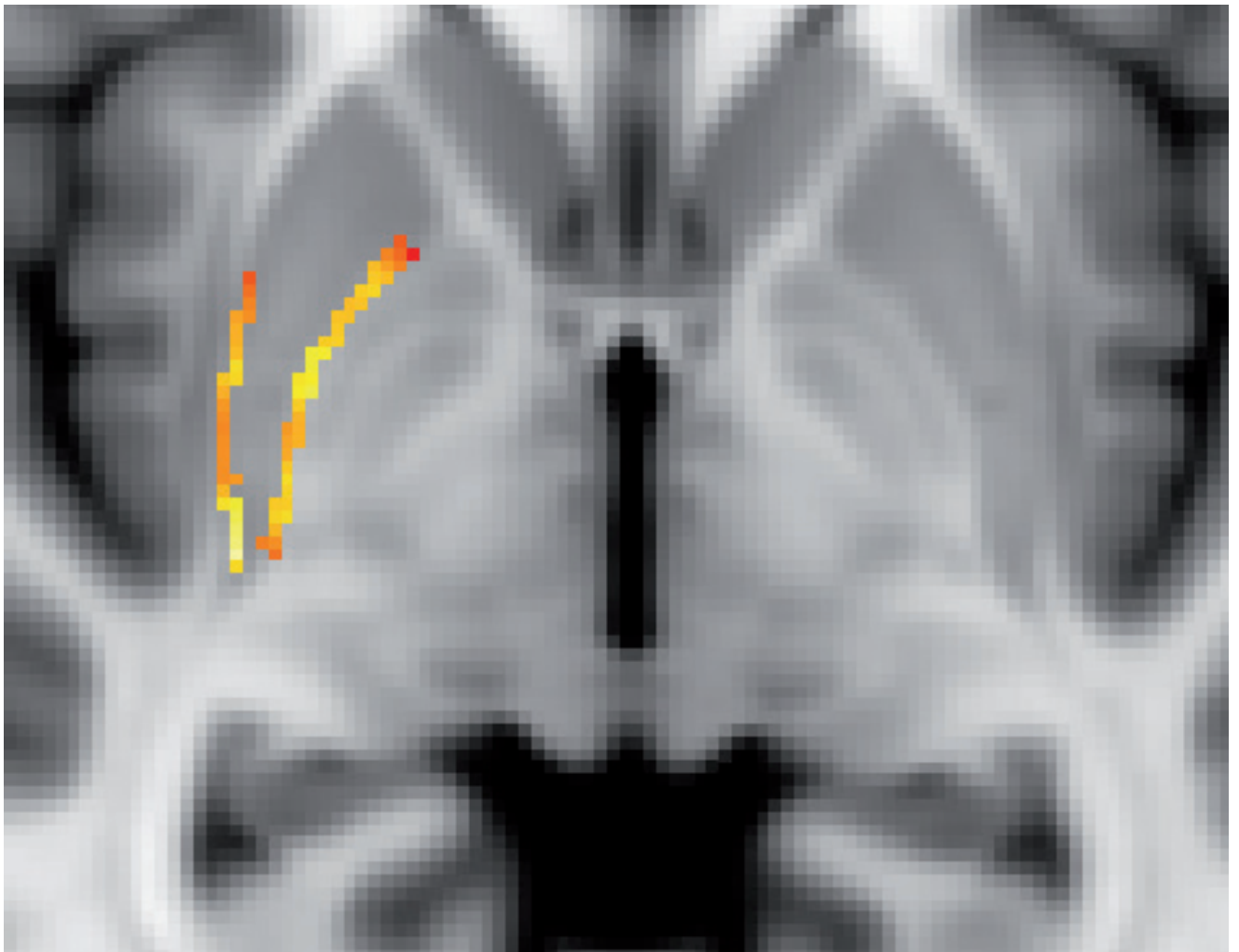


# Psychomotor disturbances in bipolar disorder – investigations using structural and functional neuroimaging



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## Abstract

Psychomotor disturbances in bipolar disorder are an expression of alterations in volition, cognition, emotion and motor control. While psychomotor disturbances remain a classic hallmark of severe mood disorders, there is limited knowledge about its mediators and neural correlates.

The general aim of this thesis was to obtain a better understanding of psychomotor disturbances in bipolar disorder. Our specific objectives were to investigate whether symptoms of psychomotor disturbances in bipolar depression relate to neural activation in frontal-striatal networks that mediate motor function, whether there is a differential activation within these frontal-striatal motor networks between depressed patients with bipolar disorder and healthy controls, and whether morphometric changes in the basal ganglia and thalamus are associated with clinical variables in euthymic bipolar disorder that may predict impairments in psychomotor function.

In **paper I**, we validated a self rating scale with respect to established observer rating scales. In a post-hoc analysis we found a psychomotor factor that we investigated further with functional magnetic resonance imaging (fMRI) in **paper II** and **III**.

In **paper II**, we investigated motor execution in patients with bipolar depression. We used task based fMRI to investigate whether self paced finger tapping would reveal any differences in neural activation between groups, and whether neural activation at different levels in the frontal-striatal motor loop is predicted by the functional deafferentation theory - framework used to explain slowed movement in Parkinson's disease. We could not confirm our hypotheses. In **paper III**, we investigated different parts of the production of voluntary movement using fMRI and a motor imagery task. We found significant between-group differences in medial parieto-occipital regions during motor imagery and all other tasks, and in cortical motor areas during motor execution. We also found decreased activations in motor regions when there was an increase in psychomotor disturbances.

In **paper IV**, we investigated whether tests of psychomotor function were associated with morphometric change in the basal ganglia or thalamus. We could not confirm our hypothesis. However, we found significant between-group differences in the shape of the right putamen in the absence of impaired psychomotor function. Shape differences were located in regions connected to frontal executive regions and motor areas. In **paper V**, we investigated morphometric differences in a subgroup of bipolar disorder characterized by greater impairment of psychomotor function in their euthymic phase. We also investigated clinical variables associated with disease expressions, and the effect of antipsychotic treatment, on morphometric change. We found that antipsychotic medication, the number of manic episodes and duration of illness were associated with local shape changes in the basal ganglia.

In summary, we found that psychomotor disturbances may be considered both a symptom and a sign, and that the neural signature of these appear to involve both structural and functional alterations in brain regions of frontal-striatal networks.



## List of publications

### Paper I

Adler M, **Liberg B**, Andersson S, Isacson G, Hetta J. Development and validation of the Affective Self Rating Scale for manic, depressive, and mixed affective states. Nord J Psychiatry 2008;62(2):130-5.

### Paper II

**Liberg B**, Adler M, Jonsson T, Landén M, Rahm C, Wahlund L-O, Wiberg-Kristoffersen M, Wahlund B. The neural correlates of self paced finger tapping in bipolar depression with motor retardation. Acta Neuropsychiatrica 2013;1(1):142-148.

### Paper III

**Liberg B**, Adler M, Jonsson T, Landén M, Rahm C, Wahlund L-O, Wiberg-Kristoffersen M, Wahlund B. Motor imagery in bipolar depression with slowed movement. Journal of Mental and Nervous Disease, October 2013 (in press).

### Paper IV

**Liberg B**, Ekman CJ, Sellgren C, Johansson A, Landén M. Subcortical morphometry and psychomotor function in euthymic bipolar disorder (submitted to Psychiatry Research: Neuroimaging).

### Paper V

**Liberg B**, Ekman CJ, Sellgren C, Johansson A, Landén M. Subcortical morphometry and psychomotor function in euthymic bipolar disorder with a history of psychosis (submitted to Journal of Affective Disorders).



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# 1 Introduction

This thesis revolves around a class of signs known as psychomotor disturbances in specific types of mental illness. In the revised eleventh edition of the Concise Oxford English Dictionary, the term psychomotor is defined as: “relating to the origination of movement in conscious mental activity”. Psychomotor activity is not just movement, it involves several general symptom categories such as sensory perception, cognition, motivation, emotion and movement (Buyukdura et al., 2011, Parker et al., 1993, Widlocher, 1983). Clinically, psychomotor disturbances display as an observable and measurable behavior that may hold important information for subtyping of mental illness (Schrijvers et al., 2008, Morrens et al., 2007). Because psychomotor activity reflects so many classes of symptoms, a better understanding of psychomotor activity may lead to a better understanding of the etiology and pathogenesis of mental illness.

Modern neuroimaging started with the introduction of ventriculography and pneumoencephalography around 1920 by Walter Dandy (Filler, 2009). Ten years later cerebral angiography enabled Egis Moniz to map blood vessels in the brain. Hormack and Hounsfield introduced computerized tomography in the 1970s for which they later received the Nobel Prize in Medicine and Physiology in 1979. Shortly thereafter molecular imaging techniques such as positron emission tomography and single photon emission tomography that used radiotracers were also developed. They allowed for the study of different aspects of metabolism and receptor systems. During this era, Paul Lauterbur and Peter Mansfield did theoretical work that laid the foundation of magnetic resonance imaging. They too received the Nobel Prize in Medicine and Physiology in 2003 for their discovery. In 1989, Seijo Ogawa wrote his seminal papers (Ogawa et al., 1990b, Ogawa et al., 1990a) on the blood-oxygen-level-dependent contrast (BOLD). This allowed for non-invasive studies of neural activation in both sexes in humans. BOLD-imaging was applied to human imaging shortly after Ogawa’s findings (Belliveau et al., 1991, Kwong et al., 1992). Today, it is clear that Ogawa’s findings marked the start of a new era in neuroimaging and the neurosciences. Greater availability of the scanning procedure, further refinements in imaging acquisition, image analysis and computational power have led to worldwide collaborations that undertake the goal of mapping neural organization in the human brain (Biswal et al., 2010).

The increased use of new neuroimaging methodology has made a great theoretical impact on psychiatry over the last 20 years. Today we can study brain

structure and brain function in vivo. This possibility has allowed us to research how morphology, activation and connectivity patterns can mediate sensory perception, cognition, motivation and movement in mentally ill patients.

To this day, an unfortunate divide between psychiatry and neurology is still evident in much research on psychiatric conditions. Despite that psychiatric and neurological assessments acknowledge the importance of sensory perception, motivation, cognition, emotion and movement. In both clinical fields there is a bias in the research questions asked. A review of functional imaging studies in mood disorders (Kupferschmidt and Zakzanis, 2011) reveal a bias in favor of emotional and cognitive aspects of mood disorders while the neurobiological correlates of sensory perception, motivation and movement remain "under-explored" in comparison (figure 1). Likewise, cognitive and emotional aspects of movement disorders and other neurological conditions are under-explored.

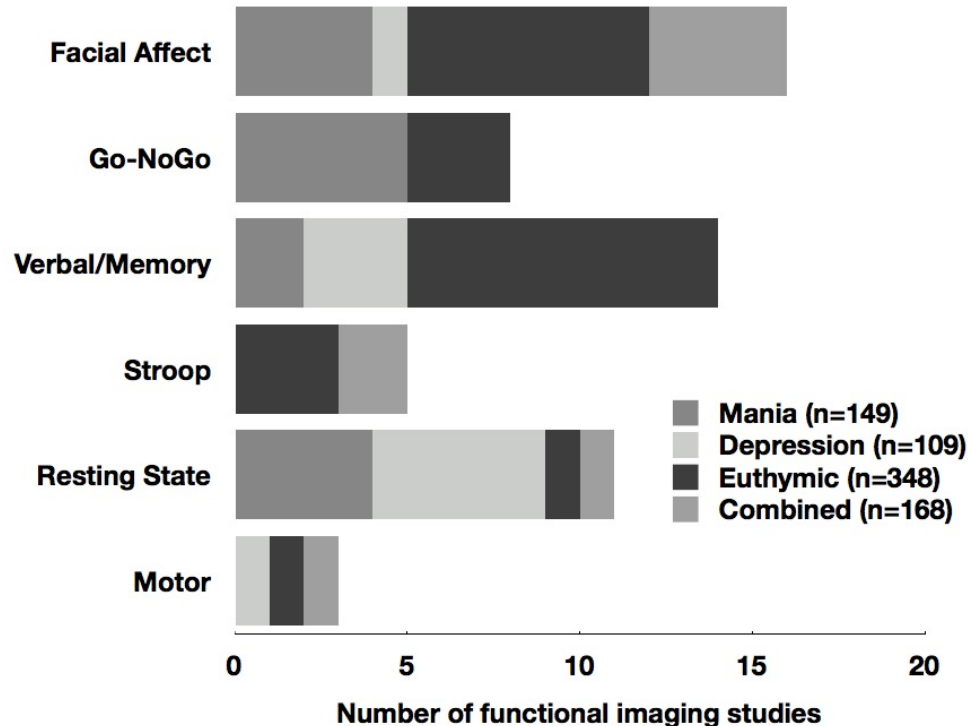


Figure 1: Studies of motor function are rare in mood disorders compared to studies of cognitive and emotional functions

The overarching aim of this thesis was to map the neural correlates of psychomotor disturbances in bipolar disorder, using both structural and functional brain imaging. We tested the hypothesis that models of psychomotor disturbance in clinically similar neurological movement disorders would apply to depression in bipolar disorder. We also investigated motor execution and higher-order

motor function in depressed patients with bipolar disorder. Finally, we investigated morphometric change, effects of clinical variables, and medication on brain regions implicated in motor control and gating of movement in particular. A broader objective of this thesis was to explore alternate strategies in understanding bipolar disorder using a psychomotor perspective.

## 1.1 Mental illness

According to the World Health Organization (WHO), "mental disorders comprise a broad range of problems, with different symptoms ... generally characterized by some combination of abnormal thoughts, emotions, behavior and relationships with others" (WHO, 2013). Mental illness has been described since ancient times. The nosology of mental illness has undergone major conceptual developments over time - a process still reflected in the continuous update of today's two major classification systems: The fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) published in 2013 (APA, 2013), and the tenth edition World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD) published in 1990 (WHO, 1990).

Table 1: Different classes of symptoms in mental illness

<i>Symptom class</i>	<i>Examples</i>
Emotion	Sadness, labile mood
Somatic	Headache, fatigue, aches, pains
Behavior	Motor slowing, agitation, tics
Perception	Hallucinations, delusions
Cognition	Memory impairment, inattention

## 1.2 Mood disorders

Mood disorders are a type of mental illness characterized by specific fluctuations in emotional function where patients display sadness, anhedonia, apathy, euphoria, or irritable mood. However, the clinical presentation of mood disorders also extends beyond the emotional domain and involves co-varying dysfunctions in cognition, perception and movement. An illustrative literary example of a mood syndrome with diurnal symptoms, sleep disturbance, depressed mood, rumina-

tion and physical presence of changes in facial expression, is given in the following description by Ray Bradbury in *Green Shadows, White Whale: A Novel of Ray Bradbury's Adventures Making Moby Dick with John Huston in Ireland*:

"I went to bed and woke in the middle of the night thinking I heard someone cry, thinking I myself was weeping, and I felt my face and it was dry. Then I looked at the window and thought: Why, yes, it's just the rain, the rain, always the rain, and turned over, sadder still, and fumbled about for my dripping sleep and tried to slip it back on."

