General conclusions
Main findings and discussion

The key contributions of this thesis to the psychosis proneness arena are summarized below.

- Psychosis proneness (positive dimension) is associated with increases in activation in predominantly prefrontal brain regions during social cognitive tasks.

- During self-reflection these increases are associated with an exaggerated self-enhancing bias. Greater activation in prefrontal, limbic and striatal regions during self-reflection may reflect an increased self-focus and attempts to reduce conflict originated by the experience of subclinical symptoms that are directed to improve self-esteem.

- In emotion regulation and Theory of Mind (ToM), increases in activation of relevant prefrontal regions may reflect compensatory efforts to reach similar performance to subjects with low levels of psychosis proneness.

- Psychosis proneness (positive dimension) is associated with increased gray matter volume in regions of the posterior cortical midline. This could reflect compensatory mechanisms for dysfunction in other brain areas, or abnormal brain maturation.

- The brain of a person with psychosis proneness (positive dimension) thus appears to show differences in function and structure. Depending on the degree of additional neurodevelopmental risk and added environmental risk factors, these differences may become dysfunctional. Its persistence may lead to the development of the florid psychotic symptoms, cognitive and social functional impairments that may ultimately result in frank psychosis.
Deficits in social cognitive processes and its neural underpinnings are thought to be key pathophysiological features of psychosis (Brunet-Gouet & Decety, 2006). The study of these processes in psychosis proneness (PP) is of timely interest given that they have been proposed as markers of vulnerability to psychiatric disorders like schizophrenia (Bora et al., 2009; Nelson et al., 2009; Phillips & Seidman, 2008).

Our first two studies in healthy subjects (without PP) lent further support to prior literature suggesting that there are specific cerebral areas whose function and interaction underlie social cognitive processes in the healthy brain. We 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. We placed special interest in the insular cortex, as this region was traditionally thought to be involved in the processing of self-related information provided it has an explicit emotional value. It remained unclear whether the insula was more generally associated with self-reflective processes. In addition, prior research had indicated that the insula is compromised in psychosis and in individuals with an At-Risk Mental State for psychosis (ARMS) (Borgwardt et al., 2008). In our study, the insular cortex appeared to have a role in generally reflecting upon self-related stimuli (i.e., attribution of personality traits to self), rather than just supporting the processing of stimuli with an explicit emotional value. As discussed in chapter 2.1.1, it is also possible that information related to the self has an intrinsic emotional value. A next step for future research would be to investigate more specifically the role of the insula in the pathophysiology of psychosis. Total insular gray matter volumes are significantly reduced in patients with schizophrenia compared to healthy controls (Saze et al., 2007). As mentioned above, reduced volume thereof has also been found in subjects with an ARMS, suggesting that insular alterations are present before illness onset (Borgwardt et al., 2008). Furthermore, it is currently proposed that self-disturbance is critical in psychosis and may predate the onset of illness (Nelson et al., 2009), therefore studies explicitly testing this hypothesis are warranted.

With regard to emotion regulation, people with schizophrenia show impairments in this ability relative to healthy controls (Penn et al., 2008). In healthy people, individual differences in the spontaneous tendency to regulate emotion are also conceptualized as an important risk factor for psychological disturbance (Gross & Munoz, 1995). In our study in healthy subjects (without PP) we observed that the neural dynamics associated with emotion regulation through reappraisal were modulated by such individual differences, as indicated by the effect of mindfulness traits on frontolimbic interactions. Furthermore, more mindfulness traits were associated with more down-regulation of experienced negative affect, as indexed by self-reported ratings of emotion experience. Our results lend further support to the idea that integrity of frontolimbic interplay is critical to the effective cognitive control of emotion (Ochsner & Gross, 2005), which is an essential feature of mental health (Gross & Munoz, 1995).

Next, we sought to investigate these processes in positive dimension PP. Deficits in emotion processing and regulation are robustly associated with schizophrenia (Aleman & Kahn 2005; Phillips et al., 2003), and may be observed in individuals with an ARMS as well as in persons at genetic risk for the disorder (Phillips & Seidman, 2008). In our study, high psychosis-prone individuals were able to down-regulate the experience of negative affect through reappraisal to the same degree than subjects with low PP. However, they showed increased neural activity during reappraisal in several regions within the prefrontal cortex (PFC), particularly in dorsomedial and ventrolateral portions, along with the anterior cingulate cortex (ACC). In addition, high psychosis-prone
subjects did not show the expected functional connectivity pattern between the PFC and the amygdala, which is known to be crucial for successful reappraisal. These findings led us to suggest that stronger PFC activation may be serving a compensatory function for decreased functional coupling between PFC-amygdala in order to effectively diminish the experience of negative emotion.

