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Social reorientation in adolescence : neurobiological changes and individual differences in empathic concern

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Social reorientation in adolescence

Neurobiological changes and individual differences in empathic concern

Sandy Overgaauw

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Social reorientation in adolescence

Neurobiological changes and individual differences
in empathic concern

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Chapter 1:

General Introduction

1.1 ADOLESCENCE AS AN IMPORTANT PERIOD FOR GAINING MATURE SOCIAL GOALS

Adolescence, which is the transition stage from childhood to adulthood, is an eventful period in life, as it encompasses major changes in physical appearance and changes in cognition, affect and social orientation. These changes are thought to be related to changes in the social environment, changes in the hormonal systems, and neurodevelopmental changes (Blakemore, 2008; Blakemore, Burnett, & Dahl, 2010). Whereas in childhood parents or caregivers play the most important role, school and playing are central elements, and the contact with friends is still quite 'simple', all of this undergoes major transformations in adolescence (Brown, 2004), and as such, this is one of the most important life period for developing mature social goals and independence.



FIGURE 1.1 | Overview of important transitions in adolescence, based on Steinberg (2005).

Adolescence is often divided into three stages: 1) early-adolescence (10–14 years old), 2) mid-adolescence (15–17 years old), and 3) late-adolescence (18–22 years old) (Steinberg, 2005; see Figure 1.1). Although researchers often refer to these stages, the boundaries are quite arbitrary, as they are largely dependent on individual differences in hormonal-, cognitive-, and social-affective levels (Blakemore, 2008; Blakemore, Burnett, & Dahl, 2010). The onset of adolescence is often marked by the onset of puberty, around age 10 for girls and around age 11.5 for boys, although also within the sexes there is large variability in the age of onset (Marshall & Tanner, 1969; Marshall & Tanner, 1970; Shirtcliff, Dahl, & Pollak, 2009). The first signs of puberty are characterized by hormonal changes related to the secretion of estrogen and testosterone leading to maturation in the ovaries and testes, which further result in the development of secondary physical features (e.g., pubic hair growth, breast development) (Shirtcliff, Dahl, & Pollak, 2009). Although puberty is often associated with bodily changes (such

as physical appearance, height, and shapes of the body), it goes beyond that, as puberty also plays a pivotal role in neurodevelopmental- and behavioral changes (Blakemore, Burnett, & Dahl, 2010).

Whereas the onset of puberty is often considered as the start of adolescence, defining the end point of adolescence is less clear. Following puberty and moving into adulthood, it is important that adolescents have acquired social and cognitive skills that are important for creating new friendships, obtaining self-confidence, being successful at an educational level, and for becoming an independent individual (Taylor, Barker, Heavey, & McHale, 2013). What is considered as the end of adolescence, and at the same time the start of adulthood, differs across cultures. In western cultures it is often indicated by the ability to manage one's life independently (Blakemore, Burnett, & Dahl, 2010).

One of the most prominent changes in adolescence is social reorientation (Blakemore & Mills, 2014; Steinberg et al., 2008). That is to say, adolescents develop more intimate relationships with peers in which mutual understanding plays an important role (Selman, 1980), they discover what it is like to be involved in a romantic relationship (Zimmer-Gembeck, 2002), and they take (social) risks by for example drinking alcohol for the first time (Brown, 2004) or showing risky driving in the presence of friends (Chein, Albert, O'Brien, Uckert, & Steinberg, 2011). These new experiences go hand in hand with the development of self-consciousness, which makes adolescents more aware of their surrounding peers, their own emotions, and the realization that their behavior will be judged by peers (Somerville & Casey, 2010; Somerville et al., 2013).

Given that adolescence is an important phase for social reorientation, eventually leading to a state of independency and individuality, empathic abilities play a crucial role in successfully reaching these goals. Examples of empathic abilities are sharing and understanding feelings of others and regulating your own emotional responses, which are crucial abilities in social interactions. How individual differences in empathic traits are related to the development of social reorientation is currently not well understood.

It is hypothesized that neural changes are related to the behavioral changes that are classified under the heading social reorientation (Somerville & Casey, 2010; Blakemore & Mills, 2014). In addition, it is hypothesized that the involvement of hormones affects social-affective functions.

Especially testosterone has proven to play an important role in risk-taking behavior during adolescence (Blakemore, Burnett, & Dahl, 2010; Peper, Koolschijn, & Crone, 2013). The current thesis has the purpose to understand the behavioral and neural underpinnings of developmental changes and individual differences in social reorientation and empathic concern across childhood and adolescence.

The questions addressed in this thesis concern: 1) how do brain regions involved in social reorientation develop in adolescence, 2) what is the role of individual differences, and 3) what is the role of pubertal development. These questions are addressed using a multi-method perspective of combining insights from self-report, task behavior, and neural activity on task tapping into components of social reorientation.

1.2 NEURODEVELOPMENTAL CHANGES IN ADOLESCENCE

An influential neural system model that aims to explain social reorientation in adolescence is the Social Information Processing model (SIPN) (Nelson, Leibenluft, McClure, & Pine, 2005; see Figure 1.2). This model describes the overall development of the brain based on three nodes: the detection node, the affective node, and the cognitive-regulation node. Each separate node represents a cluster of brain areas that mediates the processing of social information. The detection node is involved in detecting whether a stimulus is socially relevant, and for recognizing basic social characteristics (e.g. detection of faces). The anterior temporal cortex, the fusiform face area, and the superior temporal sulcus are the brain areas that are involved in this part of social information processing.

The affective node, including the nucleus accumbens (NAcc), ventral striatum (VS), hypothalamus and amygdala, attributes meaning to the perceived social information, for instance by indicating whether information is rewarding or punishing. This cluster of brain areas is thought to be more sensitive during adolescence, resulting in a stronger reaction in these brain areas compared to pre- and post-adolescence. This “hypersensitivity” is linked to changes in gonadal hormones, which affect functional and structural reorganization of the affective node regions (see Herting et al. 2014). This occurs indirectly as gonadal hormones affect neurotransmitters like dopamine, oxytocin, and serotonin that

help in the transmission of signals in the brain (e.g. social responsiveness). On a behavioral level, this hypersensitivity is claimed to enhance approaching positive stimuli and to enhance avoiding negative stimuli (Galván, 2010). In daily life, this phenomenon expresses itself in a way that adolescents are taking higher risks when peers encourage them, because being approved and socially accepted by peers is highly rewarding for adolescents (Chein et al., 2011). The downside of this medal is that adolescents who are socially rejected, avoid interactions with peers, possibly due to enhanced activation in the (social) pain related areas like the anterior insula (AI) and the anterior cingulate cortex (ACC), which often brings them in a downhill slide of more social rejection and the accompanied social pain (Masten, Telzer, Fuligni, Lieberman, & Eisenberger, 2012).

Finally, the cognitive-regulation node is involved in controlling and regulating social information (e.g. reasoning about mental states of others) and complex cognitive information (e.g. planning behavioral responses in order to reach a specific goal). The regions that are involved in this node are the dorsal medial prefrontal cortex (dmPFC) and the ventral prefrontal cortex (vPFC) (Nelson, Leibenluft, McClure, & Pine, 2005; Nelson & Guyer, 2011), regions that are still developing during mid to late adolescence, because of synaptic pruning (reduction of neurons and synapses in order to make more efficient neural structures) and myelinization (stimulates fast and guided information transmission) (Shaw et al., 2008). Notably, the detection node, affective node, and cognitive-regulation node are thought to be interrelated within the social information-processing network (Nelson, Leibenluft, McClure, & Pine, 2005).

The SIPN model shares commonalities with a second influential model, which is the dual systems model of adolescent development (Somerville, Jones, & Casey, 2010; Ernst & Fudge, 2009; Steinberg et al., 2008). This model places more emphasis on adolescent specific changes in reward seeking behavior. That is to say, mid-adolescence represents a period in which there is a peak in risk-taking behavior (e.g. having sex without protection, drinking an extensive amount of alcohol, smoking cigarettes). According to the dual systems model, the emotion regions in the brain undergo a sudden change in development, meaning that regions like the ventral striatum (a region important for reward seeking and approach behavior), and the amygdala (a region important for detecting (social) emotions), become “hypersensitive”. These regions are often indicated as subcortical regions being part of the affective node (VS and amygdala) of the SIPN model (Nelson, Leibenluft, McClure, & Pine, 2005).

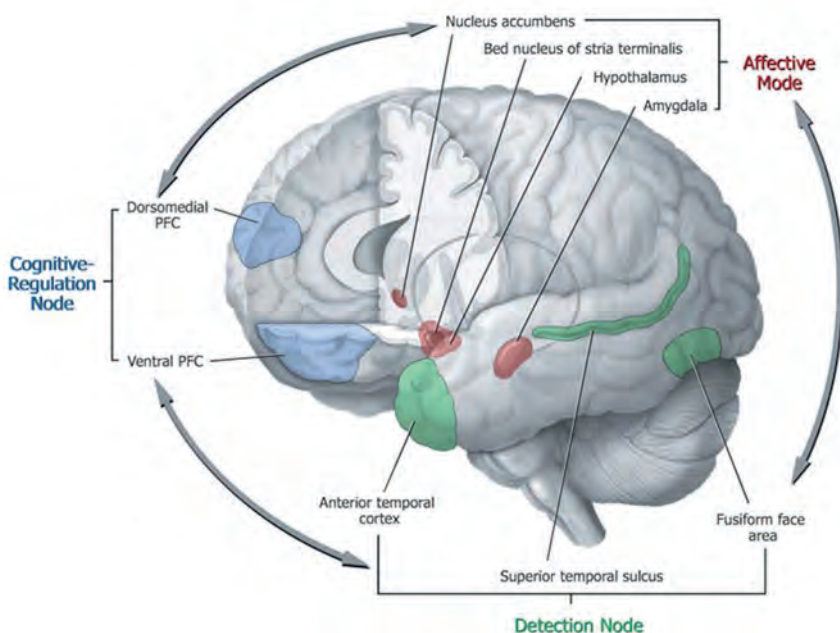


FIGURE 1.2 | Display of the regions involved in the Social Information Processing Network (SIPN) model, based on Nelson et al. (2005)

Similar to the SIPN model, the dual systems model puts emphasis on the development of the prefrontal (cortical) cortex as an important control region in the brain, although whereas the SIPN model places emphasis on both the medial and ventral parts of the prefrontal cortex, the dual systems model puts more emphasis on the lateral prefrontal cortex. The exact differentiation between functions of the medial and lateral PFC are not yet well understood, but a general finding is that the medial regions of the PFC are more involved in social information processing, such as theory of mind and self-referential processing, whereas the lateral regions of PFC are more involved in “cold” cognitive control functions such as working memory and response inhibition (Crone & Dahl, 2012; Blakemore & Mills, 2014; Luna, Padmanabhan, & O’Hearn, 2010). The maturation of the lateral prefrontal cortex continues during adolescence in terms of structure (Shaw et al., 2008) and function (Somerville, Jones, & Casey, 2010). Thus, the dual systems model presents the hypothesis that the affective system (VS, amygdala) matures faster (mid/late adolescence) than the control

system (lateral prefrontal cortex). These different developmental trajectories are leading to a discrepancy between the affective system and the control system, and seem to hinder adolescents' abilities to regulate their emotions and to inhibit impulsive reactions (Steinberg et al., 2008).

1.3 EMPATHY DEVELOPMENT FROM CHILDHOOD TO ADULTHOOD

Whereas the SIPN model provides an important working model for understanding changes in social reorientation during adolescence, less attention has been devoted to differences *between* adolescents. That is to say, some adolescents navigate through adolescence relatively well and are less sensitive to, for example, peer pressure, and develop into prosocial helping individuals with strong peer relations. In contrast, other adolescents have difficulty adapting to changing norms in peer relations and are withdrawn, lonely, suffer low self-esteem, and are likely to be at risk for internalizing disorders (Rubin, Bukowski, & Parker, 1998). The absence of social networks is strongly implicated in the development of psychopathology (Deater-Deckard, 2001). In this thesis, the hypothesis is tested that individual differences in empathy are an important predictor for behavioral and neural responses involved in social reorientation.

THE CONCEPTUALIZATION OF EMPATHY

Empathy has many different faces in terms of labels and definitions. Some of the terms that are often used to indicate empathy (or that are closely related to empathy) are: emotional contagion, empathic concern, sympathy, compassion, Theory of Mind, mentalizing, perspective taking, prosocial behavior, and altruism (for a review, see Preston & De Waal, 2002; Zaki & Ochsner, 2012; see Figure 1.3).

A consistent differentiation in the literature is the definition of empathy by two concepts: affective empathy and cognitive empathy. Affective empathy has often been defined as sharing feelings with someone by mirroring the affective state of the person who is experiencing the emotion (De Vignemont & Singer, 2006). Cognitive empathy, on the other hand, has been defined as awareness of the self, the ability to make a self-other distinction and the ability to take another person's perspective (Bernhardt & Singer, 2012).

Prosocial behavior is indicated as an ability rising from cognitive empathy, and is explained by helping someone out of compassion without taking into account self-interest.

Empathic abilities have been found to develop during childhood. An important component of affective empathy is sharing feelings, which already happens in babies, for example when all babies at the nursery start crying because one baby started expressing its sad feeling or 'cry for help/need'. This does not mean that all the babies are actually sad or in need, just that the emotion of the baby contaminated them (Decety & Meyer, 2008). Making a distinction between one's own feelings and that of someone else comes along when cognitive empathy develops, mostly around age 4 or 5, when Theory of Mind has been developed (Baron-Cohen, Leslie, & Frith, 1985). However, not all components of cognitive empathy are already in place in 5-year-old children, that is, the more advanced forms of cognitive empathy, such as perspective taking and prosocial development, develops still into adolescence (Güroğlu, van den Bos, & Crone, 2014).

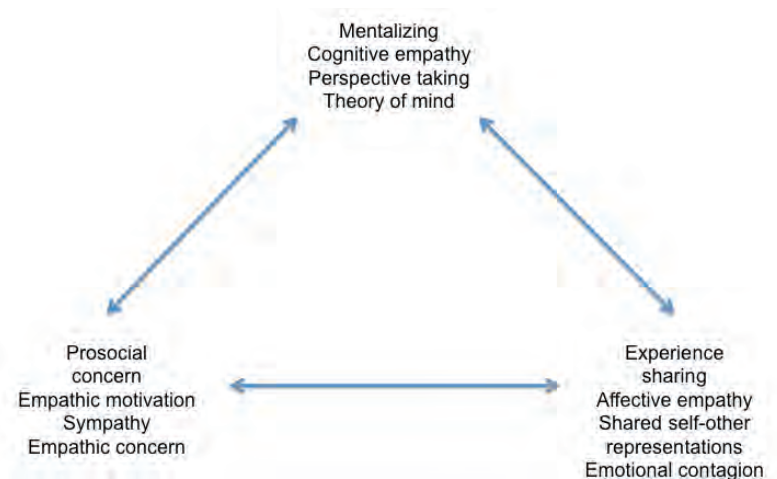


FIGURE 1.3 | Empathy encompasses different processes, which can be categorized as affective empathy, cognitive empathy and prosocial concern, based on Zaki & Ochsner (2012)

1.4 NEURAL CORRELATES OF EMPATHY

EMPATHY MODEL DECETY & MEYER

Developmental and individual differences in empathy have been described in a model by Decety & Meyer (2008), who demonstrated that empathy derives by a 'bottom-up perception action information process' in combination with a 'top-down regulation and control' information process, whereby past life experiences and specific contexts/situations are of influence. The bottom-up perception action coupling can be explained by underlying biological processes that enable people to learn and share feelings by observing action or mimicry. This biological process has been referred to as the Mirror Neuron System (MNS). When observing someone putting his hands together, the MNS provides activation in the same brain areas in the observer as in the actor, though to a lesser extent. Thus, by 'mirroring' the observed action, the mirror neurons are preparing the required brain network for actual performing an action (motor empathy). Besides facilitating action performance, the MNS is also important for perceiving the emotional state of others. Sharing emotions of others by activating the same brain areas helps in empathizing with that other person, i.e. by shared representations. The brain regions that are involved in both the perception and performance of motor empathy (most likely driven by mirror neurons are): the premotor cortex, the inferior frontal gyrus (IFG), the parietal lobule, the supplementary motor area, and the cerebellum.

The 'top-down regulation and control' information process is involved in regulating emotions that enable us to make a self-other distinction and to have self-control. Making a self/other distinction requires the ability to know if an action is performed by the self or by the other, and can be determined by: 1) non-overlapping regions in the brain, i.e. regions for self-representation are not involved in other-representations 2) awareness that neural signals of the self are giving immediate feedback, whereas motor empathy representations perceived in others require more processing. The brain regions that have been found to be important for making a distinction between the self and the other are the temporal parietal junction (TPJ) and the paracingulate cortex (PCC). The anterior insula (AI) is an example of a region that has found to become activated when you are responsible for an action, but does not activate when someone else is responsible for an action. In the latter case, the right TPJ has found to be involved (Farrer & Frith, 2002).

In sum, empathy is based on both the ‘bottom-up perception action information process’ and the ‘top-down regulation and control’ information process. Difficulties in sharing emotions can lead to shortcomings in understanding what someone else is feeling, whereas difficulties in controlling your own emotions can lead to personal distress and a lack of self-monitoring (Decety & Meyer, 2008). Determining how empathy develops on a behavioral and neural level has been studied extensively by empathy for pain.

EMPATHY FOR PAIN

The literature on the neural correlates of empathy is quite extensive and has focused on various aspects of empathy varying from empathy for physical pain, empathy for social pain (social exclusion), and empathic responses on emotions such as anger, sadness, or happiness (Bernhardt & Singer, 2012). Empathy for pain is by far the most investigated aspect of empathy (Lamm, Decety, & Singer, 2011). When seeing someone in pain, this often gives individuals an unpleasant feeling. For example when observing someone falling off his/her bike, which may lead to the feeling of falling off the bike yourself. Jackson and colleagues have studied participants’ reactions on observing pictures in which painful situations were presented (Jackson, Meltzoff, & Decety, 2005; Jackson, Brunet, Meltzoff, & Decety, 2006). The brain areas that became active while watching these disturbing pictures were the anterior insula (AI), the anterior cingulate cortex (ACC), and the anterior mid-cingulate cortex (aMCC). These regions have proven to be mainly involved in the observation of painful situations and are often referred to as the ‘pain matrix’ (Bernhardt & Singer, 2012).

The regions mentioned above have also been found to be involved in the direct experience of pain (Bird et al., 2010; Hein, Silani, Preuschoff, Batson, & Singer, 2010; Singer et al., 2004; Singer et al., 2006; Singer et al., 2008). Multiple studies have investigated empathy for pain and demonstrated overlap between the regions that became active when observing pain in others compared to experiencing pain. The observation that empathy for pain investigated by pain inflicted pictures, video clips, and by abstract visual cues leading to electric stimulation result in activation in areas that are part of the pain matrix, indicates that empathy for pain is a robust neural mechanism (Lamm, Decety, & Singer, 2011).

Besides activating pain related areas when observing painful situations, another concept is involved as well, namely the contextual or social cues.

For determining the intentions of people involved in a social situation, social cues need to be read. By reading social cues from facial expressions and posture, it is possible to understand a situation and to determine whether the behavior is morally right, wrong or neutral (e.g. harm inflicted accidentally or intentionally) (Pfeifer et al., 2009; Sinke, Sorger, Goebel, & de Gelder, 2010). The areas previously found to be involved in judging social situations and moral behavior are the TPJ, the PCC, and the amygdala (Pfeifer et al., 2009). The TPJ and PCC are regions important for making a self/other distinction and taking other persons' perspective, the oMFC is a reward and punishing related area that monitors positive or negative outcomes, and the amygdala is involved in emotional stimuli and evaluates whether situations are threatening (Decety, Michalska, & Akitsuki, 2008).

Previous studies have examined the developmental changes in activity in these empathy networks (Decety, Michalska, & Kinzler, 2012) and reported developmental changes in several key areas of the network, especially in amygdala–prefrontal cortex coupling, but much less emphasis has been placed on understanding the social–cognitive processing of empathy for pain. In addition, almost nothing is known about individual differences in these trajectories, even though studies in adults reported an important role for individual differences in empathic traits in explaining neural activity during empathy for pain (Decety & Jackson, 2004; Jackson, Brunet, Meltzoff, & Decety, 2006; Van der Heiden, Scherpiet, Konicar, Birbaumer, & Veilt, 2013). Studies that have included groups with psychopathology also show differences in empathy networks in adolescence (Decety, Chen, Harenski, & Kiehl, 2013). This thesis addresses the question how social–cognitive empathy is represented in the adolescent brain and how trait individual differences in empathy explain individual differences in neural responses to social–cognitive empathy.

1.5 OUTLINE CURRENT DISSERTATION

The studies in this thesis are inspired by the combination between the SIPN model for the development of social orientation and the Empathy model to test development and individual differences in cognitive, affective and prosocial empathy. Chapters 2 and 3 use a longitudinal design to examine developmental

changes in activity in the detection and affective nodes of the adolescent brain. Most previous research on adolescent brain development has been done cross-sectionally, which gives important information about general neural patterns associated with social and/or cognitive abilities in one or multiple (age) groups. However, the limitation of cross-sectional research is that it does not allow to follow one individual over time and to track how certain abilities change or remain stable within a person. This problem can be resolved by longitudinal research in which it is possible to examine individual trajectories for an individual.

The study presented in **Chapter 2** describes a longitudinal analysis of neural regions involved in mentalizing. Prior studies showed age related changes in the social brain network related to mentalizing, though this was only tested cross-sectionally. The goal of the fMRI study was to test whether the regions involved in mentalizing are consistently active within adolescents across time or whether regions in this network change during development.

Chapter 3 involves a combined cross-sectional and longitudinal study on the relationship between reward processing and puberty in adolescent boys and girls. The hypothesis was that the affective node of the brain, with a specific focus on the ventral striatum, would become increasingly activated in response to rewards with increase age. Second, this node was expected to show individual differences based on self-reported sensation seeking behavior. The first experiment describes a cross-sectional study in which adolescents played a risky decision task. The second experiment describes a longitudinal study of a subset of adolescents who participated in the cross-sectional study (timepoint 1) that were tested again in a follow-up two years later (timepoint 2). As such, this study aimed to examine stability, change, and individual differences in reward processing in adolescence in a cross-sectional and longitudinal comparison.

Next, the cognitive node of the SIPN model was tested in three studies, with a specific focus on cognitive empathy and prosocial behavior. First, in **Chapter 4** a new Empathy Questionnaire was validated that aims to assess different aspects of empathy (affective, cognitive and prosocial) in children and adolescents. Additionally, the study describes how these abilities are linked with positive and negative aspects of social interactions.

Next, in **Chapter 5** a behavioral study examined the role of strategic versus altruistic motivations in bargaining considerations and their developmental trajectories. The reason for using bargaining games was to measure how individuals divide a stake in which two motivational aspects are important: interest in own outcome and concern for the other player (Van Dijk & Vermunt, 2000). Considering that cognitive and prosocial empathy develops over time and that individuals differ in how empathic they behave, a bargaining game in which a stake has to be divided between self and the other can provide relevant information about cognitive empathy and prosocial behavior. More specifically, we tested whether adults show higher levels of concern for others compared to children and have more altruistic motives for offering fair distributions.

In **Chapter 6**, a cross-sectional fMRI study examines the neural responses in response to negative and positive social situations, and whether this is related to self-reported levels of empathy. We were specifically interested in testing whether the regions in the different nodes of the social brain areas were differentially sensitive to the perception of negative social and positive social situations, and whether participants differentiated between the agents in negative social and positive social situations.

Finally, **Chapter 7** integrates the previous chapters and discusses the contribution of the studies to existing literature by drawing attention to possible theoretical and practical implications.





Chapter 2:

A longitudinal analysis of neural regions involved in reading the mind in the eyes

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ABSTRACT

The ability to perceive social intentions from people's eyes is present from an early age, yet little is known about whether this skill is fully developed in childhood or that subtle changes may still occur across adolescence. This fMRI study investigated the ability to read mental states by using an adapted version of the Reading the Mind in the Eyes task within adolescents (aged 12–19) over a two-year test–retest interval. This longitudinal setup provides the opportunity to study both stability over time as well as age–related changes. The behavioral results showed that participants who performed well in the mental state condition at the first measurement also performed well at the second measurement. fMRI results revealed positive test–retest correlations of neural activity in the right superior temporal sulcus and right inferior frontal gyrus for the contrast mental state > control, suggesting stability within individuals over time. Besides stability of activation, dorsal medial prefrontal cortex showed a dip in mid–adolescence for the mental state > control condition and right inferior frontal gyrus decreased linearly with age for the mental state > control condition. These findings underline changes in the slope of the developmental pattern depending on age, even in the existence of relatively stable activation in the social brain network.

2.1 INTRODUCTION

Understanding what someone else is thinking or feeling is an important component of reading intentions, beliefs and needs of others (Baron-Cohen et al., 1999). A term that is often used to describe this ability is mentalizing, which is defined as a certain type of mental state reasoning in order to define how social cues are interpreted in the complex world of social interactions (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997). In reading the mental states of others, at least two processes are involved: a social perceptual process and a social cognitive process (Adams et al., 2009); both part of the Social Information Processing Network (SIPN; Nelson, Leibenluft, McClure, & Pine, 2005). The social perceptual process refers to 'reading' someone's mental state by direct observation of non-verbal social cues (Adams et al., 2009; Sabbagh, 2004). The social cognitive process tends to be more complex as this process enables mental reasoning about others in order to estimate intentions and its associated goal directed behavior. A key question concerns how reading mental states develops in children and adolescents. In this study, we use a longitudinal design to study the ability to infer the mental states of others by seeing only the eye region of faces across adolescence, and the brain regions involved in this process.

A task which has been used previously in adults to test brain regions involved in reading mental states is the 'Reading the Mind in the Eyes task' (RMET) developed by Baron-Cohen and colleagues (2001a). The task displays the eye region of faces, which can signal basic (e.g. happy) or complex (e.g., confused) mental states whereupon the participant needs to select the correct answer from an array of choices (Baron-Cohen, Wheelwright, Spong, Scahill, & Lawson, 2001b). As such, the task requires both social perceptual and social cognitive processes, and has been referred to as a social mentalizing task (Dal Monte et al., 2014). With an absence of ceiling effects even in typically developing adults, this social mentalizing task can be applied in studies including participants of varying ages and in both clinical and typical developing groups (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Gunther Moor et al., 2012).

With regard to neural activation, a set of studies in adults have reported robust activation in posterior superior temporal sulcus (pSTS), anterior temporal cortex (ATC), and inferior frontal gyrus (IFG) when reading mental states compared to a control condition which required gender and/or

age judgments (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Castelli et al., 2010; Gunther Moor et al., 2012). These regions have been related to different social cognitive processes (Blakemore & Mills, 2014). That is, the STS has been found to be important for predicting intentional behavior based on biological motion, i.e. non-verbal body language and facial expressions. Therefore this brain region has been associated with mentalizing and theory of mind (Blakemore, 2008; Carter, Williams, Minshew, & Lehman, 2012). The ATC, also denoted as temporal pole, is labeled as being involved in relating an emotional response to social processes involving memory, such as social recognition (Nelson, Leibenluft, McClure, & Pine, 2005; Pfeifer & Peake, 2012). The IFG, an area which is implicated in a wide variety of tasks, has been found to be involved in reading action tendency based on non-verbal and verbal cues (Liakakis, Nickel, & Seitz, 2011; Rizzolatti & Craighero, 2004; Sebastian, Viding, Williams, & Blakemore, 2010), in understanding social situations (Carter, Williams, Minshew, & Lehman, 2012), and in semantic working memory (Dal Monte et al., 2014). These brain areas together are often described as part of the 'social-brain' network, which are linked to both social perception and cognition. The areas concerning the social brain network, which are implicated in Reading the Mind in the Eyes (STS, ATC and IFG), are still developing during childhood and adolescence as was shown in several mental state reasoning studies (reviewed in Blakemore, 2008).

A prior cross-sectional study reported that 10-12-year-olds and 14-15-year-olds showed robust activation in posterior STS, ATC and IFG when performing the RMET (Gunther Moor et al., 2012). This finding was interpreted to suggest that the human system for social perception is already tuned to read the intentions of others from the eyes at a young age, consistent with the notion that children from the age of 10-12 years were already able to perform well on the RMET (Baron-Cohen et al., 2001b; Gunther Moor et al., 2012). However, 10-12-year-old children showed additional activation in medial prefrontal cortex (mPFC), bilateral IFG and the right temporal pole compared to adults, despite similar performance levels. The elevated level of activation in mPFC during early adolescence has also been reported in other studies using different social cognitive tasks (Burnett & Blakemore, 2009a; Van den Bos, van Dijk, Westenberg, Rombouts, & Crone, 2011). The researchers explained this elevated early-adolescence age effect as a refining period in which structural and functional development is still ongoing. This leads to the question whether

reading mental states is a stable characteristic which develops early (as was suggested for pSTS activity; Gunther Moor et al., 2012), or whether the neural regions involved in mentalizing undergo further specialization in adolescence (as was suggested for medial PFC, IFG and ATC; Gunther Moor et al., 2012).

The current study tested stability versus change of mentalizing while performing the RMET in adolescents using behavioral and brain measures by means of a longitudinal design. That is, longitudinal designs are imperative for testing stability because even though cross-sectional results are informative for detecting general developmental patterns, the question of whether activation is stable within individuals can only be tested using longitudinal assessment (Plichta et al., 2012; Van den Bulk et al., 2013). For example, a pattern may seem stable across time, but could still be driven by large variability within groups and across sessions.

