Chapter 7

Conclusions and future directions

Neural basis and lateralization of emotional prosody

In verbal communication, not only the meaning of the words conveys information, but also the tone of voice (prosody). Specifically, from the tone of voice we can learn about the emotional state and intentions of others. The understanding of the emotional tone of speech is highly important for successful social interaction (Mitchell and Crow, 2005). Regarding the neural substrate and the lateralization of emotional prosody perception, studies have shown discrepant results. On the one hand, it has been argued that the right hemisphere is dominant for emotional prosody; on the other hand, it has been suggested to be a function of both right and left hemisphere. This means that the extent of lateralization of emotional prosody perception is still a matter of debate.

To further disentangle the neural network involved in emotional prosody perception and its degree of lateralization, we conducted TMS studies in healthy controls. Based on imaging studies on emotional prosody, regions of interest were chosen for a transcranial magnetic stimulation study. The involvement of both right and left hemispheres was highlighted by a review on emotional prosody perception (Schirmer and Kotz, 2006). A recent imaging study revealed an association between emotional prosody perception and the left and right inferior frontal gyrus (Ethofer et al., 2006). These brain areas were the regions of interest for our first TMS study in healthy subjects, described in **chapter 2**. We designed an online TMS study to temporally reduce the activity of the left inferior frontal gyrus and the right inferior frontal gyrus separately to be able to examine whether these brain regions are critically involved in the processing of emotional prosody and of semantics in healthy subjects. The results showed significantly longer reaction times on the emotional prosody task condition after rTMS over both the right and the left inferior frontal gyrus as compared to sham stimulation and after controlling for lear-ning effects associated with order of condition. There was no difference in effect on reaction times between the right and left stimulation. These results support a bila-teral involvement of inferior frontal gyri in emotional prosody perception. In a further study described in **chapter 3**, we assumed that emotional prosody perception is a multistep process, with different brain being responsible for each step. As in various studies the right frontal and right temporal regions have been found to play a role in emotional prosody perception, these were target regions for this study. We used triple-pulse repetitive transcranial magnetic stimulation (rTMS) to shed light on the precise time course of involvement of the right anterior superior temporal gyrus and the right fronto-parietal operculum.

We hypothesized that information would be processed in the right anterior superior temporal gyrus before being processed in the right fronto-parietal operculum in right-handed healthy subjects. During listening to each sentence, a triplet of TMS pulses at 10 Hz was applied to one of the regions at one of six time points (400-1900 ms). The study confirmed that both the right anterior superior temporal gyrus and the right fronto-parietal operculum are involved in the process of emotional prosody perception. No evidence was found for sequential processing of emotional prosodic information from right anterior superior temporal gyrus to the right fronto-parietal operculum, but the results suggested parallel processing. The results showed that both areas were critically involved in the process at the same time. This time point was after 1300 ms of onset of the sentence. The effect was stronger for withdrawal emotions than for the approach emotions. This is in accordance with the approach-withdrawal hypothesis, which states that the pattern of brain asymmetry is dependent on the type of the stimulus, the right hemisphere being specialised for processing withdrawal emotions and the left hemisphere dominant for processing approach emotions (Davidson et al., 1990; Davidson, 1995). Our results suggest that emotional cues expressed in the tone of a voice can be ambiguous at the beginning of sentences, but become more apparent half-way through the sentence. This study forms the first step in disentangling the temporal involvement of different brain areas in the process of emotional prosody recognition in natural speech.

Based on the findings from **chapter 2 and 3** and earlier findings, we propose that emotional prosody perception is a multistep process. For each step, other brain areas are involved and the extent of lateralization differs. Extending on a model postulated by Wildgruber et al. (Wildgruber et al., 2006), we propose 4 successive stages to be included in the process of affective prosody perception. These stages follow after the acoustic information has come in via the thalamus (number 1 in figure 1) and the primary auditory cortex (2), pictured in figure 1, and consist of;

A) Extraction of acoustic cues of vocalizations, this takes place in the right middle and anterior superior temporal gyrus (STG) (3),

B) Identification of prosodic sequences in the right posterior STG (4) (this region has not been included in our studies),

C) Discrimination of emotional expressiveness from a set of acoustic cues, in the right FPO (5) and

D) Classifying or labelling the emotional cues as a specific emotion (e.g. fear or anger) in the bilateral inferior frontal gyri (6).

