Being left out: Neurobiological correlates of social rejection and their developmental trajectory

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CHAPTER 7

Summary and discussion

7.1 Introduction

Being included and accepted by peers is a primary goal among adolescents. The main objective of this thesis was to test the neurobiological mechanisms underlying the heightened sensitivity to peer rejection during adolescence. In particular, the empirical studies described in this thesis aimed to examine developmental changes in neural and heart rate responses to social-evaluative feedback provided by peers. An important advantage of objective biological measures is that they can provide unbiased access to processes underlying the experience of social acceptance and rejection, such as the emotional intensity or salience of these events, as well as affect regulation (Masten & Eisenberger, 2009). Neurodevelopmental models proposed that changes in social behavior that take place during adolescence are related to developmental changes in brain regions implicated in social information processing (Nelson et al., 2005). More specifically, it is hypothesized that the adolescent brain is characterized by unbalanced activity between cognitive control and affective systems, that may bias adolescents towards an increased sensitivity to social cues from peers (e.g., Casey et al., 2008a, 2008b; Nelson et al., 2005; Steinberg et al., 2008). In addition, there is increasing evidence that brain regions involved in mentalizing undergo functional changes during adolescence (Blakemore, 2008, 2010). The empirical studies in this thesis aimed to contribute to a greater understanding of developmental changes in social behavior, vis-à-vis developmental changes in neural and autonomic responses.

7.2 Summary of main findings

Chapters 2-4 of this thesis presented studies using a modified version of the Social-Jugdment task (adopted from Somerville et al., 2006). Several weeks before the experiment, participants were led to believe that peers would be forming impressions of them based on a portrait photograph. During the experiment, participants were presented with a series of unfamiliar faces of age-matched peers and were asked to predict whether they would be liked by the other person, followed by feedback indicating acceptance or rejection. The main goal of the study described in **Chapter 2** was to test the impact of social rejection on beat-by-beat heart rate responses in adults (18-25 years old). A non-social task (i.e., age-judgment task) was administered to determine the cardiac response to negative cognitive feedback. As anticipated, results revealed that feedback processing was associated with a transient heart rate slowing followed by an acceleratory recovery to baseline that was considerably delayed to unexpected social rejection. Importantly, this cardiac response was larger than heart rate changes associated with other conditions in which the feedback was not aligned with the expectations of the participant, suggesting that the impact of social rejection is stronger than the effect of expectancy violation per

se. In addition, results point to the context dependency of social rejection effects; cardiac slowing was most pronounced for rejection feedback following a positive expectation of social evaluation. The results of this study set the stage for examining developmental differences.

In **Chapter 3** of this thesis, pubertal and gender differences in sensitivity to peer rejection were tested by examining beat-by-beat heart rate responses. Specifically, the focus of this study was on the transition from childhood into early adolescence, which is marked by the onset of puberty (e.g., Forbes & Dahl, 2010). Children between 8-14 years old participated in the study and were assigned to two groups based on a self-report scale of pubertal maturation; pre-pubertal children and pubertal adolescents. The results of this study revealed larger cardiac slowing to unexpected peer rejection in pubertal adolescents relative to pre-pubertal children, most pronounced in pubertal girls. These findings support the hypothesis that heart rate sensitivity to unexpected peer rejection increases after transition into puberty, especially in girls.

The fMRI study described in **Chapter 4** had two main goals; 1) to examine the neural responses associated with expectations of social evaluation and social feedback processing, and 2) to test for developmental differences. Participants from four age groups (8-10, 12-14, 16-17, and 19-25 years old) participated in this study. The functional neuroimaging data in adults revealed activation in the vmPFC and striatum for positive compared to negative expectations of social evaluation. Age-related comparisons showed a linear increase in activity in these regions with age. With regard to feedback processing, imaging data in adults demonstrated that neural responses to social feedback differed depending on prior expectations of social evaluation. More specifically, acceptance compared to rejection feedback resulted in widespread activation following a 'like' expectation of social evaluation, but not following a 'dislike' expectation, particularly in the vmPFC and striatum. Similarly, rejection compared to acceptance feedback resulted in activation in the subcallosal cortex, striatum, OFC and lPFC following a 'dislike' expectation, but not following a 'like' expectation. Together, these findings show that neural responses to social-evaluative feedback are particularly sensitive to feedback that is aligned with an individual's own expectation of social evaluation. Age-related comparisons revealed a linear increase in activity with age in the regions reported for rejection feedback. No age-related differences were found for acceptance feedback.

