Investigation of brain function in neuropsychiatric disorder using multimodal imaging analysis

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“The universe really does look like the ultimate free lunch, fashioned from nothing; bootstrapping itself into existence by a series of demonstrable steps.”

Paul Davies

Abstract

The aim of my studies was to investigate the brain function of neuropsychiatric disorders. In the present thesis, a multimodal functional imaging analysis was used to investigate the brain function in obese and major depressive disorder (MDD) individuals, which were investigated separately in 4 studies.

MDD is a highly prevalent disorder, and the patients with MDD often have difficulties in modulating their emotions. In Study 1, a functional connectivity density (FCD) approach was used to identify abnormal connectivity for each voxel in the whole brain separately. Abnormal FCD in MDD was present in cingulate and occipital cortex; however, these particular changes have not been identified using networks or seed regions approaches. This implies an importance of abnormal functional connectivity these regions as a correlate of brain pathophysiology in a disorder of impaired reward value attribution as it is the case for depression. Therefore, in Study 3, an emotional expectancy task was investigated to study neural mechanism of biased attention in MDD patients. Findings showed that patients may lack the ability to incorporate information derived from external positive events with a corresponding down-regulation of the intrinsic focus, as reflected by high default mode network intrinsic connectivity.

Obesity also has become a global health problem is a major factor for insulin resistance and Type 2 diabetes. In contrast to MDD, obese individuals rather suffer from increased responsively towards rewarding food stimuli. In Study 2, temporal homogeneity of local resting state signals was investigated to delineate regions with specific abnormalities. Before food intake, obese men had significantly increased activity in the left putamen and decreased activity in the orbitofrontal cortex and medial prefrontal cortex relative to lean men. These results imply that obese individuals exhibit deficits in reward circuitry, which may lead to aberrant reward cue processing. In Study 4, another local resting state activity marker, ALFF, was used to

quantify the baseline neural activity during different levels of satiety. It was found that, before food intake, obese subjects had significantly increased activity in the precuneus and decreased activity in dorsal cingulate cortex (dACC) relative to lean subjects. After food intake in contrast obese subjects only showed significantly decreased activity in dACC. This implies that the obese individuals have the deficiency in the decision-making during the food reward stimuli.

To conclude, resting state activity in disorders of increased or decreased reward sensitivity is differently impaired, however, an overlap could only be found in dorsal anterior cingulate, while further differences in resting state activity suggest a rather widespread impairment which may be related to other aspects which differ between MDD and obesity.

Zusammenfassung

Das Ziel meiner Arbeit war, die Funktion des Gehirns bei neuropsychiatrischen Erkrankungen zu untersuchen. In der vorliegenden Arbeit wurde eine multimodale Analyse funktioneller Bilder benutzt um die Funktion des Gehirns von Personen mit Fettleibigkeit und Majorer Depression (MDD) in vier separaten Studien zu untersuchen.

MDD ist eine Erkrankung mit hoher Prävalenz und die Patienten mit MDD haben Schwierigkeiten in der Modulation ihrer Emotionen. In Studie 1 wurde mittels Funktioneller Konnektivitäts-Dichte (FCD) ein Ansatz benutzt um abnormale Konnektivität separat für jeden Voxel zu identifizieren. In der MDD gab es eine abnormale FCD im zingulären und occipitalen Kortex; jedoch wurden diese besonderen Veränderungen nicht durch Netzwerk oder seed-Regionen basierte Ansätze identifiziert. Die globale FCD wurde durch abnorme lokale Veränderungen in der Konnektivität und verminderte FC vom dACC zu der linken Amygdala und erhöhter FC vom OCC zur rechten supplementär-motorischen Rinde (SMA) getrieben. Dies impliziert die Bedeutsamkeit von abnormaler funktioneller Konnektivität als ein Korrelat von Pathophysiologie in einer Störung mit beeinträchtigter Attribution des Wertes von Belohnung, wie es bei der Depression der Fall ist.

Deswegen wurde in Studie 3 eine Aufgabe über emotionale Erwartung untersucht, um die neuronalen Mechanismen von verzerrter Aufmerksamkeit in MDD Patienten zu studieren. Wir fanden, dass MDD Patienten eine höhere Aktivität im dorsalen medialen präfrontalen Kortex als gesunde Teilnehmer hatten, als eine Funktion von positiver versus negativer Erwartungs-Bedingung. Die Ergebnisse zeigen, dass Patienten möglicherweise die Fähigkeit fehlt, Informationen von externen positiven Ereignissen einzubinden, was mit einer korrespondierenden Herunter-Regulation des intrinsischen Fokus einhergeht, welches auch in einer hohen intrinsischen Konnektivität des Default-Mode Netzwerkes reflektiert ist. Desweiteren fanden wir

eine signifikante positive Korrelation zwischen DMPFC PPI und SHAPS, welches Anhedonie in MDD Patienten misst. Unsere Studie demonstriert, dass Patienten mit schwerer Anhedonie ein geringeres Entkoppeln fom DMPFC zum PCC zeigen, was suggeriert, dass sie möglicherweise beeinträchtigt in der Fähigkeit sind, Informationen über externe positive Geschehnisse mit einer korrespondierenden Herunter-Regulation der intrinsischen fokussierten Aufmerksamkeit zu verbinden.

Fettleibigkeit, auch ein globales Gesundheitsproblem, ist ein bedeutender Faktor für Insulin Resistenz und Typ-II Diabetes. Im Gegensatz zu MDD leiden fettleibige Personen eher an erhöhter Ansprechempfindlichkeit für belohnende Stimuli, die Nahrungsmittel zeigen. In Studie 2 wurde die zeitliche Homogenität von lokalen Signalen im Ruhezustand untersucht, um Regionen mit spezifischen Anomalien zu unterscheiden. Vor der Nahrungsaufnahme hatten fettleibige Männer relativ zu dünnen Männern, eine signifikant erhöhte Aktivität im linken Putamen sowie verminderte Aktivität im orbito-frontalen Kortex und medialen präfrontalen Kortex. Diese Ergebnisse implizieren, dass fettleibige Männer Defizite im Belohnungs-Kreislauf zeigen, welche zu einer abweichenden Verarbeitung von Belohnungsreizen führen könnten.

In Studie 4 wurde ein weiterer lokaler Marker von Aktivität im Ruhezustand, ALFF, benutzt um die basale neuronale Aktivität während verschiedener Sättigungsstadien zu quantifizieren. Es wurde gezeigt, dass fettleibige Probanden relativ zu dünnen Probanden vor der Nahrungsaufnahme eine signifikant erhöhte Aktivität im Precuneus sowie verminderte Aktivität im dorsalen zingulären Kortex (dACC) haben. Im Gegensatz dazu zeigten fettleibige Probanden nach der Nahrungsaufnahme nur signifikant verminderte Aktivität im dACC. Wir fanden eine positive Korrelation der Aktivierung im Precuneus und Einschätzung des Hungegefühls vor der Nahrungsaufnahme, sowie eine negative Korrelation zwischen dACC Aktivierung und Plasma-Insulin Werten vor und nach der Nahrungsaufnahme. Unsere Ergebnisse deuten an, dass sowohl dACC als auch Precuneus möglicherweise eine wichtige Rolle im Essverhalten spielen: die dACC Niveaus reflektieren indirekt Maße des Glukose

Verbrauches, während der Precuneus möglicherweise die subjektive Sattheit vermittelt.

Zusammengefasst ist die Aktivität im Ruhezustand in Erkrankungen mit erhöhter oder verminderter Belohnungs-Sensitivität unterschiedlich beeinträchtigt, jedoch konnte eine Überlappung nur im dorsalen anterioren Zingulum gefunden worden, während weitere Unterschiede in der Aktivität des Ruhezustandes eine eher ausgedehnte Beeinträchtigung suggerieren, welche zu anderen Aspekten, die zwischen MDD und Fettleibigkeit differieren, in Bezug stehen könnten.

Table of Contents

List of Abbreviations

ADHD	attention deficit hyperactivity disorder
ALFF	amplitude of low frequency fluctuations
BMI	body mass index
BOLD	blood oxygen level dependent
CLIA	chemiluminescence immunoassay
CNS	central nervous system
dACC	dorsal anterior cingulate cortex
DARTEL	diffeomorphic anatomical registration using exponentiated lie algebra
DMN	default mode network
EPI	echo-planar imaging
FA	flip angle
FC	functional connectivity
FCD	functional connectivity density
FD	frame wise displacement
FDR	False Discovery Rate
fMRI	functional Magnetic Resonance Imaging
FOV	field of view
FWE	family wise error
GABA	gamma-aminobutyric acid

GM	gray matter
GMV	gray matter volume
HAMD	Hamilton rating scale for depression
HC	healthy controls
Ic	independent component
ICA	independent component analysis
KCC	Kendall's coefficient of concordance
MARDS	Montgomery-Asberg depression rating scale
MCC	mid-cingulate cortex
MDD	major depressive disorder
MNI	Montreal Neurological Institute
MPFC	medial prefrontal cortex
NBRs	negative blood oxygenation level-dependent responses
OCC	occipital cortex
OFC	orbitofrontal cortex
PCC	posterior cingulate cortex
PET	positron emission tomography
PPI	psycho-physiological interaction
ReHo	regional homogeneity
ROIs	regions of interest
SHAPS	Snaith-Hamilton pleasure scale
SN	salience network

SPM	Statistical Parametric Mapping
TE	echo time
TR	repetition time
VAS	Visual Analogue Scales
VBM	voxel based morphometry
WM	white matter
Xneg	expectancy of negative pictures
Xneu	expectancy of neutral pictures
Xpos	expectancy of positive pictures

1 Introduction

1.1 Resting state fMRI

1.1.1 Background

The human brain represents about 2% of the body weight, while accounts for about 20% of the body's energy consumption (Lennie 2003, Shulman, Rothman et al. 2004). Previous studies showed that about 60% of the energy consumption of the brain supports communication among neurons and their supporting cells (Raichle and Mintun 2006). From the cost-based analysis, the intrinsic activity is much more significant than task activity. For the resting state fMRI, the subjects are instructed to open their eyes to gaze at the fixation or keep their eyes closed, not to focus their thoughts on anything in particular, and not to fall asleep during the scanning. So resting state fMRI was used to investigate the intrinsic activity of the brain, specifically, spontaneous BOLD activity. The intrinsic activity instantiates the maintenance of information for interpreting, responding to, and even predicting environmental demands (Raichle 2006).

In the past time, the spontaneous modulation of the BOLD signal was as the noisy, which could not be attributed the task or stimulus paradigm. Last ten years, several groups studied the spontaneous BOLD activity measured in the left somatomotor cortex which is specifically correlated with spontaneous fluctuations in the right somatomotor cortex and with medial motor areas in the absence of overt motor behavior, which showed that the spontaneous BOLD activity is not random noise (De Luca, Smith et al. 2005, Fox, Snyder et al. 2006). Furthermore, an increasing number of studies are showing that these fluctuations at low (<0.1Hz) temporal frequencies are functionally relevant and correlated between regions subserving similar brain functions (Birn 2007). These BOLD signal fluctuations reflect synchronized variations

in the neuronal activity of a network of regions.

Previous study showed there is special correlation between functionally related brain regions and relate to known anatomical systems (Buzsaki and Draguhn 2004, Fox, Snyder et al. 2005). Furthermore, spontaneous BOLD fluctuations continue to inter-trial variability in measured BOLD responses and behavior (Raichle and Mintun 2006). So resting state MRI provides one important experimental approach to understanding the brain's intrinsic functional activity.

1.1.2 DMN and SN

FC method has been used to explore the interrelation between functionally related regions of the brain, and the connectivity has been characterized the functional networks, visual network, auditory network, execute control network, DMN and SN (Lowe, Mock et al. 1998, Cordes, Haughton et al. 2000, Greicius, Krasnow et al. 2003, Laufs, Krakow et al. 2003, Fox, Snyder et al. 2005, Fransson 2005, Seeley, Menon et al. 2007). Especially, DMN and SN are two core networks in cognition and emotion.

The DMN comprises several brain regions, including medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC) / precuneus, lateral and medial temporal lobes, and posterior inferior parietal lobule (Shulman, Fiez et al. 1997, Gusnard, Raichle et al. 2001), which are more active during the resting state. Since the correlated fluctuations within the resting state networks occur in the absence of an explicit task, they are often referred to as spontaneous fluctuations (Shulman, Fiez et al. 1997).

The precuneus is essential involved DMN mediated self-referential thoughts (Uddin, Kelly et al. 2009), and previous study showed that obese individuals in a hunger state engaged more in the processing information about their internal states (Tregellas, Wylie et al. 2011). On the other hand, prior studies have shown emotional attention

bias was linked to activation in the MPFC, one part of DMN, which was related to the self-referential events and emotional processing (Gusnard, Akbudak et al. 2001). Grimm and her colleagues showed that MDD is characterized by impaired deactivation in the anterior DMN during task (Grimm, Boesiger et al. 2009).

The SN consists of three main cortical areas: the dorsal anterior cingulate cortex (dACC), bilateral anterior insula, and the adjacent inferior frontal gyri (Seeley et al., 2007). Previous studies found that increased activation in SN prior to DMN attenuation (Sridharan, Levitin et al. 2008), and the SN initiate switches between DMN and brain networks of task specific engagement (Menon and Uddin 2010).

1.1.3 Analysis methods

A number of methods can be used to analyze the resting state fMRI data. In this section, I provide a brief overview of some of the statistical and mathematic approaches applied to my studies.

FC approach identifies temporal correlations of the time serious between one selected region of interest and all other voxels in the brain, which indicated that atypical FC can be attributed to changes within canonical networks (Fox and Raichle 2007). This method relies on the selection of appropriate seed voxels, which are often selected based on information either derived from task activation studies, functional neuroanatomy or even structural deficits (Craddock, Holtzheimer et al. 2009). However, resting state functional connectivity pathologies may represent a distinct neurophysiological entity, in terms of its particular distribution across brain regions and their interconnections. As such seed definition based on known deficits in other modalities may miss out crucial and unique features of atypical connectivity.

ICA approach separates the signals of the whole brain into components with

statistically independent time courses resulting in spatially distributed non-overlapping networks. The method does not require a prior selection of a seed region. ICA requires a distinction of noise and physiological signals and thus restriction on components for further analysis (Lee, Smyser et al. 2013). Due to the properties of statistical independence and uncertainty regarding the "true" numbers of independent components (IC), data could be incorrectly modeled and leave a relatively high residual variance (Hobson and Hillebrand 2006).

FCD approach, a data-driven method, could identify the major cortical and subcortical functional connectivity hubs through the regional density of functional connections (Tomasi and Volkow 2010). Global FCD was developed to reveal regions with consistent global dysconnections, even when the individual dysconnections varied across regions for different subjects or patients (Anticevic, Cole et al. 2013)**.** The FCD approach has been used to investigate children with anisometropic amblyopia (Wang, Li et al. 2014), attention deficit hyperactivity disorder (ADHD) (Tomasi and Volkow 2012), and blindness (Qin, Xuan et al. 2014). In Study 1, I compared FCD maps of resting state fMRI between MDD and healthy controls to identify regions of abnormal functional connectivity.

ReHo approach measures the coherence or similarity of low frequency fluctuations of the BOLD signal (Zang, Jiang et al. 2004), which might reflect the coherence of spontaneous neuronal activity (Logothetis, Pauls et al. 2001). ReHo assumes that a given voxel is temporally similar to that of its neighbors. Kendall's coefficient of concordance (Kendall and Gibbons, 1990) was used to measure ReHo of the time series of a given voxel with those of its nearest neighbors in a voxel-wise way (Zang, Jiang et al. 2004). In Study 2, ReHo was used as a local measure to assess differences in baseline brain activity between obese and lean men.

ALFF approach focuses on the signal temporal synchronization of low frequency fluctuation among different brain areas (Biswal, Yetkin et al. 1995) takes the amplitude

of brain activity as measured by BOLD signals in resting-state fMRI into account (Zang, He et al. 2007). In ALFF, the power spectrum of BOLD signals in the low-frequency range is used for calculating correlations to estimate the degree of functional connectivity among voxels (Zang, He et al. 2007, Chao-Gan and Yu-Feng 2010). In Study 4, ALFF used as to assess altered activity in local baseline brain activity in obese individuals before and after food intake.

1.2 Task fMRI

1.2.1 Background

Functional brain imaging has been widely used to study the neural basis of perception, cognition, and emotion (Blakemore, Smith et al. 2000, Bermpohl, Pascual-Leone et al. 2006, Disner, Beevers et al. 2011). Such studies have traditionally focused on brain regions showing task-related increase in neural activity, i.e., greater activity during an experimental task than during a baseline state.

1.2.2 PPI analysis method

PPI analysis aims to explain neural responses in one brain area in terms of the interaction between influences of other brain regions and a cognitive / sensory process (Friston et al. 1997). The PPI analysis employed a design matrix with three regressors: (i) the 'psychological variable' representing the cognitive process of interest; (ii) the 'physiological variable' representing the neural response in the seed region and (iii) the interaction term of (i) and (ii). In the study 3, PPI analysis was used to investigate the FC changes in MDD patients during the expectancy task.

1.3 MDD in fMRI studies

1.3.1 Background

MDD is a highly prevalent disorder, which is typically characterized by persistent sadness and 'down state' that dominate their lives, lacking of interest and happiness feelings in pleasurable activities (anhedonia), as well as energy exhaustion and deduced guilty feelings (Belmaker and Agam 2008, Holtzheimer and Mayberg 2011). Most of the depressive symptoms are related to the fact that MDD patients often have difficulties in modulating emotion due to severe cognitive bias processing, in which their attention and memory retrieval were inevitably prone to information that containing negative emotions (MacLeod, Rutherford et al. 2002, Disner, Beevers et al. 2011).

1.3.2 Attention bias

Attention influences the emotional experiences: I tend to experience an emotion more intensely with paying attention to this emotion. Attention mainly relays on many factors, one is the spatial directed cue which represents a top-down mechanism (Pessoa, Kastner et al. 2003); the other is the features of the recognized event or object which is a bottom-up stimulus-driven mechanism (Beck and Kastner 2005). Accordingly, there are two approaches to examine the two different attention modulation ways: the approach focus on the expectancy before the presentation of the actual stimulus is called as 'preceding attention', and the other approach focus on attention effect that appears during the period of stimulus presentation is called as 'simultaneous attention' (Bermpohl, Pascual-Leone et al. 2006).

