CHAPTER 1

General Introduction
Most of you have probably had the experience of walking down the street in a city and seeing a person you thought was acting oddly. They may have been dressed in an unusual way, perhaps disheveled or wearing an unusual collection of clothes, makeup, or jewelry that did not seem to fit any particular group or subculture. They may have been talking to themselves or yelling at someone you could not see. If you tried to speak to them, they may have been difficult to follow or understand, or they may have acted paranoid or started telling a bizarre story about the people who were plotting against them. If so, chances are that you have encountered an individual with schizophrenia or another type of psychotic disorder.

— Quote from Barch, 2019.

1.1 Schizophrenia and impaired insight

Barch (2019) described an individual who may have showed paranoid behavior and incoherent speech, making it difficult to follow or understand that person. That individual might be diagnosed with schizophrenia or another psychotic disorder. Schizophrenia is a heterogeneous disease that affects approximately 1% of the general population at some point in their lives (Lewis and Lieberman, 2000; van Os and Kapur, 2009), making it a major concern for public health. The disorder is characterized by positive symptoms such as delusions, hallucinations and disorganized speech, and negative symptoms such as affective flattening, reduced amount of speech and reduced motivation. Despite the clinical significance of psychotic disorders, its exact etiology remains unclear. Studies indicate an interaction of several neurotransmitters (i.e., dopamine and glutamate), genetic, environmental and neurodevelopmental factors as probable cause (Lieberman and First, 2018), which are all factors that may interfere with normal brain functioning.

Reconsidering that individual that you encountered on the street that was acting oddly; it is clear to you and others that their behavior is unusual. Nevertheless, the majority of patients with schizophrenia is not aware of their own symptoms and illness (Dam, 2006). This phenomenon is called impaired clinical insight. It affects 50-80% of patients with schizophrenia and it is defined as an impairment in (i) awareness of illness, (ii) attribution of symptoms to the illness, and (iii) realizing need for treatment (Amador et al., 1993). In this dissertation, the terms clinical insight and insight are used interchangeably. Impaired insight is associated with numerous negative factors such as poor treatment adherence (Lysaker et al., 2018), but also reduced use of psychological coping mechanisms (Donohoe et al., 2004; Lysaker et al., 2003) and poorer general functioning (Pini et al., 2001). In general, the majority of patients with
schizophrenia (up to 70%) can achieve remission but poor treatment adherence increases the risk of relapse (Robinson et al., 1999; van Os and Kapur, 2009). It has been shown that patients with impaired insight have poorer prognosis (Lincoln et al., 2007) and outcome in general (Schwartz et al., 1997). Moreover, current treatment options have limited success in improvement of insight (Pijnenborg et al., 2013b). Clinical trials that specifically focused on the improvement of insight showed improved insight but still left it unclear which components of these treatments led to the improvement (Guo et al., 2010; Lalova et al., 2013; Pijnenborg et al., 2019). There is a growing need for clarification of the exact etiology of impaired insight to also get a better understanding of how treatment and prognosis can be improved.

1.2 Theories of impaired insight

Several theories have been suggested to explain the etiology of impaired insight in schizophrenia, suggesting contributions of brain abnormalities, neurocognition (i.e., executive functioning, cognitive flexibility, set-shifting and self-monitoring), social cognition (i.e., self-reflectiveness and perspective taking), metacognition (i.e. “thinking about one’s thinking”), social and personal factors (i.e., stigma and personality), symptomatology and defensive denial (Vohs et al., 2016). However, a monocausal explanation of impaired insight in psychotic disorders appears unlikely, given the small to modest effect sizes (of associations between insight and these factors) that are found and the variation between patients. Therefore, in more recent years, the field is shifting towards approaching insight with less simplified, multicausal integrated explanations (Vohs et al., 2016).