Regarding self-referential processing, high psychosis-prone individuals exhibited a bias in terms of an exaggerated tendency to attribute more positive personality traits to self than to other. Although this bias (self-enhancement) is a universal human bias aimed at preserving self-esteem, when exaggerated it may lead to poor social functioning and social maladjustment (Colvin et al., 1995). Self-disturbance is a key psychopathological feature of schizophrenia (Kircher & David, 2003), which is currently thought to precede the onset of the illness (Nelson et al., 2009). Patients with schizophrenia display biases in self-referential processing, especially in attributional style, which are hypothesized to contribute to the genesis of positive symptoms such as delusions (Blackwood et al., 2001). When one’s current self falls short to one’s current standard, subsequent negative affect may generate attempts to decrease the discrepancy. If one has unusual beliefs, for instance that other people are inserting thoughts inside his head against his will, he might wonder why he deserves that, which can make him feel insecure and trigger negative emotion. This may be counterbalanced by attempts to diminish negative affect and increase self-esteem. The ACC would be a relevant region for this purpose, as observed in our experiment, given its known role in cognitive control and monitoring. Indeed, in our sample of psychosis-prone subjects the self-enhancing bias was associated with increased brain activation mainly in prefrontal (plus ACC), anterior insula, striatal (putamen) and limbic regions (amygdala). Increased activations in insular, striatal and limbic regions while processing personality traits of positive and negative valence could indicate that such traits entails an increased emotional value for these subjects (responses in insula, amygdala), which is regulated in ways that facilitate a higher rewarding value (response in putamen). That is, by attributing more positive items to self than to other, as suggested by prior literature on the nature of self-enhancing biases (Blackwood et al., 2003). In addition, it is worth noting that medial prefrontal regions including the ACC are known to be active during both resting state and self-referential processing (Gusnard et al., 2001; Lou et al., 2004; Northoff et al., 2006). Hyperactivation and hyperconnectivity in these regions during resting state have been reported in schizophrenia (Garrity et al., 2007), as well as in subjects at genetic risk (Whitfield-Gabrieli et al., 2009). This has been interpreted as reflecting an increased self-focus, that is, an enhanced focus in one’s own thoughts and feelings. Many of the positive symptoms of schizophrenia involve an exaggerated sense of self-relevance in the world, such as paranoid ideation that individuals and groups are conspiring against the person, and a blurring of internal reflection and external perception, such as hallucinations. Thus, it has been proposed that greater activity in self-referential regions may contribute to the positive symptoms and disturbances of thought that characterize schizophrenia (Whitfield-Gabrieli et al., 2009). Our results suggest that biased self-referential processing is also associated with the experience of subclinical forms of positive psychotic symptoms, in line with the notion of a psychosis continuum.

Finally, individuals with high and low PP appeared to perform equally well in Theory of Mind (ToM) processing. Findings from behavioral research in this area of social cognition in PP, all conducted also in psychometrically identified individuals, have been controversial, with four out of six reporting impaired performance (Bora et al., 2009). However, none of these previous studies had looked into brain activity while subjects performed a ToM task. We reported that individuals with high
positive dimension PP showed differences in brain activation (again) in terms of increases. In particular, increases were located within the PFC, including its anterior, dorsal medial, and lateral portions. This was interpreted as suggesting that subjects with vulnerability to psychosis required greater recruitment of prefrontal regions involved in ToM and attention in order to mentalize at the same level as non-vulnerable individuals.

This thesis thus provides evidence that healthy people with high levels of PP do not seem to show differences in performance on emotion regulation and ToM. However, they do show differences in brain activation and functional connectivity of relevant regions while performing the aforementioned tasks. We suggest that the observed increases in activation are likely to represent compensatory mechanisms at work. Patients with schizophrenia have been reported to show greater prefrontal and cingulate activation to maintain a similar level of performance to healthy controls (Callicott et al., 2003a). Notably, this is also observed in individuals at genetic risk for schizophrenia (Callicott et al., 2003b). These brain/behavior dissociations in vulnerable individuals are hypothesized to reflect that the presumed compensatory mechanisms appear to be working to a satisfactory extent (Marjoram et al., 2006).