The influence of attention on emotional experience is also found in the patients with major depressive disorder, arises from a dysfunctional interaction of bottom-up

emotional activation and top-down attention control (Mathews and MacLeod 2005). More specifically, among HC participants, attention was directed preferentially towards positive stimuli (Gotlib, Krasnoperova et al. 2004), while MDD patients had difficulties in shifting the focus of their attention to positive stimuli (Clark, Steer et al. 1994, Disner, Beevers et al. 2011). According to (Holtzheimer and Mayberg 2011), MDD patients were prone to negative state and once they entered the state, it was very difficult for them to shift to positive states. Kellough and his colleagues found that individuals in depressive episode showed increased attention towards negative stimuli and decreased attention towards positive stimuli (Kellough, Beevers et al. 2008), supported the emotional attention bias hypothesis.

Brain imaging studies revealed that many brain regions that are responsible for mood regulation were functionally disrupted in MDD patients. For example, Shafritz and his colleagues found that individuals with mood disorders required greater cognitive effort to divert attention away from negative stimuli, which was associated with the activity in the pgACC (Shafritz, Collins et al. 2006). Resting-state functional connectivity magnetic resonance imaging studies reported MDD patients showed abnormal signal fluctuations in ACC (Greicius, Flores et al. 2007), amygdala (Kong, Chen et al. 2013, Cullen, Westlund et al. 2014) and MPFC (Bremner, Vythilingam et al. 2002, Drevets 2007). Prior studies have shown emotional attention bias was linked to activation in the MPFC– one part of the DMN (Raichle, MacLeod et al. 2001), which was related to the self-referential events and emotional processing(Gusnard, Akbudak et al. 2001). Grimm and her colleagues showed that MDD was characterized by impaired deactivation in the anterior DMN during task (Grimm, Boesiger et al. 2009). However, what drives this impairment is still unclear. If MDD is characterized by deficient or biased attention, it is worthwhile to clarify that if deviant attention focus may be a result of generally increased intrinsic coupling; or if it is characterized by deviant incorporation of explicit external information, such as increased sensitivity to actual negative stimuli; or if such a bias may result from patients inability to prepare for positive stimulation and accordingly reorient their attention resources towards their

environment.

Several studies were conducted to answer the question: what were the brain mechanisms of the emotional attention bias in MDD patients? For example, Bermpohl and his colleagues used the emotional expectancy task to investigate the expectancy induced modulation of emotional pictures processing in HC group and MDD patients, and found MPFC specifically regulated attention modulation of emotion processing (Bermpohl, Pascual-Leone et al. 2006); they also found impairment of expectancy and perception interaction in dorsal MPFC (DMPFC) when the MDD patients processing emotional pictures (Bermpohl, Walter et al. 2009). However, in their experiment design, they did not distinguish positive or negative emotions, and only investigated the general emotional vs. neutral effect. Herwig and his team used unknown valence expectancy task and found when anticipating pictures of unknown valence, MDD patients showed increased activity in MPFC and dorsolateral prefrontal cortex (DLPFC) as compared to HC participants (Herwig, Bruhl et al. 2010).

The abnormal emotional recognition towards up-coming events is a part of attention bias in MDD patients; therefore in the study 3, I intend to investigate neural correlation of biased attention using an emotional expectancy task to further investigate the phenomenon.

1.4 Obesity in fMRI studies

1.4.1 Background

Obesity, a result of an imbalance of eating behavior and energy expenditure has been associated to numerous general health problems (Flegal, Graubard et al. 2005), specifically, due to its relationship to insulin resistance which is the major factor leading to Type 2 diabetes (Prince, Kuk et al. 2014).

1.4.2 Eating behavior and obesity

Generally, human eating behavior is affected by physiological, psychological, and cognitive factors (Brambilla, Dalle Grave et al. 2014, Watkins and Kim 2014, Manasse, Espel et al. 2015). Functional imaging techniques have been applied to examine differential activations in certain brain regions between obese and lean subjects. A previous study found that increased activity in hungry obese subjects when they were giving taste stimulation. (Tataranni and DelParigi 2003). Compared with lean individuals, obese individuals showed decreased brain activity in the insula, OFC and anterior medial temporal lobe (Gautier, Chen et al. 2000).

FMRI, a method to non-invasively investigate the brain as a master organ regulating homeostatic behavior, has been widely applied to the study of eating behavior. In a study by Schur et al. (Schur, Kleinhans et al. 2009), non-obese female subjects showed significantly greater activation in the brainstem, left amygdala, left OFC, bilateral striatum and occipital lobe viewing fattening food pictures compared with non-food objects. Also, Passamonti and her colleagues (Passamonti, Rowe et al. 2009) found that, compared to bland food photos, viewing pictures of appetizing food resulted in alterations in FC along the ACC and ventral striatum.

Recently, there has been increased interest in the altered activity of cerebral networks in regulating eating behavior in the obese individuals (Tregellas, Wylie et al. 2011, Kullmann, Heni et al. 2012, Garcia-Garcia, Jurado et al. 2013, Kullmann, Pape et al. 2013, McFadden, Cornier et al. 2013). The DMN and SN are considered to be two main target networks, given their crucial roles involving the integration of homeostatic signals and cognitive control. Tregellas and colleges reported altered function of the DMN in obesity individuals (Tregellas, Wylie et al. 2011). In the study of Kullmann and her colleagues, they found that the obese individuals showed augmented response in

the SN towards food stimuli (Kullmann, Heni et al. 2012). One study examined the response for food pictures before and after food intake. The researchers found that, during the pre-meal condition, obese individuals increased activation in ACC, and obese individuals increased activation in medial prefrontal cortex whatever before and after food intake. This study released that altered activation in SN was considered to be associated with the overeating through an imbalance between award processing of food stimuli and autonomic processing (Garcia-Garcia, Jurado et al. 2013).

In the Study 2 and Study 4, altered activities in baseline brain activity were assessed in obese individuals before and after food intake.

1.5 Reward system

Generally, rewards can be defined as the stimuli that positively reinforce the intensity of a behavior pattern. Food is called primary rewards as they reinforce behavior without being learned (Walter, Abler et al. 2005). Lots of studies show that obesity results from abnormalities in reward processing (Stice, Spoor et al. 2009). Based on the reinforcement sensitivity model, obese individuals show greater reactivity of brain reward systems to reinforcing foods – high fat and high sugar foods and consume more of such foods than lean individuals (Nicklas, Yang et al. 2003). Compared with lean individuals, obese individuals report that food intake is more reinforcing (Saelens and Epstein 1996), and some studies found that there is positive correlation between general sensitivity to reward and the BMI (Franken and Muris 2005, Davis, Patte et al. 2007). Consumption of palatable foods, relative to consumption of unpalatable foods, results in higher activation of the right OFC (O'Doherty, Deichmann et al. 2002). Pannacciulli and her colleagues found lower GM density in the middle frontal gyrus of the PFC in obese versus lean individuals using structural MRI (Pannacciulli, Del Parigi et al. 2006). In the study of Batterink, when required to inhibit proponent responses to appetizing food, overweight adolescents showed less activation of frontal regions

than leaner individuals (Batterink, Yokum et al. 2010).

One of the main symptoms of depression is anhedonia, the inability to experience reward and pleasure. Specially, the patients with the depressive episode are associated with anticipatory anhedonia, unwillingness to work harder for greater rewards, and impaired reinforcement learning. Anhedonia plays a more central role in depressive illness (Jensen, McIntosh et al. 2003, Kampe, Frith et al. 2003). While "anhedonia" suggests reduced pleasure upon reward consummation, accruing evidence instead relates anhedonic depression to blunted anticipatory pleasure (McClure, Berns et al. 2003), overly conservative calculation of cost/benefit ratios (McClure, Li et al. 2004), and deficits in reinforcement learning (Montague, Berns et al. 2002). In MDD individuals, the structural and metabolic activity changes had been identified throughout the reward system. Previous studies showed that MDD patients had a smaller cortical volume in the OFC and MPFC (Steffens, McQuoid et al. 2003, Caetano, Kaur et al. 2006). In one fMRI study, depressed subjects show smaller BOLD signal changes in PFC during a reversal-learning task (Tavares, Clark et al. 2008).

From the previous studies, both MDD and obesity individuals showed the abnormalities in reward system: MDD patients reduced pleasure upon reward consummation and blunted anticipatory; obese individuals show greater reactivity in reward system and less inhibit proponent response to appetizing food. In my studies, the functional MRI was used to investigate the abnormal reward function in the obese and MDD individuals.

1.6 Structure and Aims

The aims of my studies were to apply non-invasive fMRI to investigate of brain function in neuropsychiatric disorder using multimodal imaging analysis. In the 4 studies, I mainly focus on two kinds of neuropsychiatric disorders – obesity and MDD. Obesity

results from abnormalities in reward processing, and obese individuals show the hyper- responsiveness of reward circuitry to food intake. In study 2 and study 4, resting state fMRI was used to assess the baseline brain activity between obese and lean men during hunger state, and also assessed altered brain activity in obese male subjects after liquid meal. MDD patients have many symptoms linked to dysfunctional reward processing, especially; anhedonia plays a central role in depressive illness. In study 1, FCD method was used to identify regions of abnormal functional connectivity regions, which could be the correlate of brain pathophysiology in a disorder of impaired reward value. In study 3, the emotional expectancy task was used to investigate biased attention in MDD patients (Table 1).

Table 1. The structure of the studies

	Reward	Rest	Activation
MDD	Decreased	Study 1 FCD altered	Study 3 Emotion expectancy task
Obesity	Increased	Study 2 ReHo altered activity during hunger state	Study 4 ALFF altered activity during different levels of satiety

1.7 Hypothesis

I. MDD patients often have difficulties in modulating their emotions and experiencing reward and pleasure. I hypothesized that the abnormal modulation results from the abnormal functional connectivity in reward system. In Study 1, I used the FCD method to identify altered FC hubs as a correlate of brain pathophysiology in a disorder of impaired reward value attribution as it is the case for depression.

II. MDD is characterized by biased attention, I hypothesized that the biased attention results from an inability to prepare for positive stimulation and reorient attention resources towards the environment. In Study 3, I used an emotional expectancy task to investigate the abnormal activation during the positive expectancy and FC changes in MDD patients. Patients with a depressive episode are associated with anticipatory anhedonia, which reduces pleasure upon subsequent reward consummation. I also would like to find the relationship between the anhedonic level and the FC changes in the thesis.

III. I hypothesized that obese individuals suffer from increased responsively towards rewarding food stimuli, especially aberrant reward cue processing. In Study 2, I used temporal homogeneity of local resting signals to delineate regions with specific abnormality during hunger state.

IV. I hypothesized that obese individuals show disordered regulation in eating behavior and abnormal baseline neural activity during different levels of satiety. In Study 4, I used ALFF to assess alternation of local baseline brain activity in obese individuals before and after food intake.

2 Material and Methods

2.1 Study 1: Altered FCD in MDD

2.1.1 Subjects

FMRI data were obtained from twenty-one MDD patients who were recruited from the department of psychiatry and psychotherapy at the Otto von Guericke University and twenty-three age and gender matched HC participants (Table 2). According to the ICD-10 criteria, the patients were all medicated were clinically diagnosed as recurrently depressed, and severity as assessed using the 21-items HAMD (Hamilton 1960) was 17.83 ± 6.08. All patients were medicated according to clinical standards with selective serotonin reuptake inhibitor (SSRI), or noradrenalin reuptake inhibitor (NRI), or selective noradrenalin reuptake inhibitor (SNRI) alone or with new generation antidepressants including agomelatine or lithium (Supplementary table S1). Exclusion criteria included major medical illness, history of seizures, prior electroconvulsive therapy treatments, pregnancy, or general MRI-contraindications. This study was approved by the ethics committee of Otto von Guericke University, and all participants gave written informed consent.

Table 2. Demographic characteristics of study 1 participant (Zhang, Li et al. 2015)

	HC (n=23)	MDD (n=21)	Group effect P value
Gender (male/females)	14/9	12/9	0.522
Age (years)	36.65 ± 9.26	38.14 ± 11.82	0.138
HAMD	0.73 ± 1.03	17.83 ± 6.08	<0.001

2.1.2 Data acquisition

I performed the fMRI measurements on a 3 Tesla Siemens MAGNETOM Trio scanner (Siemens, Erlangen, Germany) with an EPI sequence: TR/TE = 1250/25 ms; flip angle 70°; slice thickness 5mm (no slice gap); acquisition matrix 44×44; FOV 220×220 mm^2, and voxel size 5×5×5 mm^3. Every brain volume consisted of 26 axial slices, and each functional run contained 488 image volumes. All participants were instructed keep their eyes closed, not to focus their thoughts on anything in particular, and not fall asleep during the resting state MR acquisition.

I acquired structural images using magnetization prepared rapid gradient echo sequence with the following parameters: TR/TE = 2500/4.77ms, TI=1.1s, FA=7°, bandwidth 140Hz/pixel, acquisition matrix 256×256×192, voxel size 1×1×1 mm^3.

2.1.3 Processing

2.1.3.1 Preprocessing

I preprocessed the resting-state fMRI data using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). The first 20 volumes for each subject were discarded to allow fMRI signal to reach equilibrium and participants so as to adapt to scanning noise. The 468 volumes remained were corrected for the acquisition time delay among slices. I used derived realignment to correct potential rigid head motion with thresholds (translational or rotational motion parameters less than 2mm or 2°). Then, FD from the derivatives of the rigid-body realignment estimates was calculated to reflect the mismatch of volume to volume head position (Power, Barnes et al. 2013). Several nuisance covariates (six motion parameters and their first time derivatives, average signals of the whole brain, average signals of ventricular and white matter, and time points having spike motion of FD > 0.5) were regressed from the data. I, then,

applied a band-pass filter with frequency from 0.01 to 0.08 Hz. Subject specific structural image were segmented and normalized to MNI space using DARTEL in SPM8 (Ashburner 2007). I then applied the same transformation parameters to the filtered functional images. And the derived displacement was applied to individual mean realigned functional images, which was firstly linearly coregistered with corresponding structural images. The spatially normalized functional images were then resampled to 3×3×3 mm^3 voxels.

2.1.3.2 FCD analysis

According to the study of Tomasi and Volkow (Tomasi and Volkow 2010), the global FCD, which was calculated using an in-house script, was computed as the global number of functional connections between the given voxel and all other voxels. In my study, for each subject, I calculated for all GM voxels in the whole brain.

Pearson's linear correlation identified functional connections between voxels with correlation coefficient threshold at $R > 0.6$. In order to assess the robustness of the threshold chosen, FCD maps were calculated for other two thresholds of 0.4 and 0.5. In order to increase the normality, I applied grand mean scaling the gFCD maps by dividing the gFCD of each voxel by the mean value of the whole brain gray matter of each subject. At last, the FCDs were spatially smoothed with an 8×8×8 mm^3 Gaussian kernel. The correlation of disease severity was further investigated with FCD values in regions showing significant group difference in FCD.

2.1.3.4 ICA analysis

Group ICA using the GIFT toolbox (http://icatb.sourceforge.net/) was performed with normalized fMRI data. After smoothing with a Gaussian kernel at 8 mm, I performed

standard ICA analysis, which includes four steps: (i) dimensionality reduction, (ii) application of the ICA algorithm, (iii) back reconstruction, and (iv) component calibration. In my study, 32 ICs were estimated from the fMRI data with the MDL criteria (Li, Ma et al. 2006). Visual and salience components were identified through visual inspection. I obtained the individual-level components from back-reconstruction, and the intra-network FC was scaled by z score, which reflects the degree to which the time series of a given voxel correlates with the mean time series of its corresponding component.

2.1.3.5 Seed-based FC analysis

With the preprocessing smoothed data with a Gaussian kernel at 8mm, seed-based FC analysis was calculated using REST toolbox (Song, Dong et al. 2011). The seeds defined as the regions with abnormal gFCD, include right OCC and dACC.

2.1.3.6 VBM analysis

In order to investigate structural abnormalities between MDD patients and HCs, VBM analysis was performed using SPM8. In a short, the structural image was corrected for intensity inhomogeneities, transformed into standard MNI space, segmented into GM, WM, and cerebrospinal fluid component, modulated by multiplying voxel densities with Jacobian determinants, and then smoothed using a Gaussian kernel at 8mm. Voxels with significant group differences ($P < 0.05$, corrected) could be identified with the smoothed images after a multiple comparison correction. However, the absence of a significant whole brain difference in GMV may not rule out localized influences. I also extracted their GMV for clusters of interest that show significant group differences of FCD in order to also account for potential subtle influence of local grey matter reductions in the regions showing altered FCD.

2.1.4 Statistical analysis

A two samples *t* test was performed so as to test the group differences in FCD, ICA-derived FC and seed-based FC between MDD patients and HCs with gender and age as covariates. I also checked FCD changes with the extracted GMV as a covariate to exclude the potential effect of regional structure.

For all analyses, multiple comparisons were performed using a Monte Carlo simulation in REST toolbox (corrected threshold $P < 0.05$, single voxel $P = 0.001$, 5000 simulations, FWHM = 8 mm, cluster connection radius r = 5 mm). The high initial voxel threshold was chosen to minimize false positives and also to account for smaller, but more significant, clusters of activation.

For amygdala as a small subcortical region with a priori hypothesis, the search volume for seeded connectivity changes was confined accordingly through performing a small volume correction. I applied a family wise error (FWE) correction to account for multiple comparisons within this considerably smaller volume of interest. Given the strong spread of spatiotemporal components in ICA, the main influence of each component to detect which component includes dACC or OCC was regarded for whole brain FWE corrected p-values (Figure S4).

2.2 Study 2: Altered brain activities before food intake in obese men

2.2.1 Subjects

Twenty obese men and 20 age matched lean men were recruited through poster

advertisement. According to the adjusted Chinese obesity guideline, which is an equivalent of WHO class I, obese male subjects were required to have a BMI>28 kg/m^2, and lean male subjects were required to have a BMI from 18.5 to 23.9 kg/m^2 (He, Jiang et al. 2007). They were all right-handed and no one was a smoker. They did not have a history of illicit drug dependence or alcohol abuse, and none of them were currently dieting to lose weight. All subjects gave informed consent that was written. The institutional review board of the Tianjin medical university approved this study. The methods were employed in accordance with the approved guidelines.

2.2.2 Data Procedure

All of the participants finished the paradigm between 5:30 PM and 8:00 PM. Subjects were fasted 6-8 hours before scanning on the day of the scan. After lunch, subjects were asked not ingest nothing but drinking water until the experiment began. In order to reach to satiation, subjects took a liquid formula meal (55%carbohydrate, 30% fat, 15% protein; Ensure-Plus 1.5 kcal/ml) orally, and the taste of the liquid was vanilla. The liquid meal was offered in an amount proportional to the body size of each subject. And the meal provided 40% of the personal resting energy expenditure that was assessed by indirect calorimetric analysis (Vmax Encore, Sensormedics, United States).

