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# Resting State Blood Flow and Glucose Metabolism in Psychiatric Disorders

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## 1. Introduction

Over the last 20 years, SPECT and PET, along with CT and MRI have been the main methodologies used in studies investigating psychiatric disorders. The structural alterations in patients' brains found by CT and MRI are usually quite subtle, while those found by the nuclear imaging modalities (PET and SPECT) are more pronounced. Partly for this reason, the latter methods have led to discoveries in a wide range of psychiatric disorders. In the 90s, region of interest (ROI) method provided only sketchy results due to the low spatial resolution of the nuclear imaging, but rapid progression in analytic and statistical methods in the 2000s had led to more detailed and accurate determinations of the differences in regional cerebral blood flow (rCBF) and glucose metabolic ratios (rGMR) between patients and comparison subjects. On the other hand, whereas an improved understanding of the etiology of psychiatric disorders has led to significant progress in multiple research areas, SPECT and PET studies measuring only the rCBF/rGMR distribution at rest have come to face some limitations for elucidation of the disease pathophysiology. Accordingly, at resting studies using SPECT/PET have tended to focus on certain kinds of clinical information, such as symptomatology and treatment. This review summarizes the history of at rest SPECT and PET studies, and provides a comprehensive survey in psychiatric disorders including schizophrenia, major depressive disorder, bipolar disorder and obsessive-compulsive disorder.

## 2. Schizophrenia

Functional neuroimaging has been used to elucidate patterns of increased or decreased activity within the brains of schizophrenic and normal subjects during rest and various assigned tasks, revealing that the affected parts of the central nervous system are not contained within a single brain region, but rather lie within neural networks over several brain regions. Numerous structural brain researches studies employing CT and MRI have demonstrated significant volume reductions in key brain regions such as the lateral prefrontal cortex, anterior cingulate cortex (ACC), superior temporal cortex, hippocampus/parahippocampus, striatum and thalamus in patients with schizophrenia relative to normal subjects (Shenton et al., 2001). In support of these structural alterations, functional neuroimaging studies have produced representations of abnormalities in and across these regions. Taking these results together, a variety of symptoms, including

hallucination/delusion and negative symptoms, have been attributed not to abnormalities in a single brain region but to abnormalities in a distributed network of spatially distinct regions. Furthermore, functional neuroimaging studies have demonstrated that antipsychotics have substantial effects on brain functions, and have helped to elucidate the differences in action mechanisms among them.

### 2.1 Hypofrontality and negative symptoms in schizophrenia

Ingvar and Franzen (1974) reported that patients with chronic schizophrenia showed significant reduction in the rCBF ratio of the frontal to occipital region compared to normal subjects and subjects with first-episode schizophrenia measured with $^{133}$Xe. This was the first study to report an abnormality in rCBF in schizophrenia. Following this work, several other studies examined the resting state blood flow and metabolism (Buchsbaum et al., 1982; Wolkin et al., 1985; Tamminga et al., 1992; Sachdev et al., 1997) and repeatedly reported significant decreases in patients with schizophrenia relative to normal participants. On the other hand, there have been studies showing no difference in this parameter between patients and normal controls (Gur et al., 1995; Sabri et al., 1997, Scottish Schizophrenia Research Group, 1998), or even an increase in rCBF/rGMR in patients compared to normal controls (Cleghorn et al., 1989; Ebmeier et al., 1993).

Early studies on this issue have presented very disparate results with respect to not only the presence or absence of hypoperfusion/hypomtabolism, but also, in cases in which it was present, the degree, relevant regions and correlation with symptoms of hypoperfusion/hypometabolism. The reason for these differences is presumed to be the large number of confounding factors, such as disease heterogeneity, treatment with antipsychotics, imcompleteness of results derived from the ROI method, measured value of absolute or relative data, different reference regions for relative data, measurement conditions under varied physiological states, and so on. Therefore, additional explorations with a more sophisticated study design for the drug-naïve subjects group, the same scanning conditions and reliable analytic methods are needed to reach a definitive conclusion on this issue.

As for the effects of antipsychotic medications, several studies on drug-naïve patients with first-episode schizophrenia demonstrated a significant reduction in blood flow and metabolism in the frontal cortex relative to age-matched normal controls under a resting condition (Buchsbaum et al., 1992a; Steinberg et al., 1995; Vita et al., 1995; Erkwoh et al., 1997) and task-related activation (Andreasen et al., 1992, 1997; Ashton et al., 2000) and suggested that the abnormal reduction in the prefrontal region occurs from a very early stage of the disease. With respect to the problem of analytic methods, ROI methods have been a mainstream from the 80s to late 90s, but voxel-wise methods representative of Statistic Parametric Mapping (SPM) have prevailed from the mid-90s and are the standard modality at present. This voxel-wise methods have successfully addressed two important problems in brain analyses: individual structural differences between the brains of participants and examiners' arbitress on target brain regions depending on *a priori* hypothesis. Numerical researches based on these methods have demonstrated a significant reduction in particularly the lateral, medial and orbital phases of the prefrontal cortex relative to normal controls (Andreasen et al., 1997; Ashton et al., 2000; Kim et al., 2000; Potkin et al., 2002; Lehrer et al., 2005; Molina et al., 2005a, 2005b, 2009), and these findings have shown that areas with hypoperfusion and hypometabolism were pervasive and further

accompanied by other areas with hyperperfusion/hypermetabolism within the frontal cortex (Andreasen et al., 1997; Kim et al., 2000). The measurement conditions used under rest or the performance of a given task should also be taken into consideration. Whereas most of the studies with SPECT have been conducted under a resting state, many studies using FDG-PET have performed the comparison under a cognitive task such as continuous performance task (CPT) or California verbal learning task (CVLT). This is because of the possibility that a spontaneous fluctuation of mental state under a resting condition during scanning could result in varied distribution of rGMR in the participant group as a whole. Indeed, several PET studies using CPT (Potkin et al., 2002; Molina et al., 2005a, 2005b, 2009) or a visual attention task (Lehrer et al., 2005) showed a significant reduction of rGMR in the prefrontal cortex in patients compared to normal controls, very similar to the results obtained in almost all studies under a resting state. Then, reduction of rCBF/rGMR in the prefrontal cortex in patients relative to normal controls under a static state during the performance of cognitive tasks and under a resting state collectively indicates hypofrontality.

