologies as

revealed by structural MRI. All healthy controls were free of any current or past psychiatric, neurological or systemic disorder or psychotropic medication. On the day of scanning, severity of clinical symptoms was assessed with the Hamilton Rating Scale for Depression (HAM-D, (Hamilton, 1960)) as well as the Beck Depression Inventory (BDI, (Beck et al., 1961)). The global level of social, occupational, and psychological functioning was assessed with the Global Assessment of Functioning Scale (GAF, (Spitzer et al., 1992)). One out of 25 patients with major depressive disorder received no psychotropic medication at the timepoint of fMRI assessment. All other patients received psychotropic medication as presented in Tab. S3 in the supplement. Healthy controls received no medication at the timepoint of scanning. See Tab. 3 for detailed presentation of participants´ characterization.

Table 3. Demographic and clinical characteristics for patients with major depressive disorder and corresponding healthy controls.

	MDD (n=25)	**HC** (n=25)	**MDD vs. HC**[1]
Measure	**Mean (SD)**	**Mean (SD)**	**p-value**
Age	48.76 (14.83)	44.08 (14.78)	>0.05
Sex (m/f)	12 / 13	11 / 14	
GAF	49.80 (10.53)	99.50 (1.10)	<0.001*
HAM-D	22.12 (7.06)	0	<0.001*
BDI	24.08 (6.31)	0	<0.001*
Duration of illness [years]	16.72 (10.20)		
Duration of current MDE [weeks]	16.56 (6.62)		
Number of MDEs	5.56 (2.47)		

[1]two-sample t-test; *significant for p<0.05, Bonferroni-corrected for multiple comparisons. Abbreviations: MDD, patients with major depressive disorder; HC, healthy control group; SD, standard deviation; GAF, Global Assessment of Functioning Scale; HAM-D, Hamilton Depression Rating Scale; BDI, Beck Depression Inventory; MDE, major depressive episode. Adapted table and legend taken from (Manoliu et al., in review).

2.2. Psychometric assessment

Global Assessment of Functioning (GAF). The GAF is a numeric scale representig the psychological, social and occupational functioning of the clinically assessed individual. The score ranges from 0 (no adequate information) to 100 (superior functioning) and is given in intervals of 10 points (American Psychiatric Association, 2000). The GAF was assessed in all participants.

Positive and Negative Syndrome Scale (PANSS). The PANSS is a numeric scale used to clinically assess the severity of symptoms in patients with schizophrenia. 7 positive symptoms (e.g. delusions, conceptual disorganization, hallucination), 7 negative symptoms (e.g. blunted affect, emotional withdrawal) as well as 16 general symptoms (e.g. anxiety, lack of judgement and insight) are rated within a range from 1 (not existend) to 7 (very severe). Subsequently, the subscores are summed up for each subscale, resulting in a total score for positive, negative and general symptoms. The total score of the PANSS ranges from 30 to 210 (Kay et al., 1987). The PANSS was assessed in patients with schizophrenia and corresponding groups of healthy controls.

Hamilton Rating Scale for Depression (HAM-D). The HAM-D is a numeric scale used to clinically assess the severity of depressive symptoms, including depressed mood, suicidal tendency, anxiety and disrupted sleep (Williams, 1988). In contrast to the original version, which yielded 17 items, a newer version yielding 21 items was used to assess severity of symptoms in patients with MDD. Each of these 21 items is rated by a clinician according to the severity, ranging from 0 (absence of the respective symptom) to 2, 3 or 4 points (severe presence of the respective symptom) dependent on the respective item. Subsequently, the subscores are summed up, resulting in a total score ranging from 0 to 66 (Hamilton, 1960). The HAM-D was assessed in patients with major depressive disorder and corresponding healthy controls.

Beck Depression Inventory (BDI). In contrast to the HAM-D, the BDI is a numeric self-rating scale and therefore performed by the individuals themselves instead of by the clinicians. Each of the 21 items measuring the severity of different depressive symptoms, including depressed mood, cognitive and physical symptoms (Burkhart et al., 1984) is rated within a range of 0 (absence of the respective symptom) to 3 points (severe presence of the respective symptom), thus resulting in a total score range of 0 to 63 (Beck et al., 1961). The BDI was assessed in patients with major depressive disorder and corresponding healthy controls.

2.3. Data assessment

MRI was performed on a 3 T MR scanner (Achieva, Philips, Netherland) using an 8-channel phased-array head coil (Manoliu et al., 2013a); (Sorg et al., 2013).

Structural MRI. T1-weighted structural images were acquired by using a magnetization-prepared rapid acquisition gradient echo sequence (TE = 4 ms, TR = 9 ms, TI = 100 ms, flip angle = 5°, FoV = 240 x 240 mm², matrix = 240 x 240, 170 slices, voxel size = 1 x 1 x1 mm³). T1-weigted images were subsequently used for analyses of structural properties of patients with schizophrenia, patients with major depressive disorder and healthy controls as well as for co-registration with the functional MRI images.

Functional MRI. FMRI images were acquired by using a gradient echo EPI sequence (TE = 35 ms, TR = 2000 ms, flip angle = 82°, FoV = 220 x 220 mm², matrix = 80 x 80, 32 slices, slice thickness = 4 mm, and 0 mm interslice gap; 300 volumes)

2.4. Data analysis

2.4.1. Preprocessing of structural and functional MRI data

The term preprocessing refers to several computational procedures applied to rs-fMRI data after data acquisition and before performing statistical analyses in order to remove artificial induced noise from the raw data (Huettel et al., 2009). In the current thesis, the software package „Statistical Parametric Mapping“ (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm/; (Friston, 2007)) was used for preprocessing of the rs-fMRI data. In the following, all performed steps will be presented in extensive detail.

Quality assurance. Artificial induced fluctuations of the MR signal can have various origins, including motion of the participant due to physiological activity (e.g. respiration or cardiac activity) or general restlessness during scanning and inconsistent functioning of the MRI-scanner, thus worsening the signal-to-noise ratio (SNR, (Huettel et al., 2009)). To ensure that the data quality was not affected by these possible effects, rs-fMRI data was tested for excessive head motion. Data with excessive head motion (translation > 3 mm or rotation > 1,5° between each time point or on a whole-run basis) were excluded from this study (Manoliu et al., 2013a). However, no participant had to be excluded due to artifacts induced by head motion. Since between-group differences in motion or SNR can artificially induce false positive results in consecutive statistical analyses investigating potential differences in functional connectivity between groups (Van Dijk et al., 2012), movement parameters (translational and rotational movements) as well as SNR were tested for between group differences performing two-sample t-tests, yielding no significant results ($p > 0.05$).

Coregistration. The term coregistration refers to the alignment of images originating from different scan modalities (Ashburner and Friston, 1997); (Ashburner and Friston, 2005). In the current thesis, functional and

structural MRI images were assessed successively during the scan. Since movement of the participants between the different scan sequences cannot be excluded, the functional and structural MRI images were coregistered using SPM8 for each participant.

Spatial normalization. Regarding morphologic features such as size and shape, the human brain shows a strikingly high inter-subject variability. The term normalization refers to the warping of each individual subject´s brain into a stereotaxic standard space to enable the comparability between different individuals and studies (Ashburner and Friston, 1999). In the present thesis, both functional and structural MRI data were warped into MNI (Montreal Neurological Institute) space derived from the brains of over one hundred healthy adults (Evans et al., 2012) via SPM8.

Spatial smoothing. The term spatial smoothing refers to the application of a Gaussian (normally distributed) filter to all voxels of the fMRI data to improve the validity of consecutive performed statistical tests and to increase the SNR (Kiebel et al., 1999). In the current study, all voxels were smoothed with a Gaussian Kernel with 8 mm at full width half maximum (FWHM) using SPM8.

2.4.2. Analysis of functional MRI data

Independent Component Analysis (ICA). In the current study, the “Group ICA of fMRI Toolbox” (GIFT; Medical Image Analysis Lab, The Mind Research Network, Albuquerque, NM, USA; http://icatb.sourceforge.net; (Calhoun et al., 2001)) was used to perform independent component analysis (ICA) and to decompose the preprocessed rs-fMRI data into 75 independent components (ICs). First, rs-fMRI data were concatenated and reduced performing two steps of principal component analysis (PCA). Subsequently, ICA was performed using the infomax-algorithm (Calhoun et al., 2001); (Allen et al., 2011). Since ICA is based on iterative optimization and yields therefore a certain degree of run-to-run

variability (Cole et al., 2010), the ICA-step was repeated 20 times using the implemented ICASSO software package (Himberg et al., 2004); (Allen et al., 2011) to reduce the variability of calculated components and to calculate stability indices for each component. Finally, ICA yielded 75 ICs, which were averaged across the whole group. For each participant, these averaged group components were back reconstructed into single subject space, resulting in 75 distinct ICs for each participant.

Independent components (ICs). Each IC consists of a spatial z-map reflecting component's functional connectivity pattern across space (SM) and an associated time course (TC) reflecting component's activity across time (Calhoun et al., 2001); (Allen et al., 2011); (Manoliu et al., 2013a). By correlating each pair of components´ TCs, it is possible to determine the strength of connectivity between distinct ICs (Jafri et al., 2008); (Allen et al., 2011). Throughout this thesis, functional connectivity within ICs (as indicated by components´ z-maps) will be referred to as "intra-network intrinsic functional connectivity" (intra-iFC). Functional connectivity between ICs (as indicated by correlation coefficients between ICs´ TCs) will be referred to as "inter-network intrinsic functional connectivity" (inter-iFC).

Selection of model order. The popularity of ICA in the field of neuroimaging has been strongly increasing over the last few years (Beckmann, 2012). However, the optimal choice of the ICA model-order (i.e. the number of ICs into which the rs-fMRI dataset should be decomposed) is still subject of debate (see also (Manoliu et al., 2013a)). Recently, evidence is emerging that the selection of a model-order of around 70 ICs (+/- 10) might be the optimal level to increase the chance of detecting true positive results in statistical tests investigating potential between-group differences while minimizing the risk of obtaining false-positive results (Abou-Elseoud et al., 2010). Furthermore, Allen and colleagues presented recently an analysis pipeline for ICA-based analyses based on the investigation of intrinsic functional connectivity in healthy subjects (Allen et al., 2011) by decomposing the rs-fMRI dataset

of 603 healthy adults into 75 ICs using the GIFT-software (http://icatb.sourceforge.net) (Calhoun et al., 2001). Subsequently, Allen and colleagues investigated all 75 ICs with regard to distinct features indicating whether the ICs represent intrinsic connectivity networks (ICNs) or artifacts (e.g. movement- or blood-pulsation artifacts). Finally, 28 out of 75 ICs were identified to represent ICNs. The T-maps of all 28 ICs representing ICNs were published online to allow greater comparability between studies performed by different research groups (http://mialab.mrn.org/data/hcp/RSN_HC_unthresholded_tmaps.nii, (Allen et al., 2011)). Therefore, the datasets presented in the current thesis were decomposed into 75 ICNs to maximize the statistical validity of obtained results and to ensure comparability between the different studies presented in this thesis. Furthermore, this approach yields the advantage that the identification of ICNs of interest can be performed in accordance with the reported templates (Allen et al., 2011), thus reducing the subjective bias for ICN selection (Cole et al., 2010).

Identification of intrinsic connectivity networks (ICNs). The decomposition of rs-fMRI data yielded ICNs which are well in line with known structural and functional segmentations of the human brain (Allen et al., 2011); (Abou-Elseoud et al., 2010); (Kiviniemi et al., 2009); (Smith et al., 2009); (Damoiseaux et al., 2006); (De Luca et al., 2006); (Beckmann et al., 2005). To identify the ICNs of interest in an objective and quantifiable way, those ICs representing subsystems of either DMN, SN or CEN were chosen out of the 28 templates provided online by Allen and colleagues (Allen et al., 2011), resulting in the selection of 7 distinct ICs (out of 28 templates, 3 templates represented distinct subsystems of the DMN, 1 template represented the SN, 3 templates represented distinct subsystems of the CEN, see Fig. 2 for presentation of the used templates). The aim of the next step was to obtain for each template the best fitting IC out of the 75 ICs gained via ICA. Therefore, multiple spatial regressions were performed between each of the 7 templates and all 75 ICs, respectively. For each template, the IC with the highest correlation coefficient was selected, resulting in 7 ICs

representing the 7 ICNs of interest. In accordance with the chosen templates, 3 ICs represented distinct subsystems of the DMN, 1 IC represented the SN, 3 ICs represented distinct subsystems of the CEN. For presentation of the chosen ICs, see also Fig. 6 and Tab. S4 for patients with schizophrenia during state of psychosis and their corresponding healthy controls, Fig. 7 and Tab. S5 for patients with schizophrenia during remission and their corresponding healthy controls and Fig. 8 and Tab. S6 for patients with major depressive disorder and their corresponding healthy controls.

2.4.3. Analysis of structural MRI data

Voxel-based morphometry. Functional connectivity within and between distinct ICNs can be modulated by structural alterations within the corresponding ICNs (Bonnelle et al., 2012) but also by structural anomalies within other regions of the brain (Lu et al., 2011). Since the aim of this thesis was to investigate a potential dysregulation of between-network connectivity in patients with schizophrenia and major depressive disorder regardless of anatomical anomalies, scores representing gray matter (GM) were calculated using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html; (Ashburner and Friston, 2000)) and entered in all analyses of iFC as covariate of no interest to exclude possible influences of structural anomalies on the presented results. In a first step, VBM8 corrected T1-weigted images for bias-field inhomogeneity and registered all participants´ T1-weigted images via linear and non-linear transformations (Ashburner and Friston, 2005). Then, the transformed images were divided into three distinct images, respectively, each containing a distinct tissue type (segmentation): One image represents the gray matter (GM), one image represents the white matter (WM) and one image represents cerebro-spinal fluid (CSF). All GM images were smoothed using a Gaussian kernel of 8 mm at full width half maximum (FWHM, see also section “2.4.1. Preprocessing of structural and functional MRI data” for detailed presentation of the smoothing process) and considered for further analyses. To investigate

possible structural anomalies within the groups of patients, voxel-wise two-sample t-tests were performed between each pair of groups (SA vs. corresponding healthy controls, SR vs. corresponding healthy controls and MDD vs. corresponding healthy controls, respectively) applying a threshold of $p<0.05$, FWE-corrected and $p<0.001$, uncorrected. Finally, GM scores were calculated based on the segmented GM image for each participant and entered as covariate-of-no-interest in all analyses investigating iFC.

2.5. Statistical analysis

The aim of the current thesis was to investigate a potential relationship between insular dysfunction within the SN and aberrant connectivity between DMN, SN and CEN. Therefore, it was necessary to obtain two distinct outcome measures, each reflecting a distinct property of intrinsic functional connectivity (iFC): (i) Intra-iFC, representing the FC within distinct networks (as reflected by ICNs´ SMs) and (ii) inter-iFC, representing the FC between distinct ICNs (as reflected by the correlation coefficients between ICNs´ TCs). Subsequently, the relationship between these two outcome measures was investigated as well as a possible association between both intra-iFC and inter-iFC and severity of disease-specific symptoms for each group. In the following, the statistical analyses performed will be presented in more detail.

2.5.1. Intrinsic functional connectivity within networks (intra-iFC)

To investigate the connectivity within all 7 ICNs of interest (intra-iFC), voxel-wise one-sample t-tests were performed on ICNs´ spatial maps for each group, respectively using SPM8 ($p<0.05$, family-wise-error (FWE) corrected for multiple comparisons). To investigate potential between-group differences, voxel-wise two-sample t-tests were performed on ICN´s spatial maps between each pair of groups (SA vs. corresponding HC, SR vs. corresponding HC, MDD vs. corresponding HC) using SPM 8 ($p<0.05$, FWE-corrected for multiple comparisons). To account for the possible influence of age, sex or structural anomalies on between-group differences in intra-iFC in all analyses, age, sex and total gray matter (GM) were entered as covariates of no interest.

2.5.2. Intrinsic functional connectivity between networks (inter-iFC)

To investigate the connectivity between all 7 ICNs of interest (inter-iFC), ICNs´ TCs were detrended, despiked and filtered using a fifth-order Butterworth low-pass filter with a high frequency cutoff of 0.15Hz in

accordance with a recently proposed approach (Manoliu et al., 2013a); (Allen et al., 2011); (Jafri et al., 2008). Subsequently, pairwise correlation between ICN´s TCs was investigated by the use of Pearson´s correlation. The resulting correlation coefficients were Fisher-z-transformed to enable further statistical analyses. To investigate potential between-group differences in inter-iFC, two-sample t-tests were performed on Fisher-z-transformed correlation coefficients between each pair of groups (SA vs. corresponding HC, SR vs. corresponding HC, MDD vs. corresponding HC; $p<0.05$, Bonferroni-corrected for multiple comparisons). To account for the possible influence of age, sex or structural anomalies on between-group differences in inter-iFC in all analyses, age, sex and total gray matter (GM) were entered as covariates of no interest.

2.5.3. Correlation analyses

According to a recently postulated model of large-scale brain network dysfunction in psychiatric disorders, insular dysfunction within the SN has been proposed to play a crucial role in the aberrant modulation of between-network interactions in mental disorders (Menon, 2011) and has thus been suggested to be associated with the severity of disease and state-specific symptoms in schizophrenia (Palaniyappan and Liddle, 2012) and major depressive disorder (Hamilton et al., 2013). In the following, the approach used to investigate a possible correlation between intra-iFC, inter-iFC and severity of symptoms will be presented in more detail.

The relationship between insular dysfunction and aberrant inter-iFC. To investigate the possible association between insular dysfunction within the SN and aberrant inter-network interactions, voxel-wise one-sample t-tests were calculated on SN´s spatial maps for each patient group. Then, the results were masked with the corresponding mask derived from the voxel-wise two-sample t-test between each group of patients and the corresponding group of healthy controls, respectively.

Subsequently, principle eigenvariates of the clusters located within the left and right anterior insula (AI) were extracted for each group of patients, respectively. These principle eigenvariates were correlated with the Fisher-z-transformed correlation coefficients representing the connectivity between the 7 ICNs of interest. To account for possible influences of age, sex and structural differences on possible results, partial correlation was performed with age, sex and total GM as covariates of no interest ($p<0.05$, Bonferroni-corrected for multiple comparisons). Since antipsychotic drugs have been demonstrated to have an impact on iFC (Sambataro et al., 2010), the total level of antipsychotic medication was calculated in terms of chlorpromazine-equivalent dose (CPZ, (Woods, 2003)) and entered as a further covariate-of-no-interest in all analyses investigating aberrant iFC in patients with schizophrenia (SA and SR). Patients with major depressive disorder received predominately antidepressant medication. However, since no approach similar to the calculation of CPZ is currently available to quantify antidepressant medication, the level of medication has not been introduced as additional covariate-of-no-interests in analyses investigating aberrant iFC in patients with major depressive disorder (see also section “4.5. Control parameters” for extensive discussion of this limitation).

The relationship between insular dysfunction and severity of symptoms. To investigate the possible association between insular dysfunction and disease- and state- specific symptoms, principle eigenvariates of the clusters located in the left and right AI within the SN (see above) were extracted and correlated with the severity of symptoms as measured by psychometric assessment. For patients with schizophrenia, positive and negative symptoms were assessed via PANSS (Kay et al., 1987). For patients with major depressive disorder, depressive symptoms were assessed via both HAM-D (Hamilton, 1960) and BDI (Beck et al., 1961) (see also section “2.2. Psychometric assessment”). To account for possible influences of age, sex and structural anomalies on possible results, partial correlation was performed with age, sex and total GM as

covariates of no interest ($p<0.05$, Bonferroni-corrected for multiple comparisons). For patients with schizophrenia, CPZ was additionally entered as covariate-of-no-interest (see above).

The relationship between aberrant inter-iFC and severity of symptoms. To investigate the possible relationship between aberrant between-network interactions and severity of disease- and state-specific symptoms in patients, Fisher-z-transformed inter-iFC correlation coefficients were correlated with the severity of the corresponding disease- and state-specific symptoms (as measured via psychometric assessment, see above), respectively. To account for possible influences of age, sex and structural differences on possible results, partial correlation was performed with age, sex and total GM as covariates of no interest ($p<0.05$, Bonferroni-corrected for multiple comparisons). Again, CPZ was additionally entered as covariate-of-no-interest for patients with schizophrenia (see above).

3. Results

3.1. Intrinsic connectivity networks (ICNs)

The aim of this study was to investigate a potential association between insular dysfunction within the SN and aberrant inter-network connectivity between the default mode network (DMN), salience network (SN) and central executive network (CEN) in patients with schizophrenia during acute psychosis (SA) and remission (SR) as well as in patients with major depressive disorder (MDD). Therefore, DMN, SN and CEN were identified by applying independent component analysis (ICA) on rs-fMRI data. The resulting ICs were correlated with templates representing ICNs of interest (as derived from (Allen et al., 2011), see Fig. 2 for presentation of the used templates and section “2.4.2. Analysis of functional MRI data” for detailed presentation of the identification procedure). In more detail, ICA yielded for each participant 7 intrinsic connectivity networks (ICNs) of interest: Three ICNs represented distinct subsystems of the DMN, one ICN represented the SN, three ICNs represented distinct subsystems of the CEN. A short description of all subsystems can be found below (Tab. 4, see also Tab. S4, Tab. S5 and Tab. S6 for extensive characterization of ICNs of interest, $p<0.05$, FWE-corrected). Regarding the intrinsic functional connectivity (iFC) within (intra-iFC) and between (inter-iFC) all ICNs of interest, the current results replicate almost perfectly the previously reported functional architecture of DMN (Buckner et al., 2008), SN (Seeley et al., 2007) and CEN (Fox and Raichle, 2007) (see also (Allen et al., 2011); (Abou-Elseoud et al., 2010); (Kiviniemi et al., 2009); (Smith et al., 2009); (Damoiseaux et al., 2006); (De Luca et al., 2006); (Beckmann et al., 2005)), demonstrating the validity of the applied methods and the presence of the basic functional organization of all ICNs of interest in all investigated groups. (see Fig. 6, Fig. 7 and Fig. 8 for presentation of intra-iFC within all ICNs and Fig. 3, Fig. 4 and Fig. 5 for presentation of inter-iFC between all ICNs for each group, respectively).

Table 4. Overview over the 7 ICNs of interest included in the present thesis.

ICN	Subsystems of distinct ICNs	Abbreviation (Template[1])	Key structures
DMN	anterior default mode network	aDMN (50)	medial prefrontal cortex
	inferior posterior default mode network	ipDMN (53)	medial posterior parietal cortex and angular gyrus
	superior posterior default mode network	spDMN (50)	bilateral precuneus
SN	salience network	SN (55)	bilateral anterior insula, anterior cingulate cortex
CEN	left ventral central executive network	lvCEN (34)	left inferior parietal lobule, left superior frontal gyrus
	right ventral central executive network	rvCEN (60)	right inferior parietal lobule, right superior frontal gyrus
	dorsal central executive network	dCEN (52)	left supramarginal gyrus, left inferior frontal gyrus, right supramarginal gyrus

[1]Templates were derived from (Allen et al., 2011). The number given to each template refers to each template´s respective number in the file, which contains all T-maps of interest and was made available online (http://mialab.mrn.org/data/hcp/RSN_HC_unthresholded_tmaps.nii).