The hunger rating was assessed using VAS, and with that subjects were required to rank their sensations of hunger, scaled from 0 (‘not at all hungry’) to 100 (‘very hungry’). Subjects gave the assessment before scanning in both pre-meal and post-meal conditions.

2.2.3 Data acquisition

The fMRI included two sessions, before and after the food intake. Brain imaging data were acquired with a 3 Tesla MR scanner (Signa-HDX, General Electric, United States),

and that gives an EPI sequence: TR/TE = 2000/30 ms; flip angle 90°; slice thickness 4 mm (no slice gap); matrix 64 × 64; FOV 240 × 240 mm^2, and voxel size 3.75 × 3.75 × 5 mm^3. Every brain volume was composed of 40 axial slices, and each functional run included 180 image volumes, with a total scan time of 360 s. All subjects were told that they should not focus their attention on anything in particular, and they should keep their eyes closed and not to fall asleep during the MR acquisition. Every participant in my study complied with these instructions.

Before each scan session, blood samples of subjects were taken from cubital. Plasma glucose concentrations were determined by an automated clinical chemistry analyzer (Medical Cooperation, USA) and plasma insulin concentrations by a CLIA (Siemens Diagnostics, USA).

2.2.4 Processing

2.2.4.1 Preprocessing

I preprocessed the resting-state functional image using SPM8. For each subject, the first 10 volumes of each functional time series were discarded because of the magnetization equilibrium. The 170 images remained were corrected for time delay among different slices and realigned to the first volume. Head motion parameters were calculated with estimating translation in every direction and the angular rotation on each axis for each volume. Each participant had a maximum displacement of less than 2 mm in any cardinal direction (x, y, z), and they had a maximum spin (x, y, z) less than 2°. After this step, all data were spatially normalized to the standard Montreal Neurological Institute template and each voxel was resampled to a voxel size of 3×3×3 mm cubic voxels. Further processing was carried out with REST, including temporal band-pass filtering (0.01–0.08 Hz) to reduce low-frequency drift.

2.2.4.2 ReHo analysis

In the experiment, the individual ReHo map was computed by REST. I divided such individual ReHo map with the subject's global mean KCC value within the brain mask. Standardized maps were smoothed with a Gaussian kernel (FWHM= 8 mm) for better anatomical comparability of ReHo values on a group level.

2.2.5 Statistical analysis

The two samples *t* test was performed to test differences between obese subjects and HCs, and threshold correction was performed using FDR with threshold at $p<0.05$ and with a contiguity criterion of 10 voxels.

Because of the differences between two groups before food intake, the group difference map was projected onto the mask. Within the mask, the paired t test was performed to examine the differences between before and after food intake states, and threshold correction was performed using FDR with threshold at $p<0.05$.

2.3 Study 3: Valence specific impairment of task-unspecific deactivation in DMN in MDD

2.3.1 Subjects and procedure

FMRI data were obtained from 21 MDD patients and 25 age and gender matched HC participants. Patients were clinically diagnosed according to the ICD-10 criteria and the severity was assessed using the 24-items Hamilton rating scale for depression (HAMD) and Montgomery-Asberg depression rating scale (MADRS). Snaith-Hamilton pleasure scale (SHAPS) was used as psychometric evaluation of anhedonia. Exclusion

criteria were major medical illness, history of seizures, prior electroconvulsive therapy treatments and pregnancy. This study was approved by the ethics committee of Tianjin Medical University General Hospital, and all participants provided written informed consent to participate.

The experiment was designed and presented by Presentation (Neurobehavioral Systems, http://www.neurobs.com) software. For the first 8 MDD patients and 8 HCs participants, the experimental stimuli were projected using the fMRI Hardware System (Nordic NeuroLab, NNL) into a goggle screen that wore by participants. Due to the goggle dysfunction accident, the following 13 MDD patients and 17 HCs performed the task by viewing through a viewfinder that located in the coil and the stimuli were projected through a beamer into the viewfinder. I modeled the goggle/screen effect as a non-interested regressor in the whole analysis to minimum the influence of experimental environment change.

The emotional expectancy paradigm used visual cues and pictures with different valence. A total of 60 pictures were selected from the International Affective Picture System (IAPS) (Lang, Bradley et al. 2008), and pictures were divided into positive (n=20), neutral (n=20) and negative (n=20) pictures according to the ratings of perceived valence (mean valence rating of negative: 2.06±0.54; neutral: 5.11±0.52; positive: 7.68±0.32). Pictures from this set were matched largely between valences with regard to the number of people, complexity, and semantic content.

Each picture was presented for 4 seconds. Half of the trials were preceded by an expectancy task that predicts 100% validity of the types of the upcoming stimulus; e.g., an upwards-pointing arrow indicated that a positive picture would follow (positive expectancy); a downward-pointing arrow indicated that a negative picture would follow (negative expectancy); a horizontal arrow signaled a neutral picture afterwards (neutral expectancy). Half of the pictures were preceded without any cue (unexpected pictures), meaning these pictures were followed directly after fixation. In the paradigm,

the cue-picture-mismatch events were used in order to bring new condition to the participants, therefore to increase their attention towards pictures: 15 visual cues were followed directly by fixation but not pictures. Each expectancy cue lasted 3-5 seconds; the baseline period with a fixation cross lasted 8.5-10.5 seconds (Figure 0).

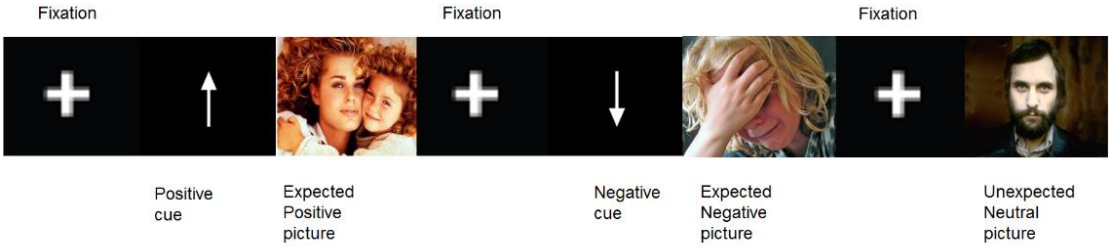

Figure 0. Paradigm for task fMRI

2.3.2 Data acquisition

MRI was performed using a 3.0-Tesla MR system (Discovery MR750, General Electric, Milwaukee, WI, USA) with an 8-channel head coil. A gradient-echo SENSE-SPIRAL (spiral in) sequence was performed using parameters of TR/TE = 1600/30 ms; FA = 60°, acceleration factor = 2, FOV = 220 mm × 220 mm; matrix = 64 × 64; slice thickness = 4 mm; gap = 0.5 mm; 36 interleaved transverse slices; voxel size 3.14×3.14×3 mm^3, and the task scan contained 710 image volumes. Sagittal 3D T1-weighted images were acquired by a brain volume sequence with the following scan parameters: TR = 8.2 ms; TE = 3.2 ms; inversion time (TI) = 450 ms; FA = 12°; FOV = 256 mm × 256 mm; matrix = 256 × 256; slice thickness =1 mm, no gap; and 188 sagittal slices.

2.3.3 Processing

2.3.3.1 Preprocessing

Data were preprocessed using SPM8. The 710 volumes were corrected for time delay between different slices and realigned to the first volume. Head motion parameters

were computed by estimating translation in each direction and the angular rotation on each axis for each volume. Each subject had a maximum displacement of less than 3 mm in any cardinal direction (x, y, z), and a maximum spin (x, y, z) less than 3°. Individual structural images were linearly coregistered to the mean functional image; then the transformed structural images were segmented into GM, white matter, and cerebrospinal fluid. The GM maps were linearly coregistered to the tissue probability maps in the MNI space. The motion-corrected functional volumes were spatially normalized to the individual's structural image using the parameters estimated during linear coregistration. The functional images were resampled into $3 \times 3 \times 3$ mm^3 voxels. Finally, all datasets were smoothed with a Gaussian kernel of $8 \times 8 \times 8$ mm^3 FWHM.

2.3.3.2 First level analysis of task data

At the single subject level, I modeled six regressors of interest and convolved with the canonical hemodynamic response function on the base of general linear model. The first 3 regressors indicated the effect of expectancy during cuing trails irrelevant of whether the picture was followed or not (expectancy of negative pictures [Xneg], expectancy of positive pictures [Xpos] and expectancy of neutral pictures [Xneu]). The last 3 regressors indicated the effect of emotion during picture display session (negative pictures [Pneg], positive pictures [Ppos] and neutral pictures [Pneu]). The voxel time series were high-pass filtered at 1/128 Hz to account for non-physiological slow drifts in the measured signal and modeled for temporal autocorrelation across scans with an autoregressive model.

2.3.3.3 PPI analysis

PPI method was used to investigate how the emotional expectancy regulated the functional connection. Briefly, PPI analyzed possible interactions between regression

slops of different regions that can be significantly tested as a measure of FC (Friston, Buechel et al. 1997). A 6 mm radius sphere around the significant peak of the second-level result from the task was created. I only investigated 'Xpos vs. Xneu' (the only condition that showed significant group difference) using PPI analysis. The extracted hemodynamics time series were deconvolved and the physiological variables were combined with the onset times for Xpos and Xneu to derive the interaction term. To obtain data of the physiological variable, I extracted the individual mean time series within a 6 mm radius sphere that centered at the maximum peak within the DMPFC seed region under the threshold of $p<0.9$ without any correction. The physiological factor was then multiplied with the psychological factor, yielded the interaction term and re-analysis in a new GLM model with 3 regressors that representing PPI, BOLD and psychological condition. Subject-specific contrast images resulting from the contrast [1 0 0], where the first column represents the interaction term, was then entered into a group analysis using a two samples t-test, and the significance threshold used for PPI analyses was $p\leq0.05$ cluster level family-wise error (FWEc) correction.

2.3.4 Statistical analysis

On the group level, several *t*-tests were conducted to check the main effect of expectancy (Xpos vs. Xneu, Xneg vs. Xneu, Xpos vs. Xneg). For second-level analysis, single subject contrasts were entered into one-sample and two-sample *t*-tests across subjects. First, statistical parametric maps were estimated for the contrast and the reverse contrasts in the healthy group (one sample *t*-test) with age and goggle/screen as covariates. Then, effects were compared between HC and depressed participants (two-sample *t*-test).

The SHAPS containing 14 items and 4 scales: if the subjects answered 'disagree' or 'totally disagree' to an item, it was assigned to a score of 1, otherwise it was 0. A total score was derived by summing the answers of each item. Higher SHAPS total scores

indicate greater anhedonia (inability to experience pleasure), and a score of 3 or higher indicates a significant reduction in the hedonic capacity (Snaith, Hamilton et al. 1995). Multiple regression analysis was conducted to investigate PPI and SHAPS correlation, SHAPS total score that described above was entered as covariates and modeled in factorial design specification.

2.4 Study 4: Altered the activity differentiates regional mechanisms subserving biological and psychological alteration

2.4.1 Subjects

Please see the 2.2.1 Subjects Part.

2.4.2 Data procedure

Please see the 2.2.2 Data procedure part.

2.4.3 Data acquisition

Please see the 2.2.3 Data acquisition part.

2.4.4 Processing

2.4.4.1 Preprocessing

I preprocessed the resting-state fMRI data using SPM8. The first 10 volumes for each subject were discarded to allow fMRI signal to reach equilibrium and participants so as to adapt to scanning noise. The 170 volumes remained were corrected for the

acquisition time delay among slices.

I used similar preprocessing steps as Study 1, more details please find 2.1.4.1 part.

2.4.4.2 ALFF analysis

ALFF maps were calculated using REST toolbox. The time courses are converted to the frequency domain using a FFT, and the square root of the power spectrum is calculated and averaged across 0.01–0.08 Hz at each voxel (Zang, He et al. 2007, Chao-Gan and Yu-Feng 2010). Then, ALFF maps were divided by whole brain mean ALFF values to normalize the global effects.

2.4.5 Statistical analysis

The two samples *t* test was performed so as to test the group differences between obese subjects and HCs with age as nuisance covariate before and after the food intake. Threshold correction was performed by a Monte Carlo simulation using REST toolbox (corrected $P < 0.05$ single voxel $P = 0.001$, 5000 simulations, FWHM = 8 mm, cluster connection radius r = 5 mm). And the ANOVA analysis was calculated for two factors group and feeding condition using full factorial design.

Then, the ROIs were selected from the previous ALFF results: dACC and precuneus. Before and after food intake, the ROIs of dACC were based on the mean activity of the voxels identified in the two samples *t* test. After liquid intake, no precuneus difference in activity could be detected, so I only selected ROI of precuneus before food intake. Then, I entered the mean value of the activation ROIs correlated with plasma insulin at the states of before and after food intake. And mean activity levels of each ROI were entered into partial correlation analyses corrected for BMI with subjective hunger ratings. In the study by Kullmann *et al.,* they found that cognitive networks were

modulated by the feeling of hunger, independent of BMI (Kullmann, Pape et al. 2013). So, in the study, I excluded the BMI component and investigated partial relationships for hunger ratings and each ROI, which was seen in its result of the contribution of the hunger rating on the activation.

3 Results

3.1 Study 1: Altered FCD in MDD

3.1.1 FCD

When at a correlation threshold of R > 0.6, MDD and HCs displayed quite similar gFCD spatial distributions (Fig. 1.1). Specifically, gFCD of both groups showed the greatest values in the posterior cingulate cortex, precuneus, and medial OCC. However, weaker gFCD was indicated in the ventral-anterior part of the temporal cortex, the basal ganglia regions, and insula.

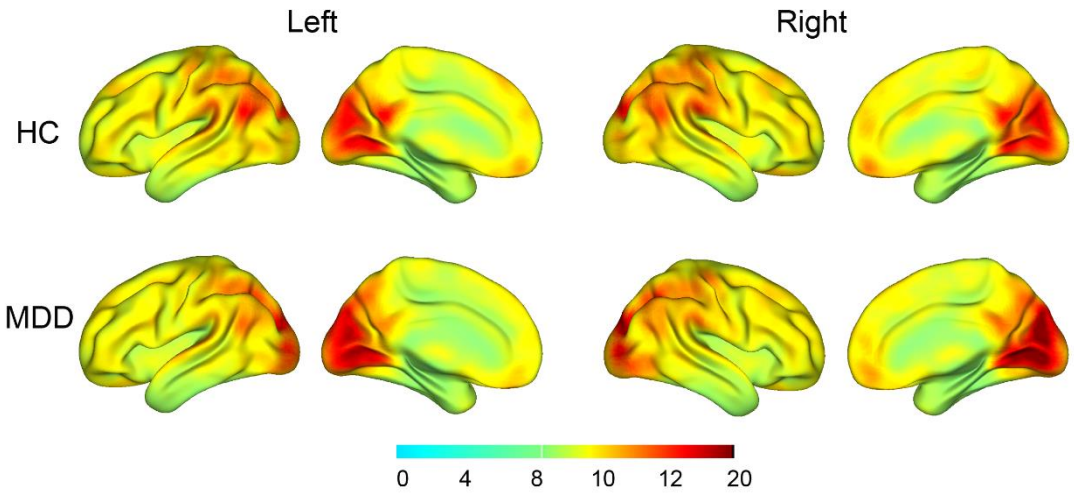

Figure 1.1 Spatial distribution of global FCD within depressed patients and healthy controls, as revealed by the results of one sample t test (correlation coefficient threshold: R > 0.6, p < 0.05, FWE corrected) (Zhang, Li et al. 2015).

As indicated by the study, in MDD subjects, there was a significant increase of gFCD in the right occipital cortex (p < 0.05, corrected, x=33, y=-93, z=9, k=34), while gFCD in the dACC showed a decreased value (p < 0.05, corrected, x=3, y=-3, z=30, k=98) as

compared with HCs (Fig. 1.2).

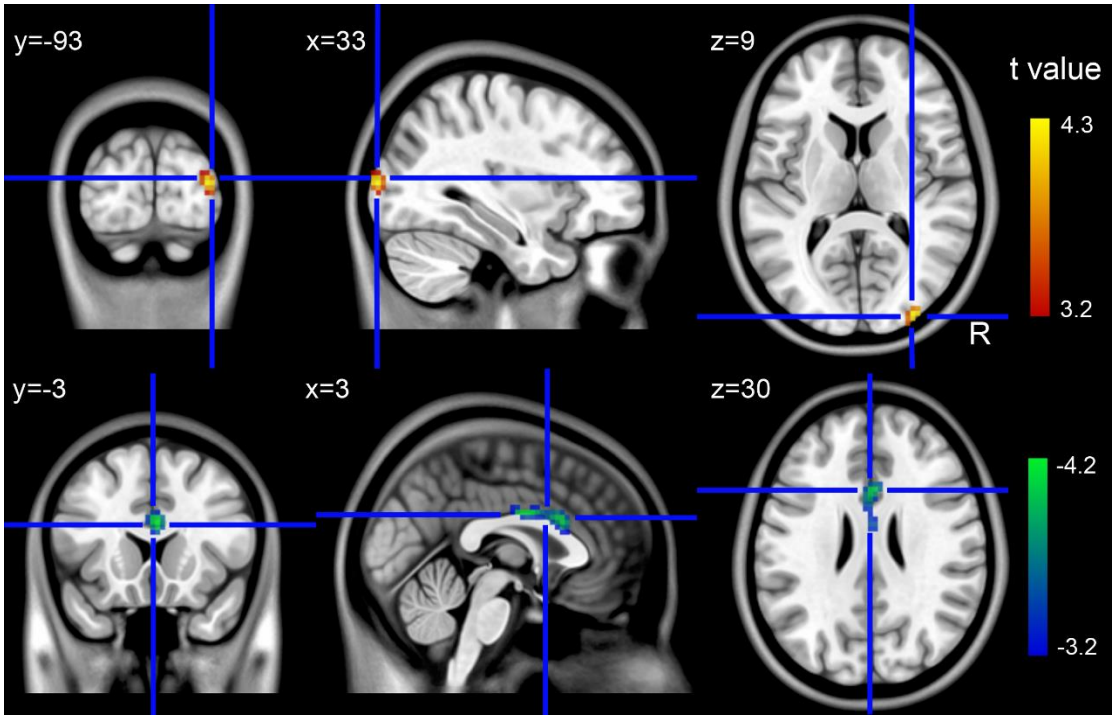

Figure 1.2 Group difference of FCD map between patient and control groups ($p < 0.05$, AlphaSim corrected). Patients showed significant increased occipital cortex (warm color) and decreased anterior mid-cingulate cortex (cold color) FCD, compared to controls. These regions with group FCD effect were then used as seeds for the FC comparison in Figure 1.3 (Zhang, Li et al. 2015).