### 1.2.1 Classification of mood disorders

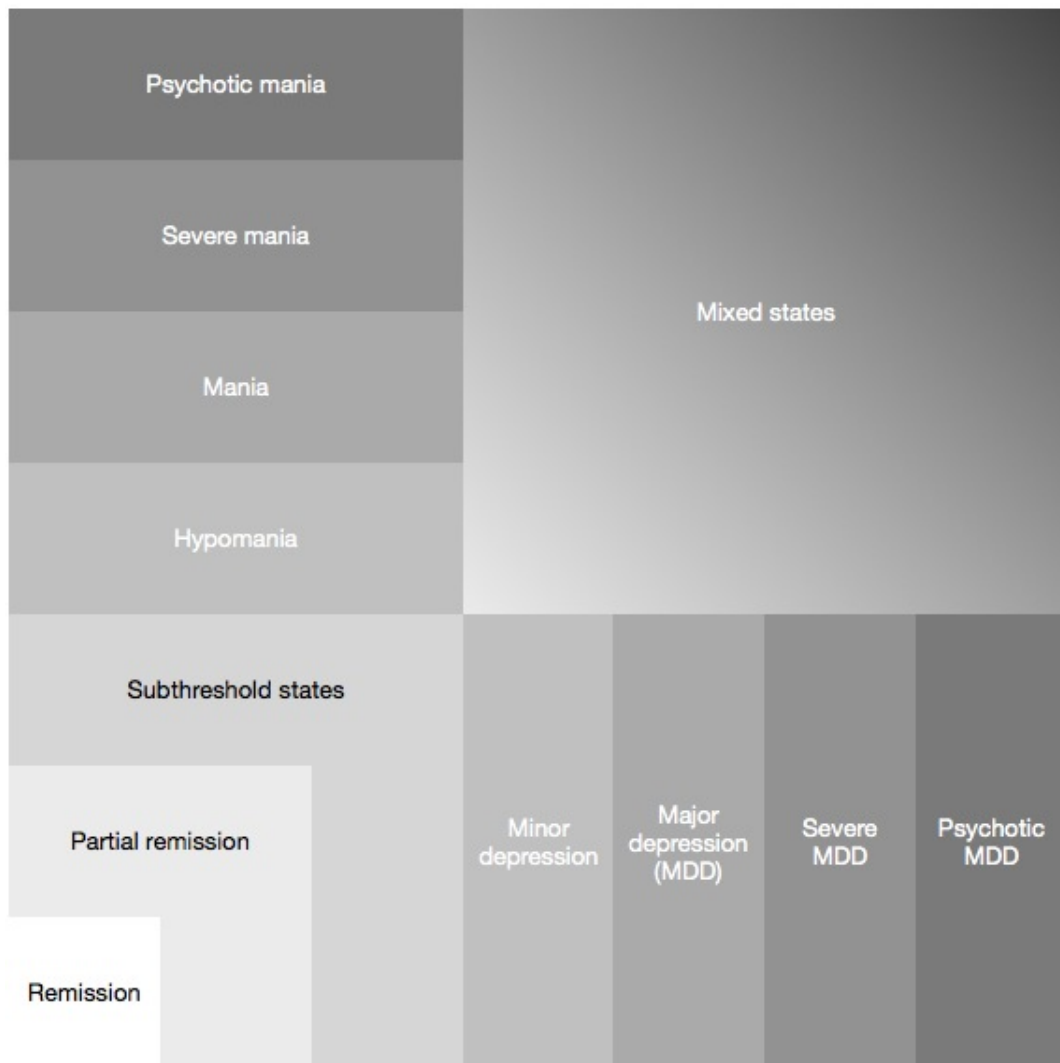
The classification of mood disorders has changed greatly over time (Angst and Marneros, 2001). In 1751 Richard Mead gave detailed descriptions of both the manic and depressed condition as separate illness entities. Almost a century later in 1854 Jean Falret and Jules Baillarger conceived of an illness that comprised both mania and depression. This view was lent support by Emil Kraepelin's empirical investigations during the 20th century into psychosis that delineated manic-depressive illness from dementia praecox (schizophrenia). This delineation exists to this day.

Since the data in this thesis was collected before the release of the fifth edition of DSM in May 2013, the text will refer to the fourth text-revised edition of DSM (APA, 2004) or the tenth edition of the ICD. The diagnostic subtypes of mood disorders are: *major (unipolar) depressive disorder*, *bipolar disorder*, *dysthymia*, and *cyclothymia*.

## 1.3 Bipolar disorder

Bipolar disorder is a brain disease characterized by episodic alteration of mood and general level of activity, but motivation, cognition, perception and motor features are also altered. Mood episodes have varying duration and patients may be free from symptoms between overt episodes, a state known as euthymia. Mood episodes can be typified as depression, mania, or as a mixture of mania and depression. Mania or manic episodes are characterized by elated mood which may include euphoria and/or irritable mood. Depression is foremost characterized by sadness, apathy and anhedonia. A depressive episode is termed "major depression" in the DSM. During episodes of mixed symptoms it may be that increased energy, irritability and racing thoughts appear at the same time as feelings of hopelessness, sadness, decreased need for sleep and suicidal ideation.

Figure 2: Spectrum of mood states (modified after Bech)



### 1.3.1 Definitions

There is a general agreement in the research and clinical communities that bipolar disorder can be divided into types I and II (Vieta and Suppes, 2008). Other classifications of bipolar disorder appear in the literature, but none of these are formally represented in the DSM or the ICD (Merikangas et al., 2007, Akiskal and Pinto, 1999, Akiskal et al., 2006, Perugi and Akiskal, 2002). Bipolar disorder type I is defined as intermittent manic and depressive episodes, although in the DSM one manic episode without depressive episodes is enough to classify the mood disorder as bipolar type I (about 1 percent of all bipolar cases). The ICD on the other hand requires a history of at least two mood episodes for all bipolar diagnoses. Bipolar type II is defined as intermittent episodes of depression and

hypomania. Hypomania shares many characteristics with mania but in general doesn't effect global functioning to the same extent that mania does, and usually does not lead to hospital admission (Merikangas and Lamers, 2012). Of those who have had hypomania, 5-15% percent go on to develop mania, thus converting from type I to type II (Benazzi, 2007). Individuals who have more than four or more mood episodes a year have a so called "rapid cycling bipolar disorder" in DSM.

### **1.3.2 Epidemiology**

Bipolar disorder was described as a "highly prevalent, highly persistent and highly impairing illness" in an overview from the National Comorbidity Service Replication (Kessler et al., 2007). Lifetime prevalence was estimated to 1.0% for type I and 1.1% for type II. Bipolar disorder usually presents for the first time around 20 years of age and it is twice as common that its first presentation is depression. However, the incidence of co-morbid anxiety is as high as 59% in bipolar disorder which may decrease the estimate for age of onset of psychiatric symptom onset to around 10 years of age. Bipolar disorder shows high numbers of persistence during a 12-month period; type II as much 73.2% of the time, followed by type I with an estimate of 63.3%. This suggests that bipolar disorder should be regarded as a chronic disease. The estimated salary-equivalent in cost productivity reaches a staggering \$14.1 billion/year for bipolar disorder in the USA or 28,011 per patient and year in Sweden (Ekman et al. 2013) .

Bipolar disorder is usually diagnosed approximately 9 years after the patients first mood episode, patients usually receive treatment 3 years after their first mood episode, more than 2 years thereafter patients are admitted to hospital or have established contact due to a suicide attempt. Despite this, another 4-5 years may elapse before the diagnosis is made (Drancourt et al., 2012). The illness may become more severe with time - a phenomenon known as "kindling" (Bender and Alloy, 2011). Periods of euthymia then have a tendency to become shorter with increasing age while the intensity of symptoms and their duration increase. People with bipolar disorder who do not receive mood stabilizing treatment have approximately four mood episodes per decade (APA, 2004).

### **1.3.3 Clinical characteristics**

Manic episodes normally may have several precipitants (Proudfoot et al., 2011). The onset is usually gradual over days, and may last as long as three months if

left untreated. Manias can present differently. They are sometimes described as being of the euphoric, irritable or delirious type. Patients may also display mood congruent psychotic symptoms such as delusions or hallucinations. According to the classification of the DSM, the diagnosis mania requires a duration of seven days (shorter if the patient is admitted to hospital). Hypomania is characterized by the same symptoms as mania, but with lower intensity and less effect on global function. The duration of hypomania can also be more variable than mania, but the diagnosis of hypomania requires a duration of at least four days. The diagnosis of mania or hypomania requires change in mood plus three other symptoms (four other symptoms of the patient only displays irritable mood). Mania and hypomania are characterized by the symptoms listed in table 2.

Table 2: Clinical characteristics of mania in DSM and ICD

<i>Item</i>	<i>Symptoms and signs</i>
1A	Elevated mood
1B	Irritable mood
2	Increased self-esteem or grandiosity
3	Decreased need for sleep
4	Increased talkativeness
5	Flight of ideas
6	Distractability
7	Increased social activities
8	Risk-taking behavior
9	Increased sexual activities (only in ICD-10)

Depressive episodes most often do not have an evident trigger. A depression often occurs in proximity of the manic episode. Depression has a gradual onset over days to weeks, and normally has a duration of at least four months if left untreated. The diagnosis major depression requires low mood, apathy and/or anhedonia plus four other symptoms. These symptoms must have occurred during at least two weeks time. The specific characteristics of a major depressive episode are given in table 3.

Sometimes symptoms of mania and depression occur during the same mood episode, a condition referred to as "mixed state" in DSM. Studies show that two thirds of all people with ongoing bipolar depression also display symptoms of mania. Sometimes this condition can exist as a sub-syndromal illness that does not fulfill the criteria for either mania or depression, but that can lead to functional impairment worse than bipolar disorder type I (Kessler et al., 2007).



Table 3: Clinical characteristics of major depression in DSM and ICD

<i>Item</i>	<i>Symptoms and signs</i>
1	Depressed mood
2	Markedly diminished interest or pleasure
3	Loss of energy or fatigue
4	Loss of confidence or self-esteem
5	Unreasonable feelings of self-reproach or excessive or inappropriate guilt
6	Recurrent thoughts of death or suicide, or any suicidal behavior
7	Diminished ability to think or concentrate, or indecisiveness
8	Psychomotor agitation or retardation
9	Insomnia or hypersomnia
10	Change in appetite (increase or decrease with corresponding weight change)

### 1.3.4 Bipolar depression

Bipolar depression refers to the depressed state in bipolar disorder. A specific definition of bipolar depression does not exist in DSM and ICD. Instead, it is considered a "major depression". Much research has focused on distinguishing the bipolar and unipolar depression from each other because of the critical treatment decisions that bipolar disorder requires. The data collected for this thesis refers to major depression in bipolar disorder type I. Therefore we will only refer to that type of bipolar depression in this text.

The depressed state is the predominant mood state for patients with bipolar disorder. One study estimates that depression is three times more common than mania or hypomania over time (Kupka et al., 2007). The age of onset for bipolar depression is earlier than for unipolar depression and at least 50% of bipolar patients first present with depression (Solomon et al., 2006, Kinkelin, 1954). Episodes may be shorter than in unipolar depression (Mitchell et al., 2001). It appears that bipolar depression resemble melancholia regardless of classification system (Parker et al., 2000). Thus, psychomotor features are prominent in bipolar depression and characterized in particular by decreased emotional reactivity, increased delay in verbal responses, slower movement, facial immobility and a increased delay in initiating movement (Mitchell et al., 2001). Interestingly, in those three samples with the most thorough rating of psychomotor disturbances it appeared that patients with bipolar depression showed a less clean symptom profile with melancholic, atypical and occasionally psychotic features. Several

studies also found that a family history of bipolar disorder and increased number of prior depressive episodes predicts bipolar depression (Perlis et al., 2006, Solomon et al., 2006).

Table 4: Characteristics of bipolar depression

<i>Symptoms and signs</i>
Hypersomnia
Leadens paralysis
Psychomotor retardation
Psychotic symptoms, pathological guilt
Manic symptoms, affective lability
Early onset of illness (before 25 years of age)
Many episodes (more than 5 episodes)
Familial risk for bipolar disorder

Compared to unipolar depression there is increased persistent and chronic unemployment in the bipolar group, indicating a greater public health burden (Zimmerman et al., 2012). However, there appears to be a lack of epidemiological data regarding bipolar depression. In a consensus document from the European College of Neuropsychopharmacology in 2007, the currently available data has "incomplete information across the life cycle, limited data on episode type, form, length and typical symptoms, limited reliable data on disability, recognition and treatment at a population level and insufficient epidemiological evidence to support independently the definition of thresholds and boundaries" (Goodwin et al., 2008).

A study comparing predominantly depressed type I bipolar patients with unipolar patients showed that unipolar patients display the same type of cognitive impairments but to a lesser degree (Borkowska and Rybakowski, 2001). One study that investigated within-subject differences between depression and euthymia found state-dependent impairment in verbal memory (Malhi et al., 2007). In their between-group comparison with healthy controls they also found that depressed subjects showed executive difficulties in form of phonemic word generation, memory problems with regard to total recall and recognition, inattention with worse Stroop-performance, and reduced psychomotor speed in both the dominant and non-dominant hand.

### 1.3.5 Euthymia

Euthymia in bipolar disorder refers to a condition where persons do not fulfill criteria for either major depression, hypomania or mania. Thus, patients display normal mood. However, the definition of euthymia varies and related terms with near identical meaning also appear in the literature. Euthymia does not have formal definition in either DSM nor ICD.

Empirical investigations of the euthymic condition in bipolar disorder indicate an ongoing disease process in brain. One study of functional recovery after first-episode mania showed that when 98% of patients do not longer fulfill the criteria of a mood episode, and 78% have achieved symptomatic recovery according to clinical ratings, then only 43% has reached functional recovery, and the degree of functional recovery also show a negative association with the duration of illness (Wingo et al., 2009).

Table 5: Characteristics of euthymia in bipolar disorder

<i>Symptoms and signs</i>
Subthreshold mood symptoms
Affective dysregulation
Cognitive impairments
Psychomotor disturbances
Relational difficulties
Unemployment
Impaired social capacity
Substance abuse

Neurocognitive impairments appear to contribute to the lack of functional recovery in bipolar disorder. Meta-analyses show impaired attention, dysfunction in episodic memory, delayed verbal memory, and impaired executive functioning as well as decreased processing speed and psychomotor speed in bipolar disorder type I (Torres et al., 2007, Robinson et al., 2006). Results in these meta-analyses are predicted by findings from our own group (Pålsson et al., 2013). The study from our group also raises the question about the effect of medication on neurocognitive functioning in euthymic bipolar disorder. This is also addressed in another meta-analysis of cognitive functions in euthymia (Bora et al., 2009).

Observed deficits during euthymia are thought to reflect a bipolar disorder trait. Since residual effects of the underlying disease are apparent in euthymic bipolar disorder, the euthymic condition has attracted interest with regard to the

identification of endophenotypes, or intermediary phenotypes, in bipolar disorder. Endophenotypes are the biological correlates that bridge gene expression to the clinical phenotype.

### **1.3.6 Etiopathogenesis**

The cause of bipolar disorder is unknown. There are pathological findings at several levels of investigation in bipolar disorder. However, there is currently no pathway that unifies all investigation levels and describes an aetiopathogenesis that leads to the clinical expression of bipolar disorder.

Bipolar disorder is highly heritable. In a population-based study of schizophrenia and bipolar disorder, the heritability estimates was 59% for bipolar disorder with a unique genetic effect of 31% (Lichtenstein et al. 2009).

Theories about the etiopathogenesis of bipolar disorder have changed over the years. Since the advent of different medications for bipolar disorder much focus has been on monoaminergic neurotransmission and specific pathways that modulate frontal-striatal brain regions and the limbic system (Drevets et al. 1997; Hasler et al. 2004; Murray et al. 2011; J. L. Price and Drevets 2012; Savitz and Drevets 2012). While no previous model has been able to fully explain the pathogenesis behind the plethora of symptoms in bipolar disorder, our knowledge of these systems have provided us with pharmacological targets that prevent suicide, and treat depression and mania.