Although earlier studies have dealt this issue with dichotomous problem; presence or absence of hypofrontality, afterward, improvements in research design and analytic methods provide more detailed information such as distributed patterns within the frontal lobe within patients' brains or the degree of difference of the finding between patients and controls. In this context, in some meta-analysis studies (Davidson and Heinrichs, 2003; Hill et al., 2004), the finding of hypofrontality has been supported and thus established as a more convictive finding in the disease.

The hypoperfusion and hypometabolism in the frontal lobe have been presumed to be closely linked with negative symptoms and cognitive impairments in schizophrenia. These notions were demonstrated by the negative relationship between negative symptoms and blood flow/metabolism (Liddle et al., 1992; Wolkin et al., 1992; Ebmeier et al., 1993; Schröder et al., 1996; Andreasen et al., 1997; Erkwoh et al., 1997; Sabri et al., 1997; Ashton et al., 2000) and the significant reductions of blood flow/metabolism in the patients group with profound negative symptoms (Potkin et al., 2002; Gonul et al., 2003a), although several negative studies have existed (Vita et al., 1995; Min et al., 1999). On the other hand, whereas the cognitive dysfunctions that have recently received so much attention are closely related with negative symptoms, the reports exploring the relationship between the impairments and at rest blood flow/metabolism are very restricted (Penadés et al., 2002; Molina et al., 2009). A hypodopaminergic state in the prefrontal cortex is presumed to underlie the negative symptoms and cognitive impairments (Lynch, 1992; Remington et al., 2011) and thus, in this context, it is noted that hypofrontality strongly suggests an important part of core pathophysiology in schizophrenia.

### 2.2 rCBF/rGMR patterns in key regions other than the frontal lobe

As for brain regions other than the frontal lobe, a number of previous studies have demonstrated substantial variations between the patients with schizophrenia and normal controls, with some reports observing increases in various activities and other reports documenting decreases, and thus no convincing consensus has been reached.

Both the lateral and medial phases in the temporal cortex have been closely related with positive symptoms, particularly hallucination and delusion. Based on accumulating evidence from fMRI studies, for example, the primary auditory cortex located in the

superior temporal cortex has been demonstrated to be closely related to auditory hallucination (Dierks et al., 1999; Lennox et al., 2000). Indeed, the first-episode and drug-naïve patients with auditory hallucinations presented higher (Horga et al., 2011) and lower metabolism (Cleghorn et al., 1992; Vita et al., 1995) compared with normal controls. Further, activity in this region was reported to be negatively associated with disorganization as a form of thought disorders (Ebmeier et al., 1993; Erkwoh et al., 1997; Sabri et al., 1997). The hippocampal and/or parahippocampal gyrus are also related with hallucination/delusion and disorganization. PET studies have shown an increase (Gur et al., 1995; Molina et al., 2005b) and decrease (Tamminga et al., 1992; Kim et al., 2000; Horga et al., 2011) in rCBF/rGMR of the regions in schizophrenia compared with normal controls, and positive (Liddle et al., 1992) and negative correlations (Schröder et al., 1996) between metabolism in the regions and hallucinations. Although these reports have very conflicting results and do not reach a definitive conclusion, they do suggest that both the lateral and medial parts of the temporal lobe are closely related with the positive symptoms.

The findings of activity within other key brain regions in schizophrenia have been very controversial. As for the striatum, several reports on drug-naïve patients have shown a significant reduction relative to normal controls (Buchsbaum et al., 1987, 1992a; Shihabuddin et al., 1998), suggesting a relation with putative neurological soft signs in the very early stage (Dazzan et al., 2004). The thalamus has a function of filtering all sensory signals from input to the cortex, and is known to play a primary role in the etiology of schizophrenia- namely, dysfunction in the correct perception of information from the external world. The activity in the thalamus has been alternatively reported to increase (Andreasen et al., 1997; Jacobsen et al., 1997; Kim et al., 2000; Clark et al., 2001) or decrease (Vita et al., 1995; Hazlett et al., 1999, 2004; Buchsbaum et al., 1996; Lehrer et al., 2005). Moreover, increases of rCBF/rGMR in the cerebellum (Andreasen et al., 1997; Kim et al., 2000; Desco et al., 2003) and the subcortical regions (Buchsbaum et al., 1998, 2007a; Desco et al., 2003) have been observed. As described above, attempts to clarify the pathophysiology of schizophrenia have focused on brain regions from the frontal and temporal cortex to the subcortical regions including the striatum, thalamus, hippocampus and cerebellum. It appears that the approach of elucidating the pathophysiology requires an integrative interpretation based on the putative aberrant networks and their correlation with symptoms. Taken together, these findings suggest that resting blood flow and metabolism studies contribute to the elucidation of the disease pathophysiology by macroscopic investigation over the whole brain and microscopic investigation focusing on key regions.