The study described in **Chapter 5** used a virtual ball tossing game, called Cyberball, to induce feelings of social rejection. More specifically, the goal of this fMRI study was to identify the neural networks that are sensitive to social exclusion and subsequent fairness considerations, and to test for developmental differences. Participants from 3 age groups (10-12, 14-16, and 19-21 years old) participated in the study and performed two tasks; first, participants played Cyberball to induce feelings of social inclusion and exclusion, followed by a Dictator game in which participants were asked to divide coins between themselves and the players who previously included or excluded them. Across

all participants, events on which participants did not receive the ball during Cyberball were associated with activation in the mPFC/vACC, subgenual ACC, and the vlPFC. In addition, a subset of areas was specifically sensitive to rejection events in the context of the exclusion game, including the insula and dACC. Together, these regions overlap considerably with the regions previously associated with exclusion blocks of Cyberball (e.g., Eisenberger et al., 2003; Masten et al., 2009), and provide additional insight in the processes that are involved in social exclusion. Age-related comparisons showed that the subgenual ACC was more strongly recruited in 10-12 year olds in the context of the exclusion game. The results of the Dictator game revealed that social exclusion clearly affected subsequent fairness considerations; players who previously excluded the participants received lower offers with more self-gain for the participants. Although all age groups most often selected the harsh punishing offer when allocating money to the excluders, adults selected the milder punishing offer more often than younger participants. Neuroimaging results showed that there was consistent activation in the TPJ, STS and the lPFC when making offers to the excluder, but that adults additionally recruited the insula and dACC.

Despite the focus of this thesis on social-evaluative feedback processing, in **Chapter 6** we aimed to chart the developmental trajectories of neural responses associated with mental state attribution. Participants from three age groups (10-12, 14-16, and 19-23 years old) participated in the study and performed an adapted version of the Reading the Mind in the Eyes task (Baron-Cohen et al., 2001a), in which photographs of the eye region of faces were presented. As anticipated, behavioral results showed that the ability to decode the feelings and thoughts of others from the eyes develops before early adolescence. For all age groups, brain activity was found in the pSTS during reading the mind in the eyes relative to a control condition using the same eyes stimuli. Only 10-12 year olds showed additional involvement of the vmPFC, bilateral IFG, and the temporal pole. Together, this pattern of developmental changes suggests that while brain regions involved in social perception (i.e., pSTS) develop early in life, the fine-tuning or functional specialization of other regions of the social brain continue during adolescence.

The results of the empirical studies described in this thesis will be discussed in the following section and integrated into the broader literature. In addition, critical considerations and suggestions for future research will be described.

7.3 General discussion and critical considerations

SOCIAL REJECTION PUTS THE BRAKES ON THE HEART

One of the main conclusions that can be derived from this thesis is that unexpected social rejection induces a prolonged heart rate deceleration. As such, the recording of heart rate changes can provide a useful window on the processing of social rejection. This finding fits well with the phasic heart rate literature showing greater heart rate deceleration in response to psychologically relevant information, such as negative performance feedback, or aversive affective stimuli (e.g., Bradley, 2009; Crone et al., 2003; Hajcak et al., 2003). Short-latency decreases in heart rate have been interpreted as a reflection of an 'orienting' response that is primarily mediated by the parasympathetic nervous system (Berntson et al., 2007; Somsen et al., 2004). Further, the context dependency of social rejection effects suggests an interplay between prior expectations of social evaluation and the valence of social feedback; that is, unexpected rejection, but not expected rejection or unexpected acceptance, elicits a strong pattern of cardiac slowing. Indeed, it has previously been suggested that both affective distress and discrepancy detection may act as complementary processes of a neural 'alarm' system (particularly the dACC) that is implicated in the processing of physical and emotional pain (Eisenberger & Lieberman, 2004). Together, these findings indicate that the parasympathetic nervous system is involved when individuals are hurt by unexpected social rejection (Chapter 2). In future studies, it would be of considerable interest to test for individual differences in the cardiac response to social rejection, such as social anxiety. Based on previous research, it could be hypothesized that individuals with high levels of social anxiety would show more pronounced heart rate slowing to negative social feedback, which may manifest in a less context dependent manner (i.e., cardiac slowing to both unexpected and expected social rejection) (Crone et al., 2005).