A well known feature of depression is the dysfunction of the hypothalamic-pituitary adrenal axis (HPA) in mood disorders (Gold and Chrousos 1985; Takahashi et al. 2009; van der Werf-Elderling et al. 2012). Patients display a dysregulated secretion of cortisol and depressed patients fail to suppress the secretion of cortisol with the dexamethasone test (Carroll 1982). This may implicate impaired glucocorticoid receptor function as the mediator of the increased secretion of cortisol (Calfa et al. 2003; Pariante and Miller 2001). It has been suggested that HPA dysfunction is a characteristic of melancholia which is characterized by psychomotor disturbance and also that it relates to cognitive functioning during euthymia (Watson et al. 2004).

Intracellular signaling pathways have received much interest in bipolar disorder. The interaction of cell surface G-proteins, and intracellular cyclic adenosine monophosphate (cAMP), protein kinase A (PKA) and brain derived neurotrophic factor (BDNF) have shown to be altered in both bipolar depression and euthymia (Carlson et al. 2006). Patients show higher cAMP stimulated PKA activity leading to changes in metabolism and gene transcription via factors such as BDNF

(Tardito et al. 2006). During all phases of bipolar illness there appears to be G-protein subunit levels that may lead to alteration of the intracellular cAMP signaling pathway. There are also alterations in calcium signaling and especially the phosphoinositide pathway that have received much interest (Belmaker 2004).

Immunological and neuroendocrine systems show changes in inflammatory markers such as cytokines across several states of bipolar disorder, and increase in activated T-cells and tumor necrosis factor alpha during acute phases of the illness (Berk et al. 2011; B. I. Goldstein et al. 2009). With regard to our interest in frontal-striatal circuitry and psychomotor slowing, there are studies that show how inflammatory markers can modulate dopaminergic tone in the basal ganglia and ascending systems, in turn leading to slowed movement, alterations in mood and reward incentives (Brydon et al. 2008; Felger and Miller 2012; Felger et al. 2013; Harrison et al. 2009).

## **1.4 Magnetic resonance imaging**

The foundation of the MRI signal depend on the magnetic properties of atomic nuclei. In short, the signal generation in MRI depend on the nuclear spins of protons in hydrogen nucleus contained in a tissue volume and placed in a static magnetic field provided by a magnet. Using a coil as a radio frequency transmitter, the nucleus can be excited with electromagnetic energy and taken from a low-energy state to a high-energy state. When the nucleus falls back into the low-energy state, magnetic oscillations from the nucleus induces current in a receiver coil. This forms the basis of the MRI signal. Other atomic nuclei but hydrogen can also be excited by manipulating the emitted radio frequency. However, most MRI examinations target hydrogen in water molecules. Since the brain contains approximately 80% water, we are able to construct an image with MRI.

By manipulating how the spin realigns with the static magnetic field of the scanner, we can determine two types of relaxation: T1, and T2. T1 relaxation refers to the realignment of spins to the scanners magnetic field. T2 relaxation depend on the so called "dephasing" of the spins of single protons when their aligned in a certain way in relation to the magnetic field. By manipulating the manner and frequency in which electromagnetic energy (RF pulses and TR=repetition time) is transmitted, and by changing time to start of signal acquisition after electromagnetic energy has been applied (TE=echo time), we are able to produce T1-weighted or T2-weighted images. In our studies, the high-resolution anatomical images are T1-weighted, and the functional images are T2-weighted.

#### **1.4.1 Structural magnetic resonance imaging**

Structural magnetic resonance imaging provides an image of grey matter/white matter contrast and morphological features of the brain. Several analysis methods then exist that allow comparison of tissue density in groups of voxels that have been aligned across individuals in a standard space. This methodology is known as voxel-based morphometry and have been frequently applied. Segmentation of grey matter, white matter, and ventricular spaces, allows for indirect measures of neurodegeneration and estimation of local thinning of the cortex at specific anatomical localizations. Manual tracing methods also exist that build upon a delineation protocol for a specific brain structure. Once the structure has been defined measures like volume, width or surface shape can be done. With regard to volume, this is perhaps the most applied analysis and is normally referred to as region-of-interest analyses. More sophisticated region-of-interest analyses have made an advent recently. These estimate local changes in shape, which have shown to be a more sensitive measure than regional volume. For example, significant changes in local shape can be detected in the absence of a significant global volume in one particular brain structure.

Diffusion magnetic resonance imaging measures the diffusion of water in the brain which allow mapping of white matter tracts and localized changes in microstructure, for example myelinization. We do not use diffusion based imaging in this thesis. However, it deserves mentioning as it has added profoundly to establishing connectivity patterns and informing theories about neural organization.

#### **1.4.2 Functional magnetic resonance imaging**

There are many methods that can be used for functional brain imaging. An example of the most common methods used in contemporary neuroscience are electroencephalography (EEG), magnetoencephalography (MEG), near-infrared spectroscopy (fNIRS), transcranial magnetic stimulation (TMS), single photon emission tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). The available methods differ with respect to the signal they measure, which in turn emerges from specific physiological processes and has limits to its resolution in space and time.

The BOLD signal is detected from distortions in the MRI scanner's magnetic field. These distortions comes from a signal loss induced by the paramagnetic properties of deoxygenated blood. Thus, the BOLD signal is a secondary measure

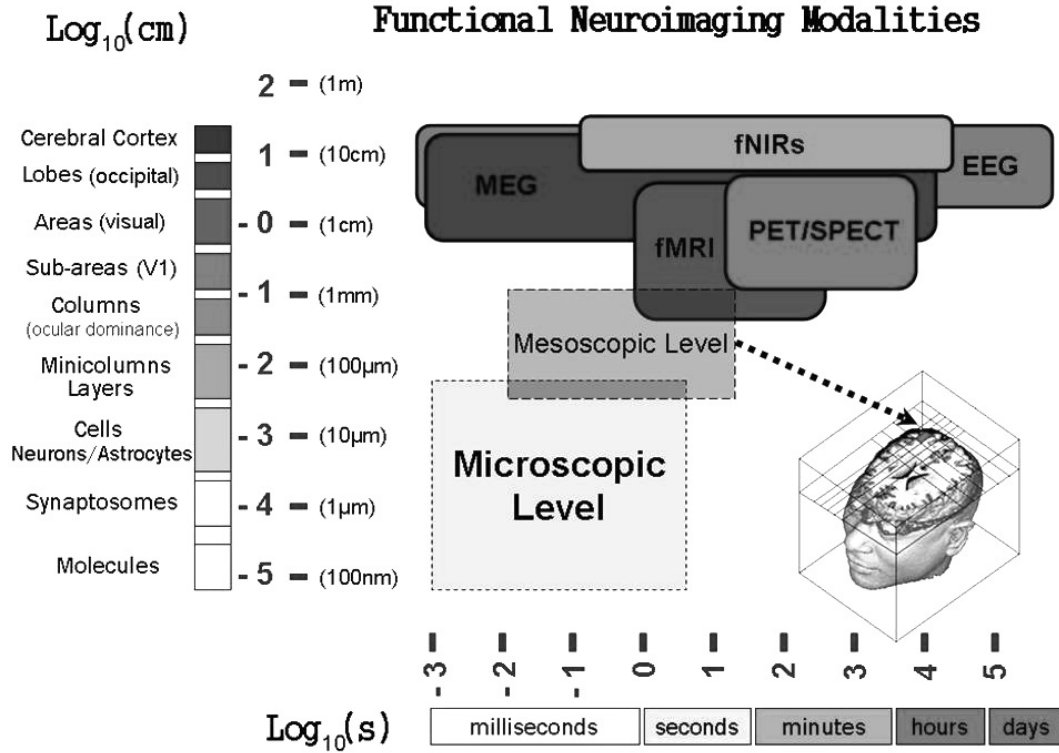


Figure 3: The spatial and temporal resolution of common functional imaging methods (with permission from Jorge Riera, PhD)

of neural activation. Several neurophysiological processes underlie the BOLD contrast used in functional magnetic resonance imaging (Lee et al. 2010; Logothetis 2008). Studies that combine functional imaging methods and electrophysiological recordings show that the BOLD signal emerges from post-synaptic activity which reflect the input to a neuronal population as well as its intrinsic processing (Lauritzen 2005; Logothetis 2003). The spatial resolution of the BOLD-signal is fractions of a millimeter up to centimeters. This means that activation of minute structures like cortical columns, and larger structures like gyri, can be estimated. The temporal resolution is usually in the order of tenths of second up to several seconds. The majority of research questions in the literature require a spatial resolution of millimeters and a temporal resolution of a seconds. Most experiments uses an average voxel size of  $55 \text{ mm}^3$ . Thus, the neural activation signal in an average voxel contains physiological information from a tissue sample of approximately  $1.65 \text{ mm}^3$  of vessels, 5.5 million neurons, 40 billion synapses, 22 km of dendrites, and 220 km of axons.

The advent of so called echo-planar imaging (EPI) was just as important as the discovery of the BOLD contrast (Mansfield 1977; Ogawa et al. 1990a). The encoding in EPI sequences greatly reduces scanning time, thereby decreasing the

Table 6: Physiological basis of BOLD

<i>Event</i>	<i>Effect</i>
Neuronal activity	Glutamate release, activation of glial cells with re-uptake of glutamate and depolarization of dendritic membrane, activation of post-synaptic calcium ion channels, post-synaptic influx of calcium ions, activation of enzymes, and production of nitric oxide, prostaglandines, and epoxyeicosatrienoic acids
Neurovascular coupling	Blood vessel dilation, increase in blood flow (rCBF)
Hemodynamic response	Washout of deoxygenated blood, decrease in ratio of deoxygenated/oxygenated blood
MRI detection	Decrease in paramagnetism, increase in T2*, increase in BOLD-signal strength, increased power in statistical parametric maps

susceptibility to motion artifacts, and allows for imaging of dynamic physiologic processes such as changes in brain metabolism. It is therefore used for the BOLD imaging. However, the EPI sequence also has drawbacks (Hutton et al. 2002). One of those is the sensitivity to susceptibility artifacts that appear in vicinity of air filled spaces. Several implicated key regions in mood disorders such as the subgenual cingulate, orbitofrontal cortex and ventromedial frontal cortex are located close to paranasal sinuses (Deichmann et al. 2002; Jezzard and Clare 1999). The EPI sequence is also more sensitive to inhomogeneities in magnetic field that may lead to decreased signals in certain regions (Holland et al. 2010).

## 1.5 Brain imaging phenotypes in bipolar disorder

Bipolar disorder is a disease where several domains of human brain function are altered. The connectivity patterns of the brain and the idea of a human connectome have become an influential concept for explaining the neural organization and interconnectivity at many levels of observation. At the macroscopic level, the lobes of the brain are connected to each other in large-scale networks that allow for interactions that mediate behaviors. A popular model with relevance to psychiatry is the idea of frontal-striatal networks. The general principle of frontal-striatal neurocircuitry is that it emanates from specific anatomical localizations in the frontal lobe, converges on specific regions of the striatum, has output via globus pallidus to the thalamus, and projects back to the frontal areas of origin. Frontal-striatal neurocircuitry is usually divided into four such closed



sub-circuits, or loops: the sensory loop, limbic loop, executive loop, and the motor loop. These loops process functionally specific information and largely remain segregated throughout the circuitry. Therefore different types of information can be studied focusing on specific target areas in these loops. Their connectivity patterns of these loops are illustrated in the picture below.

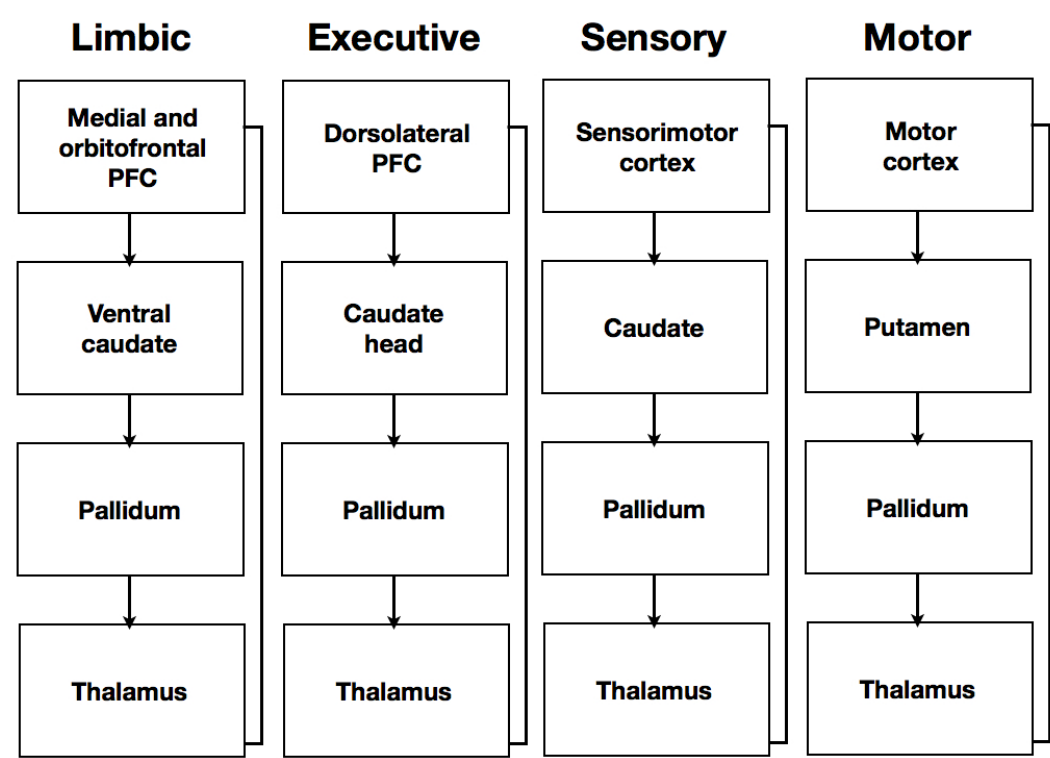


Figure 4: Frontal-striatal loops

Structural, functional and biochemical features of several brain regions are altered in bipolar disorder. As evidence has mounted it is clear that mood disorder primarily involves brain regions contributing to frontal-striatal loops at the macroscopic level: frontal lobe, basal ganglia, thalamus, limbic system, and several brain stem nuclei whose efferents modulate many of these anatomical regions (figure 5). The most inclusive map of the "anatomy of mood disorders" seems to involve anterior midline structures and lateral prefrontal brain regions.

