Summary and Discussion
Aim of the thesis
Schizophrenia is a complex psychiatric syndrome influenced by interactions between genetic and environmental risk factors. Emotion processing deficits play a key role in the disorder. Understanding the underlying mechanisms of these could help treat the disease more effectively in the future and may even potentially contribute to prevention. In this thesis, research was presented that examines various aspects of emotion processing using questionnaires, behavioral measures, functional magnetic resonance imaging (fMRI) and imaging genetics. We investigated various emotional processes such as emotion regulation, associative emotional learning and valence evaluation in three groups: patients with schizophrenia, non-psychotic first-degree relatives and healthy individuals with high levels of alexithymia.

Relatives of schizophrenia patients are an important source of information as they share part of the genetic vulnerability to develop the disorder, but without the confounds of antipsychotic medication use, severe cognitive deficits, hospitalisation or chronicity of psychosis. Studying high-risk groups gives insight into the pathophysiology of schizophrenia and may help to identify traits that are presumably core parts of the liability to the disorder.

Alexithymia is conceptualized as a personality trait characterized by difficulties in emotion regulation. More specifically, alexithymia refers to difficulties in identifying, describing and communicating emotions, difficulties in differentiating emotions from bodily sensations and diminished affect-related fantasy (Nemiah and Sifneos, 1970; Sifneos, 1973). Alexithymia is interesting because elevated levels of this trait have been reported in schizophrenia patients and in relatives of patients in previous studies (van ‘t Wout et al., 2007). Besides, alexithymia is also present in the healthy population. Therefore, studying deficits of emotion processing in the healthy population can help to understand emotional deficits in individuals with schizophrenia. At the same time, studying affective deficits in schizophrenia may provide information about what aspects of aberrant emotion processing are specifically linked to schizophrenia and how emotional processes function normally.

Emotion processing in alexithymia
In chapter two, we investigated different stages of emotion processing in healthy individuals with high verbalizing scores on the Bermond-Vorst Alexithymia Questionnaire (BVAQ) (Vorst and Bermond, 2001) compared to low-scoring individuals. We observed that individuals scoring high on the verbalizing scale scored also high on the other scales (identifying and analyzing) of the cognitive component of alexithymia, but relatively normal on the emotionalizing factor. Additionally, we investigated two emotion regulation strategies that are commonly used in daily life and lend themselves to investigation: reappraisal and suppression (John and Gross, 2004). Reappraisal is a cognitive strategy involving reinterpretation of a potentially emotion-eliciting situation into a situation with a different emotional impact. Suppression is a way of response modulation involving inhibition of emotion-expressive behavior. Reappraisal is regarded as a healthy emotion regulation strategy whereas suppression is related to unhealthy emotion regulation and less well-being. The high alexithymic group used less efficient emotion regulation strategies: they suppressed their emotions more and used less reappraisal. With regard
to cognitive-emotion processing, the alexithymic individuals performed worse at rapid recognition of emotional information from faces and at emotional mentalizing compared to the non-alexithymic group. Surprisingly, there were no specific deficits in processing of emotional language. Lane et al. (1997) suggested that in alexithymia emotional experience is blunted or absent in contrast to aposodic individuals who experience emotions fully. Thus, these two disorders rely on different mechanisms. Our study showed that individuals with alexithymia have a specific pattern of emotion processing difficulties and that the interaction of language and emotions might not be at the core of alexithymia.

**Emotion regulation in schizophrenia and relatives**

With respect to alexithymia, patients showed most difficulties on the cognitive component of the Bermond Vorst Alexithymia Questionnaire (BVAQ) comprising identifying, verbalizing and analyzing emotions. More specifically, patients reported most difficulties with analyzing and identifying their emotions, healthy controls reported the least problems with this, and the relatives were in between.

The study described in *chapter three* focused on emotion regulation, which is an important aspect of emotion processing. Difficulties in emotion regulation have, for instance, been suggested as the underlying mechanism for mood and anxiety disorders (Aldao et al., ; Eftekhar et al., 2009; Goldin et al., 2008). Recent studies have also shown that patients with schizophrenia use different emotion regulation strategies in comparison to healthy controls (Livingstone et al., 2009; van der Meer et al., 2009).

