Summary and general discussion
Patients with schizophrenia have difficulties in the processing and regulation of emotions (Kring and Elis, 2013; van der Meer et al., 2009). Furthermore, aberrant brain activation patterns during emotion processing and regulation have been reported in these patients (Morris et al., 2012; Taylor et al., 2012; van der Meer et al., 2014). The aim of this thesis was to examine whether these difficulties and aberrant neural correlates are already present in subjects at high risk for developing psychosis. To this extent, we examined brain activation during emotion processing and regulation in three groups at (putative) high risk for psychosis, namely individuals with high scores on alexithymia, individuals at genetic risk for psychosis (siblings of patients) and individuals at ultra-high risk (UHR) for psychosis. Moreover, we examined whether regions involved in emotion processing and regulation showed structural abnormalities in these increased risk groups. Examining emotion dysregulation in groups at high risk for psychosis may provide insight into emotion dysregulation as a possible vulnerability factor for developing psychosis, and subsequently, may give indications for therapies in these at-risk groups. In this chapter, the main findings of the presented studies (chapter 2-8) will be summarized briefly first. Subsequently, the findings will be discussed and recommendations for future research and clinical implications will be highlighted.

| SUMMARY |

To integrate previous neuroimaging literature on emotion processing in alexithymia, we performed a meta-analysis, presented in chapter 2. The results showed that alexithymia is associated with higher activation in the dorsal anterior cingulate cortex (ACC) during the processing of negative and positive stimuli. This may indicate stronger recruitment of neural resources, possibly due to a higher cognitive demand in individuals with high scores on alexithymia. During negative emotion processing, alexithymia was related to lower activation in 1) an emotional attention network (e.g. amygdala and visual cortex), 2) brain areas with mirror neuron properties (e.g. the dorsal premotor cortex, the parietal cortex and the supplementary motor area) and 3) the dorsomedial prefrontal cortex (DMPFC). This lower activation was suggested to underlie decreased attention to negative stimuli, poor empathic skills and emotion regulation problems related to alexithymia. Furthermore, insula and precuneus activation was lower during positive emotion processing, probably underlying lower positive affect. Taken together, these results support the hypothesis that alexithymia is associated with aberrant brain activation patterns during emotion processing, which may underlie the emotion processing difficulties that individuals with high alexithymia experience.

In chapter 3, we examined whether the two alexithymia dimensions (i.e. cognitive and affective alexithymia) are related to different morphological profiles. We found that in non-clinical individuals the cognitive alexithymia dimension was related to lower gray matter volume (GMV) in the dorsal ACC, a region suggested to be involved in emotion recognition and regulation. In contrast, the affective dimension appeared to be related to lower GMV in the medial orbitofrontal cortex (MOFC), which may play a role in emotional arousal and imagination. Furthermore, the affective dimension was associated with lower white matter volume in the superior longitudinal fasciculus which may be involved in fantasizing and imagination. These findings support the idea of two separable alexithymia dimensions as they appear to be subserved by dissociable structural correlates.

In chapter 4, we examined the hypothesis of alexithymia as an emotion regulation deficit using fMRI. The results revealed that, in a group of non-clinical individuals, alexithymia was associated with lower activation in emotion attention and recognition areas during emotion perception. However, brain activation did not differ as a function of alexithymia during
emotion regulation (i.e. suppression and reappraisal). Furthermore, individuals with high scores on alexithymia were equally capable of applying emotion regulation as individuals with low scores. These results suggest that alexithymia may arise from an early emotion perception deficit instead of compromised neural circuits subserving explicit emotion regulation.

In chapter 5, we examined whether alexithymia is associated with the degree of risk for psychosis. The results revealed that both patients with schizophrenia as well as individuals at high risk for psychosis had higher levels of cognitive alexithymia combined with low or normal levels of affective alexithymia compared to controls. Furthermore, subjects at UHR for psychosis had higher cognitive alexithymia scores compared to siblings of patients with schizophrenia. This suggests that cognitive alexithymia may be part of the vulnerability for psychotic disorders.

The aim of chapter 6 was to examine whether siblings differ from controls on gray matter volume and concentration. The results revealed no differences between these two groups on both gray matter measures. Furthermore, specifically selecting subjects on age, genetic loading or schizotypy did not alter these findings. Thus, gray matter as measured through voxel-based morphometry, might not be a suitable endophenotype for schizophrenia.

To examine the use and neural correlates of emotion regulation in subjects at genetic risk for psychosis, we performed an fMRI-study on emotion regulation in siblings of patients with schizophrenia (chapter 7). No differences were found between the sibling group and the control group on the use of emotion regulation, nor the underlying neural correlates. These non-significant findings suggest that solely being a sibling of a patient with schizophrenia by itself may not imply impaired emotion regulation capacities.