Observation had been conducted for all three correlation coefficient thresholds (R>0.4, R>0.5) (Supplementary figures S1-2) in the study results.

3.1.2 Seed-based differences of regions with gFCD abnormal

Decreased gFCD in dACC was paralleled by decreased seed-based FC of the dACC cluster to mid-cingulate cortex (x=3, y=3, z=30, k=19, Fig. 1.3A). At the same time, FC was increased for the dACC cluster towards left amygdala (x=-24, y=-3, z=-18, p<0.003, FWE, small volume corrected, Fig. 1.3B). Increased gFCD in OCC in MDD patients was

paralleled by significantly increased seed-based connectivity between the OCC cluster (revealed by FCD comparison) and occipital cortex (x=6, y=-90, z=-6, k=28, Fig. 1.3C) and right supplementary motor area (SMA, x=24, y=-15, z=72, k=24, Fig. 1.3D). No significant difference was observed on FC of dACC towards thalamus between groups.

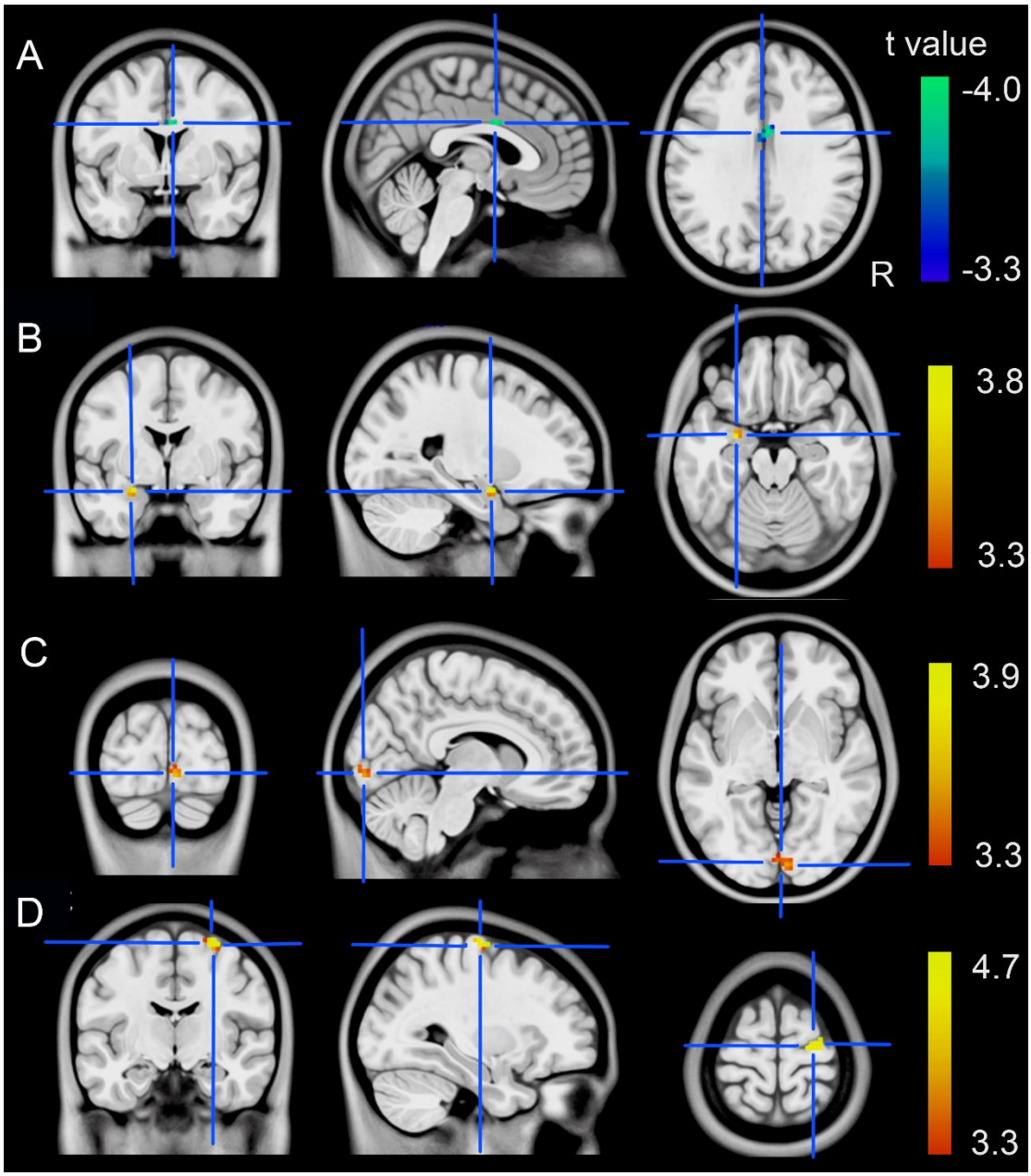

Figure 1.3 Group differences of dACC and OCC functional connectivities ($p < 0.05$, AlphaSim corrected). Patients showed significantly decreased functional connectivity towards dACC posterior sub-region (Fig. 1.3A, cold color) and increased dACC functional connectivity towards amygdala (Fig. 1.3B, warm color). Stronger

functional connectivity within OCC (Fig. 1.3C) and towards right supplementary motor area (Fig. 1.3D) was found in patients, compared to controls (Zhang, Li et al. 2015).

3.1.3 ICA

ICA revealed 32 ICs. According to the aberrant results as detected by gFCD in MDD, comparison was conducted on the group differences in FC of the salience network and visual network to verify whether ICA can also detect the functional aberrance. And as expected, no significant differences was found in FC of the two IC components between MDD and HC ($p > 0.05$, corrected, supplementary figures S3).

3.1.4 VBM

From VBM analysis, no region with significant difference of GMV between controls and depressed patients was detected on the whole brain level. But MDD patients still showed significantly deceased FCD in the mid-cingulate cortex (x = 3, y = 18, z = 24, k = 91) when compared to controls, with the local GMV of dACC as a covariate, However by contrast, the study found no regions has displayed an increased level of FCD in patients on a corrected significance level ($p<0.05$, indicated by clusters of more than 20 contiguous voxels and an individual voxel intensity threshold of $p<0.001$) when controlling the local GMV of OCC. However, when on an uncorrected level of significance ($p<0.001$, k=10 voxels), it was observed that there was an increase of FCD in the same peak locations as for the initial model. Correlation of FCD and GMV in OCC revealed no significant relationship (p=0.755, r=-0.072, MDD; p=0.07, r=-0.385, HC).

3.2 Study 2: Altered baseline brain activities before food intake in obese men

3.2.1 Behavior

Two samples *t*-test was applied to compare the group differences of plasma glucose, insulin and the rating of hunger (in the subjects with obesity and lean male subjects). My study shown that, before liquid intake, obese subjects had higher ratings of hunger than lean subjects. But, no significant difference was indicated between the two groups. The test revealed similar plasma glucose levels between lean and obese subjects before food intake. However, obese subjects showed drastically lower plasma glucose levels than lean subjects after food intake. And for the entire process, plasma insulin concentrations of obese individuals were significantly higher ($p<0.05$) than lean ones. (Table 2.1).

Table 2.1 Characteristics of the study 2 and 4 population (Zhang, Tian et al. 2015)

	Lean (n=20)	Obese (n=20)	Group effect *P* value
Age (y)	24±4	24±4	
Body weight (kg)	63.52±5.66	100.51±13.32	0.015
BMI (kg/m^2)	21.48±1.43	33.56±3.53	0.004
REE (kcal)	1627.25±175.77	2331.5±360.80	0.003
Glucose (mmol/L)			
Fasting	4.46±0.44	4.12±0.72	0.142
Post-meal	8.58±1.86	6.84±1.64	0.450
Insulin (uU/mL)			
Fasting	4.84±5.30	14.81±11.32	0.001
Post-meal	58.51±27.13	143.12±67.74	0.002
Hunger Ratings (mm)			
Fasting	71.56±9.61	72.92±13.24	0.330
Post-meal	20.63±12.89	17.06±12.99	0.738

3.2.2 ReHo

In the case of hunger state, the obese men had a significant increased activity in the left putamen, and had a significant decreased activity in the OFC, medial prefrontal cortex (MPFC) and right inferior temporal lobe (Fig. 2, $p < 0.05$, FDR corrected), when compared to the lean subjects.

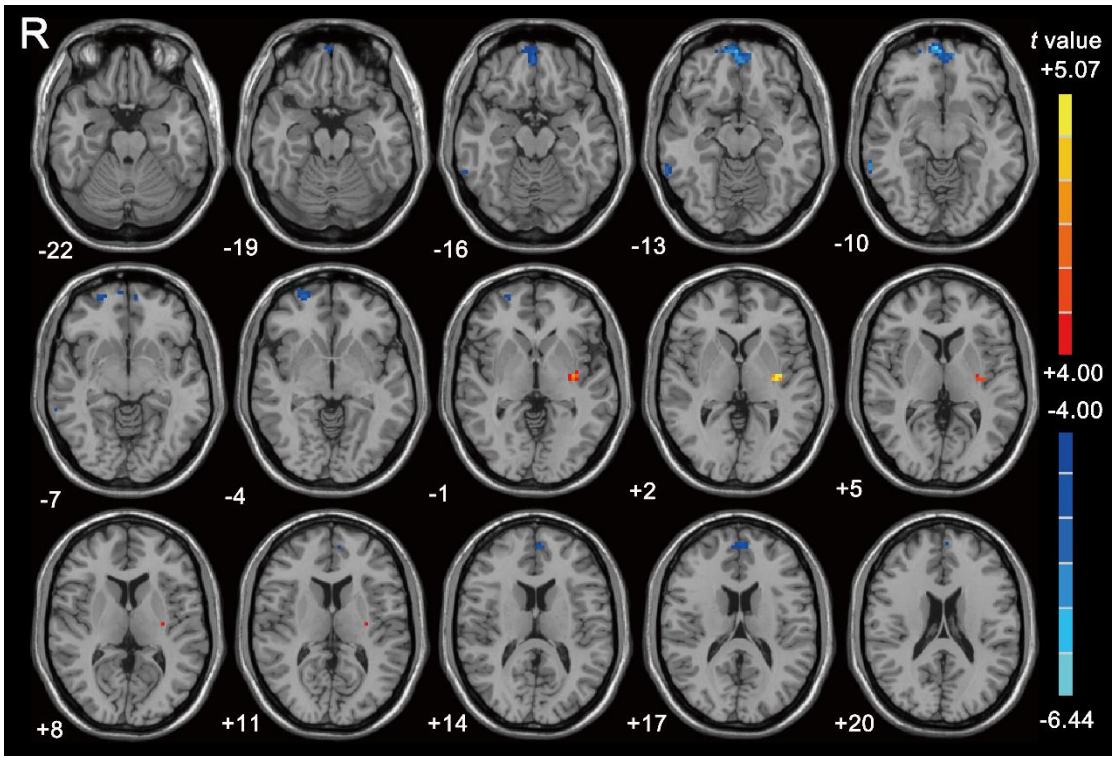

Figure 2.1. Group difference between obese subjects and controls before food intake (p< 0.05, FDR corrected). Warm and cold colors indicate obese subject-related ReHo increases and decreases, respectively (Zhang, Tian et al. 2015).

Yet, the lean men had a significant increased activity from before to after food intake in the OFC and right inferior temporal lobe. (Fig. 2.2, p < 0.05, FDR corrected), which is the same as the obese men. (Fig. 2.3, p < 0.05, FDR corrected).

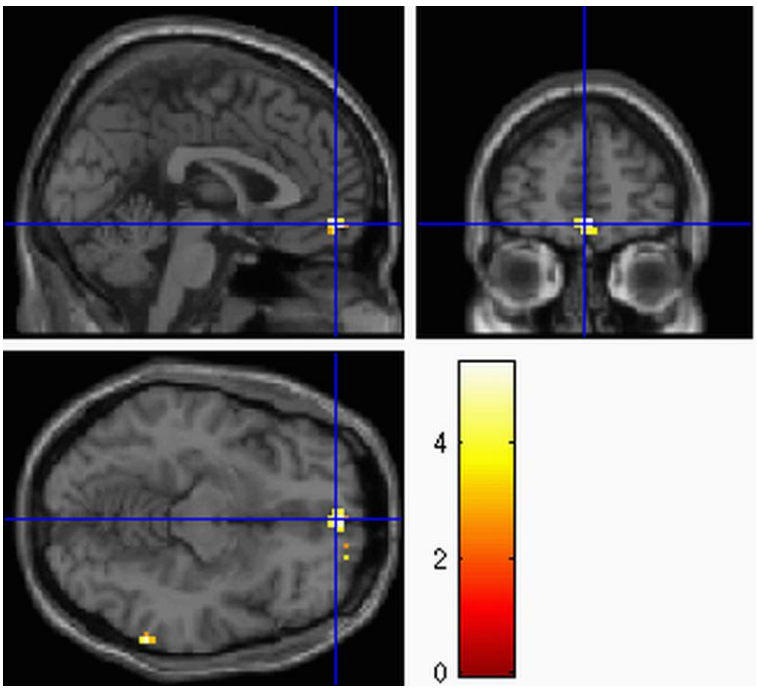

Figure 2.2. A T-statistical difference map between the fasted and the satiated state of normal controls (p< 0.05, FDR corrected). Warm colors indicate increased activity from the fasted to the satiated state (Zhang, Tian et al. 2015).

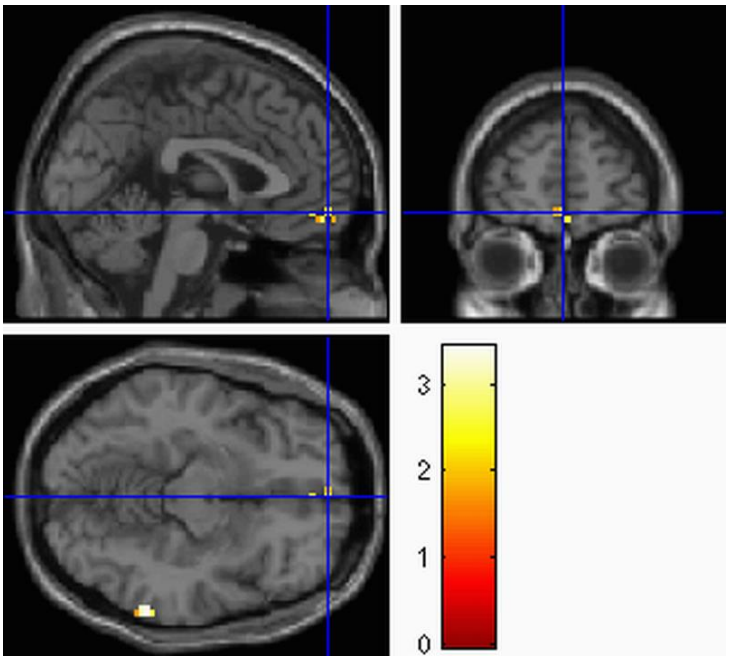

Figure 2.3. A T-statistical difference map between the fasted and the satiated state of obese subjects (p< 0.05, FDR corrected). Warm colors indicate increased activity from the fasted to the satiated state (Zhang, Tian et al. 2015).

3.3 Study 3: Valence specific impairment of task-unspecific deactivation in DMN in MDD

3.3.1 Task fMRI

All three expectancy contrasts for the comparison 'MDD vs. HC' were investigated during the study, with no obvious findings of the contrasts Xneg vs. Xneu or Xpos vs. Xneg. When comparing greater positive expectancy than neutral expectancy, MDD patients showed increased activity in the DMPFC ($p < 0.05$, FWE cluster level corrected, $x = 15$, $y = 48$, $z = 30$, $k = 390$), compared to the HCs (Fig. 3.1a). The mean values of DMPFC in the conditions of 'Xpos', 'Xneu' and 'Xneg' using MARSBAR toolbox (http://marsbar.sourceforge.net/) showed detailed activity patterns. The DMPFC signal change in patients was much higher than controls in the positive expectancy ($p < 0.05$). In other expectancies conditions, no significant difference was found between the groups (Fig. 3.1b).

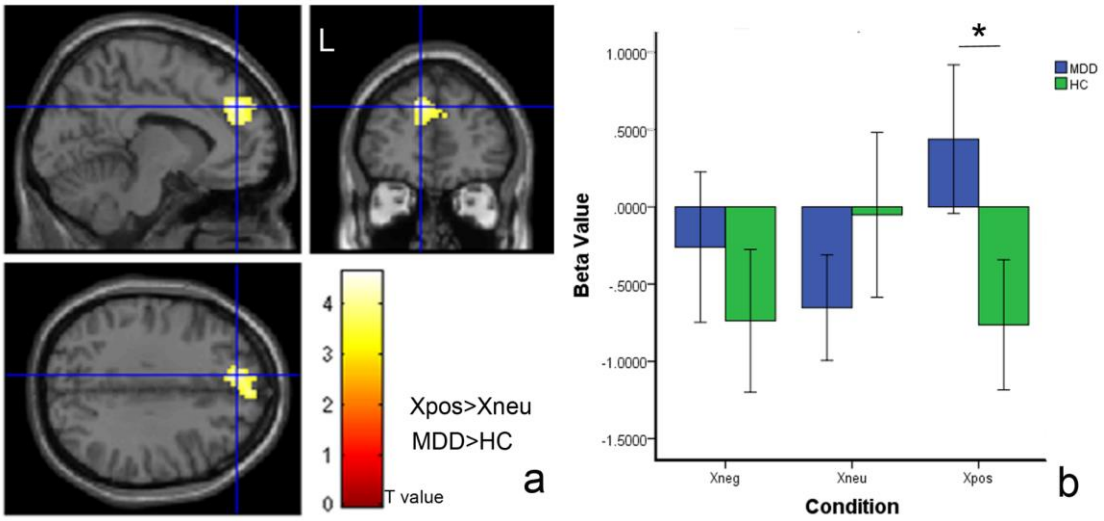

Figure 3.1. (a) Group difference of the positive vs. neutral expectancy (Xpos > Xneu) between patient and control groups (p < 0.05, cluster level FWE cor.). Patients showed significantly increased activity in the dorsal medial prefrontal cortex (DMPFC) (warm color). (b) Mean betas of the DMPFC during negative picture expectancy

(Xneg), neutral picure expectancy (Xneu) and positive expectancy (Xpos). Error bars showed the standard error of the mean. * p<0.001.