To get more insight into the neural mechanisms underlying emotion regulation strategies in individuals at increased risk for schizophrenia and schizophrenia patients, we investigated whether these groups showed differences in brain activation during reappraisal and suppression strategies compared to healthy controls.

Concerning reappraisal, patients showed less activation than controls in areas that have been related to cognitive control and emotion regulation (ventrolateral prefrontal cortex (VLPFC), dorsomedial prefrontal cortex (DMPFC) and insula) (Ochsner et al., 2002). Consistently, these areas have been shown to be less activated in schizophrenia patients during cognitive control (for a meta-analysis see Minzenberg et al., 2009).

During cognitive tasks, many studies demonstrated that frontal areas were less activated in schizophrenia patients whereas for relatives both increased and decreased activation has been shown in these areas (for a review see Fusar-Poli et al., 2007). Additionally, the anterior insula has been related to emotion processing and emotional awareness (Craig, 2009). In patients, decreased insula activation has been reported during processing of emotional stimuli (Wylie and Tregellas, 2010). Concerning suppression, our patients demonstrated less deactivation in right superior temporal gyrus extending into the posterior insula, and the DMPFC and dorsal anterior cingulate cortex. Activation of these areas has previously been associated with suppression (Goldin et al., 2008). Relatives demonstrated increased activation during reappraisal as well as suppression in prefrontal areas compared to both patients and healthy controls. Consistent with our findings in relatives, stronger PFC activation during reappraisal has also been demonstrated in psychosis-prone subjects (Modinos et al., 2010a). This increased activation might be a compensatory mechanism during emotion processing in
these individuals, while dysfunction of these areas might be a correlate of increased vulnerability to schizophrenia.

All groups were able to down-regulate their negative affect to some extent by using reappraisal or suppression. However, patients and relatives reported higher overall negative affect compared to controls. This is consistent with a study by Kring and Neale (1996), which suggests that schizophrenia patients may show similar or even stronger emotional reactivity than healthy subjects. We suggest, on the one hand, that patients are not able to recruit the required brain areas enough to down-regulate negative affect to a similar level as in controls. Relatives, on the other hand, may recruit compensatory resources as indicated by their increased brain activation. However, this may still not suffice for a reduction of negative affect to the level of controls as shown by the reported higher overall negative affect after both reappraisal and suppression.

**Associative emotional learning in schizophrenia**

Another important emotional process, that has been implicated in schizophrenia, is associative emotional learning, which is the focus of chapter four. Impairments in making an association between a word and an emotional state, may lead to difficulties in describing one’s feelings with words, which is a component of alexithymia (emotional verbalizing) (Aleman, 2005). Deficits in emotional verbalizing (van ‘t Wout et al., 2007) and associative emotional learning (Exner et al., 2004) have both been demonstrated in schizophrenia.

In this chapter, we investigated whether abnormalities in functional connectivity could underlie deficits in associative emotional learning. The abnormal functional integration of brain regions has been suggested to be an important pathophysiological mechanism of schizophrenia, also referred to as the dysconnection hypothesis (Stephan et al., 2009). Most prominently, the prefrontal cortex has been implicated in dysconnectivity in schizophrenia (Friston, 1998). Therefore, we designed an fMRI task in which participants had to remember neutral and emotional picture-word pairs and had to indicate whether they thought the pair was associated. Further, they filled in an alexithymia self-report questionnaire.

We observed that within the network involved in emotional processing patients indeed had decreased connectivity of frontal regions such as the dorsolateral prefrontal cortex (PFC), the medial PFC including the anterior cingulate cortex (ACC). Contrary to our expectations, we found no difference in connectivity of amygdala and hippocampus, which have been linked to emotional experience. Possibly, the identified differences in functional connectivity in areas related to executive control and emotion regulation underlie cognitive-emotion processing difficulties in schizophrenia. These findings are consistent with the self-reported difficulties in verbalizing, analyzing and identifying of emotions in the schizophrenia patients in combination with their self-reported intact subjective emotional arousal. The latter is consistent with recent findings of intact emotional experience in schizophrenia (van der Meer et al., 2009).