In sum, the goal of the current fMRI study was to test whether the regions of the social brain network related to mental state reasoning (Blakemore, 2008) are consistently active within adolescents across time or whether regions in this network change during development. In this study, we retested adolescents who had previously participated in the study of Gunther Moor et al. (2012) after a two-year interval. Participants between ages 10 and 16 years at the first measurement were tested again between 12 and 19 years and completed the RMET in the scanner on both occasions. Brain regions of a priori interest concerning stability over time were bilateral STS, determined based on the results of the first measurement (Gunther Moor et al., 2012). Brain regions of a priori interest concerning changes over time were mPFC, right temporal pole, and bilateral IFG (Gunther Moor et al., 2012).

2.2 METHODS

PARTICIPANTS

This longitudinal fMRI study spanned a time period of two years (min = 1.83; max = 2.42; SD = .15), with a subset of the 10- to 23 year olds who participated in the first measurement (see Gunther Moor et al., 2012). Data from the first measurement have been published before and focused on the cross-sectional developmental trajectories of brain regions involved in social mentalizing abilities. In this study, a total of 37 right-handed adolescents in the age of 12 to

19 (Mean age = 15.49, SD = 2.08; 23 females) participated again in the second measurement. For the current study, we selected all adolescents (N= 39, ages 10–16) who took part in the original study of whom 77% of the participants were scanned in the follow up (T2). The eight participants (six 14–16 year olds and two 16–18 year olds) who did not participate at the second time point (T2) were excluded based on braces or because they did not return our calls and/or e-mails. In addition to the sample reported by Gunther Moor and colleagues (2012), ten additional participants were included in the analyses of both T1 and T2. All participants followed the exact same scanning protocol. Since we focused specifically on developmental changes across adolescence, no adults were recruited for the longitudinal study.

Intelligence scores were determined during the first scanning session by two subscales of the Wechsler Intelligence Scale for Children (WISC): the subscales similarities and block design (Wechsler, 1991, 1997), and were not significantly correlated with age. Child Behavior Checklist (CBCL; Achenbach, 1991) scores on the first time point indicated no clinical thresholds and therefore did not indicate exclusion of participants at the second measurement. As a result of technical problems during the second scanning session, data from five adolescents were lost, which led to a total remaining number of 32 participants (who participated at both time points) in the final analysis (Mean age T1 = 13.2, SD = 1.95; Mean age T2 = 15.37, SD = 2.01, 20 females).

Participants provided informed consent, and for minors, parents gave informed consent. Depending on the age of the participant, a fixed amount was paid to either the parent or the participant. The Institutional Review Board of the University Medical Center approved all procedures.

EXPERIMENTAL TASK

Participants performed an adapted version of the child-version of the RMET (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001a). In this task, participants were presented with photographs of the eye region of faces during the performance of two task conditions: a mental state condition and an age/gender condition presented as a mixed block/event-related design. This design (mixed block/event-related design) is used—instead of an event-related design—in order to ensure that no executive functioning was measured because of enforced attention shifts due to a random presentation of different conditions (Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997).

The task conditions were presented in 4 blocks of 14 trials and contained 28 different black and white photographs (each photograph was displayed once in each condition) that were randomized within each block for each participant. The four blocks alternated between a mental state condition (A) or an age/gender condition (B), which were presented in an ABAB or BABA design (counterbalanced across participants). Depending on the task condition, participants were asked to either judge what the person on the photo was thinking or feeling (mental state condition) or to judge the age and gender of the person on the picture (age/gender condition). Both task conditions required participants to select one of the four simultaneously presented words that best described the photograph. In the mental state condition, the words included both basic emotion terms such as sadness, anger or happiness and more complex emotion terms like thinking, joking or being sure about something. These mental state terms were translated to Dutch by the help of native Dutch speakers (Gunther Moor et al., 2012).

The age/gender condition served as a control condition and consisted of the same pictures as shown in the mental state condition. Participants were instructed to determine whether the presented person on the picture was: 1) either younger than 60 or older than 60, and 2) a man or a woman. Based on this assessment, participants could choose from the following four response options: “younger male”, “younger female”, “older male”, or “older female”. The location of these phrases differed randomly across trials, to avoid that participants responded automatically without reading the possible answers (see Gunther Moor et al. 2012, for a complete description of the procedure). The age judgments used in the RMET were validated by 10 adults and led to a discrepancy in age judgment on three of the 28 trials. Therefore, in task performance these trials were scored as being correct in cases where the participants labeled only gender accurately.

In between trials, a jittered fixation cross was presented in the center of the screen (varying between 600 and 8000 ms). After each fixation cross, a facial stimulus was presented, accompanied by the 4 simultaneous presented words (see Figure 2.1). All stimuli remained visible for 9 seconds, though participants were required to give an answer within 8 seconds. Responses that were not made within this time frame elicited the feedback ‘Too slow’ for 1 second, signaling the end of the trial. Responses could be made by pressing a button with the index and middle fingers of the right and left hand.

The position of the response buttons mapped to the location of the four response options on the screen. Following the response, the word that was selected by the participant was displayed for the remaining length of the trial.



FIGURE 2.1 | Example of a mental state condition trial ('Reading the Mind in the Eyes Task'; Baron-Cohen et al., 2001b).

PROCEDURE

Prior to scanning, participants practiced both task conditions by performing eight practice trials. In addition, they were asked to read a list of words to make sure they understood all of the mental state terms that were used in the experiment. At the first measurement, six children between ages 10 to 12 years indicated that they did not understand one or two words on the list. Analyses showed that four of these six children made incorrect judgments on a total of 5 trials (1 or 2 trials per person), despite the explanation of the words before the fMRI session started. These trials have been excluded from further analysis to ensure that these incorrect judgments were not the result of a lack of understanding of the words. At the second measurement, a similar procedure was used and none of the participants indicated that they did not understand the meaning of a word.

During scanning, participants completed two runs of 28 trials and switched between conditions once within a run (e.g. AB–short break–AB). Both runs started with a short instruction display, explaining participants whether they would start with condition A or B. After 14 trials a display with the text ‘SWITCH’ was presented for 5 s to indicate the switch between task conditions.

DATA ACQUISITION

Prior to scanning, participants were familiarized with the scanner environment using a mock scanner. Scanning was performed using a 3.0-Tesla Philips Achieva scanner at the Leiden University Medical Center. Foam inserts that surrounded the head restricted head motion. Functional data were acquired using T2*-weighted Echo-Planar Images (EPI) (TR: 2.2 s, TE: 30 ms, slicematrix 80 x 80, FOV: 220, 35 2.75 mm transverse slices with 0.28 mm gap) during two functional runs of 153 volumes each. The first two volumes of each run were discarded to allow for equilibration of T1 saturation effects. After the functional scanning, high-resolution T2*-weighted images and high resolution T1 anatomical images were obtained.

FMRI DATA ANALYSIS

Data were analyzed using SPM8 (Wellcome Department of Neurology, London, UK). For each participant, the T1 weighted image was segmented and spatially normalized using the default parameters. The fMRI data were corrected for motion, co-registered with the T1 anatomical image and normalized to a T1 template. Templates were based on the MNI305 stereotaxic space (Cocosco, Kollokian, Kwan, & Evans, 1997). The normalization algorithm used a 12-parameter affine transformation together with a non-linear transformation involving cosine basic functions, and resampled the volumes to 3 mm cubic voxels. Data were then spatially smoothed with a 8mm FWHM isotropic Gaussian kernel. Translational movement parameters never exceeded 1 voxel (<3 mm) in any direction for any subject or scan. The participants who participated in both scanning sessions had a mean and maximum head movement of 0.08 and 2.52 mm at the first measurement and a mean and maximum head movement of 0.1 and 2.32 mm at the second measurement. Hence, head movement never exceeded 3 mm at both scanning sessions. Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction.

Statistical analyses were performed on individual participants' data using the general linear model in SPM8. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function (HRF). The onset of each presented stimulus was modeled as a separate event and was labeled as mental state or as age/gender (i.e., control) condition. The duration of the separate events was fitted based on length of the reaction time on each trial. Trials in which participants responded too slow (not within 8 seconds), or incorrect, were modeled separately as covariates of no-interest, and removed from further analysis. The modeled events based on correctly performed trials were used as covariates of interest in a general linear model along with a basic set of cosine functions that high-pass filtered the data and a covariate for run effects. The least-squares parameter estimates of height of the best-fitting canonical HRF for each condition were used in pair-wise contrasts.

The first-level analyses were group-averaged at the second-level using a fully flexible factorial design, with the factors: subject, time (T1 and T2) and condition (mental state and control). In this random effects model, we allowed for violations of sphericity by modeling non-independence across images from the same subject and unequal variances between conditions and subjects as implemented in SPM8. This analysis allowed studying main effects of Time (T1 and T2) and Condition (mental state and control) and possible interactions between Time and Condition on a whole-brain level. Task-related responses were considered to be significant at a threshold of $p < .05$ using FDR correction, with a minimum extent of 10 voxels. All brain coordinates are reported in MNI atlas space (see Table 2.1).

TABLE 2.1 | All brain coordinates based on the whole brain contrast mental state > control for N = 32 in a flexible factorial design; interconnection of subjects on T1 and T2 (FDR corrected, $p > .05$; 10 contiguous voxels).

Contrast	Region	MNI (x, y, z) coordinates	Z-value	Volume ¹ (= k_E value in SPM)
All participants: mental > control				
frontal	L Inferior Frontal Gyrus	-48, 24, -3	>8	2194
	L Inferior Frontal Gyrus	-54, 18, 18	>8	
	L Inferior Frontal Gyrus	-54, 24, 6	>8	
	Dorsal Medial Prefrontal Cortex	-9, 54, 36	5.67	142
	Dorsal Medial Prefrontal Cortex	9, 57, 33	4.96	
frontal temporal	R Superior Temporal Sulcus	48, -39, 3	6.88	906
	R Inferior Frontal Gyrus	57, 24, 6	6.81	
temporal	L Temporal Pole	-57, -6, -12	7.15	116
	R Temporal Pole	51, 12, -24	5.87	

We used the Marsbar toolbox for use with SPM8 (Brett, Anton, Valabregue, & Poline, 2002) to perform region of interest (ROI) analyses to further investigate patterns of activation for the two different time points. ROI analyses focused on brain regions of a priori interest (stability versus change) and were based on regions that were identified in the functional mask of the whole-brain analyses at T1 (mental state vs. control). Subsequently, activation in these regions were tested for stability between T1 and T2 and age-related changes in activation (see Koolschijn, Schel, de Rooij, Rombouts, & Crone, 2011 for a similar procedure). A whole-brain threshold of $p < .05$ (FDR corrected) resulted in activation in the seven task-related areas, that were activated in the mental state > control contrast at T1 (N = 32). It appeared that the left STS, the left IFG, and the left temporal pole were interconnected, as well as the right STS, the right IFG, and the right temporal pole. In order to separate the overlapping brain areas, a threshold of $p < .05$ (FWE corrected) was used for ROI extraction of these regions (see Table 2.2).

TABLE 2.2 | All brain coordinates for the seven task related ROIs based on the whole brain contrast mental state > control for N = 32 on T1 (FWE corrected > .05; 10 contiguous voxels: bilateral STS, bilateral IFG, bilateral temporal pole; FDR corrected, > .05; 10 contiguous voxels: dmPFC).

Contrast	Region	MNI (x, y, z) coordinates	Z-value	Volume ¹ (=k _E value in SPM)
All participants: mental > control				
frontal	L Inferior Frontal Gyrus	-51, 21, 18	6.22	183
	R Inferior Frontal Gyrus	54, 24, 3	5.25	24
	Dorsal Medial Prefrontal Cortex	-9, 51, 36	4.13	139
temporal	L Superior Temporal Sulcus	-51, -42, 0	6.32	197
	R Superior Temporal Sulcus	48, -36, 0	4.87	14
	L Temporal Pole	-57, -6, -12	5.44	40
	R Temporal Pole	51, -9, -21	5.20	37

The first set of analyses focused on stability within ROIs over time by correlating activity for the mental state > control condition at both time points for each region. When correlations were present, these were followed up by post hoc comparisons for the mental state > fixation baseline and control > fixation baseline conditions.

The second set of analyses assessed the effects of age on neural activation in which we used a linear mixed-effect model approach. This approach is a type of regression model that is able to account for the nested nature of the longitudinal data (participants measured multiple times). These analyses were performed using the lme4 package in R (Bates, Maechler, & Bolker, 2011). P values were determined using Likelihood Ratio Tests as implemented in the mixed() function in the afex package (Singmann, 2013). These analyses were performed on ROI activation for the contrasts mental state > control, mental state > fixation, control > fixation. For behavioral data similar analyses were performed to test for effects of age on percentage correct and reaction time (RT) in the mental state and control condition. In all models, a fixed intercept, a fixed effect of Age (linear), and a fixed effect of Age² (quadratic) as predictors to test different patterns of change across development were used. These predictor-variables were mean-centered. The nested nature of the data was modeled by including a random intercept per participant.

2.3 RESULTS

BEHAVIORAL DATA

The 2 (Condition: mental state vs. control) x 2 (Time: T1 vs. T2) repeated-measures ANOVA for percentage correct resulted in a main effect of Condition [$F(1, 31) = 101.32, p < .001$], but showed no main effect of Time or an interaction effect between Time and Condition. The main effect of Condition showed that percentage correct was higher in the control condition (Mean = 87.33%, SD = 5.67) than in the mental state condition (Mean = 66.96%, SD = 11.52). Even though percentage correct was generally lower on the mental state condition, participants performed well above chance level (25%).

To test whether there was stability in performance across sessions, we computed correlations between percentages correct in the mental state condition at T1 and T2. The analysis for mental state trials revealed a significant positive correlation between T1 and T2 ($r = .37, p = .037$; see Figure 2.2A) showing that those participants who performed well at the first measurement also performed well at the second measurement. There was no significant correlation between T1 and T2 for both the control condition ($r = .25, p = .16$), as well as for the difference score in accuracy between the mental state and the control condition.

Next, we tested performance changes by testing RT differences between conditions on correctly performed trials. For this purpose, a 2 (Condition: mental state vs. control) x 2 (Time: T1 vs. T2) repeated-measures ANOVA was performed. This resulted in a main effect of Condition [$F(1, 31) = 387.13, p < .001$], but no main effect of Time nor an interaction effect between Time and Condition. The main effect of condition showed that participants responded slower in the mental state condition (Mean = 4.03 seconds, SD = 5.37) than in the control condition (Mean = 2.94, SD = 5.42).

Correlations between RT in the mental state condition at T1 and T2 revealed a significant positive correlation ($r = .62, p < .001$, see Figure 2.2B). The same correlation analysis for the control condition also showed a significant positive correlation between T1 and T2 ($r = .86, p < .001$). These results show that those participants who responded fast at the first measurement also responded fast at the second measurement for both the mental state as the control condition. The correlation between T1 and T2 was not significant for the difference scores in RT between the mental state and control condition.

Finally, age-related changes were tested with a mixed-model approach including behavioral indices from T1 and T2. Results showed no significant age-effects on performance (percentage correct answers) for both the mental state and the control condition ($p > .1$). Also RT in the mental state and the control condition showed no significant age-effects ($p > .1$).

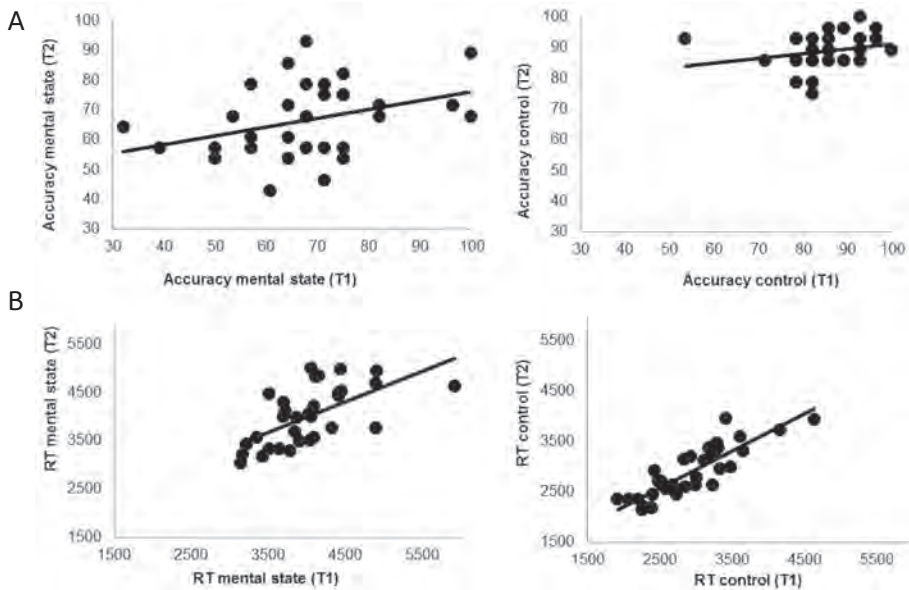


FIGURE 2.2 | (A) The correlation of the percentage correct responses in the mental state condition between T1 and T2, and the correlation of the percentage correct responses in the control condition between T1 and T2. (B) The correlation of the mean reaction time (RT) on the correct trials in the mental state condition between T1 and T2, and the correlation of the mean reaction time (RT) on the correct trials in the control condition between T1 and T2.

FMRI ANALYSES

WHOLE BRAIN CONTRASTS

The whole brain contrast involved a 2 (Condition: mental state vs. control) x 2 (Time: T1 vs. T2) ANOVA using a flexible factorial design. In the analysis, the factors 'subjects' (independence = yes, variance = equal), 'time' (independence = no, variance = equal), and 'condition' (independence = yes, variance = equal) were included to investigate the effect of time. The main effect of Condition revealed more activation in the bilateral superior sulcus (STS), bilateral inferior frontal gyrus (IFG), dorsal medial prefrontal cortex (dmPFC), and bilateral

temporal pole for mental state > control condition (see Figure 2.3, and Table 2.1). There was no main effect of Time and no Condition x Time interaction (note that even when the threshold was lowered to a lenient threshold of $p < .001$, 10 contiguous voxels, uncorrected for multiple comparisons, there were no significant effects). Thus, on a whole-brain level we find merely stability of activation over time within these mentalizing areas.

In order to further investigate patterns of stability versus change we focused on ROI analyses for the regions activated by the mental > control contrast at T1 and correlated those ROIs with activity at T2. Additionally, these ROIs were submitted to analyses testing for age-related changes in neural activity across T1 and T2.



FIGURE 2.3 | Whole brain contrast (flexible factorial design) for the main effect of mental state > control for $N = 32$; constellation of subjects on T1 and T2 (FDR corrected, $< .05$; > 10 contiguous voxels).

A TEST FOR STABILITY

First, we tested for stability by correlating activation between T1 and T2 for the ROIs extracted from the mental state > control contrast (see Table 2.2). A correlation analysis for mental state > control between T1 and T2 resulted in significant correlations in two areas (see Figure 2.4): RSTS ($r = .4$, $p = .025$; not Bonferroni corrected) and RIFG ($r = .36$, $p = .046$; not Bonferroni corrected). In order to determine to what extent the stability in RSTS and RIFG in the contrast mental state > control is driven by the mental state condition or the control condition, post hoc analyses were performed by correlating mental state > fixation and control > fixation at T1 and T2. Correlating mental state > fixation at both time points resulted in significant correlations in both RSTS ($r = .67$, $p = .001$) and RIFG ($r = .5$, $p = .004$). A correlational analysis for the control > fixation contrast between T1 and T2 resulted in a significant correlation in the RIFG ($r = .55$, $p = .001$). Together, these results indicate that activation in the right STS showed stability over time only for the mental state condition. The right IFG showed stability over time for both the mentalizing and control conditions.

The remaining post hoc tests that did not follow from the mental state > control correlation analyses are included in the supplementary material (see supplementary material Figure S2.1).

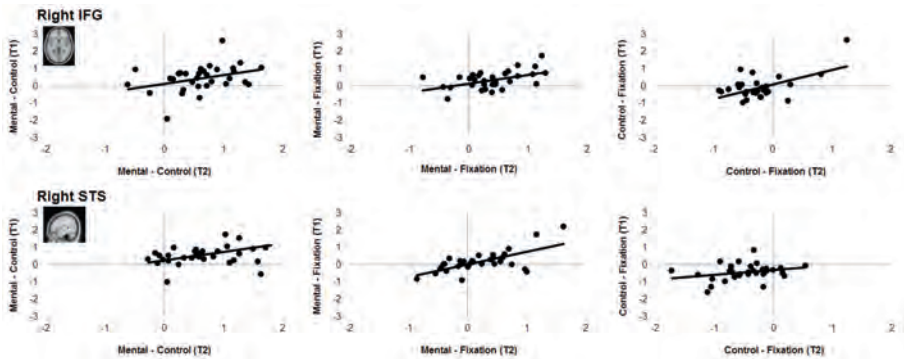


FIGURE 2.4 | Scatterplots of the correlation between T1 and T2 for the neural activation in the right IFG (54, 24, 3) and the right STS (48, -36, 0) for the contrast mental state > control, mental state > fixation and control > fixation.

A TEST FOR CHANGE

Additionally, we tested age-related changes in neural activation over time. That is to say, even though neural activation is stable over time, smaller differences between participants may appear dependent on age.

The mixed models were fitted separately for each ROI. Results for the contrast mental state > control showed significant age-effects in the right IFG and the dmPFC. Activation in the right IFG for the mental state > control contrast showed a linear decrease with age ($p = .02$; not Bonferroni corrected; see Figure 2.5). Activation in the dmPFC showed a curvilinear pattern with age; being lowest around mid-adolescence ($p < .02$; not Bonferroni corrected; see Figure 2.5). No age effects were found for the remaining areas.

Next, we performed post hoc analyses in order to determine to what extent these age effects in RIFG and dmPFC in the contrast mental state > control were driven by the mental state or the control condition. For right IFG, the mental state > fixation activation showed no significant age-related changes. Results for the contrast control > fixation showed a linear increase with age ($p = .04$; not Bonferroni corrected; see Figure 2.5). Activation in the dmPFC for the contrast mental state > fixation showed a linear decrease with age ($p = .05$; not Bonferroni corrected; see Figure 2.5). The control > fixation contrast did not show significant age-related changes.

See figure S2.2 (supplementary material) for the remaining post hoc tests that did not follow from the mental state > control contrast.

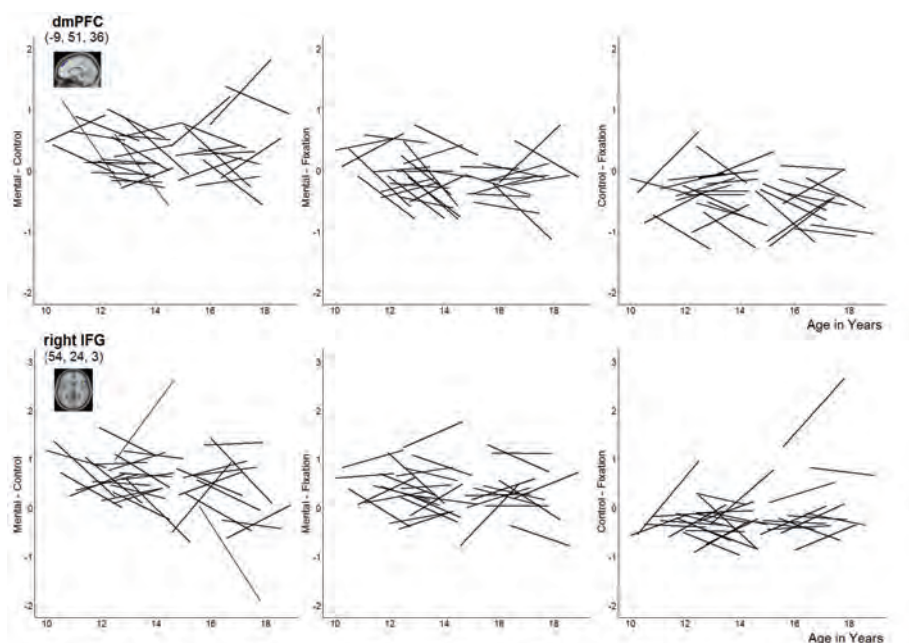


FIGURE 2.5 | Contrast values at T1 and T2 for the mental state > control, mental state > fixation and control > fixation contrasts for dmPFC (−9, 51, 36) and right IFG (54, 24, 3). The connected lines are the activation values at T1 and T2 for each participant separately. The dmPFC shows a significant quadratic dip for mental state > control and an age-related decrease for mental state > fixation. The right IFG shows a significant age-related decrease for mental state > control and age-related increase for control > fixation.

2.4 DISCUSSION

In this study we addressed the question whether reading mental states is a stable or changing characteristic during adolescence across a two-year interval. The analyses resulted in three important findings. First, behavioral results for performance on the RMET demonstrated stability in the mental state condition. This indicates that mentalizing is a relatively stable characteristic within individuals over time. Second, brain-imaging comparisons revealed stability over time in STS and IFG, two regions which have been consistently reported in neuroimaging studies using the RMET (Adams et al., 2009; Castelli et al., 2010; Dal Monte et al., 2014; Gunther Moor et al., 2012).

Third, developmental comparisons revealed age-related decreases in dmPFC and IFG, two regions that have been found to become less active across adolescence when performing social mentalizing tasks (Gunther Moor et al., 2012; Nolte et al., 2013). As such, the findings show that a social mentalizing task can expose subtle developmental changes within relatively stable social perceptual and cognitive processes.

STABLE ACTIVITY IN RSTS AND RIFG

An important question in research on the neural mechanisms of social information processing concerns whether the neural patterns we observe represent trait like characteristics that are stable across time or whether these patterns are sensitive to fluctuating emotional states. The neuroimaging studies to date which have examined longitudinal patterns, have shown that activity in subcortical brain regions associated with processing emotional phases is varying over time (Van den Bulk et al., 2013) and changes during pubertal developmental (Pfeifer et al., 2011). In addition, also in the frontal medial cortex longitudinal comparisons associated with thinking about traits of self and others are associated with change over time (Pfeifer et al., 2013). However, little is known about the test-retest reliability of the social information processing network including the cortical areas STS, IFG, and the temporal poles. The current study found evidence for stability in the right STS and the right IFG over time, suggesting that these regions are a reliable index of individual differences in mentalizing, at least as measured by the RMET.

In case of the right STS, post hoc tests showed that stability was specific for the mental state, but not for the control condition, confirming that right STS is an important region for performing the RMET (Gunther Moor et al., 2012; Nolte et al., 2013). Overall, the STS region, which has previously been identified as a component of the social detection area of the brain, is important for detecting other people's mental states and is therefore a basic component of social information processing (Nelson, Leibenluft, McClure, & Pine, 2005).

For the right IFG, stability was found for both the mentalizing condition and the control condition (mental state > control condition, mental state > fixation condition, and control condition > fixation condition). The IFG spans a large area of the lateral prefrontal cortex and has previously been related to a variety of functions such as language processing, motor control, and social understanding (Carter, Williams, Minshew, & Lehman, 2012; Fusar-Poli

et al., 2009). A recent study that compared normally developing adults with traumatic brain injured (TBI) patients showed that TBI patients performed less well on the RMET and especially the left IFG was found to be crucial for performing the task. In addition, tasks that made an appeal on the semantic working memory system correlated positively with performance on the RMET, which led the authors to conclude that the IFG plays an important role in the semantic memory components of the RMET (Dal Monte et al., 2014).

Even though stability was specifically found in the right STS and the right IFG, it should be noted that post hoc comparisons focusing on the mentalizing condition relative to fixation (instead of mentalizing relative to the control condition, presented in the supplement) revealed also stability of neural activation in left lateralized areas. Prior whole brain comparisons showed that the mental state > control contrast resulted in bilateral activation in both STS and IFG (see also Adams et al., 2009; Castelli et al., 2010; Gunther Moor et al., 2012). Thus, the current findings do not provide conclusive evidence with respect to potential lateralization effects, and the study should be replicated in the future using various samples and larger sample sizes.

AGE-DEPENDENT CHANGES IN RIFG AND DMPFC

Although the ability to judge someone's mental state is present from an early age (Nelson, Leibenluft, McClure, & Pine, 2005), the influence of hormonal changes, structural brain changes, and environmental factors can influence subtle developmental changes related to social cognition (Blakemore & Mills, 2014). Therefore, we tested whether there were regions in the social information-processing network that continued to change during adolescence. Based on previous research on adolescents, our expectation was to find age-related changes in mPFC, right temporal pole, and bilateral IFG (Gunther Moor et al., 2012, see also Blakemore, 2008; Blakemore & Mills, 2014). Longitudinal analyses are particularly useful for addressing this question because the increase in power by testing the same participants over time allowed us to detect also small within-person changes.

The first region showing age-related change was the right IFG. As was described in the previous section, this region showed relative stability over time, but age comparisons revealed also subtle developmental changes. The main contrast of mental state > control resulted in a developmental decrease over time. As such, the IFG showed the same linear age effect as was shown

in the cross-sectional study of Gunther Moor and colleagues (2012). Post hoc tests, however, showed that activity in the control condition *increased* over time, whereas activity in the mental condition did not change. Therefore, it is important to have a better understanding of the processes involved in the control condition. Several aspects of the control condition deserve attention in future studies. First, the mentalizing condition displayed different words for each trial, whereas the control condition used the same words. Even though the words were presented at different locations on each trial to avoid pre-decisions, the reading demands were much lower than in the mental state condition. Second, behavior is less stable for the control condition over time. Third, adults may have more experience with making age or gender judgments than children. Therefore, different groups may use different strategies when making age or gender judgments. Future studies disentangling the processes involved in the control condition may further reveal these possible strategy changes.