The second important finding of the cardiac studies described in this thesis is that bodily responses associated with social rejection could vary as a function of pubertal maturation and gender (Chapter 3). In line with our predictions, the delay in cardiac slowing to unexpected peer rejection was larger in pubertal adolescents relative to pre-pubertal children, and was most pronounced in pubertal girls. These results support the hypothesis of an increase in sensitivity to peer rejection after transition into puberty, and that social rejection may be particularly salient in pubertal girls (Guyer et al., 2009; Kloep, 1999; Sebastian et al., 2010a). It is possible that pubertal adolescents, especially girls, have a highly sensitive system involved in detecting and orienting attention towards peer-related negative social feedback to facilitate the processing of these signals. Moreover, results fit well with the emerging evidence suggesting puberty-specific changes on social and affective information processing (e.g., Blakemore et al., 2010; Dahl & Gunnar, 2009;

Forbes & Dahl, 2010; Silk et al., 2009). It should be noted here that exploratory analyses with age as a proxy for developmental maturation (8-10 and 11-14 years old) yielded a similar pattern of cardiac results. Whereas this finding complicates a straightforward interpretation of puberty-specific effects, it also shows that it is unlikely that developmental differences are driven by a possible bias in self-report ratings of pubertal maturation. However, in future research, it would be valuable to replicate the findings of this study using a study design that is optimized to isolate puberty-specific effects from age-effects, and by using more objective assessments of pubertal maturation (e.g., Blakemore et al., 2010; Forbes & Dahl, 2010).

A further explanation that needs to be considered for the stronger pattern of cardiac slowing to unexpected peer rejection in adolescent girls, is that peer rejection in a context of dyadic interactions might not be as emotionally salient in boys as in girls, whereas rejection from a social group (e.g., members of a sports team) might lead to other results. Indeed, it has been argued that boys generally focus more on group relationships and competitive goals, while girls place more emphasis on close emotional relationships (Bakker et al., 2010; Oldehinkel et al., 2007; Rose & Rudolph, 2006; Stroud et al., 2002). Further research is needed to gain more insight in these gender differences. In addition, a priority for future work would be to test the cardiac response to peer rejection during both the transition into and out of adolescence, by including participants from a broad age range (Casey et al., 2008a, 2008b; Steinberg et al., 2008). Ideally, longitudinal studies are needed to track developmental changes in social sensitivity over time.

NEURAL CORRELATES OF SOCIAL-EVALUATIVE FEEDBACK AND THEIR DEVELOPMENTAL TRAJECTORY

The fMRI studies described in this thesis aimed to test whether there are developmental differences in neural responses associated with social-evaluative feedback processing, that could contribute to the reported heightened sensitivity to peer rejection during adolescence (Kloep, 1999; O'Brien & Bierman, 1988; Sebastian et al., 2010a, 2011). The study with the Social-Judgment task (Chapter 4) enabled us to examine brain activation patterns during the decision phase of the task in predicting to be liked or disliked by the other person, and at the moment participants received social feedback. Interestingly, the behavioral results of this study revealed that adults more often expected to be liked by age-matched peers relative to children and adolescents. In addition, results showed that with age participants increasingly activated the vmPFC and striatum for 'like' compared to 'dislike' expectations of social evaluation. Possibly, this finding may reflect a shift in the strategy used for assessing one's own level of social status within the peer group. Adults and older adolescents may more strongly recruit brain regions involved in self-processing and mentalizing (particularly the mPFC; Amodio & Frith, 2006), which could be adaptive when taking a risk in predicting to be liked by unfamiliar peers. The age-related increase

in activation in the mPFC is inconsistent with mentalizing studies showing decreases in activation in this region between childhood and adulthood (Blakemore, 2008, 2010), but these studies did not assess expectations of social evaluation. Alternatively, this difference could point to possible functional subdivisions of the mPFC (Burnett et al., 2011).