**Emotion, genetics and brain imaging**

Psychiatric syndromes are often complex and generally not the result of one gene or a specific combination of genes. Indeed, most psychiatric syndromes and certainly schizophrenia are polygenic, genetically multifactorial and partially penetrant (see
Kendler and Eaves, 2005; Mitchell and Porteous, 2011). Polygenic refers to the fact that the disease occurs only if several genotypes are present together. Genetically multifactorial indicates that several distinct genes (or sets of genotypes) can independently cause the disease. Finally, “partially penetrant” means that nongenetic factors are required, or the disease could be inherently stochastic. Genetic differences may help explain difficulties in emotion processing and the underlying neural mechanisms both in the healthy population and in schizophrenia. The candidate gene approach focuses on genetic variation of single genes that have a theoretically relevant link to the symptoms of interest, for instance, because they code for proteins involved in neurotransmission. In chapter five, we reviewed evidence for involvement of a number of gene polymorphisms in neural activation related to emotion processing. Studies into emotional brain systems have mainly been done into 5-HTTLPR (serotonin-transporter-linked polymorphic region). This is a polymorphism in SLC6A4, the gene that codes for the serotonin transporter (5-HTT). 5-HTT removes serotonin released into the synaptic cleft, and is an important regulator of serotonergic neurotransmission. The 5-HTTLPR polymorphism is composed of a short and long allele version, the short allele has been associated with higher serotonin levels in the synaptic cleft, which has been related to increased levels of anxiety and depression. However, a number of large studies have failed to replicate these associations. The short allele has been associated with increased amygdala activation (Hariri et al., 2002), and with decreased functional connectivity between ACC and amygdala. This might result in a dysregulation of the amygdala in response to negative stimuli (Pezawas et al., 2005). All studies of the 5-HTTLPR polymorphism imply a crucial involvement of 5-HTT in emotion processing.

The catechol-O-methyltransferase (COMT) gene has a polymorphism, COMT Val158Met, that has been related to emotional behavior and its underlying neural mechanisms. Catecholaminergic neurotransmission is central to neural circuits involved in cognitive and affective processing (Heinz and Smolka, 2006). The COMT Val158Met polymorphism results in altered enzyme activity of the COMT enzyme, leading to higher dopamine levels in the prefrontal cortex in Met allele carriers. The Met allele has been associated with better cognitive functioning on the one hand, but worse emotional functioning on the other hand. At the time of our review only a few studies into COMT and emotional brain systems had been done. The Met allele has been associated with increased activation in amygdala, hippocampus and prefrontal areas during viewing of negative stimuli (Smolka et al., 2005). Additionally, the Met allele has been associated with increased hippocampal formation and VLPFC activity during the matching of fearful and angry faces (Drabant et al., 2006). More studies should be conducted into COMT and emotional brain systems, both in normal emotion processing as in disturbed emotion processing in affective disorders.

Furthermore, we discussed other gene polymorphisms which have been related to emotion processing (tryptophan hydroxylase 2 (TPH2) gene, human choline transporter (CHT1) gene, the monoamine oxidase A (MAOA) gene and the human cannabinoid1 receptor (CNR1) gene). The relevance of interaction between polymorphisms was also highlighted. Finally, we discussed X-chromosomal disorders and emotional brain functioning.

Our review shows that genes for specific aspects of neurotransmitter function impact on emotion processing in the brain. Future research should further specify the
range of genes that is involved in emotion processing, their mechanism of action, and how this is related to brain circuits involved in emotion processing.