**Structural MRI**

High PP (positive dimension) was not only associated with differences in brain function but also in brain structure. In particular, we detected differences in regional gray matter volume (GMV) in regions located within the posterior cortical midline (i.e. medial precuneus and posterior cingulate cortex). These regions play an important role, among other functions, in the processing of self-referential information. Interestingly, high psychosis-prone individuals also showed increased activation in the precuneus during self-referential processing (Chapter 4). While studies in ARMS individuals have commonly reported decreases in regional GMV, increases have also been described (Borgwardt et al., 2007a; Pantelis et al., 2003; Phillips et al., 2002). Although the reason for greater volumes is not completely understood, it has been argued that they may reflect compensation for early disturbances in other brain regions (Kawasaki et al., 2004), transient increases due to an active underlying pathological process (Meisenzhal et al., 2008), or abnormal brain maturation (i.e., delayed normal synaptic pruning) (Gotay et al., 2004). In addition, increases in GMV have been described in association with other pathologies, such as autism spectrum disorders (Palmen et al., 2005). Total brain volume increases have also been found in schizophrenia, correlated with worsening of symptoms (Garver et al., 2000). Moreover, larger precuneus has been previously reported in a VBM study of patients with schizophrenia (Antonova et al., 2005). In their study, Antonova and colleagues postulated that it would be interesting to investigate whether larger precuneus in healthy individuals is associated with greater schizotypy. Our results appeared to confirm their hypothesis. In vulnerable individuals to psychosis, increases have been proposed to reflect preexisting neurodevelopmental or maturational deficits occurring in adolescence/early adulthood. Alternatively, it is thought that they might be the morphological expression/consequence of a disease process underlying schizophrenic psychoses. In sum, the accumulated evidence for neuroanatomical correlates of different vulnerability states for psychosis and their clinical outcomes points to a complex pattern of brain abnormalities underlying different vulnerability levels of psychosis that involve not only volume reductions, but also volume increments within interconnected cortical and sub-
cortical structures (Koutsouleris et al., 2009; Lymer et al., 2006).

Finally, in patients with schizophrenia the severity of a specific positive psychotic symptom (auditory verbal hallucinations, AVHs) also influenced brain morphology. A number of regions located in the prefrontal, temporal and medial temporal lobes are long hypothesized to be key components of a network involved in AVHs (see Allen et al., 2008 for review). We observed that GMV within the left inferior frontal gyrus (IFG), a region involved in semantic processing, was positively associated with severity of AVHs. In addition, severity of AVHs influenced patterns of structural covariance between the left IFG and a number of regions within the aforementioned frontotemporal network. This supports the idea that these regions are indeed part of an intercorrelated functional network. Taken together, the results suggest that both clinical (schizophrenia patients) and subclinical (high PP individuals) positive psychotic experiences are associated with GMV alterations.

Methodological remarks and directions for future research

A number of methodological remarks must be discussed in order to aid interpreting the findings presented in this thesis in their appropriate context.

First, we selected high and low scorers on the Community Assessment of Psychic Experiences (CAPE, Konings et al., 2006) questionnaire based on the available literature on psychometrically identified PP, which has typically compared performance between groups selected upon this criterion. Moreover, it is worth noting that the distribution of PP in non-clinical samples does not show a normal distribution. Rather, it shows a half-normal distribution, with the majority of the population having very low values but a significant proportion having progressively higher values (van Os et al., 2009). Accordingly, the distance between the general mean of the distribution and the mean of the low psychosis-prone subjects is not expected to be significant. In addition, it is important to note the difference between the CAPE and other measures of proneness to psychosis such as the Launay–Slade Hallucination Scale (LSHS, Launay & Slade, 1981) or the Paranoia scale (Fenigstein & Va- nable, 1992). The items of the CAPE are more “pathological”, e.g. it does not tap on phenomena such as daydreaming. For example, the CAPE inquires whether the subject feels that he/she is being followed, that there is a conspiracy against him/her, or that there are messages in magazines or on TV specially designed for him/her. Very low levels on the CAPE are thus “normal”, whereas this is not the case for some other measures. In this light, the inclusion of average scorers would not have been expected to significantly alter the present findings. Nevertheless, future studies in PP including a control group of average scorers from the general population should help expand our findings. All experiments in this thesis have been described in sufficient detail so that the work can be repeated. Moreover, at this moment we are scanning the same fMRI protocol in a second control group, formed by subjects from a large community cohort in The Netherlands, the Tracking Adolescents’ Lives Survey (TRAILS). We aim to compare our high psychosis-prone group to this new control group (scoring 0.5 standard deviation around the mean) in order to test the replicability of results.

