Psychosis

Psychosis is a brain phenomenon that has interested researchers and clinicians from diverse fields throughout history. Efforts have been made to understand its causes, develop treatments, and ultimately prevent its occurrence. Many terms related to psychosis are nowadays also part of the everyday lexicon of people without a medical background. We might hear a friend saying that she feels “paranoid” about why somebody is not returning her calls, or we may think that our neighbor playing extremely loud music has most likely “gone mad”. Psychosis is hence integrated in our culture, as it has also been a central topic to writers, film directors, painters, musicians, and photographers. Nevertheless, there remains plenty to discover about the socio-psycho-biological factors that are responsible for such a complex phenomenon, which occurs for and by our own human brain.

The etymology of the word *psychosis* derives from the Greek “psyche”, for mind or soul, and “-osis”, for abnormal condition, literally meaning “abnormal condition of the mind”. In psychiatry, the term is applied to mental states often described as involving a “loss of contact with reality”. Psychosis may be manifested in a variety of ways, with a wide array of symptoms that affect an individual's thoughts, feelings and behaviors.

The term was first used in 1845 by the Austrian physician Ernst von Feuchtersleben, to distinguish disorders that were thought to be disorders of the mind, as opposed to “neurosis”, which was thought of as a disorder of the nervous system. In the late 19th and early 20th century, the German psychiatrist Emil Kraepelin proposed the division of the major psychoses into *manic-depressive* illness (now called bipolar disorder) and *dementia praecox* (now called schizophrenia). Kraepelin attempted to create a synthesis of the various mental disorders identified by 19th century psychiatrists by grouping diseases together based on common symptoms, in order to improve diagnosis and treatment. In Kraepelin’s classification, *manic-depressive illness* included disorders characterized by problems with mood control, where psychotic episodes appear associated with disturbances in mood, and patients will often have periods of normal functioning between episodes even without medication. These comprise “unipolar” clinical depression, bipolar disorder, and other mood disorders such as cyclothymia. Schizophrenia, however, is characterized by psychotic episodes that appear to be unrelated to mood disturbances, and most non-medicated patients will show signs of impairment also between episodes.
The term “schizophrenia” was coined 100 years ago, in 1908, by Paul Eugen Bleuler. He realized that Kraepelin’s dementia praecox was not a single disease (he referred to a “whole group” of schizophrenias), was not invariably incurable, and did not always progress to full dementia, nor did it always occur in young people (Bleuler, 1911). The main symptoms of this disease were the loosening of associations, disturbances of affectivity, ambivalence, and autism (“the four A’s”). However, the splitting of different psychological functions, resulting in a loss of unity of the personality, was the most important sign of disease in Bleuler’s conception (Stotz-Ingenlath, 2000).

Today, psychotic disorders included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994) comprise: brief psychotic disorder, delusional disorder, schizoaffective disorder, schizophrenia, schizophréniform disorder, and shared psychotic disorder. In addition, a range of other diseases of the central nervous system can produce symptoms of psychosis, originating from drug-induced states, or internal physiologic illness.

Since Kraepelin and Bleuler, psychiatrists have been observers of great progress in the development of increasingly sophisticated scientific techniques for the study of psychosis. This progress has permitted major improvements both in the study of the psychotic human brain as well as in the development of animal models of psychotic manifestations. As a result, some etiological models have been put forward in order to provide theoretical frameworks from which testable hypothesis may be derived to study causal factors and treatment development. While the understanding of the putative underlying mechanisms of psychosis has substantially advanced since the first classifications, the question of “why does it happen” is yet to be answered.

Psychosis in schizophrenia

Schizophrenia is a chronic, severe, and disabling brain disorder that has affected people throughout history. Its lifetime prevalence revolves around 1 percent, and is the third most disabling cause of disability after quadriplegia and dementia (Utsun et al., 1999). This disorder is characterized by a profound disruption in cognition and emotion, affecting the most fundamental human qualities: language, thought, perception, affect, and sense of self. It encompasses a large heterogeneity of symptoms and signs. The array of symptoms frequently includes psychotic manifestations, such as hearing internal voices or experiencing other sensations not connected to an obvious source (hallucinations) and assigning unusual significance or meaning to normal events or holding fixed false personal beliefs (delusions). No single symptom is definitive for diagnosis. Rather, the diagnosis according to the DSM-IV classification requires the presence of a chronic course (six months or greater) and psychosocial decline in addition to characteristic positive psychotic features.
Psychotic symptoms in schizophrenia

Symptoms typically begin between adolescence and early adulthood for males and a few years later for females, and usually as a result of a stressful period. Initial symptoms may include delusions and hallucinations, disorganized behavior and/or speech, and flat affect. Symptoms are usually divided into positive and negative. Positive symptoms appear to reflect an excess or distortion of normal functions. Negative symptoms appear to reflect a diminishment or loss of normal functions. The latter are difficult to evaluate because they are not as grossly abnormal as positive symptoms and may be caused by a variety of other factors (e.g., social withdrawal in response to a persecutory delusion).