In chapter 8, we studied emotion regulation in subjects at UHR for developing psychosis. The results revealed lower ventrolateral prefrontal cortex (VLPFC) activation during reappraisal in the UHR group as compared to the control group. The VLPFC is involved in the cognitive regulation of emotions and VLPFC activation has been positively related to reappraisal success. Furthermore, UHR individuals reported less use of reappraisal in daily life compared to controls. These results support the hypothesis that emotion dysregulation may already be present before the onset of a psychotic disorder.

**ALEXITHYMIA**

**The neural correlates of emotion processing in alexithymia**

Alexithymia is a putative risk factor for developing psychosis (van ‘t Wout et al., 2007; van der Meer et al., 2009) and emotion processing deficits lie at its core (Grynberg et al., 2012; Nemiah and Sifneos, 1970; Taylor et al., 1997). Therefore, in this thesis, we examined alexithymia-related neural correlates of emotion processing in order to gain more knowledge on the underlying neural basis of these deficits. As outlined in chapter 1, emotion processing is not a unitary construct, but instead consists of different phases (Smith and Kirby, 2000). The results of this thesis show that alexithymia is associated with aberrant structural and functional neural correlates involved in the early phases of emotion processing (e.g. appraisal detection and emotion generation), while the neural correlates of emotion regulation, a later phase, may remain intact.
Appraisal detection

Appraisal detection is the phase in which a relevant stimulus is detected and attention is drawn toward this stimulus (Smith and Kirby, 2000). The findings in this thesis show that alexithymia is associated with lower activation in regions involved in early appraisal detection, namely the amygdala and visual cortex (chapter 2 and 4). More specifically, these regions are responsible for early emotion detection and directing (visual) attention toward emotional stimuli (Adolphs, 2002a; Vuilleumier, 2005). The findings of abnormal activation during early appraisal detection in alexithymia are supported by two EEG studies, which showed aberrant event-related potentials (ERP) in alexithymia already during the early phases of emotion processing (Delle-Vigne et al., 2014; Goerlich et al., 2012). This aberrant activation may be specifically underlying the emotional attention deficits (Mueller et al., 2006; Suslow et al., 2003) and the emotion identification difficulties (Lane et al., 2000) in alexithymia. Recent research has supported this hypothesis by showing lower amygdala activation in high versus low alexithymia during an emotional facial identification task (Jongen et al., 2014). This lower activation was associated with worse task performance (Jongen et al., 2014). Furthermore, our findings and previous reports specifically point to an association between lower amygdala activation and the difficulties in identifying feelings in alexithymia (chapter 4; Jongen et al., 2014; Kugel et al., 2008; Pouga et al., 2010; Reker et al., 2010). Therefore, we suggest that alexithymia is related to lower activation in early appraisal detection regions, which might be specifically underlying the difficulties in identifying feelings.

Emotional stimuli may trigger associated knowledge, such as memories, which can influence appraisal detection (Smith and Kirby, 2000). For example, when seeing a dog, the memory of being bitten by a dog last month can result in a stronger appraisal detection (e.g. higher amygdala activation). It has been suggested that the (para)hippocampal formation is involved in creating this association between memories and perceived emotional stimuli (Adolphs, 2002a; Smith and Kirby, 2000). The results of chapter 4 revealed lower activation in the parahippocampus in association with alexithymia during negative emotion processing. This is in accordance with recent published data (Jongen et al., 2014). Furthermore, another recent study has shown that high levels of alexithymia combined with early life stress resulted in lower hippocampal volume (Aust et al., 2014). Even though further research on the relation between alexithymia and the (para)hippocampal complex is necessary, these findings suggest that alexithymia might be related to impaired emotional memory associations. This, in turn, can result in lower appraisal detection as the appraisal detection might be less influenced by associated knowledge.

Emotional response and emotional awareness

After appraisal detection, an emotional response is formed and, if strong enough, emotional awareness is generated (Smith and Kirby, 2000). The MOFC is a region involved in the formation of this emotional response by generating an affective state (Rothkirch et al., 2012; Rudrauf et al., 2009). The findings of chapter 3 showed that alexithymia was associated with lower GMV in this region, which was specifically related to higher scores on the affective alexithymia dimension (i.e. lower levels of emotional arousal). This suggests that in individuals with high affective alexithymia, the capacity to generate an affective state might be lower.