**Emotion processing and COMT**

As discussed in chapter five, the COMT gene is a genetic polymorphism which has received much interest in the field of emotion processing and psychiatric disorders. It has been related to both dopamine transmission and brain activation in the prefrontal cortex. As this gene might be (directly or indirectly) related to schizophrenia and has also been related to emotion processing, we wanted to investigate whether presence of the Met allele was directly related to both lower emotional verbalizing proficiency and differences in brain activation during emotion processing. Specifically, we investigated in chapter six whether COMT genotype in healthy controls would be associated with differences in activation in cortical midline structures during valence evaluation of words. Therefore, healthy controls were genotyped for COMT Val158Met polymorphism and evaluated the valence of words during fMRI.

We observed that the number of Met alleles was associated with more difficulties in verbalizing feelings. Additionally, a higher number of Met alleles resulted in lower neural activation in posterior cingulate gyrus and precuneus (cortical midline structure) during valence evaluation of words. This might be associated with lower emotional awareness, which in turn may be related to susceptibility for affective disorders. Although a recent meta-analysis did not find a direct link between COMT and schizophrenia (Okochi 2009) or depression (Lopez-Leon et al. 2008), they might be indirectly linked via an intermediate phenotype as expressed by neural systems related to emotion processing. Our finding may eventually result in new insights into the complex relationship between COMT genotype and emotional processing underlying both normal variation in affective processing and susceptibility to affective disorders.

**Integration of results of the conducted studies**

Schizophrenia is considered a non-affective psychotic disorder. However, in clinical interviews it has been demonstrated that schizophrenia is characterized by anhedonia and affective flattening. Additionally, laboratory studies have shown preserved or even stronger emotional experience and responsivity in schizophrenia patients (for an overview see Blanchard et al., 2007). In this thesis, we excluded patients diagnosed with a schizo-affective disorder, but nonetheless we found clear difficulties in emotional processing in individuals with schizophrenia. Only a few studies examined the relationship between schizophrenia, alexithymia or emotion regulation strategies (Cedro et al., 2001; Henry et al., 2008; Livingstone et al., 2009; van der Meer et al., 2009). Only one study has been published which also included relatives (van ’t Wout et al., 2007). We further established the role of alexithymia in schizophrenia patients and relatives (chapter three and four). Additionally, patients and relatives showed enhanced negative emotional experience (chapter four). Furthermore, schizophrenia patients (chapter three) reported the same pattern of employment of less healthy emotion regulation strategies as healthy participants with high alexithymia scores (chapter two). Reduced expressivity is also similar in both schizophrenia patients and alexithymic subjects (chapter two). Although there seems to be a disjunction in expression,
experience and psychophysiological components of emotions in schizophrenia, profound difficulties in emotion processing are present. Therefore, the term “non-affective” seems inappropriate to describe schizophrenia. In addition, boundaries between psychiatric disorders are not clear cut. For instance, patients with bipolar disorder, an affective disorder, often suffer from psychosis (see van Os and Kapur, 2009). Thus, schizophrenia has a clear affective component and may show more similarities with affective disorders as formerly thought.

For a complete understanding of emotion processing in schizophrenia, investigating genetics, neurobiology and behavior is important. Moreover, the integration of results from these different areas is crucial. There is a growing body of research on the neural mechanisms underlying emotion processing in schizophrenia. Most studies show an abnormal response during emotion processing in schizophrenia patients compared to controls characterized by both hyperactivity and hypoactivity in areas important for emotion processing (a.o. VLPFC, DMPFC, amygdala, hippocampus, insula) depending on the specific tasks (Aleman and Kahn, 2005; Phillips et al., 2003b) but also no differences have been reported (Anticevic, 2011; Becerril and Barch, in press; Dowd and Barch, 2010). During emotion regulation, we demonstrated that schizophrenia patients showed decreased activation in areas important for cognitive control and emotion (VLPFC, DMPFC and insula) (Ochsner et al., 2002) (chapter four).

Brain areas heavily interact with each other. Therefore, not only activation of distinct areas but also connectivity between areas may shed light on abnormalities in brain function in schizophrenia. Abnormal functional integration of brain regions has been suggested to be an important pathophysiological mechanism of schizophrenia (Friston, 1998; Stephan et al., 2009). Indeed differences in connectivity have been demonstrated in during cognitive tasks (Meyer-Lindenberg et al., 2005) and rest (Calhoun et al., 2009).