Positive symptoms

- Delusions are firmly held erroneous beliefs due to distortions or exaggerations of reasoning and/or misinterpretations of perceptions or experiences. Delusions of being followed or watched are common (persecutory delusions), as also beliefs that comments, radio or TV programs, are directing special messages to the patient (ideas of reference).

- Hallucinations are distortions or exaggerations of perception in any of the senses, although verbal auditory hallucinations (“hearing voices”) are the most common in schizophrenia.

- Disorganized speech/thinking, also described as “thought disorder”, is a key aspect of schizophrenia. The person’s speech is tangential, loosely associated, or incoherent, of sufficient severity to substantially impair effective communication.

- Grossly disorganized behavior includes difficulty in goal-directed behavior (leading to difficulties in activities of daily living), unpredictable agitation, social disinhibition, or bizarre behaviors. They may be distinguished from unusual behavior prompted by delusional beliefs by the purposelessness that characterizes disorganized behavior.

- Catatonic behaviors are characterized by a marked decrease in reaction to the immediate surrounding environment, sometimes taking the form of motionless and apparent unawareness, rigid or bizarre postures, or aimless excessive motor activity.

- Other symptoms sometimes present in schizophrenia but not consistently enough to be definitional alone include inappropriate affect to the situation or stimuli, unusual motor behavior (pacing, rocking), depersonalization, derealization, and somatic preoccupations.
Negative symptoms

- **Affective flattening** is a reduction in the range and intensity of emotional expression, including facial expression, voice tone, eye contact, and body language.

- **Alogia**, or poverty of speech, is a lessening of speech fluency and productivity, thought to reflect slowing or blocked thoughts, and often manifested as short, empty replies to questions.

- **Avolition** reflects a reduction, difficulty, or inability to initiate and persist in goal-directed behavior. Examples include loss of interest in social activities, loss of interest in activities that the person used to show enthusiasm for, or a general loss of interest.

Neurocognition

There is a long tradition in the study of neurocognitive deficits in schizophrenia, which has unveiled robust impairments in a broad range of cognitive domains. Briefly, the most consistently documented deficits include early visual processing, sustained attention, memory, executive functions, and general intelligence, together with other related psychophysiological deficits such as startle blink reflex and eye tracking (Green, 1998). In general, it is proposed that there is a broadly based cognitive impairment in schizophrenia, with varying degrees of neurocognitive deficit in a wide range of ability domains (Heinrichs & Zakzanis, 1998). In their review and meta-analysis of the evidence, the authors reported that no single test or neurocognitive construct completely separated schizophrenia from a control distribution, although the largest mean effect sizes included global verbal memory performance and full scale IQ, attention, and language function. However, while neurocognitive deficits appear to be a central feature of schizophrenia, current conceptualizations propose that such deficits do not play out a role in expressing psychosis alone. Rather, other actors are also relevant, such as aberrant dopamine transmission (a neurotransmitter relevant to psychotic symptoms), and neurodevelopmental and interpersonal deficits (Kapur, 2003). In addition, there are a number of abnormalities in brain structure and function associated with schizophrenia (Wright et al., 2000). The etiology of these brain abnormalities remains unclear, although they likely contribute to the expression of the cognitive deficits that are characteristic of the disorder (e.g., Fusar-Poli et al., 2007; Pinkham & Penn, 2006; Yoon et al., 2008).

Interestingly, neurocognitive abnormalities associated with schizophrenia have also been detected in subjects at high risk for the disorder. In particular, cognitive deficits have been observed in non-affected relatives of patients, and in subjects at clinical risk for psychosis, mainly affecting verbal memory and executive functioning (Sitskoorn et al., 2004; Pflueger et al., 2007). Interestingly, brain abnormalities associated with schizophrenia have also been observed in an attenuated form in people at clinical risk for the disorder (e.g., Borgwardt et al., 2007; Pantelis et al., 2003). Therefore, changes in brain structure and function seem to precede the onset of the illness.
Aside from neurocognitive deficits, there is growing evidence to suggest that patients with schizophrenia show prominent deficits in a number of social cognitive domains. Over the last 10 years, great interest has been placed in the issue of the cerebral implementation of social cognition, and whether in schizophrenic patients present abnormal brain activity during such processing tasks. In the present thesis, the functional magnetic resonance imaging studies focused on a number processes related to social cognition.