For the studies in structural MRI we applied voxel-based morphometry (VBM), a technique that permits comparisons of the entire brain volume at the single voxel level. We used the “op-
optimized” VBM method (Good et al., 2001) to minimize the potentially confounding effects of errors in stereotactic normalization. This method improves normalization by use of gray matter images and a gray matter template rather than anatomical (T1) images, and permits optional modulation of partitions to preserve the total amount of signal in the images. VBM has proved of good use to detect differences in regional gray matter volumes in patients with schizophrenia (Honea et al., 2005) as well as in individuals with an ARMS (e.g., Borgwardt et al., 2007b; Pantelis et al., 2003). Nevertheless, it is important to validate our findings using another method of analysis, such as a region of interest approach.

In the structural MRI study in PP, we observed a significant positive correlation between PP scores (CAPE) and depression scores (Beck Depression Inventory [BDI], Beck et al., 1996). We therefore decided to control for BDI using it as covariate of no interest in our analysis, and observed that the between-group differences in GMV remained significant. However, we did not control for depression scores in the functional MRI studies. While subjects with high PP had significantly higher BDI scores than those with low PP, it should be noted that none of the subjects had clinically relevant scores (mean score may be seen in Table 1 of Chapter 2.2.4). Unlike the CAPE, which identifies subjects with high PP based on the extremes of the distribution, the BDI has a cut-off score (13 points) upon which it is determined whether an individual is depressed or not. An association between symptoms of depression and the positive dimension of PP has been previously reported (Lewandowski et al., 2006), so that there might be an inherent difficulty to disentangle them. In consequence, the possibility that a “tendency” to have symptoms of depression influenced in part our results cannot be entirely ruled out. In order to test for this possibility, while writing this discussion chapter I have re-run all the analysis of our functional tasks adding BDI scores as covariate of no interest in the statistical designs. The results in all tasks (emotion regulation, self-reflection and theory of mind) remained unchanged. This renders more confidence in stating that the observed functional differences between groups were indeed related to psychosis proneness.

Finally, this thesis did not incorporate measures of neurocognition or social functional status. Functional decline within the last 6 months (including academic performance) was an exclusion criterion, given that on the contrary some of our subjects could already be meeting criteria for an ARMS (i.e., being already in a prodromal phase of psychosis) or a personality disorder. In addition, we investigated high-functioning individuals at the university level, so that significant differences between groups were not to be expected in neurocognitive measures such as IQ.
Implications for a model of vulnerability to psychosis

As discussed throughout this thesis, it is currently conceptualized that the experiences associated with schizophrenia and related disorders (such as paranoid delusional thinking and auditory hallucinations), which can be observed in an attenuated form in healthy people from the general population, could be regarded as the behavioral marker of an underlying liability for the disorder (van Os et al., 2009). This is consistent with the notion that psychotic symptoms might best be viewed as lying on a continuous distribution of deviancy, rather than as dichotomously deviant or nondeviant (Chapman & Chapman, 1980). Van Os and colleagues (2009) propose that this could be thought of “just as high blood pressure indicates high susceptibility for cardiovascular disease in a dose–response fashion”.

Prospective epidemiological studies have reported that about 10% of subjects psychometrically identified as psychosis-prone will go on to develop a schizophrenia-spectrum disorder (Chapman et al., 1994; Hanssen et al., 2005; Meehl, 1990). In this light, one important question to come to mind may be – *What are the mechanisms that lead from a subclinical to a clinical phenotype?*