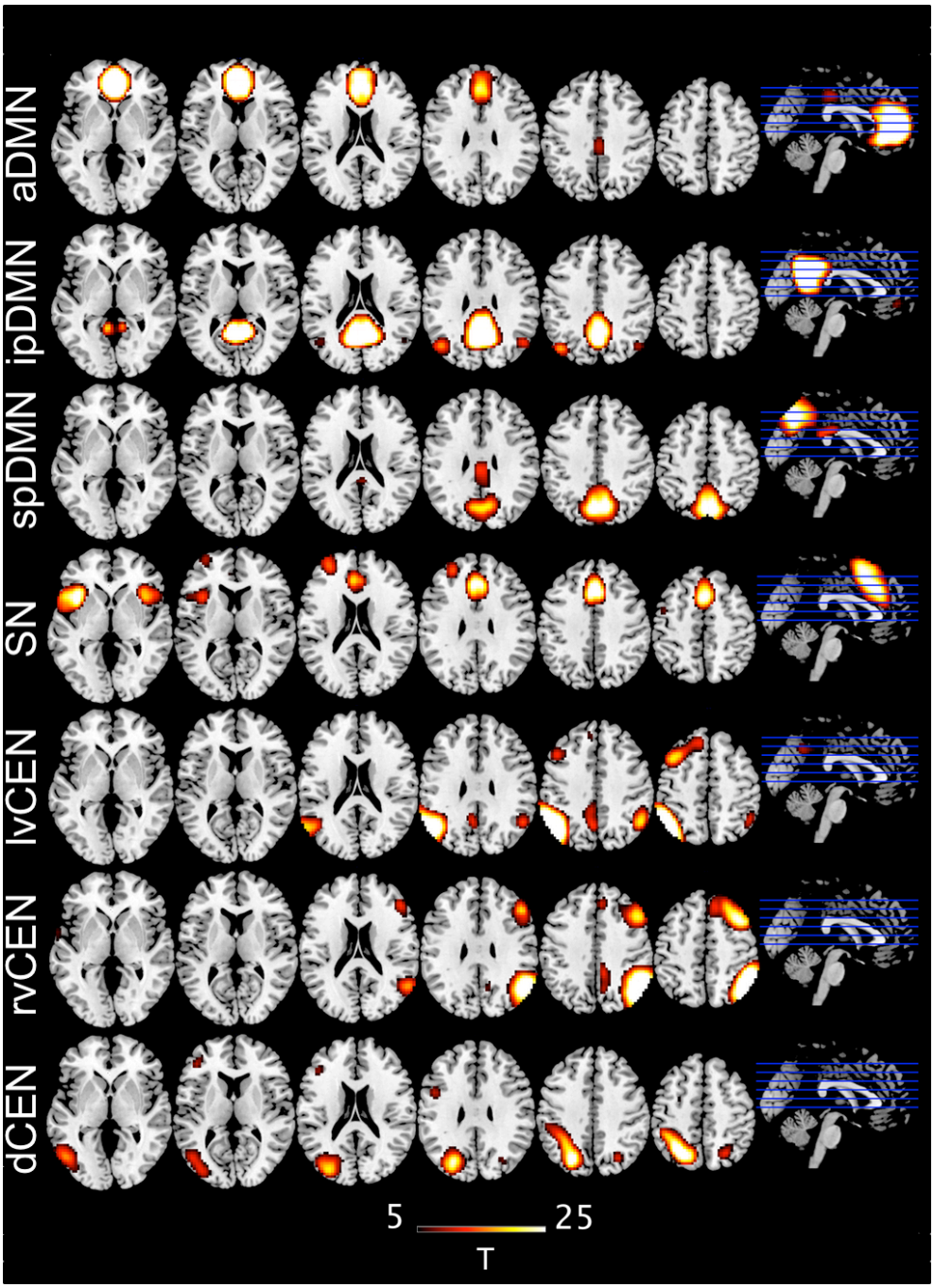

Figure 2. T-maps of intrinsic connectivity networks (ICNs) of interest as derived from (Allen et al., 2011).
Abbreviations: a/ip/spDMN: anterior/inferior posterior/superior posterior DMN; lv/rv/dCEN: left ventral/right ventral/dorsal CEN; SN: salience network. See also Tab. 4 and section "2.4.2. Analysis of functional MRI data". Figure and modified legend taken from (Manoliu et al., 2013a).

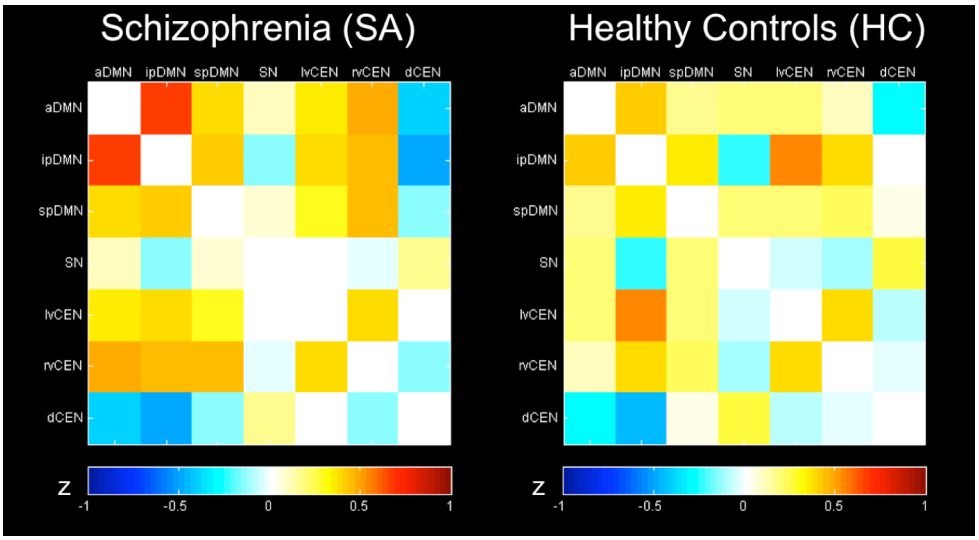

Figure 3. Inter-network intrinsic functional connectivity (inter-iFC) matrix for patients with schizophrenia during state of acute psychosis and corresponding group of healthy controls.
Pairwise Pearson's correlations between time courses of all subsystems of the the default mode network (DMN), salience network (SN), and central executive network (CEN) were Fisher-z-transformed, averaged across subjects for the group of patients with schizophrenia during state of acute psychosis and the group of healthy controls, respectively, and presented in a correlation matrix. Colors represent intensity of averaged z-scores. See also Tab. S10 for detailed presentation of inter-iFC in patients with schizophrenia during state of acute psychosis and the corresponding group of healthy controls. Abbreviations: a/ip/spDMN: anterior/inferior-posterior/superior-posterior DMN; lv/rv/dCEN: left-ventral/right-ventral/dorsal CEN. Figure and modified legend taken from (Manoliu et al., 2013a).

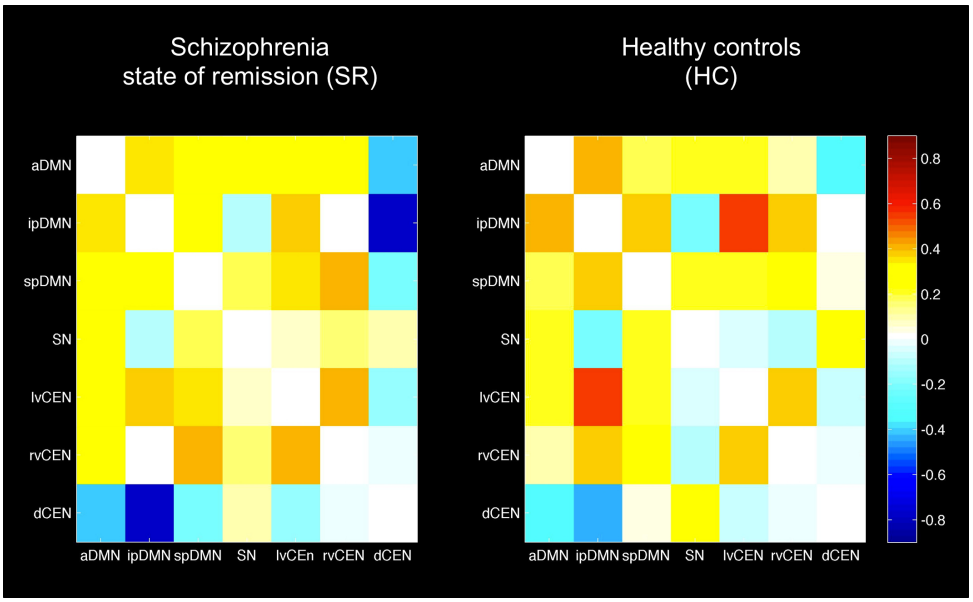

Figure 4. Inter-network intrinsic functional connectivity (inter-iFC) matrix for patients with schizophrenia during state of remission and corresponding group of healthy controls.
Pairwise Pearson's correlations between time courses of all subsystems of the the default mode network (DMN), salience network (SN), and central executive network (CEN) were Fisher-z-transformed, averaged across subjects for the group of patients with schizophrenia during state of remission and the group of healthy controls, respectively, and presented in a correlation matrix. Colors represent intensity of averaged z-scores. See also Tab. S11 for detailed presentation of inter-iFC in patients with schizophrenia during state of remission and the corresponding group of healthy controls. Abbreviations: a/ip/spDMN: anterior/inferior-posterior/superior-posterior DMN; lv/rv/dCEN: left-ventral/right-ventral/dorsal CEN. Figure and modified legend taken from (Manoliu et al., 2013b).

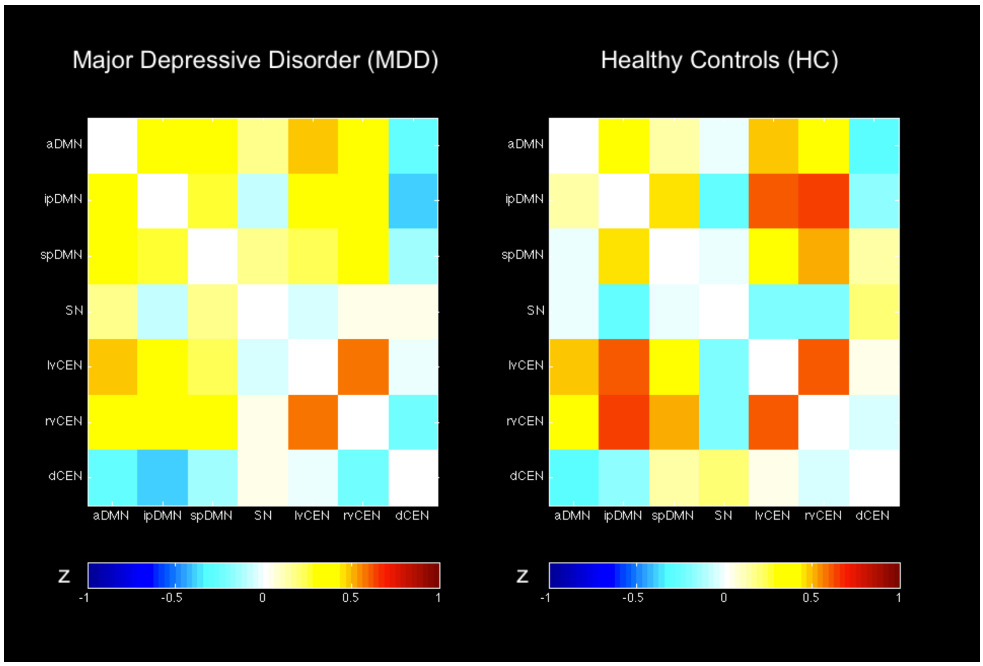

Figure 5. Inter-network intrinsic functional connectivity (inter-iFC) matrix for patients with major depressive disorder and corresponding group of healthy controls.

Pairwise Pearson's correlations between time courses of all subsystems of the the default mode network (DMN), salience network (SN), and central executive network (CEN) were Fisher-z-transformed, averaged across subjects for the group of patients with major depressive disorder and the group of healthy controls, respectively, and presented in a correlation matrix. Colors represent intensity of averaged z-scores. See also Tab. S12 for detailed presentation of inter-iFC in patients with major depressive disorder and the corresponding group of healthy controls. Abbreviations: a/ip/spDMN: anterior/inferior-posterior/superior-posterior DMN; lv/rv/dCEN: left-ventral/right-ventral/dorsal CEN. Figure and modified legend taken from (Manoliu et al., in review).

3.2. Intrinsic functional connectivity within networks (intra-iFC)

Compared to the corresponding group of healthy controls respectively, all patient groups demonstrated aberrant intra-iFC within the DMN, SN and CEN ($p<0.05$, FWE-corrected, corrected for age, sex and GM as covariates of no interest). Most importantly, all patient groups demonstrated decreased intra-iFC in the bilateral anterior insula (AI) within the SN, indicating the presence of insular dysfunction in patients with schizophrenia and major depressive disorder. Therefore, the presented results support recently formulated models of anterior insular dysfunction in psychiatric disorders (Menon, 2011), including schizophrenia (Palaniyappan and Liddle, 2012) and major depressive disorder (Hamilton et al., 2013). For detailed presentation of aberrant intra-iFC in patients, see Fig. 6 and Tab S7 for patients with schizophrenia during state of acute psychosis, Fig. 7 and Tab. S8 for patients with schizophrenia during state of remission and Fig. 8 and Tab. S9 for patients with major depressive disorder.

3.2.1. Intra-iFC in patients with schizophrenia during acute psychosis

Concerning the SN, patients with SA demonstrated decreased intra-iFC in bilateral AI as well as increased intra-iFC in the ACC (Fig. 6D). Concerning the DMN, patients with SA demonstrated decreased intra-iFC in the ACC within the aDMN (Fig. 6A) and decreased intra-iFC in the bilateral precuneus within both ipDMN and spDMN (Fig. 6B,C). Concerning the CEN, patients with SA showed heterogeneous results within all three subsystems of the CEN, including increased intra-iFC in the left middle orbital gyrus (lvCEN), left superior frontal gyrus (rvCEN) and left inferior temporal gyrus (dCEN) as well as decreased intra-iFC in the left inferior parietal lobule (lvCEN), right inferior parietal lobule (rvCEN) and right supramarginal gyrus (dCEN), suggesting increased intra-iFC within the CEN with a focus on regions located within the

frontal lobe and decreased intra-iFC within the CEN with a focus on regions located within the parietal lobe (Fig. 6E,F,G, see also Tab. S7).

3.2.2. Intra-iFC in patients with schizophrenia during remission

Concerning the SN, patients with SR demonstrated decreased intra-iFC in bilateral AI as well as increased intra-iFC in the ACC (Fig. 7D). Concerning the DMN, SR demonstrated decreased intra-iFC in bilateral ACC within the aDMN (Fig. 7A) and decreased intra-iFC in bilateral precuneus within the ipDMN (Fig. 7B). Concerning the CEN, SR demonstrated increased intra-iFC in the left inferior temporal gyrus within the dCEN (Fig. 7G). Analyses yielded no significant between-group differences within the spDMN, lvCEN and rvCEN (see also Tab. S8).

3.2.3. Intra-iFC in patients with major depressive disorder

Concerning the SN, patients with MDD demonstrated decreased intra-iFC in the bilateral AI and increased intra-iFC in the ACC (Fig. 8D). Concerning the DMN, MDD demonstrated increased intra-iFC in bilateral ACC within the aDMN (Fig. 8A), increased intra-iFC in the bilateral precuneus within the ipDMN (Fig. 8B) and both increased and decreased intra-iFC in distinct parts of the precuneus within the spDMN (Fig 8C). Concerning the CEN, patients with MDD demonstrated increased intra-iFC in the right angular gyrus and decreased intra-iFC in both the left precuneus and left middle temporal gyrus within the lvCEN (Fig. 8E), increased intra-iFC in the right postcentral gyrus within the dCEN (Fig. 8G) and No between-group differences within the rvCEN (Fig. 8F, see also Tab. S9).

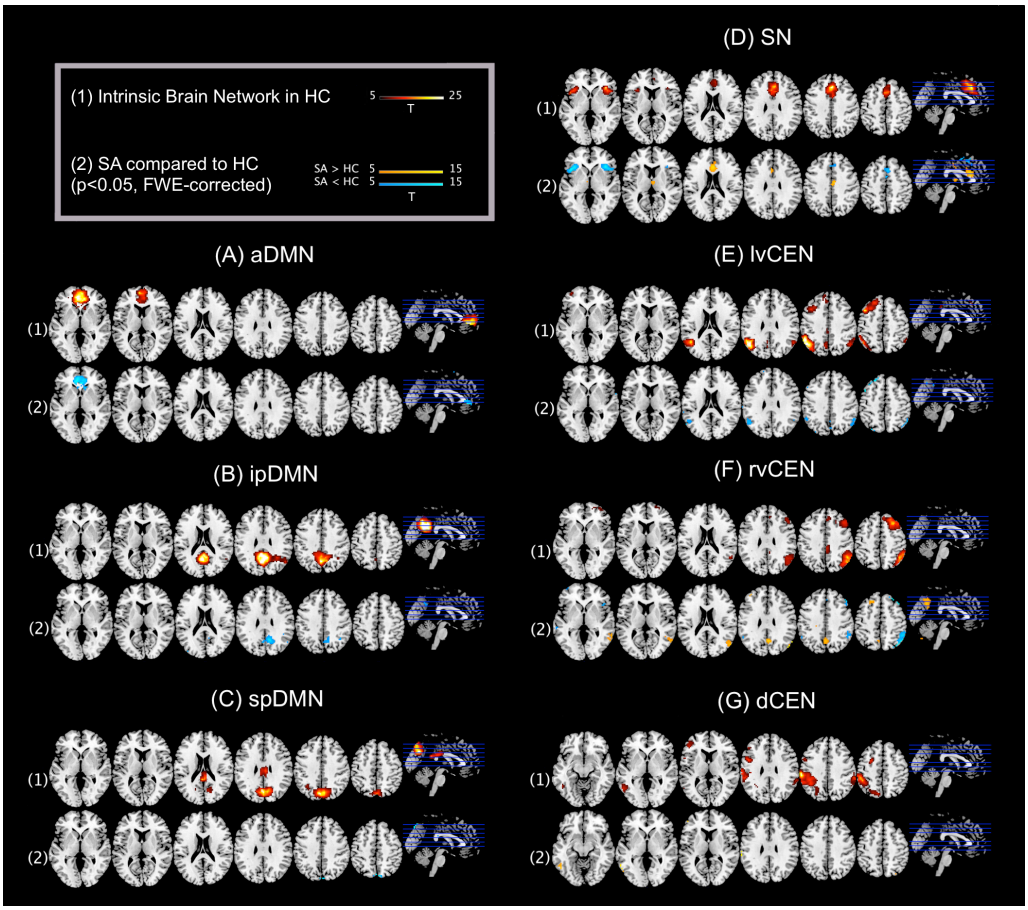

Figure 6. Intrinsic functional connectivity within (intra-iFC) the default mode network (DMN), salience network (SN) and central executive network (CEN) for healthy controls and corresponding group differences for patients with schizophrenia during state of acute psychosis.
(1) Spatial maps of selected ICs representing the default mode, salience, and central executive network (DMN, SN, CEN) were entered into voxel-wise one-sample t-tests across individuals of each group and thresholded at $p<0.05$, corrected for family wise error (FWE). Statistical parametric maps (SPMs) representing brain areas with significantly co-varying activity were superimposed on a single-subject high resolution T1 image (color scale representing t values from 5 to 25; only maps of the corresponding group of healthy controls are shown). (2) To analyze between-group differences, controls' and patients' ICs of the DMN, SN, and CEN were entered into voxel-wise 2-sample t-tests with age, sex and total GM volume as covariates of no interest and thresholded at $p<0.05$, FWE-corrected. SPMs were superimposed on a single-subject high resolution T1 image (color scale representing t values from 5 to 15). See also Tab. S4 and Tab. S7 for detailed presentation of intra-iFC for healthy controls and corresponding group differences for patients with SA. Abbreviations: SA, group of patients with schizophrenia during acute psychosis; HC, healthy control group; a/ip/spDMN, anterior/inferior-posterior/superior-posterior DMN; lv/rv/dCEN, left-ventral/right-ventral/dorsal CEN. Figure and modified legend taken from (Manoliu et al., 2013a).

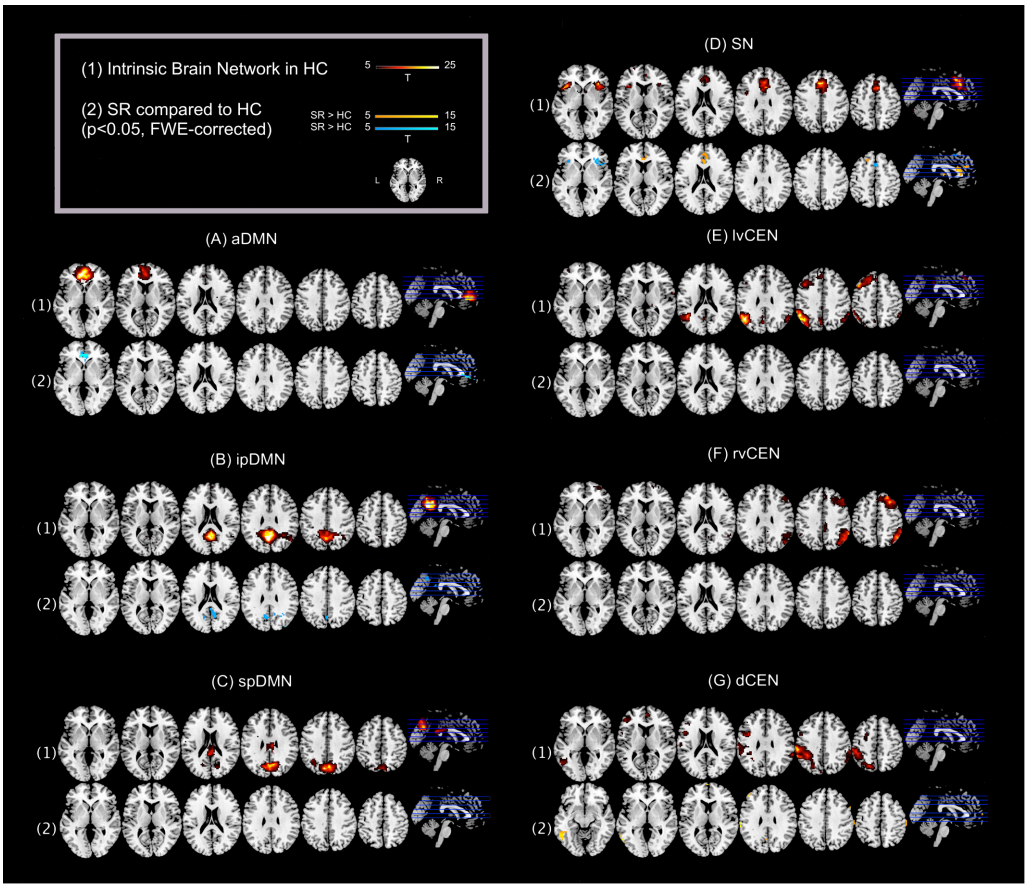

Figure 7. Intrinsic functional connectivity within (intra-iFC) the default mode network (DMN), salience network (SN) and central executive network (CEN) for healthy controls and corresponding group differences for patients with schizophrenia during remission.