Social cognition

As mentioned above, social cognition, a construct broadly referring to the cognitive processes involved in how individuals perceive, interpret, and process social information (Adolphs, 2001), is attracting increasing interest in schizophrenia research. Prompting this interest is a substantial body of work revealing that people with schizophrenia are impaired across a number of social cognitive domains (Penn et al., 2006). These include: emotion perception and regulation (how we perceive emotion in other people and how we regulate our own emotions), theory of mind (the ability that allows us to infer thoughts and intentions in other people), and self-referential processing and attributional style (how we attribute positive and negative events or personality traits to others and to ourselves).

Social cognitive deficits are relevant to the patients’ behavior for they have been directly linked to social functioning and social behavior (Couture et al., 2006). It is currently thought that the consequences of disturbances in social cognition may result in a vicious circle (Brunet-Gouet & Decety, 2006). The idea is that anxiety and discomfort provoked by abnormal perceptions and thoughts around social information may lead patients to avoid social interaction, so that social situations and interpersonal relations may lose their pleasantness and rewarding value. This lack of positive motivation for social life can, in turn, diminish the cognitive resources that are normally allocated to interpersonal problem-solving during interactions with others. Consequently, this may further impair the cognitive processing of social cues.

In the healthy brain, neuroimaging studies have provided robust evidence for the recruitment of a distributed network of neural regions during the processing of social information (Adolphs, 2001; Phillips et al., 2003a). This network primarily includes prefrontal, temporal and parietal brain regions. Several studies have revealed that patients with schizophrenia show abnormal hemodynamic response within the social cognitive circuit while processing social stimuli, particularly in the medial and lateral prefrontal cortex (PFC), medial temporal regions, and the inferior parietal lobe (Brunet-Gouet & Decety, 2006). Noteworthy, these brain abnormalities have been associated with greater severity of positive symptoms and poor social functioning (Brunet-Gouet & Decety, 2006).
Frank psychotic symptoms rarely arise “out of the blue”, with no prior mental state changes at all. In schizophrenia in particular, many authors hold that the disorder begins before the onset of psychosis (Haas & Sweeney, 1992; Häfner et al., 1993, 1994; Jones et al., 1993; Olin & Mednick, 1996). Regardless of when the actual onset of the disorder is thought of as occurring, it is useful to consider the stages leading up to frank psychosis. The term “prodrome” refers to the time period characterized by mental state features which represent a change from a person’s pre-morbid functioning, up until the onset of frank psychotic features (Yung & McGorry, 1996). It is currently proposed that the mental state thought to be a prodrome is best termed as ‘At-Risk Mental State’ (ARMS), a state that “confers high, but not inevitable risk of development of psychotic disorder in the near future” (Yung et al., 2005). In fact, prospective studies have reported that 15-40% of subjects with an ARMS will make the transition to full psychosis within 12 months (Phillips et al., 2000; Yung et al., 2004). The process of becoming psychotic creates profound psychological changes, almost always disturbing to the patient. As well as being frightening and difficult to comprehend, these experiences isolate the person from others. The consequent disruption of social networks, including family and peer relationships and schoolwork and occupational functioning, can be devastating. In addition, the timing of onset of psychosis is usually in adolescence or young adulthood, when personality development and identity issues are still being resolved. Deviant behavior during this period of untreated, unrecognized, and misunderstood psychosis may cause potentially life-threatening crises such as aggressive and suicidal behavior (Loebel et al., 1992). Increased use of substances may also occur at this time. Furthermore, effects are felt not only by the individual but by the family as well (Yung & McGorry, 1996).

The ARMS is currently defined using criteria corresponding to the Personal Assessment and Crisis Evaluation (PACE) criteria (Yung et al., 1998). In brief, the clinical features of the ARMS include one or more of the following:

- **State-based criteria**
  - Attenuated psychotic-like symptoms: low-grade positive psychotic symptoms (hallucinations, unusual thought content or suspiciousness at least several times a week and persisting for more than 1 week)
  - Brief limited intermittent psychotic symptoms (BLIPS): brief bursts of frank psychotic symptoms (hallucinations, unusual thought content, suspiciousness or conceptual disorganization lasting less than 1 week before resolving spontaneously)

- **Trait-based criteria**
  - Family history of psychotic disorder, or the individual meeting criteria for schizotypal personality disorder

...plus...

The change in mental state is clearly associated with recent marked decline in social or occupational functioning.
To date, studies of cognition in the ARMS have focused on executive functions and memory (Fusar-Poli et al., 2007; Pflueger et al., 2007), areas in which these subjects show abnormalities relative to controls. Interestingly, impairments in social cognition have also been reported in the ARMS. In particular, impairments in emotion processing (Phillips & Seidman, 2008) and theory of mind (Bora et al., 2009) have been documented, indicating that they may precede the onset of psychosis. In addition, there is evidence of disturbed self-referential processing in ARMS individuals, which has recently been proposed as a fundamental marker of vulnerability to psychosis (Nelson et al., 2009).