The second region that showed an age-related change was the mPFC. In accordance with previous studies that demonstrated a developmental decrease in mPFC involvement with increasing age (Blakemore, den Ouden, Choudhury, & Frith, 2007; Burnett & Blakemore, 2009a; Gunther-Moor, 2012), this study confirmed a developmental change in mPFC recruitment. However, the pattern of change was observed in two directions. The mental state > control contrast showed a quadratic pattern with a dip in mid adolescence, but the post hoc comparisons revealed an age-related decrease for the mental condition and a non-significant pattern for the control condition. The finding of an age-related decrease in mPFC has interesting parallels with structural changes in this area of the brain from childhood to adulthood (age 8–23; e.g. Mills, Lalonde, Clasen, Giedd, & Blakemore, 2014). The structural changes, indicated by a cubic decreasing trajectory for grey matter development and surface area, and a linear decrease of cortical thickness, could be an indicator for the functional decrease. Although, no study up till now has investigated the link between functional and structural brain imaging concerning the social brain in relation to age, larger scale longitudinal studies are necessary to test these relations. Moreover, functional studies concerning mentalizing abilities have consistently found age-related decreases in mPFC activation (Blakemore, 2008), although it is currently unclear which process accounts for this decrease in activity. Perhaps, young adolescents make more use of complex, higher-order processes for mentalizing whereas older adolescents

use more automatic social perceptual processes (Blakemore, 2008). Overall this could indicate a strategy shift from childhood to adulthood (Blakemore, den Ouden, Choudhury, & Frith, 2007). Note that some of the stimuli in the RMET task include direct gaze, which has previously been related to increased mPFC activation (Kuzmanovic et al., 2009). Although this was not the main manipulation in the current experiment, future studies should focus on the role of mPFC in direct and diverted gaze.

A limitation of this study is that the sample size was relatively small to detect more complex developmental patterns, and future studies are necessary with three or four longitudinal measurements to fit growth models. Despite this limitation, this study adds to a growing number of studies showing that longitudinal change in neural regions involved in social cognition can be detected by comparing the same individuals over two time points (Pfeifer et al., 2011; Pfeifer et al., 2013; Van den Bulk et al., 2013) and provides important information about stability and change which cannot be detected in cross-sectional comparisons.

CONCLUSION

Taken together, several studies have been performed in order to map the neural development of mentalizing abilities from childhood to adulthood and resulted in inconsistent findings. The current study used a longitudinal design and revealed stability over time in the extended social detection network (RSTS and RIFG). In addition, the current study proved that longitudinal measures are able to detect small subtle changes in activation patterns in brain regions that are involved in mentalizing, including the dmPFC and the right IFG. Although interpreting the exact processes of mentalizing that are developing during adolescence is challenging, it is likely that more complex social cognitive processes are still ongoing during adolescence.

ACKNOWLEDGMENTS

We would like to acknowledge the Autism Research Centre for the use of the 'Reading the Mind in the Eyes task'. We are grateful to Wouter van der Horst and Marthe de Jong for assistance in recruiting participants and for assistance in scanning.

2.5 SUPPLEMENTARY MATERIAL

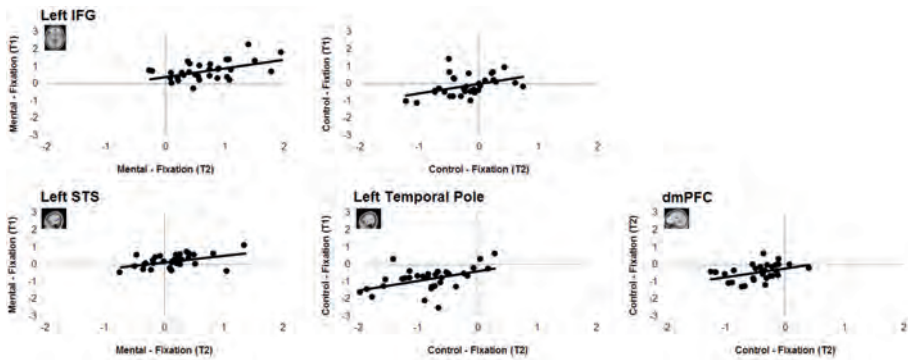


FIGURE S2.1 | We performed additional correlation analyses in order to test for stability between T1 and T2 for the remaining five ROIs (LSTS, LIFG, L temporal pole, R temporal pole, and dmPFC) performed separately for the contrasts mental state > fixation and control > fixation. Correlating mental state > fixation at both time points resulted in significant correlations in two of the five areas: LSTS ($r = .45$, $p = .009$) and LIFG ($r = .5$, $p = .003$). A correlational analysis for the control > fixation contrast between T1 and T2 resulted in a significant correlation in LIFG ($r = .42$, $p = .017$).

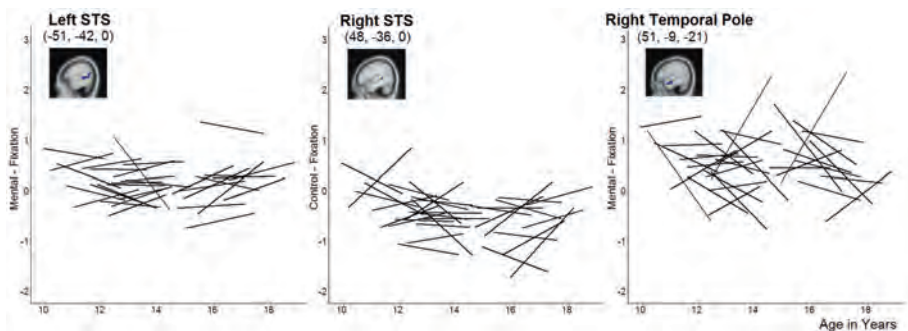
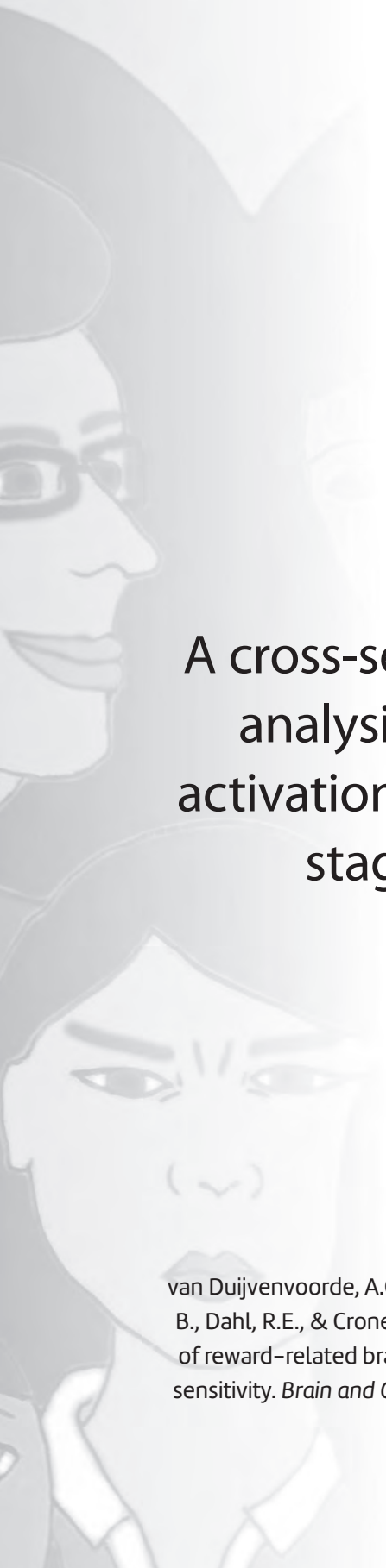


FIGURE S2.2 | Additional analyses for the contrast mental state > fixation for the remaining five areas (bilateral STS, LIFG, and bilateral temporal pole), resulted in significant age-effects in the left STS and the right temporal pole. No age effects were found for the remaining three areas. First, activation in the left STS showed a curvilinear pattern with age ($p = .02$), being lowest around mid-adolescence. Also after removing an outlier that showed the largest developmental decrease, this quadratic effect in left STS remained significant ($p = .02$). Second, contrary to our expectation concerning age-related changes in the right temporal pole for the contrast mental state > control, we did not replicate the findings of Gunther Moor and colleagues (2012) who reported higher right temporal pole activation in 10–12 years old compared to older adolescents and adults. However, a post hoc analysis of only the mentalizing condition demonstrated a linear decrease across age ($p = .01$), the quadratic effect of age was not significant. Additional analyses for the contrast control > fixation for the same remaining five areas (bilateral STS, LIFG, and bilateral temporal pole) resulted in a significant age-effect in the right STS. No age effects were found for the remaining four areas. Activation in the right STS for the control > fixation contrast showed a linear decrease with age ($p = .01$), the quadratic effect of age was significant at trend-level and showed a dip in mid-adolescence ($p = .05$).





Chapter 3:

A cross-sectional and longitudinal analysis of reward-related brain activation: effects of age, pubertal stage, and reward sensitivity

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ABSTRACT

Neurobiological models suggest that adolescents are driven by an overactive ventral striatum (VS) response to rewards that may lead to an adolescent increase in risk-taking behavior. However, empirical studies showed mixed findings of adolescents' brain response to rewards. In this study, we aimed to elucidate the relationship between reward-related brain activation and risky decision-making. In addition, we examined effects of age, puberty, and individuals' reward sensitivity. We collected two datasets: Experiment 1 reports cross-sectional brain data from 75 participants (ages 10–25) who played a risky decision task. Experiment 2 presents a longitudinal extension in which a subset of these adolescents ($n = 33$) was measured again two years later. Results showed that 1) a reward-related network including VS and medial PFC was consistently activated over time, 2) the propensity to choose the risky option was related to increased reward-related activation in VS and medial PFC, and 3) longitudinal comparisons indicated that self-reported reward sensitivity was specifically related to VS activation over time. Together, these results advance our insights in the brain circuitry underlying reward processing across adolescence.

3.1 INTRODUCTION

Adolescence is characterized as a period of hormonal changes and pronounced changes in social–affective engagement such as increases in sensation seeking and risk taking. Neurobiological models of adolescent development have suggested that adolescents are more sensitive to rewards due to a relatively increased limbic response in combination with reduced down–regulation by the prefrontal cortex and other cortical areas (Ernst & Fudge, 2009; Nelson, Leibenluft, McClure, & Pine, 2005; Somerville, Jones, & Casey, 2010). Accordingly, these models suggest that such neurobiological changes may underlie typical adolescents’ risky behaviors such as substance abuse, unsafe sexual behavior, and reckless driving (Dahl, 2004; Steinberg, 2008).

A typically found ‘reward–network’ in the brain includes dopamine–rich areas in the midbrain and their targets: striatum and medial prefrontal cortex (Blakemore & Robbins, 2012; Clark, Lawrence, Astley–Jones, & Gray, 2009; Tom, Fox, Trepel, & Poldrack, 2007). More specifically, ventral striatum (VS) has been implicated in anticipating and processing different types of rewards, as well as in producing learning signals known as prediction errors (Cohen et al., 2010; Delgado, 2007; Galván et al., 2005; Knutson, Fong, Adams, Varner, & Hommer, 2001). Similarly, medial PFC – specifically the part that overlaps with the anterior cingulate cortex (ACC) – is also related to prediction–error coding (Van den Bos, Cohen, Kahnt, & Crone, 2012), but also to action–related reward associations (Kennerley & Walton, 2011; Rushworth, Noonan, Boorman, Walton, & Behrens, 2011), and detecting the need for increased control (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). In contrast, a more ventral region of the medial prefrontal cortex, adjacent to medial orbital frontal cortex, has been implicated in coding rewards and is linked to representations of ‘value’ (Kuhnen & Knutson, 2005; McKell Carter, Meyer, & Huettel, 2010). Moreover, research indicates strong interconnections between the VS and several parts of the medial PFC. These so–called striatal–cortical loops may be important for regulating reward–related responses and subsequent goal–directed behavior (Haber & Knutson, 2010). Together, these findings suggest that goal–directed behavior (e.g., risk taking) is driven by a reward–valuation system, in which VS encodes the more ‘basic’ aspects of reward and medial PFC integrates the different aspects of the reward to represent its subjective value and is important for selecting actions and controlling behavior.

Results of previous developmental functional MRI studies suggest that adolescent decision-making may be biased by a relatively hypersensitive VS response to rewards. That is, research has indicated that adolescents (ages 13–17 years) show a larger VS response to rewards compared to children and adults (Galván et al., 2006; Padmanabhan, Geier, Ordaz, Teslovich, & Luna, 2011; Van Leijenhorst et al., 2010a; Van Leijenhorst et al., 2010b). However, other studies have indicated striatal hypo-activation in adolescents during reward anticipation (Bjork et al., 2004; Bjork, Smith, Chen, & Hommer, 2010) or have shown little differences between adolescents and adults in VS response to rewards (May et al., 2004; Paulsen, McKell Carter, Platt, Huettel, & Brannon, 2012). Moreover, only some studies have found that the VS response to rewards correlates with risk-taking behavior in every-day life (Galván, Hare, Voss, Glover, & Casey, 2007). Thus, several questions remain with respect to the specificity of the VS and medial PFC responses to rewards in adolescence and their relationship to risky behavior. For instance, it remains to be determined whether higher risk-taking in adolescence is associated with a higher VS response to rewards, a lower medial PFC response, or less functional connectivity between these areas (see also Cohen et al., 2012; Van den Bos, Cohen, Kahnt, & Crone, 2012).

Mixed findings in adolescents' reward-related brain activation might have several causes, such as differences in task design and analyses (Galván, 2010). In addition, prior contradictory findings may point toward individual differences in adolescence (Somerville, Jones, & Casey, 2010). One important source of influences on subcortical and cortical responses could be pubertal development, which may serve as an important individual difference measure in adolescents' brain activation in response to rewards and appetitive cues. That is, gonadal hormone levels significantly increase during adolescence and have both organizational and activating effects on brain functioning (Blakemore, Burnett, & Dahl, 2010; Sisk & Zehr, 2005). For instance, higher testosterone levels have been associated with increased VS activation (Forbes et al., 2010; Op de Macks, Gunther Moor, Overgaauw, Güroğlu, & Crone, 2011) and to adolescent typical risk-behavior such as experimentation with alcohol (De Water, Braams, Crone, & Peper, 2013).

Another possible source to explain individual differences in reward-related brain activation could be a persons' sensitivity to rewards. For instance, prior studies reported that activation in the VS correlated positively with self-reported 1) reward sensitivity, as measured by the behavioral approach system

(BAS) scale (Beaver et al., 2006), 2) sensation seeking, as measured by the brief sensation-seeking scale (Bjork, Knutson, & Hommer, 2008), 3) impulsivity, as measured by the psychopathic personality inventory (Buckholtz et al., 2010), and 4) real-life risk taking (Galván et al., 2007). Possibly, these personality differences in reward-related response tendencies may explain why some adolescents are more responsive to rewards than others.

In the current study we examined reward processing in adolescence in more detail. Specifically, we aimed to elucidate the relationship between reward-related brain activation, frontostriatal connectivity strength, and behavior. In addition, we focused on examining effects of age, pubertal development, and individual's self-reported reward sensitivity on reward-related brain activation. To these ends, we report two experiments using a risky decision task, in which participants could choose to take a gamble (and win or lose 10 Eurocents) or pass on this gamble (in which case nothing was gained or lost). We were specifically interested in the brain's response to rewards and losses as a result of an active gamble, since prior studies have shown that outcome monitoring is more salient when the outcomes are the result of an active choice (Rao, Kordzykowski, Pluta, Hoang, & Detre, 2008; Tricomi, Delgado, & Fiez, 2004).

In the first experiment, we reanalyzed the adolescent sample (10–16 years old) previously reported by Op de Macks et al. (2011) and added a young-adult sample (18–25 years old). The study by Op de Macks et al. (2011) primarily examined individual differences in the reward-related brain activation in relation to testosterone levels, but made no age comparisons. In the current study, we studied age, puberty, and individual difference in reward sensitivity in the same sample. The second experiment included a longitudinal extension of Experiment 1. That is, a subset of the adolescents from Experiment 1 was re-invited two years later, and completed the same risky decision task. This combined cross-sectional/longitudinal approach presents unique insights in the development of the reward system across adolescence and allows us to link changes in reward-related activation to individual's changes in behavior, age, pubertal development, and reward sensitivity.

Replicating prior studies, we expected to observe activation in VS and medial PFC when processing rewards. Second, we predicted that risk-taking propensity would be positively correlated with VS activation, negatively correlated with medial PFC activation and/or the strength of connectivity in this reward network. Third, based on prior findings we expected VS activation to

change with age (quadratic or linear). Finally, we tested whether the VS response to rewards was related to pubertal development, or to self-reported reward-sensitivity (as measured with the self-report BAS scale).

3.2 METHODS EXPERIMENT 1

PARTICIPANTS

Seventy-eight right-handed participants (50 adolescents, 28 adults) were scanned while performing a risky decision task. All participants reported an absence of neurological or psychiatric impairments (on a brief screening module) and provided written informed consent for the study (parental consent and participant assent for minors). The cross-sectional adolescent data has been reported before in Op de Macks et al. (2011), but that study focused primarily on the association between individual differences in reward-related brain activation and testosterone levels in adolescents and did not examine age effects across adolescence. The goal of this study was to extend this (cross-sectional) data set by including a sample of young adults. All procedures were approved by the local Medical Ethics Committee.

Three participants (12, 15, and 16 years old) showed head motion exceeding 3 mm during scanning and were therefore removed from further analyses. Accordingly, the final sample consisted of 75 participants (10–25 years old, Mean age = 15.9 years old, $SD = 4.1$, 47 females). Mean head motion correlated with Age, $r = -.27$, $p = .02$, but was overall low, Mean = 0.85 mm, $SD = .04$. Pubertal development was measured for all adolescents (10–16 years old, $n = 47$, 32 females), using the Pubertal Development Scale (PDS; Petersen, Crockett, Richards & Boxer, 1988)¹. No PDS scores were obtained for the young adults, since we presume all of the adult subjects have completed puberty. PDS score was positively correlated with age in the adolescent group, $r = .62$, $p < .001$.

Participants completed two subscales (similarities and block design) of the Wechsler Intelligence Scale for Children or the Wechsler Intelligence Scale for Adults in order to obtain an estimate of their intelligence quotient (Wechsler, 1991; Wechsler, 1997). Estimated IQ scores correlated negatively with Age, $r = -.4$, $p < .01$. Therefore IQ was included as a covariate of no-interest in further analyses.

¹The reason for choosing PDS as a puberty index instead of testosterone levels was because PDS measures were available for adolescents in both experiments (cross-sectional and longitudinal).

TASK

Participants performed the Jackpot Task, a risky decision task that has been used to assess developmental changes in reward processing and risk-taking behavior (Op de Macks et al., 2011; see Figure 3.1). In the Jackpot task, participants were presented with a slot machine with two of the three slots showing the same fruit. Participants were requested on each trial to choose between the risky option 'spin' (i.e., 'play' trial), or the safe option 'reset' (i.e., 'pass' trial). A 'play' decision was indexed by a button press with the right index finger; a 'pass' decision was indicated by a button press with the left index finger. The choice to play led to a monetary reward or loss (10/−10 Eurocents), whereas the choice to pass a trial led to no monetary reward or loss (0 Eurocents). The chance to win was indicated by pictures of the possible fruits for the third slot, which were visible to the participants. The chance to win varied between trials (66% versus 33%), although eventually rewards and losses occurred in 50% of the cases for both trials. Participants played 50 trials in total (30 high risk trials and 20 low risk trials) and for current analysis purposes all trials were averaged. In the prior study by Op de Macks et al. (2011) it was found that the reward-related brain activation did not differ between high and low-risk rewards. Therefore, averaging across these trials increased the power of the dependent measure. On average, there were 17 loss trials and 17 reward trials. Participants were given initial play money (2 Euros), and were instructed that they would be paid (in real money) according to the final outcome at the end of the experiment.

We focused specifically on the outcome phase after play choices, since the design was not optimal to study the feedback and the decision phase separately. That is, 'pass' trials were followed by 'reset' and 'play' trials were followed by valence feedback. Given the short time window between choice and feedback, the choice trials were confounded by feedback type. For this reason, our analysis focused on the 'play' trials, which were unpredictably followed by reward or loss.

Each trial started with a centrally presented fixation cross, followed by the stimulus presentation (3000 ms). During this time participants had to select a choice ('play' or 'reset') by a button press. Subsequently, feedback was given (reward, loss or reset) for 2000 ms. If no timely response was given, the text 'too slow!' was presented for 2000ms, followed by the next trial. This happened rarely, in less than .02 % of the trials. Between trials a fixation cross was presented for 1–6 seconds, jittered in steps of 500 and 1000 ms.

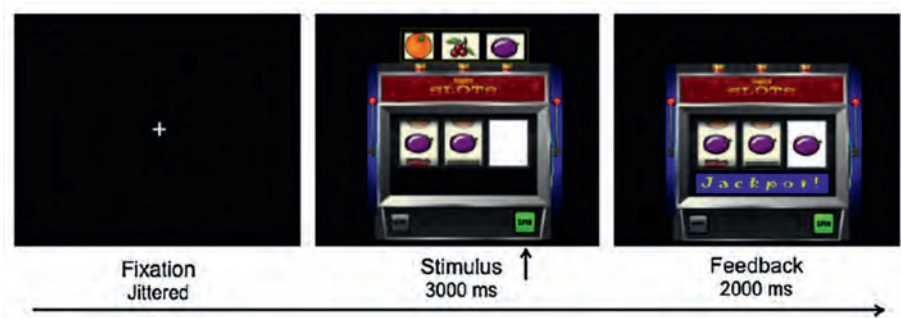


FIGURE 3.1 | The Jackpot task (Op de Macks, 2011). Example of a trial in which the participant is presented with a 1/3 chance of a reward (+10) and a 2/3 chance of a loss (-10). The participant decides to play by pressing the right button and which results in a reward (feedback screen). Reprinted from “Testosterone levels correspond with increased ventral striatum activation in response to monetary rewards in adolescents” by Z.A. Op de Macks, B. Gunther Moor, S. Overgaauw, B. Güroğlu, R.E. Dahl, & E.A Crone, 2011. Reprinted with permission.

PROCEDURE

Before entering the scanner, participants received instructions and briefly practiced the task. All scanning procedures were explained using a mock scanner. The Jackpot task was acquired in a single run that lasted approximately 5 minutes. The task was one of a battery of four tasks and was presented first in the battery (for results of the other tasks, see Gunther Moor et al., 2012) lasting a total of approximately 50 minutes. Self-report measures were administered immediately after the scan in a separate room; for the adults, the BIS/BAS questionnaire was administered at home.

REWARD SENSITIVITY

Reward sensitivity was measured using the behavioral inhibition system/behavioral approach system scale (BIS/BAS; Carver & White, 1994). A recent study examined the psychometric characteristics of the Dutch version of Carver and White’s (1994) BIS/BAS scales in two large independent samples of early and mid-adolescents; their findings confirmed that “the scales are suitable for use in research settings” (p. 500; Yu, Branje, Keijsers, & Meeus, 2011). The BIS/BAS scales consist of 24 items across four scales: one BIS scale that measures punishment sensitivity and three BAS scales that measure reward sensitivity. Note that in the current study we were specifically interested in the BAS scales. The BAS Drive scale measures the persistent pursuit of desired goals, the BAS Fun Seeking scale measures both desire for new rewards and willingness

to approach potentially rewarding events on the spur of the moment, and the BAS Reward Responsiveness scale measures the positive response to (the anticipation of) reward. Higher scores indicate greater reward sensitivity. Seventeen young adults (7 females) did not fill out the BIS/BAS scale, leaving a total of $n = 58$ who filled out the BIS/BAS scale.

MRI DATA ACQUISITION

fMRI data were acquired with a standard whole-head coil using a 3-Tesla Philips Achieva scanner. T2*-weighted echoplanar images (EPI's) were obtained during one functional run, in which the first two volumes were discarded to allow for equilibration of T1 saturation effects. Volumes covered the whole brain (38 slices; 2.75mm slice thickness; interleaved acquisition) and were acquired every 2200 ms (TE = 30 ms). A high resolution T1 image was collected at the end of each scan session, together with a high-resolution T2-weighted anatomical scan with the same slice prescription as the EPIs. Visual stimuli were projected onto a screen that was visible for participants via a mirror attached to the head coil. Head motion was restricted due to foam inserts that surrounded the head.

FMRI PREPROCESSING AND STATISTICAL ANALYSIS

Data preprocessing and analysis were conducted using SPM8 (Wellcome Department of Cognitive Neurology, London). Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction. The T1 structural image was coregistered to the functional images and segmented according to gray matter, white matter, and cerebrospinal fluid. Functional images were then spatially normalized using the normalization parameters obtained from the segmentation procedure. For seven adolescents no T1 was obtained, due to time constraints or technical problems, in which case functional volumes were spatially normalized to EPI templates. The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions. During normalization the data was re-sampled to 3-mm cubic voxels. Templates were based on the MNI305 stereotaxic space (Cocosco, Kollokian, Kwan, & Evans, 1997). Functional volumes were smoothed with a 6-mm full-width at half maximum isotropic Gaussian kernel.

Statistical analyses were performed on individual subjects' data using the General Linear Model (GLM) in SPM8. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic

response function. In a whole-brain analysis, reward and loss outcomes were modeled as single events with zero duration at the onset of the presentation of the outcome. This whole-brain analysis focused on the contrast [reward > loss]. Reset trials and trials on which the participant did not respond within the 3-s time frame were modeled separately, but were not included in contrasts.

Task-related responses were considered significant if they consisted of at least 10 contiguous voxels that exceeded a family-wise error (FWE) or a false discovery (FDR) corrected threshold of $p < .05$ (see Results). For region of interest (ROI) analyses the MarsBaR toolbox in SPM8 was used (Brett, Anton, Valabregue, & Poline, 2002).

PSYCHO-PHYSIOLOGICAL INTERACTION

To study the interplay between VS and other brain regions during processing of rewards compared to losses, functional connectivity was assessed using psychophysiological interaction (PPI) analysis (Friston et al., 1997). In PPI, functional connectivity is defined as significantly correlated hemodynamic response patterns over time between brain regions as a function of the experimental task context, here reward versus loss processing. Note that this method does not imply directionality of connectivity between regions.

The seed region in the PPI analysis was the right and left VS mask based on the reward > loss whole-brain contrast. Since VS was bilaterally activated, two separate PPIs were conducted with the right and left VS mask. By means of a peak-detection algorithm, we detected a peak voxel of activation per participant within the (left and right) VS mask. Around this peak voxel a sphere of 7 mm was drawn to create a seed ROI. After the extraction of the time course from the VS mask and the psychological vector of interest (weighting rewards with 1 and losses with -1), their interaction term was computed. This interaction regressor indicated which brain regions are functionally correlated with the respective seed VS mask. In other words, the resulting estimates from this interaction regressor express the extent to which activity in each voxel correlates with the seed region more when processing a reward than when processing a loss.

3.3 RESULTS AND DISCUSSION EXPERIMENT 1

BEHAVIOR

The average proportion of 'play' decisions was .67 (range = .28 – 1, $SD = .14$). A linear regression with proportion of plays as a dependent and Age as an independent variable showed no significant effect of Age (p 's > .1). Similar analyses with PDS score, and the BAS scales (Drive, Fun-seeking, and Reward-responsiveness) as an independent variable, also showed no significant effects of PDS or BAS scores on proportion of plays (p 's > .1). Together these results reveal that the tendency to make a risky decision was not related to age, pubertal development or individual's reported reward sensitivity. Note that this resulted in an approximately equal number of trials in the neuroimaging analyses across ages.

WHOLE-BRAIN ANALYSES

Results for the contrast [reward > loss; FWE corrected, $p < .05$, > 10 contiguous voxels] across all participants revealed bilateral VS activation and a cluster of activation in the medial PFC (see Figure 3.2). Reward-related activation was also found in the posterior cingulate cortex (PCC), and other frontal and parietal brain regions (see Table 3.1 for regions of activation and their coordinates). No significant results were found for the opposite contrast [loss > reward].

The first question we aimed to address was the relation between reward-related brain activation and proportion to play (i.e., gamble) in the Jackpot task. To detect brain regions in which reward-related activation correlated with behavior, proportion of plays was added as a regressor of interest in a whole-brain analysis [reward > loss], and IQ was included as a covariate. At an FWE corrected threshold, $p < .05$, > 10 contiguous voxels, no regions were detected. At an FDR corrected threshold of $p < .05$, > 10 contiguous voxels, proportion of plays showed a positive association with reward-related activation in VS, medial PFC, PCC, thalamus, and other frontal brain regions (see Figure 3.2 and Table 3.1 for regions of activation and their coordinates). No significant results were found for a negative association with proportion of plays. Thus, VS and medial PFC were more active following rewards, for those individuals who more often played.

The next question we aimed to address was the relation between reward-related brain activation and individual differences in BAS scores (BAS

drive, BAS Fun-seeking, and BAS reward-responsiveness). BAS subscales were added as regressors of interest in a whole-brain analysis [reward > loss, $n = 58$], and IQ was included as a covariate. At an FWE corrected threshold ($p < .05$, > 10 contiguous voxels), no regions were detected. At an FDR-corrected threshold of $p < .05$, 10 contiguous voxels, only the BAS Fun-seeking score showed a positive association with reward-related activation in VS, medial PFC, thalamus, and other frontal and parietal brain regions (see Figure 3.2 and Table 3.1 for regions of activation and their coordinates). No significant results were found for a negative association with BAS scores. Thus, VS and medial PFC were more active following rewards, for individuals who in every-day life are more willing to approach a potentially rewarding event on the spur of the moment, as measured by items such as “I’m always willing to try something new if I think it will be fun”, and “I crave excitement and new sensations” (Carver & White, 1994).

Finally, we addressed the relation between reward-related brain activation and age, based on prior studies that reported a peak in adolescence in response to rewards (Ernst et al., 2005; Galván et al., 2007; Van Leijenhorst et al., 2010a; Van Leijenhorst et al., 2010b). To detect brain regions in which reward-related activation correlated with linear and quadratic changes in age, Age and Age² were included as regressors of interest in a whole-brain analyses, with IQ included as a covariate. No results survived FWE or FDR correction. Lowering the threshold to an uncorrected $p < .001$ level, indicated a cluster of linearly increasing activity in left putamen ($x = -24$, $y = 6$, $z = 9$, 33 voxels), but no regions were found when testing for a linear decrease or a quadratic pattern. A similar whole-brain analyses to test the relation between reward-related brain activation and puberty ($n = 47$) also showed no significant cluster of activation, not even at an uncorrected threshold of $p < .001$.