(1) Spatial maps of selected ICs representing the default mode, salience, and central executive network (DMN, SN, CEN) were entered into voxel-wise one-sample t-tests across individuals of each group and thresholded at $p<0.05$, corrected for family wise error (FWE). Statistical parametric maps (SPMs) representing brain areas with significantly co-varying activity were superimposed on a single-subject high resolution T1 image (color scale representing t values from 5 to 25; only maps of the corresponding group of healthy controls are shown). (2) To analyze between-group differences, controls' and patients' ICs of the DMN, SN, and CEN were entered into voxel-wise 2-sample t-tests with age, sex and total GM volume as covariates of no interest and thresholded at $p<0.05$, FWE-corrected. SPMs were superimposed on a single-subject high resolution T1 image (color scale representing t values from 5 to 15). See also Tab. S5 and Tab. S8 for detailed presentation of intra-iFC for healthy controls and corresponding group differences for patients with SR. Abbreviations: SR, group of patients with schizophrenia during remission; HC, healthy control group; a/ip/spDMN, anterior/inferior-posterior/superior-posterior DMN; lv/rv/dCEN, left-ventral/right-ventral/dorsal CEN. Figure and modified legend taken from (Manoliu et al., 2013b).

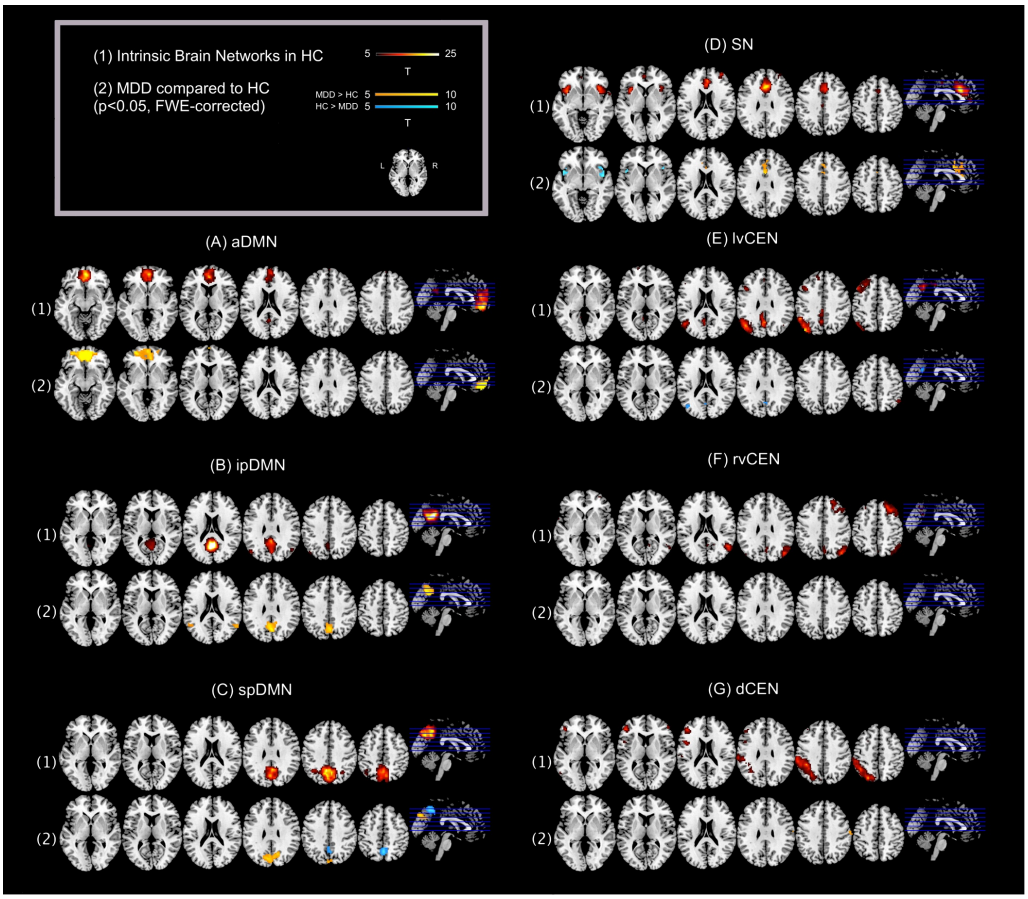

Figure 8. Intrinsic functional connectivity within (intra-iFC) the default mode network (DMN), salience network (SN) and central executive network (CEN) for healthy controls and corresponding group differences for patients with major depressive disorder.

(1) Spatial maps of selected ICs representing the default mode, salience, and central executive network (DMN, SN, CEN) were entered into voxel-wise one-sample t-tests across individuals of each group and thresholded at $p<0.05$, corrected for family wise error (FWE). Statistical parametric maps (SPMs) representing brain areas with significantly co-varying activity were superimposed on a single-subject high resolution T1 image (color scale representing t values from 5 to 25; only maps of the corresponding group of healthy controls are shown). (2) To analyze between-group differences, controls' and patients' ICs of the DMN, SN, and CEN were entered into voxel-wise 2-sample t-tests with age, sex and GM volume as covariates of no interest and thresholded at $p<0.05$, FWE-corrected. SPMs were superimposed on a single-subject high resolution T1 image (color scale representing t values from 5 to 10). See also Tab. S6 and Tab. S9 for detailed presentation of intra-iFC for healthy controls and corresponding group differences for patients with MDD. Abbreviations: MDD, group of patients with major depressive disorder; HC, healthy control group; a/ip/spDMN, anterior/inferior-posterior/superior-posterior DMN; lv/rv/dCEN, left-ventral/right-ventral/dorsal CEN. Figure and modified legend taken from (Manoliu et al., in review).

3.3. Intrinsic functional connectivity between networks (inter-iFC)

Compared to the corresponding group of healthy controls respectively, all patient groups demonstrated aberrant inter-iFC between the DMN, SN and CEN ($p<0.05$, corrected for age, sex and total GM, Bonferroni-corrected for multiple comparisons). Most importantly, all patient groups demonstrated aberrant inter-iFC between subsystems of the DMN and subsystems of the CEN, indicating the presence of aberrant interaction between DMN and CEN in patients with schizophrenia and major depressive disorder and therefore confirming recently formulated models of aberrant DMN/CEN interactions in psychiatric disorders (Menon, 2011), including schizophrenia (Palaniyappan and Liddle, 2012) and major depressive disorder (Hamilton et al., 2013). For detailed presentation of aberrant inter-iFC in patients, see Fig. 9 and Tab. S10 for patients with schizophrenia during state of acute psychosis, Fig. 10 and Tab. S11 for patients with schizophrenia during state of remission and Fig. 11. and Tab S12 for patients with major depressive disorder.

3.3.1. Inter-iFC in patients with schizophrenia during acute psychosis

Patients with SA demonstrated increased inter-iFC between the aDMN and ipDMN as well as between aDMN and spDMN, indicating an increased inter-iFC within the DMN. Furthermore, inter-iFC was increased between the aDMN and rvCEN as well as between the spDMN and rvCEN, indicating an increased inter-iFC between the DMN and CEN. Inter-iFC between the SN and any subsystem of the DMN or CEN was not altered in patients with SA (see also Fig. 9 and Tab. S10; $p<0.05$, corrected for age, sex and total GM, Bonferroni-corrected for multiple comparisons).

3.3.2. Inter-iFC in patients with schizophrenia during remission

Patients with SR demonstrated decreased inter-iFC between ipDMN and rvCEN, indicating a decreased inter-iFC between the DMN and CEN. Furthermore, inter-iFC between SN and rvCEN was increased, indicating increased inter-iFC between SN and CEN (see also Fig. 10 and Tab. S11; $p<0.05$, corrected for age, sex and total GM, Bonferroni-corrected for multiple comparisons).

3.3.3. Inter-iFC in patients with major depressive disorder

Patients with MDD demonstrated decreased inter-iFC between ipDMN and dCEN as well as between spDMN and dCEN, indicating decreased inter-iFC between the DMN and CEN. Furthermore, inter-iFC between the SN and ipDMN was increased, indicating increased inter-iFC between SN and DMN (see also Fig. 11 and Tab. S12; $p<0.05$, corrected for age, sex and total GM, Bonferroni-corrected for multiple comparisons).

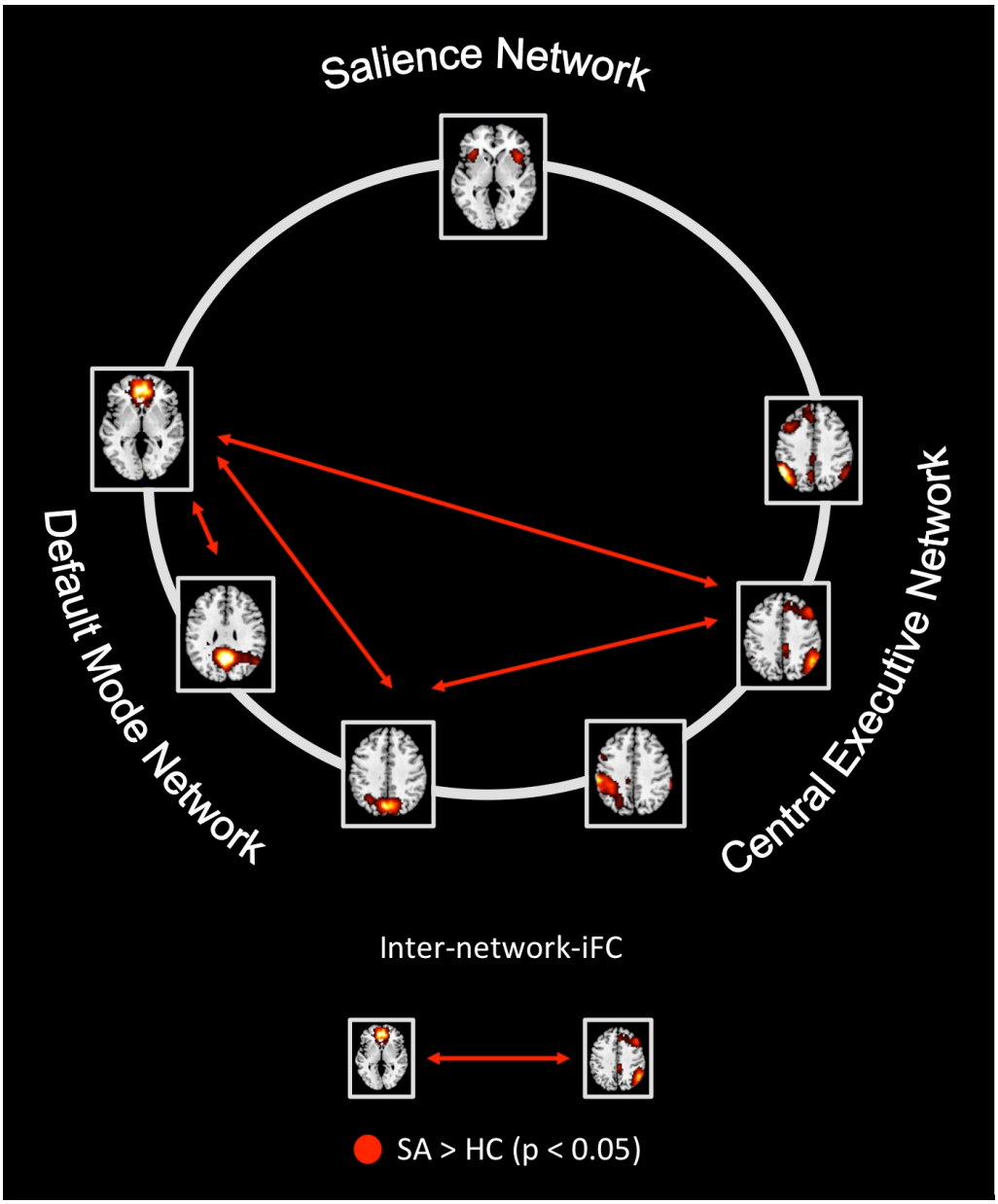

Figure 9. Between-group differences in inter-network intrinsic functional connectivity (inter-iFC) between patients with schizophrenia during state of acute psychosis and healthy controls.
Based on networks time courses, inter-network intrinsic functional connectivity (inter-iFC) was calculated by the use of Pearson's correlation between subject specific ICN timecourses (TCs). The red arrows indicate increased inter-iFC in patients compared to healthy controls (two-sample t-test, $p<0.05$, Bonferroni-corrected for multiple comparisons, see also Tab. S10). Spatial maps indicate the anterior/inferior-posterior/superior-posterior default mode network (a/ip/spDMN), left-ventral/right-ventral/dorsal central executive network (lv/rv/dCEN), and salience network (SN). All tests were corrected for age, sex and total GM volume. Abbreviations: SA, group of patients with schizophrenia during state of acute psychosis; HC, healthy control group. Modified figure and modified legend taken from (Manoliu et al., 2013a).

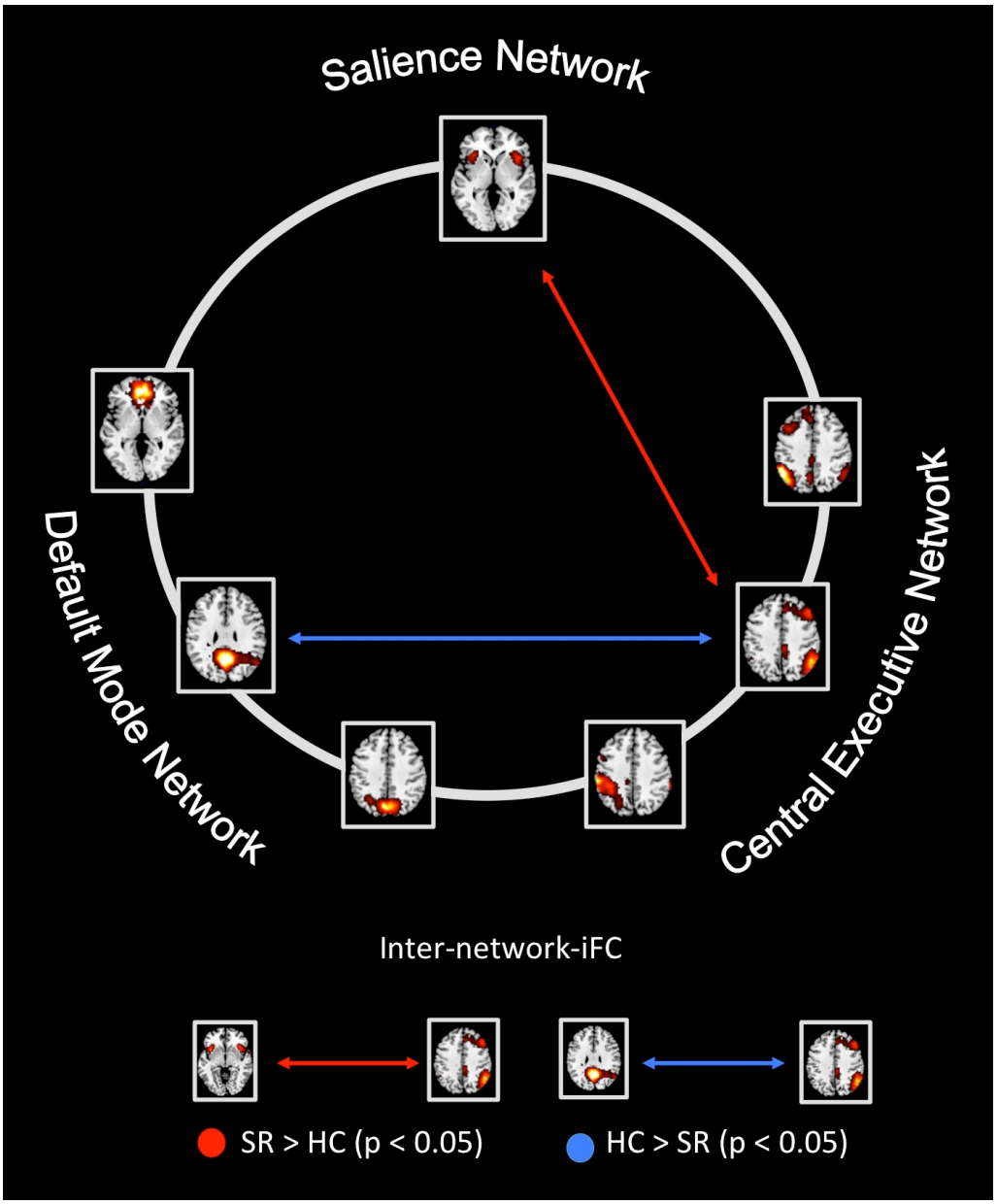

Figure 10. Between-group differences in inter-network intrinsic functional connectivity (inter-iFC) between patients with schizophrenia during state of remission and healthy controls.
Based on networks´ time courses, inter-network intrinsic functional connectivity (inter-iFC) was calculated by the use of Pearson's correlation between subject specific ICN timecourses (TCs). The red arrow indicates increased inter-iFC in patients compared to healthy controls, the blue arrow indicates decreased inter-iFC in patients compared to healthy controls (two-sample t-test, $p<0.05$, Bonferroni-corrected for multiple comparisons, see also Tab. S11). Spatial maps indicate the anterior/inferior-posterior/superior-posterior default mode network (a/ip/spDMN), left-ventral/right-ventral/dorsal central executive network (lv/rv/dCEN), and salience network (SN). All tests were corrected for age, sex and total GM volume. Abbreviations: SR, group of patients with schizophrenia during state of remission; HC, healthy control group. Modified figure and modified legend taken from (Manoliu et al., 2013b).

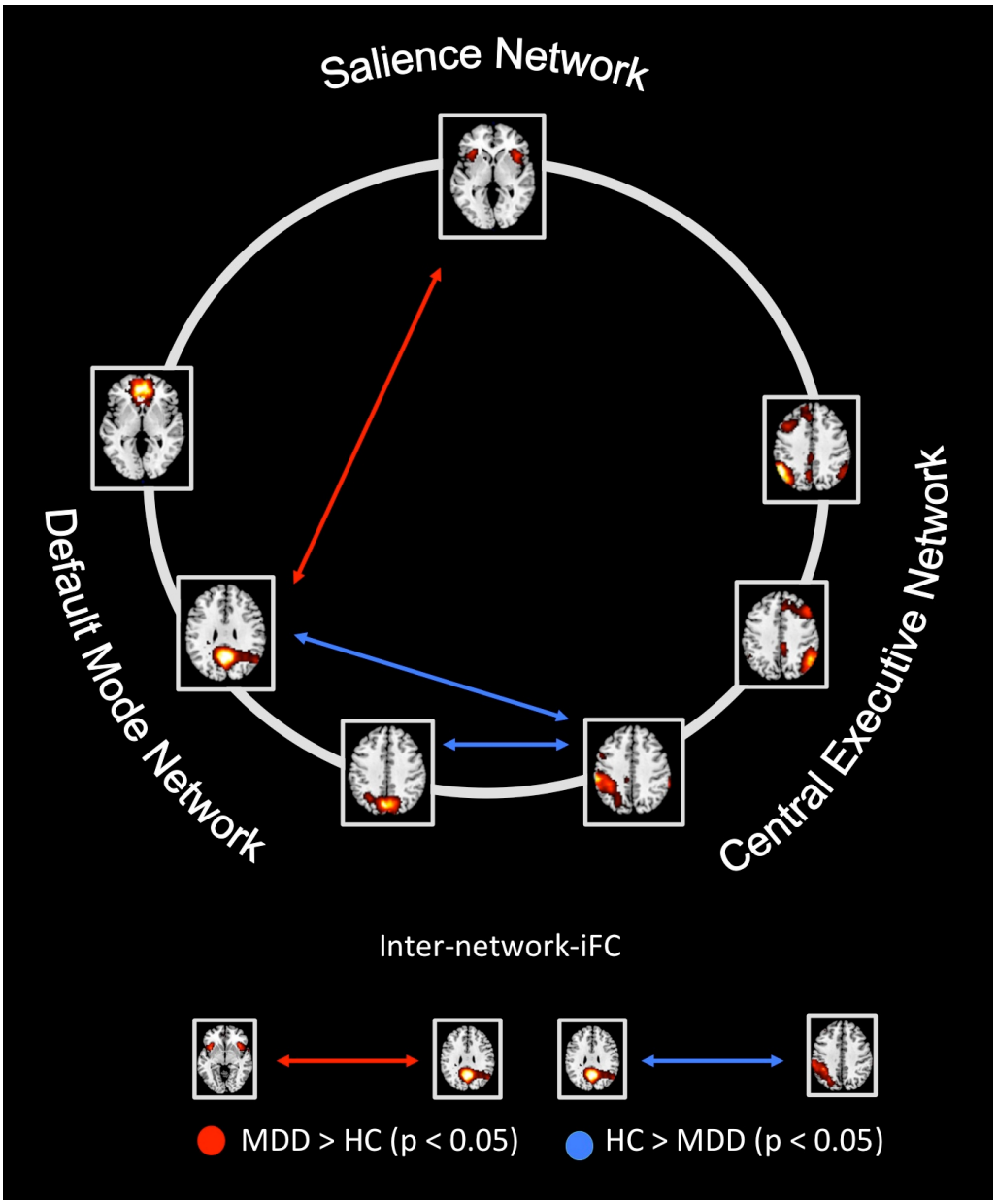

Figure 11. Between-group differences in inter-network intrinsic functional connectivity (inter-iFC) between patients with major depressive disorder and healthy controls.
Based on networks´ time courses, inter-network intrinsic functional connectivity (inter-iFC) was calculated by the use of Pearson's correlation between subject specific ICN timecourses (TCs). The red arrow indicates increased inter-iFC in patients compared to healthy controls, the blue arrows indicate decreased inter-iFC in patients compared to healthy controls (two-sample t-test, $p<0.05$, Bonferroni-corrected for multiple comparisons, see also Tab. S12). Spatial maps indicate the anterior/inferior-posterior/superior-posterior default mode network (a/ip/spDMN), left-ventral/right-ventral/dorsal central executive network (lv/rv/dCEN), and salience network (SN). All tests were corrected for age, sex and GM volume. Abbreviations: MDD, group of patients with major depressive disorder; HC, healthy control group. Modified figure and modified legend taken from (Manoliu et al., in review).

