Summary

Why?

If you heard voices speaking to you when in reality no one was talking, or if you wrongly believed that the people around you were plotting to harm you on behalf of the government, you would be suffering symptoms of psychosis. If this would impair your normal functioning, damaging your performance at work and your social relationships, you would be complying with the criteria for a diagnosis of schizophrenia.

There is a long tradition in the study of the brains of persons with psychosis, which has allowed for the identification of abnormalities in function and structure relative to healthy people. However, studying the brains of persons with schizophrenia is often complicated by the consequences of the illness - for instance the effects of antipsychotic medication, impairments in cognition (that is, of thought processes) and hospitalization. Recent studies have shown that some of the deficits associated with schizophrenia are also present in those at an elevated risk to develop it, such as people in the preceding phase (the prodrome) or relatives of patients. Therefore, it is hypothesized that such deficits could serve as markers of the illness, which would allow for early detection and intervention, and could even facilitate the development of preventive strategies.

There are healthy people in the general population who experience mild symptoms of psychosis without clinical relevance, that is, which do not affect their usual functioning and do not trigger help-seeking behavior. This has been termed psychosis proneness. Some behavioral studies have been conducted in persons with psychosis proneness, which have indicated that there is some continuity with respect to cognitive deficits. Moreover, it has been demonstrated that these individuals share, to some degree, the risk factors (genetic, prenatal, biological and environmental) associated with the development of schizophrenia. Thus, current views propose that there is an etiological continuity (in causation) between clinical and subclinical forms of psychosis (Johns & van Os, 2001; van Os et al., 2009; Verdoux & van Os, 2002). In short, that there is a continuum between normality and full-blown schizophrenia. Studying the brain of persons with psychosis proneness would allow for the study of the neurobiology (the biology of the nervous system) of some of the central features of schizophrenia without the confounding effects of antipsychotic medication, institutionalization or cognitive impairment. The aim of this thesis, therefore, was to examine the function and structure of their brain to determine whether some of the features associated with the illness are also associated with vulnerability.
for its development.

One of the most important deficits in psychosis has to do with **social cognition**, that is, the thought processes involved in how people perceive, interpret and process social information (Adolphs, 2001). People with schizophrenia show deficits in several aspects of social cognition. For instance, in the perception and regulation of emotion (how we perceive emotion in other people and how we regulate our own emotions), in **theory of mind** (the ability that allows us to infer thoughts and intentions in other people), and in **attributional style** (how we attribute positive and negative events, or personality traits, to others and to ourselves). In addition, these deficits negatively impact on the social functioning and behavior of patients with schizophrenia, and contribute to the formation of psychotic symptoms (Brunet-Gouet & Decety, 2006).

### How?

Aiming to study brain activity, we used functional magnetic resonance imaging (fMRI). When we perform an action or a mental task, specific areas of the brain are activated, which means that they will need more oxygen, and thus more blood needs to be pumped to those areas. With the help of fMRI, these changes in blood flow can be registered. This allows studying the human brain in a non-invasive way, with a technique of which there is no known contraindication for health.

Using fMRI, it has been discovered that, in the healthy brain, activity in specific networks of neurons increases while performing social cognitive tasks (including regions in the prefrontal, temporal and parietal cortices). Interestingly, patients with schizophrenia show alterations in activation of those networks when they perform such tasks (Brunet-Gouet & Decety, 2006). Recent studies have begun to show that these alterations can also be detected in persons at genetic risk to develop the illness. Thus, it has been suggested that alterations in social cognition precede the onset of the illness and may serve as markers of vulnerability (Bora et al., 2009; Nelson et al., 2009; Phillips & Seidman, 2008).

First, we tested our fMRI tasks on a group of individuals without psychosis proneness, before moving on to the study of these processes in people with that vulnerability. We asked what are the cerebral areas that the healthy brain uses to process information related to oneself, particularly when reflecting upon own personality traits. Among the regions that have been reported in previous studies as relevant to self-reflection, the **insula**, a cerebral area involved in processing bodily experiences, had received relatively little attention. Interestingly, prior research has shown that the insula is compromised in psychosis, and also in individuals in the prodrome (Borgwardt et al., 2008). In our study in healthy persons, we observed that the insula is recruited for self-reflection independently of the emotional value of the stimuli. This indicates that it has a more general role in the processing of information related to the self (which probably has an intrinsic emotional connotation) than previously thought.

The ability to regulate negative emotion is important to adequately function in a social environment, and is associated with psychological well-being (Gross & Munoz, 1995). People with schizophrenia show robust impairments in processing and regulating emotions (Penn et al., 2008). Interestingly, healthy people also differ in their ability to regulate their emotions. For example, if you were now told that reading this thesis is not free of charge it would cost 500 euros, some of you would think that this is extremely greedy, that had you been aware of this you would not have read it, and...
maybe you will even throw it out of the window. Others will perhaps feel the impulse to be carried away by the first emotional reaction, but instead you will think that perhaps life must be quite precarious for a PhD student. Thus, money might be short for a student, and even though you are not going to give the 500 euros, you might reinterpret the situation in ways that make you feel less infuriated. In other words, there are people who regulate their emotions more spontaneously, whereas others more often let themselves be carried away by a predominant emotional response. Thus, in our next experiment we studied how individual differences affect the cerebral systems involved in the regulation of negative emotion. We observed that people who tend to be more aware of and with more regulation over their emotions (measured with a questionnaire on “dispositional mindfulness”) use more effectively brain resources implicated in down-regulating negative emotion. That is, those who more naturally regulate their emotions show better modulation of cerebral dynamics involved in regulating emotion.