1.3 Measures of insight

Measures for the assessment of insight vary from single items (that can be part of a larger psychiatric interview) to detailed multi-item measures, and from self-report questionnaires to clinician-/researcher-rated (semi-)structured interviews. Both last-mentioned types of measures have their advantages as self-report scales avoid researcher/clinician bias although it can also be argued that self-report scores of patients with poorer insight might be even more biased. In this thesis, insight was measured with item 12 of the general psychopathology subscale of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) (Chapters 3 and 5), the Birchwood Insight Scale (BIS) (Birchwood et al., 1994) (Chapter 3), and the Schedule for the Assessment of Insight – Expanded (SAI-E) (David, 1990) (Chapters 4 and 5). The PANSS G12 item is
one of the most frequently used measures of clinical insight (Shad, Tamminga, Cullum, Haas, & Keshavan, 2006). It is a single-item measure based on a semi-structured interview, and correlations with other measures of clinical insight, such as the SAI-E, have shown to be strong (Sanz et al., 1998). For our studies, two trained interviewers obtained a consensus score. The Birchwood Insight Scale (BIS) is an 8-item self-rating questionnaire, consisting of three subscales measuring the three dimensions of clinical insight: awareness of illness, relabeling of symptoms and recognition of the need for treatment. The Schedule for the Assessment of Insight – Expanded (SAI-E) also measures these three subdimensions; it is a 12-item clinician/researcher-reported semi-structured interview. Several studies have confirmed these subscales with factor analyses (Dantas and Banzato, 2007; David et al., 2003; Konstantakopoulos et al., 2013).

1.4 Insight in the brain

To get a better understanding of why there is so much interindividual variability in insight, it is essential to understand the neural mechanisms underlying impaired insight. A better understanding of the neural basis of impaired insight may also help in finding better treatment options to improve it.

1.4.1 Brain structure

Studies have shown structural abnormalities in schizophrenia that are present from the early onset of illness, such as reduced gray matter volume and disrupted white matter integrity (Karlsgodt et al., 2010). Reduced gray matter volume of the medial temporal, superior temporal, and prefrontal areas was found most consistently across studies (Karlsgodt et al., 2010). Within the population of patients with a psychotic disorder, numerous studies investigated the relationship between insight and global brain volume, volume of specific regions of interest (ROIs) or voxel-based morphometry (VBM).

Brain structure can be investigated with:

- Morphometry: gray matter volume of the whole brain or of certain regions of interest (ROIs).
- Voxel-based morphometry (VBM): quantifies gray matter volume and tissue concentration per voxel. Gray matter volume is a function of cortical surface area and cortical thickness.
- Cortical thickness: quantifies thickness of the cortex.
- Diffusion tensor imaging (DTI): mapping of white matter tracts.
With regard to studies examining global brain volume, several studies found significant associations between insight and total brain volume (Flashman et al., 2000; Larøi et al., 2000; McEvoy et al., 2006; Takai et al., 1992) \(n=30\), \(n=21\), \(n=226\), \(n=57\), respectively), or more specifically, with total gray matter volume (Cooke et al., 2008; McEvoy et al., 2006) \(n=52\) and \(n=226\), respectively) or total white matter volume (Gerretsen et al., 2013; McEvoy et al., 2006) \(n=52\), \(n=226\), respectively). In contrast, six studies did not find significant associations between insight and global brain volume (Bassitt et al., 2007; David et al., 1995; Morgan et al., 2010; Palaniyappan et al., 2011; Rossell et al., 2003; Sapara et al., 2007), although some of these studies did find associations with regional brain volume (Morgan et al., 2010; Palaniyappan et al., 2011; Sapara et al., 2007). Some of these studies included relatively large samples (i.e., \(n=50\), \(n=128\), \(n=82\), \(n=57\), \(n=71\), \(n=28\), respectively), raising the question whether studies finding positive associations between global brain volume and insight represent false positive findings. The considerable variability in age, illness duration, sample sizes, statistical methods, and measures of insight between studies makes them difficult to compare.