Social cognition is of relevance in the ARMS since problems with social functioning and symptoms of emotional distress are among the commonest features of this population (Morrison et al., 2006). Previous studies have documented that those ARMS individuals who transit to psychosis have higher levels of depression than those who do not, yet no differences in anxiety, mania symptoms or levels of negative symptoms have been reported. Interestingly, these processes share overlapping neural regions, in which functional and structural deficits have been related to the ARMS (Nelson et al., 2009). To date, however, there has been no neuroimaging work on social cognition in this population. Research in ARMS subjects is of great interest given that the results may aid the investigation into the pathogenesis of psychosis and the definition of markers to predict psychosis.

Psychosis Proneness

At this point it is important to emphasize that individuals identified as having an ARMS are also characterized by experiencing significant distress and disability, and help-seeking behavior. Nevertheless, a proportion of healthy people from the community also present psychotic experiences, although these may not cause significant distress to the individual (van Os et al., 2000; Johns et al., 2004).

The concept of schizotypy describes a continuum of personality characteristics and experiences related to psychosis in the general population (Claridge et al., 1996). There is evidence to suggest that schizotypal traits fall into a factor organization similar to that in schizophrenia, consisting of positive (e.g., magical ideation, perceptual aberration), negative (e.g., physical anhedonia, social anhedonia), and disorganized (e.g., disorganized speech and behavior) symptom constellations (Claridge et al., 1996; Kerns, 2006; Liddle, 1987).

Schizotypal traits are thought to constitute a range of enduring, biologically determined, personality and cognitive traits that predispose to schizophrenia (Chapman et al., 1994; Lenzenweger, 2006). Such schizotypal traits in healthy subjects may be detected through psychometric measures (Claridge, 1997; Lenzenweger, 1994), which are used as an indicator of psychosis proneness (PP) (Meyer & Hautzinger, 2002). Accordingly, PP is conceptualized as a subclinical manifestation of the same underlying biological factors of schizophrenia-spectrum disorders (Johns & van Os, 2001; van Os et al., 2009). Psychosis-like symptoms in PP mirror the key features of schizophrenic symptoms, including paranoia, delusional thinking, and superstition, disturbed thinking and language, and poor interpersonal skills, introversion and anhedonia (Gruzelier, 2002; Raine, 1991; Vollema & van den Bosch, 1995). Thus, current views propose that there is etiological continuity between clinical (schizophrenia) and subclinical (PP) forms of psycho-
sis (van Os et al., 2009), in line with the notion of a psychosis continuum (Chapman & Chapman, 1980; Johns & van Os, 2001; Verdoux & van Os, 2002).

In addition to the behavioral similarity between PP and schizophrenia, there is thought to be a strong genetic, neurocognitive and neurobiological link between them. For example, levels of PP are increased in relatives of schizophrenia patients (Kendler et al., 1981), and levels of psychotic symptoms in patients are correlated with levels of PP in relatives (Fanous et al., 2001; Mata et al., 2003). Because compensated or non-psychotic subjects with PP are hypothesized to share a common neurodevelopmental pathway with schizophrenia (Keshavan, 1997; Murray & Lewis, 1987; Weinberger, 1987), it is expected that they will exhibit subclinical forms of the cognitive, emotional and behavioral features of the disorder. In fact, subgroups of individuals with PP exhibit a number of cognitive abnormalities that are qualitatively similar to those seen in schizophrenia, in such domains as sustained attention, executive functioning, and attentional inhibition (e.g., Lenzenweger et al., 2006). Furthermore, research in PP has revealed impairments in measures of emotional and social functioning parallel to those of schizophrenia patients (Henry et al., 2009; Horan et al., 2008; Mohanty et al., 2008; van’t Wout et al., 2004).

Given this overlap, the study of psychosis proneness offers a unique opportunity to isolate some of the pathophysiological mechanisms implicated in psychosis without confounds such as institutionalization, neuroleptic exposure, and other consequences of the illness. As mentioned earlier, levels of PP can be measured reliably and efficiently using self-administered questionnaires in healthy members of the general population (Chapman & Chapman, 1980; Chapman et al., 1994; Claridge, 1997; Hanssen et al., 2005; Konings et al., 2006; Kwapis et al., 2008; van Os et al., 2000). Such questionnaires are not offered as a system for diagnosing people, but rather as a system for labeling the deviancy of an experience. Prospective epidemiological studies have reported that about 10% of subjects psychometrically identified as psychosis-prone go on to develop a schizophrenia-spectrum disorder (Chapman et al., 1994; Hanssen et al., 2005; Meehl, 1990). Given that the prevalence of schizophrenia in the general population (according to the DSM-IV) is about 1%, being identified as psychosis-prone represents about a ten-fold increased risk for schizophrenia-spectrum disorders.