### 1.5.1 Structural and functional imaging findings

In bipolar disorder total brain grey matter volume does not appear to be altered. In the dorsolateral and dorsomedial prefrontal cortex there is less gyrification and lower grey matter volume. However, there appears to be increased grey matter volume in the ventrolateral prefrontal cortex, and grey matter loss in the

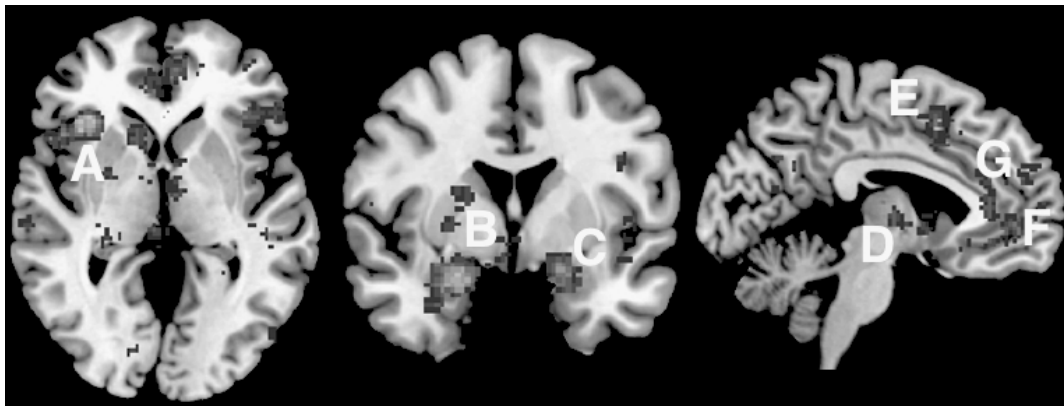


Figure 5: Brain regions that are consistently active in 109 studies of "mood". A forward inference map that represents brain areas consistently activated in relation to the search term "mood" and input to the database NeuroSynth at ([www.neurosynth.org](http://www.neurosynth.org)) in July, 2013. A=anterior insula, B=striatum, C=amygdala, D=thalamus, E=dorsal anterior cingulate cortex, F=medial frontal cortex, and G=pregenual anterior cingulate cortex.

orbitofrontal cortex (C. S. Lim et al. 2013a). One of the most reproduced findings in studies on depression is alteration of activity, metabolism, structure and biochemistry, of the subgenual anterior cingulate cortex (Mayberg et al. 1999; McNeely et al. 2008; Siegle et al. 2006). Taken together, there appears to be loss of grey matter and usually increased activity even during euthymia. In the pregenual and dorsal anterior cingulate cortex there is pronounced decreases in grey matter volume and increased activity during euthymia. It is also clear that these regions interact (Seminowicz et al. 2004). Studies show that baseline metabolism in pregenual cortex predicts treatment response, and that the degree of altered metabolism may predict response to different types of treatments for depressive states (Kennedy et al. 2007; McGrath et al. 2013). Studies show increased grey matter volume in the temporal lobe, while the activity and grey matter volume of mesial structures like the amygdala and hippocampus remain elusive, with heterogeneous results across studies (Pfeifer et al. 2008). Interestingly, with the advent of the increased interest in the "default mode network" that appear to be altered in bipolar disorder, the cuneus show increases in grey matter volume (C. S. Lim et al. 2013a; Sheline et al. 2009). A recent meta-analysis of grey matter density changes that deserves mentioning is a study by Selvaraj et al. They collected unthresholded statistical maps and carried out a meta-analysis showing that the anterior insula may play a key role in bipolar disorder (Selvaraj et al. 2012).

The question of alterations of basal ganglia in volume remain unanswered, and many studies have failed to show any changes in volume (Bonelli et al. 2006). Neuropathological investigations are sparse, but have shown decreased volume of the basal ganglia regions (Baumann et al. 1999; Bielau et al. 2005). However,

one recent study showed local shape changes in the striatum in the absence of global volume change (Ong et al. 2012). The activity of the caudate may be increased in depressive states while the activity in the globus pallidus appear to be decreased during depression (C. H. Chen et al. 2011).

In functional studies bipolar disorder patients appear to underactivate their inferior frontal regions and putamen, while there is an tendency of hyperactivation in mesial temporal regions and the basal ganglia. Interestingly, our showed a positive correlation between the number of manic episodes and grey matter density decreases in the same region (Ekman et al. 2010). Grey matter density studies (Bora et al. 2010) and meta-analyses show volumetric changes in right putamen and increased globus pallidus volumes (Arnone et al. 2009; Hallahan et al. 2011).

## **1.6 Psychomotor function**

The adjective psychomotor is commonly defined as "movement proceeded by mental activity". In accordance with a previous review of psychomotor slowing in schizophrenia, our use of the term "psychomotor" refers to the "activities and symptoms in which, rather than thinking or feeling, movement or action is the principal component, ie, in which the planning, programming, and execution of movements play a dominant role" (Morrens et al. 2007). Psychomotor function extends beyond the mere activation of peripheral motor units and contraction of muscles. It also involves a range of neurocognitive processes that contribute to motor control and determine motor actions: motor selection, motor planning, motor preparation, motor execution, action monitoring, and response inhibition (Willingham 1998). Thus, psychomotor function appears to involve both lower-order elements in movement production (Rizzolatti and Lupino 2001) and higher-order cognitive control of action (Buch et al. 2010; Duque et al. 2013; Kennerley et al. 2004; Ridderinkhof et al. 2004; Rushworth et al. 2004; Rushworth et al. 2005).

### **1.6.1 The human motor systems**

Movement can be divided into fine motor skills and gross motor skills. Fine motor skills involve small movements performed with hands, fingers, wrists, feet, toes, lips, and tongue. Gross motor skills involve larger muscle movement of the arms, legs, or entire body. Movements also have covert representations that display a functional equivalence with regard to their overt counterpart (Jeannerod and Decety 1995; Munzert et al. 2009). A division of the human motor system

that is relevant to bipolar disorder is the division into the voluntary motor system and the emotional motor system (Alheid and Heimer 1996; Holstege 1992; Nieuwenhuys 1996). It is clear that both systems may mediate the psychomotor disturbances observed in both bipolar disorder and other neurological conditions where patients display for example altered facial expression (Bologna et al. 2013), general slowing of purposeful actions (Lohr and Caligiuri 2006), and changes in postural control (Bolbecker et al. 2011; Holstege 1998).

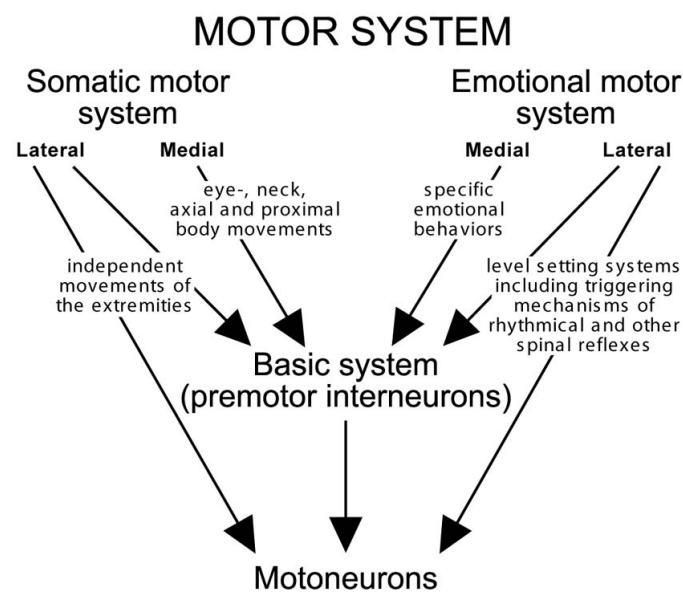


Figure 6: Human motor system (with permission from Prof. G. Holstege, PhD)

### 1.6.2 Functional anatomy of voluntary movement

The production of movement can be divided into three pre-executive parts: selection, planning and preparation, followed by execution (Rizzolatti and Luppino 2001). The anatomical correlates of the different parts of motor production have been identified and studied using electrophysiology, brain imaging and neuro-modulatory methods (Grafton and Hamilton 2007). A rostral-caudal division of motor function has been reported in several studies: selection and planning involve the prefrontal cortex, cingulate motor areas and rostral premotor areas; preparation the caudal premotor areas; and execution the primary motor cortex (Chouinard and Paus 2006; Hoshi and Tanji 2007; Nakayama et al. 2008; Picard and Strick 1996).

Retrograde tracing in primate and human imaging studies show how the connectivity of motor areas differ (Rizzolatti and Luppino 2001). The rostral premo-

tor cortex, involved in motor planning, receives input from cingulate motor regions and from prefrontal brain regions involved in higher cognitive functions such as attention, working memory and executive behavior (Luppino et al. 2003; Picard and Strick 2001). The caudal motor areas, involved in motor preparation and motor execution, have greater intrinsic connections and receive most of their input from rostral premotor cortex (Luppino et al. 1993).

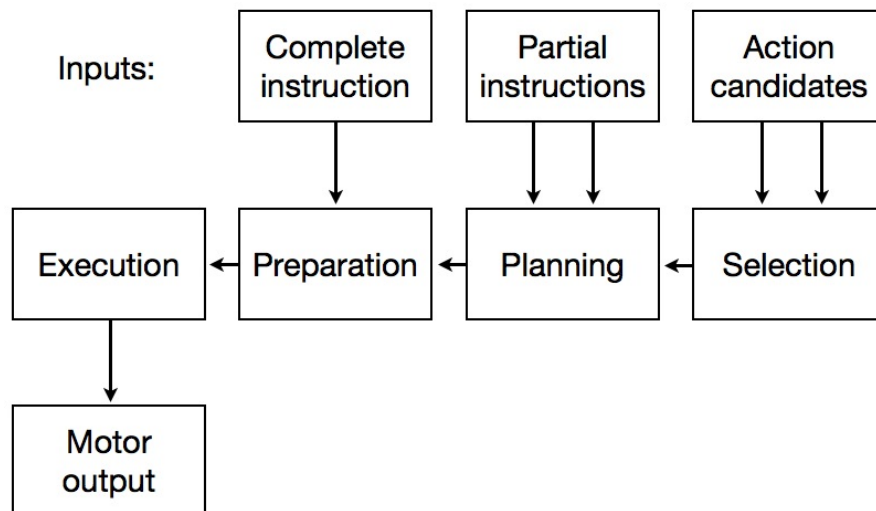


Figure 7: Motor functions in production of voluntary movement

### 1.6.3 Functional integration of emotion and movement

There are two main anatomical large-scale network models for how limbic regions interact with motor regions that could provide a framework for understanding how emotional information modulates motor function. The first of these models was initially described by Nauta who made the argument that a cortical-striatal-thalamo-cortical network provides limbic input at the subcortical level of the ventral striatum or the thalamus (Nauta 1972). Nauta's model has been expanded on to describe how the lateral prefrontal cortex interacts with limbic and paralimbic regions at the cortical level (Sheline 2006). The orbitofrontal cortex, medial frontal cortex, subgenual anterior cingulate cortex and the perigenual cingulate cortex send efferents to other subcortical limbic structures that interface with non-limbic dorsal striatal regions via the nucleus accumbens of the ventral striatum. The network projects back to cortical areas via the thalamus. The communication in this network is facilitated by dopamine which is implicated in the motor retardation, decreased motivation and cognitive deficits seen in bipolar depression (Malhi and Berk 2007; Mitchell and Malhi 2004). This model postulates

impaired control by lateral prefrontal cortex over limbic and paralimbic regions, leading to a limbic hyperactivation that eventually disinhibits the activation of the thalamus, leading to increased excitation of cortical areas (Morecraft et al. 2000).

The Nauta model was complemented by Morecraft's model. Morecraft used retrograde tracing methods to show how many limbic regions have efferents - primarily to the anterior cingulate cortex - that advance limbic signals to cortical motor regions via the cingulate motor areas. The cingulate motor areas receive most of their input from limbic areas (Morecraft and Van Hoesen 1998; Shima and Tanji 1998). The cingulate motor area has only recently been subject to structural and functional definition where its anatomical delineation and functional specificity is still a matter of debate. The region has been shown to be involved in motor responses with affective incentives. Both the rostral and the caudal part of the area have limbic afferents and it has been suggested that the region may provide one of the major interfaces where limbic signals are advanced to motor functions. This puts the region in a particularly interesting position that may hold great promise for future investigations.

#### **1.6.4 Psychomotor function in mood disorders**

Psychomotor disturbances in bipolar disorder are an expression of alterations in volition, cognition, emotion and motor control. In the 1912 edition of "Lehrbuch des Psychiatrie", Emil Kraepelin wrote the following about psychomotor retardation in his chapter on general symptomatology:

"The psychomotor retardation, which is the most important disturbance in the depressed states of manic-depressive insanity, is probably due to a similar increase in resistance. Such patients require special exertion of the will for almost every movement. All the actions are characteristically slow and weak, except when a powerful emotional shock breaks through the resistance. The retardation may become less pronounced under the influence of continued effort. In severe cases independent volitional action is almost impossible. In spite of every apparent exertion, the patients cannot utter a word or at best answer only in monosyllables, and are unable to eat, stand up, or dress. As a rule they clearly recognize the enormous pressure lying upon them, which they are unable to overcome"

#### **1.6.5 Clinical ratings of psychomotor disturbances**

The clinical signs of psychomotor disturbances can be rated with the Widlöcher, CORE and MARS scales (Parker et al. 1994; Sobin et al. 1998; Widlocher 1983).

Taken together, these rating instruments suggest that psychomotor disturbances can be divided into categories (table 7). The categories are: agitation, retardation, non-interactiveness and mental retardation (mental slowing). However, the respective contributions of cognition, motivation, emotion and movement to psychomotor disturbances have been difficult to single out (Lohr and Caligiuri 2006; Sobin and Sackeim 1997).

Table 7: Categories of psychomotor signs in the Widlöcher, MARS and CORE scales

<i>Category</i>	<i>Signs</i>
Retardation	Slowed movements (motor slowness), facial immobility (lack of facial expressivity, downcast gaze, reduced voice volume, slurring of speech), body immobility (immobility of trunk/proximal limbs), postural slumping (postural collapse), delay in motor activity, delay in responding verbally (delayed speech onset), slowing of speech rate (monotone speech), abnormal gait
Agitation	Frightened apprehension (static facial expression, abnormal staring, increased blinking, erratic eye movement), facial agitation (movement/tension in mouth), motor agitation (Increased axial truncal movement), stereotyped movements (tension in fingers and hands, hand movement, foot/lower leg movement), verbal stereotypy
Non-interactiveness	Response to social cues, emotional responsiveness, inattentiveness, poverty of associations, spontaneous speech, length of verbal responses
Mental slowing	Language and verbal flow, variety of themes spontaneously approached, richness of associations, subjective experience of ruminations, fatigability, perception of flow of time, memory, concentration, interest in habitual activities

### 1.6.6 Pathophysiology of psychomotor disturbances

Taken together, the neural correlates of psychomotor disturbances have been investigated for many years. They appear to primarily involve brainstem nuclei, midline structures and the prefrontal cortex. Thus, anatomical structures that comprise frontal-striatal networks and parts of the emotional motor system. However, many studies involve a small number of participants and have not been replicated. A review of investigations into psychomotor disturbances in depression shows deficits and decreased processing speed in both cortical brain regions, primarily in the frontal cortex, and in subcortical motor systems involved in cognition and motor control (Schrijvers et al. 2008). Nuclear imaging

studies have correlated major depression with changes in prefrontal and paralimbic metabolism (Mayberg et al. 1994) and altered dopamine transmission in subcortical structures (Meyer et al. 2001). Clinical psychomotor retardation was correlated with changes in metabolism at rest (Bench et al. 1993; Dolan et al. 1993; Mayberg et al. 1994; Videbech et al. 2002) or with indirect measures of regional dopamine transmission (Meyer et al. 2001; Meyer et al. 2006) in these studies. Functional magnetic resonance imaging (fMRI) studies using manual reaction time tasks have shown how cortical and subcortical brain regions are activated differently in patients with bipolar depression compared to healthy controls (Caligiuri et al. 2003; Caligiuri et al. 2004; Caligiuri et al. 2006; Marchand et al. 2007b; Marchand et al. 2007a).

Surprisingly few studies have investigated the relation between grey matter and psychomotor disturbances in mood disorders. One region-of-interest study of melancholic depression showed a cortical thinning of the pre-supplementary motor area, a part of the mesial premotor cortex that advances signals to motor areas from the prefrontal regions engaged in higher-order motor functions like action selection and motor planning. This thinning was found to show a positive correlation with implicit motor learning test (Exner et al. 2009). In our group we did not find a significant correlation between grey matter density and motor speed results among euthymic patients (n=53) with bipolar disorder type I (unpublished data).