3.4. The association between aberrant intra-iFC, aberrant inter-iFC and severity of symptoms

In general, all patient groups demonstrated an association between insular dysfunction (as indicated by aberrant intra-iFC) and aberrant between-network interactions (as indicated by aberrant inter-iFC). Importantly, aberrant intra-iFC within the right AI was selectively associated with aberrant DMN/CEN interactions in patients with schizophrenia as well as in patients with MDD. Furthermore, all patient groups showed a correlation between aberrant intra-iFC in the AI within the SN and severity of disease specific symptoms. In particular, aberrant intra-iFC within the right AI was consistently associated with severity of positive symptoms (SA, SR) and depressive symptoms (MDD), while aberrant intra-iFC within the left AI was associated with severity of negative symptoms (SR). Finally, patients with schizophrenia demonstrated a relationship between aberrant inter-iFC and severity of state-specific symptoms. Patients with MDD, however, demonstrated no significant correlation between aberrant inter-iFC and severity of depressive symptoms. In accordance with recent models of insular dysfunction in mental disorders (Menon, 2011), these results suggest a general association between anterior insular dysfunction, aberrant inter-network interactions and severity of disease- and state-specific symptoms in patients with schizophrenia (Palaniyappan and Liddle, 2012) and patients with MDD (Hamilton et al., 2013). For detailed presentation of associations between intra-iFC, inter-iFC and severity of symptoms in patients, see Fig. 12, Tab. S13, Tab. S16 and Tab. S19 for patients with schizophrenia during state of acute psychosis, Fig. 13, Tab. S14, Tab. S17 and Tab. S20 for patients with schizophrenia during state of remission and Fig. 14, Tab. S15, Tab. S18 and Tab. S21 for patients with major depressive disorder.

3.4.1. Correlations in patients with schizophrenia during acute psychosis

Patients with SA demonstrated a negative correlation between right AI´s intra-iFC within the SN and inter-iFC between aDMN and rvCEN, suggesting an association between right anterior insular dysfunction and aberrant DMN/CEN interactions in schizophrenia during state of psychosis (see Fig. 12, Tab. S13, $p<0.05$, partial correlations with age, sex, total GM and CPZ as covariates of no-interest, Bonferroni-corrected for multiple comparisons). Furthermore, patients with SA demonstrated a negative correlation between right AI´s intra-iFC within the SN and severity of hallucinations, suggesting an association between right AI dysfunction and severity of positive symptoms in patients with schizophrenia (see Fig. 12 and Tab. S16; $p<0.05$, partial correlations with age, sex, total GM and CPZ as covariates of no-interest, Bonferroni-corrected for multiple comparisons). Finally, patients with SA demonstrated an association between aberrant inter-iFC between aDMN and rvCEN and severity of hallucinations, indicating a relationship between aberrant inter-iFC and severity of positive symptoms in schizophrenia (see Fig. 12 and Tab. S19; $p<0.05$, partial correlations with age, sex, total GM and CPZ as covariates of no-interest, Bonferroni-corrected for multiple comparisons).

3.4.2. Correlations in patients with schizophrenia during remission

Patients with SR demonstrated a negative correlation between left AI´s intra-iFC within the SN and inter-iFC between SN and rvCEN, suggesting an association between left anterior insular dysfunction and aberrant SN/CEN interactions in schizophrenia during state of remission (Fig. 13, Tab. S14, $p<0.05$, partial correlations with age, sex, total GM and CPZ as covariates of no-interest, Bonferroni-corrected for multiple comparisons). Furthermore, patients with SR demonstrated a negative correlation between left AI´s intra-iFC and severity of negative symptoms (see Fig. 13 and Tab. S17; $p<0.05$, partial correlations with

age, sex, total GM and CPZ as covariates of no-interest, Bonferroni-corrected for multiple comparisons). Moreover, right AI´s intra-iFC within the SN was correlated with the severity of positive symptoms. However, this result did not survive correction for multiple comparisons (see Tab. S17; $p<0.05$, partial correlations with age, sex, total GM and CPZ as covariates of no-interest). Finally, patients with SR demonstrated an association between aberrant inter-iFC between SN and rvCEN and severity of negative symptoms, indicating a relationship between aberrant inter-iFC and severity of negative symptoms in schizophrenia during remission (see Fig. 13 and Tab. S20; $p<0.05$, partial correlations with age, sex, total GM and CPZ as covariates of no-interest, Bonferroni-corrected for multiple comparisons).

3.4.3. Correlations in patients with major depressive disorder

Patients with MDD demonstrated a positive correlation between right AI´s intra-iFC within the SN and inter-iFC between ipDMN and dCEN as well as between spDMN and dCEN, suggesting an association between right anterior insular dysfunction and aberrant DMN/CEN interactions in patients with MDD (Fig. 14, Tab. S15, $p<0.05$, partial correlations with age, sex and total GM as covariates of no-interest). However, these results did not survive correction for multiple comparisons (n=21). Furthermore, patients with MDD demonstrated a negative correlation between right AI´s intra-iFC within the SN and severity of depressive symptoms as measured by both HAM-D and BDI, indicating an association between right AI dysfunction and severity of depressive symptoms in patients with MDD (see Fig. 14 and Tab. S18; $p<0.05$, partial correlations with age, sex and GM as covariates of no-interest, Bonferroni-corrected for multiple comparisons). Finally, patients with MDD demonstrated no association between aberrant inter-iFC and severity of symptoms (see Fig. 14 and Tab. S21; $p<0.05$, partial correlations with age, sex and GM as covariates of no-interest).

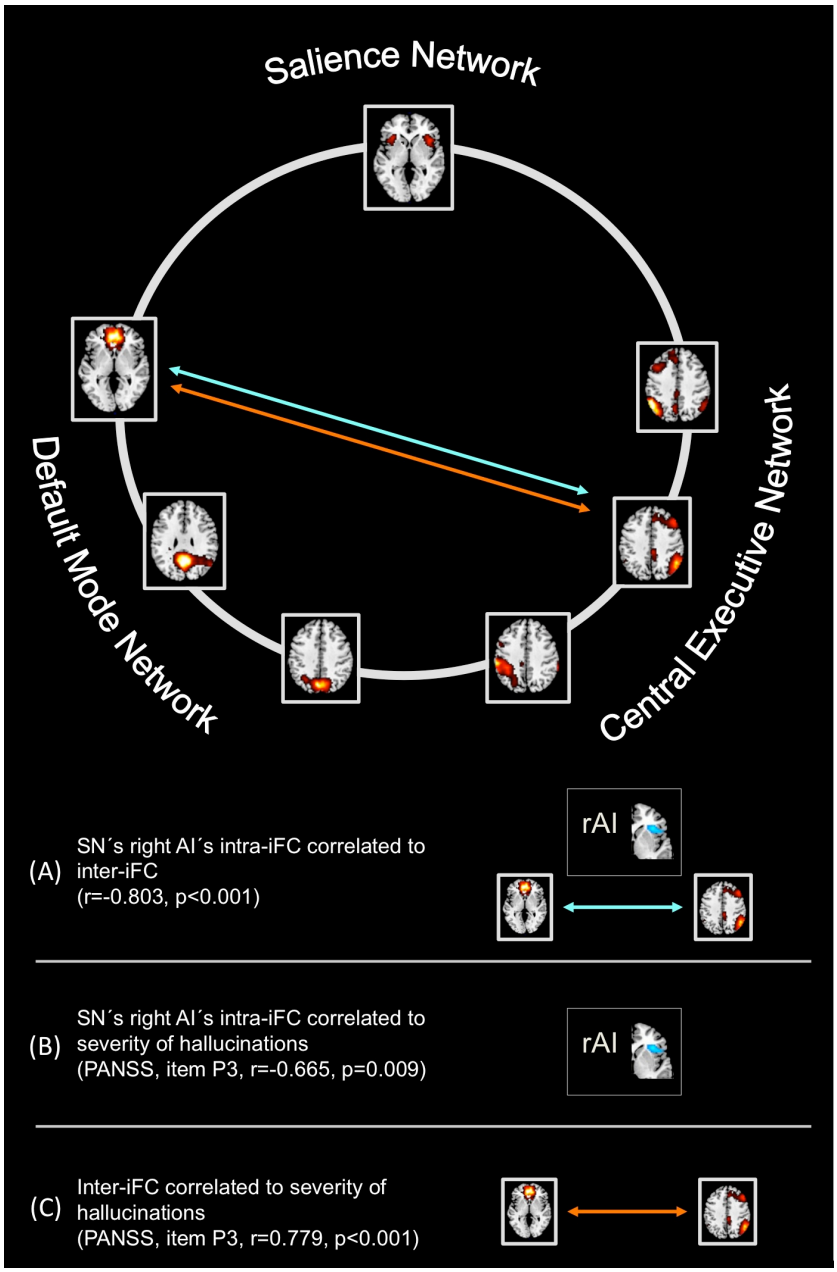

Figure 12. Associations between intra-iFC, inter-iFC and severity of symptoms in patients with schizophrenia during state of acute psychosis.

Spatial maps indicate the anterior/inferior-posterior/superior-posterior default mode network (a/ip/spDMN), left-ventral/right-ventral/dorsal central executive network (lv/rv/dCEN), and salience network (SN). In patients with SA, right AI´s intra-iFC within the SN correlated with inter-iFC between aDMN and rvCEN (panel A) as well as with the severity of hallucinations (panel B). Furthermore, inter-iFC between aDMN and rvCEN correlated with the severity of hallucinations (panel C). Partial correlations were corrected for age, sex, total GM volume and medication, Bonferroni-corrected for multiple comparisons. See also Tab. S13, Tab. S16 and Tab. S19. Modified figure and modified legend taken from (Manoliu et al., 2013a).

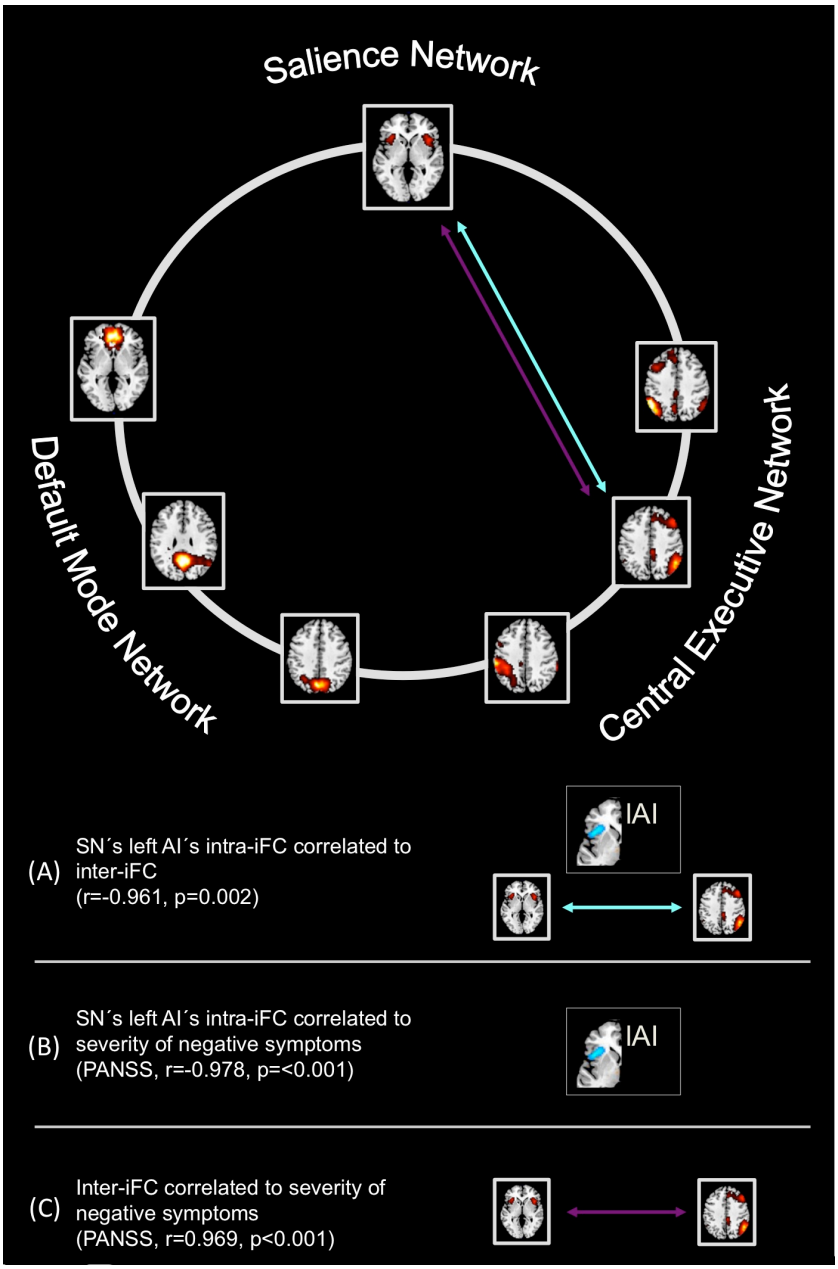

Figure 13. Associations between intra-iFC, inter-iFC and severity of symptoms in patients with schizophrenia during state of remission.
Spatial maps indicate the anterior/inferior-posterior/superior-posterior default mode network (a/ip/spDMN), left-ventral/right-ventral/dorsal central executive network (lv/rv/dCEN), and salience network (SN). In patients with SR, left AI´s intra-iFC within the SN correlated with inter-iFC between SN and rvCEN (panel A) as well as with the severity of negative symptoms (panel B). Furthermore, inter-iFC between SN and rvCEN correlated with the severity of negative symptoms (panel C). Partial correlations were corrected for age, sex, total GM volume and medication, Bonferroni-corrected for multiple comparisons. See also Tab. S14, Tab. S17 and Tab. S20. Modified figure and modified legend taken from (Manoliu et al., 2013b).

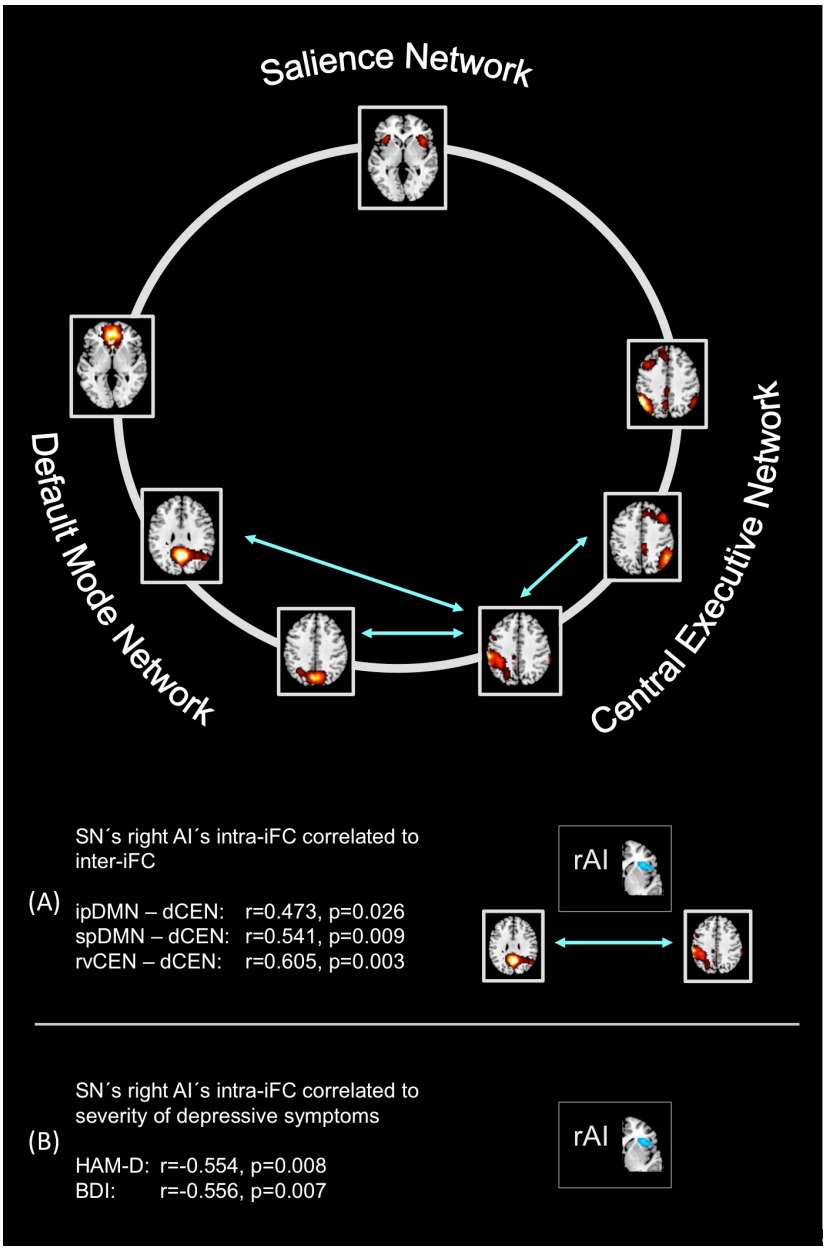

Figure 14. Associations between intra-iFC, inter-iFC and severity of symptoms in patients with major depressive disorder.
Spatial maps indicate the anterior/inferior-posterior/superior-posterior default mode network (a/ip/spDMN), left-ventral/right-ventral/dorsal central executive network (lv/rv/dCEN), and salience network (SN). In patients with MDD, right AI´s intra-iFC within the SN correlated with inter-iFC between ipDMN and dCEN, spDMN and dCEN and rvCEN and dCEN (panel A). However, these correlations did not survive correction for multiple comparisons (n=21). Furthermore, AI´s intra-iFC within the SN correlated with the severity of depressive symptoms (panel B). Partial correlations were corrected for age, sex and GM volume, Bonferroni-corrected for multiple comparisons. See also Tab. S15, Tab. S18 and Tab. S21. Modified figure and modified legend taken from (Manoliu et al., in review).

3.5. Control parameters

*Brain structure***.** To investigate possible between-group differences in anatomy, voxel-wise two-sample t-tests were performed on GM maps between each group of patients and the corresponding group of healthy controls. For all groups, analyses yielded no significant results ($p<0.05$, FWE-corrected, corrected for age and sex), suggesting no major structural anomalies in patients with schizophrenia or major depressive disorder). However, when applying a very liberal threshold ($p<0.001$, uncorrected), patients with MDD demonstrated decreased GM in several brain regions being part of the DMN and SN, including the anterior cingulate cortex, bilateral anterior insular cortex and middle temporal cortex, possibly suggesting subtle structural anomalies in patients with MDD. To investigate possible influences of structural anomalies on reported results, GM volumes were extracted for each group of patients and correlated with intra-iFC within ($p<0.05$, FWE-corrected) and inter-iFC between networks ($p<0.05$, corrected for multiple comparisons), respectively. No significant correlations were found. Furthermore, extracted GM volumes were entered as covariates-of-no-interest in all analyses of functional connectivity to account for possible effects of structural properties on FC in all groups of patients (see sections above).

Medication. Regarding possible effects of antipsychotic medication (Sambataro et al., 2010), the level of antipsychotic medication as measured via CPZ (Woods, 2003) was assessed for patients with schizophrenia and correlated with intra-iFC within ($p<0.05$, FWE-corrected) and inter-iFC between networks ($p<0.05$, corrected for multiple comparisons), respectively. No significant correlations were found. Furthermore, CPZ values were entered as covariates-of-no-interest in all analyses of functional connectivity to control for possible effects of antipsychotic medication on FC. Since no established method similar to CPZ-calculation exists currently for antidepressant medication, the level of antidepressant medication has not been entered as

covariate-of-no-interest in analyses investigating FC in patients with MDD. Please see section “4.5. Control parameters” for extensive discussion of this constraint.

4. Discussion

To investigate a possible association between anterior insular (AI) dysfunction within the salience network (SN) and aberrant inter-network connectivity between default mode- (DMN) and central executive network (CEN) as well as severity of symptoms in schizophrenia and major depressive disorder, resting-state fMRI was used to study intrinsic functional connectivity within (intra-iFC) and between (inter-iFC) intrinsic connectivity networks (ICNs) in patients with schizophrenia during state of acute psychosis and state of remission, patients with major depressive disorder and corresponding groups of healthy controls. Compared to the corresponding groups of healthy controls, all three patient groups demonstrated aberrant intra-iFC in the AI within the SN, indicating the presence of insular dysfunction in both schizophrenia and major depressive disorder. Furthermore, all groups of patients demonstrated aberrant inter-iFC between the DMN and CEN, suggesting the presence of aberrant DMN/CEN interactions in schizophrenia and major depressive disorder. Finally, aberrant intra-iFC in the AI within the SN was individually associated with the severity of disease-specific symptoms and aberrant between-network interactions in each group of patients. The results of the current thesis are perfectly in line with recently proposed models of insular dysfunction in psychopathology (Menon, 2011); (Palaniyappan et al., 2012); (Hamilton et al., 2013) and extend our knowledge about the association between insular dysfunction, aberrant between-network interactions and severity of disease- and state- specific symptoms in patients with schizophrenia and major depressive disorder, indicating a general reorganization of the DMN, SN and CEN in mental disorders.

4.1. Intrinsic connectivity networks (ICNs)

The objective of this thesis was to investigate possible re-organization of intrinsic functional connectivity (iFC) within and between the DMN, SN and CEN in patients with schizophrenia and MDD. High-model order ICA yielded 7 ICNs, each representing distinct subcomponents of DMN, SN and CEN. In general, the identified networks are well in line with previous reports of functional architecture within the DMN (Buckner et al., 2008), SN (Seeley et al., 2007) and CEN (Fox and Raichle, 2007). Particularly, the configuration of functional subsystems is in accordance with recent reports (Allen et al., 2011); (Abou-Elseoud et al., 2010); (Kiviniemi et al., 2009), indicating the presence of the basic functional architecture of all ICNs in all investigated groups. Noteworthy, analysis of inter-iFC yielded positive correlations between distinct subsystems of the DMN and CEN in all groups. Despite the inconsistency with suggested patterns of anti-correlation between DMN and CEN (Fox and Raichle, 2007), these findings match findings of a recently reported study applying high-model order ICA to investigate distinct subsystems of the DMN and CEN, respectively (Allen et al., 2011). Furthermore, a recent study investigating the temporal properties of the DMN via high temporal resolution rs-fMRI confirmed that the DMN comprises several subsystems, each characterized by it´s own characteristic pattern of temporal activity and, most notably, by it´s specific pattern of inter-iFC with other networks´ subsystems (Smith et al., 2012). Taken together, the current results suggest both the validity of applied methods and the representative nature of investigated participants.