At the moment of feedback presentation during the Social-Judgment task, we observed that acceptance feedback resulted in similar vmPFC and striatum activation in children, adolescents and adults. These results were taken to suggest that social acceptance is salient across age groups. Importantly, acceptance-related neural activity was only observed on trials in which positive social feedback was anticipated. This finding may extend the results of Somerville and colleagues (2006) showing that the vmPFC/vACC is particularly sensitive to social acceptance when people expect to be accepted. Further, the results of our study are very similar to a recent study reporting activation in reward- and self-related regions, including the nucleus accumbens and the vmPFC, in response to being liked, which was consistent across 15-24 year olds (Davey et al., 2010). In contrast to this equal sensitivity to social acceptance feedback, we observed a linear age-related increase in activity in the subcallosal cortex, lPFC, striatum and OFC for predicted social rejection. In the light of prior studies suggesting that immature function of regulatory mechanisms could contribute to a heightened sensitivity to social rejection during adolescence (Sebastian et al., 2010b, 2011), these findings may indicate that adults are better able to regulate the negative affect associated with rejection. Indeed, regions such as the lPFC, OFC and striatum has been associated with the regulation of negative affect (e.g., Ochsner et al., 2005; Wager et al., 2008), including feelings of social rejection (e.g., Eisenberger et al., 2003; Masten et al., 2009). However, an unexpected outcome in this study was the general lack of activation for the feedback condition where the negative impact of peer rejection was expected to be the highest (i.e., unexpected social rejection). This finding would suggest that the brain is particularly sensitive to social feedback that matches prior expectations of social evaluation. Further research is needed to replicate these results and to provide more insight in the exact function of the patterns of neural activation observed in this study. For instance, it will be important to collect continuous self-report ratings of emotion during scanning to better understand the affective impact of social feedback in this task.

Based on self-report ratings of distress associated with being excluded from a ball-tossing game (Cyberball), the study described in Chapter 5 enabled more insight in the negative impact of social rejection. In addition, we believe that the punishment behavior towards the excluders reported in this study further captures the affective distress caused by social exclusion, which was somewhat more pronounced in adolescents. Results revealed that all participants reported high levels of distress after the exclusion game of Cyberball, showing that social rejection is a significant threat across age groups (Baumeister & Leary, 2005). In addition, fMRI results showed a strong overlap between age groups in neural responses associated with rejection events, including regions

previously labeled as the pain network (e.g., DeWall et al., 2010; Eisenberger et al., 2003). Despite these overall similarities, we observed that the subgenual ACC was more strongly recruited in 10-12 year olds during the exclusion game of Cyberball relative to older participants. This finding could further support the findings by Masten and colleagues (2009) suggesting that the subgenual ACC plays a key role in the experience of peer rejection during adolescence. Results of their Cyberball study in 12-13 year olds showed that activity in this region correlated with higher levels of exclusion-related distress, but in this study no comparisons were made with other age groups. Further evidence for a role of the subgenual ACC in emotional distress comes from studies with clinical populations, reporting increased activity in this region in depression (e.g., Disner et al., 2011; Gotlib et al., 2005; Mayberg et al., 1999; Yang et al,. 2009). The role of the subgenual ACC in emotion processing in healthy adults is, however, more mixed (Masten & Eisenberger, 2009). Whereas some studies highlight a role of this region in the experience of negative emotions (Liotti et al., 2000; Mayberg et al., 1999), other studies point to a role of this region in positive affect and affect regulation (e.g., Burklund et al., 2007; Onoda et al., 2009). Accordingly, Masten et al. (2009) hypothesized that adolescents may show a pattern of neural activation in the subgenual ACC more similar to clinical samples, which may be related to their heightened emotional sensitivity, or the protracted development of the brain. Together, these findings suggest that early adolescents display increased activity in brain regions associated with negative affect in response to peer rejection, which may not always be reflected in self-reported exclusion distress. For future research it would be important to further delineate the role of the subgenual ACC during social rejection experiences in adolescents. For instance, it would be of interest to test whether the greater responsivity in the subgenual ACC could reflect developmental differences in emotional distress, and/or in the ability to regulate negative affect (Masten et al., 2011).