Studies on the association between insight and brain volume or cortical thickness that were either voxel-based or focused on specific regions of interest (ROIs) found associations between insight and areas distributed across the brain, predominantly in frontal but also in other areas (see Figure 1) (Asmal et al., 2018; Bassitt et al., 2007; Bergé et al., 2011; Cooke et al., 2008; Emami et al., 2016; Flashman et al., 2001; Gerretsen et al., 2013; Ha et al., 2004; McFarland et al., 2013; Palaniyappan et al., 2011; Sapara et al., 2016, 2007; Shad et al., 2006a, 2004; Tordesillas-Gutierrez et al., 2018). Some studies did not find significant associations between brain structure and insight, however (Béland et al., 2019; Buchy et al., 2017; Gerretsen et al., 2015, 2013; Morgan et al., 2010; Raj et al., 2012). Studies using other MRI-methodologies found associations between insight and abnormalities of cortical surface area of the right posterior insula (Palaniyappan et al., 2011), perfusion of the bilateral precuneus as measured with positron emission tomography (PET) (Faget-Agius et al., 2012), and hemispheric asymmetry of anteroinferior temporal lobe volume (Gerretsen et al., 2013). Thus, structural abnormalities of regions distributed across the brain have been related to insight in psychotic disorders (see Figure 1). Several studies have also related insight to brain functioning in psychotic disorders, as the relationship between brain structure and function appears complex and brain structure cannot fully explain functional dynamics (Batista-García-Ramó and Fernández-Verdecia, 2018). Brain function can be seen as a link between brain structure and patients’ clinical manifestations.
1.4.2 Brain function

Various studies investigated the relationship between insight and brain functioning with functional magnetic resonance imaging (fMRI). These studies also found that areas distributed across the brain are associated with insight during several fMRI-tasks (see Figure 2) [Bedford et al., 2012; Gerretsen et al., 2015; Sapara et al., 2014; Sapara et al., 2015; Shad & Keshavan, 2015; van der Meer et al., 2013]. Just a few regions were consistently found across several studies, however. The inferior parietal lobule and precuneus were found in several studies, and the inferior frontal gyrus and insula even more frequently. Some studies found increased activation in patients with impaired insight, while others found decreased activation. This may be explained by compensation or less efficient use of neural resources, respectively.

**Figure 1:** Schematic display of medial and lateral views of areas that showed an association between brain structure and clinical insight.

NB: Regions implicated in more than two (* in five or more) separate studies: the superior frontal gyrus, middle frontal gyrus*, inferior frontal gyrus*, insula, superior temporal gyrus*, middle temporal gyrus, inferior temporal gyrus*, cerebellum, dorsomedial prefrontal cortex, anterior cingulate cortex, ventromedial prefrontal cortex, parahippocampal gyrus and cuneus.

Functional magnetic resonance imaging (fMRI): measures brain activity indirectly with the blood-oxygen-level-dependent response, which indicates cerebral blood flow to activated brain areas.

- Task-based fMRI studies: in these studies, brain activation during different tasks can be examined. An estimation of brain activation during a certain task can be obtained by comparing brain activation during different conditions.
1.4.3 Brain connectivity and networks

So far, researchers have failed to establish a clear structural and functional substrate of insight by pinpointing specific isolated brain areas. Instead, structural and functional abnormalities have been found in a distributed network of brain regions, implying connectivity abnormalities in patients with poorer insight. Several studies investigated insight and structural or functional connectivity thus far.

Structural and functional connectivity:

- Functional (fMRI) connectivity studies: connectivity between brain regions is calculated with correlations (or similar measures) between brain activation of these regions.
- Structural connectivity studies: fractional anisotropy (FA), as measured with diffusion tensor imaging (DTI), is seen as a marker of white matter integrity.