3.3.2 PPI

During the positive vs. neutral expectancy condition, compared with HCs, MDD patients had increased FC from DMPFC towards posterior cingulate cortex (PCC) (Figure 3a, $p < 0.05$, FWE cluster level corrected, T = 4.7, x = -9, y = -36, z = 45, k = 97) and parieto-occipital cortex (Figure 3b, $p < 0.05$, FWE cluster level corrected, T = 5.15, x = -24, y = -60, z = 21, k = 60). Figure 3c show the mean PPI value between MPFC and PCC during positive vs. neutral expectancy, which revealed there is decoupling between MPFC and PCC for positive vs. neutral expectancy in controls, not in MDD patients.

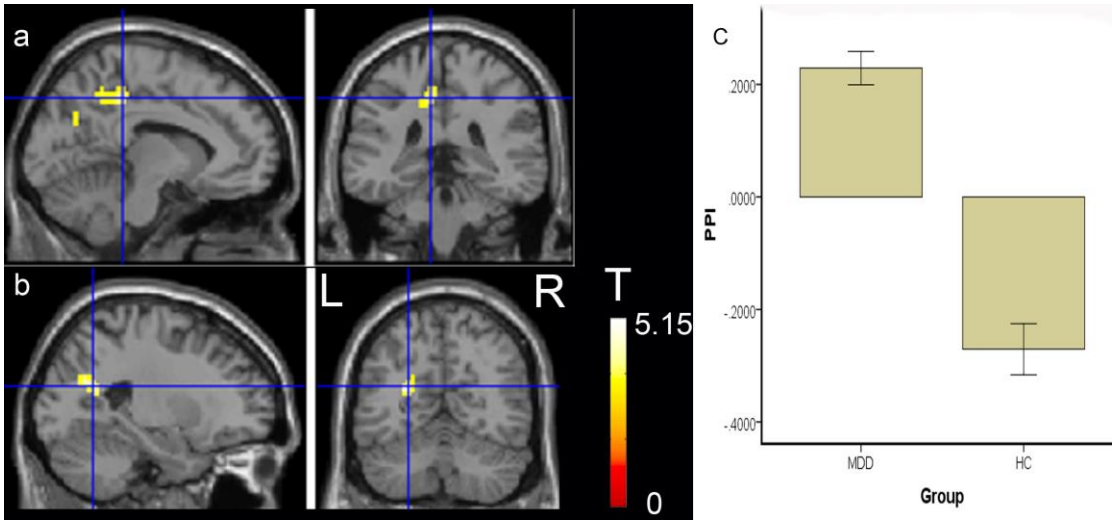

Figure 3.2. PPI group difference between patient and control groups (p<0.05, cluster level FWE cor.). Patients showed significantly increased FC from DMPFC towards PCC (a) and parieto-occipital cortex (b). (c) Mean PPI values from DMPFC towards PCC for each group, error bars depict the standard error of the mean.

3.3.3 PPI-SHAPS correlation

During the positive vs. neutral expectancy comparison, a positive correlation between PPI (DMPFC and PCC) and anhedonia as measured via SHAPS ($p<0.05$, FWE-SVC) was observed in patients. This result indicates the lowest decoupling in patients with high SHAPS scores during positive compared to neutral expectancy.

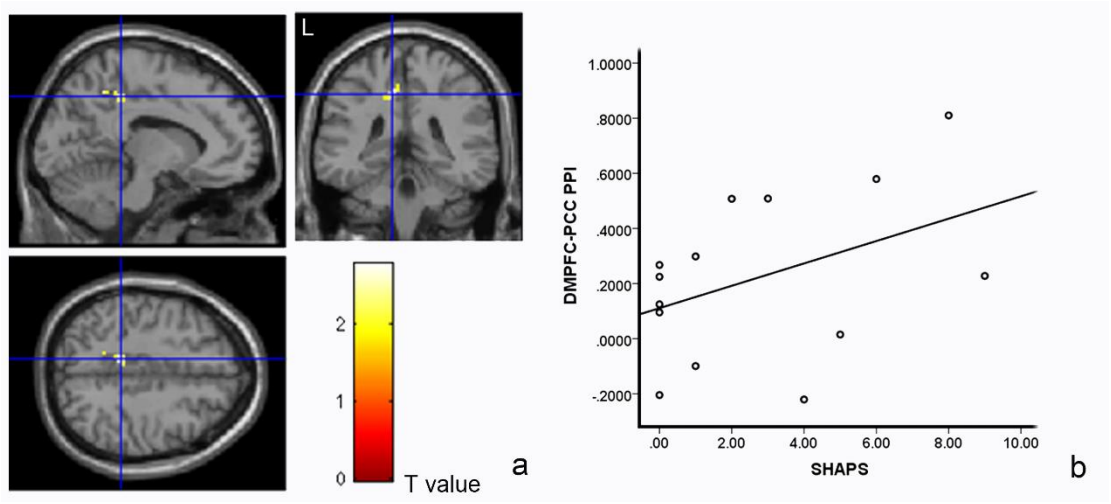

Figure 3.3. (a) The positive effect of anhedonia level on the PPI (DMPFC and PCC) with the seed of PCC in patients with MDD (warm colors) during the positive vs. neutral expectancy (Xpos > Xneu). (b) Positive correlation between SHAPS and the PPI (DMPFC and PCC) in patients ($P<0.05$, small volume and FWE corrected).

3.4 Study 4: Altered the activity differentiates regional mechanisms subserving biological and psychological alteration

3.4.1 Behavior

Please see 3.2.1 Behavior.

3.4.2 ALFF

Before food intake, obese male subjects, showed a significantly higher activity in the bilateral precuneus (Fig. 4.1, p-value < 0.05, corrected; right precuneus: x=9, y=-66, z=60, k=153; left precuneus: x=-12, y=-60, z=66, k=62) and significantly lower activity in the dACC (Fig. 4.1, p-value < 0.05, corrected, x=15, y=24, z=18, k=150), when compared to the lean control group. However, after food intake, only the lower activity in the dACC (Fig. 4.2, p-value < 0.05, corrected, x=-6, y=9, z=24, k=49) was observed compared to the control group, with no increased activity in the precuneus.

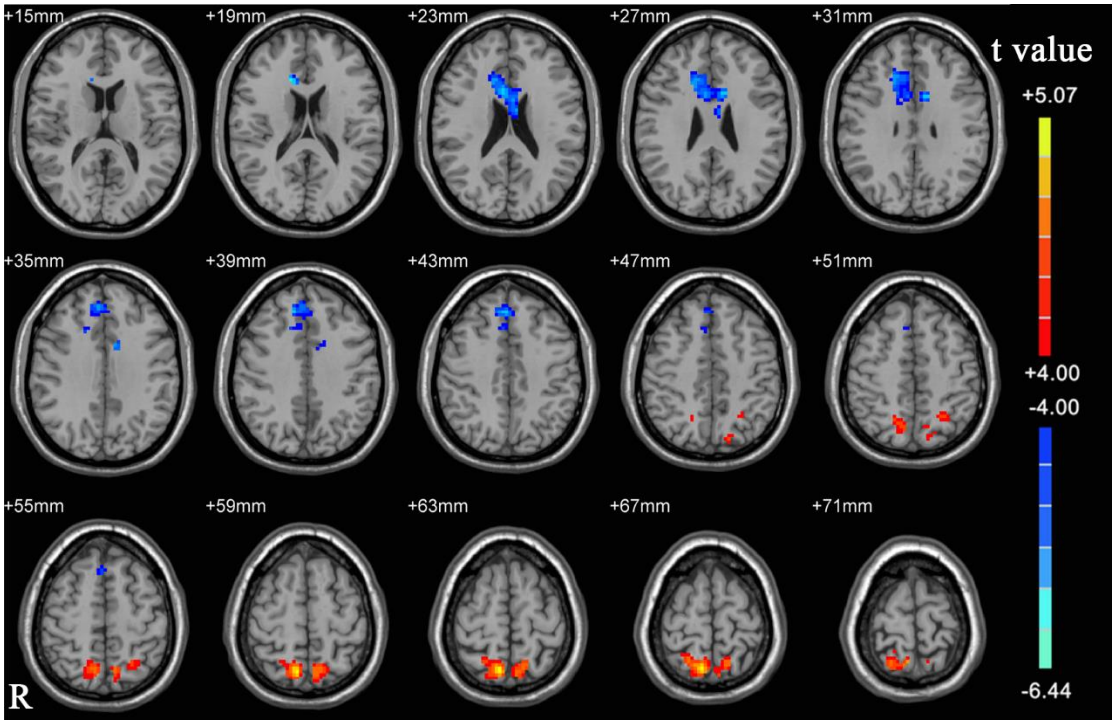

Fig 4.1. Group difference between obese subjects and controls before food intake (p< 0.05, corrected). Hot and cold colors indicate greater and lower ALFF activity in obese subject relative to healthy controls, respectively (Zhang, Tian et al. 2015).

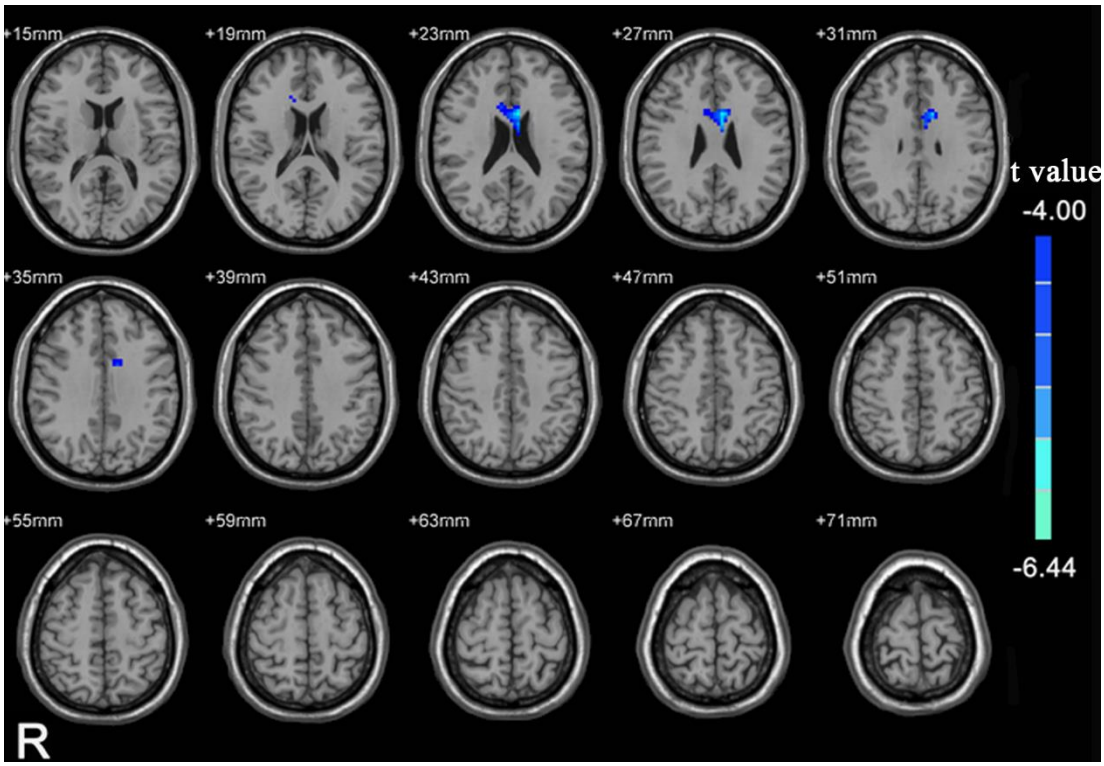

Fig 4.2. Group difference between obese subjects and controls after food intake (p< 0.05, corrected). Cold color indicates lower ALFF activity in obese subject relative to healthy controls (Zhang, Tian et al. 2015).

ANOVA revealed significant main effects of food intake condition in pericental lobule (x = -6, y = -24, z = 60, k = 202, Suppl. Fig 5B) and main effects of group on dACC (x = -3, y = 9, z = 24, k = 154, Suppl. Fig 5A).

3.4.3 Correlation

Based on these ALFF results (precuneus and dACC), then chose ROIs were chosen to correlate their mean activation levels with plasma insulin and subjective hunger ratings. There revealed a positive correlation between precuneus activation and subjects individual rating of hunger, adjusted for BMI, for conditions before food intake (r= 0.372, p<0.036; Table 4.1 and Fig 4.3). Besides, there found a significant negative correlation between dACC activation and plasma insulin before (r= -0.433, p<0.005,

Table 4.2 and Fig 4.4A) and after food intake(r= -0.492, p<0.001; Table 4.2 and Fig 4.4B).

Table 4.1 Results of the correlation between ROIs activation and the rate of hunger and plasma insulin (Zhang, Tian et al. 2015)

		Hunger rating		p	Insulin		p
		Before	After		Before	After	
dACC	Before	-0.066	-	0.719	**-0.433**	-	**0.005**
	After	-	0.189	0.299	-	**-0.492**	**0.001**
precuneus	Before	**0.372**	-	**0.036**	0.131	-	0.419
	After	-	-0.062	0.734	-	0.186	0.249

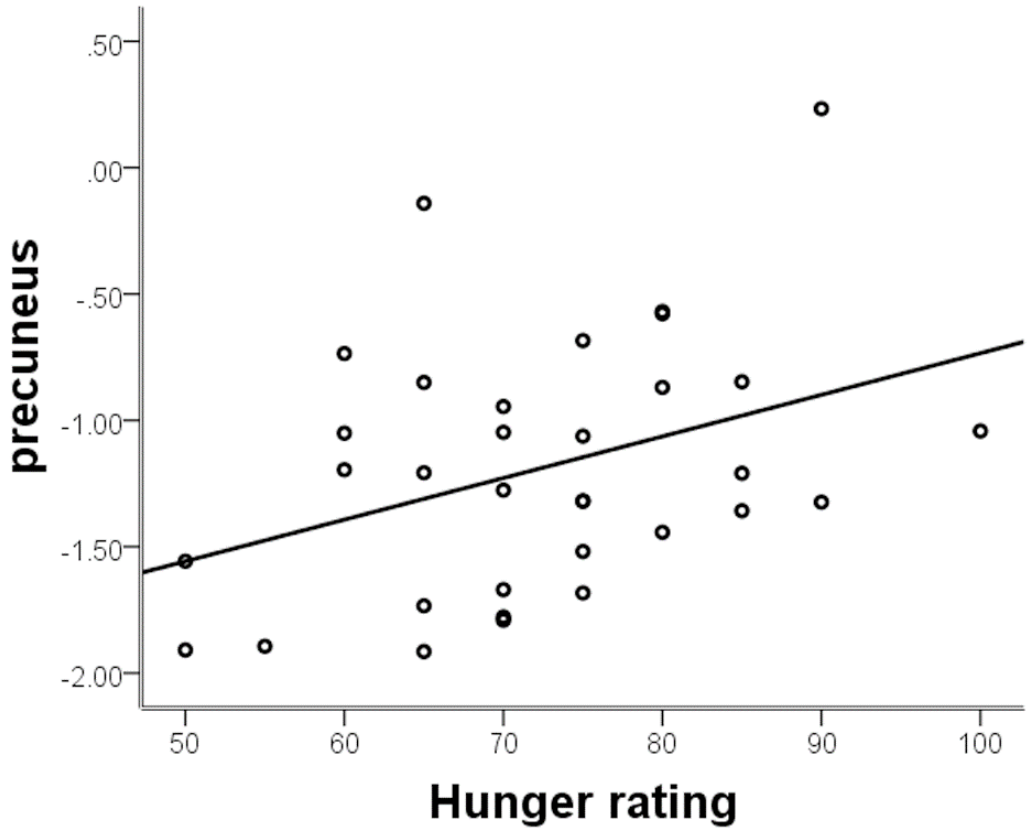

Fig 4.3. Partial correlation adjusted for BMI between the mean activity of precuneus

and hunger ratings (Zhang, Tian et al. 2015).

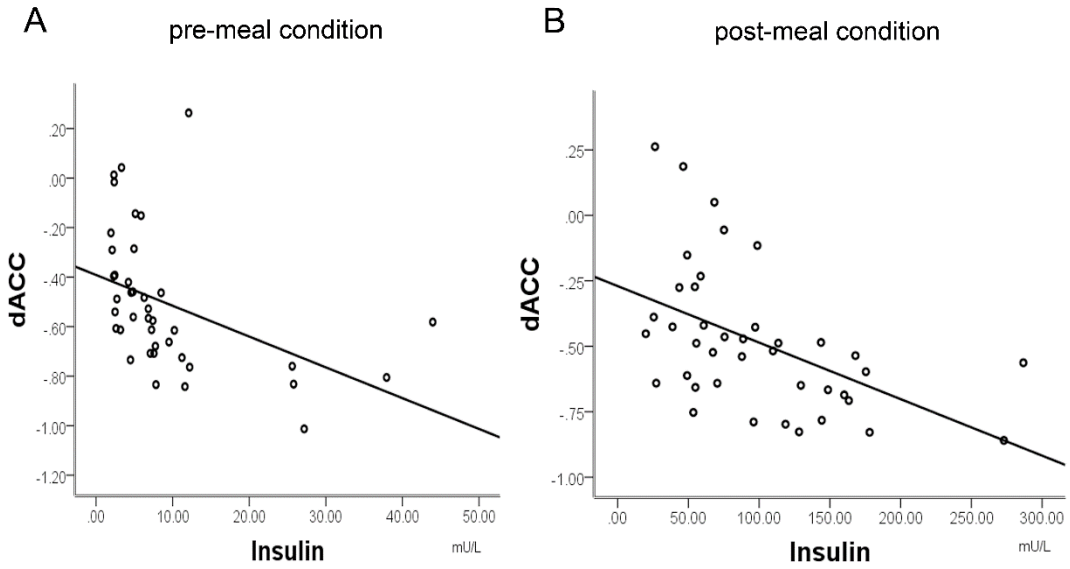

Fig 4.4. Correlation between the mean activity of dACC and plasma insulin in the pre-meal condition (part A) and the post-meal condition (part B) (Zhang, Tian et al. 2015).