Studies have shown that executive motor regions may be affected in psychomotor disturbances. A TMS study found that depressed subjects with psychomotor retardation were less able to produce output from the motor cortex than depressed patients without psychomotor retardation, or healthy controls. However, the effect was only present during maximal effort and fatigue. The findings may indicate that objective measurements of psychomotor disturbance require a great amount of load on the motor system to be informative (Loo et al. 2008). One recent study specifically addressed psychomotor functioning in depressive disorder using diffusion magnetic resonance imaging and actigraphy - an objective measure of the general activity level in an individual - and showed lower activity levels correlated with measures of differential myelination in the frontal lobe and posterior cingulate region, and a negative correlation between the same measures in the white matter beneath the primary motor cortex and in the parahippocampal region. The authors conclude that changes in psychomotor function in depressive disorder may be linked to changes in white matter in motor regions (Walther et al. 2012).



Alterations in key structures in the emotional motor system may contribute to subtypes of mood disorders and display with different degrees of psychomotor disturbances. It is possible to use transcranial ultrasound to evaluate brain stem regions where monoaminergic nuclei are located (G. Becker et al. 1994). Reduced echogenicity have been found in movement disorders with comorbid depression (T. Becker et al. 1997; Berg et al. 1999). Substantia nigra hyperechogenicity may predict parkinsonian symptoms and motor asymmetry in depression (Hoeppner et al. 2009; Walter et al. 2007b). Also, hypoechogenicity in the raphe nuclei have also been associated with depressive states which are not characterized by psychomotor symptoms (Walter et al. 2007a).

*Catatonia* deserves a special mention since it is a psychomotor state that has been more frequently investigated with neuroimaging techniques albeit by few researchers. Catatonia is a psychomotor state that can appear during a range of psychiatric conditions. In the DSM, catatonia is a seldom used classifier for subgrouping of other conditions (Francis et al. 2010). However, some researchers in the field argue that catatonia should be considered a diagnosis in its own right (Fink 1993; Fink et al. 2010; Taylor and Fink 2003). Clinically, the condition is characterized by a range of psychomotor symptoms (table 8) preferably treated with lorazepam or electroconvulsive therapy (Bush et al. 1996a, 1996b). Several signs of catatonia apply to the psychomotor disturbances in bipolar disorder both during the manic and depressed phase (Starkstein et al. 1996; Thomas 2004). Taken together, studies of catatonia point towards the possibility of right-lateralized decrease in neural activation of the medial premotor cortex, the prefrontal cortex, the orbitofrontal cortex, and the basal ganglia (Atre-Vaidya 2000; Northoff et al. 2000b; Northoff et al. 2004; Richter et al. 2010; Scheuerecker et al. 2009; Tsujino et al. 2011). However, interhemispheric disturbances appear to occur (Northoff et al. 1999b). At the microscopic level these changes are possibly linked to synaptic alterations in gamma-amino-butyric acid transmission with decreased benzodiazapine receptor binding (Iseki et al. 2009; Northoff et al. 1999a; Northoff 2000). EEG recordings of the *bereitschaftspotential* suggest that catatonic patients may have difficulties in executing and terminating movement (Northoff et al. 2000a). Thus, psychomotor disturbances in catatonia may involve alterations in synaptic function in anatomical key regions and neural networks implicated in bipolar disorder (Northoff 2002a, 2002b).

In spite of recurring descriptions of how prominent psychomotor disturbances are in mood disorders, there are very few pathophysiological models for how they emerge. Vogt considers a pathophysiological model for the emergence of

Table 8: Characteristics of catatonia

<i>Signs</i>
Excitement, stupor, mutism
Staring, posturing, grimacing
Impulsivity, automatic obedience, mitgehen
Echolalia, echopraxia, gegenhalten
Stereotypy, verbigeration, perseveration
Mannerisms, waxy flexibility, withdrawal
Combateness, grasp reflex, ambitendency
Autonomic abnormality

psychomotor symptoms in depression (Vogt 2009). According to his model there is a loss of neurons in cortical layer V in the cingulate cortex. This specifically impairs the output from cingulate motor regions to subcortical motor regions - resulting in a paucity of internally guided movement and speech. The neurodegeneration also affects the posterior cingulate cortex which leads to sensory deafferentiation and decreased susceptibility to external drivers. Clinically, this could be reflected in altered responsivity to emotional information and external events: slowed movement, anhedonia and apathy.

In Parkinson's disease, the functional deafferentiation theory has been a successful theoretical framework to explain the genesis of motor disturbances (M. R. DeLong and Wichmann 2007; M. DeLong and Wichmann 2010). This theory predicts changes in the frontal-striatal motor circuit, where decreased dopamine release in the putamen and pallidum leads to decreased subcortical output to pre- and primary motor cortices. This impairs the preparation, control and execution of movement, resulting in bradykinesia and akinesia. These features resemble those seen in bipolar depression with psychomotor disturbances.

Psychomotor disturbances in mood disorders are both clinically and theoretically informative, and hold great promise for an advanced understanding of the underlying disease.

## **2 General aim, hypothesis and objectives**

### **2.1 General aim**

The general aim was to obtain a better understanding of psychomotor symptoms in bipolar disorder.

### **2.2 Hypothesis**

We hypothesized that changes in psychomotor function in bipolar depression or euthymic bipolar disorder are mediated by alterations in frontal-striatal neuro-circuitry. This would lead to decreased activation of cortical motor areas during motor tasks which displays as slowed movement. Furthermore, we hypothesized that morphometric alterations of the basal ganglia depend on certain clinical variables previously known to affect psychomotor function.

### **2.3 Specific objectives**

1. Can a self-rating scale, constructed for the purpose of giving valid ratings of motor symptoms, be an alternative or complement to clinician-administred scales?
2. Are brain regions that mediate preparation, control and execution of movement activated differently in subjects with bipolar depression compared to healthy controls?
3. Is there an association between neural activity and clinical ratings of psychomotor symptoms in bipolar disorder?
4. Are there any differences in the morphology of the basal ganglia in bipolar disorder compared to healthy controls?
5. Do clinical variables associated with psychomotor disturbances in bipolar disorder predict morphological changes in the basal ganglia?

## 3 Methodological considerations

### 3.1 Ethics

The Local Ethics Committee in Stockholm approved the protocols (04-752/4; 2006-1397-31/4; 2005/554-31/3; 2009/1221-32; 2011/1700-32) for all three studies that were conducted in accordance with the Helsinki Declaration. All participants gave oral and written consent. No patient was under compulsory treatment at the time of recruitment.

### 3.2 Subject samples

#### 3.2.1 The first sample from Karolinska Huddinge

The first sample (**paper I**) was collected at the Southwest Psychiatric Clinic (PSSV), Karolinska University Hospital in Huddinge, Stockholm, Sweden. Geographically the area corresponds to southwest Stockholm County. The catchment area has approximately 300,000 inhabitants. The recruitment process was opportunistic. Subjects were recruited from the Affective Disorders Outpatient Unit (Affektiva Mottagningen, M59) or the PSSV inpatient wards. Thus, participants (n=61) were both inpatients and outpatients. The gender distribution was slightly uneven with an overrepresentation of females (n=37) compared to males (n=24). The average age in the sample was 44 years (17-76 years). The clinical diagnoses were bipolar disorder type I (n=37), bipolar disorder type II (n=8), unspecified (NOS) bipolar disorder (n=8), and major depressive disorder (n=8).

With respect to the distribution of diagnostic categories, we believe our cross-sectional sample is representative of the patient population enrolled at PSSV. However, we did not randomly select patients which may have introduced a sampling bias. We did purposeful sampling to obtain subjects.

#### 3.2.2 The second sample from Karolinska Huddinge

The second Karolinska Huddinge sample (**papers II-III**) was collected at the Southwest Psychiatric Clinic (PSSV), Karolinska University Hospital in Huddinge, Stockholm, Sweden. The recruitment process was opportunistic with the purpose of finding patients with apparent psychomotor disturbances. All subjects were recruited from the Affective Disorders Outpatient Unit (Affektiva Mottagningen, M59) or the PSSV inpatient wards by myself and consultant psychiatrist Mats Adler. Thus, participants (n=9) were both inpatients and outpatients. The gender

distribution was uneven with an overrepresentation of females (n=8) compared to males (n=1). The average age in the sample was 44 years (17-76 years). The clinical diagnosis of all patients was bipolar disorder type I, current major depressive episode (n=9).

The second sample from Karolinska Huddinge was not representative of the clinical population with bipolar depression at PSSV. Also, the gender distribution was not balanced. The small sample size also contributes to statistical power issues which mandated additional post-processing in the image group analysis. However, we tried to delineate a clinical phenotype that may be considered well defined with regard to the homogeneity of clinical signs and its external validity, namely bipolar depression. The prevalence of psychomotor disturbances in this group is higher than in other subclasses of depression.

### **3.2.3 The S:t Göran Bipolar Project sample**

The S:t Göran Bipolar Project sample (**papers IV-V**) was collected at the Northern Stockholm Psychiatric Clinic (NSP), S:t Göran Hospital, Stockholm, Sweden. Geographically the area corresponds to northwestern Stockholm County. The catchment area had approximately 320,000 inhabitants over 18 years of age. It is an urban area with a wide socio-economic spectrum. At the time of enrollment, all patients presented with symptoms of mania, hypomania or other symptoms and signs of bipolar disorder received initial care at this clinic. They are referred to the tertiary care bipolar outpatient unit for further assessment and treatment. The recruitment process was consecutive and took place at Affective Disorders Outpatient Unit (Affektivt Centrum). Thus, patients were outpatients (n=27). There was a slight overrepresentation of males (N=15) compared to females (n=12). In december 2012, 102 patients with bipolar disorder type 1, were enrolled in the SBP and had their brain scanned. We selected those patients (n=27) that had been scanned with MRI scanner calibration filter settings identical to controls, showed no radiological signs of disease, and had completed the following psychomotor tests: Delis-Kaplan Executive Function System (D-KEFS) tests and the Conner's Continuous Performance Test.

We selected a subsample of patients (n=20) in order to further narrow down the clinical phenotype and investigate the effects of relevant clinical variables on morphometric measures of the basal ganglia, and thalamus. The subsample was selected based on whether psychotic symptoms had ever occurred during lifetime illness. Psychotic symptoms have repeatedly been shown to worsen psychomotor function and are considered to be a researchable heuristic defining of

the most severe form of bipolar illness with response to specific somatic treatments.

The number of the bipolar disorder type I participants in the sample is substantial (n=102). However, the effect of the old calibration filter in subcortical regions was also considerable according to our gray matter density analyses. Also, all controls had been scanned with the new filter. Given the number of participants and the number of covariates we had to control for (age, gender, neuroleptics, and lithium), we chose to investigate only those patients that had been scanned with the same calibration filter settings as controls and only those who had completed the two psychomotor tests in question.

### **3.3 Clinical characterization**

In **paper I**, we used the Montgomery-Åsberg Depression Rating Scale (MADRS) as reference scale to assess the severity of depression (Asberg and Schalling 1979). We used the Hypomania Interview Guide - Clinical Version (HIGH-C) when we assessed manic symptoms (Williams et al. 1999). Furthermore, we used a modified version of The Clinical Global Impression Scale intended for use when rating patients with bipolar disorder (CGI-BP). The CGI-BP comes in two other variants: CGI-BP-D, and CGI-BP-M. These are used for global ratings of depression, and mania, respectively (Spearing et al. 1997). We were blinded to self-ratings when doing observer-ratings. All interviews were performed by authors M.A., B.L., and S.A in paper I. Inter-rating consistency was assessed for both observer rating scales.

In **papers II-III**, we confirmed the affective disorder diagnosis using the Structured Clinical Interview according to DSM-IV (SCID-I). We found that no patient fulfilled the diagnostic criteria for concurrent mania, hypomania or rapid cycling disorder. We used the Comprehensive Psychopathological Rating Scale when we assessed the severity of psychiatric symptoms and signs (Asberg and Schalling 1979). Psychomotor disturbances were rated with the CORE-scale where retardation (CORE-R) score, and total score (CORE) was calculated (Hickie et al. 1996). Patients self-rated their affective state and used the AS-18 scale investigated in paper 1. A post-hoc analysis of the data in paper 1 implicated a retardation factor (AS-18-R) whose score was calculated. We also reviewed patient files with regard to extrapyramidal side-effects of medication. We could not find any notes indicating secondary Parkinsonism around the time of scanning. All interviews, ratings, and file reviews were done by B.L. and M.A in paper II and III.

In **papers IV-V**, we used the Affective Disorder Evaluation (ADE) protocol

(Sachs et al. 2003). ADE is a structured diagnostic instrument that includes assessment of family history, childhood history, social conditions, premorbid state, somatic illness, affective disorder diagnosis according to DSM-IV, together with lifetime charting of treatments, affective symptoms and signs. We screened for other psychiatric diagnoses than bipolar disorder using the diagnostic instrument Mini International Neuropsychiatry Interview (Sheehan et al. 1998). We used the Alcohol Use Disorders Identification Test and the Drug Use Disorders Identification Test to screen for alcohol and drug abuse (Berman et al. 2005; Saunders et al. 1993). The diagnostic interviews were done by board certified psychiatrists or supervised resident psychiatrists working at a bipolar disorder outpatient unit. We also reviewed patient files and interviewed next of kin when feasible. A case review of each patient was done by a consensus panel that consisted of experienced psychiatrists specialized in bipolar disorders. Patients were excluded if they were unable to complete the standard clinical assessment, or if they were incapable of providing informed consent. Most of the assessments were done by authors M. L., C-J. E., A. J. and C. S. in paper IV and V.

### **3.4 Neuropsychological testing**

#### **3.4.1 Trails**

Trail Making Test A and B (TMT-A, TMT-B) were created to assess neuropsychological function in patients with brain injuries but has been extended to other clinical populations (Goldstein and Shelly 1972). However, they are also classic measures of "psychomotor function" in psychiatric disorders (Fowler et al. 1988). Results on TMT-A correlate with ratings in sign-based assessment of psychomotor disturbances, and decreased frontal activation, and changes in striatal morphology among depressed patients (Naismith et al. 2003; Sawa et al. 2012). They were recently included in a consensus document on neuropsychological assessment of bipolar disorders (Yatham et al. 2010). The biggest review to date on cognitive functioning in euthymic bipolar disorder found significant alterations in psychomotor function assessed with Trail Making Tests (Bourne et al. 2013). However, there has been a debate over which cognitive domain the Trail Making Tests actually assess (Bora and Pantelis 2011; Sanchez-Cubillo et al. 2009). There are strong arguments for inclusion of both the TMT-A and TMT-B in the speed processing domain, which in turn may be considered "psychomotor". However, we speculate that it may be that these tests do not fully capture the extent of psychomotor disturbance since they depend more on fine-motor function rather than

gross movements or emotional motor expressions.

Clinical psychologists assessed psychomotor disturbances in all participants by using five tests in the Trail section of the D-KEFS. Trail test 1 measures visual scanning. In Trail test 2, subjects were instructed to draw a line between numbers in ascending order (1-2-3 ... 25). In Trail test 3, subjects were instructed to draw a line between letters in ascending order (A-B-C ... X). In Trail test 4, subjects connected numbers and letters in an alternating fashion (1-B-2-C ... 12-L). In Trail test 5, subjects were instructed to draw a line across dots. The completion time is a measure of psychomotor speed.