Three studies investigated the relationship between insight and structural connectivity (as measured with diffusion tensor imaging; DTI), while four studies focused on insight and functional connectivity (as measured with resting state fMRI) in patients with psychotic disorders. Fractional anisotropy (FA) is a common measure in DTI that is seen as a marker of white matter integrity. One study found significant positive associations between awareness of symptoms as well as attribution of symptoms and fractional anisotropy of widespread areas across the brain (Antonius et al., 2011),
while another study found a positive association between insight and fractional anisotropy in fronto-occipital, cingulate, cingulate hippocampus, uncinate, and anterior corona radiata white matter tracts (Asmal et al., 2017). A last study found a specific negative relationship between insight and fractional anisotropy in the middle frontal gyrus (Ćurčić-Blake et al., 2015). In order to link insight to brain functioning, studies on functional connectivity of the brain are crucial.

Resting state functional connectivity studies on insight often implicate abnormalities of the Default Mode Network (DMN). These studies in patients with schizophrenia specifically found that poorer insight was related to lower connectivity of the anterior cingulate cortex to the rest of the anterior DMN, and lower connectivity of the precuneus within the posterior DMN (Liemburg et al., 2012), as well as higher connectivity in the DMN with the left angular gyrus (Gerretsen et al., 2014). A study on individuals at ultra-high risk of developing psychosis also found that insight was related to higher DMN connectivity between posterior cingulate cortex/precuneus and ventromedial prefrontal cortex (Clark et al., 2018). Abnormalities of other networks were also found during resting state, namely higher connectivity in the salience network with the left insula (Gerretsen et al., 2014) and lower connectivity between right posterior insula and pre- and postcentral gyri (Chen et al., 2016). Another study in patients with schizophrenia found that poorer insight was associated with higher effective connectivity from the inferior parietal lobule, posterior cingulate cortex and dorsomedial prefrontal cortex towards the ventromedial prefrontal cortex, as well as with higher effective connectivity from the inferior parietal lobule towards the posterior cingulate cortex and dorsomedial prefrontal cortex during a self-reflection task (Ćurčić-Blake et al., 2015). The authors also found lower effective connectivity from the ventromedial prefrontal cortex to the inferior parietal lobule during this task. These studies highlight the importance of studying dysconnectivity in patients with poorer insight. While diffusion-weighted imaging studies do not show a clear neural substrate of impaired insight, functional connectivity studies implicate importance of the DMN.

### 1.5 Moving focus from clinical insight to cognitive insight

The goal in this thesis is to extend knowledge on the neural basis of impaired clinical insight. However, patients might admit to being ill and realizing that they need treatment without full understanding of their illness and its consequences. It might be just a reflection of what was learned during psychoeducation or repetition of information received from their psychiatrist instead of a real understanding of their illness and
integration of their illness in their self-concept. A change in underlying beliefs might be required for a change in affect and behavior. Therefore, in this thesis, we will also extensively study a second type of insight, called cognitive insight. Cognitive insight is defined as the ability to reflect upon oneself and to not be overly certain of one’s own beliefs (Beck et al., 2004). Cognitive insight involves patients’ attributive metacognitive ability (i.e. “thinking about one’s thinking” or awareness and understanding of one’s own thought processes), and directly measures distorted thinking styles. Therefore, it is of great clinical significance, as these cognitive styles might be targeted in treatment.

Cognitive insight is measured with the Beck Cognitive Insight Scale (BCIS), which consists of two subscales: self-reflectiveness (9 items) and self-certainty (6 items) (Beck et al., 2004). Good cognitive insight is reflected by a high composite index score (i.e. self-reflectiveness minus self-certainty), a high self-reflectiveness score and a low self-certainty score. These two factors have been confirmed in quite a few populations (Buchy et al., 2012b; Favrod et al., 2008; Gutiérrez-Zotes et al., 2012; Kao and Liu, 2010; Uchida et al., 2009). Processes that might underlie cognitive insight are self-monitoring, and processing and regulation of one’s own state and performance. Cognitive insight also requires abilities necessary for integrating new information into one’s own thought processes and re-evaluating one’s own beliefs. As such, it is assumed to reflect higher-order (meta-)cognitive functioning, to a stronger extent than may be the case for clinical insight.