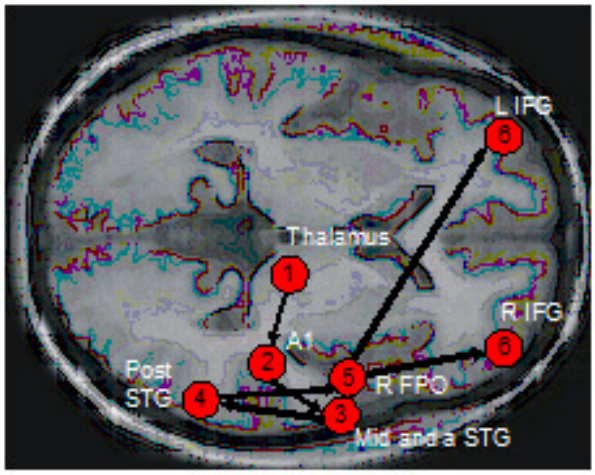

Figure 1 Model of emotional prosody perception as a multi-step process. Adapted from Wildgruber et al. (2008). A 1 = primary auditory cortex, STG = superior temporal gyrus, FPO = fronto-parietal operculum, IFG = inferior frontal gyrus. A = anterior. The process of emotional prosody perception includes four stages that follow after the acoustic information has come in via the thalamus (1) and the primary auditory cortex (2). The four stages are: A) Extraction of acoustic cues of vocalizations, this takes place in the right middle and anterior superior temporal gyrus (STG) (3), B) Identification of prosodic sequences in the right posterior STG (4) (this region has not been included in our studies), C) Discrimination of emotional expressiveness from a set of acoustic cues, in the right FPO (5) and D) Classifying or labelling the emotional cues as a specific emotion (e.g. fear or anger) in the bilateral inferior frontal gyri (6). Results from chapter 3 revealed parallel processing instead of sequential.

Overall, it can be concluded that the process of emotional prosody perception is bilateral but asymmetrical, with a predominance of the right hemisphere. The different steps need to be studied further to disentangle the brain areas responsible for each step. This could also be of interest for patient groups who show impairments in vocal emotion perception. They might be impaired in one of the sub-processes, while others might be intact. Some studies have already concluded that patients with schizophrenia have a deficit in the early processing of acoustic features underlying the impairments in decoding emotion based on speech intonation (Matsumoto et al., 2006;Leitman et al., 2005). This might point to an abnormality at the level of temporal areas more than in frontal areas. Future studies are needed to further clarify the relation between a deficit in analyzing fundamental acoustic features and its contribution to the impairment in the recognition of emotional prosody in schizophrenia. Furthermore, studies should be designed to examine which of the sub-processes are impaired, and which are intact in schizophrenia. Clarifying this may help in finding ways to ameliorate the ability to correctly identify emotional prosody perception.

Emotional prosody perception in schizophrenia

Results from **chapter 2 and 3** have shown that the neural basis of emotional prosody perception includes frontal and temporal areas, with a predominance of the right hemisphere in healthy subjects. Furthermore, an important characteristic of emotional prosody processing is its temporal pattern (**chapter 3** and (Schirmer and Kotz, 2006; Wildgruber et al., 2006). Abnormalities in frontal and temporal regions and their connections have been shown in schizophrenia (Sommer et al., 2001;Mitchell et al., 2004;Dollfus et al., 2005). For example, fMRI studies revealed decreased language lateralization in schizophrenia as compared to healthy controls (Sommer et al., 2001;Weiss et al., 2006). Interestingly, also with regard to emotional prosody, a reduced degree of the normal right-lateralised temporal lobe response has been shown in schizophrenia (Mitchell et al., 2004). As specialization of one hemisphere for a certain function has been theorized to be important for the speed and clarity of information processing (Hugdahl and Westerhausen, 2009;Hugdahl, 2000), reduced lateralization of emotional prosody perception is expected to result in impairments in this function.