Furthermore, chapter 3 showed lower GMV in the dorsal ACC in relation to alexithymia. This region has been associated with the cognitive processing of emotions and is thought to be involved in processes such as emotion recognition and emotional awareness (Etkin, 2010;
Etkin et al., 2011). This lower dorsal ACC volume may indicate a lower functional capacity of this region, which could support the proposed inverted U-shape hypothesis from chapter 2. This inverted U-shape hypothesis suggests that during simple emotion processing tasks, such as passive viewing of emotional pictures, activation of the dorsal ACC is higher in alexithymia compared to controls, which may reflect a compensatory mechanism. When task difficulty increases, for example when identification of emotional stimuli is required, this activation may drop and hence, task performance may decline. This hypothesis was proposed because the meta-analysis in chapter 2 revealed higher dorsal ACC activation in alexithymia, while several other studies had reported lower activation in this region (Kano et al., 2003; Karlsson et al., 2008; Moriguchi et al., 2007). Furthermore, such an inverted U-shape of ACC activation has previously been reported in patients with obsessive compulsive disorder (Koch et al., 2012).

Recently, two new studies on the neural correlates of alexithymia reported lower ACC activation in individuals with high alexithymia (Chester et al., 2014; Jongen et al., 2014). The first study provided support for the inverted U-shape hypothesis as lower dorsal ACC activation was found during a more cognitive demanding emotion recognition task (Jongen et al., 2014). Furthermore, this task was more difficult for individuals with alexithymia than controls as reflected by their lower performance (Jongen et al., 2014). The second study reported lower dorsal ACC activation in alexithymia during a social exclusion task (Chester et al., 2014). This result might be explained by a second hypothesis regarding the diverse findings on dorsal ACC activation in alexithymia, which was originally proposed by Kano and Fukudo (2013) and further described in chapter 2. This hypothesis suggests that stimuli with a physical context, such as pain, might elicit higher dorsal ACC activation in alexithymia. This hypothesis was based on several studies showing higher ACC activation in alexithymia during pain-related tasks (Kano et al., 2007; Moriguchi et al., 2007). Based on indications that the neural correlates of social exclusion and pain are quite similar (Kross et al., 2011), one would expect higher dorsal ACC activation in alexithymia during social exclusion. However, Chester et al. (2014) reported lower ACC activation related to alexithymia. This discrepancy might be explained by the suggestion that social exclusion during a cyberball task (as applied by Chester et al., 2014) is less intense than physical pain or social exclusion in daily life and the emotional content might therefore be more difficult to detect (Kross et al., 2011). This could indicate that individuals with alexithymia might have experienced more difficulties in identifying social exclusion in the study of Chester et al. (2014), which could explain the lower dorsal ACC activation. If dorsal ACC activation dropped due to higher task difficulty, this would be in line with our inverted U-shape hypothesis of dorsal ACC activation in alexithymia. However, this hypothesis regarding the findings of Chester et al. (2014) remains speculative as no behavioral measures on the level of experienced rejection were included during this task.

Taken together, recent literature provides further support for the inverted U-shape hypothesis of dorsal ACC activation in alexithymia, which might be caused by lower capacity of this region as reflected by the lower dorsal ACC volume. This suggests that when emotional responses are strong enough to reach awareness, individuals with alexithymia might experience difficulties recognizing and analyzing these feelings due to aberrant functioning of the dorsal ACC.

**Emotion regulation**

After the generation of a subjective emotional state, emotion regulation may take place to change this emotional response (Gross, 1998). Alexithymia has long been regarded an
emotion regulation deficit (Aleman, 2005; Taylor et al., 1997; Taylor and Bagby, 2004). Therefore, we suggested in chapter 2 that the lower DMPFC activation found in association with alexithymia during emotion processing might have been underlying emotion regulation difficulties. However, in chapter 4, we examined the neural correlates of emotion regulation and did not find any activation differences related to alexithymia. Furthermore, individuals with high levels of alexithymia were equally capable of down regulating their negative affect through emotion regulation as individuals with low alexithymia levels. It is possible that the lower DMPFC activation found in chapter 2 did not reflect less efficient emotion regulation as this is not the only function of this region. The DMPFC is also involved in the generation of the emotional response and subsequently, the formation of an affective state (Kober et al., 2008; Phillips et al., 2003). Therefore, the lower DMPFC activation during emotion processing reported in our meta-analysis (chapter 2), may also indicate abnormalities during the generation of an affective state. Another possibility is that the lower DMPFC activation reflected difficulties with implicit emotion regulation, instead of explicit emotion regulation, since implicit regulation often takes place when people are presented with negative stimuli (Gyuruk et al., 2011). In our emotion regulation task (chapter 4), participants were explicitly trained and cued to perform emotion regulation, which might have made it less difficult to regulate negative affect. Furthermore, we should acknowledge the possibility that our emotion regulation task may not have been difficult enough to find subtle emotion regulation deficits. For example, we used static photographs which are probably more easy to regulate than real life situations (for more discussion on the emotion regulation task, see page 169). Future research should use more realistic stimuli, such as movie clips, to further examine emotion regulation in alexithymia. However, our results do show that when explicitly trained and cued to perform reappraisal in a lab-based setting, the neural correlates of emotion regulation appear intact in alexithymia.