Overall, the findings of neuroimaging studies to date suggest that the neural mechanisms underlying social rejection experiences continue to develop during adolescence. In Chapter 1 of this thesis several neurobiological models of adolescent development were described, including the SIPN model (Nelson et al., 2005). In particular, these models proposed that changes in emotional and social behavior during adolescence could be the result of unbalanced activity between cognitive control and affective systems. More specifically, the adolescent brain is believed to be characterized by earlier functional maturation of affective brain circuitry relative to a more gradual maturation of prefrontal areas important for regulatory control (e.g., Casey et al., 2008a, 2008b; Nelson et al., 2005). The question then arises whether this imbalance could bias adolescents towards a heightened emotional sensitivity to peer rejection. While only a limited number of studies have yet explored this question, the studies of Sebastian and colleagues (2010b, 2011) and our study (Chapter 4) indeed suggest that there is a (linear) increase in activity with age in regions which have been associated with the regulation of

negative affect in response to peer rejection (i.e., lPFC). These findings fit well with these models suggesting that brain regions involved in affect regulation are among the latest regions reaching functional maturity.

However, in order to account for non-linear shifts in social and emotional sensitivity from childhood into adulthood, both affective and regulatory brain circuitry should be considered together (e.g., Casey et al., 2008a, 2008b; Somerville et al., 2010a). If immature function of regulatory brain regions would be the basis for the heightened sensitivity to peer rejection during adolescence, this would not explain why adolescents are more sensitive to social rejection than children. In addition, brain regions that are involved in the affective processing of social stimuli are believed to highly sensitive to the increase of gonadal hormones at the onset of puberty (Nelson et al., 2005; Steinberg et al., 2008). Yet, neuroimaging evidence in support of enhanced neural responses in affective brain regions to peer rejection during adolescence is still limited. The results of our Cyberball study (Chapter 5) showed that the subgenual ACC was more strongly recruited in 10-12 year olds during social exclusion relative to older participants. While we cannot conclude from this study whether this neural response shows a U-shaped developmental pattern (since no comparisons with younger participants were made), this finding can provide a useful starting point for exploring developmental differences in affective brain regions. Further, the specificity of this effect in 10-12 year olds suggests that this finding may coincide with the onset of puberty, which should be tested in more detail in future studies.

It is important to note that, despite evidence for age-related differences in the processing of social rejection, studies also point to large similarities in neural and behavioral responses to social-evaluative feedback across age groups (e.g., Masten et al., 2009; Sebastian et al., 2011). These findings could be taken to suggest that social acceptance and rejection is salient across ages. It is possible that these social experiences may yield strong, uniform reactions across individuals, limiting the degree of age-related variance (Lissek et al., 2006). Indeed, it can be hypothesized from an evolutionary point of view that it would be adaptive to develop the neurobiological mechanisms underlying social attachment and bonding early in life (e.g., Lieberman & Eisenberger, 2009; MacDonald & Leary, 2005). Further, these age-related similarities raise questions concerning the experimental manipulation of social-evaluative experiences. Given the increased importance of peers during adolescence, teenagers are believed to be particularly sensitive to social rejection by peers. However, to date, not all studies investigated the impact of peer rejection, but tested for rejection experiences in general (not necessarily by peers). In addition, in studies aiming to simulate the experience of peer rejection, these feelings are typically induced through cover stories about age-matched peers. For future research it would be important to make the role of peer evaluation more explicit, for instance by the real presence of peers in the laboratory setting, or by simulating interactions between teenagers in the social media (see for a nice example the 'Chatroom Interact task' reported

by Silk et al., 2011). We believe this could enhance the sensitivity to detect age-related differences in the experience of social rejection.

To further improve our understanding of the neural substrate of social rejection in adolescence, there are several methodological issues that need to be considered. Whereas in the fMRI studies described in this thesis participants of multiple age groups were included, other studies typically included participants of only one or two age group(s) (Masten et al., 2009; Sebastian et al., 2010b, 2011). The use of a narrow age range limits the possibility to test for linear and non-linear patterns of activation with age. In addition, in some prior studies only females were included (Sebastian et al., 2010b, 2011). Our cardiac results described in Chapter 3, as well as results of other studies, suggest that gender is an important moderating variable in the processing of social rejection (Stroud et al., 2002). A priority for future fMRI studies would be to test the impact of peer rejection from middle childhood into adulthood, ideally by the use of longitudinal designs or a careful selection of age groups (Luna et al., 2010), and with sufficient power to test for gender differences. Further, an exciting avenue for future studies would be to test for age and gender differences in how different regions interact in response to social rejection, for instance by using functional connectivity analyses (e.g., Hare et al., 2008; Zaki et al., 2007).