4 Discussion

4.1 Two neuropsychiatric disorders

In my studies, I concentrated on MDD and obesity these two neuropsychiatric disorders. There is growing evidence that major depressive disorder and obesity share common health complications, such as cardiovascular disease and type II diabetes mellitus (Bender, Zeeb et al. 2006, Mezuk, Eaton et al. 2008, Gafarov, Panov et al. 2014), which could be explained by an unhealthy lifestyle (Galper, Trivedi et al. 2006, Strine, Mokdad et al. 2008). And, many studies have examined the association between depression and obesity and reported obese individuals have 5 times the risk of MDD than the non-obese (Moussavi, Chatterji et al. 2007, Roy-Byrne, Davidson et al. 2008, Hewer, Fuessl et al. 2011). Furthermore, several studies provided biological explanations for the association between MDD and obesity - the inflammatory system of both two disorders people is dysregulated (Bornstein, Schuppenies et al. 2006, Vreeburg, Hoogendijk et al. 2009). In the study of Afari and his colleagues, they found depression and obesity shared genetic risk factors, which based on a community-based sample of twins (Afari, Noonan et al. 2010). My studies investigated these two neuropsychiatric disorders separately: Study 1 and Study 3 investigated MDD, Study 2 and Study 4 investigated obesity; while I found the common character among them: abnormalities in reward system. In Study 1, MDD subjects showed significantly increased FCD in the right OCC, while FCD in the dACC was reduced compared with healthy controls. This implies an importance of abnormal functional connectivity these regions as a correlate of brain pathophysiology in a disorder of impaired reward value attribution as it the case for depression. In Study 2, I found that, before food intake, obese men had significantly increased activity in the left putamen relative to lean men, and decreased activity in OFC. This study supports the hypothesis that there is a hyper-functioning reward circuitry in obese individuals, in which the frontal cortex may fail to inhibit the striatum, and consequently lead to overeating and obesity. In Study 3,

MDD patients had greater activity in MPFC than healthy participants as a function of positive vs. neutral expectancy condition. The PPI results revealed a significant group difference of task dependent coupling from MPFC towards PCC during positive vs. neutral expectancy condition, and a positive correlation between PPI of PCC and SHAPS in patients. My findings would be consistent with the hypothesis that patients may lack of the ability to incorporate information derived from external positive events with a corresponding down-regulation of the intrinsic focus. In Study 4, before food intake, obese subjects had significantly increased activity in the precuneus and decreased activity in dACC relative to lean subjects. After food intake in contrast obese subjects only showed significantly decreased activity in dACC. I further found precuneus activation positively correlated with hunger ratings before food intake, and there was negative correlation between dACC activation and plasma insulin levels before and after food intake. The study quantified the baseline neural activity during different levels of satiety and indicated that both dACC and precuneus may play an important role in eating behavior.

4.2 Eating behavior design

In the previous studies of eating behavior, the researches usually used the task state to investigate the brain activity during the specific stimuli (Schur, Kleinhans et al. 2009). Schur and his colleagues used the food pictures to investigate the brain activity (Schur, Kleinhans et al. 2009). Recently, there have been increased studies using functional connectivity method to investigate the brain networks (Tregellas, Wylie et al. 2011, Kullmann, Heni et al. 2012, Garcia-Garcia, Jurado et al. 2013) in obesity. However, this method relies on the selection of the regions of interest, which are based on the specific hypothesis (Craddock, Holtzheimer et al. 2009). I used the resting state method to investigate spontaneous brain during the before and after food intake states. The method focuses on the local brain activity during the resting state.

There are two factors regulating the reward processing, which are hunger and food intake (Drewnowski, Maillot et al. 2009). Hunger affects the reward processing, which motivates people to eat. Previous studies showed that hunger makes food more palatable (Berridge 2004), so hunger is a significantly important factor to investigate the eating behavior. Food intake could lead to satiety, which makes food less palatable (Rolls, Rolls et al. 1981). Calorie content and palatability are two factors influence food intake, so I used the same taste liquid meal and the ingestion quantity is in amount proportional to body size of each subject.

Each subject was scanned twice. For the first time scanning, subjects were asked to fasted 6-8 hours, not to ingest anything except pure water. All subjects reached to the hunger state at the first time scanning. For the scanning, I would like to find the abnormal brain activity in obese individuals during the hunger state. However, I did not estimate the quantity of water ingested during the fasted duration, which is one limitation of my design. The quantity of ingested water would influence the distension of stomach, which would have an effect on the brain responses.

All subjects had ingested the liquid meal, which is in an amount proportional to each subject's body size, and then whey took the second time scanning. For the scanning, I would like to find the abnormal brain activity in obese individuals after food intake. In my experiment, I used the vanilla liquid meal, the taste of which could be accepted by all subjects. However, the degree of palatability of the liquid meal for the subjects was not estimated, which is a crucial effect on the brain activity.

4.3 Altered baseline brain activities in obese men during hunger state

In Study 2, the ReHo method was used to examine spontaneous brain in lean and obese men.

The obese men, before food intake, had significantly decreased activity in the OFC and MPFC. In one VBM study by Walther and his colleagues (Walther, Birdsill et al.), there is the negative correlation between BMI and gray matter volumes in OFC and cerebellar regions. A study in functional neuroimaging found that obese individuals showed reduced activation in the frontal regions, including the superior frontal gyrus, middle frontal gyrus, ventrolateral prefrontal cortex, medial prefrontal cortex, and OFC, as compared to lean individuals (Batterink, Yokum et al.). The primate MPFC contains the secondary taste cortex, which receives projections directly from the primary taste cortex (Baylis and Moore 1994). This secondary taste cortex represents the reward value of taste, in which its taste neurons only respond to food when the animal is hungry (Rolls, Critchley et al. 1999). According to my study (Zhang, Tian et al. 2015), OFC plays a crucial role in eating behavior, and obese individuals show less inhibitory control during hunger state and lead to eat more food than healthy controls.

The dorsal striatum, known as a key component of the reward system, plays a role in consumed food reward (Stice, Spoor et al. 2008, Stice and Knowlton 2008). Activation in the caudate and putamen were negatively related to future weight gain for participants with attenuated dopamine signaling (Stice, Spoor et al. 2008, Stice and Knowlton 2008). Previous studies showed that, when normal subjects were hungry compared to when they were sated, the left putamen was activated (Stice, Spoor et al. 2008, Stice and Knowlton 2008). According to my published paper, I interpreted obese men had significantly increased the synchronicity of activity in the left putamen before food intake, which may mean that dopamine was released more in the striatum of the obese men (Zhang, Tian et al. 2015).

Whatever before and after food eating, the rating of hunger in obese and lean subjects were similar, which indicates that the desire of hunger were similar between the two groups (Flint, Raben et al. 2000). The study by Tataranni and his colleagues (Tataranni, Gautier et al. 1999) fielded similar results. However, the activity of the brain regions

was inconsistent with the VAS results. Before food intake, compared to the lean individuals, the obese ones, had remarkably elevated brain activity in the left putamen, which may indicates that obese men had a desire to eat more than the lean men did, but they did not acknowledge this feeling.

4.4 Altered the activity differentiates regional mechanisms subserving biological and psychological alteration

In Study 4, the ALFF method was used to examine spontaneous brain in lean and obese men.

In the study, I found obese individuals had a significantly greater activity in the precuneus only in hunger state, not in satiety state. In the previous studies, the precuneus, belongs to DMN (Fox and Raichle 2007), mediated self-referential thoughts (Uddin, Kelly et al. 2009). Obese individuals before food intake is engaged in the processing information about their internal states (Tregellas, Wylie et al. 2011). Zhang and his colleagues interpreted increased precuneus activity at the same time as the activity in the DMN as a representation of increased self-focus and processing of subjective feeling of hunger (Zhang, Tian et al. 2015). I also found there is a positive correlation between hunger rating and the activity of precuneus during hunger state. In the study of Tataranni, they found that, compared to satiety state, the precuneus brain activity is greater in the hunger state (Tataranni, Gautier et al. 1999). My results are parallel to their findings, especially, there is no significant difference of precuneus between groups after food intake.

The dorsal ACC forces the integration of highly relevant sensory stimuli (Seeley, Menon et al. 2007), and activates in response to metabolic stress, hunger and pleasurable feeling (Craig 2002). Previous studies showed that, compared to lean subjects, the obese individuals increased activation in ACC in response to food pictures (Martin,

Holsen et al. 2010, Stice, Yokum et al. 2010). One fMRI study using decision-making takes showed that dACC plays role in reward based decision-making (Bush, Vogt et al. 2002). In study 4, I investigated the neural baseline activity before and after food intake, and found that, compared to lean subjects, lower activity of dACC in obese men. According to Manasse's food anticipation study, obese subjects showed hyper-responsivity in the reward system during food cue stimuli (Manasse, Espel et al. 2015). I thought dACC is a code region to encode the reward value of food cues (Zhang, Tian et al. 2015). In one PET study by Gautier and colleagues, obese individuals also showed reduced activity in the ACC, compared to HCs (Gautier, Chen et al. 2000).

According to my published paper, I thought ACC is an important region with altered activity in obesity; its functional role seems to deviate from that of the precuneus (Zhang, Tian et al. 2015). Its baseline aberration, whatever before and after food intake, is reflected by insulin measures. Previous work indicated insulin is an important hormone to regulate appetite and food intake (Zhao and Alkon 2001), and the signal of insulin could affect the mental activity about the current energetic supply. The studies by Gautier and his colleagues found insulin takes the negative correlated with the activation of the OFC and precuneus after food intake (Tataranni, Gautier et al. 1999, Gautier, Chen et al. 2000). In Study 4, I found the insulin concentration of obese individuals, compared to lean ones, were significantly higher, and there is a negative correlation between insulin and the activation of dACC before and after food intake. My previous study interpreted that the obesity and plasma insulin levels have essentially influence on the activation of dACC, supporting food intake via basic metabolic mechanisms and potentially independent from subjective motivation (Zhang, Tian et al. 2015)

4.5 ReHo and ALFF analysis

For ReHo analysis, Kendall coefficient of concordance (KCC) was used for measuring

the similarity of the time series within a functional cluster based on the regional homogeneity hypothesis, and 27, 19 or 7 nearest neighboring voxels were defined as a cluster and a KCC value (range 0–1) was given to the voxel at the center of this cluster (Zang, Jiang et al. 2004).

In ALFF analysis, the fMRI time series was transformed to a frequency domain with a FFT and then the power spectrum was obtained. Since the power of a given frequency is proportional to the square of the amplitude of this frequency component of the original time series in the time domain, the square root was calculated at each frequency of the power spectrum and the averaged square root was obtained across a frequency band at each voxel.

ReHo and ALFF are two widely used approaches in characterizing the local brain features of resting state fMRI data, which have been used to investigate schizophrenia, Alzheimer's disease, autism spectrum disorders, attention deficit hyperactivity disorder and so on. I firstly use these two methods investigate obesity. These two methods have been widely used to explore local functional abnormalities in a variety of brain disorders. In the Study 2 and Study 4, the two approaches were used to investigate altered activities in local baseline brain activity in obese individuals before and after food intake. Using two kinds of analysis approaches, I got the different results of the same subjects' sample. In the previous studies, the ALFF and ReHo have been used to identify functional abnormalities in neuropsychiatric disorders. However, studies of ALFF and ReHo have yielded inconsistent results (Liu, Liu et al. 2006, Chen, Xu et al. 2013, He, Deng et al. 2013, Ren, Lui et al. 2013, Yu, Chien et al. 2014). Though these two approaches are characterized the local brain features of resting state fMRI, they reflect the different physical activity. The ReHo reflects the similarity of spontaneous neural activity, among spatially adjacent brain tissues (Zang, Jiang et al. 2004), while the ALFF quantifies the strength or intensity of low-frequency oscillations embedded in the baseline neural activity (Zang, He et al. 2007). Previous studies found that ReHo and ALFF methods were demonstrated to be stable to noise interference (Li,

Kadivar et al. 2012), and one-sample *t* test results of two methods were strongly correlated (Yuan, Di et al. 2013). Yan and his colleagues also used the two methods to investigate the same subjects (Chao-Gan and Yu-Feng 2010) (Figure 5.1). From the figure 5.1, I could found the activations of MPFC, precuneus and cingulate cortex are different between these two methods analysis, and these regions are my main finding areas. So I got the different results based the two kinds of approaches, and I interpreted my results from the different directions, one is loss control (Study 2), the other is self-referential thoughts (Study 4).

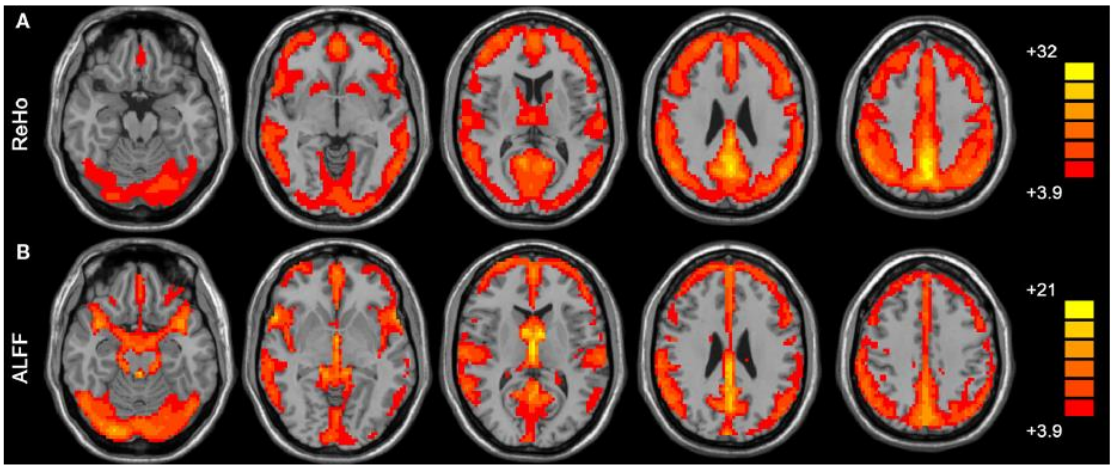

Figure 5.1 ReHo (A) and ALFF (B) methods revealed the pattern during the resting state. The statistical threshold was set at $t > 3.89$ ($P < 0.0001$) for one-tailed *t*-tests and cluster size >135 mm^3 (Chao-Gan and Yu-Feng 2010).

4.6 Altered FCD in MDD

In Study 1, the FCD method was firstly used to observe the aberrant global connectivity in resting state fMRI measure in patients with major depression. FCD would be able to detect different connectivity profiles of certain regions even if their disconnectivity patterns would spatially vary across individuals (Anticevic, Brumbaugh et al. 2013). In such, deviant FCD could mainly be interpreted as a sign of affection of regions property within a whole network. According to Buckner et al (Buckner 2010), FCD could rapidly

provide insight into global properties of connectivity and identify regions of the brain referred to as hubs. Hubs are nexuses of connectivity hypothesized to allow efficient integration across widely distributed brain areas (Bullmore and Sporns 2009), and such hub function could be effectively disrupted as a sum of disconnection. As a support for such general network effects, abnormal graph metrics have been shown to exist (Zhang, Wang et al. 2011), especially for between module connectivities (Lord, Horn et al. 2012). In my study, I found however that the clusters of abnormal FCD were significantly dysconnected to specific brain regions, limiting this interpretation for my finding. Interestingly, these secondary seed-based analyses revealed a great relevance of concomitant changes of locally restricted FC in that OCC was increasingly connected to clusters within OCC and dACC was decreasingly connected with dACC in patients.

While ICA was found to be highly reproducible (Damoiseaux, Rombouts et al. 2006), it seems to restrict connectivity estimates of the regions observed here too much towards deviant connectivity of the underlying independent spatiotemporal component, ignoring the variability of subcomponents. This would be especially supported by the local dysconnections of the two regions of altered FCD since these would also be detectable by ICA if they would sufficiently correlate with the IC time-courses. What I cannot say at this stage is how far other dysconnections with a less regionally consistent pattern would also contribute to the mean difference in FCD across groups. Related follow-up questions could ideally investigate the independence of FCD and specific connection changes in an independent and sufficiently powered clinical sample.

The dACC, involved in relaying top-down cognitive inputs in the context of the cognitive model (Ochsner and Gross 2005), showed reduced functional connectivity with limbic regions in individuals with depression (Greicius, Flores et al. 2007). Impaired connectivity was discussed to contribute to attenuated cognitive control and therefore to increase awareness and conscious processing of negative stimuli (Disner, Beevers et al. 2011). When I followed up on deviant connectivity towards amygdala,

the increase in FC seems counterintuitive. While specific investigations of reduced FC of this dACC portion towards amygdala have not been reported, one would have hypothesized rather the opposite given existing knowledge and concepts. Actually, Anand et al suggested that decreased resting-state connectivity between the dorsal ACC and limbic areas associated with increased amygdala responses to negative stimuli in individuals with depression (Anand, Li et al. 2005). Previous electrophysiology studies found that dACC consist of a mixture of functionally distinct cells, especially anticipate targets (Gehring and Willoughby 2002) and encode reward values (Sanfey, Hastie et al. 2003, Sanfey, Rilling et al. 2003). So, reduced local connectivity within this dACC region would be rather consistent with reduced activation or cognitive control, which would be in line with decreased processing of positive information (Disner, Beevers et al. 2011). And Chang and colleagues found that ACC activation respect foregone rewards (Chang, Wu et al. 2013). So the abnormal connection of dACC showed the region correlated with the brain pathophysiology of impaired reward value attribution, especially foregone rewards.

I also found the MDD subjects showed significantly increased FCD in the OCC along with increased local FC and towards and right frontal cortex. In the previous studies, the OCC plays role in the pathology of depression has been investigated for changes in the concentrations of γ-aminobutyric acid (GABA), which is the major inhibitory neurotransmitter in the brain. And the study using proton magnetic resonance spectroscopy (1H-MRS) found that medication-free depressed patients showed the significantly lower level of GABA levels in this region (Sanacora, Mason et al. 1999, Sanacora, Gueorguieva et al. 2004). Meanwhile, cortical GABA concentration was found to be inversely correlated with BOLD responses (Northoff, Walter et al. 2007), suggesting that the excitation/inhibition cortical balance controls the functional neuroimaging measures (Muthukumaraswamy, Edden et al. 2009). Likewise, Donahue and colleges reported that GABA concentration in the visual cortex is inversely correlated with BOLD signal variations and with cerebral blood flow (Donahue, Near et al. 2010), suggesting a link between neurochemical and MR-measured

hemodynamic responses. A recent study in seasonal depressive disorder patients using graph theory also showed group differences on the level of hub nodes in OCC (Borchardt, Krause et al. 2014). In the same study, hyper-connectedness and hyper-efficiency was also found in occipital cortex in patients. Although the visual cortex was not part of the major resting state connectivity investigation in MDD, neither by implementing this region as a seed nor by including visual independent components (Dutta, McKie et al. 2014), my findings, together with those by Borchardt et al, may however motivate to include visual cortex into systematic investigations in the future.