### 2.3 Impacts of antipsychotics on blood flow and metabolism

Antipsychotics have some significant effects on brain blood flow and metabolism, and are presumed to be closely related to the potency of neuroleptics. All antipsychotics commonly induce dopamine (DA) D2 receptor antagonistic actions, resulting in the most direct action for improvement of delusions and hallucinations. Traditionally, typical antipsychotics such as haloperidol, an almost pure DA D2 blocker, had been widely used. But more recently, atypical antipsychotics have become the mainstay in the clinical practice. These atypical antipsychotics can reduce the extra-pyramidal symptoms and improve the negative symptoms and cognitive impairments by an antagonistic action on the 5-HT 2A receptors. Functional neuroimaging studies have provided important insights about the differences in pharmacological action and treatment effect among a diverse range of antipsychotics, and the subsequent functional changes in the central nervous system.

A number of previous studies have shown that typical neuroleptics such as haloperidol reduce blood flow and metabolism in the frontal lobe. These effects were repeatedly replicated in studies of both acute (Bartlett et al., 1998; Lahti et al., 2005) and chronic administration (Bartlett et al., 1991; Buchsbaum et al., 1992b; Miller et al., 1997, 2001; Lahti et al., 2003). Further, whereas haloperidol was reported to be related with hypoperfusion and hypometabolism in the hippocampus in terms of amelioration of positive symptoms (Lahti et al., 2003), increases of rCBF/rGMR in the motor cortex induced by haloperidol were presumed to be related with extra-pyramidal symptoms (Molina et al., 2003; Buchsbaum et al., 2007), and the decrease in activity in the occipital cortex following haloperidol treatment might be related with sedative effects (Bartlett et al., 1991; Desco et al., 2003; Lahti et al., 2003).

An increase in rCBF/rGMR in the basal ganglia in patients with schizophrenia by neuroleptics, in particular haloperidol, is the most consistent finding among numerous reports on antipsychotics. This has been replicated very well in the acute effect (Lahti et al., 2005) as well as the chronic effect (Buchsbaum et al., 1987, 1992a, 2007a; Miller et al., 1997, 2001; Scottish Schizophrenia Research Group, 1998; Corson et al., 2002; Desco et al., 2003; Lahti et al., 2003). The increase of blood flow and metabolism in this area is presumed to be due to increases of activity in the post synapses through upregulation of DA D2 receptors induced by a potent blocking action of the receptor by haloperidol (Miller et al., 1997; Corson et al., 2002). This notion is in line with the increase of volume in this area following haloperidol treatment in structural MRI studies (Shenton et al., 2001).

Studies on the effects of atypical antipsychotics on brain perfusion/metabolism have become to be examined based on more detailed neuronal substrates than studies on typical antipsychotics by appearance of voxel wise analysis. Although risperidone has less effect on the reduction of blood flow in the frontal lobe than haloperidol (Miller et al., 2001), the drug induces a significant reduction in the prefrontal cortex relative to baseline (Berman et al., 1996; Liddle et al., 2000; Ngan et al., 2002; Molina et al., 2008). In the basal ganglia, the degree of increase in blood flow/metabolism by risperidone is likely smaller than that by haloperidol (Liddle et al., 2000; Miller et al., 2001). Liddle et al. (2000) demonstrated that treatment with risperidone for 6 weeks showed a significant positive relation between decrease in the hippocampus and decrease in reality distortion, suggesting that the hippocampus is an important target area of risperidone.

Olanzapine is likely that its effect of blood flow/metabolism in the frontal lobe is lesser than that by risperidone (Gonul et al., 2003b; Molina et al., 2005c; Buchsbaum et al., 2007b).

Clozapine, the gold standard among the atypical neuroleptics, has a pharmacological profile with weaker blockade of DA D2 receptors and broader actions for multiple receptors than other atypical antipsychotics, and these characteristics are presumed to be related to its superior clinical efficacy relative to other neuroleptics. Interestingly, several previous studies have reported that clozapine induced a significant reduction in blood flow/metabolism in the prefrontal cortex (Potkin et al., 1994, 2003; Cohen et al., 1997; Lahti et al., 2003; Molina et al., 2005d, 2008). On the other hand, increases in several parts of the prefrontal cortex, including the ACC (Lahti et al., 2003) and decreases in the hippocampus (Lahti et al., 2003; Potkin et al., 2003) have been shown by some studies, supporting the drug's clinical actions such as ameliorations of delusions/hallucinations and cognitive impairments. Indeed, responders to clozapine exhibited more prominent changes in blood flow/metabolism above mentioned rather than non-responders (Potkin et al., 2003; Molina

et al., 2008). These complex patterns induced by clozapine have been suggested to be strongly related to the drug's superior clinical characteristics.

### 2.4 Conclusion

Functional neuroimaging studies performed in schizophrenic subjects under a resting state have made progress in the accumulation of findings on hypoperfusion/hypometabolism in the frontal lobe. It is noted that the hypofrontality is closely related with negative symptoms. On the other hand, the brain regions relevant to positive symptoms are still clearly unknown. The studies performed thus far have well explored the effects of various antipsychotics on the brain blood flow and metabolism, but neuroleptic-induced reductions in blood flow/metabolism in the prefrontal cortex have been obscure in terms of their relationship with the improvement of positive symptoms or secondary negative symptoms. By contrast, alteration in the limbic regions or the medial phase of the temporal cortex, such as the hippocampus, has been shown to be related with positive symptoms, and functional neuroimaging studies have contributed to detection of the origin of positive symptoms.

## 3. Major Depressive Disorder

Functional neuroimaging studies measuring at-rest brain perfusion and metabolism in patients with major depressive disorder (MDD) have demonstrated that the etiology of the disease is closely linked with multiple components of the frontal lobe, temporal lobe, parietal lobe, limbic/paralimbic regions, and basal ganglia. Recent knowledge on affection and perception acquired from multiple human and animal research fields strongly support the findings that have been observed within depressive patients' brains in neuroimaging studies. Although a number of functional neuroimaging studies for MDD have been conducted to date, the results were varied widely among the studies. However, a sequence of inconsistent findings on MDD has demonstrated that depressive patient groups consist of highly heterogeneous subtypes, and that the etiology of depression contains multiple symptoms.