The decreased connectivity, as described in this thesis, in patients in areas related to cognitive control and emotion regulation during associative emotional learning may constitute a neural basis for the self-reported difficulties in identifying, analyzing and verbalizing their feeling. In addition, the absence of differences in connectivity as well as brain activation in regions associated with emotional memory and experience, might underlie the similar level of reported emotional experience (chapter four). Partly in line with our results, very recently, Anticevic et al. (2011) demonstrated that in schizophrenia patients amygdala recruitment and reported experience of emotion were similar as in controls during a perceptual decision task with emotional distracters. Importantly, patients showed a weaker prefrontal-amygdala coupling, and this predicted negative symptoms.

In addition to studying neural processes in patients, individuals at increased genetic risk for schizophrenia might provide important information with regard to pathophysiological mechanisms of the disorder. However, research on the neural basis of emotion processing in relatives is scarce. Only two studies have been published about this topic (Habel et al., 2004; Venkatasubramanian et al., 2010). They reported during viewing negative emotional expressions decreased frontal (Venkatasubramanian et al., 2010) and amygdala activation (Habel et al., 2004; Venkatasubramanian et al.). We, for the first time, investigated the neural mechanisms underlying emotion regulation in patients, relatives and controls. Relatives showed increased activation during down-regulation of negative affect. This points towards the employment of more resources in relatives and might reflect a compensatory mechanism (chapter four). For cognitive
processing, a compensatory mechanism in relatives has also been proposed (MacDonald et al., 2009). Indeed, differences in emotion regulation and its underlying neural mechanisms in individuals at increased genetic risk might point towards a vulnerability marker for schizophrenia.

With respect to genetics, no gene or combination of genes is characteristic of a complex disorder as schizophrenia. A gene might be closer to a specific trait, that is also present in the disease, than to a complex psychiatric syndrome. With regard to the COMT gene and emotion processing, we demonstrated that Met allele carriers in the healthy population have more difficulties in emotional verbalizing (chapter six). Schizophrenia and COMT genotype have been associated because both are related to differences in dopamine transmission and prefrontal functioning. If a relationship between COMT and schizophrenia is demonstrated, the Val allele has been reported to have a higher incidence in schizophrenia (Voisey et al., in press) but with inconsistent results (Okochi, 2009). Additionally, Caspi et al. (2005) demonstrated that the use of cannabis is associated with risk for psychotic symptoms only in carriers of the COMT Val158 allele. Concluding from our results, it would be expected that the Met allele would be more present in schizophrenia patients because they reported more difficulties in emotion processing (chapter two and three) as did the Met allele carriers (chapter six).

As effects of genetic variation on the level of the brain might be more direct than on complex behavior, combining imaging and genetics might help clarify differences in emotion processing both in the healthy population and in schizophrenia (see Meyer-Lindenberg and Weinberger, 2006). With regard to the effect of COMT genotype on neural mechanisms underlying emotion processing, a higher number of Met alleles resulted in lower activation in posterior cingulate gyrus (PCC) during valence evaluation in healthy individuals (chapter six). Interestingly, during the same task, a similar activation pattern as in Met allele carriers was demonstrated in schizophrenia patients in our lab (Liemburg et al. in preparation). Possibly, the COMT gene has differential effects on brain activation in healthy participants and patients with schizophrenia. Indeed, Prata et al. (2009) found that during a verbal fluency task the Val allele was associated with greater fronto-temporal activation in patients with schizophrenia but found the opposite effect in controls. Additionally, similar effects of the COMT gene on working memory performance were reported in a meta-analysis (Barnett et al., 2008) with opposing directions in schizophrenia patients and controls.

In addition, no single gene can account for all variance in emotion processing. For instance, several neuromodulators (e.g. dopamine and serotonin) with different genes important for their functioning, are implicated in emotion processing. Besides, interactions between genes contribute to differential effects on cognitive and emotion processing (chapter five).