In subjects with an ARMS, positive symptoms of psychosis have been found to be most strongly predictive of subsequent transition to psychosis (Parker & Lewis, 2006). Positive symptoms such as auditory verbal hallucinations (AVH) occur in approximately 10-15% of the general population, of whom only a small proportion has a clinically relevant psychotic disorder. A comprehensive study on such individuals reported that, although healthy subjects with AVH did not meet criteria for a psychotic disorder, there was a pronounced increase on schizotypal tendency and family loading for psychiatric disorders (Somm et al., 2008). In that study, individuals who experienced AVH with negative content experienced higher distress from the voices and had lower global functioning. The authors hypothesized that not the presence of hallucinations per se but rather the negative emotional content of the voices and the perceived distress appear to constitute an important difference between more benign positive experiences and psychopathology. Thus, it appears of importance to study cognitive-emotional processes in individuals at heightened risk for psychosis, especially in relation to positive symptomatology, in order to aid understanding of the pathophysiology of psychosis.

In summary, the psychometric high-risk method uses questionnaires to identify persons who exhibit a number of personality and cognitive abnormalities that resemble those that occur in psychosis. In addition, like persons at familial high risk, higher levels of PP predict future conversion to schizophrenia (e.g., Chapman et al., 1994). Although PP shares an extensive array of similarities with schizophrenia in terms of genetic
and environmental risk factors, individuals with PP have less severe cognitive disturbances than patients and lack the debilitating symptoms of clinical schizophrenia. An additional advantage of the PP paradigm is the possibility to study protective mechanisms that differentiate psychosis-prone individuals from people with frank psychosis. Hence, research in these subjects should facilitate the determination of relevant etiological factors, and may ultimately hasten the development of prophylactic treatment interventions.

Behavioral evidence

Behavioral research in psychosis proneness has revealed a number of cognitive deficits similar to those seen in schizophrenia (Siever & Davis, 2004). In particular, deficits in episodic memory (Mitropoulou et al., 2002; Voglmaier et al., 1997) and executive function (Trestman et al., 1995) have been reported. Few behavioral studies have investigated social cognition in PP. Thus far, this research has revolved around the following domains, which are areas of consistently reported deficits in schizophrenia.

- *Emotion processing*. Phillips & Seidman (2008) recently reviewed the available evidence for deficits in emotion processing in at-risk samples (i.e., psychosis proneness, genetic high risk and ARMS). Emotion deficits were examined across different dimensions: perception, expression, experience, and psychophysiological response. According to this review, PP has been associated with impaired emotion perception, which seemingly depends on symptom subtype (negative, positive, disorganized), with results being more robust in the positive subtype. In particular, subjects with the positive subtype have been found to misidentify expressions of emotion in faces as well as in tone of voice. People with positive PP report increased emotionality on self-report, in terms of increased emotional confusion and ambivalence to emotion. Positive PP has also been associated with increased nonspecific skin conductance response to negative stimuli.

- *Theory of mind (ToM)*. A recent meta-analysis by Sprong et al. (2007) reported that there is substantial evidence to consider a mentalizing impairment as susceptibility indicator for schizophrenia. Nevertheless, two studies out of the six included in that meta-analysis did not find differences in performance between subjects with high and low psychosis proneness. Bora et al. (2009) performed a review on ToM in schizophrenia, and included the same 6 studies in PP. The studies identifying a relationship between high PP and ToM impairment appeared to not be free from shortcomings such as the use of different instruments for the definition of PP, as well as for the assessment of ToM. In addition, the two studies with better recruitment procedure found no relationship between ToM and PP. Thus, behavioral results in this area are somewhat inconsistent. There is evidence to suggest, however, that individuals at genetic risk for schizophrenia show impaired ToM, paired with altered brain activation in ToM-relevant brain regions (Marjoram et al., 2006). Following the notion that some of the positive symptoms of schizophrenia reflect an impairment in the ability to infer the mental states of others (Frith & Corcoran, 1996), and that schizotypal experiences analogous to positive symptoms of schizophrenia predict poorer mentalizing (Pickup, 2006), ToM difficulties would be most strongly associated with positive psychotic experiences. To date, no study had investigated brain
activation during ToM processing in psychosis proneness.

- **Self-referential processing – attributional style of personality traits.** Patients with schizophrenia express cognitive biases in the processing of self-related information. For instance, they may display distorted attributions of positive and negative events as means of maintaining self-esteem, by limiting conscious awareness of negative aspects of the self (Bentall et al., 1994). Patients tend to overattribute negative events to external agents, and positive events to internal causes. This phenomenon is related to the genesis of positive symptoms, such as delusions (Bentall et al., 2001). Interestingly, research in clinical and genetic high-risk groups has reported abnormalities in self-referential processing, as well as in brain function and structure of associated regions, suggesting that self-disturbances may be a trait marker of vulnerability (Nelson et al., 2009). In psychosis-prone individuals, paranoid ideation symptoms have also been associated with perceptions of the self (Martin, & Penn, 2001). Although there is evidence for self-disturbance in people with PP (Meehl, 1962, 1989), the neural mechanisms relevant to self-referential processing had never been studied in these individuals.