Chapter 4 describes a quantitative review on emotional prosody perception in patients with schizophrenia. Understanding the intonation in speech is crucial for social communication. It gives information about the feelings and intentions of others. Being impaired in this function may contribute to miscommunications.

A growing body of evidence shows that patients with schizophrenia are impaired in emotion processing. This might even be one of the most pervasive disturbances in schizophrenia, which may contribute to social isolation. Our meta-analysis revealed a large effect size (d = 1.2) for the perception of emotional prosody. This indicates that the performance of patients with schizophrenia was more than one standard deviation lower than that of healthy control subjects on tasks of emotional prosody perception. When we compare this d value to the effect sizes reported in previous meta-analyses of cognitive function in schizophrenia, it would rank among "The most powerful and reliable neuroscience findings in schizophrenia research" (Heinrichs, 2001). We also found a large effect size (d = 1.1) for the expression of emotional prosody in schizophrenia, although the interpretation of the result due to the limited number of studies included, must be done with some reserve. The results support the view that emotional abnormalities may be a key dysfunction in schizophrenia (Aleman and Kahn, 2005). Furthermore, emotional prosody perception seems to be a trait deficit as opposed

to a state deficit. Two studies have shown that the deficit already exists in the early years of the illness (Kucharska-Pietura et al., 2005; Edwards et al., 2001). Additionally, Kee and colleagues showed that subtle deficits in emotion perception are detec-table in healthy siblings of schizophrenia patients, when multiple measures of both vocal and affect perception were taken together (Kee et al., 2004). This means that emotional prosodic comprehension deficits cannot be merely an artefact of duration of illness, treatment or institutionalisation as the deficit seems to be stable over time. Studies have shown that a general prosodic comprehension deficit in patients with schizophrenia can be ruled out as they have no difficulty comprehending non-emotional prosody (Murphy and Cutting, 1990;Pijnenborg et al., 2007).

Similar disturbances in the perception of emotional prosody that have been described in patients with schizophrenia, have also been reported in right hemisphere damage patients (Ross et al., 2001). The studies that were included in our meta-analysis did not provide enough information to be able to analyze the influence of severity of psychopathology and symptom clusters on the ability to identify emotional prosody. This relationship was studied in **chapters 5 and 6**.

Clinical correlates of emotion perception in schizophrenia

Chapter 5 describes a study examining the relationship between the ability to identify emotional prosody and symptom clusters in schizophrenia. In our meta-analysis only studies were included that compared a group of schizophrenia patient with a group of healthy controls, based on these studies nothing could be concluded with regard to the relation between symptom clusters and emotion perception. Studies examining this relationship have however been published, these are studies that did not include healthy control groups. Their results are however mixed. Some studies on emotional prosody perception and symptomatology found a relationship with negative symptoms (Bach et al., 2009a;Leitman et al., 2005;Edwards et al., 2001). Positive symptoms (Poole et al., 2000;Shea et al., 2007;Rossell and Boundy, 2005) and disorganization symptoms (Poole et al., 2000;Bozikas et al., 2004;Leitman et al., 2005) have however also been related to emotional prosody perception. Others, however, found no relationship between vocal affect recognition and symptoms (Ross et al., 2001;Kucharska-Pietura et al., 2005). To further clarify the clinical correlates of emotional prosody perception in schizophrenia, we investigated a group of 83-patients, who performed an emotional language task with a prosody and a semantics condition, including two

emotions: anger and fear. Symptomatology was described by the five clusters of symptoms of schizophrenia psychopathology according to the five-factor mode resulting from a ten-fold cross-validation study of the scores of a large sample of Dutch and Belgian in and out patients with schizophrenia: Positive, Negative, Disorganization, Excitement and Emotional distress (van der Gaag et al., 2006). Results showed that patients with more Positive symptoms and patients with more Disorganization symptoms were more impaired in correctly identifying negative emotions from the intonation of voice. No relation was found between severity of negative symptoms and the ability to understand emotional prosody. These findings suggest that patients with disorganized symptoms and with positive symptoms are expected to have trouble in social interaction when it comes to vocal communication. This demonstrates that the associations of vocal affect recognition with cognitive and behavioural features of schizophrenia, are not simply a by- product of social withdrawal and blunted affect.