Studies on the effects of antidepressants on brain perfusion and metabolism have reported the relatively consistent finding that abnormal activity in the key brain regions relevant to depression could be normalized by successful treatment. However, no reliable markers on response prediction have been available to date in the imaging studies. On the other hand, studies of electroconvulsive therapy (ECT), an established treatment modality for refractory depression, have suggested that its effective mechanism is involved in the inhibitory process within subjects' brains that occurred immediately following the ECT course.

### 3.1 Abnormalities in multiple prefrontal cortex and limbic regions in MDD

Earlier functional neuroimaging studies on depression have reported significant reduction in rCBF/rGMR in the frontal lobe or prefrontal cortex in patients with depression relative to normal subjects (Baxter et al., 1989; Martinot et al., 1990; Bench et al., 1992). However, several subsequent studies with the voxel based analyses have failed to confirm this finding (Skaf et al., 2002; Videbach et al., 2002; Bonne et al., 2003). Great progression made in research on human and animal emotion and perception has elucidated that the frontal lobe and limbic/paralimbic systems are tightly involved in affective and perceptive controls, including mood, attention, decision-making, anxiety, behaviors dependent on

reward/punishment, and so on. It is, therefore, very reasonable that hypoactivity in the frontal lobe is observed in subjects with depression relative to normal subjects. Inconsistent results among the previous studies mentioned above, suggest great heterogeneity of patients with the disease. Therefore, a number of confounding factors, such as age, sex, brain organic condition (ischemia and atrophy), pharmacotherapy (drug class, dose and duration), and disease stage (acute or remit), could easily affect brain activity, leading to a varied distribution of rCBF/rGMR in the patient group as a whole.

Studies with careful sample selection, in which subjects who were, for example, in a drug-naïve state or in withdrawal from antidepressants for several weeks, were careful selected in order to reduce the heterogeneity have reported significant hypoperfusion and hypometabolism in the dorsolateral prefrontal cortex in subjects with depression relative to normal controls (Kimbrell et al., 2002; Gonul et al., 2004). The reduction in activity in this region was the most consistent finding among those in the frontal lobe as a whole. Additionally, rCBF and rGMR in the dorsolateral prefrontal cortex were negatively correlated with the severity of depression (Baxter et al., 1989; Martinot et al., 1990; Hurwitz et al., 1990; Bonne et al., 1996; Kimbrell et al., 2002; Gonul et al., 2004). Subanalyses of each symptom have shown the degree of psycho-motor retardation and the activity in the prefrontal cortex to be negative correlated (Bench et al., 1993; Dolan et al., 1993; Videbach et al., 2002). Although increased activities in the ventrolateral prefrontal cortex and OFC have been suggested by a sequence of studies by Drevets (Drevets et al., 1992, 1997; Drevets, 1999, 2000), other studies did not sufficiently examine these areas. With respect to the medial prefrontal cortex and ACC, although most studies with relatively large ROIs in this area, observed hypoperfusion and hypometabolism (Hurwitz et al., 1990; Bench et al., 1992, 1993; Bonne et al., 1996; Mayberg et al., 1997; Videbach et al., 2002; Gonul et al., 2004), several detailed studies on these regions demonstrated decreased activities in the dorsal medial prefrontal and dorsal ACC (Kimbrell et al., 2002; Fitzgerald et al., 2008) and increased activities in the rostral ACC (Drevets, 1999; Konarski et al., 2007). In particular, the latter region was suggested that the greater perfusion and metabolism was, the better clinical response to antidepressant treatment was predicted (Mayberg et al., 1997).

As for the limbic region, increases in rCBF/rGMR in the amygdala (Drevets et al., 1992; Abercrombie et al., 1998; Videbach et al., 2002) and caudate (Gonul et al., 2004; Périco et al., 2005) were observed in patients with depression relative to normal subjects. The subgenual ACC, a component within the paralimbic system, was hypoactive in patients with unipolar depression (Drevets et al., 1997; Skaf et al., 2002; Fitzgerald et al., 2008), but also in patients with bipolar depression (Drevets et al., 1997). The caudate was also reported to show hypometabolism (Baxter et al., 1985; Drevets et al., 1992). These reductions in activity in anatomically small areas, such as the subgenual ACC and caudate, might be due to the partial volume effects (Krishnan et al., 1992; Drevets, 2000). The ventrolateral prefrontal cortex, including the subgenual ACC, has closely reciprocal connectivities with the amygdala, hypotharamus and brain stem, and disturbances of these networks could lead to the hypersensitivity to failure, pathological guilt and exaggeration of self-esteem shown in patients with MDD.