In conclusion, alexithymia seems to be related to functional and structural correlates in regions involved in appraisal detection, the generation of emotional responses and the awareness thereof. This pattern resembles the pattern of lower activation in patients with schizophrenia during emotion processing (Taylor et al., 2012; Li et al., 2010). However, while in patients lower prefrontal activation during emotion regulation has been found (van der Meer et al., 2014; Morris et al., 2012), the neural correlates of emotion regulation appear to be intact in alexithymia. At least, when individuals with alexithymia are explicitly trained and cued to perform emotion regulation. This suggests that alexithymia might be more an emotion perception and generation deficit than an emotion regulation disorder.

The two dimensions of alexithymia

As described in chapter 1, it has been suggested that alexithymia might not be a uniform construct, but may comprise of two different dimensions, a cognitive and affective alexithymia dimension (Vorst and Bermond, 2001). The cognitive dimension consists of the identifying, analyzing and verbalizing subscales, while the affective dimension consists of emotionalizing and fantasizing (Vorst and Bermond, 2001). Based on these dimensions, different alexithymia types have been proposed (Bermond et al., 2007). Type-I alexithymia is characterized by high levels of both cognitive and affective alexithymia. Individuals with type-I alexithymia therefore experience lower levels of emotional arousal and fantasizing, together with impaired emotional cognition (e.g. difficulties in identifying, analyzing and verbalizing feelings). In contrast, type-II alexithymia is characterized by high levels of cognitive alexithymia together with low or normal levels of affective alexithymia. This indicates that individuals with type-II alexithymia have normal or heightened levels of
emotional arousal, while the cognitions accompanying these emotions (such as verbalizing and analyzing emotions) are impaired (for a schematic representation of the alexithymia dimensions and types, see Figure 1.1 in chapter 1). These alexithymia types and dimensions have been psychometrically identified (Bailey and Henry, 2007; Bermond et al., 2007; Vorst and Bermond, 2001). However, there has been some debate on whether they actually exist (Bagby et al., 2009). It has been previously suggested that the two alexithymia dimensions might be related to separable neural correlates, which could support the existence of these two dimensions (Bermond et al., 2006; Larsen et al., 2003; Wingbermühle et al., 2012). However, as outlined in chapter 2, most neuroimaging literature solely focused on the cognitive alexithymia dimension, because the most applied alexithymia questionnaire (TAS-20) does not assess the affective dimension (Bagby et al., 1994).

The structural and functional imaging results described in this thesis indicate that the two alexithymia dimensions are related to dissociable neural correlates. The cognitive dimension was related to lower activation in appraisal detection regions, such as the amygdala and visual cortex (chapter 2 and 4). This result is in agreement with the study of Pouga et al. (2010), the only other fMRI study examining the neural correlates of the two alexithymia dimensions. They reported an association between the cognitive dimension (e.g. identifying subscale) and lower amygdalar activation, which also indicates that the cognitive dimension might be specifically related to the aberrant activation during early appraisal detection in alexithymia. In line with this hypothesis, an EEG study of Goerlich et al. (2012) showed that aberrant early ERP components, related to appraisal detection, were associated with the cognitive dimension, but not the affective dimension.

In relation to the affective dimension, no aberrant activation patterns were found in this thesis (chapter 4). This finding is in contrast with the study of Pouga et al. (2010), who reported higher ACC and lower premotor cortex activation in association with the affective dimension. Surprisingly, the results of our meta-analysis (chapter 2) showed this pattern of higher ACC and lower premotor activation in relation to the cognitive dimension. One explanation for this could be that these activation patterns might be specifically related to type-I alexithymia (i.e. high levels on both the cognitive and affective dimension).