Thus, in the current study, we found no evidence for a peak in the brain’s response to rewards in mid-adolescence, and weak evidence for a monotonic age-related increase in reward-related activation. Instead, these results indicate that reward-related brain activation was predominantly related to propensity to play and self-reported individual differences in fun seeking across adolescence².

² When including BAS-subscales (Drive, Fun seeking, and Reward responsiveness), proportion of plays, Age, and IQ as a covariate of no interest in one whole-brain analyses the reported effects generally remained. Only proportion of plays showed a weaker effect, in which an association with reward-related activity was observed specifically in medial PFC and at an uncorrected threshold of $p < .001$, >10 contiguous voxels

FUNCTIONAL CONNECTIVITY

A final question was whether *connectivity* in a VS–medial PFC network was related to proportion of plays and other individual difference measures. For this purpose, two whole-brain PPI analyses with left VS and right VS masks from the whole-brain analysis (see Figure 3.2, upper panel) as seed regions showed that processing rewards compared to losses enhanced functional connectivity between VS and medial PFC (including ACC and dorsal medial PFC regions; FDR corrected, $p < .05$, >10 contiguous voxels). Analyses for left VS and right VS pointed to partly overlapping regions, including medial PFC, visual cortex, and other frontal–parietal brain regions. However, functional connectivity with left VS showed an additional cluster in right anterior insula (see Figure 3.3A and supplementary Table S3.1 and S3.2 for functionally connected regions and their coordinates).

We extracted the strength of functional connectivity between medial PFC and left VS, medial PFC and right VS, and right anterior insula and left VS for each participant. We tested whether the strength of these functional connections was correlated with individual's proportion of plays, age, pubertal development, and BAS-scores. Results indicated no significant results for functional connectivity strength between medial PFC and (left and right) VS. However, functional connectivity between right anterior insula and left VS was related to proportion of plays in the task, in which larger connectivity was related to a lower number of plays, $r = -.30$, $p < .02$ (see Figure 3.3B).

SUMMARY EXPERIMENT 1

Taken together, whole-brain analyses revealed that rewards compared to losses activated a reward-related brain network, including VS and medial PFC. Whole-brain results indicated that reward-related activation in these regions was positively associated with proportion of plays and self-reported reward sensitivity (as measured by BAS Fun Seeking-score). PPI analyses indicated increased functional connectivity after reward compared to losses between bilateral VS and (dorsal) medial PFC. Functional connectivity between left VS and right anterior insula also increased after rewards compared to losses, and this connectivity was associated with attenuated risky decision-making.

These cross-sectional results led to specific points of focus for the longitudinal analyses in Experiment 2. That is, in Experiment 2 we examined whether reward-related activation of VS and medial PFC [as defined by reward > loss activation] was related to changes in behavior, age and/or pubertal stage, and self-reported reward sensitivity over time.

TABLE 3.1 | Coordinates for the brain regions showing activation for the Reward > Loss contrast and brain regions showing a positive correlation in the reward > loss contrast with proportion of plays and self-reported BAS Fun-seeking, peak voxels are reported at cluster level. PFC = prefrontal cortex, VS = ventral striatum, ACC = Anterior Cingulate Cortex, BA = Brodmann Area.

Anatomical Area	MNI coordinates (mm)				
	Cluster Size	x	y	z	Z-max value
<i>Reward > Loss, FWE corrected $p < .05$, > 10 contiguous voxels</i>					
L VS	100	-15	15	-6	6.87
R VS	32	12	9	-9	6.23
R ACC (BA24)	38	6	0	33	5.46
L Posterior Cingulate Cortex	213	-6	-36	36	6.23
L Lateral PFC	88	-42	45	12	6.36
L Superior Frontal Gyrus	106	-21	33	45	6.76
L Superior Frontal Gyrus	99	-12	66	15	6.22
R Middle Frontal Gyrus	16	39	9	54	5.34
R Precentral Gyrus	58	21	-27	60	5.93
R Precentral Gyrus	12	42	-15	60	5.57
L Precentral Gyrus	23	-21	-30	60	5.71
R Putamen	11	30	-12	-12	6.10
L Thalamus	25	-6	-18	9	5.25
L Angular Gyrus	75	-39	-69	39	5.55
R Inferior Parietal Lobe	32	42	-42	57	5.31
R Superior Parietal Lobe	15	18	-54	66	5.00
L Middle Temporal Gyrus	10	-57	-45	6	5.09
L Occipital Lobe/Lingual Gyrus	1830	-12	-78	-15	7.82
<i>Proportion of plays, FDR corrected, $p < .05$, > 10 contiguous voxels</i>					
R ACC/ (Para)cingulate Gyrus	887	3	45	18	4.43
R (Para)cingulate Gyrus	72	9	18	45	3.47
L ACC (BA24)	20	-3	12	24	2.98
R Lateral PFC	131	45	15	48	3.84
L Middle Frontal Gyrus	24	-27	9	54	3.38
R Middle Frontal Gyrus	11	30	12	57	3.11
R Superior Frontal Gyrus	20	18	42	39	3.35
L Inferior Frontal Gyrus	59	-39	24	-9	3.61

TABLE 3.1 | Continued

Anatomical Area	MNI coordinates(mm)				
	Cluster Size	x	y	z	Z-max value
R Inferior Frontal Gyrus (BA9)	41	51	9	24	3.79
R Inferior Frontal Gyrus (BA47)	12	45	21	-6	2.85
L Precentral Gyrus	67	-45	-3	45	4.38
L Postcentral Gyrus	56	-51	-21	48	3.38
R Supplementary Motor Area	39	3	6	60	3.51
R Thalamus (including striatum)	339	9	-21	12	4.36
R Middle Temporal Gyrus	25	45	-54	6	3.15
L Posterior Cingulate Cortex	23	-3	-45	6	3.13
L Intracalcarine Cortex	191	-24	-66	9	4.28
L Precuneus / Occipital Lobe)	3047	-15	-54	39	5.26
<i>BAS Fun-seeking scale, FDR corrected, $p < .05$, > 10 contiguous voxels</i>					
L ACC	135	-9	33	9	4.65
R ACC (BA24)	17	9	21	27	3.05
L Paracingulate Gyrus	16	-6	24	45	3.37
L VS (putamen)	235	-18	12	-9	4.08
R VS (putamen)	18	27	-3	-3	3.23
L Brainstem	103	-9	-21	-12	4.18
R Superior Frontal Gyrus	58	15	33	48	3.97
R Middle Frontal Gyrus	22	33	21	42	3.53
L Middle Frontal Gyrus	87	-33	27	45	3.46
R Inferior Frontal Gyrus	24	42	33	0	3.41
R Cingulate Gyrus	87	15	6	45	4.01
L Precentral Gyrus	14	-45	0	33	3.42
R Insula	38	27	24	9	3.82
R Insula	11	36	6	0	3.06
R Parietal Lobe (Precuneus)	77	15	-48	39	3.63
R Parietal Lobe (Angular Gyrus)	15	36	-51	39	3.32
L Parietal Lobe (Angular Gyrus)	13	-33	-60	39	2.98
R Superior Parietal Lobe	11	15	-51	69	3.22
L Intracalcarine Cortex	19	-3	-69	15	3.18
L Occipital Lobe / PCC	2261	-15	-45	-3	4.88
L Occipital Lobe (Cuneus)	34	-21	-72	18	3.45
L Lateral occipital cortex	14	-12	-84	36	3.26
L Lateral occipital cortex	11	-45	-63	21	2.89

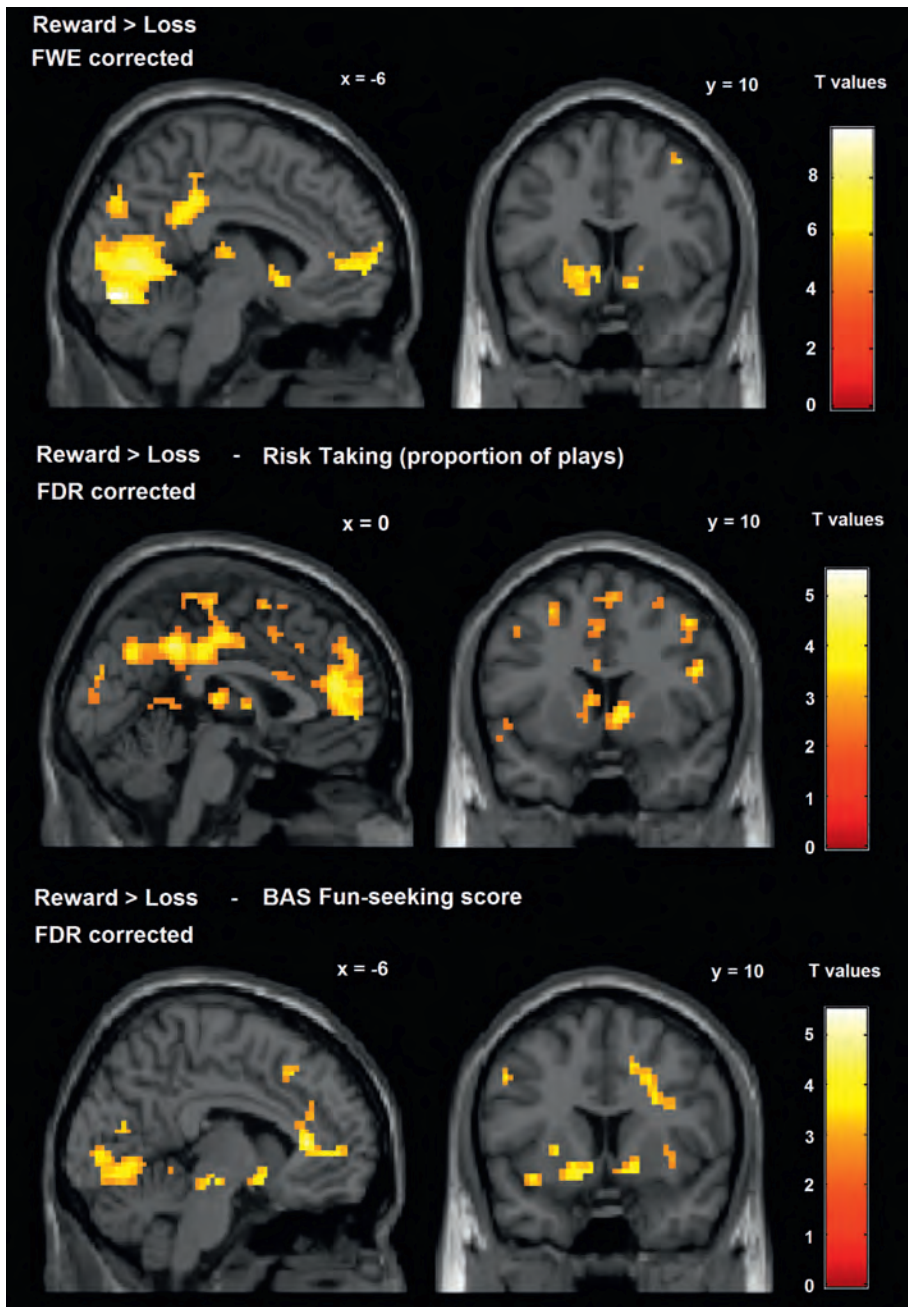


FIGURE 3.2 | Whole-brain results for the contrast [reward > loss] for all participants, at an FWE corrected threshold of $< .05$, > 10 contiguous voxels (upper panel). Whole brain results for the contrast [reward > loss], displaying regions that showed increased activation with increased number of plays (middle panel) and displaying regions that showed increased activation with increasing BAS Fun-seeking score (lower panel). Both results are reported at an FDR corrected threshold of $< .05$, > 10 contiguous voxels.

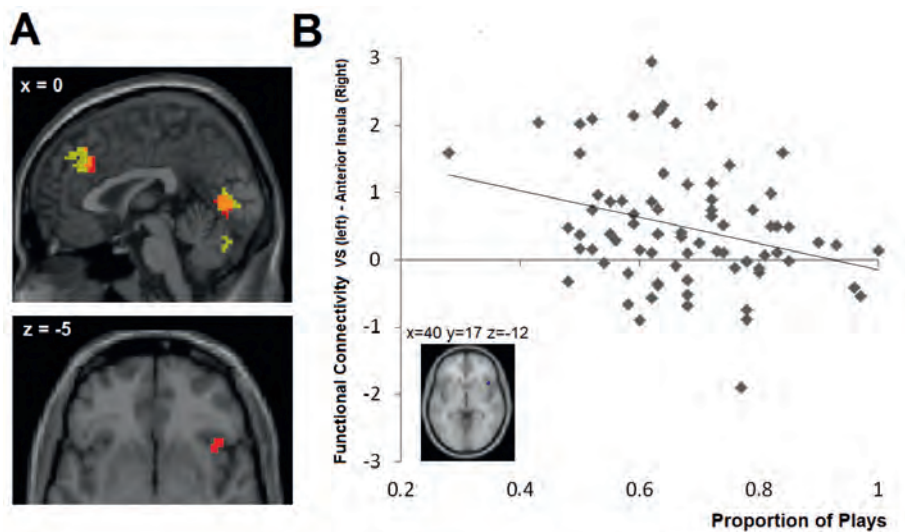


FIGURE 3.3 | (A) Whole-brain results for the psycho-physiological interaction regressor with a seed region in left VS (red) and right VS (yellow) – orange indicates overlap – at an FDR-corrected threshold of $< .05$, > 10 contiguous voxels. The interaction regressor shows regions that enhance functional connectivity with VS (left and right respectively) when processing rewards compared to losses. (B) Scatterplot depicting the positive association between functional connectivity between left VS–right anterior insula and proportion of plays.

3.4 METHODS EXPERIMENT 2

PARTICIPANTS

A subset of the adolescents from Experiment 1 ($n = 33$) were scanned again approximately two years later, and were administered the same risky decision task. The goal of this study was to extend this dataset with a longitudinal sample. All participants signed informed consent (parental consent and participant assent for minors) and procedures were approved by the local Medical Ethical Committee.

Two participants showed head motion exceeding 3 mm during scanning at time point 2 (T2) and were therefore removed from further analyses. For longitudinal analyses, 31 adolescents were included at time point 1 (T1) and T2 (T1: 10–16 years old, Mean age = 13.1 years old, SD = 2.0; T2: 12–19– years old, Mean age = 15.3 years old, SD = 2.1, 18 female). The average time difference between the first and second scan was 2.13 years (1.8 – 2.3 years old, SD = .14). The average head motion on T1 was significantly correlated with Age at T1,

$r = -.41, p < .05$, however, head motion at T2 was not related to Age at T2, $p = .2$. Note that the mean head motion was low at both time points (T1: Mean = .1 mm, SD = .05; T2: Mean = .09 mm, SD = .04).

Similarly to T1, PDS scores at T2 were positively correlated with age at T2 ($r = .39, p < .05$). A repeated measures ANOVA indicated an increase in pubertal development from T1 to T2, $F(1, 30) = 32.8, p < .001$, that did not differ significantly between boys (Mean PDS increase = .83) and girls (Mean PDS increase = .76), $p = .8$.

The task, procedure, and MRI acquisition in Experiment 2 were identical to those described in Experiment 1.

FMRI PREPROCESSING AND STATISTICAL ANALYSIS

Data preprocessing and analysis was conducted using SPM8 (Wellcome Department of Cognitive Neurology, London). Preprocessing steps in Experiment 2 were identical to those described in Experiment 1.

Two types of statistical analyses were performed on this longitudinal dataset. First, we used the ROIs defined based on the whole-brain analysis [reward > loss] in the cross-sectional study (left VS, right VS, and medial PFC) to examine longitudinal changes in neural activation related to changes in behavior, age, pubertal development, and individual's reward sensitivity. Second, we performed a whole-brain analysis on the longitudinal dataset within the GLM framework, with a $2(\text{reward, loss}) \times 2(\text{T1, T2})$ repeated measures ANOVA (flexible factorial design). The latter analysis allowed for a whole-brain inspection of a main effect of outcome [reward > loss], a main effect of time [T2 > T1], and an interaction between the contrast [reward > loss] $\times$ time.

3.5 RESULTS AND DISCUSSION EXPERIMENT 2

BEHAVIOR

The proportion of plays in the adolescent longitudinal sample was .62 ($SD = .13$) for T1 and .63 ($SD = .11$) for T2. A correlational analysis between T1 and T2 showed that proportion of plays was significantly correlated across sessions ($r = .41, p < .02$), however, this correlation also indicates there was a fair amount of within-individual differences in choice behavior across time.

A set of linear regressions with proportion of plays at each time point as a dependent and Age (continuous) at each time point as an independent variable showed that Age did not significantly predict behavior on T1 and T2 (respectively) nor did Age on T1 predict the change in behavior from T1–T2. Similarly, BAS subscales and PDS scores at T1 and T2 did not predict proportion of plays on T1 and T2 (respectively) nor predicted scores on T1 the change in behavior from T1–T2. (p 's > .05). Thus, risk-taking propensity was generally stable across time and was not related to developmental factors and individual differences.

ROI ANALYSES

We extracted individual activation values for the longitudinal dataset from the ROI masks used in the cross-sectional whole-brain analysis and focused on the contrast [reward > loss] in left VS ($x=-16, y=11, z=-5$), right VS ($x=16, y=11, z=-5$), and medial PFC ($x=-6, y=55, z=7$). These ROIs were chosen to enable comparison with Experiment 1. A repeated measures ANOVA was performed for each ROI with reward-related activation at T1 and T2. There was no effect of Time (i.e., Age) on brain activation in the VS and medial PFC. An additional correlational analysis for each ROI between reward-related activation at T1 and T2 showed no significant correlations over time within these ROIs.

We performed a linear regression [backward selection] with proportion of plays, PDS score, BAS scores, and IQ as independent and brain activation in an ROI [reward > loss] as a dependent variable. The same analysis was repeated with Age instead of PDS scores. These regression analyses were performed for behavioral scores and brain activation at T1, T2, and the change in behavioral scores and brain activation between T1 and T2.

The regression for medial PFC at T1 showed no significant results of any of these predictors. The regression analysis for left VS at T1 showed that BAS Fun-seeking score, Beta = .51, $p < .01$, and pubertal developmental score, Beta = .32, $p < .05$, were positively associated with left VS activation. A regression analysis for right VS at T1 showed that BAS Fun-seeking score was positively associated with right VS reward-related activation, Beta = .51, $p < .01$. A similar set of regressions for T2 showed no significant effects of Age, proportion of plays, PDS or BAS scores on reward-related brain activation at T2.

Crucially, regression analyses were performed with the change over time in reward-related activation in medial PFC, Right VS, and Left VS as

dependent variables, and the change over time in proportion of plays, PDS score, and BAS scores as independent variables. The regression for medial PFC showed no significant results of any of these predictors. A regression for left VS showed that the change in BAS Fun-seeking score was positively associated with the change in reward-related activation in left VS, $\text{Beta} = .38, p < .05$. A regression for right VS showed that the change in BAS Fun-seeking score was positively associated with the change in reward-related activation in Right VS, $\text{Beta} = .36, p < .05$ (see Figure 3.4).

These results suggest that an increased VS response to rewards is associated with increased self-reported fun seeking; this relationship is independent of developmental factors, such as age and pubertal development.

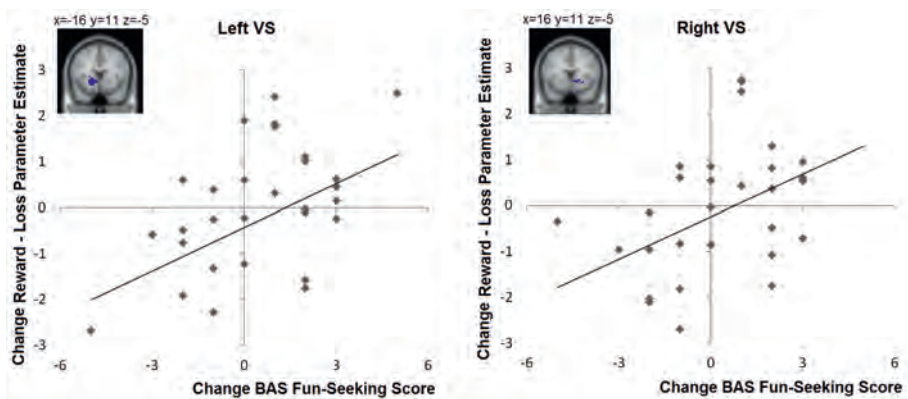


FIGURE 3.4 | Scatterplots for the change in reward > loss activation (T1-T2) and the change in left and right Ventral Striatum (VS) and self-reported Fun-seeking.

WHOLE-BRAIN ANALYSIS

To ensure that the pre specified ROIs did not prevent us from observing brain regions that showed changes in activation over time when processing rewards compared to losses, we performed a whole-brain 2 (reward, loss) $\times$ 2 (T1, T2) repeated measures ANOVA (flexible factorial design) on the longitudinal dataset.

Results for the main effect of outcome [reward > loss] across all participants resulted in VS activation (right) and a cluster of activation in the medial PFC (see Figure 3.5). Reward-related activation was also found in the PCC and visual cortex (see supplementary Table S3.1 for regions of activation and their coordinates). No significant results were found for the opposite contrast

[loss > reward]. The interaction term between reward-loss $\times$ time showed no significant results at FWE or more lenient corrected thresholds (FDR $p < .05$ and uncorrected $p < .001$).

Thus, even though correlations in ROI activation values indicate intra-individual variability in brain activation, there was a strong main effect of reward-related activation at the group level.

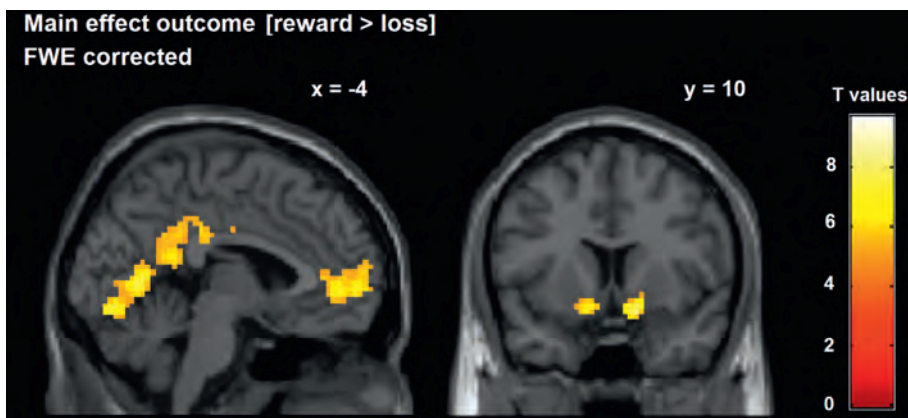


FIGURE 3.5 | Whole-brain results for the main effect of outcome [reward > loss] for all participants in T1 and T2 from a 2×2 flexible factorial ANOVA. Results are shown at an FWE-corrected threshold of $< .05$, > 10 contiguous voxels.

3.6 GENERAL DISCUSSION

The goal of this study was to examine stability, change, and individual differences in reward processing in adolescence. We first examined the relation between brain and behavior in the context of reward processing and risky decision-making. Second, we examined the effects of age, pubertal development, and reward sensitivity on reward-related brain activation in a cross-sectional and longitudinal comparison. To these ends, Experiment 1 utilized a risky decision task in a cross-sectional sample of adolescents and young adults. Experiment 2 was a longitudinal extension, in which an adolescent subset was re-studied using the same paradigm two years later.

For the current study, we used a task in which participants had the opportunity to 'play' or 'pass'. The advantage of this design is that rewards and losses are thought to be more meaningful when there is an active choice to

play (Rao et al., 2008; Tricomi, Delgado, & Fiez, 2004). Therefore, the analyses were focused on the brain responses to reward and loss following play trials. As expected, monetary rewards resulted in robust activation in the bilateral VS and medial PFC in the cross-sectional sample (Delgado, 2007; Knutson et al., 2001).

The longitudinal analysis confirmed these findings by revealing activation in a highly similar reward-related network including most predominantly VS and medial PFC. These activation patterns are in line with the functional roles of these regions, such as the coding of reward throughout various stages of decision making for the VS (Liu et al., 2007), and action regulation and control for the medial PFC (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Rushworth, Mars, & Summerfield, 2012). We, however, did not observe brain activation in the ventral medial PFC and the adjacent orbital frontal cortex. Given that these regions have been related to the representation and the comparison of value during risky choice (Kuhnen & Knutson, 2005; Rushworth et al., 2011), it may be that these regions are more readily activated in response to choice than outcome processing.

Interestingly, no results were found for the opposite contrast (i.e., loss > reward), suggesting that the brain regions involved in winning and losing overlap. This finding is supported by previous findings that also showed no results for the contrast no-gain versus gain in a similar design (e.g., Van Leijenhorst et al. 2010a). A possible explanation could be that in the current context negative feedback was not a learning signal and therefore there was no activation greater for loss than gain (Van Duijvenvoorde & Crone, 2013).

A whole-brain analysis showed that the propensity to play (i.e., to choose the risky option) was related to increased reward-related activation in both VS and medial PFC. That is, participants who generally played more often showed, as expected, increased activation in VS, but also increased activation in medial PFC after rewards compared to losses. Previous studies demonstrated that activation in medial PFC regions during decision-making was related to increased risk-taking tendencies (Van Leijenhorst et al., 2010a; Xue et al., 2009; but see Eshel, Nelson, Blair, Pine & Ernst, 2007), which is consistent with its role in reward-related action tendencies (Rushworth et al., 2011; Rushworth, Mars, & Summerfield, 2012). The current study extends previous findings by showing that medial PFC activation during outcome processing was positively related to the tendency to choose a risky option in a cross-sectional sample.

DEVELOPMENTAL CHANGES AND INDIVIDUAL DIFFERENCES

A current debate in the literature concerns the VS response to rewards in adolescence. Prior studies have reported both increases and decreases in mid-adolescence, although this may depend also on task demands (Bjork, Smith, Chen, & Hommer, 2010; Galván, 2010; Richards, Plate, & Ernst, 2013). In a prior study by Op de Macks et al. (2011), which involved a subset of participants reported in this study, it was found that reward-related brain activation correlated positively with testosterone levels, in both boys and girls. This led us to hypothesize that reward-related activation would peak in mid-adolescence, as can be expected based on adolescent-typical changes in the dopamine system (Galván, 2010; Luciana & Collins, 2012). However, a comparison with a sample of young adults (18–25 year olds) did not show developmental differences related to age or puberty. Only at lower (uncorrected) thresholds, reward-related activation in left putamen increased linearly with age. Thus, these results report no direct evidence for a peak in adolescent VS activation and suggest that individual differences in adolescence may be more important.

Indeed, this study showed that reward responses in the VS were related to the extent to which participants reported to be fun seeking in everyday life. Previously, Galván et al. (2007) reported that neural responses to rewards in adolescence could be partly explained by individual differences in risk-taking behavior in everyday life. It was previously reported in a large behavioral developmental study including 935 participants between ages 10 and 30 that self-reported sensation seeking peaks in mid-adolescence (Steinberg et al., 2008). Possibly, findings in prior studies of heightened VS activation in adolescents compared to adults were driven especially by risk-seeking adolescents. The current study provided further evidence for this hypothesis by showing that within individuals, changes in fun seeking over time correlated positively with changes in reward-related VS activation. This longitudinal extension provides a strong case for the role of individual differences in reward-seeking behavior, which may bias some adolescents to respond more strongly to rewards than others. Further study is needed to study how hyperactivity in VS is related to individuals' learning and decision-making.

FUNCTIONAL CONNECTIVITY

The next question concerned whether there was functional connectivity between VS and medial PFC. In the current study a functional connectivity

analysis in the cross-sectional sample indicated increased connectivity between VS and medial PFC after processing rewards compared to losses. Contrary to expectations we did not find a relation between VS–medial PFC functional connectivity and task-related behavior (i.e., proportion of plays). Instead, increased functional connectivity was found between VS and insula after rewards compared to losses, and the strength of this functional connectivity was related to individuals' risky decision-making. That is, greater connectivity was associated with an attenuated tendency to play, suggesting a potentially regulatory role of the insula (see also Cho et al., 2012). Indeed, insula activation has been implicated in saliency detection (Menon & Uddin, 2010), harm avoidance (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003), and risk processing (Mohr, Biele, & Heekeren, 2010). However, given the low number of trials in the current study, these results need to be interpreted carefully.

Previous work also indicated a relation between frontostriatal structural connections and choice behavior, in which higher integrity of frontostriatal white-matter tracts was associated with less impulsive choice behavior, suggesting that the PFC has a regulatory role over the VS (Peper et al., 2012). However, other findings demonstrated that more mature white-matter tracts in the frontal cortex (corpus callosum, connecting left and right prefrontal and orbital frontal cortex), is related to increased engagement in risky behaviors (Berns, Moore, & Capra, 2009). These mixed findings indicate the need to further study how frontostriatal connections influence risk taking in adolescence.

LIMITATIONS

There are a couple of critical aspects to take into account when reporting and comparing studies on risk and reward processing (Galván, 2010). First, studies may differ in the component of the decision-making process targeted (e.g., decision-making, cue/anticipation, and outcome). Due to its task design the current study focused specifically on outcome processing. However, future studies may profit from analyzing both decision-related and outcome-related responses (see also Barkley-Levenson, van Leijenhorst & Galván, 2013; Paulsen et al., 2012; van Leijenhorst et al., 2010a). Also, the current task was not aimed toward decomposing influences of risk, expected value, and reward that may drive individuals' decision making. Combinations in future paradigms will be valuable to further disentangle these components of decision-making.