### 3.2 Change of rCBF/rGMR induced by antidepressants and ECT

Antidepressant agents are shown to be effective for 50-60% patients with MDD (Hirschfeld et al., 2002), and only 20-35% of patients reach remission (Mann, 2005). While diverse classes

of antidepressants are available in clinical practice at present, studies on the effect of specific antidepressants on brain perfusion or metabolism and the studies on the relationship between clinical improvement and the brain activity induced by antidepressants have been very restricted, and, further, the few such studies that exist usually have very small sample sizes. According to previous studies on these issues, aberrant regions at baseline prior to initial treatment in subjects with MDD appear to be normalized, particularly in responders to the agent. However, it is very uncertain whether the abnormalities can be recovered to a level similar to that in normal subjects (Baxter et al., 1985, 1989; Tutus et al., 1998; Ishizaki et al., 2008) or remain to a certain degree (Hurwitz et al., 1990; Martinoti et al., 1990). The discrepancies among these studies might be due to differences in class, dose of antidepressant, diverse treatment durations, different definitions of effectiveness or recovery of symptoms, or small sample sizes. Several selective serotonin reuptake inhibitors (SSRIs; paroxetine and citalopram) and serotonin and noradrenaline reuptake inhibitors (SNRIs; venlafaxine) in some well-designed studies have been examined most extensively in terms of their effects on brain perfusion/metabolism in patients with MDD. However, although several key regions, such as the frontal, temporal, parietal, and limbic regions and the basal ganglia, have been widely found to be relevant areas affected by the depressants studied, consistent findings on the combination of the relevant areas or their change directions have been very scarce. With respect to the prediction of the response to antidepressants, the greater the perfusion in the ACC (Mayberg et al., 1997), rectul gyrus (Buchsbaum et al., 1997), and lateral prefrontal cortex (Joe et al., 2006; Brockmann et al., 2009) prior to treatment was, the better the expected response. On the other hand, a decrease in rCBF/rGMR prior to treatment in the ACC (Brody et al., 1999; Konarski et al., 2009), lateral prefrontal cortex (Navarro et al., 2004) and hippocampus/basal ganglia/thalamus (Milak et al., 2009) led to a good treatment response. Therefore, the studies on this issue to date have failed to confirm conclusions.

ECT is usually indicated the patients with MDD who have been treatment-resistant to antidepressants. While this modality provides a relatively high rate of response for these patients, the understanding of its mechanism of action remains very poor. During seizures induced by ECT, evident reductions in rCBF/rGMR occurred over large brain areas (Takano et al., 2007). Afterwards, hypoperfusion and hypometabolism, to a lesser degree than during the seizure, in several brain regions, including the prefrontal region, have continued for a maximum of several months. This findings is presumed to be related to clinical responsiveness (Prohovnik et al., 1986; Rosenberg et al., 1988; Guze et al., 1991). However, some studies have demonstrated significant increases in rCBF in several brains (Bonne et al., 1996; Kohn et al., 2007). These discrepancies might be due to several confounding factors, such as procedural-related factors including anesthetics and electrode replacements, or to varying durations between the termination of the ECT course and imaging scanning.

### 3.3 Conclusion

The etiology of depression is strongly suggested to be related to the frontal lobe and limbic/paralimbic regions. However, the highly heterogeneity of patients with depression could lead to inconsistent results observed among studies. In addition, assessing the results in anatomically small areas or components with obscure boundaries, such as the subgenual ACC, amygdala, and OFC, is very difficult, and this serious problem in the interpretations of these regions stems from the effects of volume reduction in these regions in patients with

depression relative to normal. With respect to antidepressants and ECT, their mechanisms have been under examination.

## 4. Bipolar Disorder

Bipolar Disorder is characterized by distinctive affective labile episodes of manic/hypomanic state and/or depressive state. Concurrently, cognitive dysfunctions such as impairments of attention, working memory and executive function usually accompany the disease. Based on recent careful clinical observations, lifetime prevalence, including all bipolar II disorder, subthreshold bipolar disorder and drug-induced manic/hypomanic episode, is up to 5% (Merikangas et al., 2007). About 60% of patients with bipolar disorder are misdiagnosed as having MDD, and further, one-third of patients experience any psychiatric symptoms for more than 10 years before a correct diagnosis is made (Hirschfeld et al., 2003). Therefore, understanding the pathophysiology of bipolar disorder is very important for exact diagnosis and effective treatment. In neuroimaging studies on bipolar disorder, however, there have been a number of difficulties with the research, such as difficulty in recruiting patients with mania into the study and with safely scanning them, and the large heterogeneity within such patient groups in terms of affective state and disease subtype. Therefore, neuroimaging studies conducted to date have tended to have small sample sizes. Also, almost all studies on bipolar disorder have employed depressive patient groups combining cases of bipolar and unipolar depression, and the data acquired to date in manic and euthymic patients have been relatively restricted compared to the findings in depressive patients. In this context, resting state rCBF/rGMR studies on bipolar disorder have appeared to be inconsistent (Stoll et al., 2000; Strakowski et al., 2000). Still, recent resting state studies are providing a cortical-anterior subcortical dysfunction model of the disease pathology through several kinds of examination, including studies on mania and comparative studies between bipolar and unipolar depression (Keener and Phillips, 2007; Pan et al., 2009).

### 4.1 Bipolar mania

There have been few studies on manic patients, and those that have been performed have been largely biased by very small sample size, patients with manic level that can cooperate with study, and continuous pharmacotherapy consisting of a mixture of mood stabilizers, antidepressants and antipsychotics. In these studies, rCBF/rGMR reduction in the prefrontal cortice, particularly the ventral prefrontal cortex and increase in the subcortical areas compared to normal controls have been relatively consistent, providing cortical-subcortical or cortical–limbic/paralimbic regions impairment as a disease model in bipolar disorder. Decrease in brain perfusion/metabolism in the frontal cortex has been reported in the lateral prefrontal cortex at rest (al-Mousawi et al., 1996; Bhardwaj et al., 2010; Brooks III et al., 2010) and during cognitive tasks (Blumberg et al., 1999; Rubinsztein et al., 2001) and in the orbitofrontal cortex at rest (Blumberg et al., 1999) and during cognitive tasks (Blumberg et al., 1999; Rubinsztein et al., 2001). On the other hand, increases of rCBF/rGMR have been reported in the dorsal ACC (Rubinsztein et al., 2001), caudal ACC (Blumberg et al., 2000) and ventral/subgenual ACC (Drevets et al., 1997; Blumberg et al., 2000; Brooks III et al., 2010) and the head of the caudate (Blumberg et al., 2000; Brooks III et al., 2010). Goodwin et al. (1997) reported that in patients with relapsed manic episodes following withdrawal of

lithium, increase of rCBF in the ACC was positively correlated with manic symptoms. These findings lead to and partly support the anatomical-functional hypothesis that while the orbitofrontal and lateral prefrontal impairments are related with affective/impulsive dysregulation and cognitive dysfunction, respectively, compensatory functional hyperactivity reflects the findings of increase in the ACC and limbic/paralimbic regions observed in resting-state studies (Keener and Phillips, 2007; Pan et al., 2009).