4.2. Intrinsic functional connectivity within networks (intra-iFC)

All three patient groups showed aberrant intrinsic functional connectivity (intra-iFC) within the DMN, SN and CEN. Considering the hypothesis of the current study, it is of particular interest to note that all three groups showed aberrant intra-iFC in the anterior insula (AI) within the SN, supporting recently formulated models of anterior insular dysfunction in psychiatric disorders (Menon, 2011), including schizophrenia (Palaniyappan and Liddle, 2012) and major depressive disorder (Hamilton et al., 2013). Furthermore, the findings within the DMN and CEN were well in line with the current literature, demonstrating the representativeness of the investigated patients as well as the validity of the methodological approach. Taken together, current results suggest a robust reorganization of DMN, SN and CEN in psychiatric disorders, such as schizophrenia and major depressive disorder. In the following sections, all findings regarding aberrant intra-iFC within the DMN, SN and CEN will be extensively discussed for each group of patients, respectively.

4.2.1. Intra-iFC in patients with schizophrenia during acute psychosis and remission

Salience Network. Regarding the SN, patients with schizophrenia demonstrated decreased intra-iFC within the bilateral AI and increased intra-iFC within the ACC during acute psychosis and remission. Furthermore, aberrant intra-iFC within the right AI was associated with the severity of positive symptoms during psychosis (see Fig. 12 and Tab. S16) and remission (see Tab. S17, not significant after correction for multiple comparisons (n=21)), while aberrant intra-iFC within the left AI was associated with the severity of negative symptoms (see Fig. 13 and Tab. S17). These results are in line with recently formulated models of insular dysfunction in schizophrenia (Palaniyappan and Liddle, 2012), which has been suggested to be associated with both aberrant between-network interactions and severity of symptoms (Menon, 2011) and

present even during psychotic remission (see also section “4.4. The association between aberrant intra-iFC, aberrant inter-iFC and severity of symptoms” for detailed discussion of these associations). In general, insular dysfunction within the SN in patients with schizophrenia might lead to aberrant assignment of salience to internally generated perceptions, thus explaining patients´ difficulties to discriminate between self-generated perceptions and externally perceived stimuli, possibly explaining positive symptoms such as hallucinations (Kapur, 2003); (Palaniyappan et al., 2012). Furthermore, aberrant salience is suggested to modulate the processing of rewarding events, conceivably explaining both disrupted learning and negative symptoms in schizophrenia (Gradin et al., 2011). Therefore, the described presence of AI dysfunction in schizophrenia during both psychosis and remission is well in line with the current literature and suggests that insular dysfunction might be a characteristic feature of schizophrenia, regardless of the current state of disease. Although the first study derived from this thesis was the first study to demonstrate decreased intra-iFC in the AI within the SN at the time point of publication (Manoliu et al., 2013a), these findings have been confirmed in the meantime by Moran and colleagues, who applied a different methodological approach to investigate iFC within the insula in patients with schizophrenia (Moran et al., 2013).

Default Mode Network. Regarding the DMN, patients with schizophrenia during state of acute psychosis demonstrated decreased intra-iFC within as well as increased inter-iFC between the subsystems of the DMN (see Fig. 6, Fig. 9 as well as Tab. S7 and Tab. S10), suggesting an increased iFC within the DMN. During psychotic remission, only decreased intra-iFC within distinct subsystems of the DMN was still present, while the increased inter-iFC between DMN´s subsystems demonstrated during psychosis was absent. (see Fig. 7, Fig. 10 and Tab. S8, Tab. S11). These results are in accordance with the current literature, reporting a relationship between increased intra-iFC within the DMN and the presence of psychosis in patients with schizophrenia (Garrity et al.,

2007). However, it is to note that heterogeneous alterations of iFC within the DMN have been reported (Whitfield-Gabrieli and Ford, 2012), including both increased (Whitfield-Gabrieli et al., 2009) and decreased (Camchong et al., 2011) intra-iFC within the DMN. It has been discussed that the application of different methodological approaches and investigation of inhomogeneous patient samples including patients during different states of disease or patients with schizoaffective disorder (Woodward et al., 2011) might explain these inconsistent results. To avoid these methodological problems, only patients meeting the criteria for schizophrenia according to DSM-IV (American Psychiatric Association, 2000) were included and investigated in different groups in accordance to their state of disease. Subsequently, a standardized pipeline for ICA-based analysis of rs-fMRI data (Allen et al., 2011) was applied to identify and analyze the networks of interest in a robust and reproducible way. Taken together, the findings presented in the current thesis might contribute to a better understanding of the inconsistent findings of aberrant intra-iFC within the DMN in patients with schizophrenia reported in the literature.

Central Executive Network. Regarding the CEN, patients with schizophrenia during state of acute psychosis demonstrated increased intra-iFC with a focus on regions within the frontal lobe and decreased intra-iFC with a focus on regions located within the parietal lobe while patients during remission demonstrated increased intra-iFC in the temporal lobe only (see Fig. 6 and Fig. 7 as well as Tab. S7 and Tab. S8). Disruption of the CEN is a characteristic feature of many mental disorders, including schizophrenia (Woodward et al., 2011). In particular, studies investigating the iFC within the CEN reported both increased and reduced intra-iFC in patients with schizophrenia (Rotarska-Jagiela et al., 2010). Therefore, the current results are well in line with recent studies and extend the current knowledge about altered intra-iFC in patients with schizophrenia by indicating that aberrant iFC within the CEN might be dependent on the state of disease in schizophrenia.

4.2.2. Intra-iFC in patients with major depressive disorder

Salience Network. Regarding the SN, patients with MDD showed decreased intra-iFC in the bilateral AI as well as increased intra-iFC in the ACC (see Fig. 8 and Tab. S9). Furthermore, aberrant intra-iFC within the right AI was associated with the severity of symptoms (see Fig. 14 and Tab. S18) and aberrant inter-iFC between DMN and CEN (see Tab. S15, not significant after correction for multiple comparisons (n=21)). These results are in line with studies reporting aberrant iFC within the AI in patients with MDD (Horn et al., 2010); (Sliz and Hayley, 2012) and recently formulated models of insular dysfunction in major depressive disorder (Hamilton et al., 2013), which has been suggested to be associated with both aberrant between-network interactions and severity of symptoms (Menon, 2011). A detailed discussion of these associations is presented in section “4.4. The association between aberrant intra-iFC, aberrant inter-iFC and severity of symptoms”. In general, insular dysfunction within the SN might induce aberrant salience towards rewarding events, which has been shown to be associated with anhedonia in patients with MDD (Gradin et al., 2011) and/or aberrant salience towards self-referential thoughts, possibly underlying depressive symptoms, such as rumination (Hamilton et al., 2011b). Especially since the AI is also critically involved in emotional processing (Craig, 2002); (Craig, 2009), the current results represent a further hint towards the relevance of insular dysfunction for patients with MDD.

Default Mode Network. Patients with major depressive disorder demonstrated increased intra-iFC within two subsystems of the DMN (i.e. aDMN and ipDMN) as well as mainly increased intra-iFC within the spDMN (see Fig. 8 and Tab. S9). Furthermore, patients with MDD demonstrated a trend to increased inter-iFC between aDMN and spDMN (see Tab. S12, not significant after correction for multiple comparisons (n=21)), suggesting an increased iFC within the DMN. These results are in accordance with the current literature, reporting increased iFC within

the DMN of patients with MDD during rest (Greicius et al., 2007); (Broyd et al., 2009); (Posner et al., 2013). In addition to increased iFC during rest, patients with MDD show decreased activation patterns of the DMN during evaluation-tasks of positive and negative stimuli (see (Hamilton et al., 2013) for review), suggesting that the DMN-mediated evaluation of self-oriented stimuli and/or thoughts might be more receptive to internally-generated reflections than to perceived external stimuli (Hamilton et al., 2013). Taking these observations into consideration, the current results provide further evidence for the important role of disrupted DMN-mediated self-related cognitive processes in patients with major depressive disorder.

Central Executive Network. Regarding the intra-iFC within the CEN, patients with MDD demonstrated heterogeneous alterations, including increased intra-iFC in the right angular gyrus and decreased intra-iFC in the left precuneus and left temporal gyrus (see Fig. 8 and Tab. S9). These results are in accordance with previous studies reporting altered activity within the angular gyrus, temporal gyrus and precuneus in patients with MDD (Fitzgerald et al., 2008a) and support the notion that the CEN, which is involved in demanding goal-directed cognitive activity, shows aberrant iFC in patients with MDD (Fitzgerald et al., 2008b). Furthermore, these results extend our knowledge by providing first evidence for the suggested concept, that the reported heterogeneous results within the CEN in patients with MDD might reflect alterations within distinct sub-systems of the CEN, each maintaining characteristic tonic (resting-state) or phasic (affective response) cognitive processes (Hamilton et al., 2013). Future studies investigating the behavioral relevance of distinct subsystems of the CEN might contribute to a better understanding of the frequently reported heterogeneous alterations within the CEN in patients with MDD.

4.3. Intrinsic functional connectivity between networks (inter-iFC)

All three patient groups showed aberrant intrinsic functional connectivity (inter-iFC) between the DMN, SN and CEN. Considering the hypothesis of the current thesis, it is of particular interest to note that all three groups showed aberrant inter-iFC between the DMN and CEN, supporting recently formulated models of aberrant DMN/CEN interactions in psychiatric disorders (Menon, 2011), including schizophrenia (Palaniyappan and Liddle, 2012) and major depressive disorder (Hamilton et al., 2013). Furthermore, the findings within the DMN and CEN are well in line with the current literature, demonstrating the representativeness of the investigated patients as well as the validity of the methodological approach. Taken together, current results suggest a robust reorganization of the interactions between DMN, SN and CEN in schizophrenia and major depressive disorder. In the following sections, all findings regarding aberrant inter-iFC between the DMN, SN and CEN will be extensively discussed for each group of patients, respectively.

4.3.1. Inter-iFC in patients with schizophrenia during acute psychosis and remission

Regarding the inter-iFC between DMN and CEN, patients with schizophrenia during state of acute psychosis showed aberrant inter-iFC between the aDMN and rvCEN as well as between the spDMN and rvCEN (see Fig. 9 and Tab. S10), while patients with schizophrenia during psychotic remission demonstrated aberrant inter-iFC between ipDMN and rvCEN (see Fig. 10 and Tab. S11), indicating a robust presence of aberrant DMN/CEN interactions in schizophrenia. Furthermore, the aberrant inter-iFC between the aDMN and rvCEN was associated with the severity of hallucinations in patients during psychosis, indicating a link between aberrant DMN/CEN interactions and psychopathology. A detailed discussion of these associations is presented in section “4.4. The association between aberrant intra-iFC,

aberrant inter-iFC and severity of symptoms". These results are perfectly in line with recent studies (Skudlarski et al., 2010); (Hasenkamp et al., 2011) reporting aberrant recruitment of anticorrelated DMN and CEN in patients with schizophrenia and proposed models, which suggest that schizophrenia is characterized by aberrant engagement and disengagement of the internally-oriented DMN and externally-oriented CEN (Williamson, 2007), possibly underlying patients´ difficulties to discriminate between internally-generated and externally-perceived stimuli (Menon, 2011). The current results extend these findings by showing that aberrant DMN/CEN interactions are associated with aberrant intra-iFC within the AI and not only present during state of acute psychosis but also during state of remission. The notion that aberrant inter-iFC is also present during psychotic remission is further supported by the finding that patients during remission showed aberrant inter-iFC between the SN and CEN (see Fig. 10 and Tab. S11), which again was associated with the severity of negative symptoms and left AI dysfunction (see section "4.4. The association between aberrant intra-iFC, aberrant inter-iFC and severity of symptoms" for detailed discussion of these associations). Taken together and in accordance with recently formulated models of aberrant DMN/CEN interactions in schizophrenia (Palaniyappan and Liddle, 2012), current results provide additional evidence for aberrant between-network interactions in patients with schizophrenia and extend the current knowledge by demonstrating that these alterations are partly robust disease-specific features and partly modulated by the presence of psychosis.

4.3.2. Inter-iFC in patients with major depressive disorder

Patients with MDD showed decreased inter-iFC between the ipDMN and dCEN as well as between the spDMN and dCEN, suggesting a decreased inter-iFC between the DMN and CEN (see Fig. 11 and Tab. S12). Furthermore, both findings showed a trend to significant association with aberrant intra-iFC in the right AI within the SN (see Tab.

S15, not significant after correction for multiple comparisons (n=21)), indicating an association between insular dysfunction and aberrant DMN/CEN interactions in patients with MDD (a detailed discussion of these associations is presented in section “4.4. The association between aberrant intra-iFC, aberrant inter-iFC and severity of symptoms”). These results support the concept that disrupted engagement and disengagement of DMN-mediated, self-referential and CEN-mediated, goal-directed cognitive activity might underlie several symptom dimensions, which are characteristic for MDD (Hamilton et al., 2013). In particular, a recent study investigating the relationship between the DMN´s and CEN´s activity in patients with MDD demonstrated increased dominance of DMN´s activity compared to CEN´s activity in patients with MDD, which was furthermore associated with the severity of ruminations (Hamilton et al., 2011b). Furthermore, patients with MDD showed increased inter-iFC between the SN and DMN (see Fig. 11 and Tab. S12), suggesting a heightened relevance of DMN-mediated cognitive processes in terms of SN-mediated salience mapping, supporting recent models of aberrant inter-network connectivity due to AI/SN dysfunction in MDD (Menon, 2011). Taken together, the current findings provide further evidence for the presence of aberrant DMN/CEN interactions in patients with MDD, supporting the notion that disrupted disengagement of DMN-mediated self-related cognitive activity might be a characteristic feature of MDD, potentially facilitating disease-specific symptoms, such as depressive rumination.

4.4. The association between aberrant intra-iFC, aberrant inter-iFC and severity of symptoms

All group of patients showed an association between aberrant intra-iFC in the AI within the SN, aberrant between-network interactions and severity of disease-specific symptoms. In particular, aberrant intra-iFC in the right AI was associated with aberrant DMN/CEN interactions (SA, MDD) and severity of psychotic (SA, SR) and depressive (MDD) symptoms, while aberrant intra-iFC in the left AI was associated with aberrant SN/CEN interactions and severity of negative symptoms (SR). Recently suggested models postulate that anterior insular dysfunction might lead to dysfunctional modulation of between-network interactions (Sridharan et al., 2008); (Menon and Uddin, 2010); (Uddin et al., 2011). In particular, aberrant engagement and disengagement of the internally-oriented / self-related DMN and externally-oriented / goal-directed CEN might be associated with aberrant detection and mapping of salient internal or external stimuli and/or events (Menon, 2011), possibly giving rise to disease-specific symptom dimensions (Palaniyappan and Liddle, 2012); (Hamilton et al., 2013) via distinct disease-specific pathways (Menon, 2011). The current results strongly support these models and extend our knowledge about insular dysfunction and DMN/SN/CEN reorganization in mental disorders by providing first evidence for a link between aberrant intra-iFC within the AI, aberrant inter-iFC between networks and severity of disease-specific symptoms. In the following, these relations will be presented and linked to the current literature for patients with schizophrenia and patients with MDD in separate sections.

4.4.1. Correlations in patients with schizophrenia during acute psychosis and remission

In line with the presented hypothesis and recently formulated models (Menon, 2011); (Palaniyappan and Liddle, 2012), patients with schizophrenia demonstrated both aberrant intra-iFC in the right and left AI within the SN (see Fig. 6, Fig. 7 and Tab. S7, Tab. S8) and altered

inter-iFC between DMN, SN and CEN as a function of state of disease (see Fig. 9, Fig. 10 and Tab. S10, Tab. S11). Furthermore, aberrant intra-iFC within the AI and aberrant intra-iFC between distinct networks were associated with each other and correlated with the severity of state-specific symptoms. In particular, aberrant intra-iFC within the right AI was associated with aberrant DMN/CEN interactions and severity of positive symptoms in psychosis (see Fig. 12, Tab. S13 and Tab. S16) and showed a trend to significant correlation with positive symptoms during remission (see Fig. 13 and Tab. S17; not significant after correction for multiple comparisons). The missing significance could be explained by small statistical power due to the limited size of patient sample during remission (n=12) and/or small variance of positive symptoms in patients during psychotic remission, see also section “4.6. Limitations”). Aberrant intra-iFC within the left AI was associated with aberrant SN/CEN interactions and severity of negative symptoms in remission (see Fig. 13 and Tab. S14, Tab. S17). All tests were corrected for age, sex, gray matter and level of antipsychotic medication (as measured with CPZ), making it thus very unlikely that the presented results are influenced by these factors. Taken together, the current results demonstrate a link between insular dysfunction, aberrant between-network interactions and severity of state-specific symptoms in patients with schizophrenia as a function of state of disease.

The current results support recently suggested models of insular dysfunction within the SN in schizophrenia, facilitating aberrant between-network interactions and thus distinct characteristic symptoms both during psychosis and psychotic remission (Palaniyappan and Liddle, 2012). Following points provide further support of this notion: (1) The right AI has been demonstrated to critically modulate between-network interactions in healthy subjects (Sridharan et al., 2008); (Menon and Uddin, 2010); (Uddin et al., 2011). (2) Structural and functional alterations within the AI are among the most frequent reported findings in schizophrenia and have been shown to be associated with the severity of positive and negative symptoms (Glahn et al., 2008); (Ellison-

Wright et al., 2008); (Koutsouleris et al., 2008); (Ellison-Wright and Bullmore, 2009); (White et al., 2010); (Palaniyappan et al., 2011); (Gradin et al., 2013); (Moran et al., 2013). (3) The current results confirm postulated models suggesting a link between insular dysfunction and aberrant DMN/CEN engagement and disengagement, which is potentially contributing to the presence of positive symptoms during psychosis and negative symptoms during remission (Palaniyappan and Liddle, 2012). In particular, aberrant assignment of salience to internally generated and externally perceived stimuli is proposed to cause abnormal recruitment of cognitive networks, thus resulting in abnormal behavioral responses (Menon, 2011). (4) Shortly after the presented results have been reported (Manoliu et al., 2013a), another study confirmed aberrant right AI modulation of DMN/CEN interactions in patients with schizophrenia and reported an association with the severity of cognitive symptoms (Moran et al., 2013). Therefore, the current results strongly suggest that AI dysfunction is a characteristic feature of schizophrenia and might contribute to the emergence of state-specific symptoms in patients with schizophrenia via aberrant modulation of between-network interactions.

It is to note that the presented findings indicate an asymmetric dysfunction of the AI in patients with schizophrenia depending on the state of the disease. While aberrant intra-iFC within the right AI was associated with aberrant DMN/CEN interactions and severity of positive symptoms during psychosis (see Fig. 12, Tab. S13 and Tab. S16), aberrant intra-iFC within the left AI was associated with aberrant SN/CEN interactions and severity of negative symptoms during remission (see Fig. 13, Tab. S14 and Tab. S17). These findings are in line with the described asymmetric representation of interoceptive information in the right and left AI, which has been proposed to stem from the asymmetric configuration of the peripheral autonomic nervous system (Craig, 2009). In general, the right AI is more linked to the sympathetic nervous system, whereas the left AI is more linked to the parasympathetic nervous system (Craig, 2002). Therefore, it has been

suggested that the right AI is associated with “sympathetic” emotions induced by arousal-increasing stimuli such as pain or aversive stimuli, whereas the left AI is more related to positive emotions, including joy, relaxation and romantic or maternal love (Craig, 2009). The right AI´s role in modulating behavioral responses in the context of arousal and the left AI´s role in processing emotions (Craig, 2009) might explain, why right AI dysfunction was consistently linked with aberrant DMN/CEN modulation contributing to the rise of positive symptoms, while left AI dysfunction was linked with the severity of negative symptoms which are mainly characterized by diminished social interactions and rigid affect, possibly via impaired responses to pleasant stimuli and rewards (Gradin et al., 2013). This notion is further supported by studies reporting an association between structural anomalies within the AI and severity of positive and negative symptoms in patients with schizophrenia (Koutsouleris et al., 2008); (Palaniyappan et al., 2012). Taken together, the current results provide first evidence for an association between the asymmetric organization of the AI, lateralized insular dysfunction and distinct symptom dimensions as a function of state of disease in patients with schizophrenia. It is to note, however, that asymmetric insular dysfunction was not explicitly tested within a unified statistical framework. Therefore, further studies exploring this observation are necessary to allow for a better understanding of the significance of the AI´s asymmetric dysfunction in schizophrenia.

4.4.2. Correlations in patients with major depressive disorder

In line with the presented hypothesis and recently formulated models (Menon, 2011); (Hamilton et al., 2013), patients with major depressive disorder demonstrated decreased intra-iFC in bilateral AI within the SN (see Fig. 8 and Tab. S9) and decreased inter-iFC between both ipDMN and dCEN as well as between spDMN and dCEN (see Fig. 11 and Tab. S12). Additionally, patients demonstrated increased inter-iFC between the SN and DMN (see Fig. 11 and Tab. S12). Aberrant intra-iFC within the right AI was associated with the severity of depressive symptoms as

assessed via both HAM-D and BDI (see Fig. 14 and Tab. S18) and demonstrated a trend to significant correlation with aberrant DMN/CEN interactions (the latter being not significant after correction for multiple comparisons (n=21), see Tab. S15). All tests were corrected for age, sex and gray matter, making it thus very unlikely that the presented results are influenced by these factors. Taken together, the current results demonstrate a link between insular dysfunction, aberrant between-network interactions and severity of depressive symptoms in patients with major depressive disorder.

These results are line with the hypothesis that dysfunction within the right AI might be associated with aberrant DMN/CEN interactions, therefore causing disease-specific symptoms in patients with MDD (Menon, 2011). This notion is supported by several observations: (1) The right AI has been shown to play a critical role in modulating DMN/CEN interactions in healthy subjects (Sridharan et al., 2008). (2) Structural and functional alterations within the right AI are among the most regular reported findings in patients with MDD (Savitz and Drevets, 2009); (Diener et al., 2012); (Sliz and Hayley, 2012); (Hamilton et al., 2013). (3) The present results confirm previously postulated models of insular dysfunction in MDD, which suggested a link between aberrant AI-modulated network-switching, aberrant engagement and disengagement of internally-oriented DMN-mediated activity and externally-oriented CEN activity, and severity of depressive symptoms in patients with MDD (Uddin et al., 2011); (Menon and Uddin, 2010); (Menon, 2011). (4) The present results are further supported by findings reported by Hamilton and colleagues (Hamilton et al., 2011b), who found that the right AI demonstrated altered activity at the onset of DMN/CEN activity, which in turn was associated with the severity of ruminations. Furthermore, a recent meta-analysis demonstrated, that the right AI showed decreased activity during switching between affective and cognitive control tasks (Diener et al., 2012). Thus, presented results provide first evidence for a direct relationship between

right AI dysfunction within the SN, aberrant DMN/CEN interactions and general severity of depressive symptoms in patients with MDD.