Second, it is important to consider the task contrast and/or baseline used across studies. That is, while this study used a typical contrast of reward vs. loss, future studies may benefit from a neutral baseline (e.g., including a neutral condition) to distinguish whether differences in reward processing are due to differences in the brain responses to reward or responses to loss. Alternatively, parametric modulation of rewards and losses (e.g. Tom, Fox, Trepel, & Poldrack, 2007; Xue et al., 2009) may be a promising approach in distinguishing reward versus loss-related activation across development.

Third, even though the current longitudinal sample is an important starting point, the sample size is relatively small for detecting subtle developmental changes. We aimed to present these data as evidence that change scores are informative for understanding developmental patterns. In future studies, larger sample sizes will allow us to make stronger inferences about developmental trajectories. Related, the relative low number of trials for each contrast (i.e., on average, 17 reward and 17 loss trials) could hinder the detection of age-related changes. While previous fMRI studies reported developmental changes in reward processing based on similar numbers of trials per condition (i.e., 18 trials per condition; Bjork et al., 2004; Ernst et al., 2005), these studies included more than two conditions, suggesting the need for a larger number of trials in future studies.

Finally, task context may be driving age-related changes in risk-taking or brain activation. For instance, a recent study suggested that adolescents may be more ambiguity-tolerant, instead of more risk-tolerant compared to adults, indicating they are more likely to take a risk under conditions of unknown probabilities (i.e., an ‘ambiguous’ decision-situation) compared to known probabilities (i.e., a ‘risky’ decision-situation) (Tymula et al., 2012). Future studies are important for disentangling adolescent sensitivities across different decision contexts, such as risky, ambiguous, or social decision contexts.

CONCLUSION

In the current study, we used a risky decision task to investigate neurodevelopmental changes (cross-sectional and longitudinal) in the processing of rewards and its relation to task-related behavior (i.e., the proportion of play choices), age, pubertal development, and individuals’ reward sensitivity. Adolescence is characterized as a period of increased reward sensitivity and risk taking, but it remains unclear whether changes in reward-

related brain activation drive the changes in risk-taking behavior. The results of the experiments reported here advance our understanding of the potential mechanisms underlying reward processing and risky decision-making in adolescence. Specifically, these results indicated that increased activation within a network of brain regions responsive to rewards — including VS and medial PFC — is related to an increased tendency to play and heightened self-reported fun seeking. Longitudinal comparisons confirmed the association between VS activation and individual’s fun seeking. Furthermore, we observed increased connectivity between VS and medial PFC after rewards versus losses, but only the increased functional connectivity between VS and insula was associated with attenuated risky decision-making. Future challenges lie in unraveling how localized brain activation and frontostriatal connections are related to changes in risk taking across adolescence and in creating paradigms that are sensitive to individual and developmental differences in risk-taking tendencies.

3.7 SUPPLEMENTARY MATERIAL

TABLE S3.1 | Coordinates for the brain regions showing greater functional connectivity during rewards than losses with a left and a right ventral striatum seed. Peak voxels reported at cluster level with FDR corrected < .05, > 10 contiguous voxels. SFG = superior frontal gyrus, SMA = supplementary motor area, BA = brodmann area.

Anatomical Area	MNI coordinates (mm)				
	Cluster Size	x	y	z	Z-max value
<i>Ventral Striatum (seed) Left</i>					
L Paracingulate Gyrus	144	−6	30	33	4.01
R SMA / Medial Frontal Gyrus	10	9	−12	51	3.93
R Lateral PFC	15	51	36	24	3.58
R Inferior Frontal Gyrus / Insula	37	45	21	−6	3.71
R Precentral Gyrus	56	42	−9	42	4.21
R Inferior Parietal Lobe	22	48	−33	48	3.68
L Inferior Parietal Lobe	41	−45	−45	42	3.64
R Superior Parietal Lobe	132	27	−39	60	4.01
L Precuneus	26	−21	−66	48	3.30
R Lateral Occipital Cortex	1320	30	−81	24	5.26

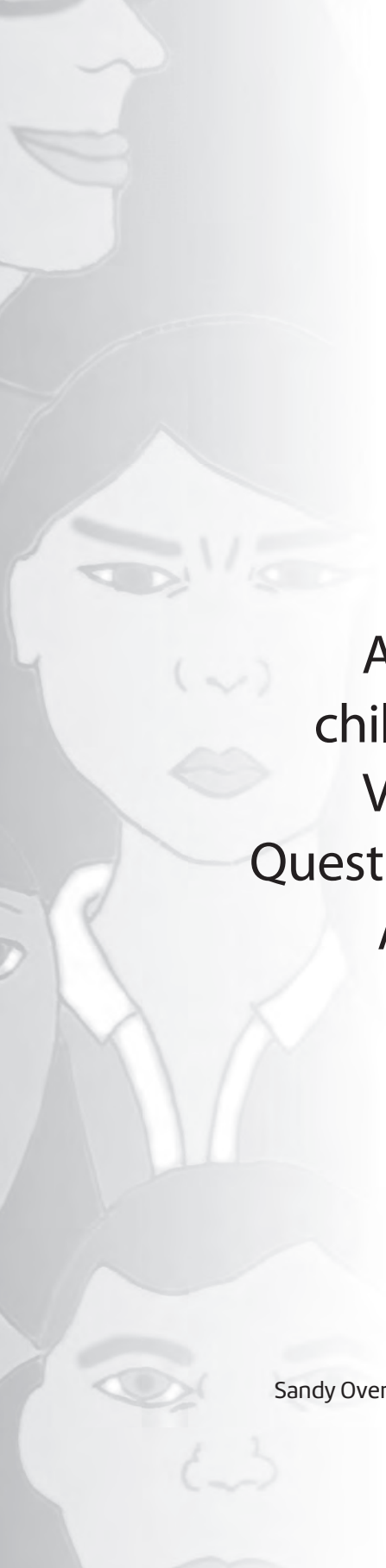
TABLE S3.1 | Continued

Anatomical Area	MNI coordinates (mm)				
	Cluster Size	x	y	z	Z-max value
L Occipital Fusiform Gyrus	188	-39	-69	-15	4.73
L Cerebellum	45	-6	-75	-27	3.54
<i>Ventral Striatum (seed) Right</i>					
R SFG / Paracingulate Gyrus	157	6	36	45	4.18
R Anterior Cingulate Cortex	11	12	15	33	3.47
R Lateral PFC	10	-48	9	42	3.42
R PrecentralGyrus	38	51	6	39	3.80
R PostcentralGyrus	44	36	-21	39	3.90
R Hippocampus	17	36	-21	-9	3.91
L Precuneus (BA 7)	23	-24	-57	54	3.46
R Precuneus (BA 7)	90	24	-57	48	4.22
R Lateral Occipital Cortex/ Precuneus	14	9	-78	51	3.67
R Lateral Occipital Cortex	2005	27	-81	24	5.36
L Cerebellum	15	-12	-66	-21	3.90

TABLE S3.2 | Coordinates for the brain regions showing activation for the main effect of outcome [Reward > Loss] across T1 and T2. Peak voxels are reported at cluster level with FWE corrected < .05, > 10 contiguous voxels. ACC = anterior cingulate cortex, PCC = posterior cingulate cortex.

Anatomical Area	MNI coordinates (mm)				
	Cluster Size	x	y	z	Z-max value
<i>Reward > Loss</i>					
R Ventral Striatum	91	15	9	-15	6.99
L Ventral Striatum	47	-15	3	-12	6.65
R ACC (BA32)	184	3	48	-3	6.14
R PCC (BA23)	12	3	-12	33	5.09
L Superior Frontal Gyrus	18	-21	36	45	5.32
R Lateral Occipital Cortex	182	30	-84	15	6.52
L Lateral Occipital Cortex	183	-24	-87	21	7.46
L Lateral Occipital Cortex	22	-48	-69	-12	5.80
L Lingual Gyrus / Fusiform Gyrus	724	-15	-78	-15	>8.0





Chapter 4:

Assessing empathy across childhood and adolescence: Validation of the Empathy Questionnaire for Children and Adolescents (EmQue-CA)

Sandy Overgaauw, Carolien Rieffe, Eveline A. Crone, Berna Güroğlu.

ABSTRACT

Empathy plays an important role in socio-emotional functioning. In this study, 1262 children and adolescents (10–15 year olds) performed the newly developed Empathy Questionnaire for Children and Adolescents (EmQue-CA) that was tested on reliability, construct validity, and concurrent validity. The EmQue-CA aimed to assess three components of empathy: Affective Empathy, Cognitive Empathy, and Prosocial Motivation. A Principal Components Analysis confirmed the three-factor model representing these three components. Reliability analyses demonstrated high construct consistency of the scales. The scales showed high construct validity, as the three concepts of the EmQue-CA were positively correlated with Empathic Concern (Affective Empathy) and Perspective Taking (Cognitive Empathy), scales of the well-validated Interpersonal Reactivity Index (Davis, 1980). With regard to concurrent validity, higher empathy was related to more awareness of others' emotions, higher friendship quality, less focus on own affective state and lower levels of bullying behavior. The EmQue-CA is a reliable and valid empathy instrument useable for both typically and atypically developing (e.g. Severe Language Impairment, Autism Spectrum Disorder, disruptive behavior disorder) children and adolescents aged ten and over.

4.1 Introduction

Empathy is defined as the ability to read, share, and understand emotional states of others (Mehrabian & Epstein, 1972). It entails two separate but intertwined components: affective and cognitive empathy (Chakrabarti & Baron-Cohen, 2006). Affective empathy refers to sharing an emotional state of others; cognitive empathy is the ability to understand emotional states of others, also referred to as 'perspective-taking' (Decety & Jackson, 2004; Preston & De Waal, 2002). Feeling compassion for a suffering person is the result of this combined ability to share and understand emotions. These skills are crucial to think of ways to help the suffering person or to act upon these thoughts, often indicated by the term 'prosocial behavior' (Eisenberg, 2000; Jolliffe & Farrington, 2006; Goudena et al., 2007). In this sense, the tendency to act upon this empathic sharing and understanding in a prosocial manner forms the third crucial component of empathy, which we will label 'Prosocial Motivation'. Examining this third component of empathy is particularly important during childhood and adolescence, as prosocial behavior has found to be crucial for adaptive social-emotional functioning.

Empathic skills have a large impact on how children and adolescents act toward individuals in their social group. Children with higher empathic skills are generally better able to regulate their emotions, show less aggression, and act more prosocially (Eisenberg, 2000; Pouw, Rieffe, Oosterveld, Huskens, & Stockmann, 2013). These skills are important for bonding with primary caregivers, friends, and other eminent people (Knafo, Zahn-Waxler, Van Hulle, Hyun Rhee, & Robinson, 2008). Cognitive empathy predicts high quality friendships, involving mutual reciprocity and stability (Soenens, Duriez, Vansteenkiste, & Goossens, 2007). However, cognitive empathy without the affective component can result in bullies, who are emotionally less affected by others' emotions, tormenting defenseless peers (Jolliffe & Farrington, 2006). In similar vein, affective empathy without the motivation to emotionally support the suffering person could hamper rather than strengthen the relationship (Pouw et al., 2013). Therefore, it is useful to have an instrument that disentangles all three components of empathy (affective- and cognitive empathy, and prosocial motivation), as development might be disharmonic, which could result in symptoms of psychopathology. An instrument that can identify the different components of empathy on each of these skills enables

professionals working with children in a clinical setting to focus on specific deficits in empathic behavior.

4.1.1 Empathy measures

Albeit sharing feelings with others (affective empathy) has been included in existing empathy questionnaires (Davis, 1980; Hawk et al., 2013; Jolliffe & Farrington, 2006; Lietz et al., 2011; Mehrabian & Epstein, 1972), as well as the understanding of these feelings (cognitive empathy) (Baron-Cohen & Wheelwright, 2004; Davis, 1980; Hawk et al., 2013; Hogan, 1969; Jolliffe & Farrington, 2006; Lietz et al., 2011), the corresponding tendency to behave supportive to the person in distress to date has been mainly neglected (Rieffe, Ketelaar, & Wiefferink, 2010). Moreover, due to difficult grammar constructions, many of the existing questionnaires for empathy are less suitable for children with language impairments, as we often see in children with Specific Language Impairment (SLI; Durkin & Conti-Ramsden, 2007), ASD (Pouw et al., 2013), and/or hearing impairments (Ketelaar, Rieffe, Wiefferink, & Frijns, 2013). Therefore, we designed an empathy questionnaire for children and young adolescents, accessible to children from the age of ten, and also easy to understand for less well developing children and adolescents, consisting of the following three scales: 1) Affective Empathy: a scale that measures the extent to which the subject feels for the emotion of the suffering person, 2) Cognitive Empathy: a scale that measures the extent to which the subject also understands why the person is in distress, and 3) Prosocial Motivation: a scale that measures the extent to which the subject is also inclined to actually help or support the suffering person.

4.1.2 Present study

The current study aimed to examine the construct and concurrent validity of the Empathy Questionnaire for Children and Adolescents (EmQue-CA) based on a dataset of participants aged 10–15. For the construct validity, we examined links of the EmQue-CA scales with two scales of the Interpersonal Reactivity Index (IRI), which is a commonly used measure for empathy across adolescence (Davis, 1980; Hawk et al., 2013). We expected positive correlations between the scales Empathic Concern (Affective Empathy) and Perspective Taking (Cognitive Empathy) of the IRI with the Affective and Cognitive Empathy scales of the EmQue-CA respectively.

To examine concurrent validity, the associations of the EmQue-CA scales with related concepts have been examined. Concerning intrapersonal functioning, it was expected that adolescents high on Affective Empathy would be less focused on their own internal affective states (i.e. lower scores on the scales Differentiating Emotions and Bodily Awareness of Emotions of the EAQ, the Emotion Awareness Questionnaire), but give more importance to be informed about others' affective states (i.e. higher scores on scale Attending to Others' Emotions, EAQ) (Rieffe & De Rooij, 2012). Furthermore, it was expected that adolescents scoring high on Cognitive Empathy and Prosocial Motivation would be more focused on others' emotions (i.e. higher scores on the scale Attending to others' Emotions), and show a negative or no relationship with Differentiating Emotions and Bodily Awareness of Emotions.

Concerning interpersonal functioning, it was expected that adolescents high on Affective Empathy would bully less (De Wied, Goudena, & Matthys, 2005; Menesini, Camodeca, & Nocentini, 2010; Rieffe, Camodeca, Pouw, Lange, & Stockmann, 2013; Stavrinides, Georgiou, & Theofanous, 2010; Warden & Mackinnon, 2003) and have better friendship qualities as these adolescents feel for another peer in distress. Moreover, reporting higher friendship qualities was also expected to be related to Cognitive Empathy, as understanding why someone feels distressed is important for maintaining good social relationships. For Cognitive Empathy in relation to Bullying there was no clear expectation. In fact, there is a controversy in the literature suggesting on the one hand that bullies are high on Cognitive Empathy, which makes them the so-called cold-blooded intelligent bullies (Rieffe et al., 2013; Sutton, Smith, & Swettenham, 1999). And on the other hand, the literature suggests that adolescents high on Cognitive Empathy would bully less because of a better understanding of the causes for the distress and thus better know how to support this person (Kokkinos & Kipritsi, 2011). Additionally, we expected that adolescents who are more inclined to help the person in distress (high scores on Prosocial Motivation), bully less, and have better friendship qualities.

Our final aim of this study was to examine empathy development across childhood and adolescence by studying age differences for the three empathy components assessed by the EmQue-CA (Van der Graaff et al., 2014). We hypothesized that empathic abilities in general would show age related increases, though with prudence as the literature shows inconsistencies (Eisenberg, Cumberland, Guthrie, Murphy, & Shepard, 2005; Lockwood, Seara-

Cardoso, & Viding, 2014; Mestre, Samper, Frías, & Tur, 2009; Davis & Franzoi, 1991). Additionally, we took the role of gender into account. We expected affective empathy to remain stable with age in girls and to show a decrease with age in boys. Concerning cognitive empathy we hypothesized that both boys and girls would show a developmental increase (Taylor, Barker, Heavey, & McHale, 2013; Van der Graaff et al., 2014). For prosocial motivation our expectation was to find an increase in prosocial motivation with age, stronger in girls.

4.2 METHOD

4.2.1 Participants

In total 1262 children and adolescents aged between 10 and 15 years participated in the study (Mean age = 13.24; SD = 1.68; 50% girls). All participants were recruited from local elementary and high schools with different levels of education, including preparatory schools for vocational secondary education and university. From the 974 participants (77% of the sample), a total of 124 (13%) children attended elementary school, 222 (23%) attended secondary vocational education, 175 (18%) attended higher general secondary education, and 453 (46%) attended secondary science education.

TABLE 1 | Sample sizes, gender distribution (%), mean age and standard deviation (SD) in years of the participants from six age groups.

	10 years	11 years	12 years	13 years	14 years	15 years
Number of participants	159	134	194	280	279	216
Female (%)	79 (50)	73 (54)	86 (44)	144 (51)	143 (51)	106 (49)
Mean age	10.3	11.25	12.59	13.44	14.39	15.47
SD age	.32	.30	.27	.29	.28	.27

Note. The Chi square analyses indicated that gender distribution did not differ across the age groups ($\chi^2(5) = 5.16, p = .40$; see Table 1).

4.2.2 Procedures

Both schools and parents provided written consent for participation. Data collection took place at school. The participants were given classical instructions where it was emphasized that participation was entirely anonymous and voluntary and that there were no right or wrong answers. They could ask questions any time during the data collection session, which was part of a larger session and

lasted 45 minutes on average. The university ethical committee approved the procedures and questionnaires.

4.2.3 Measures

Empathy Questionnaire for Children and Adolescents (EmQue-CA). This self-report measure consists of 19 items grouped in three scales: Affective Empathy (7 items), Cognitive Empathy (6 items), and Prosocial Motivation (6 items; see Figure 1 for a complete list of all items). Participants were asked to rate to what extent the description was true for them on a 3-point scale: 1) not true, 2) somewhat true, and 3) true (Pouw et al., 2013). All questions were formulated positive, where higher scores reflected higher empathic abilities. Mean scores were calculated per scale.

Interpersonal Reactivity Index (IRI). Two scales of the IRI (Davis, 1980) were obtained from subsamples of this study: Empathic Concern (e.g., 'I am often quite touched by things that I see happen'; N = 171), and Perspective Taking (e.g., 'I believe that there are two sides to every question and I try to look at them both'; N = 1145). From this point forward, the Empathic Concern scale will be referred to as Affective Empathy, and the Perspective Taking scale will be indicated with Cognitive Empathy. Both scales contained 6 items; each item was rated on a 5-point Likert scale with 0) completely untrue, 1) not quite true, 2) in between, 3) quite true and 4) completely true. The construct consistency between the items of the scales was good (see Table 2).

Emotion Awareness Questionnaire (EAQ). Three scales of the well validated EAQ were included in a subsample of this study (Rieffe, Oosterveld, Miers, Meerum Terwogt, & Ly, 2008; N = 171): Differentiating Emotions (7 items; e.g. 'Sometimes, I feel upset and I have no idea why'), Bodily Awareness of Emotions (5 items; e.g. 'When I am scared or nervous, I feel something in my tummy') and Attending to Others' Emotions (5 items; e.g. 'If a friend is upset, I try to understand why'). All items were answered on a 3-point scale with 1) not true, 2) sometimes true, 3) often true. Mean scores were calculated per scale. The items of the scales showed good construct consistency (see Table 2).

Friendship Quality Scale (FQS). We used an adapted version of the FQS (Bukowski, Hoza, & Boivin, 1994; N = 863) containing 28 items assessing five aspects of friendship quality: companionship, help, security, closeness, and conflict. Participants were asked to indicate how much each item was true for their relationship with their best friend on a 5-point Likert scale ranging from (1)

not true to (5) completely true. Based on a previously reported subdivision of the questionnaire in two separate factors (Demir & Urberg, 2004), exploratory factor analyses were performed to make a distinction between positive and negative friendship quality. Here we included the positive friendship quality factor with a total of 13 items (e.g., 'My friend and I help each other'). Sum scores were calculated and higher scores indicated higher relationship quality. Cronbach's Alpha of .90 showed high construct consistency of the positive Friendship Quality Scale (see Table 2).

Olweus Bully/Victim Questionnaire (OB/VQ). Self-reported bullying was assessed using the well-validated OB/VQ (Olweus, 1986; N = 967). Participants were asked to indicate how often they engaged in different acts of bullying in the last six months on a 5-point scale with answers varying from (1) I haven't bullied other children to (5) several times a week. Sum scores of the six bullying items were used to indicate engagement in bullying. The consistency of the bullying subscale is high with a Cronbach's Alpha of .80 (see Table 2).

4.2.4 Statistical analyses

In order to assess the construct validity of the EmQue-CA, we first examined the intended three-factor structure and conducted a Principal Component Analyses (PCA) with varimax rotation. The three factors were based on the previously established scales and required that each intended item would show a factor loading of at least $> .40$ on their key factor. Furthermore, the inter-factor correlations were computed to demonstrate diversity between the scales, and Cronbach's alphas were computed to examine construct consistencies. Next, we examined the associations between the Affective and Cognitive Empathy scales of the EmQue-CA with the scales Affective Empathy and Cognitive Empathy of the IRI respectively. The concurrent validity of the EmQue-CA was also tested, for which we examined the associations between the three EmQue-CA scales with emotion awareness, friendship quality, and bullying behavior. Finally, we applied Fisher r -to- Z transformation to calculate a value of Z to assess the possible significance of the difference between boys and girls for the correlations between the scales of the EmQue-CA and the scales of the IRI, EAQ, FQS and OB/VQ, and age.

4.3 Results

4.3.1 Factor structure, internal consistency and construct validity

A Principal Component Analysis (PCA) on all 19 items was performed with three factors (see Figure 1). All items loaded on the intended factor, except for one item that failed to load on the intended factor for Cognitive Empathy and was thus removed ('I often don't understand why someone gets angry'). Cronbach's alphas of the three scales of the EmQue-CA indicated good internal consistencies for the scales: Affective Empathy .68, Cognitive Empathy .64, and Prosocial Motivation .75 (see Table 2). The mean scores in Table 2 show that girls score higher on Prosocial Motivation, but not on the other scales. Correlations between all three scales were significant (see Table 3), also when analyzed per age group, but still below .60, so there was no collinearity. Additionally, correlations for the Affective and Cognitive empathy scales of the EmQue-CA correlated positively with the IRI scales ($r(164) = .36; p < .01$ and $r(1138) = .34; p < .01$, respectively).

4.3.2 Concurrent validity

To study the concurrent validity of the EmQue-CA, we examined the relationship between the EmQue-CA scales and related constructs (see Table 3). As expected, the results showed negative correlations between Affective Empathy with Differentiating Emotions ($r(117) = -.28; p < .01$) and Bodily Awareness of Emotions ($r(117) = -.28; p < .01$). Cognitive Empathy and Prosocial Motivation were related positively to higher scores on the EAQ scale Attending to Others' Emotions ($r(117) = .43; p < .01$; and $r(117) = .22; p < .05$ respectively).

When we examined the relationships of the EmQue-CA scales with indices for social functioning, we found that Friendship quality correlated positively with Affective Empathy ($r(862) = .36, p < .01$), Cognitive Empathy ($r(863) = .30, p < .01$), and Prosocial Motivation ($r(863) = .42, p < .01$). Bullying, on the other hand, correlated negatively with all three scales of the EmQue-CA (Affective Empathy: $r(966) = -.14, p < .01$; Cognitive Empathy: $r(967) = -.20, p < .01$; Prosocial Motivation: $r(863) = -.42, p < .01$). Moreover, all correlations reported in this section remained significant after controlling for age. Additionally, the means for the related constructs have been calculated separately for boys and girls (see Table 2). Results revealed gender differences only for Bullying, boys bullying more often than girls. The other constructs did not show gender differences.

To assess the significance of the difference between boys and girls on relationships between scales of the EmQue-CA and other variables in this study, we applied Fisher r-to-Z transformation (see Table 3). Fisher transformations showed that the correlation between Affective Empathy and Differentiating Emotions differed significantly between boys and girls, resulting in only a significant negative relationship for boys ($Z = -2.3$; $p < .05$). The correlation between Prosocial Motivation and Attending to Others' Emotions also showed gender differences ($Z = 2.78$; $p < .01$), resulting in a significant negative correlation for boys but not for girls. Additionally, Cognitive Empathy measured by the EmQue-CA and Cognitive Empathy measured by the IRI showed a difference between boys and girls, girls showing a significant stronger positive correlation than boys ($Z = -2.63$; $p < .01$).

TABLE 2 | Construct consistencies of the three scales of the Empathy Questionnaire for children and adolescents (EmQue-CA).

	Number of items	N	Cronbach's Alpha	Inter-item correlation	Mean (SD) boys	Mean (SD) girls
EmQue-CA						
Affective Empathy	7	1253	.68	.23	1.85 (.34)	2.18 (.35)
Cognitive Empathy	5	1255	.64	.26	2.36 (.38)	2.51 (.36)
Prosocial Motivation	6	1258	.75	.33	2.42 (.42)*	2.66 (.34)*
IRI						
Affective Empathy						
Cognitive Empathy	6	171	.73	.31	2.25 (1.02)	2.50 (.94)
	6	1145	.69	.27	2.45 (.66)	2.63 (.66)
EAQ						
Differentiating Emotions						
Bodily Awareness of emotions	7	117	.75	.30	2.39 (.45)	2.34 (.41)
Attending to others' emotions	5	117	.79	.43	1.93 (.44)	1.68 (.42)
	5	117	.61	.24	2.37 (.40)	2.62 (.33)
Friendship Quality						
Bullying	17	863	.90	.37	60.05 (10.73)	68.79 (9.98)
	6	908	.80	.42	.94 (.59)*	.67 (.49)*

Note. Using independent t-tests, the means indicated with a * denote significant group differences ($p < .05$).



FIGURE 1 | Principal Component Analysis with the three factor model of the Empathy Questionnaire for Children and Adolescents (EmQue-CA).

4.3.3 Relation of EmQue-CA scales with age

Results showed a positive correlation between Age and Affective Empathy: $r(1253) = .10, p < .01$, a negative correlation between Age and Prosocial Motivation: $r(1258) = -.14, p < .01$, and no correlation between age and Cognitive Empathy. However, when testing for group differences for the correlations of the EmQue-CA scales and age between boys and girls by applying Fisher r -to- Z transformation to calculate a value of z , results showed a significant difference for Affective Empathy and Age ($z = -2.30; p < .05$). Girls showed a positive relationship between age and Affective Empathy ($r(627) = .20, p < .01$), whereas there was no significant relationship for boys (see Table 3).

TABLE 3 | Correlations between the scales of the EmQue-CA and the scales of the IRI, EAQ, friendship quality, and bullying.

	Affective Empathy (boys/girls)	Cognitive Empathy (boys/girls)	Prosocial Motivation (boys/girls)
EmQue-CA			
Affective Empathy	1	.37**	.46**
Cognitive Empathy	.37**	1	.42**
Prosocial Motivation	.46**	.42**	1
Age	.02/.20**	.04	-.14**
IRI			
Affective Empathy	.33**	.19*	.21**
Cognitive Empathy	.35**	.25**/.39**	.40**
EAQ			
Differentiating Emotions	-.46**/-.06	-.08	-.06
Bodily Awareness of Emotions	-.26**	-.02	-.18
Attending to Others' Emotions	.25**	.42**	.37**/-.14
Friendship quality	.36**	.30**	.42**
Bullying	-.15**	-.20**	-.27**

Note. * $p < .05$, ** $p < .01$. Correlations are only presented separately for boys/girls when they significantly differed when tested by the Fisher r -to- Z transformation. All correlations remained significant when corrected for age.

4.4 Discussion

In this study we examined the construct and concurrent validity of the EmQue-CA, a newly developed questionnaire for Children and Adolescents, that aims to assess the three major components that empathy consists of: Affective Empathy (feeling for the other person in distress), Cognitive Empathy (understanding where the distress comes from), and the urge that one can feel to help the other person in distress, which was labeled as Prosocial Motivation. The outcomes of this study confirm the three-factor structure. Moreover, the three identified scales (Affective Empathy, Cognitive Empathy, and Prosocial Motivation) show good internal consistencies, as well as correlations with related constructs in the expected directions. Both indices for social functioning (friendship quality and bullying) were associated with all three EmQue-CA scales.

The negative correlations between Affective Empathy and the scales Bodily Awareness of Emotions and Differentiating Emotions were as expected. Children and adolescents who were more focused on other people's distress

as assessed by the Affective Empathy scales, were less focused on their own internal state, as assessed by Bodily Awareness of Emotions. Prior studies have also shown that children or adolescents who were too much occupied by their own internal state, were not paying sufficient attention to the outside world and other people (Rieffe, & de Rooij, 2012). In order to sense the feelings of another person, one needs to overcome the idiosyncratic focus and be able to focus on the other person's feelings instead. A willingness to Attend to Others' Emotions was positively correlated with all three EmQue-CA scales, but most strongly with Cognitive Empathy. This makes sense as affective aspects of empathy, that is, the tendency to feel for the other person is supposed to be innate (Decety & Meyer, 2008), and triggered by the mirror neuron system, but the cognitive aspect of empathy, that is, understanding why the other person feels distressed, requires a genuine interest in the other person, which is reflected in the EAQ scale that measures a person's tendency to Attend to Others' Emotions. Unlike the affective empathy skill, cognitive empathy might more strongly reflect an intention, a skill that people can apply or not, depending on their social goals. In this sense, cognitive empathy reflects a higher order reflection than affective empathy (Decety & Meyer, 2008).