**Neurobiological evidence**

Neuroimaging studies in schizophrenia have demonstrated that cognitive impairment in patients may be associated in part with anomalous cortical activity in the prefrontal cortex (PFC). Among the various cognitive deficits found in schizophrenia, impaired executive functioning is among the most widely observed, and is consistently associated with impaired function of the PFC (Weinberger et al., 1986). The most common interpretation has been the existence of a general deficit in prefrontal function in schizophrenia, which has been traditionally termed hypofrontality (Andreasen et al., 1997). However, later quantitative meta-analysis of the literature have reported that, while patients with schizophrenia do exhibit reduced activation in the dorsolateral portion of the PFC during working memory tasks, this co-occurs with activation increases in other brain regions, including other portions of the PFC (Glahn et al., 2005). Increased frontal pole activity is also seen in verbal episodic memory studies (Heckers et al., 1998; Ragland et al., 2001), and has been attributed to increased retrieval effort in the patient sample. Indeed, a recent meta-analysis of executive functioning in schizophrenia reported that the disorder is associated with both decreases and increases in neural activation (Minzenberg et al., 2009). Functional increases in this population have been commonly interpreted as compensatory in nature.

Overall, evidence of reduced activation in dorsolateral portions of the PFC and increased activity in other regions (such as the anterior cingulate cortex, and limbic regions such as the amygdala and the insula) seems to be consistent with the notion that schizophrenia disrupts or reverses the normal functional connectivity of prefrontal and limbic structures and represents a disconnection syndrome (Andreasen et al., 1999; Friston & Frith, 1995; Hoffman, 1997; Weinberger et al., 1992). Thus, the hypofrontality vs. hyperfrontality account of the altered function of the frontal cortex in schizophrenia is strongly challenged by current evidence. Considering that it is not one brain re-
region alone but rather a distributed network which is engaged by task demands, reduced regulation of this network by the dorsolateral PFC might lead patients to increase engagement of other processes to maintain task performance, such as attentional, mnemonic, and monitoring functions. In addition, differential activation is also seen in limbic regions such as the amygdala and the insula, which could reflect differential emotional reactivity to task demands in patients with schizophrenia (Minzenberg et al., 2009).

Besides impairments in the cognitive domain, patients with schizophrenia also show deficits in emotion processing, as indicated by a markedly reduced ability to perceive, process and express facial emotions (Mandal et al., 1998; Morrison et al., 1988; Mueser et al., 1996; Streit et al., 2001). Functional magnetic resonance imaging studies have suggested that abnormalities in the amygdala are crucial to deficient emotion processing (Gur et al., 2002; Schneider et al., 1998; Taylor et al., 2002). Interestingly, there is evidence of structural abnormalities in the amygdala also in individuals at genetic risk for schizophrenia (van Rijn et al., 2005).

In subjects with vulnerability to psychosis, it has been argued that prefrontal activity may reflect islands of preserved or compensatory function (Siever et al., 2002). For example, Buchsbaum and colleagues (1997) showed that subjects with schizotypal personality disorder recruited frontal lobe areas during executive functioning performance differently than healthy controls, and did not simply show reduced activation. As mentioned above, it has been shown that patients with schizophrenia display hyperactivation of the PFC when they perform equally to healthy controls in a cognitive task (Callicott et al., 2003), in line with the notion that prefrontal activity increases reflect a compensatory mechanism. Subjects with high levels of psychosis proneness may also show differences in brain activation during task performance relative to subjects with low levels. The only previous study to date using brain imaging techniques in subjects psychometrically identified as psychosis-prone (positive dimension) reported differential prefrontal activation during an affective interference task (Mohanthy et al., 2005). The authors reported that these subjects showed significant increases in activation in dorsolateral and ventrolateral portions of the prefrontal cortex, as well as in limbic regions such as the hippocampus and the amygdala during maintenance of attentional set in the presence of negative emotional distractors (Emotional Stroop task). Such increases were interpreted as greater effort to inhibit strongly interfering emotional stimuli in order to achieve normal behavioral performance.