Taken together, emotion processing differs in schizophrenia patients, relatives, and individuals with high alexithymia scores. In addition, neural mechanisms underlying emotion processing show different patterns in these groups. Also, COMT genotype effects emotion processing and its underlying neural mechanisms. For a complete understanding of emotional processing in schizophrenia further research is needed. Individuals at increased risk might provide important information on how genetic influences contribute to emotion processing differences and vulnerability for psychiatric disorders. Hence, high-risk individuals should be included in emotion processing studies. Additionally, other genetic polymorphisms and gene-gene interactions should be taken into account. Finally,
integrating brain, behavior and genetics would help clarify emotion processing and its underlying mechanisms both in the healthy population and in psychiatric disorders.

Methodological considerations and future research
In this thesis, we investigated emotion processing using different measures ranging from self-report questionnaires to fMRI and imaging genetics in different populations. The obtained results in the different experiments were not always easy to compare and several considerations are in order. I will also present some directions for future investigations.

During associative learning of emotional picture-word pairs, we found that patients had decreased connectivity in areas related to cognitive control and emotion regulation such as the dorsolateral prefrontal cortex and the medial prefrontal cortex including the anterior cingulate cortex. We found no evidence of differences in brain activation between patients and controls. During reappraisal of negative emotional pictures however, patients demonstrated decreased brain activation in ventrolateral prefrontal cortex, dorsomedial prefrontal cortex (DMPFC) and insula. No connectivity analysis on these data has been performed yet, but it may be very informative as differences in connectivity have been implicated in emotion regulation ability (Ochsner et al., 2002). For instance, the tendency to be mindful has been related to increased connectivity between DMPFC and amygdala (Modinos et al., 2010b). Moreover, in psychosis-prone subjects less prefrontal-amygdala coupling during reappraisal has been reported (Modinos et al., 2010a). Also, differences in connectivity have already been demonstrated in patients during associative learning (chapter four), working memory and rest (for a review see Calhoun et al., 2009). We hypothesize that connectivity between prefrontal areas, important for cognitive control, and limbic areas, important for emotional experience might be attenuated in our patients during emotion regulation as they were less able to down-regulate their negative affect. In relatives, we predict the same pattern as patients, also consistent with Modinos et al. (2010a).

With regard to sample selection, in the studies on emotion processing and COMT and in relation to alexithymia (chapter two and six, respectively), we included university students, who on average function at a high level. This may limit the generalizability of the findings. Despite the homogeneity of the groups, we were able to define specific emotion processing deficits in these groups. However, people with very high levels of alexithymia, e.g. patients with psychosomatic complaints, may be more impaired and present a broader range of emotion processing deficits. Possibly, studying alexithymia and emotion processing difficulties in these patients will provide information about course of the illness. Regarding the COMT polymorphism, we included relatively young participants (mean age 21 years with standard deviation 5 years). As methylation of the COMT gene (influenced by aging, nutrition and life events, amongst others) can lead to changes in gene activity, different results may be achieved in older samples due to epigenetic mechanisms (cf. Abdolmaleky, 2006).

In the studies into schizophrenia (chapter three and chapter four), we chose to include a stable patient sample with relatively low levels of symptomatology. We did not distinguish between positive and negative symptoms. Reduced amygdala activation in schizophrenia patients has been related to flat affect (Aleman and Kahn, 2005; Fahim et al., 2005). Thus, patient samples with pronounced negative symptoms may demonstrate
different activation patterns from other patients. Therefore, investigating patients characterized by specific symptoms might add important information to reported difficulties in emotion processing.

An important limitation might be the use of medication. Most of our patients used antipsychotic medication while control participants and relatives did not. This might have influenced task performance and brain activation in patients. It has been suggested that antipsychotic medication reduces brain activation. However, studies including medication-free patients show similar results as studies examining patients on medication with regard to brain activation, emotional expressivity and emotional experience (see Aleman and Kahn, 2005). In addition, studies into relatives of schizophrenia patients might provide important information about the disorder without the confounding effects of medication or chronicity of psychosis (chapter three). Of note, as a large proportion of patients has to use medication chronically, it is also important to understand how they function on medication.