### **3.4.2 Continuous performance test**

The Continuous Performance Test is test of sustained attention and response inhibition (Egeland and Kovalik-Gran 2010). In theory, the test also targets key structures implicated in the brain phenotype of bipolar disorder: the dorsolateral prefrontal cortex, the right inferior frontal gyrus, and the orbitofrontal cortex (Aron et al. 2003; Aron and Poldrack 2005, 2006; Berkman et al. 2009; Chen et al. 2011; Ekman et al. 2010; Frodl et al. 2010). A review also suggests that the cognitive subcomponents in the test can be mapped onto different neurotransmitters modulated by pharmacological treatments for bipolar disorder (Aron and Poldrack 2006). Clinically, the test is sometimes used to measure cognitive and behavioral components in attention-deficit-hyperactivity-disorder. However, the test also identifies alterations in euthymic bipolar disorder patients (Bora et al. 2006). Thus, we chose the test because one of its outcome variables (Overall Hit Reaction Time) relate to information processing in specific neural networks implicated in anatomical studies of bipolar disorder type I.

In Conner's Continuous Performance Test, participants were required to press the space bar whenever any letter except "X" appeared on the computer screen. The interstimulus intervals were 1, 2 and 4 seconds with a display time of 250 milliseconds. The test consisted of 6 blocks and 3 sub-blocks, each containing 20 trials. The presentation order of the different interstimulus intervals varied between blocks. Overall Hit Reaction Time (milliseconds) was calculated from all responses.



## 3.5 Stimulus protocols in functional imaging

### 3.5.1 Experimental paradigms

Model-based experiments are based on the idea that there are task specific brain activations that can be compared between groups (Price and Friston 2002). Most functional imaging experiments accord with this idea. For example, in this thesis we investigate the neural correlates of motor function in bipolar disorder by using different types of experimental paradigms that activates frontal-striatal motor regions in both patients and controls. Several types of designs exist in model-based imaging. In general, these can be grouped into blocked designs, event-related designs and mixed designs (Amaro and Barker 2006).

Blocked designs are based around an on/off structure and subsequent analyses are usually of the subtractive type (Mechelli et al. 2003). For example, any task during on-periods are contrasted with off-, or rest-periods, to provide a map of task specific activations. Blocked designs are preferably used to investigate localization of activation and have been widely used since the infancy of functional imaging. However, blocked designs have drawbacks in that many tasks have an intrinsic chronometry, and the expectation and the maintenance itself of a task induces habituation and unwanted cognitive efforts. The magnitude of BOLD signal change is between 0.5-5% depending on the efficiency of the design.

Event-related designs are commonly used for the estimation of the degree of activation a stimulus elicits (Dale 1999). Stimuli are usually randomly presented and elaborate ways of optimizing presentation order exist (Friston et al. 1999; Wager and Nichols 2003). The task may then be contrasted with null conditions or another stimulus. Event-related designs avoid some of the problems with blocked designs, as randomized presentation order minimizes habituation and expectation. On the other hand, the magnitude of the BOLD signal change is less than in blocked designs which requires more events in order to detect significant activity. The magnitude of BOLD signal change is between 0.1-0.5% depending on the efficiency of the design.

Model-free experiments revolve around the idea that there are localized changes in metabolism or altered functional connectivity between specific networks at different scales over time (Smith 2004). Model-free experiments are exploratory. One example of a model-free experiment is resting-state functional MRI. As the name implies, while in the scanner, subjects rest. These types of studies have gained great interest and have provided insight into the development of the functional organization of the human brain (Biswal et al. 2010; De Luca et al. 2006; Fair et

al. 2008). In particular, the mapping of the so called "default mode network" has been important to the field of mood disorders (Greicius et al. 2007; Kuhn and Gallinat 2011; Sheline et al. 2010). However, there is still ongoing development of the methods used for scanning and analyzing resting-state data (Beckmann et al. 2005; Cole et al. 2010). Different mathematical concepts are used in post-processing (Pereira et al. 2009). Some of the more prevalent ones are: independent component analysis, principal component analysis, and various machine learning methods.

### 3.5.2 Finger tapping

The finger tapping test is measure of motor speed. It can be performed in various ways. Tapping can be guided by an external stimulus or done at the subject's own pace. This is important as self initiated tapping targets different neural networks compared to externally paced tapping (Allison et al. 2000; Joliot et al. 1998; Riecker et al. 2003). A quantitative meta-analysis of various types of finger tapping show how tapping predictably activates the premotor cortex, the primary motor cortex and striatal regions (Witt et al. 2008). Self initiated tapping appears to target anatomical regions that are midline structures associated with effortful control, motor control and volition (Witt et al. 2008). Common outcome measures of the finger tapping test are: time to initiation (response time) and tapping frequency.

The test can be used to distinguish between localized pathologies in neurological disorders (Shimoyama et al. 1990). Motor asymmetry and lateralization can also be assessed (Caligiuri et al. 2004; Lohr and Caligiuri 1995). Previous studies of finger tapping have failed to show any significant differences between depressed patients and controls (Lim et al. 2013). Correlation analyses in a molecular neuroimaging study showed that tapping frequency is significantly associated with striatal dopamine binding capacity (Meyer et al. 2006). However, given the prominent status of psychomotor disturbances in mood disorders, very few studies have been made.

In **paper II**, all participants performed finger tapping while in the MRI-scanner, following instructions on a computer screen shown to them using a mirror. Before the experiment started, participants were shown how to perform finger tapping, defined as a thumb-index finger opposition of the right hand. Participants were asked to tap as quickly as possible. The experiment had an on/off design consisting of 20 s of finger tapping followed by 20 s of rest. During the first second of each on-period the instruction 'tap' was presented. The screen then turned black

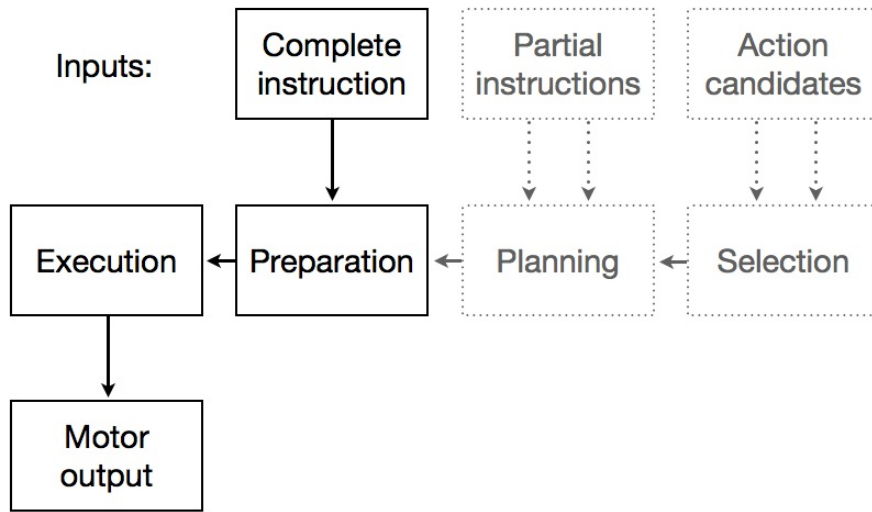


Figure 8: Motor functions tested in voluntary finger tapping

and the task was performed followed by rest. The stimulus cycle was repeated seven times. The total functional scanning time was 280 s.

Two areas of concern in our studies of motor execution (**paper II-III**) is that our results suggest a motor asymmetry, and that we failed to record the tapping frequency of subjects. Since subjects did not do bilateral finger tapping, we cannot infer about either interhemispheric changes that neurophysiological studies have predicted, nor do we have behavioral control for the action that brain activation data predicts.

### 3.5.3 Imaginary finger tapping

Motor imagery is a widely used experimental paradigm that is used to study cognitive aspects of motor control (Jeannerod and Decety 1995). The idea behind motor imagery is that cognitive motor processes such as motor imagery and observation of movements share the same neural representations in the voluntary motor system (Decety 1996; Hanakawa et al. 2008; Lotze and Halsband 2006). Reviews of various types of motor imagery show that motor imagery predictably activates the premotor cortex, the primary motor cortex and striatal regions, usually with more rostral localization of cortical activity on the border of the prefrontal cortex and motor regions (de Lange et al. 2008; Munzert et al. 2009; Munzert and Zentgraf 2009). Thus, motor imagery allows for the study of pre-executive motor functions: planning and preparation of movement (Hoshi and Tanji 2007; Nakayama et al. 2008). To our knowledge there are no functional neuroimaging studies of motor imagery in affective disorder patients. A recent study of mental hand rotation in major depression found that the number of depressive episodes

may increase performance errors in motor imagery tasks (Chen et al. 2013). However, their study does not explicitly target the pre-executive or executive parts in movement production.

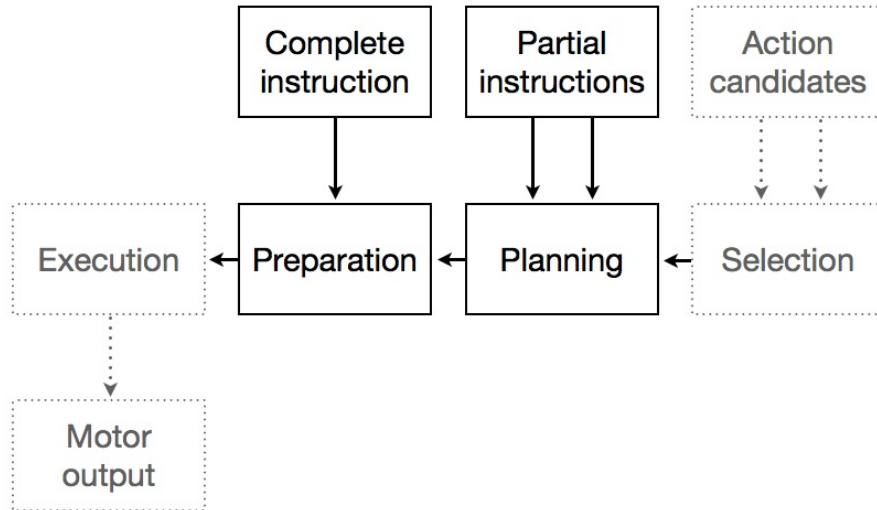


Figure 9: Motor functions in motor imagery of voluntary movement

In **paper III**, all participants did finger tapping with their right hand (motor execution), imagined performing finger tapping (motor imagery) with their right hand, or imagined a familiar place (control for unspecific imagery). While in the MRI scanner they followed instructions on a computer screen shown to them using a mirror. The experiment was an on/off design consisting of 20 s of task performance and 20 s of rest. The total cycle time was 80 s. During the first second of each on-period the task instruction was presented ("rest", "imagine a familiar place", "imagine performing finger tapping" or "perform finger tapping"). The task was performed during the whole duration of the block while the screen turned black. The task order was semi-randomized. The stimulus cycle was repeated 5 times. The total functional scanning time was 400 seconds. Before the experiment started, participants were shown how to perform finger tapping, defined as a thumb-index finger opposition. Participants were asked to tap as quickly as possible.

### 3.6 Image analysis

#### 3.6.1 Statistical parametric mapping

Statistical parametric mapping software was created alongside the technical innovations in MRI and increased availability of scanning facilities. The majority of

neuroimaging results are presented by superimposing statistical results (or statistical parametric maps, "SPMs") on brain images in order to show the location and magnitude of difference. Several analysis softwares exist today. Perhaps the most widely used ones are SPM, AFNI, and FSL. The output from an MRI analysis is usually in the form of SPMs displaying patterns of structural or functional connectivity. This output is a measure of how brain regions covary in time or space.

Effective connectivity measures can also be modeled. These refer to the extent by which different brain regions may influence each other during task performance (Friston et al. 2003; Friston 2011).

Peaks in SPMs are presented in the form of co-ordinate tables that describe the anatomical localization of significant differences. In most cases the inference rely on atlases that contain histological maps, connectivity maps or gross anatomical maps (Devlin and Poldrack 2007; Van Essen and Dierker 2007). Thus, information from brain images can be made in several ways and this clearly affects the inference we can make from them.

### **3.6.2 Vertex-based morphometry**

In **papers IV-V**, we used tools from the FSL (version 5.0.2) software suite to analyze structural T1 weighted images. We used the FIRST tool (version 1.2) for segmentation of the following subcortical brain structures in both hemispheres; caudate nucleus, putamen, pallidum and thalamus (Patenaude et al. 2011). FIRST is an automated, user-independent, model based registration and segmentation tool. Each anatomical structure that FIRST is able to segment has a default setting from 336 manual tracings done in the brain scans of both healthy, neurological and psychiatric subjects. These manual tracings provide a starting point (prior) for the automated segmentation.

The FIRST analysis pipeline involves several parts. The first step involves a two stage affine registration to standard space (Jenkinson and Smith 2001). The first stage is a standard 12 degrees of freedom registration to the standard space template. The second stage applies a 12 degrees of freedom registration using a subcortical mask to exclude voxels outside the subcortical regions of interest. Thus, the initial registration is further refined with respect to subcortical structures. In the second step, the segmentation is done. The segmentation is done using priors from the manually segmented images. The segmentation is based on the intensity in T1-weighted scans. During the third step, boundary application is applied that further refines the delineation of the outlined structures. This

three step procedure computes meshes for structures that represent the surface of these anatomical structures and their volumetric outputs. A mesh represents the same number of vertices in every subject, and each single vertex roughly corresponds to the same point in space across individuals. However, in the case of shape difference this point has a perpendicular displacement with regard to the mean surface of the structure. All types of output images were visually inspected by B.L.

The parameter estimates were calculated for all surface voxels using the general linear model. In our between-group analyses, we added use of neuroleptics and/or lithium as covariates in the regression model in order to remove their potential confounding effects. In our within-group correlation analyses we also added age and gender as covariates. We used the program Randomise (Nichols and Holmes 2002) for non-parametric permutation based inference ( $n = 5000$ ). We corrected for multiple comparisons in all analyses. We tested for local changes in size or shape in any direction using an F-test.

We calculated intracranial volume using the SIENAX tool. Each brain was segmented into three tissue types: grey matter, white matter and cerebrospinal fluid. We defined intracranial volume as the sum of those tissue volumes. We also used SIENAX to calculate a scaling factor for each participant (Smith et al. 2004). This was derived from the difference in size of each individual brain in relation to the MNI152 standard brain. We used this scaling factor to normalize all volumetric measures in each subject. Left ( $n=1$ ) and right ( $n=2$ ) caudate volumetric data from the patient group was excluded due to faulty segmentation of the periventricular surfaces or the head part. Right putamen volumetric data from the control group ( $n=1$ ) was excluded due to faulty segmentation of the whole anatomical structure. This data was also excluded in the shape analysis.