Cognitive insight reflects one’s own judgements about the self but one can argue whether self-judgements of individuals with poor cognitive insight are correct, given that no measure of behavior is included. However, in the initial study describing the BCIS, the investigators observed significant correlations in the expected direction between the BCIS composite index score and being aware of a mental disorder as measured with the Scale to Assess Unawareness of Mental Disorder (SUMD; rated by a clinician) (Amador et al., 1993), between the self-reflectiveness subscale scores and being aware of delusions as measured with the SUMD, and between change in BCIS-scores and change in positive and negative symptoms (Beck et al., 2004). Several other studies from other research groups have also shown reliability and validity of the BCIS, and that it can distinguish patients with psychosis from patients without psychosis and healthy individuals (Riggs et al., 2012). Additionally, several studies showed increased self-certainty (i.e. poorer cognitive insight) in individuals with at-risk mental state (Uchida et al., 2014) or at clinical high risk for psychosis (Kimhy et al., 2014). Thus, altogether, results of previous studies suggest that individuals can objectively rate their experiences (Riggs et al., 2012).
1.5.1 Brain structure
Studies in patients with a psychotic disorder related cognitive insight to brain structure by either examining brain volume of certain regions of interest or per voxel. Two studies examining the association between cognitive insight and gray matter volume of hippocampal areas found relations between hippocampal volume and cognitive insight or self-certainty specifically (Buchy et al., 2010; Orfei et al., 2017). No significant associations were found for self-reflectiveness (Buchy et al., 2010; Orfei et al., 2017). Another study did not find any significant associations between self-reflectiveness or self-certainty and hippocampal volumes (Buchy et al., 2016). The last study included only 15 patients, however, while Buchy et al. (2010) and Orfei et al. (2017) included 61 and 45 patients, respectively. Whole brain VBM or cortical thickness studies found an association between self-reflectiveness and the right ventrolateral prefrontal cortex (Buchy et al., 2016; Orfei et al., 2013), and between self-reflectiveness and widespread areas across the brain (Buchy et al., 2016). For self-certainty, one study did not find significant associations (Orfei et al., 2013), while the other found involvement of the ventrolateral prefrontal cortex and other widespread areas across the brain again (Buchy et al., 2016).

**Figure 3:** Schematic display of medial and lateral views of areas that showed an association between brain structure and cognitive insight.
NB: only one region (i.e. the hippocampus) was implicated in more than 2 studies.

1.5.2 Brain function
fMRI-studies on cognitive insight found significant associations between the composite index score and activation of the left dorsolateral prefrontal cortex, left parahippocampal gyrus, right posterior cingulate cortex, and right inferior parietal lobule (during a reality evaluation and recognition task) (Lee et al., 2015). With
regard to self-reflectiveness, significant associations were found with activation of the ventromedial prefrontal cortex (during a self-reflection task) (van der Meer et al., 2013), bilateral ventrolateral prefrontal cortex (during an external source memory task) (Buchy et al., 2015) and left parahippocampal gyrus and right inferior parietal lobule (during a reality evaluation and recognition task) (Lee et al., 2015). On the other hand, no significant associations were found between the composite index score and brain activation during a self-reflection task (van der Meer et al., 2013), or between self-certainty scores and brain activation during a self-reflection task (van der Meer et al., 2013) or external source memory task (Buchy et al., 2015). Lastly, a PET-study on cognitive insight found a negative association with perfusion in right fusiform gyrus, left precuneus, bilateral superior temporal gyrus and bilateral insula, and a positive association with perfusion of left orbito-frontal gyrus (Caletti et al., 2017).