Besides the functional activation differences, the results of chapter 3 revealed that the two alexithymia dimensions were also related to separable structural correlates. The affective alexithymia dimension was related to lower gray matter volume in the MOFC, which is suggested to be an emotion induction region (Rothkirch et al., 2012), and lower white matter volume in the superior longitudinal fasciculus, which is involved in fantasizing and imagination (Andrews Hanna et al., 2010; Makris et al., 2005). These structural abnormalities could be underlying the lower emotional arousal and lower levels of fantasizing in individuals with high affective alexithymia levels. Higher levels on the cognitive dimension, on the other hand, were related to lower dorsal ACC volume. Together with the recent finding of lower cingulate volume in association with lower levels of affective alexithymia (Goerlich-Dobre et al., 2014), this may point to a specific role of lower cingulate volume in type-II alexithymia (i.e. high levels of cognitive alexithymia and low or normal levels of affective alexithymia). This hypothesis of lower ACC volume in type-II alexithymia seems contradictory to the hypothesis of higher ACC activation in type-I alexithymia. However, lack of growth, atrophy or death of dendrites and neurons (possible reasons for lower ACC volume) do not necessarily imply lower activation, as the structural alterations may be associated with biochemical changes that enhance excitability, e.g. through disinhibition or compensatory activation of neighboring tissue. Future research should examine the relation between ACC volume and function in subjects specifically selected on type-I and type-II alexithymia.
Unraveling the neural correlates of the two alexithymia dimensions and alexithymia types is of great relevance as it has been shown that different patterns of scores on the two alexithymia dimensions might be related to different forms of psychopathology (Moormann et al., 2008a). For example, it was recently shown that somatoform disorders seem more related to type-I alexithymia, while borderline personality disorder was related to type-II alexithymia (Moormann et al., 2008a). Furthermore, type-II alexithymia has previously been related to schizophrenia (van ’t Wout et al., 2007; van der Meer et al., 2009). In chapter 5, we confirmed that patients with schizophrenia indeed show a type-II alexithymia pattern. Furthermore, we found that the degree of vulnerability for psychosis was related to higher levels of cognitive alexithymia and lower or normal levels of affective alexithymia. Especially this type-II alexithymia pattern was related to higher levels of negative symptoms in the controls and siblings, which strengthens the idea that type-II alexithymia might be a vulnerability factor for schizophrenia.

Combined, these results indicate that alexithymia might not be a one-dimensional construct but rather seems to consist of at least two separable dimensions. Furthermore, these dimensions seem to be differently related to brain activation, brain structure and the vulnerability for psychopathology, such as schizophrenia.

| EMOTION REGULATION IN SUBJECTS AT HIGH RISK FOR PSYCHOSIS |

Whereas emotion regulation difficulties have been well established in schizophrenia (see chapter 1), little to no research had yet been performed on emotion regulation in subjects at increased risk for psychosis. Therefore, in this thesis, we examined whether individuals at (putative) high-risk for developing psychosis differed from controls in the use and underlying neural correlates of two emotion regulation strategies, expressive suppression and cognitive reappraisal.

Expressive suppression

Expressive suppression (i.e. the inhibition of emotion-expressive behavior) is an emotion regulation strategy that has been associated with negative outcomes, such as lower levels of positive affect and life-satisfaction (Gross, 2002), and is therefore considered a less efficient emotion regulation strategy compared to reappraisal. Patients with schizophrenia appear to use expressive suppression more than controls (Kimhy et al., 2012; van der Meer et al., 2014). In this thesis, we examined whether subjects at increased risk for psychosis also report more use of expressive suppression.

The results revealed that only high levels of alexithymia were associated with more use of suppression (chapter 4), which is in line with previous reports (Kessler et al., 2010; Swart et al., 2009; Wingenfeld et al., 2011). Furthermore, the results of chapter 2 showed that alexithymia is related to lower activation in MNS regions. These regions are involved in emotion expressive behavior (Carr et al., 2003) and recent research has shown that during suppression, activation in these regions is lower compared to performing mimicry (Vrticka et al., 2013). This may indicate that the reported higher frequency of suppression in alexithymia is related to lower MNS activation during emotion processing. Future research should correlate MNS activation to suppression in individuals with alexithymia. Furthermore, examining facial expression through electromyographic recordings in alexithymia and relating this to brain activation could give further insight in these relations.
Although siblings and UHR individuals did show higher levels of alexithymia (chapter 5), they did not report more use of suppression (chapter 7 and 8). This discrepancy is difficult to explain, however this finding corroborates the report of non-significant differences between siblings and controls on suppression in a smaller sample (van der Meer et al., 2014). It might be that instead of a general extensive use of suppression in these at risk groups, only siblings and UHR individuals with high levels of alexithymia apply more expressive suppression. However, more research is needed before conclusions can be drawn. Besides the absence of behavioral differences, no brain activation differences during expressive suppression were found between siblings and controls (chapter 7). Furthermore, alexithymia was not related to differential neural correlates during suppression (chapter 4). This finding is in agreement with the fact that no behavioral indications of difficulties in the use of suppression were found, i.e. all groups reported to use this strategy to the same extent or even more compared to controls and were capable of down-regulating negative affect through suppression.