A pathway to psychosis

While an accurate account of the pathophysiological mechanisms that lead to psychosis remains to be provided, there is substantial evidence for the role of a number of risk factors in the expression of a particular liability into a psychotic disorder. Nien-dam et al. (2009) have recently put forward a model summarizing vulnerability-related and progressive abnormalities in brain anatomy that are hypothesized to contribute to the manifestation of the clinical symptoms, cognitive impairment, and psychosocial dysfunction associated with progression toward psychosis in individuals with an ARMS. Although the onset of schizophrenia does not usually occur until adolescence or early adulthood, a number of insults throughout the pre-, peri-, and postnatal developmental periods are believed to increase the risk for developing schizophrenia. For instance, it has been shown that hypoxic complications during birth predict increased gray matter loss in those who develop schizophrenia (Cannon et al., 2002). During early development, it is hypothesized that early brain vulnerabilities such as reduced synaptic plasticity (Friston, 1998), hippocampal dysgenesis (Wood et al., 1997), and/or disruption of white matter integrity (Davis et al., 2003) affect later developmental processes in the brain. These later processes, such as aberrant synaptic pruning (McGlashan & Hoffman, 2000), peak during adolescence and are hypothesized to contribute to the onset of schizophrenia, and to the “disconnectivity” that appears to be characteristic of the disorder (Friston, 1998). Of course, various environmental triggers may interact with these brain changes. Epidemiological evidence suggests that psychosocial stress and/or early substance use may precipitate the onset of the disorder (Bebbington et al., 1993; Sugranyes et al., 2009). Ultimately, alterations in normal brain maturation (progressive gray and white matter changes) that take place during adolescence may have a large impact on the brain dysfunction seen in the prodromal phase of psychosis. For instance, it has been shown that ARMS individuals who go on to develop schizophrenia show differential gray matter loss over one year, relative to those who do not convert (Sun et al., 2009). Although the etiology of such changes in brain structure is unknown, they likely contribute to the overt expression of cognitive impairment in a variety of domains, including social cognition, that are observed in patients with established illness (e.g., Pinkham & Penn, 2006; Yoon et al., 2008).
Moreover, abnormalities in dopamine transmission, an excitatory neurotransmitter relevant to positive and negative symptoms of psychosis, have been reported not only in those with frank psychosis but also in subjects with proneness to psychosis (reviewed in Howes & Kapur, 2009). Deterioration in cognitive functions may accelerate during the prodromal period, in association with changes in brain functioning that lead to the development of florid psychotic symptoms (Feinberg, 1982; McGlashan & Hoffman, 2000) and functional decline in a variety of domains (Cosway et al., 2000).

Niendam and colleagues thus propose a comprehensive model for the putative pathway leading to psychosis, which would intuitively embrace the proportion of psychosis-prone subjects that go on to develop a clinically-relevant outcome. We nevertheless do not have data on these variables from our participants. That is, we do not know the degree of neurodevelopmental and environmental risk that our psychosis-prone participants are faced with. We do know, however, that they 1) had accessed higher education (they were university students), 2) lived in a relatively small city in a wealthy country, 3) were not using drugs, and 4) did not experience a decline in global functioning or academic performance over the 6 months prior to scanning. Hence, our participants would seem to have rather “protective” factors, or be at reduced risk, which might explain in part the absence of overt behavioral deficits in our experiments and the differences in brain activation that were tentatively interpreted as compensatory. The cross-sectional nature of our studies prevents us to elucidate whether the observed differences in brain function and structure may or may not ultimately lead to a full-blown psychotic disorder. According to current theoretical conceptualizations, this is likely to depend on the degree of neurodevelopmental and environmental risk that the person with PP is additionally exposed to (van Os et al., 2009).

With regard to factors that are relevant to the expression of a clinical outcome in individuals with high PP, emotional appraisal and degree of intrusiveness of the psychotic experiences have been found to be important determinants (Hanssen et al., 2005). This was also evident in a recent study with healthy subjects from the general population who experienced auditory verbal hallucinations (Sommer et al., 2008). Some individuals, faced with psychotic experiences, may develop distress and help-seeking behavior through dysfunctional attributions or coping styles, whereas others may not (Bentall et al., 2001; Birchwood et al., 2000; Garety, et al., 2001). Interestingly, in this thesis we detected differences in activation within neural correlates of emotion regulation and self-reflective processing in subjects with high positive PP. It is tempting to propose that, in the absence of added neurodevelopmental and environmental risk factors, the brain of an individual with PP may have the capacity to deploy compensatory resources that could ultimately prevent subclinical experiences to become clinically relevant. In light of the myriad of changes that occur during development in vulnerable individuals, future investigations should seek to examine whether changes in brain regions associated with social cognition undergo further changes in time, as well as how these relate to changes in global functioning, in order to determine if risk for transition is more closely associated with dynamic progressive changes. Such findings will set the stage for targeted interventions that can be applied to those at greatest risk for illness and long-term functional impairment.
A pathway to what psychosis?