Another issue that deserves mentioning is that different experimental tasks to induce feelings of social rejection may elicit distinct patterns of neural activation. Indeed, it is likely that task structure has an impact on the affective dynamics of social rejection. For instance, whereas the Social-Judgment task requires the processing of explicit judgments about social-evaluation, the Cyberball induces feelings of social rejection by excluding participants during a ball-tossing game. An important next step will be to gain more insight in psychological and neural processes underlying different kind of rejection experiences (Kross et al., 2007). One way of testing this would be to systematically examine the impact of social rejection by different interaction partners and different forms of rejection (e.g., rejection by same or opposite sex peers, rejection based on physical appearance or academic achievement, acute or a more gradual build-up of social rejection). One a related note, it would be of interest to test whether adolescents are more sensitive to specific forms of social rejection relative to adjacent developmental stages. Ultimately, this line of research has the potential to increase our understanding of the neurobiological mechanisms involved in social rejection and their developmental trajectory.

Finally, an interesting point to acknowledge is the different pattern of results obtained by cardiac and fMRI measures using the same experimental paradigm (Chapters 2-4). That is, although cardiac slowing was most pronounced for unexpected social rejection, neuroimaging results revealed widespread activity in response to expected social acceptance, and to a lesser extent to expected social rejection. These results seem to suggest that the heart and brain are differentially sensitive to social-evaluative feedback in the context of this task. However, there are several plausible explanations that need

to be considered. First, phasic heart rate changes may be particularly involved in the quick detection and adaptive allocation of attention towards salient information in the environment, such as unexpected social rejection (Porges, 2003; Thayer & Brosschot, 2005). Brain responses on the other hand may also reflect processes involved in the higher-level appraisal of social and emotional information (Kalisch et al., 2006). Second, the discrepancy between findings could reflect a difficulty to capture the specific timing of the heart rate response associated with unexpected social rejection in the fMRI signal, since fMRI is limited in temporal resolution (Wager et al., 2007). To overcome this problem, we recently started a study using the conjoint measurement of cardiac and electrical measures of brain activity (EEG).

PROTRACTED DEVELOPMENT OF BRAIN REGIONS INVOLVED IN MENTALIZING

Besides studies on social-evaluative feedback processing, this thesis described a study on developmental changes in neural activity associated with mind-reading from the eyes (Chapter 6). In particular, results of this study revealed that the pSTS was similarly recruited in both adolescents and adults, supporting the SIPN model of Nelson and colleagues (2005) suggesting that brain regions involved in social perception (i.e., the 'detection' node) develop early in life. In addition, it was observed that 10-12 year olds additionally recruited the mPFC, IFG, and the temporal pole when reading the mind in the eyes. Results of this study fit well with previous fMRI studies on mentalizing showing increased activity in prefrontal areas (particularly the mPFC) in adolescents relative to adults (e.g., Blakemore et al., 2007; Burnett et al., 2009; Pfeifer et al., 2007; Wang et al., 2006), and could extend these findings to more basic social-perceptual processes involved in mentalizing.

Yet, the question still remains why brain regions involved in mentalizing show a protracted functional development across adolescence, despite early maturation of mentalizing skills at a behavioral level. Previously, it has been hypothesized that these age-related differences in neural activation may reflect maturational processes involved in the fine-tuning of neural systems, particularly in the mPFC (Blakemore, 2008, 2010). Alternative explanations may relate to the functional role of the regions to perform these tasks. It is possible that children rely more on social semantic knowledge during mentalizing, due to less experience with mental state terms or mentalizing. Prior studies demonstrated that abstract social semantic information necessary to understand the mental states of others is subserved by the same brain regions involved in theory of mind, including the mPFC and the temporal poles (Mitchell et al., 2005a; Ross & Olson, 2010; Zahn et al., 2007). Finally, age-related differences in functional activity could hint toward the use of different strategies (e.g., Burnett & Blakemore, 2009a; Crone & Ridderinkhof, 2011; Luna et al., 2010). For instance, it has been suggested that adolescents might

employ a less automatic, more explicit strategy for mentalizing (Burnett & Blakemore, 2009a, 2009b), or a 'self-oriented' strategy by simulating in the self what another person is thinking or feeling (Burnett et al., 2009; Moriguchi et al., 2007).