Taken together, these results suggest that the extensive use of suppression might be an illness-related feature because it is found in patients with schizophrenia rather than in siblings and UHR individuals. However, as alexithymia was related to the use of suppression further research should examine the combined effect of higher levels of alexithymia and suppression on the risk for psychosis. Furthermore, we should note that self-report and peer-report measures of expressive suppression are only moderately correlated (John & Gross, 2003). Thus, it could be possible that subjects at high-risk were less capable of evaluating their own expressiveness. Therefore, future research should include peer assessments to evaluate the role of expressive suppression in individuals at risk for psychosis.

Cognitive reappraisal

In contrast to expressive suppression, the use of cognitive reappraisal has been related to positive outcomes such as higher levels of positive affect and well-being (Gross, 2002). Previous research has shown that patients with schizophrenia report less use of reappraisal compared to controls (Kimhy et al., 2012; Livingstone et al., 2009; van der Meer et al., 2009) and show lower prefrontal activation during reappraisal (Morris et al., 2012; van der Meer et al., 2014). We examined whether groups at high risk for psychosis also report less use of reappraisal and whether the neural correlates underlying reappraisal show signs of impairment in these groups.

The results showed that both siblings of patients with schizophrenia and subjects with high levels of alexithymia reported equal use of cognitive reappraisal as controls. The equal use of reappraisal in siblings further extents the non-significant findings on reappraisal in sibling reported by van der Meer et al. (2014), while the findings in alexithymia were in contrast with our expectations based on previous reports (Stasiewicz et al., 2012; Swart et al., 2009). However, research on the association between alexithymia and reappraisal are inconsistent as others also failed to show significant associations between alexithymia and reappraisal (Geenen et al., 2012; Weiss et al., 2012). Furthermore, the results did not show any aberrant brain activation patterns during cognitive emotion regulation in these groups (chapter 4 and 7). Moreover, no structural differences in prefrontal regulation regions were found (chapter 3 and 6). In contrast, individuals at UHR for psychosis did report less use of cognitive reappraisal compared to controls and showed lower activation of the VLPFC during reappraisal (chapter 8). The VLPFC is an important region during reappraisal as this region is responsible for the cognitive regulation of emotions (Ochsner et al., 2002) and related to reappraisal success (Wager et al., 2008). Therefore, lower activation during reappraisal in
this area might indicate emotion regulation difficulties in the UHR group. In a study of Modinos et al. (2010), the neural correlates of another high risk group for psychosis were studied during reappraisal. This risk group consisted of healthy students with elevated scores on schizotypy. The results revealed higher activation in the high schizotypy group in several regulation areas, among them the VLPFC. The authors suggested that this higher level of activation might have served as a compensatory mechanism (Modinos et al., 2010b). Combined, these results show that in siblings and healthy individuals with high levels of alexithymia, the neural capacity to regulate emotions may be intact. Subjects with higher levels of schizotypy, but good overall functioning, are also still capable of cognitively regulating emotions, however they seem to need compensatory brain activation (Modinos et al., 2010b). When subclinical psychotic symptoms are combined with lower social functioning (UHR group), this compensatory mechanism appears to no longer work, resulting in lower prefrontal activation which may hamper the use of cognitive reappraisal.

Emotion dysregulation thus might be specific for subjects at UHR for psychosis and patients with schizophrenia. This substantiates the idea that emotion dysregulation may already occur in the prodromal phase of psychosis (Fowler et al., 2012). Emotion dysregulation is associated with lower social functioning, higher levels of negative affect and higher levels of anxiety (Gross, 2002). All of which are linked to the vulnerability for psychosis (Cornblatt et al., 2012; Fusar-Poli et al., 2014a). Furthermore, one could speculate that emotion dysregulation might play a role in delusion formation as previous research has shown that individuals with hallucinations in combination with high levels of negative affect have a greater chance of developing delusions (Hanssen et al., 2005; Krabbendam et al., 2005). This leads to the hypothesis that intact use of cognitive reappraisal might serve as a protective factor against psychosis.