When studying emotion perception in schizophrenia, it is also interesting to look at misattribution patterns: what emotion do patients perceive if they do not perceive the correct emotion? More specifically, in **chapter 6** misattribution patterns are studied for neutral facial expressions and neutral prosodic expressions that are misperceived as being emotional. In this study we tested the hypothesis of aberrant salience on misattribution patterns in emotion perception (Kapur, 2003). Although the attribution of aberrant salience to neutral stimuli has been mainly implicated in the genesis and persistence of positive symptoms of schizophrenia, we hypothesized that such misattribution in emotion perception would also affect other symptom dimensions, e.g. disorganization symptoms, negative symptoms and emotional distress. Thirty-seven patients with schizophrenia performed vocal and facial emotion recognition tasks. Symptomatology was again described by the 5 factors of the PANSS according to the five-factor model of Van der Gaag et al. (2006). Regression analyses revealed that misclassifying neutral expressions as angry or anxious predicted severity of symptoms in 3 out of 5 PANSS factors (van der Gaag et al., 2006): Disorganization symptoms, Excitement and Emotional distress. This could not be explained by difficulties in attention and working memory. The unpredicted relation with excitement may be understood clinically. Misattribution of negative emotional value to neutral expressions could result in higher levels of excitement (e.g. poor impulse control, hostility, and uncooperativeness). These results suggest a contributing role for attribution biases in the symptom dimensions Disorganization, Emotional distress, and Excitement,

which might be explained by an internal salience generator.

Clinical implications: treatment of emotional prosody perception

From the literature, including our studies, it is clear that deficits in emotional prosody perception can be regarded among the most prominent cognitive deficits in schizophrenia (**Chapter 4**). Emotion perception is one of the domains of social cognition. Social cognition concerns all information processing underlying social interaction (Brothers, 1990). Schizophrenia patients are known to have deficits in other domains of social cognition as well, such as attributional style and theory of mind. A recent review found clear and consistent relationships between functional outcome measures and domains of social cognition, especially between social and emotional perception and functional outcome (Couture et al., 2006). Social functioning is thought to be the most important outcome measure of schizophrenia. Findings on the relationship between social outcome and impairments in emotion perception stress the importance of taking emotional prosody perception seriously. Therefore, we recommend defining social cognition, including emotion perception in others, as an important aspect of schizophrenia and thus as one of the primary treatment targets within psychiatric rehabilitation. Emotion perception should be taken into account in diagnosis, treatment and clinical guidance. If emotion perception can be reliably improved it may lead to better interpersonal relationships, social competence and community functioning (Combs et al., 2008).

Impairments in emotion perception have also been found to be predictors of low tolerance for emotional distress (Hooker and Park, 2002;Hodel et al., 2004). Furthermore, in schizophrenia, low stress tolerance might deteriorate already existing psychopathology (Nuechterlein et al., 1992). Results from our studies described in **chapter 5 and 6**, revealed that impairments in emotion perception are related to different symptom dimensions, instead of merely with symptoms reflecting social withdrawal and flat affect. Because of these relationships between emotion perception and symptoms dimensions, impairments in emotion processing might improve, at least at a certain extent, in reaction to medication or other interventions targeting symptom clusters.

Recent investigations on the neural substrate of affective dysfunction in schizophrenia show abnormal amygdala activation during emotion recognition tasks (Pinkham et al., 2008;Hall et al., 2008) and during social decision-making (Baas et al., 2008). Such findings indicate that normalization of amygdala responses may help to ameliorate emotion processing.