The positive relationship between friendship quality and empathy is in line with our expectations and confirms the importance of empathic abilities for social interactions irrespective of gender (Allemand, Steiger, & Fend, 2014; Soenens, Duriez, Vansteenkiste, & Goossens, 2007). High levels of empathy also corresponded with low levels of bullying behavior, indicating the protective role of empathic abilities in the motivation for offending. The finding that boys reported higher bullying behavior compared to girls is in line with previous studies on physical aggression (Warden & Mackinnon, 2003). To further unravel the specific role of empathy in social interactions during childhood and adolescence, examining how these components are related to the development of both positive and negative relationships is particularly important.

Empathy is an important tool for adaptive social interactions, which emphasizes the importance of investigating these abilities more thoroughly, especially in less well developing groups that may be delayed in or missing one or more components of empathy. Different studies already denoted the possibility of higher levels of affective empathy, combined with lower levels of cognitive empathy in children and adolescents with Autism Spectrum Disorder

(ASD), creating tension for these children who might then have no idea how to react adaptively when affectively aroused (Pouw et al., 2013). In contrast, the rule-breaking behavior of children and adolescents diagnosed with Oppositional Defiant Disorder (ODD) or Conduct disorder (CD) could be due to lower levels of affective empathy, which in turn could hinder them in forming and maintaining friendships with peers (Taylor, Barker, Heavey, & McHale, 2013). Future studies could focus on the development of empathic abilities in less well developing groups (e.g. SLI, ASD, and ODD/CD) and on the relationship with the person they empathize with. In the past, Meyer and colleagues (2013) for example showed that empathy for friends activated brain areas important for sharing emotions, whereas empathy for strangers activated a brain network that is involved in reasoning about others' intentions. Perhaps this could explain the inconsistencies in the literature concerning the development of empathy.

Furthermore, our results showed a developmental increase in Affective Empathy in girls, a developmental decrease in Prosocial Motivation in both boys and girls, and no age related changes for Cognitive Empathy. The finding that Affective Empathy is higher in girls than in boys was in accordance with previous findings that indicate that girls are more tended to share emotions with friends and other eminent people (Taylor, Barker, Heavey, & McHale, 2013). The age related increase deviates from previous findings, though this could be explained by differences in selected age groups. It could be that Affective Empathy increases in early adolescence and stabilizes around mid-adolescence (Van der Graaff et al., 2013). The absence of age related differences in Cognitive Empathy was against expectations, as previous research demonstrated developmental increases in both boys and girls. A possible explanation could be that cognitive empathy develops from mid-adolescence onwards, as Van der Graaff and colleagues reported an age effect between 13 and 18 (Van der Graaff et al., 2013). Finally, the developmental decrease in Prosocial Motivation in both boys and girls was unexpected and cannot be readily explained by previous findings. However, it should be noted that the differences in means levels of Prosocial Motivation in the different age groups are rather small and the reported age differences should be replicated and interpreted with caution (see Table S1).

Taken together, the EmQue-CA presents a significant contribution to the knowledge on empathic abilities in children and adolescents. Particularly, the scale assessing Prosocial Motivation presents a valuable addition to existing questionnaires measuring empathy. Future studies should further focus on

the development of empathic abilities, as empathy has found to be of great importance in forming and maintaining social relationships that are crucial for learning how to follow social rules.

Supplementary material

TABLE S1 | Mean and standard deviations of scores of the Empathy Questionnaire for children and adolescents (EmQue-CA): per scale and age group.

	N	10 years M (SD)	11 years M (SD)	12 years M (SD)	13 years M (SD)	14 years M (SD)	15 years M (SD)
Affective Empathy	1253	1.93 (.39)	1.97 (.35)	1.95 (.36)	2.05 (.38)	2.05 (.38)	2.04 (.41)
Cognitive Empathy	1255	2.37 (.4)	2.43 (.37)	2.4 (.36)	2.43 (.37)	2.44 (.37)	2.43 (.38)
Prosocial Motivation	1258	2.63 (.36)	2.6 (.34)	2.48 (.36)	2.56 (.4)	2.47 (.45)	2.47 (.41)





Chapter 5:

Fairness considerations when I know more than you do: Developmental comparisons

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ABSTRACT

The Ultimatum Game (UG) is a valuable paradigm to study fairness considerations. Here, we tested developmental differences between altruistic and strategic motivations in fairness considerations using a version of the UG with hidden conditions. Participants were proposers and could divide coins between themselves and an anonymous other. Hidden information conditions involved division of coins where some coins were only visible to the participant (e.g., 8/2 condition where, from the total of 10 coins, 8 coins were visible to both players and 2 coins only visible to the proposer). In total, 22 young adults and 79 children between ages 8 and 13 played multiple one-shot versions of the UG with hidden conditions with anonymous others. Overall analyses confirmed validity of the task and showed that participants of all age groups had strategic intentions. Specific task analyses revealed that adults divided the coins equally in the standard UG conditions, but gave less to the second player in the hidden information conditions. The developmental comparisons revealed an age $\times$ condition interaction, such that adults and 10- to 12-year-old children differentiated between standard and hidden conditions more than 8- to 9-year-old children. These findings indicate that young children have a basic understanding of different strategic motives, but that behavior of adults and older children is driven more by strategic intentions.

5.1 INTRODUCTION

Making fairness related decisions is a common and important component of social interactions. These decisions are based on different underlying motives, including the relevance of true fairness and the need to comply with generally applicable social norms (Rilling & Sanfey, 2011). Experimental tasks based on economic exchanges have proven successful in examining people's strategies in bargaining situations and the factors that influence their decision-making. One of these tasks is the well-known Ultimatum Game (UG). In this two-player bargaining game, the first player (i.e., the proposer) makes an offer to divide the stake, for example 10 coins, between the two players. The second player (i.e., the responder) decides either to accept or reject the proposed division. If the offer is accepted, the coins are divided according to the offer of the proposer. In case the responder rejects the proposed offer, both parties receive nothing (Güth, Schmittberger, & Schwartz, 1982).

Many studies have examined what motivates proposers to offer an equal distribution instead of a "game theoretic" smallest possible offer in the UG context (Fehr & Schmidt, 2006). Contrary to what might be expected, people are not always primarily motivated to maximize their own outcome and seem to care for equality. A commonly given explanation is that proposers are motivated by considerations of fairness (Binmore, Morgan, Shaked, & Sutton, 1991; Pillutla, Murnighan, & Keith, 1996; Fehr & Schmidt, 2006; Reuben & van Winden, 2008, 2010), which might be partially caused by the acquired social norms of our society (Sally & Hill, 2006; Tomasello & Vaish, 2013). However, besides the "altruistic" willingness to be fair (Kagel, Kim, & Moser, 1995; van Dijk & Vermunt, 2000; Kohler, 2011), players might also be motivated by the fear of rejection (van Dijk, de Cremer, & Handgraaf, 2004), resulting in strategic action (Güth, Schmittberger, & Schwartz, 1982; Binmore, Shaked, & Sutton, 1985). That is, if the offer is beneficial for the proposer but not for the responder (i.e., an unfair split), the responder may reject the offer. In this case, the responder prefers that both parties receive nothing over an unfair split. Thus, the proposer in the UG may wish to maximize self-profit, but may take the perspective of the responder who might reject an unfair offer, resulting in the socially desirable fair offer. In this case, fairness requires the ability to take the perspective of others into account (Güroğlu, van den Bos, & Crone, 2009; Steinbeis, Bernhardt, & Singer, 2012). In short, fairness considerations might be based on two different

processes: a true belief in fairness (i.e., an altruistic motivation), and a fear for rejection (i.e., a strategic motivation).

DEVELOPMENTAL COMPARISONS

Several studies have shown that children under the age of 7 prefer distributions in their own favor and that preference for fair distributions increases with age (Benenson, Pascoe, & Radmore, 2007; Fehr, Bernhard, & Rockenbach, 2008; Gummerum, Hanoch, & Keller, 2008; Blake & Rand, 2010; Blake & McAuliffe, 2011). These developmental differences between ages 3–4 and 8 years have been interpreted as an increased preference for equity (Fehr, Bernhard, & Rockenbach, 2008; Tomasello & Vaish, 2013). For example, Blake and McAuliffe (2011) examined inequity aversion among 4- to 8-year-olds, where participants could use an apparatus that divided candy by pulling a green or a red handle, which allowed them to either accept or reject the offer. The game consisted of two conditions: disadvantageous inequity (1/4) and advantageous inequity (4/1). In both conditions the alternative distribution was the equity distribution (1/1), controlling for a default rejection tendency. Interestingly, only the 8-year-olds showed a preference for fairness in both advantageous and disadvantageous inequity conditions, willing to sacrifice their own coins in order to provide equity in the advantageous inequity condition.

This developing preference for fairness over self-interest across childhood is thought to partly depend on the acquisition of perspective taking (PT) abilities, which enables children to take another person's view (Harbaugh, Krause, & Liday, 2003; Takagishi, Kameshima, Schug, Koizumi, & Yamagishi, 2010). This progressing ability to take the perspective of others, which is defined here as the ability to understand thoughts and intentions by others and willingness to act on this understanding, can subsequently result in the development of strategic behavior. One way of examining strategic intentions behind fairness considerations is comparing offers made by proposers in the UG and the Dictator Game (DG). The DG differs from the UG in the way that proposals in the DG cannot be rejected by the receiver; the proposed offer determines the outcome for both players. If fairness is the driving force behind offering equal distributions, the proposals should be the same in both experimental games. Indeed, prior studies have demonstrated that fair proposals increase with age in the UG relative to the DG, with the greatest change occurring between ages 7 and 10 years (Harbaugh, Krause, & Liday, 2003; Leman, Keller, Takezawa, &

Gummerum, 2008; see also Steinbeis et al., 2012, who replicated the same finding in children between ages 6 and 13 years).

Güroğlu et al. (2009) studied proposer behavior in 9–18 year olds using an adapted version of the DG and the UG, which was developed to study the role of PT. This experimental variant, also referred to as the mini-UG, gave proposers two options for distributing 10 coins. One offer was always an unfair distribution (8 coins for proposer, 2 for responder), and this offer was presented next to another distribution which could be: 2 coins for the proposer and 8 for the responder (hyper-fair condition), 5 coins for both (fair condition), or 10 coins for the proposer and none for the responder (hyper-unfair condition). The findings showed that with increasing age, participants were increasingly strategic in the offers they made, such that they differentiated more between the three conditions based on the alternative distribution that was presented.

Taken together, prior developmental studies show evidence for an increase in offers in the UG between ages 7–8 and 12–13 years, suggesting a developmental change in fairness considerations in this period. The comparison between UG and DG behavior suggests that even young children are able to act strategically (Harbaugh, Krause, & Liday, 2003), but that these strategic intentions increase with age (Steinbeis, Bernhardt, & Singer, 2012). This leads to the question whether the developmental changes in UG offers can indeed be attributed to strategic (i.e., higher offers out of fear for rejection) rather than altruistic (i.e., higher offers because of equity/fairness preference) motivations behind fairness considerations.

DISSOCIATING ALTRUISTIC VERSUS STRATEGIC CONSIDERATIONS

Several researchers have employed a modified version of the UG with hidden information conditions in order to dissociate between altruistic and strategic considerations in UG offers (Kagel, Kim, & Moser, 1995; van Dijk, de Cremer, & Handgraaf, 2004; van Beest, Steinel, & Murnighan, 2011). Hidden information refers to information that is only available to the proposer and that can be used in his/her own benefit. For example, it can be the case that the proposer has 10 coins to share with the responder, but the responder thinks that there are only 8 coins in the game (i.e., 8/2 condition where from the total of 10 coins, 8 coins were visible to both players and 2 coins only visible to the proposer). If the proposer's decision was based on altruistic motivations, he or she would offer 5 coins (a true fair split). However, if the proposer is motivated by strategic considerations, he or

she would offer 4 coins to the responder, knowing that the responder will *think* this is a fair split. These hidden information conditions give the proposer the opportunity to act in an *altruistically* fair manner or in a *seemingly* fair manner, by making a strategic offer and using the hidden information to maximize self-gain (Kagel, Kim, & Moser, 1995; van Dijk, de Cremer, & Handgraaf, 2004; Koning et al., 2011).

Prior studies demonstrate the influence of various sorts of hidden information on proposer behavior in adults. Overall, it was found that proposers make more equal offers in complete information conditions than in the hidden information conditions and take advantage of hidden information by making seemingly fair offers and maximizing self-gain (Camerer & Loewenstein, 1993; Straub & Murnighan, 1995; Rapoport & Sundali, 1996; Murnighan & Saxon, 1998; van Beest, Steinel, & Murnighan, 2011). The UG with hidden information therefore proves valuable to answer questions related to the development of fairness considerations based on altruistic versus strategic motivations.

THE CURRENT STUDY

In the present study, we asked children between ages 8–13 and adults to play the role of the proposer in the hidden information version of the UG. Our main expectation was to find an increase in strategic fairness with age. Specifically, we expected adults to make higher offers than children in the complete information trials compared to the hidden information trials, based on the assumption that adults are better able to take the perspective of others and make strategic offers based on what they are willing to receive themselves (Page & Nowak, 2002). This pattern of behavior was expected to emerge between ages 8 and 13 (Harbaugh, Krause, & Liday, 2003; Blake & McAuliffe, 2011; Steinbeis, Bernhardt, & Singer, 2012). We also aimed to investigate the role of PT skills in fairness considerations across adolescence using a self-report index of PT abilities.

5.2 MATERIALS AND METHODS

PARTICIPANTS

In total there were 101 participants, including 22 adults between ages 18 and 25 years (Mean age = 20.23, SD = 1.23, 5 males and 17 females) and 79 children between ages 8 and 13 years. The children were divided into four age groups:

8- to 9-year-olds (Mean age = 8.5, SD = .27, 4 boys and 10 girls), 10-year-olds (Mean age = 10, SD = .71, 7 boys and 11 girls), 11-year-olds (Mean age = 11.41 SD = .28, 14 boys and 13 girls), and 12-year-olds and older (Mean age = 12.37, SD = .32, 13 boys and 7 girls; see Table 5.1). Of this sample, eight participants were excluded because of missing data and eight because they were extreme outliers (e.g., only pressing button “1” for the whole task). All children were recruited from elementary schools and participated voluntarily with the consent of the school and their parents. Adults were contacted through a university recruitment program and were tested in a quiet laboratory, comparable to the test session of the children.

TABLE 5.1 | Descriptives of sample sizes, gender distribution, and mean age in years (SD) of the five age groups.

	Group				
	1	2	3	4	5
Number of participants	14	18	27	20	22
Female	71%	61%	48%	35%	77%
Mean age	8.5	10	11.41	12.32	20.23
SD	.27	.71	.28	.32	1.23

THE HIDDEN ULTIMATUM GAME

The computer task was a variant of the classical UG. Written instructions were presented on the computer screen. Participants were told that they had to divide a certain number of coins, each with a value of 1 Euro, between themselves and the anonymous second players (i.e., the responders); the participants were told that the game was played online through an Internet connection with the responders. They were also told that the responder could accept or reject the offer they made: if the responder rejected the offer, both players would receive nothing; if the offer was accepted, the coins would be distributed as suggested by the participant. Subsequently, they were informed about the existence of two kinds of stakes: stakes with complete information and stakes with hidden information. In case of the complete information, both players were aware of the amount of coins in the game. In case of hidden information, only the proposer knew the total amount of coins that could be shared, and the responder was not aware that there was hidden information.

The task consisted of 15 conditions with three levels for the total number of coins (8, 9, or 10 coins in the game) and five levels for the number of

hidden coins (0, 2, 3, 4, or 5 hidden coins). Each condition was offered twice in a random distribution yielding a total number of 30 trials. Each trial started with a fixation cross with duration of 1 s, followed by the stimulus, which was response terminated. Hidden information trials involved blue coins visible to both the proposer and the responder, and white coins only visible to the proposer (see Figure 5.1). When the stimulus appeared, the proposer could make an offer from 0 to a maximum of 8, 9, or 10 coins (depending on the condition) by pressing an associated key on the keyboard. After the proposer made the offer, a screen appeared for 3 s, which signaled that the receiver was making his/her decision. The decision of the receiver was not presented to the proposer to avoid learning effects. Following the decision-time screen, a feedback screen of 5 s was presented which summed up the offer and indicated what the proposer would retain if the offer would be accepted.

THE INTERPERSONAL REACTIVITY INDEX

In order to measure the cognitive component of empathy, participants filled out the PT subscale of the Interpersonal Reactivity Index (IRI; Davis, 1980). This self-report questionnaire has been used extensively with children and adolescents before (Litvack-Miller et al., 1997; Eisenberg et al., 1999; Gleason et al., 2009). The PT subscale explicitly measures the cognitive tendency to see things from the point of view of others, without necessarily experiencing any affective response. The subscale consists of six items to be answered on a five point Likert scale with completely untrue, in between, and completely true. Cronbach's alpha for the PT subscale was .71.

PROCEDURES

All participants were tested in a quiet laboratory or classroom. They were told that they were going to play an online game with anonymous same-age others from a different school or university. In reality, the other person was not present and waiting time was computer-simulated. It was explained that the computer would randomly choose trials at the end of the experiment, which would be paid to the participants as well as to the second players. It was thus emphasized that their final reward depended on their choices during the game *and* the acceptance of the offers by the responder.

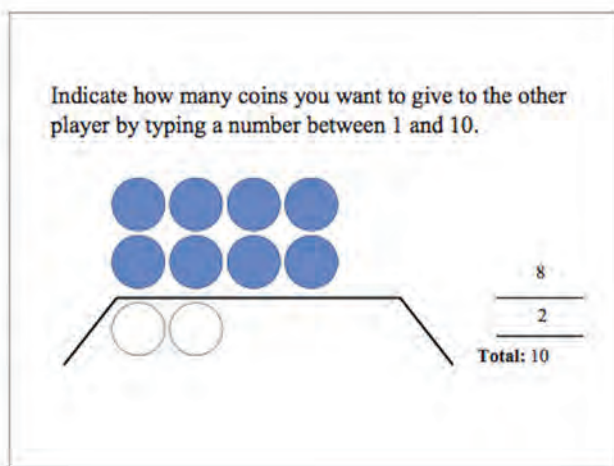
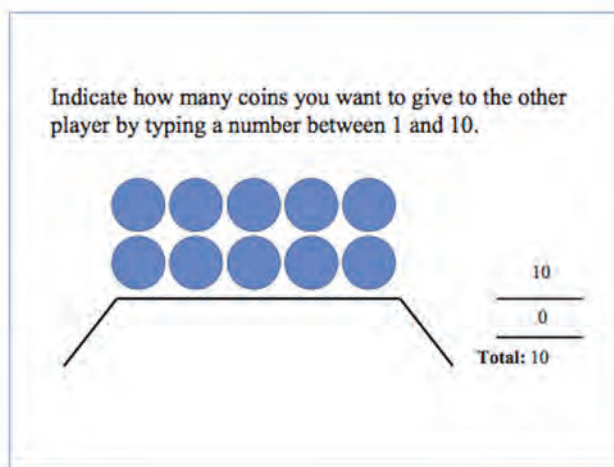


FIGURE 5.1 | Complete and incomplete information conditions visible to the participant in the role of proposer. The blue coins indicate visibility to both proposer and responder. The white coins indicate a hidden condition and are only visible to the proposer.

To make sure that the youngest participants also understood the instructions, the experimenters read the instructions out loud and used chocolate coins to explain the concept. They were explained that there were no right or wrong answers and that they could rely on their own judgment. After the instructions, the task was completed individually on a laptop computer. The task started with eight practice trials, followed by 30 experimental trials. The task was self-paced and all participants completed the game within 15 min. Following the task, the participants filled out the IRI questionnaire (Davis, 1980).

The children were told beforehand that they could choose a small present from the money they would earn in the game. All of the presents the children could choose from had approximately the same value. Adults were told that they would receive the money they had won during the game. All adults were paid a fixed amount of 6.50 Euros (approximately 8 dollars). Neither children nor adults indicated to have any doubts about the genuineness of the task and/or the outcome of their payments.

5.3 RESULTS

PRELIMINARY ANALYSES IRI

In order to examine age differences in PT skills on the self-report scale of the IRI, we first performed a univariate analysis of variance (ANOVA) with PT as the dependent variable and age group as a fixed factor. Results showed a main effect of age [$F(4, 89) = 3.65, p < .01$], which indicates that the age groups differed on their PT skills. Tukey *post hoc* tests demonstrated a difference between the youngest and the oldest age group, where 20-year-olds scored significantly higher than the 8/9-year-olds (Mean age = 15.95, SD = 2.73 and Mean age = 10.75, SD = 4.79, respectively). The remaining age groups did not differ from each other (10-year-olds: Mean age = 14.06, SD = 6.47, 11-year-olds: Mean age = 13.4, SD = 3.14, 12-year-olds: Mean age = 12.47, SD = 3). The correlation between age and PT skills was also significant ($r = .29, p < .01$).

PRELIMINARY ANALYSES HIDDEN UG

First, we tested whether the context of the 15 conditions resulted in different offers. A 3 (total coins) $\times$ 5 (hidden coins) repeated measure ANOVA across participants indeed resulted in a main effect of total number of coins [$F(1, 88) = 103.29, p < .01$], as well as a main effect of the number of hidden coins [$F(1, 88) = 425.72, p < .01$]; there was no significant interaction. First, as can be seen in figure 5.2, participants offered a higher amount of coins when there were more coins to be divided. Second, participants gave fewer coins when there was more hidden information. Thus, the main effects validated that the task was successful in measuring fairness considerations under hidden conditions.

The interaction between 3 (total coins) $\times$ 5 (hidden coins) $\times$ 5 (age group) was not significant. One reason for not finding age effects in this general analysis

could be the large number of conditions, which undermined smaller age effects in strategic intentions. The unequal trials (counting up to an uneven number of total coins) were added for exploratory reasons, in order to see how participants would act in reaction to trials in which the participants are forced to choose an unequal distribution. A limitation of these trials is that it is not possible to distinguish between altruistic and strategic trials when the total number of trials is unequal (in essence, on these trials). For this reason, we performed additional tests on the equally numbered trials and as can be seen in the subsequent analyses, when we tested for specific comparisons for fairness considerations, the expected age effects emerged. Next, we present how these considerations are present in different age groups.

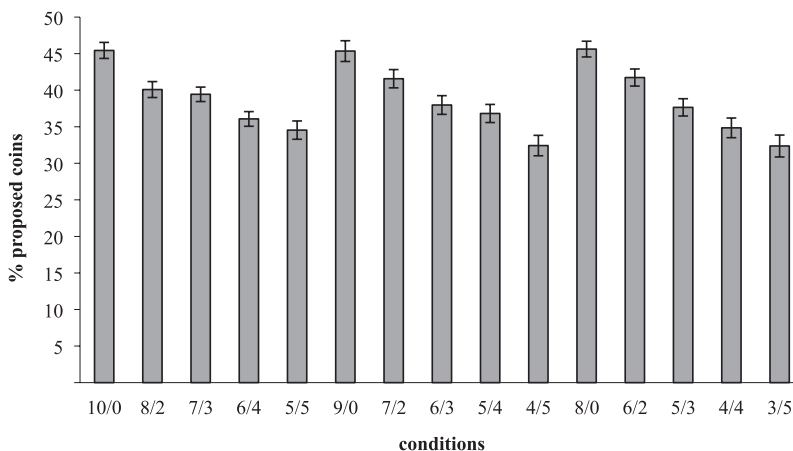


FIGURE 5.2 | Mean offers and standard errors of offers made in the three complete information conditions (10/0, 9/0, and 8/0) and the 12 hidden information conditions with two (8/2, 7/2, and 6/2), three (7/3, 6/3, and 5/3), four (6/4, 5/4, and 4/4), and five hidden coins (5/5, 4/5, and 3/5).

In our analyses examining age effects, we only included the offers that contained an even number of coins (total 8 or total 10), and an even number of hidden coins (0, 2, or 4). These trials were selected because they allow for direct comparisons of one factor while keeping other factors stable (e.g., 8/0 versus 8/2 tests for the role of hidden information while keeping total number of coins stable). Thus, the analyses below focus on specific questions targeted in this experiment. See table 5.2 for an overview of mean offers per condition and age group.

TABLE 5.2 | Descriptives of mean offers of the fifteen conditions in five age groups.

	Mean age									
	9 yr		10 yr		11 yr		12 yr		20 yr	
Total of 10 coins	M	SD	M	SD	M	SD	M	SD	M	SD
10/0	4.17	(.71)	4.47	(1.05)	4.70	(.75)	4.50	(1.1)	4.88	(.61)
8/2	3.38	(1.46)	4.08	(1.23)	4.04	(1.03)	4.12	(.93)	4.33	(.48)
7/3	3.83	(1.27)	3.83	(1.06)	3.70	(.84)	4.15	(1.06)	4.10	(.54)
6/4	3.25	(1.12)	3.83	(1)	3.70	(.84)	3.56	(1.09)	3.64	(.73)
5/5	3.33	(1.8)	3.86	(1.26)	3.36	(.9)	3.32	(1.26)	3.43	(.75)
Total of 9 coins										
9/0	3.79	(2.15)	4.28	(1.27)	3.88	(.99)	4.12	(.96)	4.38	(.59)
7/2	3.29	(1.42)	3.75	(1.44)	3.68	(1.04)	4.03	(.86)	3.88	(.31)
6/3	3.25	(1.79)	3.53	(1.27)	3.22	(.82)	3.71	(1.03)	3.38	(.5)
5/4	3.54	(1.5)	3.61	(1.36)	3.32	(.78)	3.03	(1.14)	3.14	(.48)
4/5	2.79	(1.66)	3.14	(1.29)	2.94	(1)	2.97	(1.15)	2.71	(.9)
Total of 8 coins										
8/0	3.08	(1.08)	3.81	(.88)	3.60	(.79)	3.65	(.77)	4.10	(.54)
6/2	3.21	(1.36)	3.31	(.96)	3.22	(.75)	3.50	(.9)	3.38	(.5)
5/3	2.71	(.94)	3.33	(1.28)	2.94	(.75)	3.24	(1.05)	3.00	(.55)
4/4	2.71	(1.34)	2.94	(1.38)	2.84	(.66)	2.68	(1.2)	2.60	(.74)
3/5	2.50	(1.9)	2.86	(.97)	2.54	(.95)	2.59	(1.18)	2.52	(.75)

The first question concerned whether there were age differences in the *no-hidden information condition*. A repeated measure analysis (ANOVA) with amount of coins (two levels: 10/0 versus 8/0) as a within-subjects factor and age group (five levels) as a between subjects factor yielded the expected main effect of amount of coins [$F(1, 88)=80.09, p < .001$] and a marginally significant main effect of age [$F(4, 88)=2.35, p = .06$]. *Post hoc* Tukey comparisons on the age effect revealed that the 20-year-old group offered significantly more than the 8- to 9-year-old group, with the other groups showing intermediate scores.

The second question concerned whether the age groups were differentially sensitive to hidden information *when this increased the total number of coins available*. A repeated measure analysis (ANOVA) with hidden coins (two levels: 8/2 versus 8/0) as a within-subjects factor and age group (five levels) as a between subjects factor yielded a main effect of hidden coins [$F(1, 88)=12.13, p < .01$] and a main effect of age [$F(4, 88)=2.99, p < .05$]. There was no hidden coin $\times$ age group interaction. The main effect of hidden coins showed that all participants offered more coins when more coins were available in the hidden information condition (8/2) compared to the complete information condition (8/0; see Figure 5.3). The age effect was examined using Tukey's *b post hoc*

tests and the results showed that 8/9-year-olds kept significantly more coins for themselves by making lower offers in both conditions than the 10-year-olds and the 20-year-olds. Ten and 11-year-olds did not differ significantly from the other age groups.

Third, in order to examine age differences in strategic motivations, we compared conditions with varying amounts of hidden coins, *when this decreased the total number of coins available*. A repeated measure analysis (ANOVA) with hidden coins (three levels: 8/0 versus 6/2 versus 4/4) as a within-subjects factor and age group (five levels) as a between-subjects factor again yielded a main effect of hidden number of coins [$F(1, 88)=55.32, p < .01$] and a marginally significant interaction between hidden coins and age group [$F(4, 88)=2.27, p < .07; \eta^2_n = .1$, see Figure 5.4].

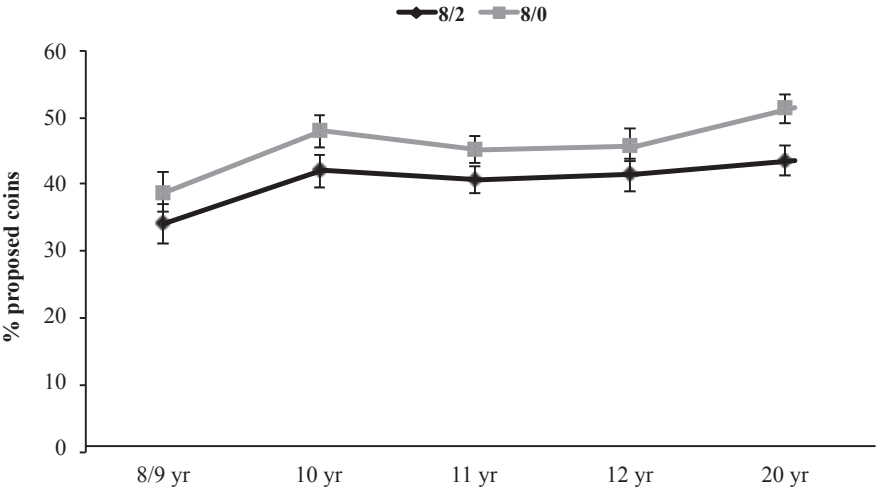


FIGURE 5.3 | Mean amount of proposed coins and standard errors in the complete 8/0 condition versus the hidden 8/2 condition in all age groups.