CONSIDERATIONS AND FUTURE IMPLICATIONS

Sample characteristics

In this thesis, three samples with a putatively increased risk for psychosis were examined. However, these groups are not solely at high risk for psychosis. For example, higher levels of alexithymia have also been found in autism (Berthoz et al., 2013), depression (Berthoz et al., 1999) and anxiety (Honkalampi et al., 2000). Furthermore, non-psychotic psychiatric disorders are more often found in siblings of patients with schizophrenia and UHR individuals compared to controls (Addington et al., 2012a; Maier et al., 2002). Therefore, the reported emotion processing and regulation abnormalities in this thesis might not be specific for the risk of psychosis, but may play a more general role in the development of psychopathology. Previous research has reported lower use of reappraisal in other psychiatric samples (e.g. pathological gamblers and depression) (Joormann and Gotlib, 2010; Williams et al., 2012). Furthermore, lower prefrontal activation during reappraisal has been reported in subjects at high risk for depression (Felder et al., 2012). This indicates that indeed emotion dysregulation might be a more general vulnerability factor for psychopathology. Future research should examine the association between specific symptoms and emotion dysregulation (and the neural correlates thereof) to gain insight into whether emotion dysregulation is related to specific or more general symptoms of psychopathology. Furthermore, performing longitudinal studies to examine whether emotion dysregulation is related to the conversion to psychosis could provide valuable information which may improve the prediction of a transition to psychosis.
Furthermore, siblings of patients with schizophrenia form a very heterogeneous sample. For example, some siblings may carry more genetic risk variants or encounter more traumatic life events, which makes them more vulnerable for psychosis than others. As outlined in chapter 6 and 7, this heterogeneity might explain the divergent and negative findings in this group. Selecting siblings based on specific characteristics (as performed in chapter 6), may provide insight into the underlying causes of these divergent findings. Furthermore, previous research has shown that different groups of siblings with different cognitive profiles can be distinguished (Quee et al., 2014). Future research should examine if it is also possible to divide siblings into groups with different affective functioning profiles.

In this thesis, alexithymia was assessed with a self-report inventory as this is the most common way to examine alexithymia. Self-report measures are reliant on reflecting one’s own emotions, which is limited in individuals with alexithymia. Therefore, future research should include both self-report and observer-rated measures to assess alexithymia, such as the structured interview based on the Beth Israel Hospital Psychosomatic Questionnaire for alexithymia (Sriram et al., 1988). Furthermore, as outlined in this discussion, our results indicate that the two alexithymia dimensions are related to separable neural correlates. These two alexithymia dimensions can be used to distinguish separate types of alexithymia. Type-I alexithymia is related to high levels of both cognitive and affective alexithymia, which indicates that individuals experience low levels of emotional arousal and difficulties with accompanying emotional cognitions. Type-II alexithymia, on the other hand, is related to high levels of cognitive alexithymia but normal or low levels of affective alexithymia, which indicates normal to high levels of emotional arousal but impaired emotional cognitions. These alexithymia types seem to be related to different forms of psychopathology (e.g. Moormann et al., 2008a; chapter 5). Therefore, studying the neural correlates of these different alexithymia types may provide information on the neural correlates underlying the risk for different forms of psychopathology. In this thesis, we took a first step by examining the neural correlates of the two alexithymia dimensions. However, future research should focus on selecting individuals with specifically type-I or type-II alexithymia to examine if the different combinations of alexithymia scores are indeed related to different neural correlates.

Task-related considerations

In chapter 4, 7 and 8, an emotion regulation task was applied. Although this task consistently activated regions in accordance with previous literature, some considerations regarding this task should be mentioned.

All the emotion regulation tasks presented in this thesis applied a late cueing method in which the cue to reappraise was given after stimulus presentation. This method was chosen to allow subjects to have a naturalistic response to the emotional stimulus before regulation took place. However, this late cueing method may have caused the amygdala to habituate early (Ochsner et al., 2012), which could explain why we did not find any deactivation of the amygdala during reappraisal in our tasks. Future research should examine emotion regulation applying an early cueing paradigm to examine reappraisal in subjects at UHR for psychosis. This type of research could give insight into whether or not the lower prefrontal activation found during reappraisal in this group (chapter 8) is also related to less deactivation of the amygdala.

Second, research has shown that during reappraisal the activation in the prefrontal cortex is inversely correlated to amygdala activation (Banks et al., 2007). Unfortunately, we were unable to reliably study this fronto-limbic connection because the regulation blocks of
the emotion regulation task were too short (4s). Future research should therefore apply longer regulation times, or a block design, in order to examine functional connectivity patterns during reappraisal in individuals with an increased vulnerability for psychosis.

As mentioned in chapter 1, neuroimaging literature on expressive suppression is much more scarce compared to the literature on reappraisal. This is possibly due to the fact that correct application of the suppression strategy is difficult to control. Studying expressive suppression in individuals at high risk for psychosis, as well as in patients, is of great interest as these groups display fewer emotional expressions (Kring and Elis, 2013). Integrating electromyographic measurements or recording facial expression during scanning could provide more information on expressive suppression and the underlying neural correlates in both patients and subjects at high risk for psychosis.

The studies presented in this thesis only examined emotion regulation in lab-based settings. However, it would be interesting to examine whether our findings also translate to emotion regulation in daily life. Therefore, we suggest to apply momentary assessment studies on emotion regulation (as applied in Farmer and Kashdan, 2012) in subjects at increased risk for developing psychosis. It would be interesting to examine whether the lower VLPFC activation in the UHR group is related to emotion dysregulation in daily life. Furthermore, in this thesis we were unable to detect emotion dysregulation in individuals with high levels of alexithymia and siblings of patients with schizophrenia in a structured lab-setting. However, it is possible that in the more complex daily life without explicit instructions, these individuals do report some difficulties in emotion regulation.