What about people with psychosis proneness? Do they show differences in the neural systems implicated in social cognition? First, we administered a questionnaire to measure subclinical psychotic experiences (positive type, that is, strange perceptions and unusual beliefs), the Community Assessment of Psychic Experiences (Stefanis et al., 2002) to 600 university students. Two groups of 20 persons with high and low psychosis proneness were ultimately recruited, and we investigated between-group differences in brain activation while they performed three tasks on social cognition: emotion regulation, attribution of personality traits, and theory of mind.

We did not find significant differences in behavioral performance between the groups in the ability to regulate emotion, or in theory of mind. However, participants with high psychosis proneness showed more brain activity than participants with low psychosis proneness during these tasks, mainly in regions of the prefrontal cortex (the frontmost part of the brain). Furthermore, we examined interactions (functional connectivity) between regions of the prefrontal cortex involved in cognitive control (controlling which responses we give) and the limbic system (where automatic responses to an emotional stimulus are produced). Such interactions are thought to be crucial for the optimal regulation of negative emotion. Besides the observed prefrontal increases in activation, individuals with high psychosis proneness did not show the expected interactions between prefrontal and limbic systems.

With regard to the attribution of personality traits, we observed that people with high psychosis proneness showed an exaggerated tendency to attribute more positive traits to themselves than to others. This is called “self-enhancing bias”. While this phenomenon is a universal human tendency with the function to protect self-esteem, when exaggerated it is known to be associated with social maladjustment (Colvin et al., 1995). This phenomenon is common in patients with schizophrenia, particularly related to positive symptoms such as delusions (Bentall et al., 1994). On the brain level, we also observed increases in activation, mainly in regions of the prefrontal cortex, associated with this self-enhancing bias in people with high psychosis proneness.

The goal of this thesis was to study not only brain function but also brain structure, given that structural abnormalities are known features in schizophrenia (Wright et al., 2000), and in individuals in the prodrome (Borgwardt et al., 2007; Pantelis et al., 2003). Thus, we examined putative differences in gray matter volume (the surface of the brain, where we have the bodies of the neurons) using a semi-automated technique called Voxel-Based Morphometry (VBM). People with high psychosis proneness showed more volume in areas of the so-called “cortical midline” (the medial part of the brain between the left and the right halves). These are relevant areas for the processing of self-related information, and volume
hallucinations, “hearing voices”) would modulate brain volume in people with schizophrenia. Severity of hallucinations was measured with a self-report questionnaire. Using VBM, we observed that more severe hallucinations were associated with more gray matter volume in a brain region involved in semantic processing (the left inferior frontal gyrus, an area that falls behind the left temple). Moreover, we reported that volume in the left inferior frontal gyrus and volume in other (frontal and temporal) regions that constitute a network involved in speech production and monitoring vary together as a function of the severity of the hallucinations.

Finally, our results also suggest that gray matter volume is associated with positive psychotic symptoms both in their clinical and subclinical forms. In our last experiment, we moved to the endpoint of the continuum in order to investigate how a specific positive psychotic symptom (i.e., auditory verbal hallucinations, “hearing voices”) would modulate brain volume in people with schizophrenia. Severity of hallucinations was measured with a self-report questionnaire. Using VBM, we observed that more severe hallucinations were associated with more gray matter volume in a brain region involved in semantic processing (the left inferior frontal gyrus, an area that falls behind the left temple). Moreover, we reported that volume in the left inferior frontal gyrus and volume in other (frontal and temporal) regions that constitute a network involved in speech production and monitoring vary together as a function of the severity of the hallucinations.

What?

The above figure depicts a summary of main findings from our studies in psychosis proneness. The picture outside the box is a three-dimensional view of the surface of the standard brain. Across a variety of tasks on social cognition, we observed that individuals with high psychosis proneness showed increases in activation relative to subjects with low psychosis proneness. These increases are depicted in a red-color scale, overlaid on the standard brain. During the processing of self-related information, increases in brain activation were associated with an exaggerated tendency to attribute more positive traits to self than to others. This could be interpreted as indicative of an increased self-focus (the tendency to be more self-referent), fruit of attempts to reduce conflicts originated by the experience of subclinical psychotic symptoms, in order to improve self-esteem. In regards to the regulation of negative emotion and theory of mind, the observed increases in activation may reflect compensatory efforts to attain equal performance to people with low psychosis proneness. The bottom picture shows regions in which subjects with high psychosis proneness exhibited increased gray matter volume. This was thought to reflect compensatory mechanisms for disturbances in other parts of the brain, or abnormal brain maturation.
So, what can we say about psychosis proneness? This thesis suggests that psychosis proneness is associated with differences in brain activation and functional connectivity during social cognitive tasks, as well as with differences in brain morphology. Thus, there appear to be differences in the brain of a person with psychosis proneness. If the vulnerable individual is exposed to added environmental risk factors (e.g., drug use), these brain differences may become dysfunctional, and their persistence may lead to fully-developed psychotic symptoms, as well as to the cognitive and social impairments that may ultimately result in frank psychosis.

Future studies in people from the general population with a longitudinal focus should illuminate whether the observed differences may have predictive value. The same tasks used in this thesis will now be implemented by other researchers in our team in people in the prodrome, as well as in patients with schizophrenia, aiming to examine brain changes in different phases of the illness. It should be taken into account that about 10% of people with psychosis proneness will go on to develop a schizophrenia-spectrum disorder (Chapman et al., 1994; Hanssen et al., 2005; van Os et al., 2009). This could be related to the success of the brain for compensation, and to the presence/absence of added environmental risk factors. This thesis represents a promising first step in the study of the neurobiology of psychosis proneness, and encourages further research in the field.

References