Intra-iFC was decreased in both left and right AI within the SN in patients with MDD. However, only the right AI was associated with the severity of depressive symptoms and showed a trend to significant correlation with aberrant inter-iFC between the DMN and CEN. These results are in accordance with the current literature, suggesting a prominent role of the right AI in modulating DMN/CEN interactions in healthy subjects (Sridharan et al., 2008). Furthermore, only the right AI showed abnormal activation response at the onset of DMN- and CEN activity in patients with MDD during rest, while the left AI showed no association with DMN/CEN activation and deactivation (Hamilton et al., 2011b). This finding might be explained by the asymmetric organization of the left and right AI ((Craig, 2002), see above). In more detail, the right AI is activated in response to arousing stimuli and interoceptive perceptions, including physical (Craig, 2009) and mental pain, such as social rejection (Eisenberger et al., 2003); (Kross et al., 2011). As a reaction to perceived stimuli, the right AI facilitates the engagement and disengagement of distinct cognitive systems in order to generate an adequate behavioral response (Menon and Uddin, 2010). Especially since it has been demonstrated that the sympathetic activity is increased in patients with MDD (Barton et al., 2007), the current results might represent a first hint towards an association between right AI dysfunction, aberrant sympathetic activity and abnormal interoceptive processing in MDD. Taken together, present findings strongly support suggested models of abnormal AI modulation of inter-network connectivity in MDD (Menon, 2011); (Hamilton et al., 2013), extending the current knowledge by demonstrating a direct association between aberrant intra-iFC in the AI within the SN, aberrant DMN/CEN interactions and severity of depressive symptoms in patients with MDD.

4.5. Control parameters

Brain structure. When applying a standard-threshold of $p<0.05$, FWE-corrected, voxel-wise investigations of between-group differences yielded no significant results for all three groups of patients. However, when applying a more liberal threshold ($p<0.001$, uncorrected), patients with MDD showed decreased GM volume in several regions, which are part of the DMN or SN. To account for possible influences of structural anomalies on iFC, total GM volumes were extracted and correlated with intra-iFC within and inter-iFC between networks ($p<0.05$, corrected for multiple comparisons), yielding no significant results. Furthermore, GM scores were entered as covariates-of-no-interest in all analyses of iFC, making it thus very unlikely that the reported results in iFC are explained by structural anomalies. However, both approaches assume linearity and do therefore not exclude non-linear effects of structural anomalies on iFC. Since the nature of the association between structural properties and functional connectivity is still not completely understood, further studies are necessary to better understand the possible effect of structural anomalies on iFC within and between ICNs in both healthy subjects and patients with mental disorders.

Medication. Psychotropic medication has been demonstrated to have an effect on iFC (Sambataro et al., 2010); (Delaveau et al., 2011). However, the patient samples investigated in scope of this thesis were predominately medicated. Regarding patients with schizophrenia, the amount of antipsychotic medication was calculated via CPZ (Woods, 2003), correlated with scores representing intra-iFC and inter-iFC (yielding no significant results) and entered as covariates-of-no-interest in all analyses investigating iFC. However, following the above-mentioned argumentation, investigating or correcting for potential linear relationships does not exclude the possibility of non-linear effects of antipsychotic medication on iFC in patients with schizophrenia. Regarding patients with MDD, the level of antidepressant medication could not be taken into account for analyses of iFC since no well-

established method comparably to the calculation of CPZ is currently available to quantify the amount of antidepressant medication. Therefore, no linear relationship between the level of antidepressant medication and scores of iFC could be investigated. However, there is evidence that the obtained results are not due to antidepressant medication. In the current study and in line with the literature (Greicius et al., 2007); (Broyd et al., 2009), patients with MDD showed increased intra-iFC within the DMN. Recently, Posner and colleagues (Posner et al., 2013) applied rs-fMRI within the framework of a double-blind, placebo-controlled trial investigating the effect of duloxetine, a serotonin and noradrenaline reuptake inhibitor, on iFC within the DMN in patients with dysthymia, a mood disorder characterized by similar alterations in iFC (i.e. increased intra-iFC within the DMN) as MDD. Compared to placebo, duloxetine was associated with a decrease of the initially increased iFC within the DMN in patients with dysthymia (Posner et al., 2013), suggesting that antidepressant medication might contribute to a normalization of aberrant iFC within the DMN in affective disorders. This finding might represent a hint that the results presented in the current study are not explained by but found despite the level of medication. However, it is evident that it is principally not possible to rule out that reported results have been modulated by possible effects of antipsychotic and/or antidepressant medication on iFC in patients with schizophrenia and MDD. Further studies investigating the relationship between aberrant intra-iFC within and inter-iFC between ICNs in un-medicated patients are necessary to replicate the results of the current thesis.

4.6. Limitations

In addition to the two aspects discussed in the previous section, various methodological considerations have to be taken into account.

Sample size. In the current thesis, iFC was investigated in 18 patients with schizophrenia during psychosis, 12 patients with schizophrenia during remission, 25 patients with MDD and corresponding groups of healthy controls, respectively. Particularly the sample size of patients with schizophrenia during remission was rather small. It is to note that a small sample size reduces the power of applied statistical tests, resulting in a higher risk of obtaining false negative results (type-II-error). Therefore it is presumable that not all anomalies in iFC were detected by the applied statistical tests. At the same time, however, small sample sizes yield a relatively low risk for obtaining false positive results (type-I-error), suggesting the robust nature of the presented results. Nonetheless, the presented results should be replicated in larger patient samples.

Psychiatric co-morbidities. Although patients with schizophrenia yielded no co-morbidities, 14 out of 25 patients were diagnosed with a mental co-morbidity. In particular, 6 patients with MDD were diagnosed with generalized anxiety disorder, 5 were diagnosed with dependent personality disorder and 3 were diagnosed with somatization disorder. It is to note, however, that MDD is a largely heterogeneous mental disorder, which is characterized by a broad range of duration of illness, number of major depressive episodes, family history and especially psychiatric co-morbidities. To assess potential alterations in a representative group of patients with MDD, we applied the inclusion and exclusion criteria reported by Hennings and colleagues, who investigated clinical characteristics and clinical outcome in 842 patients with MDD including patients with the above-mentioned co-morbidities (Hennings et al., 2009).

Independent Component Analysis. Over the last couple of years, ICA has emerged as a very popular method to investigate rs-fMRI data. However, few methodological constraints remain still unresolved, including the subjective bias of IC identification and the rather arbitrary selection of the number of ICs to be estimated based on the preprocessed rs-fMRI data (Cole et al., 2010). To avoid these potential problems, two findings were of particular interest: (1) Recently, it has been demonstrated that a model order (i.e. number of ICs to be estimated) around 70 +/- 10 offers the possibility to investigate all known functional subsystems of ICNs while yielding the lowest risk to obtain false-positive results (Abou-Elseoud et al., 2010). (2) Consequently, Allen and colleagues investigated ICNs in 603 healthy individuals by performing high-model-order ICA, obtaining 75 ICs out of which 28 ICs represented distinct ICNs and were published online ((Allen et al., 2011), see also section “2.4.2. Analysis of functional MRI data”). In the current thesis, the approach proposed by Allen and colleagues was adopted to investigate potential DMN/SN/CEN reorganization in patients with schizophrenia and MDD. Therefore, it was possible to identify the ICNs of interest in an automated and objective way via spatial correlation of the obtained ICs with aforesaid T-maps (see also section “2.4.2. Analysis of functional MRI data” for detailed presentation of the applied identification procedure).

BOLD-signal. Over the last decades, fMRI has swiftly become a widely applied method for mapping neuronal activity supporting cognitive processes in-vivo, thus contributing to a better understanding of the brain´s functional organization and the neurobiological basis of human cognition. However, it is to note that neuronal activity is not measured directly via fMRI but rather inferred from local fluctuations of deoxygenated hemoglobin via BOLD-contrast ((Logothetis, 2002); (Viswanathan and Freeman, 2007), see also section “1.2.1. From BOLD-signal to resting-state functional connectivity”), while the neurophysiological correlates of the measured BOLD-activity are still not completely understood and subject of considerable debate (Bandettini,

2012b). Firstly, vascular structures occupy only 3% of a typical-sized voxel, while the rest is covered by intervascular space consisting of glia cells, neurons and synapses (Logothetis, 2008). Therefore, it has been argued that the BOLD signal fails to distinguish between distinct neuronal processes, including function-specific activation, neuromodulation, excitation and inhibition (Logothetis, 2008). First studies investigating the link between neuronal activity and BOLD-signal in a multimodal way suggested that the BOLD signal is more closely associated with synaptic activity than neuronal spiking activity (Viswanathan and Freeman, 2007). However, a recent study by Karl Deissenroth´s group applying a novel integrated technology combining optogenetic control of inputs with high-field fMRI assessment found that a local stimulation of excitatory neurons causes positive BOLD signals both at the initial location and in downstream targets distant from the location of the applied stimulus (Lee et al., 2010). Secondly, although glia cells have been shown to maintain the neurovascular coupling, it is still unclear to which extent astrocyte-specific properties might modulate the local BOLD-signal (Gurden, 2013). Thirdly, a recent study showed that the physiological mechanisms underlying the increase and decrease of BOLD-signal are quite different, in particular regarding their localization within different cortical layers (Goense et al., 2012). Indeed, each cortical layer displays its own characteristic hemodynamic mechanism, resulting together in the overall signal assessed via fMRI (Bandettini, 2012b). Taken together, these novel insights into the nature of the BOLD-signal illustrate the importance and necessity of future studies investigating the neuronal activity by using a multimodal approach to better understand the underlying neurophysiology. Notwithstanding these current limitations, it has become evident that fMRI represents currently the best available possibility to gain insight into the brain´s basic functional architecture and, which is of particular interest for clinical neuroscience, to generate regionally and/or functionally defined testable hypotheses, which might set the stage for simultaneous multimodal investigations, assessing fMRI, neurochemical

properties and electrical neuronal activity, preferably in a non-invasive way in vivo (Logothetis, 2008).

4.7. Psychopathological implications

Over the last decade, a growing number of neuroimaging studies have examined the functional architecture of the human brain during rest. Theoretical frameworks focusing on the reorganization of large-scale networks in mental disorders provide the possibility to investigate the neural correlates of psychiatric disorders such as schizophrenia and MDD by exploring potential alterations within and between well-known intrinsic connectivity networks. Based on the assumed contribution of these networks to higher cognitive functions in healthy subjects as derived from several task-studies, it is possible to deduce the significance of possible alterations within and between these networks for distinct cognitive processes. Aberrant cognitive processes, on the other hand, might underlie distinct disease-specific symptom dimensions in mental disorders.

Recently, it has been proposed that aberrant cognitive processes might be induced by abnormal organization of distinct networks maintaining higher cognitive functions, such as the DMN, SN and CEN. The DMN maintains internally-oriented / self-referential cognitive processes (Buckner et al., 2008). The CEN maintains externally-oriented / goal-relevant cognitive processes (Fox and Raichle, 2007). Under normal conditions, the coordination between these two networks is mediated by the AI within the SN (Sridharan et al., 2008). Disrupted functional connectivity of the AI within the SN may contribute to aberrant switching between DMN-mediated, self-referential and CEN-mediated, goal-directed processes, giving rise to abnormal behavioral reactions to internal and/or external stimuli and events (Menon and Uddin, 2010). In the following, potential psychopathological implications will be presented for patients with schizophrenia and MDD, respectively.

Potential psychopathological implications for patients with schizophrenia. In the current study, anterior insular dysfunction as well as aberrant between-network interactions correlated with the severity of

positive and negative symptoms in patients with schizophrenia. During psychosis, right AI dysfunction and aberrant DMN/CEN interactions correlated with the severity of hallucinations. During remission, left AI dysfunction and aberrant SN/CEN interactions correlated with the severity of negative symptoms, such as emotional and passive / apathetic emotional withdrawal. Numerous studies propose that hallucinations are related to self-generated inner speech (McGuire et al., 1995), while negative symptoms such as passivity are associated with self-generated actions (Blakemore et al., 2000); (Palaniyappan and Liddle, 2012). In healthy individuals, these internally generated actions and perceptions do not generate proximal salience under normal circumstances. According to Palaniyappan and Liddle´s model of insular dysfunction in schizophrenia (Palaniyappan and Liddle, 2012), the term proximal salience refers to a transitory interoceptive state, which results from the appraisal of the current relevance of internally or externally perceived stimuli and events to induce the adequate behavioral response to these stimuli via AI facilitated regulation of CEN-mediated actions and/or DMN-mediated cognitive processes. In patients with schizophrenia, however, insular dysfunction within the SN as well as the consecutive aberrant AI/SN-mediated modulation of DMN/CEN interactions is disrupted, therefore possibly causing both aberrant salience mapping to internally-generated thoughts and actions as well as abnormal behavioral responses to these internally generated stimuli. In particular, the perception of inner thoughts/speech and actions can reach such a high level of salience, that patients with schizophrenia loose the ability to distinguish whether these stimuli were internally-generated or perceived from the external world, thus giving rise to distinct disease-specific symptoms, such as hallucinations and delusions. While hallucinations might represent the direct experience of salient internally generated stimuli, delusions might represent the individual´s cognitive struggle to make sense of these perceptions (Kapur, 2003).

Potential psychopathological implications for patients with MDD. In the current study, insular dysfunction within the right AI correlated with the severity of depressive symptoms and demonstrated a trend to correlation with aberrant DMN/CEN interactions in patients with MDD. Several decades ago, Aaron T. Beck presented a cognitive theory of depression (Beck, 1967); (Beck and Alford, 2009). He suggested, that depressive symptoms might be caused by negative biases in emotion and cognition, which lead to an aberrant interpretation of perceived internal and external stimuli and therefore to a negative-biased view of the world and oneself (Mathews and MacLeod, 2005); (Willner et al., 2012). In general, most depressive patients are permanently processing and evaluating negative information. The disability to disengage these negatively biased cognitive processes is a characteristic feature of patients with depression and might contribute to the rise of disease-specific symptoms, such as depressive rumination (Gotlib and Joormann, 2010); (Hamilton et al., 2013). In terms of large-scale network frameworks, the coordination between DMN-mediated (internally-oriented/self-referential) and CEN-mediated (externally-oriented/goal-directed) activity is modulated in healthy individuals by the SN, particularly by the right AI within the SN (Sridharan et al., 2008). In patients with MDD, AI dysfunction might lead to an aberrant modulation of DMN/CEN interactions, therefore causing difficulties to disengage extensive DMN-mediated, self-referential cognitive activity. Indeed, increased dominance of DMN activity has been showed to be associated with the severity of depressive rumination and with aberrant patterns of activity of the right AI in patients with MDD (Hamilton et al., 2011b). Together with difficulties to engage CEN-mediated, externally oriented cognitive processes, possibly due to AI dysfunction, these findings might explain, why depressive patients fail frequently to disengage the processing of negatively-biased thoughts, leading to further worsening of depressive symptoms.

4.8. The “triple network model of psychopathology”: open questions and future directions

The presented results are strongly suggesting a link between traditional cognitive theories and modern large-scale network theories in patients with schizophrenia and major depressive disorder, contributing to a better understanding of the neurobiology underlying these mental disorders. However, the “triple network model of psychopathology” also raises questions, which still have to be answered.

The link between DMN/SN/CEN reorganization and findings outside the triple network model. Currently, it is still unclear whether and how frequently reported findings beyond the DMN, SN and CEN are linked with the model of DMN/SN/CEN reorganization in mental disorders. In particular, it has been argued that the “triple network model” misses to account for other common findings in mental disorders, such as aberrant activity within the auditory cortex in patients with schizophrenia (Williamson and Allman, 2012) or aberrant activity in subcortical regions, such as the striatum during task and rest in patients with schizophrenia (Murray et al., 2008); (Sorg et al., 2013) and major depressive disorder (Hamilton et al., 2011a); (Gradin et al., 2011). Taking this into account, a recent study investigated the relationship between the SN and reward-processing regions in the striatum and found aberrant connectivity between these two systems in patients with schizophrenia, suggesting a relevant modulatory role of the striatum for SN activity via processing of reward-signals (Gradin et al., 2013). This finding supports the concept of “motivational salience”, which suggests that aberrant dopamine-modulated reward-prediction error processing alters the motivational value of external stimuli and/or internal events after the initial stimulus has been appraised (Kapur, 2003), therefore linking the concept of disrupted salience to the concept of aberrant reward-based learning in patients with schizophrenia (Murray et al., 2008); (Fletcher and Frith, 2009) and major depressive disorder (Robinson et al., 2012). Further studies investigating the link between findings within and outside the

triple network model are necessary to understand the associations and potential influences of other frequently reported findings, especially within subcortical regions, on DMN/SN/CEN reorganization in patients with schizophrenia and major depressive disorder.

The link between DMN/SN/CEN reorganization and neurochemical anomalies. Although neurochemical anomalies, particularly aberrant dopaminergic neurotransmission, has been demonstrated for several mental disorders, including schizophrenia (Howes et al., 2009); (Howes et al., 2012); (Fusar-Poli and Meyer-Lindenberg, 2013a); (Fusar-Poli and Meyer-Lindenberg, 2013b) and depression (Nestler and Carlezon, 2006); (Meyer et al., 2006); (Hamilton et al., 2013), it is still unclear how neurochemical anomalies are associated with aberrant reorganization of DMN, SN and CEN in mental disorders. Since dopamine plays a crucial role in reward processing and learning in healthy individuals particularly via modulation of the activity of reward-mediating neuronal populations within the striatum and the midbrain (Kapur, 2003), it has been suggested that aberrant dopaminergic neurotransmission might underlie aberrant learning and motivational salience in patients with schizophrenia (Murray et al., 2008) and major depressive disorder (Robinson et al., 2012), which might represent a potential link to the robust DMN/SN/CEN reorganization in these disorders by modulating SN activity (Gradin et al., 2011). However, while first evidence for a dopamine-sensitive modulation of SN activity is emerging in healthy individuals (Cole et al., 2012), the direct link between aberrant dopaminergic neurotransmission and aberrant SN activity in patients with mental disorders is still missing. Studies simultaneously assessing iFC within and between DMN, SN and CEN via fMRI as well as dopaminergic neurotransmission via PET, for example using the presynaptic tracer (18)-F-DOPA in the same individual are necessary to provide the missing direct link between aberrant dopaminergic neurotransmission and iFC within and between DMN, SN and CEN in patients with mental disorders.

The specificity of DMN/SN/CEN reorganization for distinct symptom dimensions and mental disorders. In the current study, patients with schizophrenia and MDD showed an association between aberrant intra-iFC in the AI within the SN and aberrant inter-iFC between DMN, SN and CEN. Although the described patterns of functional DMN/SN/CEN reorganization were not identical, they showed great similarities, suggesting that the mechanisms suggested by the "triple network model of psychopathology" might represent rather a "final common pathway" of different mental disorders than the underlying cause of these anomalies, which might be highly individual for distinct psychiatric disorders, including genetic, metabolic and/or social factors. In particular, measured DMN/SN/CEN reorganization might be triggered by disease-specific structural or functional neurobiological alterations, e.g. striatal anomalies in patients with schizophrenia (Sorg et al., 2013) or hippocampal anomalies in patients with major depressive disorder (Drevets et al., 2008). Furthermore, studies directly comparing DMN/SN/CEN reorganization between different mental disorders within a unified statistical framework are still missing. Currently, all findings stem from studies comparing potential alterations in intrinsic functional connectivity between a distinct group of patients and matched healthy controls, making it therefore difficult to infer to which extent the reported findings are specific for each mental disorder solely based on the used study design. Theoretically, described findings might represent only certain aspects, which are characteristic for mental disorders in general but not coding specific disease-relevant mechanisms in particular. Future studies investigating potential similarities and differences between different mental disorders as well as potential disease-specific causes underlying the reorganization of large-scale brain networks in various mental disorders are necessary to better understand the potential specificity of reported findings.

Taken together, the question whether the triple network model of psychopathology (Menon, 2011) can be extended in such a way to account for these current restrictions is of particular interest to better

understand the similarities and differences between distinct mental disorders in particular and the neurobiology of mental disorders in general.

5. Conclusion

The current thesis provides first evidence for a direct association between insular dysfunction within the SN, a robust functional reorganization of intrinsic connectivity networks mediating cognition and the severity of disease specific symptoms in psychiatric disorders, including positive symptoms in patients with schizophrenia during acute psychosis, negative symptoms in patients with schizophrenia during psychotic remission and global depressive symptoms in patients with major depressive disorder. These results strongly support the “triple network model of psychopathology”, which suggests that disrupted AI/SN modulation of DMN-mediated, self-referential/internally oriented and CEN-mediated, goal-directed/externally oriented cognitive processes might cause abnormal behavioral responses to perceived external stimuli and internal events and thus be a characteristic feature of severe mental disorders, including schizophrenia and major depressive disorder. Therefore, the presented findings represent a link between modern large-scale brain network theories and traditional cognitive theories of psychopathology, give an insight into the functional neurobiology underlying schizophrenia and major depressive disorder as well as its potential behavioral implications for mental disorders in general and represent a first step towards a functional neuroimaging-based biomarker for mental disorders.

To be able to understand the architecture of the human brain, it is inevitable to investigate different neurobiological levels within a unified theoretical framework, including the genetic, molecular, cellular, large-scale and behavioral level. Considering the complexity of the human brain and the limitations of each methodological approach currently applied in human neuroscience, it becomes evident that a multimodal approach has become almost indispensable for future studies, which intend to explore the functional architecture of the human brain an its behavioral relevance in health and disease. Regarding (almost) non-invasive neuroimaging, biochemical properties can be assessed via

PET, neurophysiological properties can be inferred from analyses applying EEG or MEG, structural properties can be investigated via structural MRI or DTI and the mapping of the large-scale functional architecture of the brain can be assessed via fMRI. Especially simultaneous assessments using hybrid systems, such as modern PET/MR scanners or assessing EEG during fMRI scan sessions represent promising approaches to investigate direct associations between the respective outcome measures. Taken together, only a future integration across available modalities as well as across known brain functions will offer the chance to better understand the function and dysfunction of the human brain. In this context, the methods and results presented in the current thesis provide a contribution to the current and future understanding of the neurobiology underlying human behavior by establishing a methodological approach to investigate cognitive-relevant large-scale brain networks and, perhaps more importantly, by generating regionally and functionally specific hypotheses for future multimodal imaging studies investigating the neurobiological underpinnings of mental disorders.

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7. Supplement

Table S1. Individual subject medication protocol and dosage for patients with schizophrenia during state of acute psychosis

Participants	Scan during acute state of psychosis
1	20 mg Olanzapine
2	100 mg Clozapine, 80 mg Ziprasidone
3	30 mg Olanzapine, 15 mg Aripiprazole
4	10 mg Olanzapine, 5 mg Risperidone
5	30 mg Olanzapine, 5 mg Risperiodone
6	*NO medication*
7	12,5 mg Olanzapine, 6 mg Paliperidone
8	*NO medication*
9	20 mg Olanzapine
10	400 mg Quetiapine, 9 mg Paliperidone
11	30 mg Olanzapine, 50mg Clozapine
12	30 mg Olanzapine, 5 mg Risperidone
13	400 mg Quetiapine, 5 mg Risperidone
14	25 mg Olanzapine, 50 mg Clozapine
15	200 mg Amilsupride, 15 mg Aripiprazol
16	30 mg Olanzapine, 400 mg Quetiapine
17	15 mg Olanzapine
18	200 mg Clozapine, 12mg Paliperidone

Table taken from (Manoliu et al., 2013a).