### 4.2 Bipolar depression

Although there have been more reports on bipolar depression than on mania, the findings from this body of work are rather confusing. This may be due, at least in part, to the design of these studies. That is, earlier studies have frequently used a disease group combining cases of unipolar and bipolar depression, and when they have compared bipolar depression with other conditions, they have alternatively used normal healthy subjects, patients with unipolar depression and subjects with mania/euthymia as the comparison group. Moreover, the different studies have different target regions (ACC, subgenual prefrontal cortex and amygdala). With respect to the cortex, although few reports demonstrated any regions with hyperperfusion and hypermetabolism in bipolar depression relative to normal controls, areas with hypoperfusion/hypometabolosm in the patients compared to normal controls spread very broader in the lateral prefrontal (Baxter et al., 1985, 1989; Ketter et al., 2001; Brooks III et al., 2009a), medial prefrontal (Baxter et al., 1985; Bauer et al., 2005; Brooks III et al., 2009a), subgenual ACC (Drevets et al., 1997; Brooks III et al., 2009a), temporal lobe (Baxter et al., 1985; Ketter et al., 2001; Bhardwaj et al., 2010), occipital lobe (Baxter et al., 1985; Ketter et al., 2001) and parietal lobe (Baxter et al., 1985; Ketter et al., 2001). On the other hand, hyperperfusion/hypermetabolism have also been observed in the subcortical or limbic/paralimbic areas, including the amygdala (Ketter et al., 2001; Drevets et al., 2002; Bauer et al., 2005; Mah et al., 2007), subgenual ACC (Drevets et al., 1997; Bauer et al., 2005; Mah et al., 2007), ventral striatum (Bauer et al., 2005), caudate nucleus (Ketter et al., 2001; Mah et al., 2007), and putamen (Ketter et al., 2001; Mah et al., 2007), nucleus accumbens (Ketter et al., 2001; Mah et al., 2007), thalamus (Ketter et al., 2001; Bauer et al., 2005) and cerebellum (Bauer et al., 2005).

There have been a few reports comparing patients with bipolar depression and bipolar mania within the same study. Examination of the subgenual ACC (Brodmann area 25) by Drevets et al. (1997) demonstrated clear distinction of increased activity when mania and decreased activity when depression, and growing attention has been paid to this area as a mood-state marker in bipolar disorder. However, some subsequent studies showed higher metabolism in the depressive state (Bauer et al., 2005; Mah et al., 2007), indicating a failure to conform. The inconsistency among studies on small anatomical area such as the subgenual ACC may be related to shortcomings in the characteristics of nuclear imaging, such as insufficient spatial resolution of the scanner or inaccurate normalization to the standard brain (Drevets et al., 2002).

### 4.3 Euthymia

Although manic state and depressive state represent clinically extreme and opposite symptoms, neuroimaging findings on the two states are relatively similar. Thus, a cortical-subcortical model raises some questions as to whether this model means trait marker in the

disease, or whether reliable mood-state markers in the disease exist. In this context, studies on euthymia will be more and more important for addressing these issues.

Some studies on patients with euthymic state compared to normal controls have reported a decrease of rCBF/rGMR in the lateral prefrontal (Culha et al., 2008; Brooks Ⅲ et al., 2009b) and ACC (Culha et al., 2008) at rest, and the lateral prefrontal (Krüger et al., 2003) and OFC (Blumberg et al., 1999; Krüger et al., 2003) during cognitive tasks or symptom-provocation. On the other hand, regions with increased perfusion/metabolism were observed in the subcortical areas such as the amygdala (Brooks Ⅲ et al., 2009b) and parahippocampus (Brooks Ⅲ et al., 2009b) at rest. Krüger et al (2003, 2006) in symptom-provocation studies demonstrated that although increased rCBF in the subgenual ACC seen in normal controls was deficit in euthymic patients, increased perfusion in the dorsal ACC was observed only in the patients. Though there have been very few studies conducted on euthymia, patients with euthymia appear to show a decrease of rCBF/rGMR in the prefrontal cortex and an increase in rCBF/rGMR in the subcortical areas, according to previous reports. These notions are comparable to recent clinical observations that patients in a euthymic state show significant cognitive impairments identical to the distinctive pathological states of mania and depression (Kessing, 1998; Elshahawi et al., 2011), and they are in preparatory stage to relapse fragile to stress (Swann, 2010), but not asymptomatic state not meeting manic and depression.

### 4.4 Conclusion

Functional neuroimaging studies on bipolar disorder have demonstrated hypoactivity in the cortex, particularly the ventral prefrontal cortex, and concurrent hyperactivity in the subcortical or limbic/paralimbic regions. To data, however, this knowledge has not reflected the clinical bipolarity of mania and depression and thus remains a trait marker. Furthermore, these findings cannot be distinguished from those of other psychiatric disorders, including unipolar depression. Studies with more sophisticated designed and larger sample size will be needed in the future.