However, to avoid the use of these post-hoc interpretations, there is need of a theoretical framework that could account for these developmental differences in a wide range of mentalizing tasks. In particular, we suggest that a priority for future work would be to find out whether the ability to understand the mental states of others requires a general level of abstract thinking that still develops during adolescence, or whether regions of the social brain may be less functionally defined during adolescence, followed by an increase in functional specialization or task selectivity with age (Johnson et al., 2009). Further, a promising direction for future studies would be to design experimental tasks that avoid ceiling effects at a young age (Burnett et al., 2011). Using an advanced mentalizing task, a recent study by Dumontheil et al. (2009) showed improvement in performance across adolescence. More specifically, the authors hypothesized that the interaction between mentalizing and executive functions continues to develop during adolescence.

7.4 Challenges and future directions

In the previous section, the main findings and conclusions of the empirical studies described in this thesis are discussed, as well as suggestions for future research. In this final section, several challenges and future directions at a more general level will be addressed that could improve our understanding of adolescent brain development and social behavior.

STRUCTURE AND FUNCTION RELATIONSHIPS

An important assumption in neurobiological models of adolescent development is that age-related changes in behavior are related to changes in neural activation and information processing, which in turn are related to the structural maturation of the brain (e.g., Burnett et al., 2011; Casey et al., 2008a, 2008b; Nelson et al., 2005). Despite the growing body of evidence showing a protracted structural and functional development of the adolescent brain, it is still for the most part unknown how changes in brain structure, such as synaptic pruning or myelination, might be related to brain function and behavior (see Luna et al., 2010; Somerville & Casey, 2010). On the one hand, it has been suggested that synaptic pruning might lead to less neural activity, resulting in a decrease in activity in brain regions with age. Indeed, some studies report that higher magnitude of activity could reflect neural inefficiency or increased effort, and that the extent of activation may shift from diffuse to more focal patterns of activation with age (e.g., Casey et al., 2005; Durston et al., 2006; Galvan et al., 2006). Alternatively, it has been suggested that synaptic pruning may facilitate the recruitment of more complex computations or a greater capacity to

perform a task, resulting in increased activity in specific regions with age (e.g., Bunge et al., 2005; Crone et al., 2006b; Sebastian et al., 2011). Similarly, it is still largely unknown how myelination affects changes in neural activity (Luna et al., 2010). There is a critical need for studies tracking the relationship between changes in brain structure, function and performance, ideally by the use of longitudinal designs (e.g., Crone & Ridderinkhof, 2011; Durston et al., 2006).

One recent promising theoretical framework for brain development highlights the dynamic interplay between structure and function relationships across development. According to this view of 'interactive specialization' (Johnson, 2010; Johnson et al., 2009), cognitive functions emerge as a consequence of bi-directional interactions between the brain and environmental factors, resulting in a reorganization of interactions between brain regions. Brain regions may begin with poorly defined functionality, followed by a process of functional specialization that could be driven by experiences. As such, the same behavior could be supported by different patterns of neural activation during development. This theory contradicts the 'maturation account', which suggests that specific cognitive functions come 'on-line' as the brain regions to perform a specific task reach and adult-level of functioning caused by intrinsic factors (i.e., genetics, neuroanatomical) (Johnson, 2010). The challenge for the future would be to test whether the theory of 'interactive specialization' could account for developmental differences in neural activity across adolescent development, and to explore how experiences could shape brain development.