### 3.6.3 Functional imaging

In **papers II-III**, imaging data was analyzed using the FSL 4.1.5 software (FMRIB, Oxford University, UK). Data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98. The timeseries data is very sensitive to head motion because minor displacements of signal may give rise to signal changes far greater than the BOLD signal. In **paper III**, we excluded volumes with sharp spikes of motion using "fsl motion outlier". Each of the identified volumes were added as separate explanatory variables in the regression model at the subject level. The original time-series data was left unaltered. This type of motion correction was not done in **paper II**. In **papers II-III**, we used the MCFLIRT tool,

and each subject's run was corrected for head motion (Jenkinson et al. 2002). To account for time difference in slice acquisition, we performed slice-timing correction using Fourier-space time-series phase-shifting. Because each voxel's intensity over time in the image is analyzed, it is desirable to analyze as few voxels as possible. This is with respect to both computational time, but it also to decrease the need for multiple comparisons correction. Thus, we used the BET tool to remove non-brain tissue (Smith 2002). We smoothed functional data to increase the signal-to-noise ratio without reducing valid activation, compensate for anatomical variability after registration, and to permit application of Gaussian random field theory for the corrected statistical inference. We used a Gaussian kernel set to full-width half-maximum 8 mm. Also, we normalized the grand-mean intensity of the entire four-dimensional dataset by a single multiplicative factor, and filtered out physiological noise (breathing patterns, heartbeats, pulsations in cerebrospinal fluid) using high-pass temporal filtering set to 100 s. Registration from high resolution structural to standard space was done using affine linear registration (Jenkinson and Smith 2001). The parameter estimates were calculated for all brain voxels using the general linear model, and contrast images comparing each condition of interest with the others or rest (i.e., the baseline). Our patient sample had a different gender distribution than our control group. Additionally, neuroleptics may affect psychomotor performance. Therefore we added gender and use of neuroleptics as co-variables in the regression model in order to remove their potential confounding effects. The time-series statistical analysis was carried out with local autocorrelation correction (Woolrich et al. 2001). The higher-level analysis was carried out using FMRIB's Local Analysis of Mixed Effects (FLAME) stage 1 and stage 2 with/without automatic outlier detection (Beckmann et al. 2003; Woolrich et al. 2004; Woolrich 2008; Woolrich et al. 2009). Z (Gaussianised T/F) statistic images in the whole-brain analysis were thresholded using clusters determined by Z 2.3 and a (corrected) cluster significance threshold of  $p=0.05$  (Worsley et al. 1996). In the region-of-interest analysis the statistic images were thresholded using a (corrected) voxel significance threshold of  $p=0.05$  (Worsley et al. 1996). The correction for multiple comparisons was done using Gaussian Random Field theory. Anatomical and histological labels for stereotaxic co-ordinates were retrieved from the probabilistic Harvard-Oxford Cortical Atlas, and the Julich Histological Atlas (Desikan et al. 2006; Eickhoff et al. 2006; Eickhoff et al. 2007).

## 4 Results and discussion

### 4.1 Symptoms of psychomotor disturbances

In **paper I**, we created a clinical self rating scale (Affektiv Skattningsskala, AS-18) that we believed could separate depressive, manic and mixed states. We evaluated the rating scale with reference to established observer based rating scales. Blinded to self ratings, we assessed patients with affective disorder (n=55) that had completed the AS-18. We rated their symptoms and signs of affective disorder using well established observer based rating scales for assessment of depression and mania. We found that the AS-18 correlated well with observer ratings and could be used for self rating of the severity of current affective state. However, what is more important within the framework of this thesis is that in a post-hoc factor analysis of the AS-18 results we found that data separated in to three factors. Two of these were characterized by symptoms of depression or mania. However, the factor analysis also showed a third "retardation" factor. This third factor described 14.9% of the variance in data, and was characterized by having the three highest loadings on "low energy" (0.83), "retardation" (0.79), and "slow thinking" (0.74). Thus, we found that there was possibility of self rating of psychomotor disturbance. We investigated this "retardation" factor further in relation to neural activation during movement in **papers II-III**.

### 4.2 Signs of psychomotor disturbances

In **paper II**, we investigated the neural correlates of psychomotor speed in the depressive phase of bipolar disorder type I. We used fMRI and scanned subjects with current bipolar depression (n=9) and healthy controls (n=12) while they performed self paced finger tapping. Since many of the psychomotor disturbances in bipolar disorder resemble those seen in the neurological movement disorder Parkinson's Disease, we also investigated whether the *functional deafferentiation theory* applies to psychomotor disturbances in bipolar disorder.

Neither our whole-brain analysis, nor our region-of-interest analysis in **paper II** could establish any significant differences between patients and controls. In an exploratory post-hoc analysis where we used a less stringent statistical threshold, we found significant differences between patients and controls in the medial and lateral prefrontal cortex during self paced finger tapping. However, a qualitative description of the activation pattern in **papers II-III** show that fewer voxels were activated in frontal-striatal and thalamic regions that make up the "motor loop".



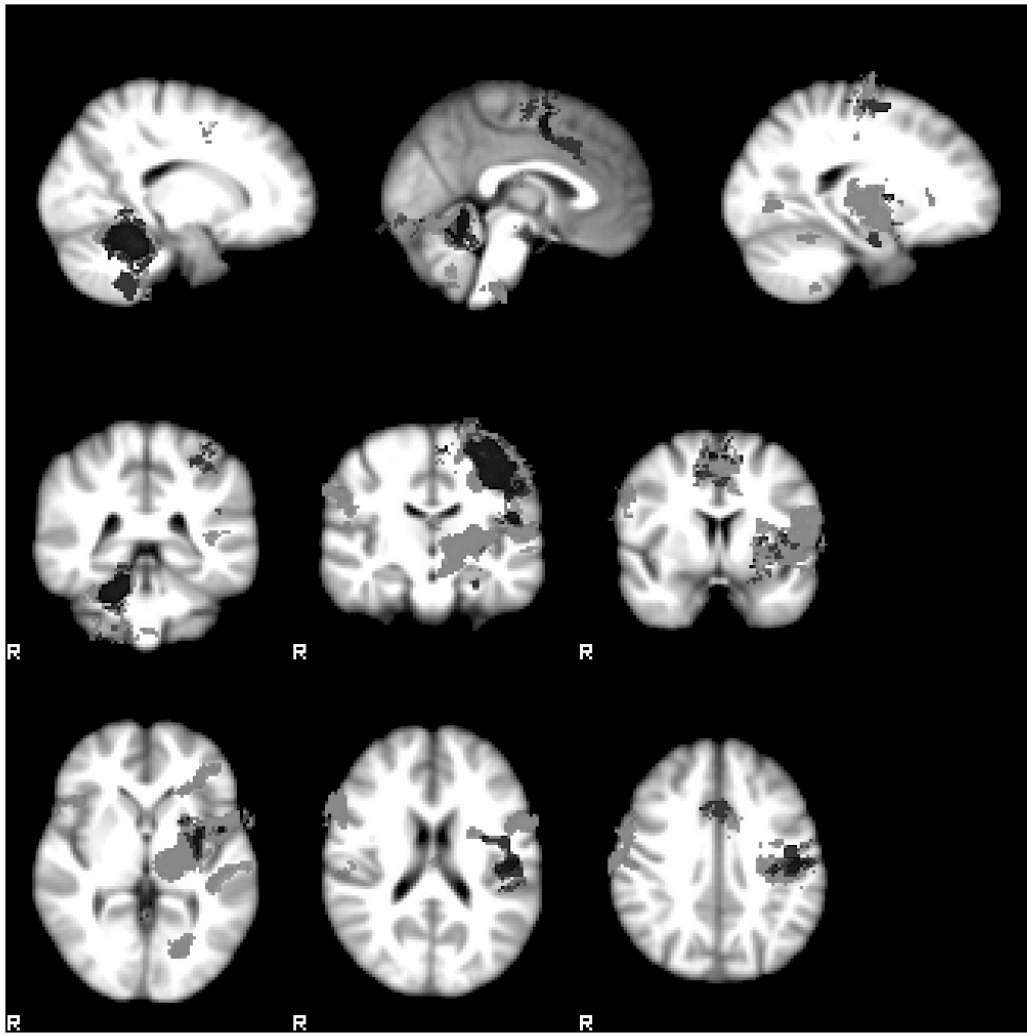


Figure 10: Neural activation patterns during motor execution

It also appears that there was a motor asymmetry with less activation of the contralateral hemisphere during right hand finger tapping. We also found that activations in the patient group appears to involve midline regions responsive to affective modulation of motor behavior. We reason that the lack of significant differences is due to statistical power issues because of the low number of participants. This study show that self paced finger tapping activate the same regions in patients with bipolar depression and healthy controls. This implies that finger tapping may be a good experimental paradigm for assessing changes in frontal-striatal and thalamic regions that mediate movement. We did not find a significant statistical association between either sign-based measures (CORE, CORE-R), or symptom-based measures, of psychomotor disturbances (AS-18, AS-18-R). Furthermore, the *functional deafferentiation theory* did not predict activation patterns in our data.

In **paper III**, we investigated different parts of movement production in the depressive phase of bipolar disorder type I. We used fMRI and scanned subjects with current bipolar depression (n=9) and healthy controls (n=12) while they imagined or executed self paced finger tapping. Our aim was to investigate whether brain regions that mediate selection, planning, and preparation, and execution of movement are activated differently in depressed patients with bipolar disorder type I. We did not find any significant differences in neural activation of frontal-striatal motor areas during motor imagery. Instead we found a significant difference in right posterior medial parieto-occipital regions.

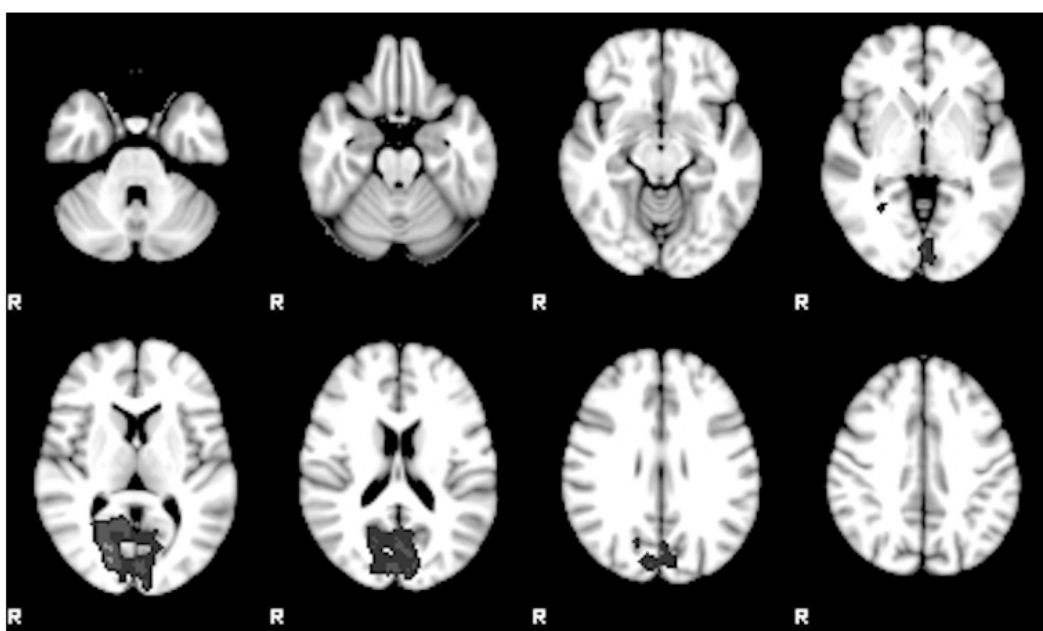


Figure 11: Neural activation patterns during motor imagery (patients-controls)

During motor execution, controls activated more than patients in right lateral occipital cortex, right posterior medial parietal cortex, right parietal lobules, left temporal cortex, right lateral dorsal premotor cortex, left ventral premotor cortex, inferior frontal gyrus bilaterally, left posterior insula, lateral prefrontal cortex bilaterally, and the frontal poles. We also found that patients activated the posterior medial cortex significantly more than controls during all tasks. In **paper III**, we also found statistically significant and negative correlations between sign-based ratings of psychomotor disturbance, and symptom-based ones in medial premotor cortex, primary motor cortex, and lateral ventral premotor cortex. We conclude that many stages in the production of voluntary movement may be altered in bipolar depression.

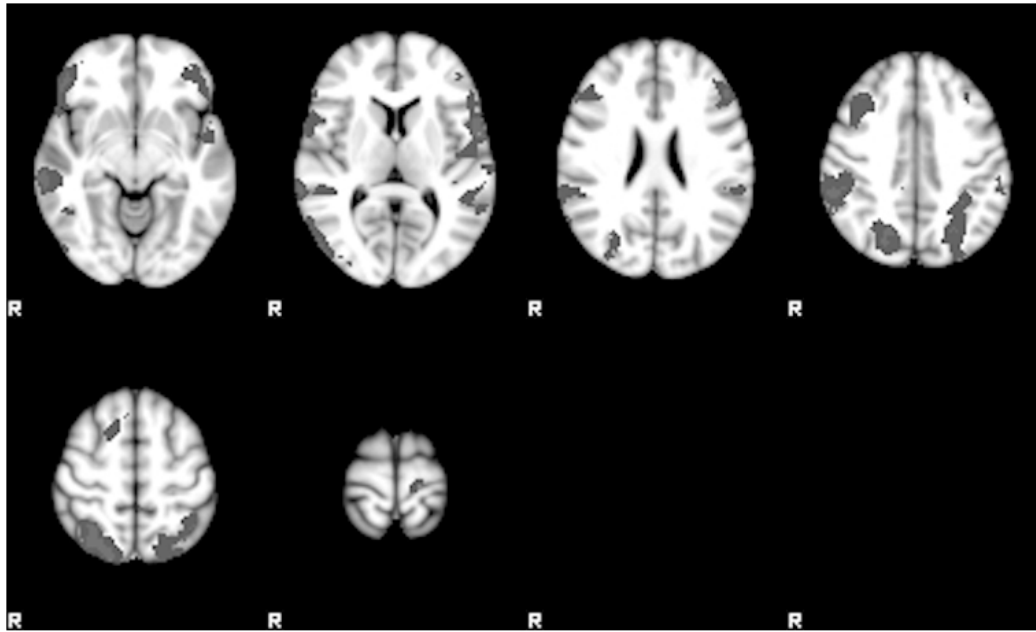


Figure 12: Neural activation patterns during motor execution (controls-patients)

### 4.3 Causes of psychomotor disturbances

In **paper IV**, we hypothesized that test results from the D-KEFS Trails or Conner’s CPT would predict morphometric changes in the basal ganglia or thalamus in euthymic patients with bipolar disorder. We also assessed between-group morphometric differences by investigating both global volumes and local changes in shape. We did not find any significant associations between global volume, local shape, and psychomotor measures. There was no significant between-group difference in any of the psychomotor measures apart from visual scanning abilities. However, we found significant changes in local shape between patient and controls. This change was localized in the right dorsal putamen (figure 13). According to probability based anatomical classification, the connectivity of these regions involve frontal executive regions and motor areas. We conclude that even in the absence of psychomotor disturbances, regions involved psychomotor function are altered, and this may reflect the underlying disease in bipolar disorder.