Another possible treatment option could be to directly target the social cognitive deficits by intervening at the level of social cognition. Various studies have been described on the effectiveness of psychosocial interventions that target different domains of social cognition, these have been reviewed elsewhere (Kern et al., 2009;Kurtz and Mueser, 2008;McGurk et al., 2007;Mueller et al., 2009). Relatively few of these treatment programs also targeted emotion perception. A recent meta-analysis reviewed the efficacy of social cognitive skills training (Kurtz and Mueser, 2008). Moderate average effect sizes were found for improving community or institutional functioning and for negative symptoms, supporting the efficacy of social skills training to improve psychosocial functioning (Kurtz and Mueser, 2008). The meta-analysis of Kurtz and Mueser did not include emotion perception as a therapeutic component of the social cognitive remediation approaches (Kurtz and Mueser, 2008). Another meta-analysis on efficacy of social cognitive remediation in schizophrenia patients did embrace social emotional perception among other social cognitive areas, this domain was however not analyzed separately (Mueller et al., 2009). Conclusions from this meta-analysis were again that social cognitive remediation, in combination with various other treatment modalities, does lead to improvements of social cognitive skills. Moreover, generalizability to other domains of functioning and symptoms through social cognitive remediation was found (Mueller et al., 2009).

Searching through the literature, nineteen studies were found that investigated the efficacy of psychosocial interventions in schizophrenia on the ability to correctly identify emotions in others. As proposed by Penn, these interventions can be conceptualized as either "targeted", focussing on a specific ability, here emotion perception, or "broad-based", including cognitive remediation (Penn et al., 2005). To begin with the targeted interventions, a first hopeful conclusion is that emotion perception can be improved by treatment sessions. Methods like mimicry (Penn and Combs, 2000;Frommann et al., 2003), training discrimination with or without the verbalization of the characteristic features of facial affect (Frommann et al., 2003;Wolwer et al., 2005;Russell et al., 2006;Russell et al., 2008) all improved emotion perception directly after treatment. Factors that seemed to enhance the effects of training were monetary reinforcement (Penn and Combs, 2000), attentional prompts (Combs et al., 2006;Combs et al., 2008), repetition (Marsh et al., 2009) and integration into real world situations (Frommann et al., 2003;Wolwer et al., 2005). Interestingly, one training session was found to be enough to improve emotion perception (Penn and Combs, 2000). With regard to the durability of these effects on emotion

perception and the generalizability to social functioning, not much can be concluded from the studies describing interventions targeting emotion perception. The studies that did report on durability of the improvements, showed sustained improvements of emotion perception after one week, with weak generalizability to other emotional tasks (Combs et al., 2006;Combs et al., 2008;Russell et al., 2008). When evaluating the efficacy of the broad-based interventions, some of the studies were promising. Results from these studies highlight some important characteristics for durability and generalizability of improvements in emotion perception and social functioning. First, the training should be longer than twelve weeks (Hodel et al., 2004;Sanz et al., 2009). Second, maintenance sessions are necessary to sustain improvements. Third, the treatment program should encompass in vivo exercises. Fourth, based on the findings described in **chapter 6** we recommend to also include neutral expressions, because these are found to be often misperceived as being emotional by people with schizophrenia. This has been conceptualized as the aberrant salience hypothesis; In the absence of effective treatment, patients with a psychosis related to schizophrenia exhibit aberrant salience (Kapur, 2003). Furthermore, motivation and attention are always important to enhance treatment effects. Social cognition has been conceptualized as consisting of three components: 1) Emotion perception (the ability to identify the affect expressed by others) and social perception (the ability to ascertain social cues from behaviour provided in a social context, which includes, but is not limited to, emotion cues), 2) Attributional style (causal explanations given for positive and negative outcomes) and 3) Theory of mind (the ability to understand others' intentions or perspectives) (Couture et al., 2006;Penn et al., 2007). Emotion perception and social perception are often grouped together as they are both closely tied to social knowledge (Couture et al., 2006). Equal attention should be paid to all three domains in social cognition training programs. Not only facial emotion but also vocal emotion perception should be included in the treatment program. Understanding emotional prosody gives us crucial information of emotions and intentions of others. If the perception of emotions and intentions in others can be improved, this may lead to improved social functioning and a better quality of life for persons with schizophrenia (Green et al., 2005). Results from social cognitive skills trainings are promising, they should be more extensively implemented and tested in randomized controlled trials with the inclusion of a training of emotion perception.