PUBERTAL HORMONES AND SEX DIFFERENCES

A second important direction for future research is to test in detail how hormonal changes associated with the onset of puberty could impact brain development and behavior. This line of research is essential to support and further refine theoretical models on adolescent brain development, in which often a key role for puberty is suggested (see Blakemore et al., 2010). In particular, it is hypothesized that pubertal hormones could modulate activity in affective brain regions which may lead to increased emotional reactivity in adolescence (Dahl & Gunnar 2009; Forbes & Dahl, 2010; Nelson et al., 2005; Steinberg, 2008). Recently, there is indeed increasing evidence that structural and functional changes in the brain coincide with the onset of puberty, and that the effects of pubertal hormones could be gender-specific (e.g., Blakemore et al., 2010; Peper et al., 2011). Further, the cardiac results described in Chapter 3 reveal that bodily responses associated with social information processing could vary as a function of both pubertal maturation and gender. However, to date the number of studies that have considered the role of gender and pubertal hormones in social and emotional development is still limited. Because age and puberty are often highly correlated, research on pubertal development poses several challenges for an optimal study design. Future studies should try to disentangle age and puberty-specific effects by using a narrow age range in which participants only differ

in terms of pubertal status, or by using longitudinal analyses to account for individual differences in timing and tempo of puberty. In addition, more research is needed to test the reliability of different methodologies to assess pubertal development (i.e., self-report measures, physical examinations, hormone concentrations) (e.g., Blakemore et al., 2010; Dorn & Biro, 2011; Forbes & Dahl, 2010; Silk et al., 2009). Finally, research on the effects of puberty has the potential to yield insight in the emergence of gender differences in psychological disorders during adolescence (e.g., Angold et al., 1998; Oldehinkel & Bouwma, 2011).

Individual differences: towards clinical implications

Even though knowledge about normative brain development is critical to aid the understanding of pathways leading to mental disorders, a priority for future research would be to test in more detail for individual differences in social and emotional development. Adolescence is a time of transition marked by major biological and psychological changes, as well as a sharp increase in mental disorders, such as anxiety, depression, and addiction (e.g., Calkins, 2010; Davey et al., 2008; Oldehinkel & Bouwma, 2011). More specifically, it has been proposed that the temporary imbalance between earlier functional development of affective brain regions relative to a more gradual maturation of brain regions important for regulatory control may expose adolescents to certain vulnerabilities (Casey et al., 2010; Nelson et al., 2005), which is nicely illustrated in a study by Hare and colleagues (2008). The results of this study revealed that adolescents showed increased activity in the amygdala in response to fearful facial expressions relative to children and adults, which decreased with repeated exposure to the fearful faces. Importantly, individual differences in anxiety predicted the extent of this habituation; individuals with higher levels of anxiety showed less habituation of the amygdala, which was associated with less functional connectivity between the PFC and the amygdala. The authors interpreted this effect as indicating that the adolescent brain seems to be more reactive to emotional stimuli that increases the need for regulatory control, placing individuals with less regulatory control at a risk for mental health problems (see also Casey et al., 2010). Indeed, increased subcortical relative to prefrontal activity has been implicated in several affective disorders, such as depression and anxiety (e.g., Guyer et al., 2008; McClure et al., 2007). Similarly, it would be of considerable interest to test for individual differences in neural responses to peer rejection, which may explain why some adolescents are at a greater risk for developing mental disorders after negative peer experiences. The 'rejection sensitivity model' (Downey & Feldman, 1996) would be an interesting framework for understanding these individual differences. According to this model, rejection sensitivity could be characterized by a greater tendency to anxiously expect, readily perceive, and intensely react to social rejection, which may be the result of early rejection experiences with significant others (Butler et al., 2007; Kross et al., 2007; London et al., 2007).

To further elucidate the pathways for mental health problems during adolescence, it would be important to increase our understanding of the complex interplay between biological vulnerabilities and environmental challenges in the life of teenagers. The transition into adolescence is marked by a dramatic set of changes, such as the increased importance of peers, a greater degree of autonomy and independence, and greater academic demands. At the same time, the body of teenagers undergoes major changes (Steinberg & Morris, 2001). The emergence and co-occurrence of these changes may serve as specific stressors during this period in life that could exacerbate the imbalance between affective and regulatory brain regions (see Hare et al., 2008). Research on genetic and environmental risk factors will be vital to understand the role of individual differences in social and emotional development in this critical period in life.