**Figure 4:** Schematic display of medial and lateral views of areas that showed an association between brain function and cognitive insight. NB: only one region (i.e. the inferior frontal gyrus) was implicated in more than two studies.

One study on cognitive insight in healthy individuals found a positive association between self-reflectiveness and activation of the right ventrolateral prefrontal cortex, and between self-certainty and midbrain activation during an external source memory task (Buchy et al., 2014). Taken together, the number of studies conducted on the neural correlates of cognitive insight is too low to draw strong conclusions. Nonetheless, the picture that emerges is that quite some regions across the brain have been associated with cognitive insight.
1.5.3 Brain connectivity and networks

Just a few studies investigated structural and functional connectivity in relation to cognitive insight thus far. Structural connectivity studies on cognitive insight were based on DTI-data or structural covariance of cortical thickness. Three DTI studies did not find significant associations between fractional anisotropy and cognitive insight [Buchy et al., 2016; Ćurčić-Blake et al., 2015; Orfei et al., 2013]. A study describing a seed-based analysis of structural covariance with a seed in the ventrolateral prefrontal cortex found a significant positive association between self-certainty and covariance of the ventrolateral prefrontal cortex, on the one hand, and the right superior frontal gyrus (dorsomedial frontal gyrus) and right pars triangularis on the other hand (Kuang et al., 2017). No significant associations with self-reflectiveness were found (Kuang et al., 2017). Only one study examined resting state functional connectivity thus far; a significant negative association was reported between self-certainty and connectivity in the dorsal attention network with the left inferior frontal cortex (Gerretsen et al., 2014).

1.6 Moving towards a different approach

In this thesis, we will focus on brain connectivity. The communication and integration of information between distant brain areas reveals important information of considerable added value in addition to structure or activation of specific regions. After all, it is the parallelly distributed patterns of activation of brain networks (i.e., neural synchrony) that underpins mental abilities. Studies described in this thesis will add to the literature with regard to three main aspects: we will (1) not only focus on specific regions or networks but also on global brain functioning, (2) examine dynamic functional connectivity instead of static functional connectivity, and (3) we will take a multimodal approach examining insight with data from different MRI-modalities. Previous studies were all focused on specific networks and connectivity within these networks. Healthy brain functioning, however, requires a balance between segregation (i.e., segregation of the brain into subnetworks that are specialized in specific functions) and integration (i.e., good communication within and between subnetworks) in order to allow efficient information transfer between subnetworks and across the brain. Therefore, in this dissertation, we will not only focus on specific regions or networks but we will also examine global brain functioning based on structural (gray matter and DTI) and functional (resting state fMRI) connectomes. Additionally, all previous studies examined static functional connectivity (i.e., mean connectivity over a scan session) which does not provide information on fluctuations of functional networks over time. It has been increasingly suggested that transitions between neurocognitive states are important for neurocognitive
processes. Therefore, in this thesis, we will examine dynamic functional connectivity to get more insight into separate mental states during resting state and how they relate to insight. And last, most—but not all—earlier studies did not examine insight with data from different MRI-modalities, while combining imaging techniques allows us to concurrently investigate special mechanisms in one individual. Therefore, in order to get a more comprehensive view of brain abnormalities in poor insight, we will examine brain connectivity with data from different MRI-modalities, namely Proton Magnetic Resonance Spectroscopy (1H-MRS), task-based fMRI, resting state fMRI, brain volume and DTI. In this manner, information obtained with functional MRI can provide a link between brain structure (as measured with 1H-MRS, brain volume and DTI) and clinical manifestations of impaired insight.