4.7 Valence specific impairment of task-unspecific deactivation in DMN in MDD

In study 3, I found the anterior part of DMPFC, a region that was previously identified to be associated with attention proceeding deficient of emotional pictures perception in MDD patients, was also related to emotional expectancy dysfunction. More specifically, the positive expectancy showed impaired deactivation in MDD as compared to HC group, but not negative or neutral expectancies. The PPI result revealed a significant MDD related FC impairment from DMPFC towards PCC and parieto-occipital cortex as a function of positive greater than neutral expectancy. This was driven by a significant decoupling between DMPFC and PCC during positive vs. neutral expectancy conditions in HC group, which was absent in patients. To my knowledge, this is the first study that observed deficient intra-DMN FC during specifically positive emotional expectancies, which underlies deficient DMN deactivation in MDD patients.

Previous studies have indicated that the activity in DMPFC was involved in cognitive tasks, e.g., appraisal and expression of negative emotion (Etkin, Egner et al. 2011), internal cued conditions such as pleasant vs. unpleasant stimuli (Gusnard, Akbudak et

al. 2001) or expected vs. unexpected pictures (Walter, Matthia et al. 2009), to engage action monitoring (Amodio and Frith 2006), etc. More importantly, DMPFC is a key region during emotional attention processing, for example, it showed stronger activity when the participants viewing positive pictures than negative pictures (Bermpohl, Pascual-Leone et al. 2006), or showed smaller signal decreased during emotional judgment (Northoff, Heinzel et al. 2004). Therefore, it is reasonable that the deficient BOLD response in DMPFC was often related to mental disorders such as MDD. A previous clinical study found increased activity in the left DMPFC and PCC in healthy group during expected vs. unexpected emotional pictures perception, but this effect was absent among MDD patients (Bermpohl, Walter et al. 2009). Insufficient deactivation in left DMPFC of MDD patients for positive pictures perception was then observed in the same study, which suggested that MDD patients showed DMPFC dysfunction in correctly processing external positive information leading to impaired preparation and thus reduced attention gain of positive events. However, in the above mentioned study, the researchers were not able to check the positive expectancy condition, because the expectancy cues did not differentiate into positive and negative emotion. My experiment incorporated the valence effect during expectancy, and abnormal positive expectancy activation was successfully discovered in DMPFC among MDD patients, which added clinical evidence that MDD patients showed DMPFC dysfunction in correctly processing the internal positive information (expectancy).

DMPFC is an anterior and essential part of DMN, and the negative blood oxygenation level-dependent responses (NBRs) in regions of DMN have been related to rumination, autobiographical memory, self-referential information processing, and various emotional-cognitive tasks (Gusnard, Akbudak et al. 2001, Raichle, MacLeod et al. 2001, McKiernan, Kaufman et al. 2003, Fransson 2005, Grimm, Schmidt et al. 2006, Grimm, Boesiger et al. 2009, Whitfield-Gabrieli and Ford 2012, Zhu, Wang et al. 2012). The NBRs is a result of high neuronal resting-state activity that inhibited during tasks, due to goal-directed external stimuli related attention resources allocation (Greicius and Menon 2004, Fox, Snyder et al. 2005, Fransson 2005). Grimm and her colleagues found

MDD patients showed abnormal NBRs in the anterior DMN (mostly the ventromedial prefrontal cortex, shorten as VMPFC) when performing emotion perception and emotion judgment tasks (Grimm, Boesiger et al. 2009). The follow-up study from (Grimm, Ernst et al. 2011) found the MDD patients' DMPFC (as well as VMPFC) showed reduced NBRs during self-related judgment and passive viewing; and most interestingly, they found a correlation between valence and self-relatedness rating for positive (but not negative) emotional pictures in healthy group - which was opposite in MDD that patients only showed significant correlation for negative emotional pictures. Taken together, MDD patients were less attracted by positive emotions – an emotion that supposed to cause stronger deactivation in the anterior DMN during both passive perception and active anticipation/judgment; therefore in my study, the patients showed less deactivation (even showed activation instead of deactivation as compared to HC group) in the DMPFC when expecting positive pictures.

Based on my hypothesis, I was interested in finding out the intra- or inter- DMN network FC that seeded in the anterior DMN (the left DMPFC) and modulated by the valence dependent expectancy. The PPI result revealed a significant DMN decoupling between anterior DMN and posterior DMN (PCC) as a function of positive vs. neutral expectancy in HC group, however, the positive stimuli induced decoupling was impaired in MDD patients. A stronger resting-state FC between posterior and anterior DMN in MDD patients than healthy group was identified by (Berman, Peltier et al. 2011), and they also found the rumination scores were positively correlated with the FC – strongly supported the notion that increased intra-DMN FC indicated stronger rumination in MDD patients. Although the previous study only reported rs-FC evidence of increased intra-DMN (anterior-posterior DMN) connectivity in MDD patients, a very recent study reported a similar FC (from subgenual anterior cingulate cortex [sgACC] to PCC) was also increased when the MDD patients performing the external focus task (Belleau, Taubitz et al. 2015). The same study also found a decreased FC in executive and salience networks during the external focus task in MDD patients, which may be a result of the increased intra-DMN FC. In other words, in order to 'normally'

performing a task that requires external focus (such as expecting a positive emotional picture when detected an upwards-pointing cue), the internal focused rumination has to be interrupted to reallocate neural resources to the outside world, therefore the FC between anterior and posterior DMN that related to rumination has to be disconnected. However, due to the obsessive negative rumination in MDD patients, the intra-DMN decoupling cannot be proceeded, and the increased resting-state intra-DMN FC is still strong during positive expectancy (or even stronger than neutral expectancy). My finding is in line with above mentioned studies and within an independent patients group, supported a positive valence dependent DMPFC-PCC decoupling deficient mechanism that underlie the rumination symptom of MDD patients.

Consistent with the impaired attention focus toward external events in the case of positive expectancies, I found a correlation between DMPFC PPI and SHAPS in MDD patients. SHAPS allows measuring the anhedonia, which is one important character of many MDD patients (Gorwood, Corruble et al. 2008). Specifically, the patients with the depressive episode are associated with anticipatory anhedonia and impaired reinforcement learning (Jensen, McIntosh et al. 2003, Kampe, Frith et al. 2003). Anhedonia research has flourished with the development of a basic literature that describes partially dissociable neural systems for reward anticipation versus consummation (Knutson, Adams et al. 2001) and for learning cue-reward. While anhedonia suggests reduced pleasure upon reward consummtion, accruing evidence instead relates anhedonic depression to blunted anticipatory pleasure (McClure, Berns et al. 2003). Impaired NBR in DMN has also be found to discern highly anhedonic MDD patients from those patients with anhedonia and this deficit to downregulate DMN activity during actual perception of emotional stimuli was related to a glutamatergic deficit in the MPFC (Walter, Henning et al. 2009). In contrast to this previous study, I however found a deficit in the dorsal portion, which was now apparent even before actual picture presentation. The previous association of anhedonia related lack of DMN downregulation during consumatory processes could thus be extended towards

deficient preparational mechanisms during anticipation of positive events.

Moreover, I added evidences to previous clinical studies on either increased rs-FC or task induced deactivations in MDD patients, by showing that both effects can be linked within the same paradigm. Importantly, I found that in patients, the effect of impaired network decoupling as a function of limited attention refocusing towards external demands in the context of potentially meaningless positive expectancy, can be observed already during the anticipation period. I also provided novel findings that differed from two similar previous studies, of which (Herwig, Bruhl et al. 2010) did not observed the DMPFC effect during pleasant vs. neutral expectancy, and (Bermpohl, Walter et al. 2009) only reported a valence dependent effect during perception. One potential reason may be that of changes in design as in Bermpohl et al, (2009) the picture periods followed expectancies with fixed duration, which may lead to difficulties to disambiguate expectancy and picture related responses. Other potential reasons for finding expectancy related differences may be that the sample size further was slightly larger than the one reported in Bermpohl et al 2009 (n=21 vs. n=15 patients) and the use of a 3 Tesla scanner may have further increased the signal to noise ratio to detect group differences. In contrast, severity, gender distribution and medication status seem to be rather comparable and thus may not have to be considered the primary sources for the new findings. Nevertheless, it needs to be acknowledged, that this my observation is the first of its kind in an Asian patient group, while potential differences in brain correlates of depression neither between Chinese and German clinical samples nor between Asian and Caucasian groups have never been systematically observed to my knowledge (Han and Northoff 2008).

4.8 Reward deficiency

Anhedonia is one of the main symptoms of MDD, which is the loss of interest in previously rewarding activities. Depressive patients reduce the hedonic capacity,

which should be possible to gain from one single activity. The symptom of MDD reflects deficits in reward circuitry (Hardin, Pine et al. 2009). In Study 1, MDD subjects showed significantly decreased FCD in the dACC compared with healthy controls. The dACC involved in relaying top-down cognitive inputs in the context of the cognitive model (Ochsner and Gross 2005). Previous electrophysiology studies found that dACC consist of a mixture of functionally distinct cells, especially anticipate targets (Gehring and Willoughby 2002) and encode reward values (Sanfey, Hastie et al. 2003, Sanfey, Rilling et al. 2003). Reduced connectivity within dACC region would be rather consistent with reduced activation or cognitive control, which would be in line with reduced processing of positive information (Disner, Beevers et al. 2011). I inferred that the dACC correlated with the brain pathophysiology of impaired reward value attribution. MDD patients showed increased prefrontal cortex activation while evaluating outcomes (Forbes, Christopher May et al. 2006). In Study 3, I found that positive expectancy showed impaired deactivation in MDD patients compared to HCs. In this case, MDD patients showed abnormal in processing external positive information, leading to impaired preparation and reduced attention gain of positive events. PPI results found the positive stimuli induced decoupling was impaired in MDD patients, and impaired NBR in the DMN has been found to discriminate highly anhedonic MDD patients. This identified anhedonia patients may have an impaired ability in incorporating information about the positive events with a corresponding down regulation of intrinsically focused attention.

Lots of studies show that obesity results from abnormalities in reward processing (Stice, Spoor et al. 2009). Based on the reinforcement sensitivity model, obese individuals show greater reactivity of brain reward systems to reinforcing foods – high fat and high sugar foods and consume more of such foods than lean individuals (Nicklas, Yang et al. 2003). Consumption of palatable foods, relative to consumption of unpalatable foods, results in higher activation of the right OFC (O'Doherty, Deichmann et al. 2002), and Pannacciulli and her colleagues found lower GM density in the middle frontal gyrus of the PFC in obese versus lean individuals using structural MRI

(Pannacciulli, Del Parigi et al. 2006). In my study, during the hunger state, I found that obese individuals had significantly increased activity in the left putamen and decreased activity in the OFC and MPFC relative to lean men, which identified there is a hyper-functioning reward circuitry in obese individuals. In the obesity study, each subject received the meal in an amount proportional to his or her body size, and each subject experienced similar satiation after food intake. While I thus eliminated the possibility to provide less energetic supply to the obese subjects, a reward deficient processing mode would still expect reduced rewarding value for the same amount of relative caloric intake (Stice, Spoor et al. 2009). So in the study, I could not find the evidence for an increased group difference after food intake, which may have been possible at different caloric levels.

4.9 Limitations

Several methodological limitations were identified to my experimental design.

Study 1. In the future studies, I should increase sample sizes to overcome ambiguities on the reliability of the findings. These studies should try to include drug naive patients to control for effects of antidepressant treatment. Such studies however come with their own limitations, given that this may introduce a bias for comparably younger patients with limited potential to compare to older populations, while currently medicated older patients may show long term effects of prior treatment durations. Thus standardization of acquisition and analysis strategies may be crucial aspect in order to accumulate evidence across a number of independent studies, given that no perfect study may exist to address all relevant questions related to abnormal resting state behavior in major depression (Zhang, Li et al. 2015).

Study 2 and Study 4. Firstly, I did not find nucleus accumbens, which is an important region of the reward system. The reason may be, in the study, each subject was given

the liquid meal of the small caloric amounts, which may result in different levels of reward system responses. Secondly, I only used the male subjects. In the study of Del Parigi et al, they showed that sex-specific brain responses to a meal (Del Parigi, Chen et al. 2002). Furthermore, male and female obese individuals may follow different routes and accordingly have an effect of BMI (Aldhoon-Hainerova, Zamrazilova et al. 2014, Bosch, Steinberger et al. 2015). I should increase the sample sizes and involve both gender subjects in the future research. Thirdly, obesity has been associated with the alternation of affection and cognition (Bayol, Farrington et al. 2007, Borer 2010). In the current studies, any psychological tests or questionnaires were tested by subjects. Fifthly, when considering time by region interaction on the correlation of insulin and hunger ratings on dACC and precuneus activity, one needs to carefully consider that no information on a suited post-meal cluster for precuneus can be chosen, in contrast to dACC, which showed significant differences at both time points. The non-significance of correlation between hunger rating and precuneus activity thus may not fully exclude long-term association between these two dimensions. At last, I did not monitor whether all subjects open eyes or fall asleep during the resting state scanning using the special equipment. After the each scanning session, a technician checked with each subject whether this was rally done or not. (Zhang, Tian et al. 2015, Zhang, Tian et al. 2015).

Study 3. The findings in the study should be considered in light of certain limitations. Additional study is needed for independent testing of the PPI results by using larger sample sizes, although the DMPFC finding during the positive vs. neutral expectancy is in line with the previous work. Given the patients with MDD in the present study have various depressive episodes and received different antidepressant treatments, future research is needed to further evaluate the activity in the DMPFC for valence-dependent expectancy by controlling for the antidepressant treatment and depressive episode.

5 Conclusions

The work presented in the thesis report altered brain function in two neuropsychiatric disorders, MDD and obesity, which are reward deficiency disorders.

MDD patients showed decreased reward sensitivity. I demonstrated changes of whole brain connectivity of individual brain regions in MDD patients. MDD subjects showed abnormal global and local functional connectivity in dACC, which plays an important role in reward-based decision-making. This implies an importance of abnormal functional connectivity region as a correlate of brain pathophysiology of impaired reward value attribution as it the case for depression. Furthermore, the emotional expectancy task was used in MDD patients to study the neural mechanism of biased attention in MDD. I identified impaired deactivation for positive valence dependent expectancy in DMPFC, a core region in anterior DMN. Impaired anterior to posterior DMN FC during positive expectancy. The altered DMN activity may be related to rumination and neglect of positive information. And, anhedonia MDD patients may have an impaired ability in incorporating information about external reward stimulation.

Obesity individuals showed increased reward sensitivity. Temporal homogeneity of local resting state signals was investigated to delineate regions with specific abnormality. During hunger state, obese subjects had increased activity in the left putamen and decreased activity in OFC and MPFC, which implies obese individuals' exhibit deficits in reward circuitry. Frontal cortex may fail to inhibit the striatum during reward cue processing, which may lead to overeating. Another local resting state activity marker, ALFF, was used to quantify the baseline neural activity during different levels of satiety. My findings indicated that both dACC and precuneus might play an important role in eating behavior. DACC, a core region involved in reward-based decision-making, was decreased in activity before and after food intake. This would be

in line with the observation that obese individuals may have a deficiency in decision making during the food reward stimuli. Abnormal precuneus activation was found before food intake in obese subjects, which implies that this region could be directly related to increased subjective motivation towards food reward.

To conclude, resting state activity in disorders of increased or decreased reward sensitivity is differently impaired, however, an overlap could only be found in dACC, while further differences in resting state activity suggest a rather widespread impairment which may be related to other aspects which differ between MDD and obesity.

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7 Supplemental tables and figures

Supplementary Table S1

Subject	Age	Sex	Citalopram	Paroxetin	Fluoxetin	Venlafaxine	Mirtazapin	Duloxetine	Agomelatine	Lorazepam	Quetiapine	Chlorprothixen	Zymbalta
1	44	f			+		+						
2	38	m		+			+						
3	52	m							+				
4	23	f											
5	40	m					+			+			
6	30	m				+	+		+	+			
7	26	m				+	+						
8	56	f				+	+						
9	57	f					+						
10	56	f	+										
11	40	m	+										
12	28	m								+			
13	26	f						+			+		
14	22	m				+	+						
15	24	f	+										
16	41	m					+			+		+	
17	26	m								+	+		
18	33	m					+						
19	47	m					+						
20	50	f					+						
21	42	f											+

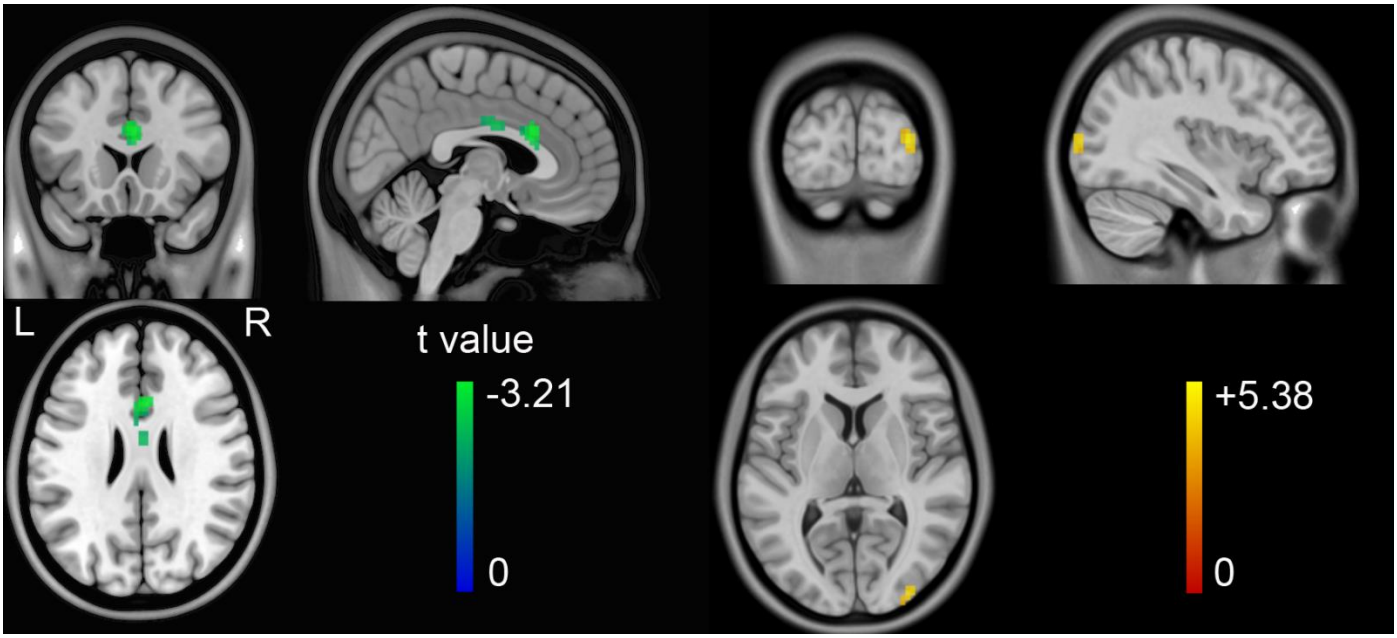

Figure S1. Group difference of functional connectivity density (FCD) map between patient and control groups (correlation coefficient threshold: R > 0.4, uncorrected p < 0.001). Hot and cold colors indicate increased and decreased global FCD in depressed patients, respectively.