With regard to brain morphology, schizophrenia is known to be associated with volumetric brain abnormalities, which can be detected with structural magnetic resonance imaging (MRI) methods. Areas of particular interest in schizophrenia are temporal, frontal, striatal and thalamic areas (Shenton et al., 2001). Longitudinal MRI studies suggest that changes are progressive, in particular in the initial couple of years of the illness, and are associated with functional outcome (Keshavan et al., 2005). Brain volumetric abnormalities have also been detected in the ARMS (Borgwardt et al., 2007; Meisenzahl et al., 2008; Pantelis et al. 2003), as well as in first-degree relatives and healthy co-twins of patients with schizophrenia (Baare et al., 2001; Hulshoff Pol et al., 2004; Lawrie et al., 1999; Seidman et al., 1999; Staal et al., 2000). These early abnormalities associated with increased vulnerability to psychosis are thought to reflect developmental or later maturational processes in adolescence and early adulthood (Borgwardt et al., 2007). To date, no study has investigated neuroanatomy in healthy people with psychosis proneness. This represents an important gap given the previously mentioned considerations on a continuum between PP and frank psychosis, and the methodological advantages of studying clinically unaffected subjects with PP, as for example treatment with antipsychotics is known to affect gray matter volumes (Scherk & Falkai, 2006).
Imaging the vulnerable brain

Functional and structural MRI provide the opportunity to gain insights as to whether differences at the brain level precede the onset of psychosis. It is proposed that brain changes in psychosis may be better conceptualized as anomalous trajectories of brain development (Pantelis et al., 2007). Although the pathological processes underlying such changes remain unclear, it is speculated that they may reflect anomalies in genetic and/or other endogenous mechanisms responsible for brain maturation, as well as adverse effects of intense or prolonged stress or other environmental factors (Wood et al., 2008). Considering that first psychotic episodes usually occur in late adolescence, the study of individuals with vulnerability to psychosis in this period of their lives provides a unique opportunity to identify brain changes associated with vulnerability prior to illness onset.

Functional MRI (fMRI)

fMRI provides high resolution, noninvasive reports of the increase in blood flow to the local vasculature that accompanies neural activity in the brain. This technique facilitates visualization of the blood-oxygen level dependent (BOLD) response in a given brain region. It is, thus, an indirect measure of brain activity, of the underlying electrical signal. When participants perform a task inside the scanner, we are actually studying whether the ratio of oxygenated hemoglobin in the blood associated with a particular brain region is statistically greater under one experimental condition than under another experimental condition. fMRI is currently widely applied as research tool to better our understanding of the neural circuits whose malfunctioning may lead to symptoms of major psychiatric disorders, such as schizophrenia. fMRI is thus used, among other methods, to help elucidate why these symptoms actually occur, what the brain bases of these symptoms are, so that one day we might be able to inform illness prevention and treatment.

Figure 1. Functional MRI allows for the visualization of the hemodynamic response in brain regions that are engaged during a given task. The image depicts loci of activation (in red) on a cutout of the standard human brain (MRIcron).
Structural MRI

Aside from brain function, this thesis also focused on brain structure (in particular, regional gray matter volume), using a Voxel-Based Morphometry (VBM) approach. VBM is a whole-brain, unbiased objective technique used to characterize brain differences \textit{in vivo} using structural magnetic resonance images (Mechelli et al., 2005a).

VBM studies in normal subjects have focused on the impact of learning and practice on brain structure, leading to the finding that environmental demands may be associated with changes in gray and white matter in the human brain. This method has also been successful in identifying gross structural abnormalities, such as those observed in herpes simplex encephalitis, multiple sclerosis and Alzheimer’s disease. In addition, VBM has been useful in characterizing subtle changes in brain structure in a variety of diseases associated with neurological and psychiatric dysfunction. In schizophrenia, VBM has proved to be effective for the detection of regional gray matter volume abnormalities relative to healthy controls (Honea et al., 2005). Noteworthy, such abnormalities have been detected in an attenuated form in subjects with an ARMS relative to healthy controls, as also between ARMS subjects who converted to psychosis relative to those who did not (e.g., Pantelis et al., 2003; Borgwardt et al., 2007).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{brain_structural_mri.png}
\caption{The cerebral cortex is a highly folded sheet of gray matter (GM) that lies inside the cerebrospinal fluid (CSF) and surrounds a core of white matter (WM). With VBM we can study differences in GM or WM volume between populations of interest.}
\end{figure}
This thesis comprises seven empirical studies in different populations of interest – healthy individuals without PP, healthy individuals with PP as measured by self-report questionnaire, and patients with schizophrenia. The principal aim of this work was to examine the psychophysiology of PP using an integrative neuroimaging approach, using experimental techniques drawn from cognitive psychology, functional and structural neuroimaging.