To be able to develop proper intervention methods, future studies should aim at clarifying the neurocognitive processes underlying the deficits of emotion percep-

tion in schizophrenia. To this end, studies should also use designs that are more similar to real-world situations. The experimental condition should not only include standardized sentences, but also real-world conversations. As far as we know one study has been published with this purpose (Huang et al., 2009).

Avenues for future research

Findings from our studies in healthy controls revealed that frontal and temporal brain regions are implicated in emotional prosody perception with a predominance of the right hemisphere (**chapter 2 and 3**). Patients with schizophrenia have been shown to have severe impairments in this function (**chapter 4**). These findings in combination with the relationships that were found with certain symptom dimensions (**chapter 5 and 6**) might indicate that the neural basis of these symptom clusters may be overlapping with the neural basis of emotional prosody processing, i.e. including temporal and frontal areas. The exact neural bases of both emotional prosody perception and symptom clusters, however, remain to be investigated.

Furthermore, impairments in emotional prosody perception in schizophrenia (**chapter 4**) indicate that alterations in the right hemisphere might play a role in schizophrenia as this hemisphere has been shown to be important for emotional prosody (**chapter 2 and 3** and (van Rijn et al., 2005;Adolphs et al., 2002)). These findings support the hypothesis that symptoms in schizophrenia can be consequences of not only left but also right-hemisphere abnormalities (Cutting, 2006; Mitchell and Crow, 2005). This means that the influential theory on the genesis of schizophrenia that links abnormalities of left hemisphere functions to the development of psychosis (Crow, 2000) may be complemented by abnormalities in right hemisphere (social) functions. A few imaging studies have indeed shown aberrant activation during emotional prosody perception in schizophrenia patients as compared to healthy controls (Mitchell et al., 2004;Bach et al., 2009b). Their results however, are contradictory. One study reported a reversal of the normal right-lateralized temporal response to emotional prosody in patients with schizophrenia as compared to healthy controls (Mitchell et al., 2004). Bach et al. however concluded the opposite (2009b), patients in their study showed an increased right-lateralization of prosody processing at the level of the temporal and parietal cortex. Our group is currently working on a combined functional Magnetic Resonance Imaging (fMRI) guided – Transcranial Magnetic Stimulation (TMS) study to clarify the neural substrate and extent of lateralization of emotional prosody perception in schizophrenia patients.

Another syndrome that has been associated with anomalous lateralization of language function (van Rijn et al., 2008) and increased risk of psychosis (Hyde and Lewis, 2003) is Klinefelter Syndrome (KS). KS is characterised by the presence of an extra X chromosome in males (47, XXY karyotype). Both left and right hemispheric language functions have been shown to be impaired in KS. A recent study found relative difficulties in a group of KS in the recognition of emotional prosody and in the recognition of emotional semantics (van Rijn et al., 2007). Van Rijn et al. also found that men with KS show high levels of schizophrenia spectrum pathology (2006). Difficulties in recognizing social cues together with the structural brain abnormalities associated with the XXY karyotype, suggest that a genetic mechanism involving genes on the X chromosome might lead to disturbances in the development of social cognition in XXY men. To further study a relation between the X-chromosome and the degree of lateralization of language functions, we are currently conducting a combined fMRI-TMS study to test the extent of lateralization of emotional prosody perception in KS. If men with Klinefelter show the same pattern of lateralization of emotional prosody perception as schizophrenia patients, which is what we predict, this would gives clues about a genetic basis of this aberrant lateralization, namely, located on the X-chromosome. This shared genetic basis, located on the X-chromosome, would underlie social dysfunction in both schizophrenia and Klinefelter Syndrome. With these studies, we hope to further elucidate the neural underpinnings and its genetic basis of emotional prosody perception in schizophrenia and in Klinefelter Syndrome, in order to be able to develop proper intervention methods in the future.

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