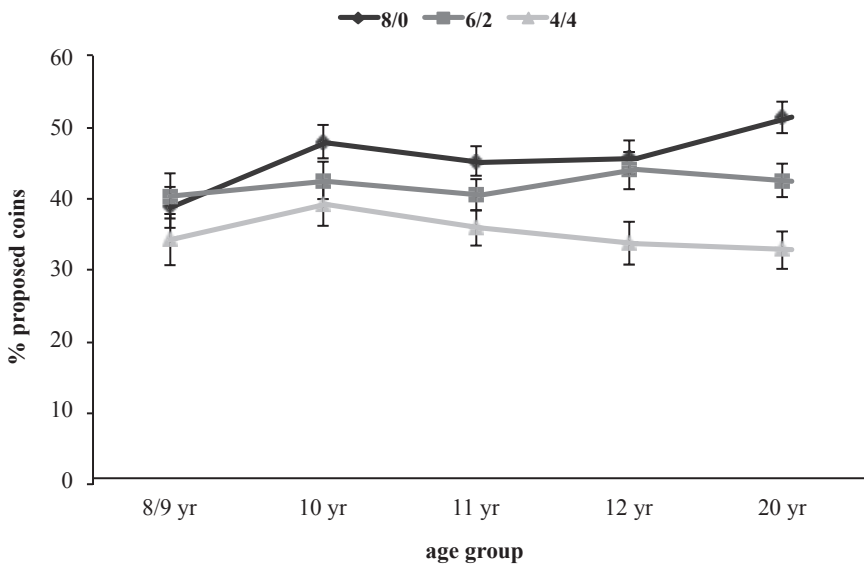


FIGURE 5.4 | Mean amount of coins and standard errors offered in the 3 conditions with a total number of 8 coins (i.e., 8/0, 6/2, and 4/4) in five age groups.

To examine whether offers in complete information conditions were significantly different from offers made in the hidden conditions within age groups, a repeated measure (ANOVA) *post hoc* analysis was conducted between the conditions 8/0, 6/2, and 4/4 for each age group separately. The results demonstrated that all age groups differentiate between the three conditions [all F_s (1, 16–24) > 9.91, p 's < .01], except for the youngest age group (8/9-year-olds).

The same analysis was performed for the 10 coins condition. Here, the repeated measure analysis (ANOVA) with hidden coins (three levels: 10/0 versus 8/2 versus 6/4) as a within-subjects factor and age group (five levels) as a between-subjects factor again yielded a main effect of hidden number of coins [$F(1, 88) = 53.16$, $p < .001$]. Contrary to what we expected, neither a main effect for age ($p = .17$) nor an interaction between hidden coins and age group ($p = .66$) was significant. Thus, the age differences were restricted to specific conditions, which could indicate that the 8- to 9-year-old group has more variance in responding yielding only some of the age effects significant. In order to determine whether this was the case, we have performed an independent

t-test to measure the homogeneity between the different age groups for each condition separately. Levene's test for equality of error variances showed that there was no significant variance between age groups in case of the conditions: 8/0, 8/2, and 6/4. The remaining conditions did show unequal variance between age groups, such that variance was larger in the youngest groups compared to the older age groups: 10/0 ($p < .01$), 6/2 ($p < .05$), and 4/4 ($p < .01$).

Next, we were still interested in testing whether there would be a difference when selecting only the youngest and the oldest age group, based on visual inspection of the graphs. A repeated measure analysis (ANOVA) with hidden coins (three levels: 10/0 versus 8/2 versus 6/4) as a within-subjects factor and age (two levels: 8/9-year-olds versus 20-year-olds) as a between-subjects factor yielded the expected main effect of condition [$F(1, 31)=32.11, p < .01$] and the expected main effect of age [$F(1, 31)=5.23, p < .05$]. This result is consistent with previous findings reporting lower offers by 8/9-year-olds compared to adults. We note though that this is a *post hoc* analysis and should be interpreted with caution.

LINKS WITH PERSPECTIVE-TAKING

To examine whether PT changes over time related to the offers made in the UG, correlations were computed between UG conditions and the PT scale of the IRI. The scale did not correlate with coins offered in the complete information conditions (8/0). In contrast, the PT scale was positively related to the number of coins offered in the hidden information condition 8/2 ($r = .21, p < .05$) and related marginally to the hidden information condition 6/4 ($r = .19, p = .06$), and 4/4 ($r = .19, p = .06$). This scale identifies the participants who are able to adopt the perspective of others in real life situations (Davis, 1980). Thus, this association seems to indicate that the hidden information condition required PT.

After controlling for age, PT was positively related to the number of coins offered in all hidden conditions, except for the 8/2 ($r = .23, p < .05, N = 87$) condition: 6/2 ($r = .21, p < .05, N = 87$), 6/4 ($r = .24, p < .05, N = 87$), and 4/4 ($r = .28, p < .01, N = 87$). There were no significant correlations with the complete information conditions (8/0 or 10/0).

In addition, we also performed a mediation analysis in order to be able to determine whether PT has a mediating role in the age differences in UG behavior. In the first regression model, age was found to be significantly

and positively associated with PT ($b_1 = .32, p < .01$). In regression model two, the association between PT and amount of coins offered in the 8/2 condition was found to be significantly and positively associated ($b_2 = .23, p < .05$). The third regression model found that age and amount of offered coins in the 8/2 condition were significant and positively associated ($b_3 = .21, p < .05$). Finally, when age and PT were included in the same model, the association between age and amount of coins offered in the 8/2 condition was no longer significant ($b_4 = .3, p < .08$), fulfilling the requirements for full mediation. The Sobel Test confirmed that PT fully mediated the association between age and amount of coins offered ($p < .01$). Thus, older participants who scored higher on the self-report PT subscale made higher offers in the specific case of the 8/2 condition. No mediation effects were found for the other conditions.

5.4 DISCUSSION

The goal of this study was to examine the role of strategic versus altruistic motivations in fairness considerations and their developmental trajectories. The results of this study show that by age 8/9 children already show strategic fairness considerations. All participants reduced the number of coins offered when information was hidden, showing that the ability to use strategies already develops at a young age. Specific follow up comparisons revealed age differences in how children and adults used strategies. That is, in standard proposal situations (i.e., with no-hidden information), adults proposed more fair offers than 8/9-year-old children, with children between ages 10 and 12 showing an intermediate pattern. The results further show that by age 8/9 children distinguish less between the hidden and no-hidden information conditions compared to adults who clearly differentiated based on the impending information. It should be noted that it was only in a subset of the conditions that children in the age of 8/9 years-old acted less strategically than adults. Yet, these results may indicate that adults are in certain situations more strategic than children. Below, we interpret these results in the light of our hypotheses.

The first hypothesis that was tested was whether adults show higher levels of concern for others and have altruistic motives for offering fair distributions. The results from the current study suggest the development of more strategic motives during late childhood, given that proposed offers in the

complete information conditions increased with age. The average amount of coins adults proposed to the other party in complete information conditions was approximately 50% compared to an average of 40% of the youngest age group. This age-related increase in offers made in complete information conditions is consistent with prior results (Harbaugh, Krause, & Liday, 2003; Güroğlu, van den Bos, & Crone, 2009; Steinbeis, Bernhardt, & Singer, 2012). Consistent with this point of view, Epley et al. (2004) performed an experiment in which participants had to take the visual perspective of the other person, to see objects from their point of view. The results showed that adults compared to children viewed solutions from different perspectives and were better in controlling their self-centered tendency in taking perspective of others. In this study, strategic motivations can possibly explain the increased prosocial behavior in adults, where they make fair offers to maximize their own outcomes (Reuben & van Winden, 2010). People tend to offer higher amounts when they reason about what other people will find acceptable and what is accepted according to social norms (Straub & Murnighan, 1995). The fear of being rejected by their counterpart prevents proposers to make a low offer (van Dijk & Vermunt, 2000; van Dijk, de Cremer, & Handgraaf, 2004).

The hypothesis of increases in strategic fairness considerations finds support in the analyses of the hidden conditions. The hidden, or incomplete information, conditions allowed for the comparison of offers where information was not available to the responder. All participants were strategic and offered less in the hidden, conditions compared to when all information was available to the responder. At the same time, all participants were also altruistic, because they did not lower their offer to 50% of what was visible to the responder (for example, even in the 4/4 condition, participants offered on average 2.8 coins, which is more than 2 coins which would have been considered a fair split by the responder). A comparison of age groups revealed lower offers by children and adults in case of the hidden 8/2, 6/2, and 4/4 conditions. Adults offered approximately 45% of their amount in the 8/2 condition, and children offered approximately 40%. In case of the 6/2, and 4/4 conditions, however, the offers of children and adults were no longer different from each other. These findings indicate that children already have a basic understanding of different strategic motives, but that behavior of adults is more consistent and seems to be more driven by strategic intentions.

Previous studies already pointed out that adult proposers like to benefit from a favorable situation (Kagel, Kim, & Moser, 1995; van Dijk, de Cremer, & Handgraaf, 2004; Koning et al., 2011). The current findings show that children showed a small decrease in number of coins proposed to the other player under hidden conditions, whereas adults dropped their offers to a much less altruistic, self-interested level compared to the complete information condition. Possibly, this reflects more self-oriented decision-making in case of more hidden information in the older age groups. One interpretation of this developmental difference is that the age-related increase in levels of PT, which allows individuals to predict what others find fair or unfair. This hypothesis is supported by our findings that behavior in the hidden conditions was correlated with self-reported PT skills and the outcomes of the mediation analyses revealing that self-reported PT mediates the relation between age and strategic UG behavior.

A second possible mechanism which can explain the developmental difference is the increase in inhibitory control with increasing age. An intriguing study by Steinbeis et al. (2012) revealed a correlation between strategic UG behavior (indexed by the difference score of the UG and the DG) and performance on the stop-signal task, a measure for response inhibition. These differences were associated with developmental changes in the contribution of the dorsolateral prefrontal cortex (DLPFC), a brain region known to develop across childhood and adolescence. Thus, it is possible that besides PT, the ability to control impulsive choices also contributes to the development of strategic bargaining. For example, Steinbeis et al. (2012) described that young children (age 6–9) can already point out when a division is unfair. Yet it is only with increasing age that they act strategically accordingly.

Taken together, this study showed that between ages 8 and 13, children offer more to others in the UG, but also become more strategic in fairness consideration. These findings were interpreted in terms of increasing levels of PT and impulse control. One aspect which received less attention in this study was the role of individual differences. Takagishi et al. (2010) recently reported that half of the children younger than six already reject unequal offers. Thus, there are important individual differences in fairness considerations among children, which can have influenced the robustness of the findings in this study, especially in the younger children. Future studies would therefore greatly benefit from following children's fairness behavior longitudinally, and

relate this development to individual differences in personality, empathy, and prosocial behavior (Eisenberg, Cumberland, Guthrie, Murphy, & Shepard, 2005).

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Chapter 6:

Behavior and Neural Correlates of Empathy in Adolescents

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ABSTRACT

This study examined neural correlates of empathy in adolescence while observing harmful acts. A total of 32 participants (aged 12–19 years) viewed pictures depicting negative (offenders inflicting intentional harm) and positive (friends socializing) social situations. After viewing each picture, participants could allocate hypothetical points to either the offender or the victim in a dictator game. Behaviorally, participants of all ages acted prosocially towards victims, fairly towards positive individuals and punishingly towards offenders. Brain imaging analyses showed that viewing negative situations was associated with more activation in the bilateral intraparietal lobule and the superior temporal sulcus (STS), whereas viewing positive situations was associated with more medial prefrontal cortex and left temporal parietal junction activity. Analyses testing for associations between brain activity and self-reported empathy showed that the STS was correlated negatively with reports of understanding others' distress and the willingness to help others. Together, the findings suggest that adolescents show similar prosocial behavior, as previously reported in adults with greater STS activity, when observing negative social acts that is modulated by an individual's empathy for others.

6.1 INTRODUCTION

Adolescence is marked by pronounced social-cognitive and social-affective changes, requiring the acquisition of new social skills and providing new challenges with important repercussions for the development of social relationships (Dahl, 2004). An important component for behaving adequately in response to others' emotions and behavior is empathy. Empathy is often defined as the ability to feel and read (affective) mental states of others, which helps us to understand and predict their intentions (Decety, Michalska, & Akitsuki, 2008; Nummenmaa, Hirvonen, Parkkola, & Hietanen, 2008). In childhood and adolescence, empathic skills play an important role in how children and adolescents act toward individuals in their social group. For example, children who report higher empathic skills are better able to regulate their emotions and act in more prosocial ways towards others (Greimel et al., 2010; Knafo, Zahn-Waxler, van Hulle, Robinson, & Rhee, 2008; Rieffe, Ketelaar, & Wiefferink, 2010). The current study aimed to investigate the neural underpinnings of individual differences in empathic concern in adolescence in the evaluation of intentional negative social situations involving offenders and victims.

Empathy has previously been described as consisting of the following three components: 1) affective empathy, defined as the capability to identify with another person's emotions, 2) cognitive empathy, defined as the ability to understand these emotions and reason about affective states, and 3) mentalizing, which refers to the ability to reason about cognitive states (Kramer, Mohammadi, Donamayor, Samii, & Munte, 2010; Walter, 2012). The latter component provides an important mechanism that enables us to differentiate between one's own and others' feelings. To put it briefly, empathy empowers us to feel and understand others' emotions, and provides us with a regulatory system to counteract possible overarousal resulting from such an empathic reaction (Lamm, Batson, & Decety, 2007).

Previous neuroimaging studies have suggested that mentalizing is specifically linked to the medial prefrontal cortex (mPFC), an area that has been found to be crucial for social information processing. Studies on people with a lesion in this brain area have shown that these patients were not able to read others' mental states based on nonverbal cues (Gupta, Tranel, & Duff, 2012; Shamay-Tsoory & Aharon-Peretz, 2007) and neuroimaging studies report that this region is consistently engaged in mentalizing tasks (Blakemore, 2008). In

addition, neuroimaging studies showed that the superior temporal sulcus (STS), the temporal parietal junction (TPJ) and the intraparietal sulcus (IPS) are involved in processing intentional and goal-directed behavior of others (Iacoboni, 2009; Vander Wyk, Voos, & Pelphrey, 2012; Van Overwalle, 2009). For example, Kramer et al. (2010) found that when interpreting dyadic interactions with empathic content, there was increased activation in the STS, but not in single-person situations, indicating the important role of the social context.

Furthermore, mentalizing areas are differentially sensitive to observing positive and negative social situations. That is to say, it was previously found that observing pain was associated with increased activation in the IPS and STS, whereas observing happy scenarios was associated with increased activation in the mPFC and TPJ (Morelli, Rameson, & Lieberman, 2012). The mPFC is thought to code the emotional value of social display, as this region is more engaged when viewing social situations with more positive valence ratings (Winecoff et al., 2013). In other words, neural regions involved in observing social scenarios seem to be differentially sensitive to negative (e.g. harmful or painful) and positive (e.g. happy) social events.

Developmental neuroimaging studies have suggested that the transition from an egoistic form of empathy in young children to a more reciprocal concern for other people in adulthood (Hoffman, 1990; Nakao & Itakura, 2009) is driven by the development of brain areas which support mentalizing (Decety & Svetlova, 2012; Nelson, Leibenluft, McClure, & Pine, 2005). For example, it was previously shown that bilateral TPJ was more active in response to different mental states in adults compared to children (Gweon, Dodell-Feder, Bedny, & Saxe, 2012; Saxe, Whitfield-Gabrieli, Pelphrey, & Scholz, 2009). In addition, several studies showed that during adolescence this network of mentalizing areas (TPJ, STS, mPFC) becomes increasingly active when reasoning about complex social emotions (Burnett & Blakemore, 2009b) or incorporating intentionality of others into decision making (Güroğlu, Van den Bos, van Dijk, Rombouts, & Crone, 2011; Van den Bos, McClure, Harris, & Fiske, 2007). These studies lead to the hypothesis that brain regions associated with empathy-related mentalizing develop during adolescence. Given that cognitive empathic skills increase during adolescence (Van der Graaff et al., 2014), an important question concerns whether individual differences in empathic ability predict neural activity associated with empathy-related mentalizing.

In the present study we examined neural responses in adolescence when viewing pictures of negative and positive social situations and how these responses relate to self-reported levels of empathy. We were specifically interested in neural responses when viewing negative social situations in which a person intentionally inflicts pain on someone else (attention directed to either the victim or the offender) and positive social situations (attention directed to one of the happy people). Using this manipulation, we tested whether regions in the mentalizing network (TPJ, STS, mPFC), that are known to develop during adolescence, were differentially sensitive to the perception of negative or positive social situations. It is currently unknown whether higher levels of empathy are related to enhanced activity in the mentalizing brain areas such as the mPFC, TPJ, STS and IPS due to increased mentalizing capacities (i.e. related to a higher degree of 'feeling' for the other) or due to a better ability to downregulate empathic responses (i.e. related to better self-other differentiation and regulation).

Following Decety et al. (2012), we tested whether participants differentiated between the agents in harmful and positive social events by examining subsequent punishing behavior. Decety et al. (2012) previously examined punishment behavior of children, adolescents and adults (4–37 year olds) after observing harmful events. They found milder punishment with increasing age of agents who intentionally harmed a person. Based on these findings, participants played a hypothetical dictator game after observing harmful acts. The dictator game involves transfer to or sharing of money with others. Specifically, participants played dictator games with agents who harmed others, were being harmed, or were present in a positive social event. We predicted that less money would be allocated to offenders compared to victims or people in a positive social situation (Decety, Michalska, & Kinzler, 2012). This manipulation was used to validate that participants differentiated between social conditions.

6.2 METHODS

PARTICIPANTS

In total, 37 right-handed and typically developing adolescents between the ages of 12 and 19 years old participated (Mean age = 15.5, SD = 2.09, 14 males

and 23 females). Initially, we contacted 50 participants who were in the database for individuals who expressed willingness to participate in research; 13 of these participants could not participate due to braces, a clinical diagnosis or because they did not respond to our calls and/or e-mails. From the 37 participants who participated in the scanning session, we excluded data from 5 participants due to movement (> 3 mm, $n = 4$) or incomplete data ($n = 1$); this resulted in a final sample size of 32 participants. Participants were recruited from different secondary schools and through our subject recruitment database. Parents of adolescents under 18 years of age and participants over 18 were asked to give written consent. After participation, participants received a monetary incentive. The institutional review board of the university medical center approved all procedures before the start of the study.

EXPERIMENTAL TASK: EMPATHY-DICTATOR GAME

Participants performed an empathy-dictator game (EDG), in which they were presented with social situations involving individuals involved in a negative or a positive social situation. Following Decety et al. (2012), we tested whether participants differentiated between the agents in negative and positive social situations by examining subsequent punishing behavior. After viewing each situation, they were asked to distribute coins between themselves and another person depicted in the social situation. In a dictator game, the participant decides how to divide a certain stake (e.g. coins) between themselves and another player, thereby making a balance between concern for one's own gain and concern for others. The current study used a modified dictator game that allowed us to examine whether participants differentiated between victims and offenders in their evaluation of harmful acts. In the current version of this coin distribution game the participants were given four fixed distributions of coins as options where they could choose from rather than allowing them to make a choice of 1–10 coins. We predicted that less money would be allocated to offenders compared to victims or persons in positive situations (Decety, Michalska, & Kinzler, 2012).

The social situations showed either negative social situations (involving inflicting intentional harm on another person) or positive social situations. In the harmful social situations, participants were asked to either focus on the offender or on the victim. Thus, three conditions were created (negative offender, negative victim, positive happy person). Each condition consisted of 15 stimuli

and these were presented in a random order. Fifteen adults, who were asked to score the different situations on how harmful they were, validated the 45 stimuli beforehand. Each situation contained at least 2 people of the same age group as the participant. A brief sentence describing the event was shown on the screen below the picture. The person with whom the participant was asked to share coins was indicated with an arrow pointing to him/her. Even though there were only positive social interactions in the positive condition, an arrow was inserted also in these conditions, pointing at 1 of the individuals in the picture in order to balance processing demands related to the arrow. In short, the person indicated by the arrow was either a victim, an offender or a person with positive affect (Figure 6.1).

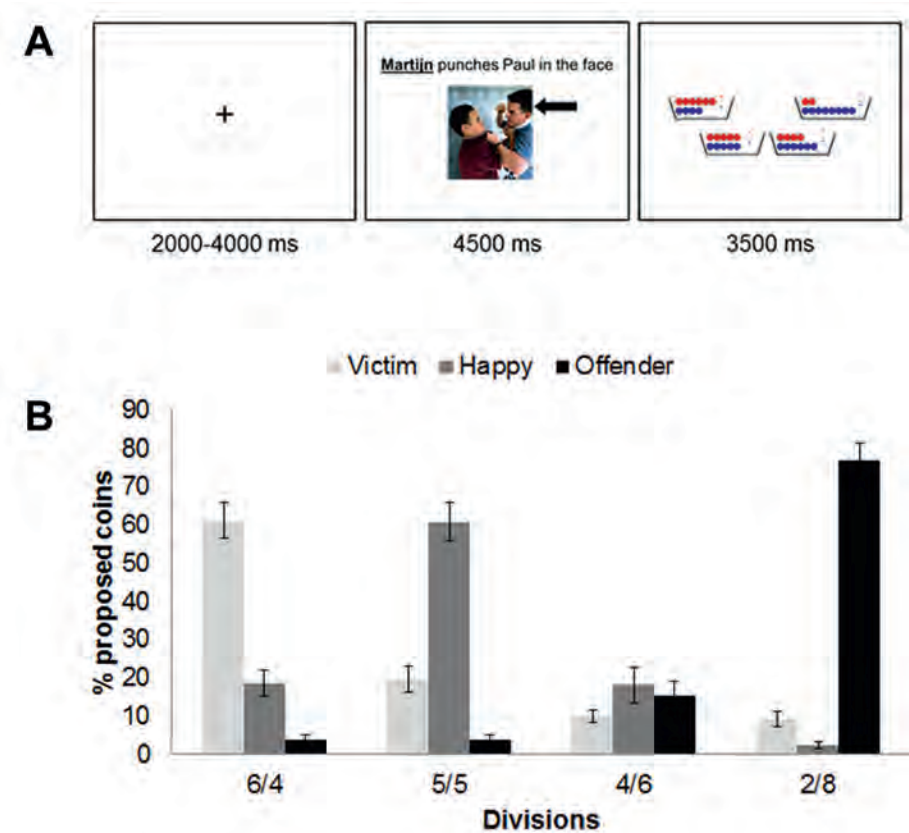


FIGURE 6.1 | Task display. Each trial consisted of a stimulus presented for 4.5 s followed by a dictator screen presented for 3.5 s. The stimulus could be a harmful act by an offender, a harmful act to a victim or a positive stimulus. The dictator game requires an allocation choice out of 4 options (see text for explanation). b Percentage allocated coins to an offender, a victim or a positive person.

Prior to the presentation of each stimulus, a jittered fixation-cross appeared for a duration between 2,000 and 4,000 ms. Subsequently, the stimulus was presented for 4,500 ms. After the stimulus, a selection screen was shown with four options to divide coins: a prosocial offer (6/4; 6 coins for the other and 4 coins for the participant), an equal offer (5/5), an offer that is slightly more advantageous for the participant (4/6) and an unfair offer (2/8). This screen was presented for 3,500 ms, during which the response was made. In case participants did not respond within this time window, a screen with the message 'Too late' was displayed. This occurred in less than 2% of the trials, which were further discarded from the analyses.

BEHAVIORAL MEASURES: THE EMPATHY QUESTIONNAIRE

Participants completed 18 items of the Empathy Questionnaire (EmQue-CA; Pouw et al., 2013), a self-report with three scales: contagion (7 items), which refers to affective empathy (e.g. When a friend is upset, I feel upset too), understanding (5 items), which reflects cognitive empathy (e.g. When a friend is angry, I tend to know why) and support (6 items), which reflects the tendency to act prosocially (e.g. If a friend is sad, I want to do something to make it better). Answers could be given on a 3-point scale: 1) not true, 2) sometimes true and 3) often true. All 18 questions were formulated positively, with higher scores reflecting higher empathic abilities. Mean scores were computed and used for the analyses (minimum score = 1, maximum score = 3). Scores on all three scales were normally distributed, with skewness as follows: .27 (SE = .414) for contagion, -1.02 (SE = .414), for understanding, 1.02 (SE = .414) and -1.93 (SE = .414) for support. Cronbach's alphas of the three scales of the EmQue-CA. were as follows: contagion: .73, understanding: .64, and support: .75.

FMRI DATA ACQUISITION

E-prime software (Psychology Software Tools, Inc., Pittsburgh, Pa., USA) and a rear projection system were used for the stimuli presentation. Scanning was performed using a 3-tesla Philips Achieva scanner at the Leiden University Medical Center. Functional data were acquired using T2 * -weighted echo-planar images (TR = 2.2 s, TE = 30 ms, slice-matrix = 80 × 80, FOV = 220, 35 transverse slices of 2.75 mm with 0.28-mm gap) during one functional run of 259 volumes. The first 2 volumes of this run were discarded to allow for equilibration of T1 saturation effects. After the functional scanning,

high-resolution T2 * -weighted images and high-resolution T1 anatomical images were obtained.

FMRI DATA ANALYSIS

Image processing was carried out with SPM8 (Wellcome Department of Cognitive Neurology, London, UK). For each participant, the T1-weighted image was segmented and spatially normalized using the default parameters. The fMRI data were corrected for motion, co-registered with the T1 anatomical image and normalized to a T1 template. Templates were based on the MNI305 stereotaxic space (Cocosco, Kollokian, Kwam, & Evans, 1997). The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions, and resampled the volumes to 3-mm cubic voxels. Data were then spatially smoothed with an 8-mm FWHM isotropic gaussian kernel. Due to excessive head movement, 4 participants were excluded. The remaining participants did not exceed 1 voxel (<3 mm) in any direction for any scan. Mean and maximum head movement was 0.1 and 2.91 mm. Images were corrected for differences in timing of slice acquisition, followed by rigid body motion correction.

Statistical analyses were performed on group data using a random-effects model using one-sample *t* tests. The fMRI time series data were modeled by a series of events convolved with a canonical hemodynamic response function. The modeled events based on correctly performed trials were used as covariates of interest in a general linear model along with a basic set of cosine functions that high-pass filtered the data. The least-squares parameter estimates of height of the best-fitting canonical hemodynamic response function for each condition were used in pair-wise contrasts. The presentation of the social situation and the presentation of the decision screen were modeled as zero-duration impulse functions. Trials on which participants did not respond within the 3,500-ms time frame (i.e. too late screen) were not included in the contrasts of interest. The first-level analyses were group averaged at the second level and further analyzed using one-sample *t* tests. Activation related to processing negative and positive social situations were examined by contrasting negative social situation > positive social situations and vice versa. Activation related to empathy for processing of harmful acts was examined by focusing on two contrasts: trials where the arrow pointed at the offender versus positive situations (offender > positive) and trials where the

arrow pointed at the victim versus positive situations (victim > positive). To test for differences in neural responses to offenders versus victims, we examined the contrasts offender > victim and victim > offender.

We used the MarsBar toolbox in SPM8 (Brett, Anton, Valabregue, & Poline, 2002) to perform region of interest (ROI) analyses to further investigate patterns of activation for the three conditions and to correlate neural activation with the self-report scales for empathy and average prosocial behavior on the empathy-dictator game. ROIs were defined based on functional masks of the whole-brain analyses (FWE corrected, $p < .05$, at least 10 contiguous voxels) and were averaged across all the voxels in the cluster, resulting in a mean value per ROI for each condition for each participant. All brain coordinates are reported in MNI atlas space.

6.3 RESULTS

SELF-REPORTED EMPATHY

Mean scores on the scales of the EmQue-CA are: contagion: 2.21 (SD = .41), understanding: 2.54 (SD = .36), and support: 2.58 (SD = .42).

EMPATHY-DICTATOR GAME

As can be seen in figure 6.1B, participants differentiated between the offender, the victim and the person in the positive situations in their allocation of coins. The 3 (person) $\times$ 4 (choice) repeated-measures ANOVA resulted in the expected person $\times$ choice interaction ($F_{1, 32} = 366.85, p < .001; \eta^2 = .92$). The most frequent allocation for the positive person was an equal (5/5) distribution of coins (Mean = 60.85%), whereas the most frequent allocation for the victim was a prosocial (6/4) distribution (Mean = 61.18%) and an unequal (2/8) distribution for the offender (Mean = 77.07%). These findings confirm that participants clearly differentiated between the different conditions.

FMRI RESULTS: WHOLE-BRAIN CONTRASTS

We first examined the contrasts offender > victim and victim > offender in order to investigate differences in neural activation when focusing on offenders versus victims in observing a social situation. These contrasts yielded no differences in neural activation, thus these two conditions were combined as a 'negative situation' condition.

Next we examined the negative situation > positive situation and the reversed contrasts. The negative situation > positive situation contrast resulted in more activation in the right STS (RSTS: 51, -57, 6), the left STS (LSTS: -51, -60, 6), the right inferior parietal lobule (RIPL: 63, -30, 33) and the left inferior parietal lobule (LIPL: -57, -33, 24) when observing negative acts (Figure 6.2). The reverse contrast of positive situation > negative situation resulted in increased activation in the mPFC (-3, 57, 3) and left TPJ (LTPJ: -42, -69, 30; Fig. 6.3). The coordinates of all peak activations in both contrasts are reported in table 6.1.