## 5. Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) has a lifetime prevalence of 2-3% (Weissman et al., 1994). OCD is characterized by persistent and recurrent thoughts that invade conscious awareness against a patient's will (obsessions) and is further usually accompanied by ego-dystonic, ritualistic behaviors that the patient is obliged to perform in order to prevent overwhelming anxiety (compulsions). Patients with OCD form a more homogeneous group than those with other psychiatric disorders, and this perhaps accounts for the fact that previous functional neuroimaging studies have provided relatively consistent findings on aberrant brain regions in this disorder, which include the OFC, ACC, caudate nuclei, thalamus and so on. That is, the etiology of OCD has been presumed to follow a cortico-subcortical model. Functional neuroimaging techniques have contributed substantially to the exploration of these areas relevant to the disorder. Furthermore, recent reports on treatment intervention for OCD have strongly suggested that selective serotonin reuptake inhibitors (SSRI) and cognitive behavior therapy (CBT), both established treatment approaches, raise some effects on patients' brain blood flow and metabolism, and further normalize aberrant regional perfusion and metabolism within these networks in treatment responders.

### 5.1 Dysfunction of the orbitofrontal-subcortical circuit in OCD

The basal ganglia is a candidate abnormal area in OCD to which great attention was initially paid. The reason for this is a high rate of patients with obsessive symptoms were found to have certain diseases, such as Von Economo encephalitis (Schilder, 1938), Sydenham's chorea (Swedo et al., 1989) and Tourette's syndrome (Nee et al., 1980), which have presumed to be impaired in the basal ganglia. Afterwards, functional neuroimaging studies on OCD have focused on the striatum, in particular caudate nucleus as aberrant region within patients' brains and concurrently have successively detected some abnormal brain areas such as the OFC, ACC and thalamus in patients with OCD, when compare them with normal healthy subjects. In this context, researchers have proposed a dysfunction of cortico-striatum-thalamus-cortical network as an etiological model of OCD (Modell et al., 1989; Baxter et al., 1996; Saxena et al., 1998).

It has been classically recognized that the cortico-subcortical network consists of direct and indirect pathways. The thalamus in the network has a gating function which filters all stimuli from the outer world and receives two main inputs from the striatum. The one is the direct pathway where signals from the striatum input to the thalamus via the globus pallidus internal/substantial nigra and the other is the indirect pathway where signals from the striatum input to the globus pallidus internal/substantial nigra through the globus pallidus external or subthalamic nucleus, and are further sent to the thalamus. Afterwards, feedback signals from the thalamus are sent to the cortex. These pathways consist of neurotransmissions combined with excitatory signals by glutamate and inhibitory signals by GABA. The direct pathway inputting to the thalamus disinhibits the thalamus (reinforcement of positive feedback) and the indirect pathway inhibits the thalamus (negative feedback), thereby helping to maintain the balance of the system (Alexander and Crutcher, 1990). In patients with OCD, it is presumed that this circuit represents an imbalance of hyperactivity. In the dysfunctional network, impairment in the striatum leads to an insufficient gating function of the thalamus, resulting in cortical hyperactivities. In this context, the direct pathway in the patients with OCD predominates over the indirect pathway. In terms of symptom-relations, the striatum is essentially involved in unconscious acquisition of the initial process of action or behavior, and hypermobilization of the impaired striatum could lead to compulsive symptoms in the manner of ritual behaviors, in order to normalize the undesirable thoughts or anxieties occurring via the dysfunctional thalamus. On the other hand, these invasive thoughts and excess anxieties would relate with hyperactivity in the OFC and ACC, respectively.

Previous functional neuroimaging studies in subjects at rest or undergoing symptom-provocation have implicated an increase in rCBF/rGMR in the OFC (Baxter et al., 1987, 1988; Benkelfat et al., 1990; Horwitz et al., 1991; Rubin et al., 1992, 1995; McGuire et al., 1994; Alptekin et al., 2001), ACC (Swedo et al., 1989; Horwitz et al., 1991; Perani et al., 1995), caudate nucleus (Baxter et al., 1987, 1988; Diler et al., 2004; Saxena et al., 2004), putamen (Benkelfat et al., 1990; Perani et al., 1995) and thalamus (McGuire et al., 1994; Perani et al., 1995; Alptekin et al., 2001; Saxena et al., 2001, 2004), strongly suggesting hyperactivities in the cortico-subcortical loop in patients with OCD. However, other studies have demonstrated inverse results, i.e., decreases in the OFC (Crespo-Faccoro et al., 1999; Busatto et al., 2000), ACC (Busatto et al., 2000), caudate nucleus (Rubin et al., 1992, 1995; Edmonstone et al., 1994; Lucey et al., 1995, 1997), putamen (Edmonstone et al.,

1994) and thalamus (Martinot et al., 1990; Lucey et al., 1995). These discrepancies were presumed to be due to varied treatment duration of serotonin reuptake inhibitors (SRIs) (Rubin et al., 1995), or to childhood- or adult-onset of the disease (Geller et al., 1995), presence or absence of comorbidity disorders such as MDD or tic disorder (Crespo-Faccoro et al., 1999; Hoehn-Saric et al., 2001) and the measurement of different parameters (brain blood flow or metabolism). Interestingly, whereas SPECT studies tended to indicate a decrease in rCBF, FDG-PET studies tended to show an increase in rGMR in the key regions in the disease, suggesting a possibility of uncoupling between brain blood flow and glucose utilization (Whiteside et al., 2004). At the very least, these regions are closely involved in the pathophysiology of OCD.

Studies on the relation between the symptom severity and the degree of abnormality in these areas have presented very varied results and failed to provide consistent findings.