First, we tested our fMRI tasks on a group of individuals without PP (Part 2.1, Imaging the Healthy Brain) before moving on to the study of the same processes in people with such vulnerability. We began by asking which areas are recruited in the healthy brain to process information related to one’s self, particularly when reflecting upon own personality traits. Among the cerebral areas that had been previously reported as relevant to self-reflection, the cortical midline structures had been most commonly discussed. Nevertheless, the insula, an area involved in processing bodily experiences, thus also related to processing information related to self, had received relatively little attention in studies of self-reflection. This region was traditionally thought to be involved in the processing of self-related information providing it had explicit emotional value. However, the particular role of the insula in self-reflective processes remained unclear. Interestingly, there is evidence to suggest that the insula is compromised in psychosis and also in individuals with an ARMS (Borgwardt et al., 2008), leading to the recent proposal that self-disturbance might be a trait marker of psychotic vulnerability (Nelson et al., 2009). We thus first sought to study neural activity associated with self-reflection as compared to that associated with reflecting upon another person, or with general semantic knowledge, in a sample of healthy subjects. We tested the hypothesis that a number brain regions would be specifically recruited for self-reflection on personality traits, particularly in the cortical midline, and including the anterior insular cortex. This work is presented in Chapter 2.1.1.

The ability to regulate negative emotion is critical to adaptively respond to the distressing experiences we may encounter in everyday life (Gross & Munoz, 1995). People with schizophrenia show robust impairments in processing and regulating emotions (Penn et al., 2008). Interestingly, healthy individuals also differ in the tendency to regulate emotions, insofar as some regulate emotion more spontaneously, while others more often let themselves be carried away by a prepotent emotional response. In recent years, the relevance of studying the influence of such individual differences on brain circuits supporting emotion regulation has been emphasized for their putative role as risk factors for psychological disturbance (Gross & John, 2003). Individual differences in emotion regulation abilities may be reliably measured with self-report questionnaires (Gross & John, 2003). Dispositional mindfulness refers to the ability to be more aware of, detached from and regulatory of current ongoing experience (Baer et al., 2004). In fact, the few available neuroimaging studies on subjects trained in mindfulness strategies have reported differential activity in prefrontal and limbic regions, that is, overlapping systems to those involved in emotion regulation (Lutz et al., 2008). Theoretically, having more or less dispositional mindfulness skills would imply being more or less regulatory of current emotional states. However, no study to date had investigated whether individual differences in the tendency to be spontaneously mindful are associated with differential recruitment of an emotion regulation brain circuitry. Thus, in Chapter 2.1.2 we tested the novel hypothesis that the neural dynamics relevant to emotion regulation would be influenced by individual differences in dispositional mindfulness, in healthy individuals without PP.

Next, these fMRI tasks were applied to individuals with high levels of positive dimension PP...
(Part 2.2, Imaging the Vulnerable Brain) in order to examine putative differences in brain activation relative to subjects with low PP during emotion regulation (Chapter 2.2.1), self-reflection (Chapter 2.2.2), and theory of mind (Chapter 2.2.3). Of note, the study on theory of mind was conducted in collaboration with Dr. Simone Shamay-Tsoory, from the University of Haifa, Israel. Based on the literature in schizophrenia and the (behavioral) studies in psychosis-prone individuals, we hypothesized that high PP would be associated with differential activation within brain systems relevant to each of those aspects of social cognition (mainly within regions of the PFC).

Not only functional but also structural brain abnormalities have been repeatedly described in schizophrenia, and appear to be associated with the ARMS. However, no study to date had used structural MRI to examine the brains of subjects with PP. Thus, in Chapter 2.2.4 we sought to investigate differences in regional gray matter volumes between subjects with high and low PP, using VBM. We hypothesized that subjects with high PP would show differences in regions previously involved in studies of schizophrenia and the ARMS (i.e., inferior frontal cortex, insula, cingulate cortex, temporal regions, and the parietal lobe).

Finally, we moved to the endpoint of the psychosis continuum (Part 2.3., Imaging the Psychotic Brain) to investigate whether the severity of a positive symptom with clinical relevance (i.e., auditory verbal hallucinations, AVH) would modulate patterns of structural covariance in the brains of patients with schizophrenia. Structural covariance refers to the co-variation in regional (gray matter) volumes between different brain regions (Mechelli et al., 2005b). A number of regions express altered patterns of structural covariance in patients with schizophrenia relative to controls (Mitelman et al., 2005; Wible et al., 1995; Woodruff et al., 1997). However, the relation between these alterations and a specific psychotic symptom was unknown. Thus, we studied a sample of patients with schizophrenia and medication-resistant AVH to test the hypothesis that structural covariance between a number of regions which are part of a neural network involved in speech production and verbal monitoring would depend on overall severity of AVH. This was also a VBM study, presented in Chapter 2.3.1.

Of note, the two structural MRI studies are the fruit of a 5-month working visit at the Neuroimaging Section in the Institute of Psychiatry, King’s College London, in collaboration with Prof. Philip McGuire and Dr. Andrea Mechelli.

General consideration

In the chapters presenting findings on individuals with psychosis proneness, the terms “psychosis proneness” and “psychometric schizotypy” are indistinctively used. Both terms were used in reference to the same construct given that levels of psychosis proneness were assessed with a questionnaire, that is, a psychometric measure for the detection of subclinical psychotic experiences in the general population.
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