**Schizophrenia-spectrum disorders.** Regarding the possible clinical outcomes of the subclinical psychotic phenotype, prospective epidemiological studies have reported that about 10% of subjects psychologically identified as psychosis-prone will go on to develop a schizophrenia-spectrum disorder (Chapman et al., 1994; Hanssen et al., 2005; Meehl, 1990). A high score on a questionnaire measuring schizotypal personality traits such as the one used in this thesis is therefore conceptualized as a phenotypic marker for possible development of psychosis (Chapman et al., 1994; Squires-Wheeler et al., 1991). Scales measuring positive schizotypy demonstrate characteristics of vulnerability indicators to schizophrenia and schizophrenia-spectrum disorders (Horan et al., 2008). Prior research on the association between schizophrenia-spectrum disorders and persons identified as being at heightened risk on the basis of their psychometric profiles have shown that such individuals have significantly elevated rates of avoidant, schizotypal, and paranoid personality disorders (Gooding et al., 2007; Thaker et al., 1993). Despite this overlap, subjects with PP are not psychosocially impaired and do not qualify for such a diagnosis (Lenzenweger, 1998). Psychometric scales serve a broader objective of predicting proneness to psychosis as opposed to a specific vulnerability to DSM schizophrenia (Thaker et al., 1993). Thus, such scales are related to psychosis, but it is less clear whether they are specifically related to schizophrenia. In this light, the results from our studies should be interpreted in reference to healthy people with proneness to psychosis as measured by self-report questionnaire, which have about tenfold increased risk for psychosis than people without such proneness, and among whom there are subjects who may be sharing overlapping features with schizotypal and paranoid personality disorder. Only longitudinal studies with larger samples should be able to elucidate the potential prognostic value of the observed neurobiological differences for predicting a specific psychiatric outcome.

**Non-schizophrenia psychosis.** Our findings in PP also merit some discussion in regards to non-schizophrenia psychosis. Previous studies examining symptom dimensions in schizotypy (Lewandowski et al., 2006) and schizophrenia (Ermsley et al., 1999) have consistently reported a much stronger relationship of mood symptoms with the positive than with the negative dimension. Chapman et al. (1994) reported that young adults identified as having positive PP exhibited markedly elevated rates of mood disorders at 10-year follow-up assessment relative to control and anhedonic participants. Affective dysregulation is thought to occur across the continuum of schizotypy, and it appears to be best conceptualized as part of the positive schizotypy dimension. Recent findings of an association between positive schizotypy and mania and hypomania through the Wisconsin Schizotypy Scales (Kwapil et al., 2008) was interpreted as consistent with the similarities in symptoms and genetic liability between mood and nonmood psychoses (Cardno et al., 1999). The cross-sectional nature of the present studies does not allow for the elucidation of whether alterations in the neural dynamics underlying social cognitive processing may have the potential to discriminate between schizophrenia or non-schizophrenia psychosis, or are common to both. As mentioned above, our results are restricted to subjects with proneness to psychosis, but it is not so clear what specific diagnosis would they have were they to progress to a clinical outcome.
Conclusion

In summary, this thesis was concerned with mechanisms that are central to disease susceptibility rather than a consequence of the disorder. These mechanisms appeared to relate to differences in brain function and structure, as well as to biased self-referential processing. Figure 1 depicts a conceptual model of the possible mechanisms underlying continuity/discontinuity between subclinical and clinical expressions of psychosis, derived from the integration of our results within current theoretical accounts (Niendam et al., 2009; van Os et al., 2009).

Figure 1. Psychosis proneness (subclinical phenotype) may become clinically relevant depending on the degree of neurodevelopmental brain susceptibility and environmental risk that the person is additionally exposed to. This thesis reports that psychosis proneness is associated with differences in brain function and structure. A vulnerable brain that leads to psychosis proneness might have capacity for compensation in the absence of added risk factors. This compensation could ultimately impede the development of a clinical outcome (blue pathway). Alternatively, given a higher degree of neurodevelopmental and environmental risk, brain differences associated with the subclinical phenotype may become dysfunctional, leading to the overt neurocognitive/social cognitive impairments, functional decline and exacerbation of psychotic symptoms that may eventually result in the clinical phenotype, that is, a psychotic outcome (orange pathway).

Whether the described brain differences associated with high PP are protective mechanisms that protect from frank psychosis should be clarified by further studies with a longitudinal focus, including larger samples and assessing genetic, prenatal/obstetric, and environmental risk factors throughout neurodevelopment and childhood. Such studies may also help ascertain normal or abnormal trajectories of brain development, as brain imaging findings in individuals at risk for psychosis across different stages seem to reside in regions (frontal and temporal cortices) which are dynamically changing during normal maturation.
References


Friston KJ. 1998. The disconnection hypothesis. Schizophr Res 30, 115-125.


Summaries