### 5.2 Change following intervention by SRIs and cognitive-behavior therapy

Previous studies have replicated well that aberrant findings of rCBF/rGMR relevant to OCD-related regions could be normalized by pharmacological intervention of SRIs. Treatment of clomipramine, a tricyclic antidepressant, over several months could normalize regional blood flow or metabolism in the OFC and/or caudate nucleus from significant increase level prior to intervention compared to normal controls (Benkelfat et al., 1990; Swedo et al., 1992; Rubin et al., 1995). Also, intervention by two SSRIs, paroxetine and fluoxetine, provided similar results to clomipramine; increased rCBF/rGMR in the OFC and/or caudate nucleus at baseline were reduced significantly following treatment with paroxetine (Saxena et al., 1999, 2002; Hansen et al., 2002; Diler et al., 2004) and increased rCBF/rGMR in the ACC/caudate nucleus/thalamus at baseline decreased significantly after fluoxetine treatment (Hoehn-Saric et al., 1991; Baxter et al., 1992). Furthermore, in most of these studies, responders in clinical symptoms to pharmacological intervention tended to show a significant decrease relative to baseline, whereas non-responders showed no change by the treatment (Benkelfat et al., 1990; Baxter et al., 1992; Swedo et al., 1992; Saxena et al., 1999; Hoehn-Saric et al., 2001; Diler et al., 2004; Ho Pian et al., 2005). With respect to response prediction, several studies have found that the lower the brain blood flow or metabolism in relevant regions prior to treatment was, the greater was the reduction in OCD symptoms (Benkelfat et al., 1990; Saxena et al., 1999). In addition, there were significant correlations between decrease of metabolism at baseline in the OFC or caudate nucleus and improvement of OCD symptoms (Benkelfat et al., 1990; Swedo et al., 1992; Baxter et al., 1992). However, studies on significant response predictors have been very restricted and reliable parameters on response prediction have never been explored to date.

CBT, interestingly, also appears to normalize increased rCBF/rGMR in some relevant areas, including the caudate nucleus (Baxter et al., 1992; Schwartz et al., 1996; Nakatani et al., 2003) and thalamus (Saxena et al., 2009). Additionally, responders to CBT exhibited greater reduction in the caudate nucleus from baseline to CBT intervention than did non-responders (Schwartz et al., 1996). Although there have been few studies up to now on the alteration of brain function before and after CBT, growing notions on the effects of CBT on brain functions within subjects would address some important issues on whether the functional brain change induced by SRIs is a direct consequence of their pharmacological actions, or a state consequence occurring regardless of treatment approaches.

### 5.3 Depression as a comorbidity with OCD

Although most studies have been directed to the patients with OCD without MDD, in clinical practice OCD patients frequently have major depression as a comorbidity; approximately one-third of OCD patients also have MDD (Rasmussen and Eisen, 1992; Weismann et al., 1994), whereas 22-38% of patients with MDD have obsessive-compulsive symptoms (Kendell and DiScipio, 1970). Thus, notions acquired from studies performed on pure OCD patients without depression might deviate from the actual pathophysiology of OCD. Further, since SRIs and CBT are commonly effective for improvement of both OCD and MDD, exploration of the neuronal substrates shared by the two diseases might provide very valuable information for understanding the etiology.

Saxena et al. (1999) demonstrated that patients with concurrent OCD and MDD showed a significant reduction in metabolism in the hippocampus similar to that of patients with MDD alone. Furthermore, treatment with paroxetine for patients with concurrent OCD and MDD induced a reduction of rGMR in the ventral lateral prefrontal cortex, which was similar to the findings in patients with MDD alone, but did not show a decrease in the OFC and caudate nucleus like that seen in the patients with OCD alone (Saxena et al., 2002). These findings suggested that patients with concurrent OCD and MDD had the pathophysiology of MDD, and thus may constitute a distinctive subtype within OCD, such that both the etiologies of OCD and MDD should be considered carefully when devising a treatment strategy.

### 5.4 Conclusion

Functional neuroimaging studies on OCD have provided much more consistent findings than structural MRI studies. That is, in patients with OCD, some important regions in the cortical and subcortical areas present with hyperactivity and are normalized by pharmacotherapy. Since improvements by SRIs and CBT occur in only about half of patients (responders), further neuroimaging studies controlled by treatment intervention are strongly needed.

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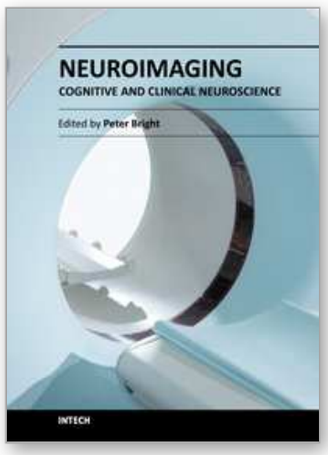


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The rate of technological progress is encouraging increasingly sophisticated lines of enquiry in cognitive neuroscience and shows no sign of slowing down in the foreseeable future. Nevertheless, it is unlikely that even the strongest advocates of the cognitive neuroscience approach would maintain that advances in cognitive theory have kept in step with methods-based developments. There are several candidate reasons for the failure of neuroimaging studies to convincingly resolve many of the most important theoretical debates in the literature. For example, a significant proportion of published functional magnetic resonance imaging (fMRI) studies are not well grounded in cognitive theory, and this represents a step away from the traditional approach in experimental psychology of methodically and systematically building on (or chipping away at) existing theoretical models using tried and tested methods. Unless the experimental study design is set up within a clearly defined theoretical framework, any inferences that are drawn are unlikely to be accepted as anything other than speculative. A second, more fundamental issue is whether neuroimaging data alone can address how cognitive functions operate (far more interesting to the cognitive scientist than establishing the neuroanatomical coordinates of a given function - the where question).

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