Table S2. Individual subject medication protocol and dosage for patients with schizophrenia during state of acute remission

Participants	Scan during state of remission
1	400 mg Clozapine
2	*NO medication*
3	2 mg Risperidone
4	*NO medication*
5	12,5 Olanzapine
6	*NO medication*
7	*NO medication*
8	300 mg Clozapine
9	600 mg Quetiapine
10	600 mg Amisulpride, 400 mg Quetiapine
11	600 mg Quetiapine, 5 mg Risperidone
12	450 mg Clozapine, 15 mg Aripiprazole

Table taken from (Manoliu et al., 2013b).

Table S3. Subjects' medication protocol and dosage for patients with major depressive disorder

Number of patients	Medication (mean dose)
Mono-therapy (n=7)	
n = 3	Citalopram 30mg/d
n = 3	Sertraline 200mg
n = 1	Mirtazapine 30mg/d
Dual-therapy (n=12)	
n = 5	Citalopram 37.5mg/d and Mirtazapine 30mg/d
n = 2	Citalopram 40mg/d and Venlafaxine 225mg/d
n = 3	Venlafaxine 225mg/d and Mirtazapine 30mg/d
n = 1	Citalopram 30mg/d and Quetiapine 200mg/d
n = 1	Sertraline 200mg/d and Mirtazapine 30mg/d
Triple-Therapy (n=5)	
n = 2	Citalopram 30mg/d, Venlafaxine 187.5mg/d and Amisulprid 200mg/d
n = 2	Citalopram 30 mg/d, Mirtazapine 30mg/d and Quetiapine 200mg/d
n = 1	Venlafaxine 22 mg/d, Mirtazapine 30mg/d and Quetiapine 200mg/d

Table S4. Intrinsic connectivity networks in the healthy control group of patients with schizophrenia during state of acute psychosis (referring to Fig. 6).

Anatomical Region	L / R / Bi	cluster	Z-score	p-value*	MNI (x,y,z)[1]
(A) Anterior Default Mode Network					
Medial Prefrontal Cortex	L	922	>8.00	<0.001	-3 45 -3
Medial Prefrontal Cortex	R	"	>8.00	<0.001	9 42 -3
(B) Inferior Posterior Default Mode Network					
Medial Posterior Parietal Cortex	L	1192	>8.00	<0.001	-3 -63 30
Medial Posterior Parietal Cortex	R	"	>8.00	<0.001	6 -57 33
Angular Gyrus	R	"	5.77	<0.001	48 -57 27
(C) Superior Posterior Default Mode Network					
Precuneus	Bi	806	>8.00	<0.001	-3 -66 33
Posterior Cingulate Cortex	Bi	211	7.43	<0.001	-3 -42 21
Inferior Parietal Lobule	L	47	5.88	<0.001	-30 -54 42
(D) Salience Network					
Anterior Cingulate Cortex	Bi	802	>8.00	<0.001	0 27 39
Insula Lobe	R	278	>8.00	<0.001	36 27 -3
Insula Lobe	L	233	7.18	<0.001	-30 24 -9
(E) Left Ventral Central Executive Network					
Inferior Parietal Lobule	L	729	>8.00	<0.001	-48 -63 33
Superior Frontal Gyrus	L	535	7.67	<0.001	-42 15 51
Inferior Parietal Lobule	R	180	6.17	<0.001	54 -57 30
Precuneus	L	67	6.06	<0.001	-6 -66 39
Inferior Frontal Gyrus	L	44	5.82	<0.001	-45 33 -18
Posterior Cingulate Cortex	L	19	5.21	0.005	0 -36 33
(F) Right Ventral Central Executive Network					
Inferior Parietal Lobule	R	619	>8.00	<0.001	48 -66 36
Middle Frontal Gyrus	R	661	7.72	<0.001	30 24 45
Middle Cingulate Cortex	R	70	6.07	<0.001	6 -30 36
Cerebellum	L	18	5.68	<0.001	-33 -66 -36
Middle Orbital Gyrus	R	62	5.63	<0.001	39 54 -6
Superior Frontal Gyrus	R	"	5.53	0.001	24 60 6
(G) Dorsal Central Executive Network					
Supramarginal Gyrus	L	1016	>8.00	<0.001	-60 -30 39
Inferior Frontal Gyrus	L	150	6.81	<0.001	-48 6 27
Supramarginal Gyrus	R	123	6.72	<0.001	60 -36 39
Middle Frontal Gyrus	L	115	6.69	<0.001	-24 9 60
Middle Temporal Gyrus	L	99	6.66	<0.001	-51 -60 -3
Inferior Frontal Gyrus	L	94	6.34	<0.001	-48 33 27

*one-sample-t-test, significant for $p<0.05$, FWE-corrected for multiple comparisons, cluster-threshold > 15 voxel. [1] MNI, Montreal Neurological institute; L, left hemisphere; R, right hemisphere; Bi, bilateral. Table and legend taken from (Manoliu et al., 2013a).

Table S5. Intrinsic connectivity networks in the healthy control group of patients with schizophrenia during state of remission (referring to Fig. 7).

Anatomical Region	L / R / Bi	cluster	Z-score	p-value*	MNI (x,y,z)[1]
(A) Anterior Default Mode Network (aDMN)					
Medial Prefrontal Cortex	L	451	6.88	<0.001	-6 45 0
Medial Prefrontal Cortex	R	"	6.73	<0.001	6 39 -3
(B) Inferior Posterior Default Mode Network (ipDMN)					
Medial Posterior Parietal Cortex	L	579	>8.00	<0.001	-3 -60 30
Medial Posterior Parietal Cortex	R	"	6.80	<0.001	6 -51 24
Angular Gyrus	R	"	6.55		48 -57 27
(C) Superior Posterior Default Mode Network (spDMN)					
Precuneus	Bi	344	6.53	<0.001	-9 -75 36
Inferior Parietal Lobule	L	"	4.77	<0.001	-33 -37 39
Posterior Cingulate Cortex	Bi	57	5.90	<0.001	-3 -36 24
(D) Salience Network (SN)					
Anterior Cingulate Cortex	Bi	255	6.19	<0.001	-3 27 39
Insula Lobe	L	77	5.91	<0.001	-39 18 -3
Insula Lobe	R	66	5.90	<0.001	36 27 0
(E) Left Ventral Central Executive Network (lvCEN)					
Inferior Parietal Lobule	L	412	6.87	<0.001	-48 -63 33
Superior Frontal Gyrus	L	137	6.16	<0.001	-39 21 51
Middle Frontal Gyrus	L	"	5.65	<0.001	-3 39 42
Inferior Parietal Lobule	R	42	5.00	<0.001	60 -51 39
Precuneus	L	33	4.86	<0.001	-6 -69 39
(F) Right Ventral Central Executive Network (rvCEN)					
Inferior Parietal Lobule	R	229	6.00	<0.001	42 -69 45
Middle Frontal Gyrus	R	167	6.54	<0.001	30 24 45
Middle Cingulate Cortex	R	70	5.25	<0.001	9 -27 36
Middle Orbital Gyrus	R	22	4.81	<0.001	30 57 -6
(G) Dorsal Central Executive Network (dCEN)					
Supramarginal Gyrus	L	300	6.35	<0.001	-60 -30 39
Inferior Temporal Gyrus	L	24	5.96	<0.001	-51 -57 -6
Inferior Frontal Gyrus	L	12	5.20	<0.001	-48 3 33
Supramarginal Gyrus	R	7	5.19	<0.001	63 -42 30

*one-sample-t-test, significant for $p<0.05$, FWE-corrected for multiple comparisons, cluster-threshold > 5 voxel. [1] MNI, Montreal Neurological institute; L, left hemisphere; R, right hemisphere; Bi, bilateral. Table and legend taken from (Manoliu et al., 2013b).

Table S6. Intrinsic connectivity networks in the healthy control group of patients with schizophrenia during state of remission (referring to Fig. 8).

Anatomical Region	L / R / Bi	cluster	Z-score	p-value	MNI[1] (x, y, z)
(A) Anterior Default Mode Network (aDMN					
Medial Prefrontal Cortex	L	1224	>8.00	<0.001	0, 50, -14
Medial Prefrontal Cortex	R	"	>8.00	<0.001	6, 47, -5
Posterior Cingulate Cortex	Bi	47	6.14	<0.001	0, -55, 19
(B) Inferior Posterior Default Mode Network (ipDMN)					
Precuneus	L	937	>8.00	<0.001	-3, -52, 22
Precuneus	R	"	>8.00	<0.001	3, -55, 19
Angular Gyrus	L	40	7.33	<0.001	-45, -73, 37
Angular Gyrus	R	17	6.06	<0.001	48, -67, 31
(C) Superior Posterior Default Mode Network (spDMN)					
Precuneus	R	1444	>8.00	<0.001	6, -64, 43
Precuneus	L	"	>8.00	<0.001	0, -79, 43
Angular Gyrus	L	"	6.20	<0.001	-36, -58, 40
Angular Gyrus	R	56	6.15	<0.001	36, -58, 37
(D) Salience Network (SN)					
Anterior Cingulate Cortex	Bi	948	>8.00	<0.001	0, 23, 28
Anterior Insula	L	432	>8.00	<0.001	-39, 14, -11
Anterior Insula	R	400	>8.00	<0.001	51, 17, -11
Middle Frontal Gyrus	R	92	6.52	<0.001	33, 53, 22
(E) Left Ventral Central Executive Network (lvCEN)					
Angular Gyrus	L	653	>8.00	<0.001	-45, -67, 31
Inferior Parietal Gyrus	L	"	7.82	<0.001	-51, -52, 31
Precuneus	L	310	7.60	<0.001	-3, -61, 31
Middle Frontal Gyrus	L	345	6.73	<0.001	-45, 17, 49
Inferior Temporal Gyrus	L	24	6.27	<0.001	-63, -49, -17
Superior Medial Gyrus	L	33	5.55	<0.001	-9, 41, 40
(F) Right Ventral Central Executive Network (rvCEN)					
Superior Frontal Gyrus	R	481	7.46	<0.001	30, 26, 52
Angular Gyrus	R	488	7.40	<0.001	42, -73, 40
Precuneus	R	94	6.68	<0.001	3, -61, 25
Middle Frontal Gyrus	L	25	6.49	<0.001	-24, 17, 58
Temporal Pole	L	10	5.71	<0.001	-57, 11, -11
(G) Dorsal Central Executive Network (dCEN)					
Supramarginal Gyrus	L	1099	7.79	<0.001	-60, -34, 37
Inferior Frontal Gyrus	L	182	7.22	<0.001	-45, 38, 7
Inferior Frontal Gyrus	L	109	7.04	<0.001	-48, 8, 22
Inferior Temporal Gyrus	L	161	6.75	<0.001	-57, -55, -11
Superior Frontal Gyrus	L	35	6.31	<0.001	-24, 5, 64

*one-sample-t-test, significant for $p<0.05$, FWE-corrected for multiple comparisons, cluster-threshold > 10 voxel. [1] MNI, Montreal Neurological institute; L, left hemisphere; R, right hemisphere; Bi, bilateral. Table and legend taken from (Manoliu et al., in review).

Table S7. Altered intra-iFC in patients with schizophrenia during state of acute psychosis compared to healthy controls (referring to Fig. 6)

Anatomical Region	L / R / Bi	cluster	Z-score	p-value*	MNI (xyz)[1]
(A) Anterior Default Mode Network					
(a) SA > HC					
-					
(b) SA < HC					
Anterior Cingulate Cortex	Bi	213	>8.00	<0.001	9 39 -3
(B) Inferior Posterior Default Mode Network					
(a) SA > HC					
-					
(b) SA < HC					
Precuneus	Bi	92	6.93	<0.001	9 -57 33
(C) Superior Posterior Default Mode Network					
(a) SA > HC					
-					
(b) SA < HC					
Precuneus	Bi	43	>8.00	<0.001	3 -78 48
(D) Salience Network					
(a) SA > HC					
Anterior Cingulate Cortex		75	6.24	<0.001	-3 21 24
Anterior Cingulate Cortex	R	21	6.24	<0.001	6 -9 36
(b) SA < HC					
Insula Lobe	R	125	7.17	<0.001	36 27 0
Insula Lobe	L	120	7.09	<0.001	-42 18 3
SMA	Bi	28	5.64	<0.001	3 18 51
(E) Left Ventral Central Executive Network					
(a) SA > HC					
Middle Orbital Gyrus	L	24	7.7	<0.001	-45 48 -9
(b) SA < HC					
Middle Frontal Gyrus	L	80	>8.00	<0.001	-42 15 54
Inferior Parietal Lobule	L	14	7.07	<0.001	-36 -78 42
Angular Gyrus	L	44	6.61	<0.001	-57 -63 27
Inferior Parietal Lobule	R	52	6.58	<0.001	54 -57 48
(F) Right Ventral Central Executive Network					
(a) SA > HC					
Angular Gyrus	R	91	>8.00	<0.001	51 -72 30
Cuneus	R	70	6.24	<0.001	3 -63 33
Superior Frontal Gyrus	L	21	5.57	<0.001	-18 30 51
(b) SA < HC					
Inferior Parietal Lobule	R	116	>8.00	<0.001	48 -63 48
Superior Frontal Gyrus	R	30	>8.00	<0.001	30 30 54
Middle Frontal Gyrus	R	23	7.27	<0.001	45 24 48
(G) Dorsal Central Executive Network					
(a) SA > HC					
Inferior Temporal Gyrus	L	28	6.86	<0.001	-54 -63 -6
(b) SA < HC					
Right Supramarginal Gyrus	R	11	6.41	<0.001	63 -42 36

*two-sample-t-test with age, sex and total GM volume as covariates of no interest, significant for p<0.05, FWE-corrected for multiple comparisons. cluster-threshold > 10 voxel. [1]MNI, Montreal Neurological institute; L, left hemisphere; R, right hemisphere, Bi, bilateral. Table and legend taken from (Manoliu et al., 2013a).

Table S8. Altered intra-iFC in patients with schizophrenia during state of remission compared to healthy controls (referring to Fig. 7)

Anatomical Region	L / R / Bi	cluster	Z-score	p-value*	MNI (x,y,z)[1]
(A) Anterior Default Mode Network (aDMN)					
(a) SR > HC					
-					
(b) SR < HC					
Anterior Cingulate Cortex	Bi	179	>8.00	<0.001	9 42 -3
(B) Inferior Posterior Default Mode Network (ipDMN)					
(a) SR > HC					
-					
(b) SR < HC					
Precuneus	R	21	5.71	<0.001	12 -60 24
	L	23	5.37	0.001	-9 -60 30
(C) Superior Posterior Default Mode Network (spDMN)					
(a) SR > HC					
-					
(b) SR < HC					
-					
(D) Salience Network (SN)					
(a) SR > HC					
Anterior Cingulate Cortex	Bi	33	5.83	<0.001	0 27 12
(b) SR < HC					
Insula Lobe	R	18	5.68	<0.001	36 27 0
Insula Lobe	L	8	5.08	<0.001	-27 27 9
(E) Left Ventral Central Executive Network (lvCEN)					
(a) SR > HC					
-					
(b) SR < HC					
-					-
(F) Right Ventral Central Executive Network (rvCEN)					
(a) SR > HC					
-					
(b) SR < HC					
-					
(G) Dorsal Central Executive Network (dCEN)					
(a) SR > HC					
Inferior Temporal Gyrus	L	111	7.52	<0.001	-54 -52 -21
(b) SR < HC					
-					

*two-sample-t-test with age, sex and total GM volume as covariates of no interest, significant for $p<0.05$, FWE-corrected for multiple comparisons. cluster-threshold > 5 voxel. [1]MNI, Montreal Neurological institute; L, left hemisphere; R, right hemisphere, Bi, bilateral. Table and legend taken from (Manoliu et al., 2013b).

Table S9. Altered intra-iFC in patients with major depressive disorder compared to healthy controls (referring to Fig. 9)

Anatomical Region	L / R / Bi	cluster	Z-score	p-value	MNI (x, y, z)
(A) Anterior Default Mode Network (aDMN)					
(a) MDD > HC					
Medial Orbitofrontal Gyrus	R	635	>8.00	<0.001	6, 47, -14
Medial Orbitofrontal Gyrus	L	"	>8.00	<0.001	0, 65, 4
(b) MDD < HC					
-					
(B) Inferior Posterior Default Mode Network (ipDMN)					
(a) MDD > HC					
Precuneus	L	292	>8.00	<0.001	0, -64, 28
Precuneus	R	"	6.25	<0.001	9, -52, 31
(b) MDD < HC					
-					
(C) Superior Posterior Default Mode Network (spDMN)					
(a) MDD > HC					
Precuneus	R	275	6.91	<0.001	15, -64, 28
Precuneus	L	"	6.77	<0.001	-12, -70, 25
(b) MDD < HC					
Precuneus	R	157	7.14	<0.001	3, -61, 46
Precuneus	L	13	5.95	<0.001	-6, -49, 58
(D) Salience Network (SN)					
(a) MDD > HC					
Anterior Cingulate Cortex	Bi	168	6.54	<0.001	0, 8, 34
(b) MDD < HC					
Insula lobe	R	65	5.05	0.007	48, 14, -2
Insula lobe	L	53	4.91	0.017	-42, 11, -8
(E) Left Ventral Central Executive Network (lvCEN)					
(a) MDD > HC					
Angular Gyrus	R	23	5.34	0.002	51, -61, 46
(b) MDD < HC					
Precuneus	L	26	5.52	<0.001	0, -64, 25
Middle Temporal Gyrus	L	24	5.48	<0.001	-42, -70, 19
(F) Right Ventral Central Executive Network (rvCEN)					
(a) MDD > HC					
-					
(b) MDD < HC					
-					
(G) Dorsal Central Executive Network (dCEN)					
(a) MDD > HC					
Postcentral Gyrus	R	19	5.58	<0.001	63, -16, 40
(b) MDD < HC					
-					

*two-sample-t-test with age, sex and total GM volume as covariates of no-interest, significant for p<0.05, FWE-corrected for multiple comparisons. cluster-threshold > 10 voxel. [1]MNI, Montreal Neurological institute; L, left hemisphere; R, right hemisphere, Bi, bilateral. Figure and legend taken from (Manoliu et al., in review).

Table S10. Inter-network intrinsic functional connectivity (inter-iFC) in patients with schizophrenia in state of acute psychosis and healthy controls and corresponding group differences (referring to Fig. 3 and Fig. 9).

Inter-iFC	SA		HC		SA vs. HC[1]	
	Mean	SD	Mean	SD	Direction	p-Value
aDMN - ipDMN	0.673	0.117	0.422	0.163	SA>HC	*<0.001**
aDMN - spDMN	0.402	0.207	0.181	0.145	SA>HC	*<0.001**
aDMN - SN	0.106	0.206	0.200	0.186	HC>SA	0.201
aDMN - lvCEN	0.366	0.169	0.215	0.168	SA>HC	0.024
aDMN - rvCEN	0.477	0.145	0.111	0.174	SA>HC	*<0.001**
aDMN - dCEN	-0.398	0.182	-0.312	0.141	HC>SA	0.136
ipDMN - spDMN	0.424	0.276	0.368	0.247	SA>HC	0.431
ipDMN - SN	-0.137	0.170	-0.221	0.197	SA>HC	0.186
ipDMN - lvCEN	0.392	0.258	0.554	0.185	HC>SA	0.044
ipDMN - rvCEN	0.444	0.176	0.383	0.153	SA>HC	0.180
ipDMN - dCEN	-0.487	0.220	-0.449	0.173	HC>SA	0.709
spDMN - SN	0.064	0.192	0.211	0.194	HC>SA	0.014
spDMN - lvCEN	0.302	0.257	0.207	0.246	SA>HC	0.458
spDMN - rvCEN	0.464	0.272	0.226	0.180	SA>HC	*0.001**
spDMN - dCEN	-0.133	0.222	0.051	0.195	HC>SA	0.006
SN - lvCEN	0.019	0.214	-0.046	0.254	SA>HC	0.467
SN - rvCEN	-0.031	0.206	-0.109	0.239	SA>HC	0.247
SN - dCEN	0.182	0.188	0.265	0.185	HC>SA	0.086
lvCEN - rvCEN	0.382	0.227	0.383	0.211	HC>SA	0.774
lvCEN - dCEN	0.031	0.149	-0.080	0.186	SA>HC	0.093
rvCEN - dCEN	-0.156	0.201	-0.008	0.191	HC>SA	0.020

[1] two-sample t-test controlled for age, sex and total GM volume. Italics indicate $p<0.05$, *significant for $p<0.05$, Bonferroni-corrected for multiple comparisons (n=21). Abbreviations: SA, group of patients with schizophrenia during acute psychosis; HC, healthy control group; inter-iFC, inter-network intrinsic functional connectivity; a/ip/spDMN: anterior/inferior-posterior/superior-posterior DMN; lv/rv/dCEN: left-ventral/right-ventral/dorsal CEN; SN: salience network. Table and modified legend taken from (Manoliu et al., 2013a).

Table S11. Inter-network intrinsic functional connectivity (inter-iFC) in patients with schizophrenia in state of remission and healthy controls and corresponding group differences (referring to Fig. 4 and Fig. 10).

Inter-iFC	SR (n=12)		HC (n=12)		SR vs. HC[1]	
	Mean	SD	Mean	SD	Direction	p-Value
aDMN - ipDMN	0,351	0,188	0,424	0,200	HC>SR	0,266
aDMN - spDMN	0,328	0,195	0,138	0,141	SR>HC	*0,034*
aDMN - SN	0,274	0,148	0,152	0,188	SR>HC	0,141
aDMN - lvCEN	0,261	0,168	0,157	0,124	SR>HC	0,078
aDMN - rvCEN	0,312	0,131	0,105	0,173	SR>HC	*0,011*
aDMN - dCEN	-0,411	0,223	-0,318	0,121	HC>SR	0,473
ipDMN - spDMN	0,268	0,123	0,317	0,295	HC>SR	0,563
ipDMN - SN	-0,094	0,178	-0,301	0,194	SR>HC	0,052
ipDMN - lvCEN	0,387	0,195	0,545	0,195	HC>SR	0,14
ipDMN - rvCEN	0,003	0,143	0,371	0,107	*HC>SR*	*<0.001**
ipDMN - dCEN	-0,782	0,195	-0,523	0,126	HC>SR	*0,008*
spDMN - SN	0,171	0,193	0,149	0,148	SR>HC	0,988
spDMN - lvCEN	0,343	0,176	0,162	0,267	SR>HC	0,076
spDMN - rvCEN	0,418	0,197	0,190	0,192	SR>HC	*0,021*
spDMN - dCEN	-0,222	0,216	0,032	0,229	HC>SR	0,066
SN - lvCEN	0,071	0,134	-0,140	0,240	SR>HC	0,066
SN - rvCEN	0,166	0,157	-0,177	0,237	*SR>HC*	*0,002**
SN - dCEN	0,109	0,176	0,260	0,147	HC>SR	0,088
lvCEN - rvCEN	0,410	0,166	0,359	0,223	SR>HC	0,609
lvCEN - dCEN	-0,150	0,230	-0,119	0,159	HC>SR	0,678
rvCEN - dCEN	-0,025	0,195	-0,088	0,168	SR>HC	0,289

[1]two-sample t-test, controlled for age, sex and total GM volume. Italics indicate $p<0.05$, *significant for $p<0.05$, Bonferroni-corrected for multiple comparisons (n=21). Abbreviations: SR, group of patients with schizophrenia during remission; HC, healthy control group; inter-iFC, inter-network intrinsic functional connectivity; a/ip/spDMN: anterior/inferior-posterior/superior-posterior DMN; lv/rv/dCEN: left-ventral/right-ventral/dorsal CEN; SN: salience network. Table and legend taken from (Manoliu et al., 2013b).