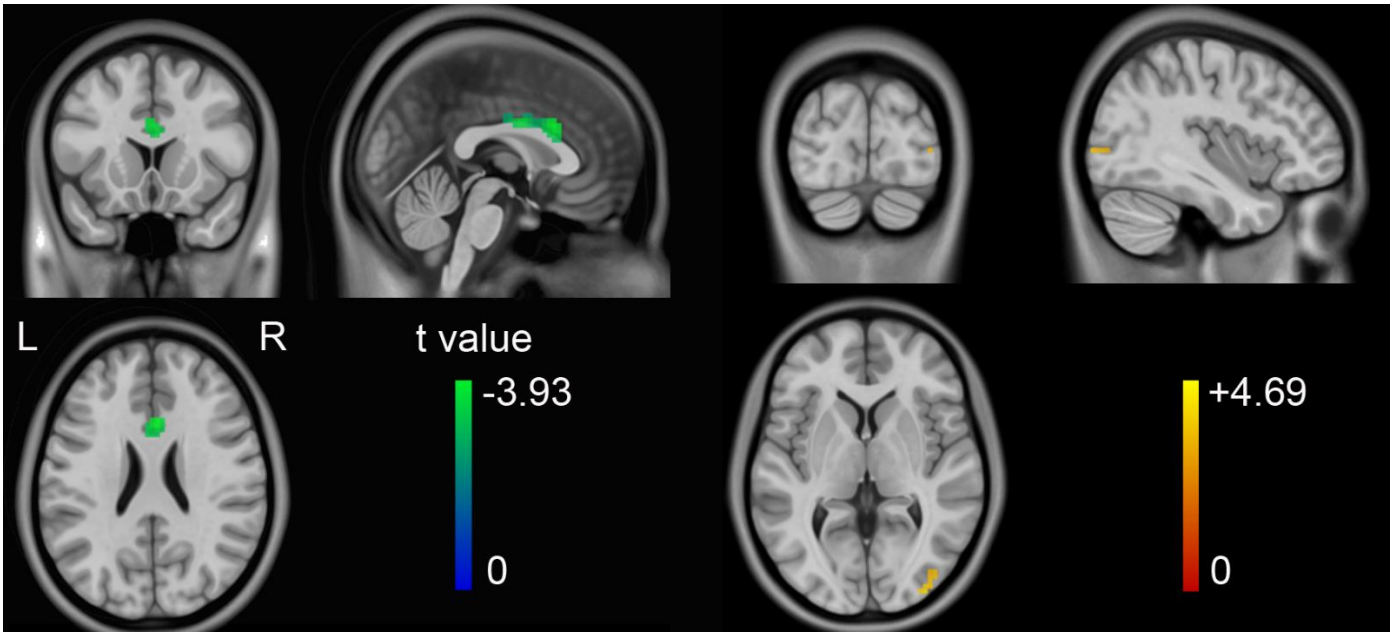

Figure S2. Group difference of functional connectivity density (FCD) map between patient and control groups (correlation coefficient threshold: R > 0.5, uncorrected p < 0.001). Hot and cold colors indicate increased and decreased global FCD in depressed patients, respectively.

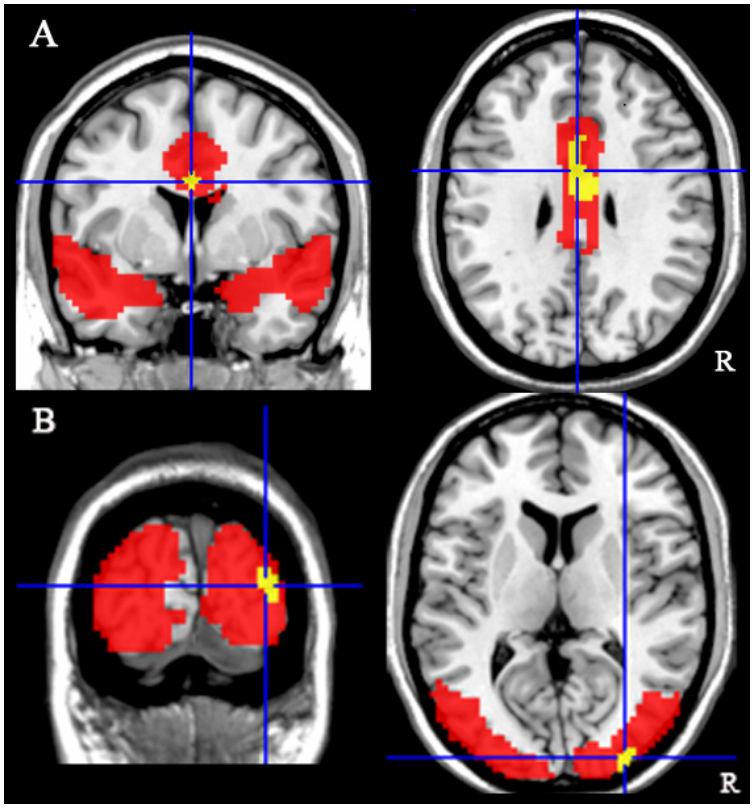

Figure S3. Spatial distributions of the salience and visual networks ($p < 0.05$, FWE correction), identified using individual component analysis (ICA).

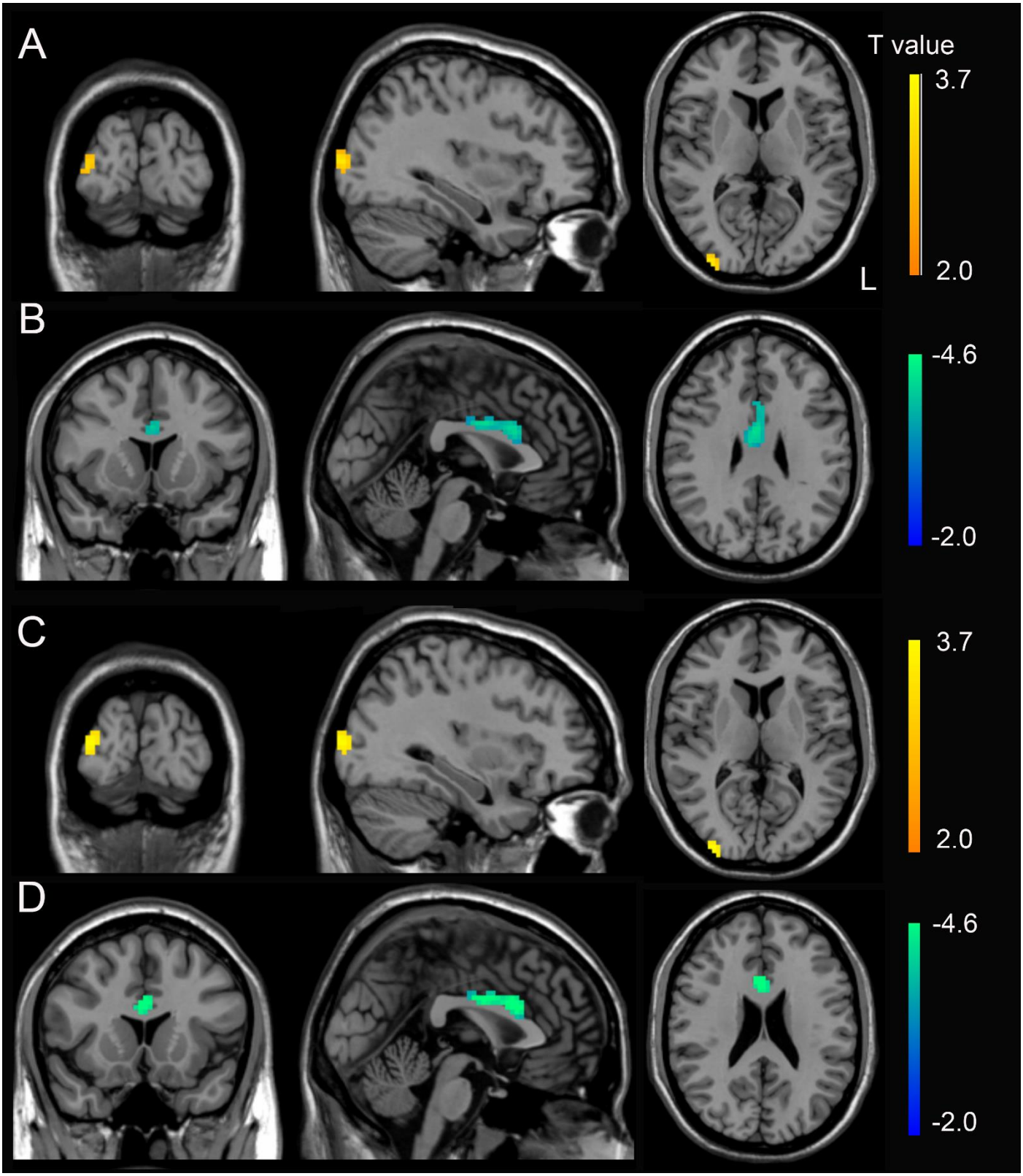

Figure S4. Group difference of functional connectivity density (FCD) map between patient and control groups, with the gray matter volume (GMV) of mid-cingulate cortex and occipital cortex as covariates, respectively.

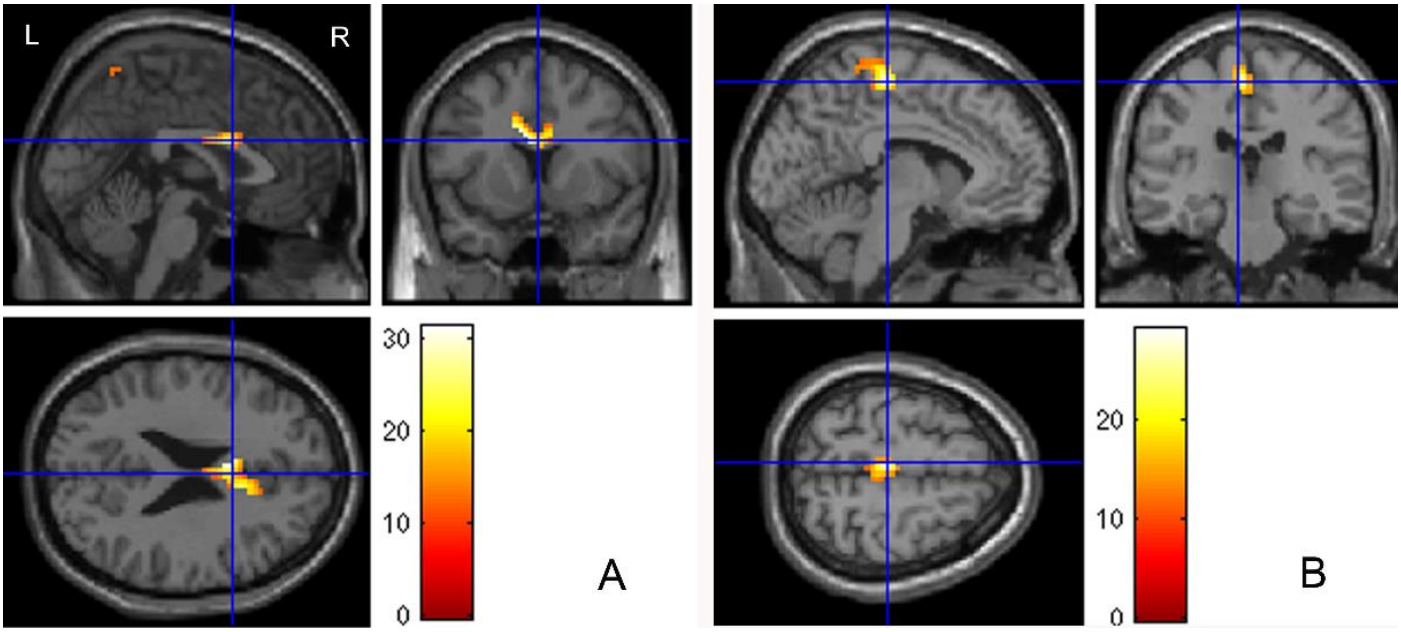

Figure S5. The results of main effect of group (in red, A) and feeding condition (in red, B) in the change of ALFF, revealed by the full factorial design in SPM8.

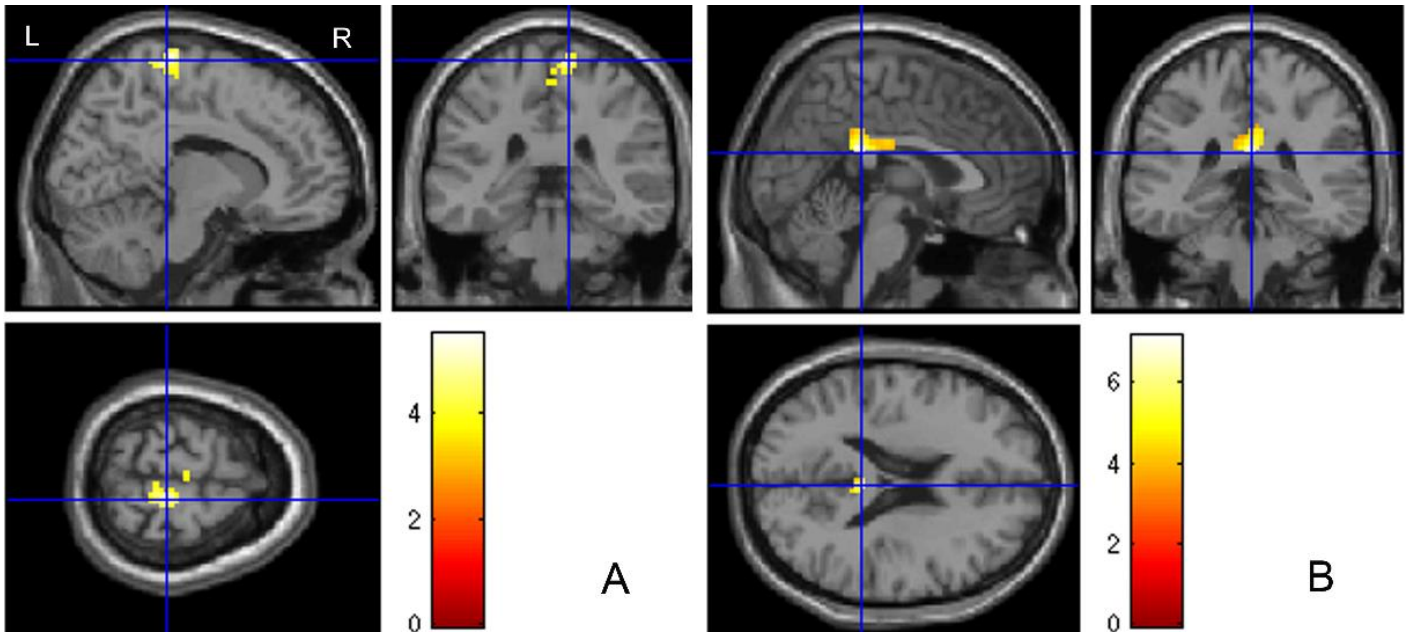

Figure S6. The result of effect of the meal (ie before vs after) in group of healthy controls (in red, A) and obese subjects (in red, B).

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9. Lebenslauf

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10. Publications

Journals

Zhang B., Tian D.R., Yu C.S., Zhang J., Tian X., von Deneen K. M., Zang Y. F., Walter M., Liu Y. J., Altered baseline brain activities before food intake in obese men: A resting state fMRI study. Neurosciences Letters (2015), 584 (1):156–161.

Zhang B., Tian D.R., Yu C.S., Li M., Zang Y. F., Liu Y. J., Walter M., Altered baseline brain activity differentiates regional mechanisms subserving biological and psychological alterations in obese men. Scientific Reports (2015), 5, 11563; doi: 10.1038/srep11563.

Zhang B.*, Li M.*, Qin W., Demenescu L. R., Metzger C., Bogerts B., Yu C., Walter M., Altered functional connectivity density in major depressive disorder at rest. European Archives of Psychiatry and Clinical Neuroscience, (2015), DOI 10.1007/s00406-015-0614-0.

Zhang B. *, Li S. *, Zhuo C., Li M., Safron A., Genz A., Qin W., Yu C., Walter M., Altered task-unspecific deactivation in the default mode network is depending on valence in patients with major depressive disorder. Submitted.

Conferences

Zhang B., Li M., Zhuo C., Li S., Qin W., Lord A., Martin M., Yu C., Bogerts B., Depression alters the functional connectivity response to the negative emotional anticipation, 2015. The 19th Annual Meeting of the Organization for Human Brain Mapping, Honolulu, USA.

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Zhang B., Metzger C., van Tol M.-J., Osoba A., Horn D., Tempelmann C., Bogerts B., Walter M., Resting-state fMRI in depression alters dorsomedial prefrontal cortex connectivity between networks, 2013. 9. Mitteldeutsche Psychiatrietage, Jena, Germany.

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Machts J.*, **Zhang B.***, Metzger C., van Tol M.-J., Kaufmann J., Bittner D., Abdulla S., Kasper E., Schuster C., Prudl J., Kollewe K.., Petri S., Dengler R., Walter M., Vielhaber S., Resting-state functional connectivity in amyotrophic lateral sclerosis, 2012. Third Biennial International Conference on Resting-State Functional Brain Connectivity, Magdeburg, Germany

Zhang B., Metzger C., van Tol M., et al., Depression alters dorsolateral prefrontal cortex response to anticipated picture viewing, 2012. The 16th Annual Meeting of the Organization for Human Brain Mapping, Beijing, China

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Erklärung

Hiermit erkläre ich, dass ich die von mir eingereichte Dissertation zu dem Thema

“Investigation of brain function in neuropsychiatric disorder using multimodal imaging analysis”

selbständig verfasst, nicht schon als Dissertation verwendet habe und die benutzten Hilfsmittel und Quellen vollständig angegeben wurden.

Weiterhin erkläre ich, dass ich weder diese noch eine andere Arbeit zur Erlangung des akademischen Grades doctor rerum naturalium (Dr. rer. nat) an anderen Einreichtungen eingereicht habe.

Magdeburg, 14.10.2015