Psychotic symptoms in bipolar disorder predicts the most severe forms of psychomotor disturbances. Psychomotor impairments is also more pronounced during the euthymic phase of bipolar disorder when psychotic symptoms do not occur. In **paper V**, we therefore chose a subgroup of bipolar disorder patients that had been psychotic. We investigated whether there was an association between the morphology of the basal ganglia and thalamus, and psychomotor function, duration of illness, number of mood episodes, or treatment with neuroleptics. We

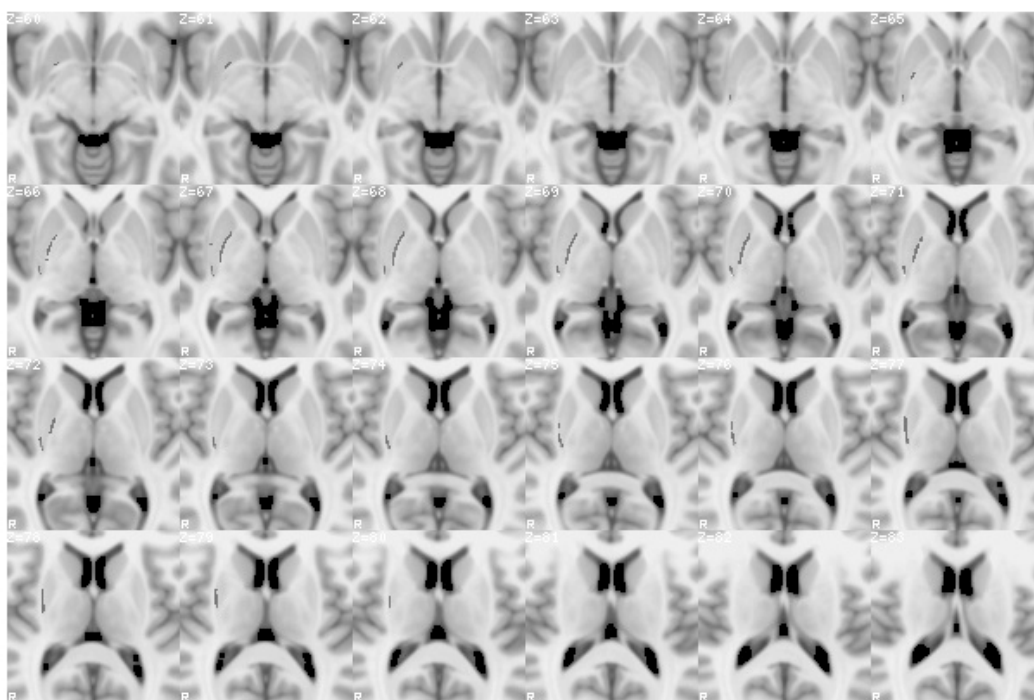


Figure 13: Local shape changes in right dorsal putamen

also investigated between-group differences in relation to controls. We found that there were no significant between-group differences in global volume or shape. We found decreased motor speed in patients compared to controls. However, we found that variables hypothetically associated with disease expression; duration of illness and number of manic episodes, were associated with local shape changes in the right striatum (figure 14) and left putamen and left pallidum (figure 15), respectively. Also, treatment with antipsychotics predicted local shape changes in the right globus pallidus.

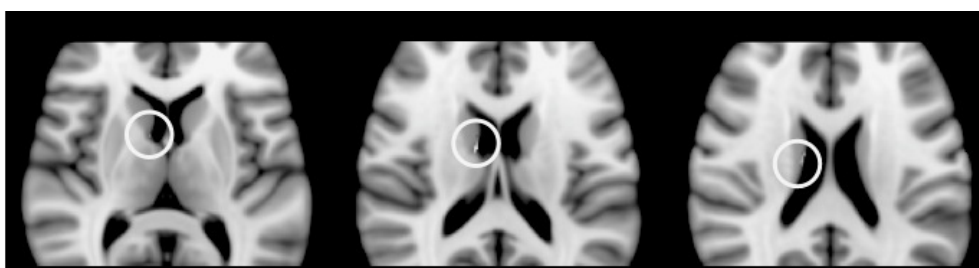


Figure 14: Number of manic episodes and shape changes in the right striatum

We conclude that clinical variables implicated in disease expression were significantly associated with shape changes in the basal ganglia, and that the negative effect of antipsychotics on psychomotor disturbances may be expressed in

the right globus pallidus.

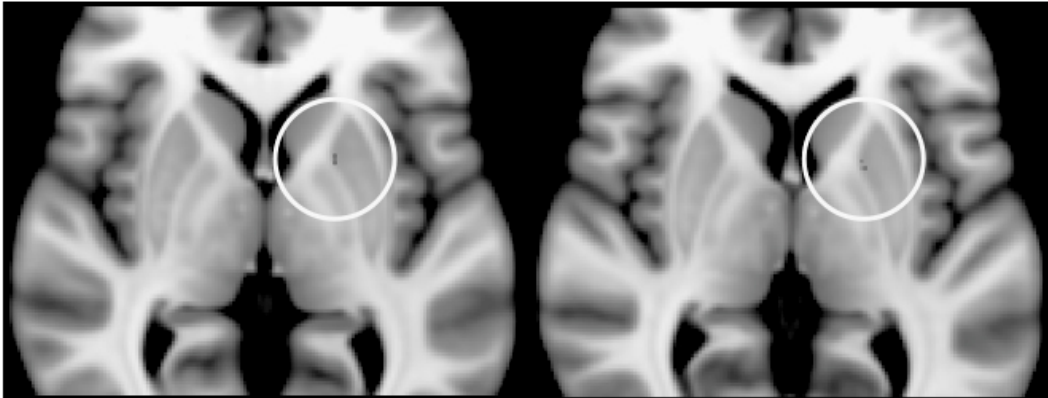


Figure 15: Duration of illness and shape changes in the left putamen and left pallidum

## 4.4 General discussion

In this thesis, we tested the hypothesis that psychomotor disturbances in bipolar disorder are mediated by alterations of frontal-striatal neural networks leading to functional deafferentiation of cortical motor areas and slowed movement. We used clinical ratings, right-hand tests of psychomotor function and brain imaging to formally test this hypothesis. In **paper I**, we found that symptoms of psychomotor disturbances could be self rated. In **paper II**, a formal test of the functional deafferentiation model disproved our hypothesis. In **paper III**, we confirmed decreased neural activation of cortical motor areas in patients with bipolar disorder. In **papers II-III**, there were less activated voxels in the right hemisphere in patients during right-hand motor tasks. In **paper IV**, we found between-group differences in right dorsal putamen shape. In **paper V**, we found significant associations between putative disease expression variables. We also found that treatment with antipsychotics predicts morphometric changes in the basal ganglia.

### 4.4.1 Study design, samples and power

There are limitations to the study designs used in this thesis. **Paper I** is an observational, non-consecutive, case-series study. **Papers II-III** are experimental case-control studies. **Papers IV-V** are observational, naturalistic, cross-sectional and consecutive case-control studies. Case-control studies are usually unrepresentative of the target population, but are more feasible to set up than recruiting

thousands of subjects in order to achieve a sample representative of the population. However, non-longitudinal cross-sectional studies can only determine correlations, and preclude inference about cause-effect relationships, because they cannot determine the temporal sequence between exposure and outcome. Thus, the direction of the correlation in case-control studies cannot normally be determined. There may be exceptions to this rule if pre-existing constitutional factors are prevalent. A naturalistic study makes it difficult to control for factors that might affect outcome measures. Case series studies are hampered by possibility selection bias which limits their generalizability.

There are also limitations in terms of statistical power in **papers II-III**. To have a representative sample of bipolar depression at the Affective Disorders Outpatient Unit in PSSV in these studies, a sample size of 80 patients, at a 95% confidence level with sample error of 5% would be needed. In **papers II-III** there are few patients ( $n=9$ ). This clearly limits the generalizability of our results. However, it is worth considering that the significant between-group differences in **paper III** may imply large effect sizes. Such effects may have important clinical significance. We believe this justifies smaller samples when there is an informed and clinically relevant hypothesis. A recent trend in the neuroimaging community has been to gather large materials or meta-analyze previous studies in order to investigate possible brain phenotypes of psychiatric disorders. However, the success of such investigations depend on the homogeneity of the clinical phenotype under investigation. Thus, minor studies may be of great value in the clinical environment.

#### 4.4.2 Image acquisition

There is an inherent methodological bias in neuroimaging research because of the different types of equipment, scanner settings, and different imaging protocols that are used. No consensus has yet been reached about how to harmonize protocols in order to be able to compare data across sites. It may even be that software and hardware upgrades of equipment at the same site make it difficult to collect longitudinal data. Data may also have been collected with certain brain regions in mind. This is very important in psychiatric studies that use functional imaging using the EPI sequence. They may have to sacrifice good signal quality in certain brain regions in order to optimize them in others, for example in the subgenual cingulate cortex, orbitofrontal cortex or frontal poles. Other acquisition variables that affect data are voxel size, slice positioning, the number of slices, the strength of the magnetic field, field homogeneity, and the scanning

order of different sequences. Thus, a number of acquisition variables may determine successful sampling.

This variability in instrument settings highlights the importance of using meta-analytical techniques when summarizing results to infer about imaging signatures of specific diagnoses. However, other issues like publication bias and the quest for only positive findings complicates these methodological matters further.

#### **4.4.3 Image content**

The clinical utility of imaging in bipolar disorder is a question of the content of information in the image. In the clinical investigation of suspected neurodegenerative disease, a brain scan is praxis. This scan focuses on information about the media temporal cortex so that any thinning of the hippocampus may be identified as an indication of degenerative disease. A similar praxis may be in the future of clinical investigation of bipolar disorder, perhaps focused on the basal ganglia, the anterior cingulate cortex, medial temporal cortex, and prefrontal cortex. Neuropathological studies have shown decreased volume of basal ganglia structures in bipolar disorder (Baumann et al. 1999; Biellau et al. 2005).

Structural alterations in well defined brain structures as seen in imaging data can emerge from different types of pathophysiological processes. In the context of our findings of structural change there are several other studies that suggest the meaning of the changes in shape and volume that we observe. In a multimodal imaging study on methamphetamine abuse, known to affect striatal regions, the authors suggested that changes in striatal volume could be linked to water content, or a tertiary increase in cell volume because of inflammation, secondary to changes in blood-barrier integrity because matrix degrading proteases (Chang et al. 2007). A study of pharmacological effects on striatal morphology showed that exposure to the dopamine blocking agent haloperidol led to localized changes in striatal volume, which implies that receptor density may contribute to volumetric change (Tost et al. 2010). As previously mentioned, there are studies that show how inflammatory markers can modulate dopaminergic tone in the basal ganglia and ascending systems, in turn leading to slowed movement, alterations in mood and reward incentives (Brydon et al. 2008; Felger and Miller 2012; Felger et al. 2013; Harrison et al. 2009). Hypothetically, inflammatory processes may lead to covarying alterations of basal ganglia volume, dopaminergic tone, and psychomotor slowing.

#### 4.4.4 Image analysis

An image analysis involves arbitrary decisions that may change the outcome of the results. Some of the most important of these decisions are not independent from each other. Informed decisions are a prerequisite in order to get valid results. Some of the most common parameters that can be adjusted are filter parameters that remove physiological noise, spatial smoothing that improves signal-to-noise ratio in data, and the choice of thresholding technique and alpha-level to avoid statistical errors. Type I and type II errors are a concern in MRI image analysis. Type I refers to false positives, and type II to false negatives. There has been a strong bias in the neuroimaging community towards addressing primarily type I error. Type II error is just as much of a concern, especially with the advent of more quantitative meta-analytical techniques.

In most neuroimaging datasets a univariate statistical approach is used to analyze images. A typical MRI volume usually contains thousands of voxels. A test of 100000 voxels with an alpha level of  $p=0.001$  would result in 100 false positives. Thus, each voxel tested for significance demands correction for multiple comparisons. Traditional Bonferroni correction has been found to be too conservative for MRI scans, which come with features that require other methods to be optimal. A voxel is the "atomic" component in an image. However, voxels are not independent of each other in MRI scans. In structural images, neighboring voxels may share information due to partial volume effects and head movement. In functional images, the hemodynamic response used to model the BOLD signal is dispersed in time over several scan volumes, and effects of head movement and anatomical normalization also contribute further. Also, during pre-processing, smoothing procedures decrease the independence between voxels. "Activated" voxels also tend to cluster. Therefore so called "topological" methods are used for controlling for statistical error (Worsley 1996). A reasonable approach for controlling type I error is a two-way procedure where a cluster-forming threshold (in most of our studies  $p=0.005$ ) determines which voxels to test at  $p=0.05$ . However, the measures taken to control for false positives are at the expense of type II error. This means that subtle effects may be hard to detect, and that there is a bias towards large effects, and these are typically seen in particular regions where the BOLD signal is strong, and many times not in regions of interest to psychiatry. Meta-analyses have the power to detect smaller effects in individual studies and compensate for "low power to detect subtle but real effects" (Lieberman and Cunningham 2009). Given the potential bias and problems that exist in harmonizing protocols this becomes problematic if we wish to infer from imaging data.



#### **4.4.5 Forward and reverse inference**

Neuroimaging provides the means for researchers to infer about the role of certain brain regions in clinical domains such as emotion, sensory perception, motivation, cognition, or movement. The conclusions we draw from neuroimaging data can generally be inferred in two different ways: through forward inference or reversed inference. Forward inference refers to mapping of the neural correlates of certain cognitive functions. However, forward inferences are only as good as the theories to which they pertain, and thus highlight the importance of a continuous struggle to delineate clinically meaningful subtypes of bipolar disorder. This is very much the ongoing practice in the neuroimaging community where we infer about the brain phenotype in bipolar disorder by using DSM. Reverse inference refers to the inference about cognitive functions from looking at brain features. In most cases it is preferable to avoid reverse inference in order to gain insight into the specifics of cognitive functions. However, in research on bipolar disorder, reverse inference may also be useful in discovering intermediary phenotypes that can improve clinical outcomes.

#### **4.4.6 Challenging current diagnoses**

During the last decade, the idea of endophenotypes or intermediary phenotypes that bridge genotypic expression and clinical phenotype has been used as a research strategy to elucidate the pathophysiology of affective disorders. However, the starting point for selection in most studies relies on a nosology that many researchers find unsatisfactory. There are few imaging studies that have investigated subtypes of depression in relation to the number of studies that been published on major depression. While some studies acknowledge the familial component in patient selection to "homogenize" the sample, many studies characterize the effect of confounding covariates like gender, age, or global level of functioning. While it is important to control for these factors, they remain unspecific with regard to the illness, and provide limited contributions to further development of psychiatric nosology. Thus, current diagnoses are usually not challenged.

In his seminal work on the distinction between bipolar and unipolar illness, Carlo Perris investigated 138 bipolar patients and 139 unipolar subjects with affective disorder during 13 years in Sundsvall, Sweden (Perris 1966). Together with the work of Jules Angst in Switzerland, this work laid down the foundation of modern nosology in affective disorders. Yet, there is no imaging study to date

that has validated this dichotomy in spite of the available number of subjects and retrospective clinical data.

#### **4.4.7 A putative model for psychomotor disturbances in bipolar disorder**

Based on the results in this thesis, we speculate the following: the left-lateralized motor asymmetry during movement of the contralateral hand in the patient group in **papers II-III**, the right-side morphometric alterations in right dorsal putamen in **paper IV**, the associations between disease expression variables and right-side morphometric alterations in basal ganglia in **paper V**, implicate the possibility of right-side functional deafferentation. We recognize the possibility that the right hemisphere should be investigated further in relation to psychomotor function in bipolar disorder.

Given the importance of dopamine in bipolar disorder, subcortical motor control and cortical cognitive functions, we speculate that there may be a dopaminergic model useful for understanding psychomotor disturbances in bipolar disorder. In **paper II**, we found an increased activation in ventromedial prefrontal regions that signal to brainstem dopaminergic nuclei. These nuclei have diverging dopamine projections to key regions in the frontal-striatal networks. It may be that functional alterations in these dopaminergic brainstem nuclei could lead to changes in the target regions of nigrostriatal and mesocortical dopamine pathways, thus leading to changes in the control, preparation and execution of movement in bipolar disorder.

#### **4.4.8 Future perspectives**

Perhaps one of the key problems in the imaging literature is how few longitudinal studies there are that try to map the expression of a natural course of bipolar disorder. Given the substantial individual burden and societal cost and of bipolar disorder, it is also surprising how few studies there are on bipolar depression which is the predominant pathological state in bipolar disorder over time.

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