Table S12. Inter-network intrinsic functional connectivity (inter-iFC) in patients with major depressive disorder and healthy controls and corresponding group differences (referring to Fig. 5 and Fig. 11).

Inter-iFC	MDD (n=25)		HC (n=25)		MDD vs. HC	
	Mean	SD	Mean	SD	Direction	p-value
aDMN - ipDMN	0,412	0,281	0,313	0,250	MDD > HC	0,088
aDMN - spDMN	0,340	0,247	0,131	0,244	MDD > HC	*0,003*
aDMN - SN	0,183	0,223	-0,020	0,248	MDD > HC	*0,029*
aDMN - lvCEN	0,485	0,250	0,494	0,209	HC > MDD	0,684
aDMN - rvCEN	0,410	0,231	0,380	0,191	MDD > HC	0,896
aDMN - dCEN	-0,266	0,233	-0,294	0,184	MDD > HC	0,593
ipDMN - spDMN	0,274	0,221	0,466	0,189	HC > MDD	0,062
ipDMN - SN	-0,070	0,185	-0,276	0,224	MDD > HC	*0,002**
ipDMN - lvCEN	0,383	0,245	0,616	0,203	HC > MDD	*0,005*
ipDMN - rvCEN	0,427	0,208	0,629	0,205	HC > MDD	*0,019*
ipDMN - dCEN	-0,393	0,235	-0,162	0,184	HC > MDD	*0,001**
spDMN - SN	0,160	0,202	-0,018	0,261	MDD > HC	0,054
spDMN - lvCEN	0,244	0,243	0,431	0,215	HC > MDD	0,080
spDMN - rvCEN	0,395	0,193	0,509	0,247	HC > MDD	0,438
spDMN - dCEN	-0,134	0,208	0,131	0,217	HC > MDD	*<0,001**
SN - lvCEN	-0,044	0,173	-0,209	0,217	MDD > HC	*0,027*
SN - rvCEN	0,048	0,216	-0,194	0,277	MDD > HC	*0,021*
SN - dCEN	0,043	0,217	0,201	0,204	HC > MDD	*0,026*
lvCEN - rvCEN	0,580	0,248	0,602	0,202	HC > MDD	0,901
lvCEN - dCEN	-0,030	0,248	0,056	0,199	HC > MDD	0,120
rvCEN - dCEN	-0,230	0,222	-0,055	0,245	HC > MDD	*0,021*

[1] two-sample t-test controlled for age, sex and total GM volume. Italics indicate $p<0.05$, *significant for $p<0.05$, Bonferroni-corrected for multiple comparisons (n=21). Abbreviations: MDD, group of patients with major depressive disorder; HC, healthy control group; inter-iFC, inter-network intrinsic functional connectivity; a/ip/spDMN: anterior/inferior-posterior/superior-posterior DMN; lv/rv/dCEN: left-ventral/right-ventral/dorsal CEN; SN: salience network. Table and legend taken from (Manoliu et al., in review).

Table S13. Partial correlations between intra-iFC in the right/left AI within the SN and inter-iFC between intrinsic connectivity networks of interest in patients with schizophrenia in state of acute psychosis (referring to Fig. 12).

Inter-iFC	right AI		left AI	
	r-score	p-Value	r-score	p-Value
aDMN - ipDMN	-0.336	0.240	0.268	0.354
aDMN - spDMN	-0.626	*0.017*	0.338	0.237
aDMN - SN	0.074	0.802	-0.168	0.566
aDMN - lvCEN	-0.129	0.660	-0.031	0.916
aDMN - rvCEN	-0.803	*<0.001**	0.405	0.151
aDMN - dCEN	-0.014	0.961	-0.208	0.476
ipDMN - spDMN	-0.475	0.086	0.168	0.566
ipDMN - SN	-0.127	0.665	-0.157	0.592
ipDMN - lvCEN	0.031	0.916	-0.042	0.887
ipDMN - rvCEN	-0.591	*0.026*	0.468	0.091
ipDMN - dCEN	-0.365	0.199	-0.129	0.661
spDMN - SN	0.296	0.305	-0.179	0.541
spDMN - lvCEN	-0.519	0.057	0.177	0.544
spDMN - rvCEN	-0.386	0.173	0.214	0.462
spDMN - dCEN	0.071	0.809	-0.203	0.487
SN - lvCEN	0.325	0.258	0.107	0.715
SN - rvCEN	0.111	0.706	-0.264	0.362
SN - dCEN	-0.187	0.521	0.204	0.485
lvCEN - rvCEN	-0.048	0.870	-0.092	0.755
lvCEN - dCEN	-0.124	0.672	-0.059	0.841
rvCEN - dCEN	0.106	0.719	-0.154	0.599

Italics indicate $p<0.05$, *significant for $p<0.05$, after Bonferroni-correction for multiple comparisons (n=21). Partial correlation, corrected for age, sex, total GM volume and chlorpromazine equivalent dose (CPZ). Abbreviations: a/ip/spDMN: anterior/inferior posterior/superior posterior DMN; lv/rv/dCEN: left ventral/right ventral/dorsal CEN; SN: salience network; AI: anterior insula. Table and legend taken from (Manoliu et al., 2013a).

Table S14. Partial correlations between intra-iFC in the right/left AI within the SN and inter-iFC between intrinsic connectivity networks of interest in patients with schizophrenia in state of remission (referring to Fig. 13).

Inter-iFC	right AI		left AI	
	r-score	p-Value	r-score	p-Value
aDMN - ipDMN	0,056	0,916	-0,603	0,205
aDMN - spDMN	-0,015	0,977	0,507	0,305
aDMN - SN	-0,671	0,145	-0,009	0,987
aDMN - lvCEN	0,232	0,658	0,392	0,442
aDMN - rvCEN	0,101	0,849	0,793	0,06
aDMN - dCEN	-0,604	0,204	0,605	0,204
ipDMN - spDMN	0,306	0,555	-0,698	0,123
ipDMN - SN	-0,05	0,925	0,038	0,943
ipDMN - lvCEN	0,672	0,144	-0,132	0,803
ipDMN - rvCEN	0,819	*0,046*	-0,24	0,646
ipDMN - dCEN	-0,374	0,466	0,293	0,572
spDMN - SN	-0,034	0,949	0,84	*0,036*
spDMN - lvCEN	0,049	0,926	-0,236	0,653
spDMN - rvCEN	-0,407	0,423	-0,597	0,21
spDMN - dCEN	-0,28	0,591	0,493	0,321
SN - lvCEN	-0,602	0,206	0,238	0,65
SN - rvCEN	0,207	0,695	-0,961	*0,002**
SN - dCEN	-0,528	0,281	0,956	*0,003*
lvCEN - rvCEN	0,356	0,488	-0,491	0,322
lvCEN - dCEN	-0,779	0,068	-0,037	0,945
rvCEN - dCEN	-0,362	0,481	0,319	0,538

Italics indicate $p<0.05$, *significant for $p<0.05$, Bonferroni-corrected for multiple comparisons (n=21). Partial correlation, corrected for age, sex, total GM volume and chlorpromazine equivalent dose (CPZ). Abbreviations: a/ip/spDMN: anterior/inferior posterior/superior posterior DMN; lv/rv/dCEN: left ventral/right ventral/dorsal CEN; SN: salience network; AI: anterior insula. Table and legend taken from (Manoliu et al., 2013b).

Table S15. Partial correlations between intra-iFC in the right/left AI within the SN and inter-iFC between intrinsic connectivity networks of interest in patients with major depressive disorder (referring to Fig. 14).

Inter-iFC	right AI		left AI	
	r-score	p-value	r-score	p-value
aDMN - ipDMN	-0,24	0,282	-0,23	0,304
aDMN - spDMN	-0,195	0,383	0,108	0,633
aDMN - SN	0,285	0,198	-0,204	0,362
aDMN - lvCEN	0,243	0,277	-0,001	0,998
aDMN - rvCEN	-0,3	0,174	-0,043	0,851
aDMN - dCEN	0,412	0,056	0,135	0,548
ipDMN - spDMN	-0,24	0,282	0,118	0,602
ipDMN - SN	0,087	0,702	0,059	0,793
ipDMN - lvCEN	0,11	0,627	-0,325	0,14
ipDMN - rvCEN	-0,403	0,063	-0,051	0,823
ipDMN - dCEN	0,473	*0,026*	0,453	0,034
spDMN - SN	0,33	0,134	-0,201	0,369
spDMN - lvCEN	-0,23	0,302	0,205	0,359
spDMN - rvCEN	-0,403	0,063	0,318	0,15
spDMN - dCEN	0,541	*0,009*	-0,057	0,8
SN - lvCEN	0,249	0,263	-0,117	0,605
SN - rvCEN	0,416	0,054	-0,118	0,601
SN - dCEN	-0,045	0,843	-0,119	0,598
lvCEN - rvCEN	-0,266	0,232	0,186	0,406
lvCEN - dCEN	0,097	0,669	-0,147	0,514
rvCEN - dCEN	0,605	*0,003*	0,019	0,932

Italics indicate p<0.05, *significant for p<0.05, Bonferroni-corrected for multiple comparisons (n=21). Partial correlation, corrected for age, sex and total GM volume. Abbreviations: a/ip/spDMN: anterior/inferior posterior/superior posterior DMN; lv/rv/dCEN: left ventral/right ventral/dorsal CEN; SN: salience network; AI: anterior insula. Table and legend taken from (Manoliu et al., in review).

Table S16. Partial correlations between intra-iFC in the right/left AI within the SN and severity of hallucinations (P3) and delusions (P1) in patients with schizophrenia during state of acute psychosis (referring to Fig. 12).

Positive PANSS subscores	right AI		left AI	
	r-score	p-Value	r-score	p-Value
Delusions (P1)	-0.358	0.208	0.490	0.076
Hallucinations (P3)	-0.665	*0.009**	0.487	0.078

Italics indicate p<0.05, *significant for p<0.05, after Bonferroni-correction for multiple comparisons (n=4). Partial correlation, corrected for age, sex, GM volume and chlorpromazine equivalent dose (CPZ). Abbreviations: AI: anterior Insula; PANSS: Positive and Negative Syndrome Scale. Table and legend taken from (Manoliu et al., 2013a).

Table S17. Partial correlations between intra-iFC in the right/left AI within the SN and severity of positive and negative symptoms in patients with schizophrenia during state of remission (referring to Fig. 13).

PANSS scores	right AI		left AI	
	r-score	p-Value	r-score	p-Value
Total Positive Symptoms	0,886	*0,019*	-0,553	0,255
Total Negative Symptoms	0,141	0,789	-0,978	*0,001**

Italics indicate p<0.05, *significant for p<0.05, Bonferroni-corrected for multiple comparisons (n=4). Partial correlation, corrected for age, sex, total GM volume and chlorpromazine equivalent dose (CPZ). Abbreviations: AI: anterior Insula; PANSS: Positive and Negative Syndrome Scale. Table and legend taken from (Manoliu et al., 2013b).

Table S18. Partial correlations between intra-iFC in the right/left AI within the SN and severity of symptoms in patients with major depressive disorder (referring to Fig. 14).

Symptom scores	right AI		left AI	
	r-score	p-Value	r-score	p-Value
HAM-D	-0,554	*0,008**	0,103	0,649
BDI	-0,556	*0,007**	-0,320	0,888

Italics indicate p<0.05, *significant for p<0.05, after Bonferroni-correction for multiple comparisons (n=4). Partial correlation, corrected for age, sex and GM volume. Abbreviations: AI: anterior Insula; HAM-D: Hamilton Depression Rating Scale; BDI: Beck Depression Inventory. Table and legend taken from (Manoliu et al., in review).

Table S19. Partial correlations between inter-iFC and severity of hallucinations (P3) and delusions (P1) in patients with schizophrenia in state of acute psychosis (referring to Fig. 12).

Inter-iFC	Delusions (P1)		Hallucinations (P3)	
	r-score	p-value	r-score	p-value
aDMN - ipDMN	0.054	0.854	-0.122	0.677
aDMN - spDMN	0.064	0.828	0.445	0.111
aDMN - SN	0.385	0.175	0.116	0.693
aDMN - lvCEN	-0.027	0.926	0.312	0.278
aDMN - rvCEN*	0.382	0.178	0.779	*0.001**
aDMN - dCEN	0.074	0.801	0.274	0.344
ipDMN - spDMN	-0.083	0.778	0.283	0.327
ipDMN - SN	0.475	0.086	0.190	0.514
ipDMN - lvCEN	-0.043	0.885	-0.055	0.852
ipDMN - rvCEN	0.673	*0.008*	0.534	*0.049*
ipDMN - dCEN	0.539	*0.047*	0.406	0.149
spDMN - SN	-0.200	0.494	-0.209	0.474
spDMN - lvCEN	-0.007	0.980	0.638	*0.014*
spDMN - rvCEN	0.176	0.548	0.309	0.282
spDMN - dCEN	0.034	0.909	-0.039	0.895
SN - lvCEN	0.207	0.477	-0.065	0.825
SN - rvCEN	0.040	0.891	-0.016	0.957
SN - dCEN	-0.328	0.253	0.032	0.913
lvCEN - rvCEN	0.019	0.947	0.322	0.261
lvCEN - dCEN	0.360	0.206	0.310	0.282
rvCEN - dCEN	-0.167	0.567	0.230	0.429

Italics indicate $p<0.05$, *significant for $p<0.05$, after Bonferroni-correction for multiple comparisons (n=21). Partial correlation, corrected for age, sex, GM volume and chlorpromazine equivalent dose (CPZ). Abbreviations: a/ip/spDMN: anterior/inferior posterior/superior posterior DMN; lv/rv/dCEN: left ventral/right ventral/dorsal CEN; SN: salience network. Table and legend taken from (Manoliu et al., 2013a).

Table S20. Partial correlations between inter-iFC and severity of positive and negative symptoms in patients with schizophrenia in state of remission (referring to Fig. 13).

Inter-iFC	Total Positive Symptoms		Total Negative Symptoms	
	r-score	p-Value	r-score	p-Value
aDMN - ipDMN	0,443	0,379	0,595	0,213
aDMN - spDMN	-0,254	0,627	-0,574	0,233
aDMN - SN	-0,717	0,109	0,135	0,799
aDMN - lvCEN	-0,152	0,774	-0,402	0,429
aDMN - rvCEN	-0,243	0,643	-0,869	*0,025*
aDMN - dCEN	-0,764	0,077	-0,463	0,355
ipDMN - spDMN	0,361	0,482	0,597	0,211
ipDMN - SN	-0,184	0,727	-0,016	0,977
ipDMN - lvCEN	0,807	0,052	0,071	0,893
ipDMN - rvCEN	0,844	*0,034*	0,105	0,844
ipDMN - dCEN	-0,166	0,753	-0,129	0,808
spDMN - SN	-0,256	0,624	-0,865	*0,026*
spDMN - lvCEN	-0,03	0,955	0,188	0,722
spDMN - rvCEN	-0,115	0,828	0,643	0,169
spDMN - dCEN	-0,327	0,526	-0,362	0,481
SN - lvCEN	-0,615	0,194	-0,073	0,89
SN - rvCEN	0,555	0,253	0,969	*<0,001**
SN - dCEN	-0,686	0,133	-0,9	*0,014*
lvCEN - rvCEN	0,396	0,437	0,486	0,329
lvCEN - dCEN	-0,728	0,101	0,179	0,735
rvCEN - dCEN	-0,509	0,302	-0,228	0,663

Italics indicate $p<0.05$, *significant for $p<0.05$, Bonferroni-corrected for multiple comparisons (n=21). Partial correlation, corrected for age, sex, total GM volume and chlorpromazine equivalent dose (CPZ). Abbreviations: a/ip/spDMN: anterior/inferior posterior/superior posterior DMN; lv/rv/dCEN: left ventral/right ventral/dorsal CEN; SN: salience network. Table and legend taken from (Manoliu et al., 2013b).

Table S21. Partial correlations between inter-iFC and severity of depressive symptoms in patients with major depressive disorder (referring to Fig. 14).

Inter-iFC	HAM-D		BDI	
	r-score	p-value	r-score	p-value
aDMN - ipDMN	0,076	0,735	0,082	0,716
aDMN - spDMN	0,098	0,664	0,009	0,969
aDMN - SN	-0,048	0,833	-0,214	0,34
aDMN - lvCEN	0,029	0,896	0,195	0,386
aDMN - rvCEN	0,398	0,067	0,429	0,047
aDMN - dCEN	0,054	0,811	-0,057	0,8
ipDMN - spDMN	-0,024	0,916	0,058	0,797
ipDMN - SN	-0,055	0,808	-0,282	0,203
ipDMN - lvCEN	-0,155	0,49	-0,116	0,609
ipDMN - rvCEN	0,305	0,167	0,199	0,375
ipDMN - dCEN	0,059	0,794	-0,119	0,597
spDMN - SN	0,039	0,864	-0,114	0,614
spDMN - lvCEN	0,128	0,57	-0,008	0,971
spDMN - rvCEN	0,178	0,429	0,203	0,364
spDMN - dCEN	0,11	0,626	-0,041	0,856
SN - lvCEN	-0,107	0,637	-0,243	0,277
SN - rvCEN	-0,306	0,167	-0,371	0,089
SN - dCEN	0,101	0,656	0,004	0,987
lvCEN - rvCEN	0,504	*0,017*	0,353	0,108
lvCEN - dCEN	-0,109	0,629	-0,142	0,527
rvCEN - dCEN	-0,289	0,193	-0,315	0,153

Italics indicate p<0.05, *significant for p<0.05, after Bonferroni-correction for multiple comparisons (n=21). Partial correlation, corrected for age, sex and GM volume. Abbreviations: a/ip/spDMN: anterior/inferior posterior/superior posterior DMN; lv/rv/dCEN: left ventral/right ventral/dorsal CEN; SN: salience network. Table and legend taken from (Manoliu et al., in review).

Publications

1. Publications derived from this thesis

Aberrant Dependence of Default Mode / Central Executive Network Interactions on Anterior Insular Salience Network Activity in Schizophrenia.

Manoliu A, Riedl V, Zherdin A, Mühlau M, Schwerthöffer D, Scherr M, Peters H, Zimmer C, Förstl H, Bäuml J, Wohlschläger AM, Sorg C.

Schizophrenia Bulletin, 2013. In press, ePub ahead of print (2013 March 21th).

Insular dysfunction reflects altered between-network connectivity and severity of negative symptoms in schizophrenia during psychotic remission.

Manoliu A, Riedl V, Doll A, Bäuml JG, Mühlau M, Schwerthöffer D, Scherr M, Zimmer C, Förstl H, Bäuml J, Wohlschläger AM, Koch K, Sorg C.

Frontiers in Human Neuroscience, 2013. In press, ePub ahead of print (2013 May 20th).

Insular dysfunction within the salience network is associated with severity of symptoms and aberrant inter-network connectivity in major depressive disorder.

Manoliu A, Meng C, Brandl F, Doll A, Tahmasian M, Scherr M, Schwerthöffer D, Zimmer C, Förstl H, Bäuml J, Riedl V, Wohlschläger AM, Sorg C.

In review.

2. Oral presentations derived from this thesis

Impaired insular regulation of brain networks in schizophrenia psychosis.
Manoliu A, Riedl V, Neufang S, Zherdin A, Myers N, Mühlau M, Zimmer C, Förstl H, Bäuml J, Wohlschläger AM, Sorg C.
18th Annual Meeting of the Organization for Human Brain Mapping, June 10-14th, 2012 in Beijing, China.

Impaired insular regulation of brain networks in schizophrenia psychosis.
Manoliu A, Riedl V, Zherdin A, Mühlau M, Zimmer C, Förstl H, Bäuml J, Wohlschläger Am, Sorg C.
Kongress der Deutschen Gesellschaft für Psychiatrie und Psychotherapie, November 24th, 2012 in Berlin, Germany.

3. Poster presentations derived from this thesis

Aberrant insular regulation of brain network interactions in schizophrenia.
Manoliu A, Riedl V, Neufang S, Zherdin A, Myers N, Mühlau M, Zimmer C, Förstl H, Bäuml J, Wohlschläger AM, Sorg C.
18th Annual Meeting of the Organization for Human Brain Mapping, June 10-14th, 2012 in Beijing, China.

Aberrant insular regulation of brain network interactions in schizophrenia.
Manoliu A, Riedl V, Neufang S, Zherdin A, Myers N, Mühlau M, Zimmer C, Förstl H, Bäuml J, Wohlschläger AM, Sorg C.
Opening Symposium of the TUM-Neuroimaging-Center (TUM-NIC), July 12th, 2012 in Munich, Germany.

4. Further publications, which are not part of this thesis

Increased Intrinsic Brain Activity in the Striatum Reflects Symptom Dimensions in Schizophrenia.

Sorg C*, Manoliu A*, Neufang S, Myers N, Peters H, Schwerthöffer D, Scherr M, Mühlau M, Zimmer C, Drzezga A, Förstl H, Bäuml J, Eichele T, Wohlschläger AM, Riedl V.

(*equal contribution)

Schizophrenia Bulletin. 2013; 39: 387 – 395.

Asymmetric Loss of Parietal Activity Causes Spatial Bias in Prodromal and Mild Alzheimer's Disease.

Sorg C*, Myers N*, Redel P, Bublak P, Riedl V, Manoliu A, Perneczky R, Grimmer T, Kurz A, Förstl H, Drzezga A, Müller HJ, Wohlschläger AM, Finke K.

(*equal contribution)

Biological Psychiatry. 2012; 71: 798-804.

Patterns of cognitive performance in Subcortical Ischemic Vascular Disease (SIVD).

Scherr M, Krenn Y, Sorg C, Manoliu A, Trinka E, Förstl H, Staffen W, Bergmann HJ, Kirschner M, McCoy M.

The Journal of Neuropsychiatry and Clinical Neurosciences, accepted on Dec 12th, 2012.

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