In the meta-analysis of chapter 2, we showed that alexithymia was associated with lower activation in the insula and precuneus during the processing of positive stimuli. These results were suggested to be related to the lower positive affect reported by individuals with alexithymia. However, these results were based on a small number of studies, so further research on the neural correlates of positive emotion processing in alexithymia is needed. In general, neuroimaging research in the field of psychotic disorders has mainly focused on the processing and regulation of negative emotional stimuli, including the studies presented in this thesis. Although negative emotion processing is of great relevance in studying psychosis, possible impairments in positive emotion processing should not be overlooked. For example, anhedonia, the inability to experience pleasure from enjoyable events, is a symptom of schizophrenia. Furthermore, anhedonia has been reported in siblings of schizophrenia patients (Velthorst et al., 2012), UHR individuals (Valmaggia et al., 2013) and alexithymia (Tchanturia et al., 2012). It would be interesting to examine the relation between anhedonia and the ability to up-regulate positive emotions. Up-regulating positive affect is a cognitive emotion regulation strategy which increases the positive affect in response to positive stimuli (Giuliani et al., 2008). As this regulation strategy relies mainly on the same neural correlates as the reappraisal of negative events (Kim and Hamann, 2007), deficits in emotion regulation might also be underlying anhedonia in both patients with schizophrenia and individuals at increased risk for psychosis.

CLINICAL IMPLICATIONS

The findings in this thesis show that the degree of risk for psychosis is associated with higher levels of alexithymia (chapter 5). Clinicians have occasionally reported individuals with alexithymia as treatment-resistant or avoidant because they do not seem to respond to psychodynamic psychotherapy treatments (Lumley et al., 2007; Taylor et al., 1997; Vanheule et al., 2011). Such treatment resistance is possibly not caused by unwillingness of the
alexithymic patient, but merely caused by an incapability of introspecting and verbalizing their feelings (Lumley et al., 2007; Taylor et al., 1997; Vanheule et al., 2011). Therefore, interventions designed for schizophrenia patients or subjects at increased risk for psychosis, should keep in mind that therapeutic interventions that rely on these processes might not work in these groups because of the higher levels of alexithymia. Rather, patients with high levels of alexithymia seem to better respond to more cognitive-behavioral treatments (Lumley et al., 2007; Vanheule et al., 2011). We therefore recommend cognitive-behavioral treatments in patients with schizophrenia and individuals at UHR for psychosis with high levels of alexithymia.

Our results indicate that UHR individuals may be impaired in the application of cognitive reappraisal (chapter 8). Although replication and further research is needed, this gives rise to the idea of implementing emotion regulation training in the UHR group. Previous research has shown that subjects at UHR for psychosis benefit from cognitive-behavioral therapy (CBT), as this results in lower transition rates (van der Gaag et al., 2012; van der Gaag et al., 2013) and lower levels of psychotic symptoms (Morrison et al., 2012). However, the levels of depression and anxiety do not change through CBT compared to treatment as usual (Morrison et al., 2012; van der Gaag et al., 2012). Combining CBT with a specific emotion regulation training has been shown to be effective in reducing negative affect and depression in a mixed psychiatric sample (Berking et al., 2008). Higher levels of negative affect are reported to precede psychosis (Fowler et al., 2012) and the UHR group shows aberrant emotion regulation patterns which could underlie these higher levels of negative affect (chapter 8). Therefore, including emotion regulation training in CBT might be a valuable addition to the interventions for individuals at UHR for psychosis.

| CONCLUDING REMARKS |

Schizophrenia has long been viewed as a cognitive disorder. However, over the last two decades research has also focused on the emotion processing difficulties in schizophrenia (Aleman and Kahn, 2005). In this thesis, we showed that these emotion processing difficulties already occur in individuals at increased risk for developing psychosis. Schizophrenia and the vulnerability to this disorder are associated with higher levels of cognitive alexithymia which may impair early appraisal of emotional significance. Furthermore, in the UHR group emotion dysregulation may occur. Emotion dysregulation might contribute to poorer outcomes in this group as it is associated with psychopathology and poorer social dysfunction. Moreover, emotion dysregulation may lead to higher levels of negative affect which could increase the chance of a transition to psychosis. These results show that difficulties with emotion processing and emotion dysregulation are not solely related to schizophrenia or psychosis but may be part and parcel of the vulnerability for psychosis. This further substantiates the need of emotion-related research in psychotic disorders as this might result in better prediction of the transition to psychosis and could provide more targeted interventions.