1.7 Aim and outline of chapters

The main aim of this thesis is to increase knowledge on the neural substrates of clinical and cognitive insight. In different chapters, we will investigate insight with distinct MRI-modalities and methodologies that give complementary information on how brain connectivity is related to insight to get a more comprehensive view of the neural substrate of insight. We will take a hypothesis-driven approach focusing on specific regions or networks in chapters 3-4, while taking a whole brain data-driven approach in chapters 5-6. The following objectives will be investigated in the consecutive chapters: (1) functional and structural brain correlates of insight by performing a systematic review and meta-analysis on all neuroimaging studies conducted on clinical and cognitive insight in patients with a psychotic disorder (chapter 2), (2) how clinical insight relates to levels of a marker of neuronal integrity in the white matter of the prefrontal cortex in patients with a psychotic disorder (chapter 3), (3) how clinical and cognitive insight relate to brain activation and connectivity during an emotion regulation task in patients with schizophrenia (chapter 4), (4) how variability in gray matter connectome characteristics relate to clinical and cognitive insight in patients with a psychotic disorder (chapter 5), (5) how dynamic functional connectivity during resting state relates to cognitive insight in healthy individuals (chapter 6), and (6) how variability in gray matter and DTI connectome characteristics relate to cognitive insight in healthy individuals (chapter 6).

In chapter 2, all studies are integrated to get a clear picture of brain regions associated with clinical and cognitive insight. This chapter is followed by four empirical chapters, of which three are conducted with patients with a psychotic disorder and one with healthy individuals only.
The systematic review and meta-analyses performed in chapter 2 show that widespread areas across the brain have been associated with impaired insight, suggesting impaired neural connectivity. Therefore, in chapter 3, we are interested in white matter connectivity of the dorsolateral prefrontal cortex as this area has been associated with impaired clinical insight consistently. We measure concentrations of the neurometabolite N-acetylaspartate in the white matter of the left dorsolateral prefrontal cortex in patients with a psychotic disorder, as N-acetylaspartate is seen as a marker of neuronal integrity. A reduction of this marker in this area might suggest dysconnectivity as it may indicate impaired functioning of axons, for example because of reduced myelination, causing abnormal neural connectivity (Du et al., 2013; Tang et al., 2007). In this chapter, we relate clinical insight to N-acetylaspartate concentrations in 88 patients with a psychotic disorder.

In chapter 4, we investigate how clinical and cognitive insight relate to brain activation and connectivity during emotion regulation in 30 patients with schizophrenia. It has been suggested that in order to have good insight, one needs to be able to regulate their negative emotions given the stigma and negative emotions that are associated with a schizophrenia diagnosis. Connectivity between different areas can be studied with an abundance of methods that provide different information and can be used to answer different questions. In chapter 4, we calculate connectivity with generalized psychophysiological interaction (gPPI), with which connectivity modulated by task can be calculated between seed regions and the rest of the brain.

In chapter 5, we move from the hypothesis-driven approach to a whole brain data-driven approach focusing on the gray matter connectome. Gray matter connectomes can be created based on gray matter similarity. They represent networks with which we might be able to bridge the gap between functional and white matter networks as these networks appear to be somewhere in between with regard to their variability over time. In this chapter, we use tools from graph theory to calculate complex network measures with which we can relate whole brain global structural brain connectivity to clinical and cognitive insight in 114 patients with a psychotic disorder.

In chapter 6, we examine cognitive insight in 58 healthy individuals by combining data of three MRI-modalities: resting state fMRI, gray matter volume and DTI. From resting state fMRI data, one can calculate functional connectivity between regions when individuals are not engaged in any task. Functional connectivity, and dynamic functional connectivity specifically, can be calculated with different measures but in this chapter, we calculate functional connectivity based on phase coherence. We create functional connectivity matrices per time point per individual after which we can
calculate several measures that describe functional connectivity states that individuals go through during scanning. We relate cognitive insight to measures such as switching frequency between states, probability of being in a certain state, time spent in a certain state and switching probabilities between the different states. Additionally, we create gray matter and DTI connectomes and calculate graph metrics to relate whole brain global structural (gray matter and DTI) connectivity to cognitive insight.

Last, in chapter 7, results of all studies will be summarized and integrated, and limitations of our studies and future perspectives will be discussed.