**Clinical implications**

In this thesis, we investigated important emotion regulation strategies, reappraisal and suppression. Our findings may give directions for clinical implications that could help bridge the gap between fundamental knowledge and implications for treatment.

We demonstrated that schizophrenia patients use less reappraisal. Moreover, the neural mechanisms underlying reappraisal were different in schizophrenia. There is some evidence that psychological treatment or cognitive training might alter neural pathways involved in reappraisal. Bryant et al. (2008) demonstrated that activation of the amygdala and anterior cingulate cortex in response to fearful faces predicts the success of cognitive behavioral treatment in patients with post-traumatic stress disorder. On the basis of this study, Hartley and Phelps (2010) suggest in their review that success of therapy depends on functional integrity of neural circuitry and the success with which individuals are able to use these regulatory mechanisms. Recently, Haut et al. (2010) reported that after cognitive training regions in the prefrontal cortex (DLPFC, ACC, frontopolar cortex) showed an increase in activation. The extent to which the activity increased, predicted behavioral improvement. Also, Eack et al. (in press) demonstrated in patients with early course schizophrenia greater preservation of gray matter volume in medial temporal regions and increased gray matter volume of the left amygdala after a 2-year cognitive enhancement therapy, including social-cognitive exercises (e.g. perspective taking and emotion management). Less gray matter loss in medial temporal regions and increases in amygdala were related to improved cognition. Interestingly, these regions are implicated in social cognition. While relatives show difficulties in emotion processing and differences in underlying brain activation patterns (chapter three), it might be of importance to investigate whether high-risk groups might also benefit from the neuroprotective effect of cognitive enhancement therapy. A recent review from Smyth and Arigo (2009) concludes that emotion regulation interventions may improve health and well being in at-risk and clinical populations. Future research should elucidate if emotion regulation processes might benefit from treatment or training specifically targeting brain areas involved in emotion regulation both in psychiatric disorders and in individuals at increased risk for psychiatric disorders.
We showed that schizophrenia patients, relatives (chapter three) and individuals with high alexithymia levels (chapter two) used more suppression as emotion regulation strategy compared to controls. The use of suppression has been negatively related with well-being (Gross and John, 2003) and increased stress (John and Gross, 2004). Stress has been implied as a factor important for the onset of psychosis. As relatives are already at increased risk for developing psychosis, increased stress might be detrimental, and suppression might thus be an inadequate strategy. Therefore, a different use of emotion regulation strategies might be helpful to reduce stress.

Training or therapy focused on awareness, recognition and regulation of emotions might be beneficial for individuals using suppression as emotion regulation strategy. Greenberg (Greenberg, 2002) proposed one such approach, named “emotion-focused therapy”. In this approach, patients are taught how to become aware of their emotions, to understand their bodily reactions, and to express emotion in a context appropriate way. Although not specifically designed for patients with schizophrenia, their relatives or alexithymic individuals, it could be tailored to each individual. This might lead to better understanding and regulating emotions in individuals with emotion processing difficulties.

Mindfulness, rather popular at the moment, might also be useful for better emotion regulation. Mindfulness is defined as paying total attention to the present moment with a non-judgmental awareness of inner and outer experience. Mindfulness based interventions seem helpful in reducing stress and could be useful for the treatment of physical and mental disorders (for a review see Chiesa and Serretti, in press). Most importantly, recent studies point towards effectiveness of mindfulness based therapy in schizophrenia (Chadwick et al., 2009) with a positive effect on cognition and affect (Taylor et al., 2009).

In sum, although clinical implications were not the direct target of the research presented in this thesis, more knowledge regarding the nature of emotional abnormalities in schizophrenia can ultimately lead to a better clinical understanding and hence pave the way for novel treatment strategies.