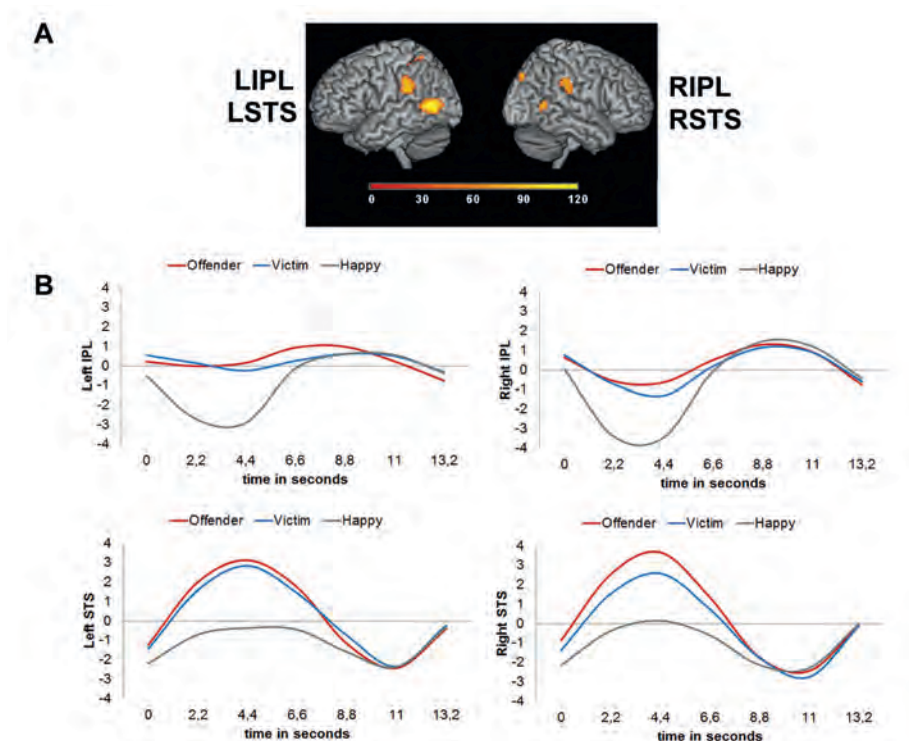


FIGURE 6.2 | Neural responses in the contrast negative situation > positive situation showing activation in bilateral IPL and bilateral STS (FWE corrected at $p < .05$, at least 10 contiguous voxels). b Time series for bilateral IPL and bilateral STS. The colored horizontal bar represents the t values. For the coordinates, cluster sizes and statistical values for each active cluster we refer to table 6.1. The time series are presented in TRs of 2.2 s, where 0 marks the onset of the stimulus presentation. Note that the activation pattern in IPL is showing deactivation at the onset of stimulus presentation, which is not uncommon for social mentalizing areas [16, 27]. LSTS = Left superior temporal sulcus; RSTS = right superior temporal sulcus.

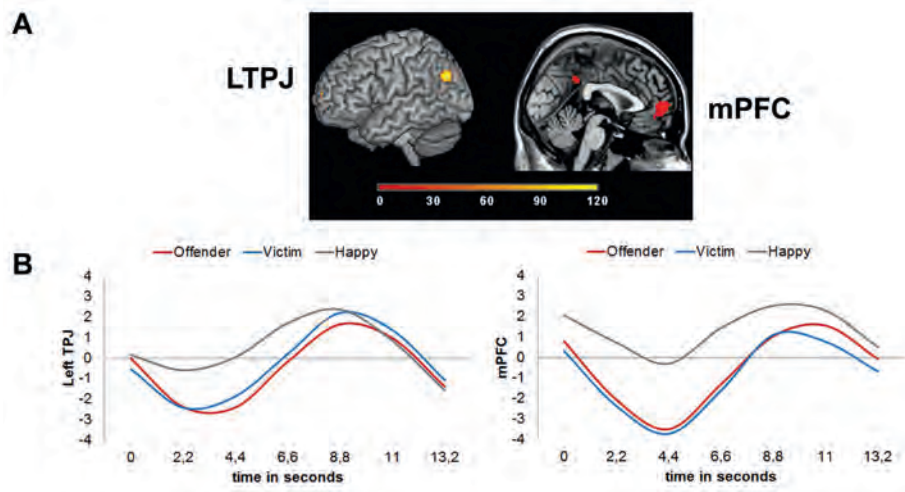


FIGURE 6.3 | (A) Neural responses in the contrast positive situation > negative situation showing activation in the mPFC and LTPJ (FWE corrected at $p < .05$, at least 10 contiguous voxels). (B) Time series for vmPFC and LTPJ. The colored horizontal bar represents the t values. For the coordinates, cluster sizes and statistical values for each active cluster we refer to table 6.1. The time series are presented in TRs of 2.2. s, where 0 marks the onset of the stimulus presentation. Note that the activation pattern in vmPFC and TPJ is showing deactivation at the onset of stimulus presentation, which is not uncommon for social mentalizing areas [27]. LTPJ = Left temporal parietal junction.

TABLE 6.1 | All brain coordinates based on the whole brain contrasts negative situation > positive situation and positive situation > negative situation (FWE corrected, $< .05$; 10 contiguous voxels).

Contrast	Region	MNI (x, y, z) coordinates	Z-value	Volume ¹ (=k _e value in SPM)
All participants: negative > positive				
	L Superior Temporal Sulcus	-51, -60, 6	6.96	213
	R Superior Temporal Sulcus	51, -57, 6	5.66	23
	L Inferior Parietal Lobule	-57, -33, 24	6.14	91
	R Inferior Parietal Lobule	63, -30, 33	5.58	28
	Precuneus	24, -81, 39	5.93	19
All participants: positive > negative				
	Medial Prefrontal Cortex	-3, 57, 3	5.81	100
	L Temporal Parietal Junction	-42, -69, 30	5.64	33
	Hippocampus	-24, -21, -18	5.68	11
	Cingulate Gyrus	0, -45, 36	5.58	34

FMRI RESULTS: CONNECTION BEHAVIOR AND NEURAL ACTIVATION

To test whether there was a relationship between neural activity for negative situation > positive situation to subsequent behavior in the dictator game, an average prosocial offer score (positive outcome for responder) was created by averaging across the percentage chosen 6/4 and 5/5 divisions for each condition (offender, victim, happy person) separately. Subsequently, a correlation analysis with neural activity in the four ROIs extracted from the contrast negative situation > positive situation (LSTS, RSTS, LIPL, RIPL) and average prosocial offer scores, separately for each condition (offender, victim, happy person), showed that the R was negatively related to subsequent prosocial scores when dividing coins with offenders ($r = -.35$, $p < .05$, not Bonferroni corrected). Thus, more RIPL activity was associated with less prosocial and more punishing behavior. The other correlations were not significant.

Similar correlation analyses with neural activity in the two ROIs extracted from the contrast positive situation > negative situation (mPFC, LTPJ) and average prosocial and antisocial offer scores showed no relationship between the frequency of prosocial or antisocial offers and neural activity in mPFC or LTPJ.

FMRI RESULTS: SELF-REPORTED EMPATHY ANALYSIS

Next we examined the relation between neural activation in the same ROIs extracted from the whole-brain analyses (bilateral STS, bilateral IPL, mPFC, LTPJ) and empathy. For this purpose, we performed correlation analyses between the difference scores for the negative situation > positive situation and scores on the empathy scales. There was a negative correlation between neural activation in LSTS (for negative situation > positive situation) with empathic understanding ($r = -.40$, $p < .05$) and support ($r = -.47$, $p < .01$), but not for contagion. Thus, adolescents who reported a better understanding of others' distress and who were more willing to help showed less activation in the LSTS during negative social interactions (involving intentional harm), whereas adolescents who reported lower levels of understanding and support showed more activation in LSTS for negative social interactions (Figure 6.4). There were no other correlations found. See table 6.2 for correlations among the three scales.

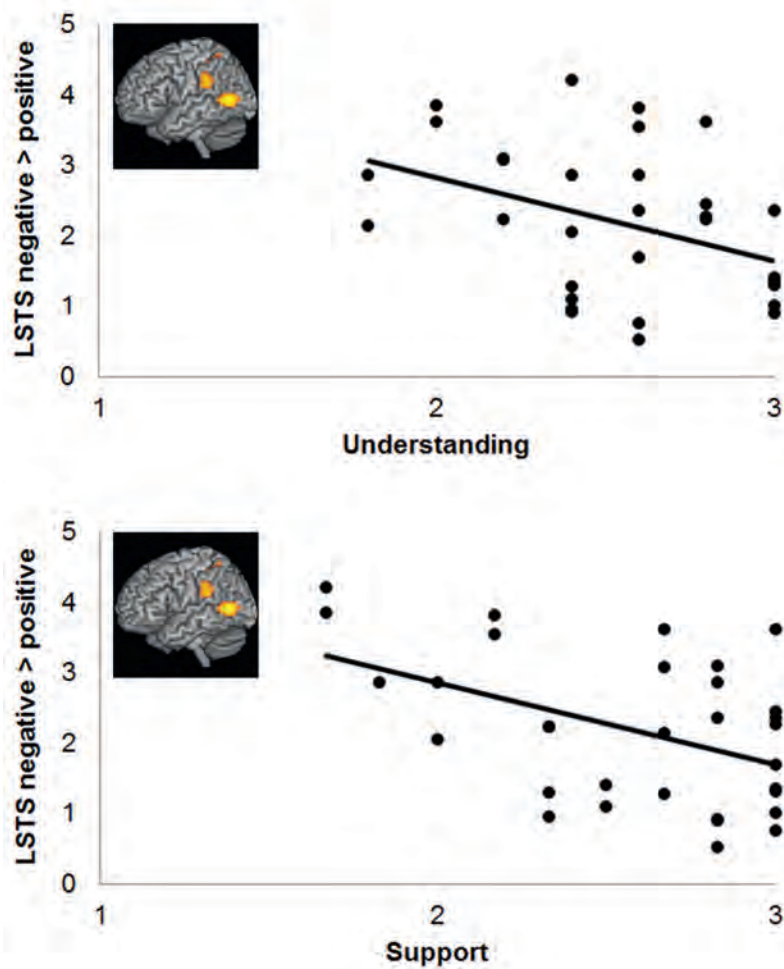


FIGURE 6.4 | Correlation between neural activation in LSTS for ROI values in the contrast negative situation > positive situation and self-reported empathic support and understanding – ROI based on whole-brain analyses for the main contrast negative situation > positive situation (FWE 0.05 corrected, at least contiguous 10 voxels; coordinates $x = -51$, $y = -60$, $z = 6$; see table 6.1). LSTS = Left superior temporal sulcus.

TABLE 6.2 | Correlations between the six task related ROIs and the scales of the Empathic Concern Questionnaire (ECQ), and age. * < .05, ** < .001

	RSTS	LIPL	RIPL	mPFC	LTPJ	Contagion	Understanding	Support	Age
Negative > positive									
LSTS	.64**	.48**	-.62	-.16	.60**	-.08	-.40*	-.47**	-.21
RSTS		.39**	.39*	-.31	-.20	-.11	-.17	-.17	-.34
LIPL			.82**	-.40	-.09	-.31	-.34	-.29	-.13
RIPL				-.20	.06	-.13	-.18	-.18	-.16
Positive > negative									
mPFC					.60**	-.13	-.07	-.18	.34
LTPJ						-.13	-.15	-.00	.11
ECQ							.35	.52**	-.22
Contagion								.48**	-.19
Understanding									-.27
Support									

6.4 DISCUSSION

In the current study we investigated neural activation in response to viewing negative and positive social situations during adolescence. Specifically, we tested which neural regions were sensitive to witnessing harmful acts and how these patterns of brain activity were related to social behavior and self-reports of empathy. The behavioral results showed that participants treated others differentially during the empathy-dictator game depending on the preceding social behavior of the person: they acted more prosocially toward victims, more punishingly toward offenders and more fairly toward persons involved in positive social situations. These behavioral findings indicate that empathy in the evaluation of negative social situations, involving intentionally harmful acts and harmed victims, is present in adolescents (Decety, Michalska, & Kinzler, 2012; Vaish, Carpenter, & Tomasello, 2009; Zelazo, Helwig, & Lau, 1996).

Brain regions in the mentalizing network (TPJ, STS, mPFC) were examined to determine whether they were more active when observing negative (harmful) relative to positive social situations. The imaging findings showed that stimuli depicting victims and offenders were both associated with stronger activation in bilateral STS and IPL. These findings are consistent with prior studies showing that these regions are involved in predicting intentional behavior, perspective taking and mentalizing (Bruneau, Pluta, & Saxe, 2012; Danziger, Faillenot, & Peyron, 2009; van der Heiden et al., 2013). The STS has not been consistently found in all studies that showed physically painful situations (Jackson, Brunet, Meltzoff, & Decety, 2006; Jackson, Meltzoff, & Decety, 2005; Lamm, Decety, & Singer, 2011). Possibly, this region is sensitive to the context in which the harm-inflicting acts occur, as Kramer et al. (2010) found that only in the case of dyadic interactions (as in the current study) increased STS activation was found. In the current study we draw attention to the actors in the situation by pointing an arrow and giving a short written explanation, which may have resulted in more mentalizing in social interactions involving intentional harm.

In order to investigate possible individual differences in neural responses to harmed (victims) or harming people (offenders) in the time span of adolescence, we related neural activation to individual differences in empathic traits. We focused on the domains of empathy: contagion (affective empathy), understanding (cognitive empathy) and support (tendency to act prosocial) as distinct predictors of empathy on neural activity. We found a negative correlation

of LSTS activity when adolescents were looking at harmful acts and self-reports of empathic understanding and support. The higher the understanding- and support-related empathy skills the less STS activity – previously been shown to be involved in social perception (Gallagher & Frith, 2003). This finding is consistent with previous work showing the involvement of the STS when taking ‘other perspective’ versus ‘self-perspective’ (van der Heiden et al., 2013). It is possible that adolescents with lower empathy skills are more involved in their own perception than in the other. The RIPL showed a similar effect, that is to say, more IPL activity when observing offenders was associated with less prosocial, more punishing, behavior, although this effect was weaker than the STS effect and did not survive correction for multiple comparisons. Taking these results together, the current results suggests that STS (and IPL) may be more involved in thinking about intentions when observing harmful acts and this effect is stronger in adolescents who report lower understanding and support (Ruby & Decety, 2004). In future research, it will be interesting to test these questions using connectivity analyses, as these analyses give information about communication between brain regions.

The reversed contrast of positive versus negative situations resulted in an increase in hemodynamic activity in the mPFC and LTPJ. This effect is consistent with a previous study of Morelli et al. (2012), in which they found similar regional activity in adults when observing pictures of happy people relative to neutral pictures. Morelli et al. (2012) argued that individuals interpret physical pain by watching a person harming another, whereas situations with a more positive valence require evaluating the situation as a whole. Others have suggested that the ventral mPFC (vmPFC) tracks reward more generally based on social emotional stimuli (Winecoff et al., 2013). Although the current results are in line with these previous findings, vmPFC activation has also been found when adults observed pictures of intentionally negative acts (Decety, Michalska, & Kinzler, 2012). However, the paradigm used in these prior studies (Decety, Michalska, & Kinzler, 2012) contained pictures of only body parts without showing faces. Even though this effect was reported for negative situations, these stimuli could still make an appeal on the abilities to judge and evaluate a social situation (Morelli, Rameson, & Lieberman, 2012). Therefore, future studies are needed to clarify the role mPFC and TPJ play in evaluating social stimuli.

Contrary to prior studies, there was no consistent activation in the anterior cingulate cortex (ACC), insula and amygdala when observing harmful situations. ACC activation is often linked to affective rather than cognitive empathy (sympathizing with someone's pain and experiencing the pain yourself; Singer, Critchley, & Preuschoff, 2009; Singer et al., 2004). One possibility is that playing the dictator game after each social situation caused participants to predecide while observing the social acts rather than only experiencing the primary impact of observing pain. Alternatively, this outcome could be explained by the stimuli used in the current study. The negative stimuli depict an intention for a harmful social act, whereas previous studies focused on the mirror system for experiencing pain and empathizing with pain experienced by another (Lamm, Decety, & Singer, 2011). Future studies should focus on the role of the ACC in affective and cognitive components of empathy.

Some limitations of this study deserve further attention. First, the adolescents clearly differentiated in their sharing treatment of others depending on whether the other was a victim, an offender or a person involved in a positive social situation, and this behavior was consistent across trials. A disadvantage was that therefore it was not possible to compare social and antisocial responses following observation of the same social interactions (e.g. participants almost always punished offenders, therefore we could not investigate neural responses to treating the offender fairly). In addition, given that we used restricted choice options, the positive options (6/4 and 5/5) were less generous than the negative options (4/6 and 2/8), which could have primed participants to make more greedy choices. Second, the sample size was relatively small with an unequal division between boys and girls, which impacted our power to investigate the unique contribution of gender to empathic abilities. Considering developmental trajectories of girls (13–18 years old) scoring high on both affective and cognitive empathy (Van der Graaff et al., 2014), it would be interesting for future research to investigate to what extent empathic abilities are mediated by gender differences. Furthermore, it would be interesting to investigate the predictive role of age in combination with specific, context-dependent and individual empathic abilities for prosocial behavior. In order to detect age-related changes, future longitudinal studies should examine whether these relations are based on trait versus state characteristics and their stability patterns across adolescence (Lindenberger, von Oertzen, Ghisletta, & Hertzog, 2011).

Taken together, our findings highlight the involvement of social brain networks when observing negative (IPL and STS) and positive social situations (mPFC and TPJ) during adolescence. The neural correlates of empathy are important for understanding the mechanisms underlying the development of social behavior during this period (Rameson, Morelli, & Lieberman, 2011). Our findings emphasize an important role of individual differences in empathy at the social and neural levels of social cognition. Clearly, future studies that examine the impact of accidental harmful acts (Akitsuki & Decety, 2009; Decety & Michalska, 2010; Decety, Michalska, & Akitsuki, 2008), gossiping or social exclusion (Masten, Morelli, & Eisenberger, 2011) may further our understanding of empathy and social pain. The current study provides a first step in this direction.

6.5 SUPPLEMENTARY MATERIAL

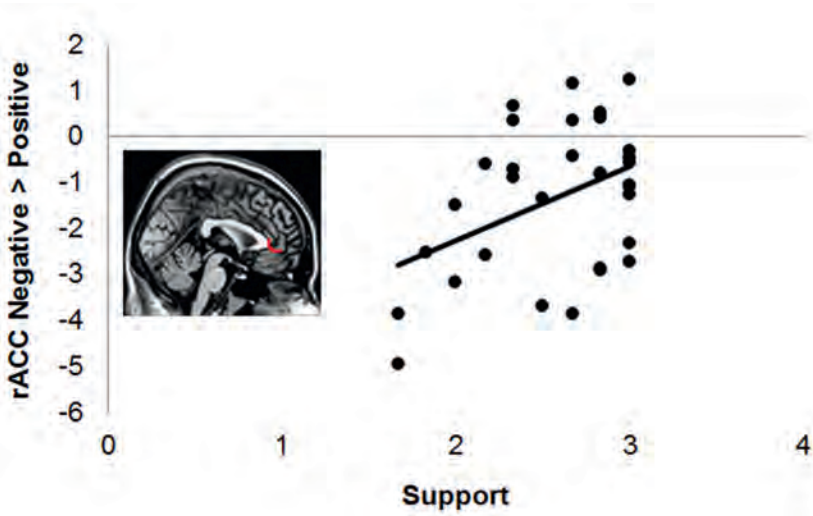


FIGURE S6.1 | Neural activation in the rostral ACC (3, 45, -3, 17 voxels, $Z = 3.84$) in the contrast negative situation > positive situation with the support subscale as regressor ($< .001$ uncorrected, at least 10 contiguous voxels). No other clusters were detected for this contrast.

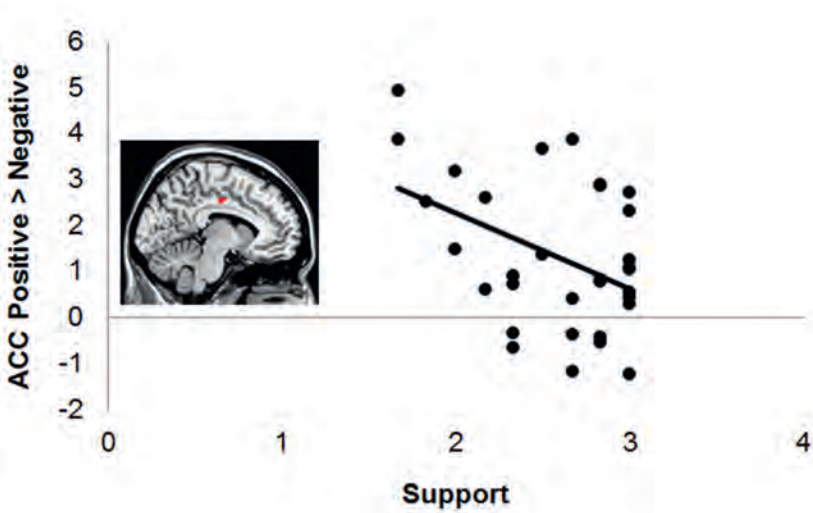


FIGURE S6.2 | Neural activation in the dorsal ACC (-9, -12, 42, 10 voxels, $Z = 3.55$) in the contrast positive situation > negative situation with the support subscale as regressor ($< .001$ uncorrected, at least 10 contiguous voxels). No other clusters were detected for this contrast.





Chapter 7:

Summary & Discussion

7.1 ADOLESCENCE AS AN IMPORTANT PERIOD FOR GAINING MATURE SOCIAL GOALS

The general aim of this dissertation was to investigate developmental changes and individual differences in social reorientation during adolescence on a behavioral and neural level, with a specific focus on empathy. More specifically, the studies described in this dissertation focused on: stability, change, and individual differences in the neural correlates of reading the mind in the eyes in a longitudinal sample (10–19 year olds) (Chapter 2), stability, change, and individual differences in reward processing in a longitudinal sample (10–25 year olds) (Chapter 3), the self-report assessment of empathy in adolescence in relation to social interactions with peers (10–15 year olds) (Chapter 4), empathic concern in the behavioral evaluation of fairness (8–13 year olds and 18–25 year olds) (Chapter 5), and neural correlates of empathic concern in the evaluation of positive and negative social interactions (12–19 year olds) (Chapter 6).

The studies in this thesis were inspired by research showing that during adolescence social reorientation takes place, which enhances the importance of social skills as social networks with peers become central elements in the adolescent's life. The key question of this dissertation is: how social decision-making processes of adolescents are related to developmental changes and/or on individual differences in empathic concern.

7.2 NEURODEVELOPMENTAL CHANGES IN READING MENTAL STATES AND IN RISK-TAKING: A LONGITUDINAL APPROACH

Over the last decennia, fMRI research has been performed in order to unravel the complex functions of the brain and to get a more profound understanding of the development of specific brain regions, their connectivity, and their relationship with for example hormonal changes. Some researchers have classified the brain by nodes (detection node, affective node, and cognitive-regulatory node) to describe how brain regions are involved in and interact during social information processing (Nelson, Leibenluft, McClure, & Pine, 2005). Other theories have made distinctions between cognitive and affective systems (purportedly cortically and subcortically regulated) to indicate how the development of

specific regions are involved in adequate or non-adequate social-emotional functioning (Ernst & Fudge, 2009; Somerville, Jones, & Casey, 2010; Steinberg et al., 2008). Decety and Meyer (2008) proposed the involvement of biological processes (MNS) in the perception of actions, and how this relates to processing information about emotions of self, versus emotions of others (Decety & Meyer, 2008). These neurodevelopmental theories were the starting points for examining developmental changes and individual differences in social reorientation and the role of empathy.

The study in Chapter 2 described a longitudinal study (two-years interval) on mentalizing (i.e. reasoning about mental states of others; Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997). In this study, adolescents performed the Reading the Mind in the Eyes task in which they were asked to indicate the mental state of the person presented in the picture, in which only the eye region of faces was shown (mental state condition). The control condition that was included in the RMET contained the same pictures as in the mental state condition, though in the control condition participants were asked to indicate gender (man or woman) and age (younger than 60 or older than 60) based on the following choice options: younger male, younger female, older male, and older female.

Behavioral results showed that the percentage correct trials was high in both early adolescents (10–14 years old) and mid-to-late adolescents (15–19 years old), and that the percentage correct trials at the first measurement was correlated with the percentage correct trials at the second measurement. This indicates that from the age of 10, adolescents are already able to read mental states of others based on only the eye region of faces, and that individuals who performed well at the first time point also performed well at the second time point two years later. Mentalizing is a higher order form of Theory of Mind and helps in predicting goal directed behavior of others by taking the perspective of others and by reasoning about their mental state. Since predicting intentional behavior of others helps in understanding a social situation, it could also help in social interactions with peers. Therefore, it would be interesting to test in future research whether high performers on the RMET (high percentage correct trials in the mental state condition), report higher quality of friendships and have higher popularity ratings according to peers.

On a neural level, the longitudinal study on reading the mind in the eyes demonstrated activity in bilateral superior temporal sulcus (STS), bilateral

inferior frontal gyrus (IFG), bilateral temporal pole, and dorsal medial prefrontal cortex (dmPFC) for the whole brain contrast (mental state versus control). These regions are part of both the detection node (STS, temporal poles, IFG), and the cognitive-regulation node (dmPFC) of the SIPN model (Nelson, Leibenluft, McClure, & Pine, 2005). Of these areas, the right STS and the right IFG showed stability within individuals over time. The right STS only showed stability in the mental state condition, whereas the right IFG showed stability for both the mental state and the control condition. This indicates that the regions important for detecting emotions from the eyes are relatively stable within adolescents, which is in line with performance on the task at both time points. Yet, although the right IFG showed stability over time, an age-related decrease was found as well.

In the dmPFC, a quadratic as well as a linear decrease age-effect was found for mental state reasoning. These findings suggest that the activity patterns of the two regions in the PFC (right IFG and dmPFC), which are important role in mentalizing, change over time. The ongoing maturation of this area in combination with gaining experience and becoming an independent adult could indicate a possible strategy shift in how adolescents read mental states.

The ventral striatum (VS) is part of the affective node of the Social Information Processing model (Nelson, Leibenluft, McClure, & Pine, 2005), which is often involved in processing rewards. Besides the involvement of the VS in receiving rewards, the VS is also involved when taking risks in the presence of peers and during positive social interactions (Cheng, Chen, Lin, Chou, & Decety, 2010; Chein et al., 2010; Guyer et al., 2008).

In the study presented in Chapter 3, participants played a gambling task presented as a slot machine. The paradigm consisted of 2 conditions: a high-risk condition (a winning chance of 66%), and a low-risk condition (a winning chance of 33%). On each trial, the participant had the option to play (chance of winning or losing 10 Eurocents) and to pass (no gain or loss). On a behavioral level, both the cross-sectional and the longitudinal study showed that all individuals took more risks in the low-risk than the high risk condition, but age, puberty (Petersen, Crockett, Richards, & Boxer, 1988), and scores on the BAS scales (Drive, Fun-seeking, and Reward-responsiveness; Carver & White, 1994) were not related to risk-taking behavior as measured by the amount of 'play'-decisions.

On a neural level, both the cross-sectional and the longitudinal study described in Chapter 3 underlined the involvement of the VS in response to rewards, together with medial prefrontal cortex (mPFC) activity. For the reversed contrast (loss versus gain) no activity was shown. In contrast to what was hypothesized beforehand, no peak in VS activation was found around mid-adolescence (Casey, Getz, & Galván, 2008; Giedd et al., 1999; Gogtay et al., 2004; Paus, 2005; Sowell et al., 2003; Steinberg, 2008; Steinberg, 2010). Although previous research on the dual systems model described that mid-adolescence is a representative period during which most risk-taking and sensation-seeking behavior is most prominently present, some contradictory findings have been reported as well (Willoughby, Good, Adachi, Hamza, & Tavernier, 2013). For example, some studies showed that risk-taking behavior increases linearly during adolescence instead of peaking around mid-adolescence (Hooshmand, Willoughby, & Good, 2012). In addition, peaks in risk-taking can occur later than during mid-adolescence, for example, substance use has been found to increase when adolescents are around 17/18 years old. Hooshmand and colleagues (2012) explained this high level of risk-taking in late adolescents, by the fact that it is legal to buy alcohol from the age of 18, which increases the opportunity to drink alcohol. Additionally, the transition to College/University can stimulate the alcohol use since drinking is socially accepted at Colleges and Universities and an easy way to meet new people and bond with them (Connor, Psutka, Cousins, Gray, & Kypri, 2013). However, others have found that pubertal development is an important predictor for initiating alcohol use, which is often interpreted as a biological influence on risk-taking behavior (De Water, Braams, Crone, & Peper, 2013). Thus, more longitudinal research with larger samples is necessary to examine the separate influences of biological and environmental factors in risk-taking behavior and neural responses to risk and reward.

Interestingly, risk-taking behavior as measured by choosing to play in both high-risk and low-risk trials was positively related to activation in the VS and the mPFC (gain versus loss). The propensity to play was also related to increased connectivity between the left VS and the right anterior insula (AI). Furthermore, there was a relationship between VS activation and self-reported fun seeking. Increased activation in the VS was positively related to high scores on the fun seeking scale of the BAS, which indicates that processing gain or loss is sensitive to individual differences. This finding was reinforced by the longitudinal comparison, which showed that changes in fun-seeking

scores were correlated with change in brain activation. In other words, those adolescents who showed an increase in fun seeking over time also showed an increase in VS activation over time. Moreover, those adolescents who showed a decrease in fun seeking over time also showed a decrease in VS activation over time. Together, these results highlight that the affective node of the SIPN model is sensitive to individual differences in states. These findings may also indicate why developmental differences are not consistently reported across studies. In some studies, the selected adolescents may have a different high risk-taking propensity in real-life than other adolescents, and this may explain individual differences in VS activation (Galván, Hare, Voss, Glover, & Casey, 2007).

7.3 EMPATHY DEVELOPMENT IN ADOLESCENCE: A MULTI-METHOD APPROACH

Empathic abilities have been measured in multiple ways, for example by observational research (Ketelaar, Rieffe, Wiefferink, & Frijns, 2013), behavioral tasks (e.g. bargaining games) (Van Dijk & Vermunt, 2000), and questionnaires (Baron-Cohen & Wheelwright, 2004; Davis, 1980; Hawk et al., 2013). Yet, there are still controversies about how empathy should be measured. In Chapter 4, the validation of a new empathy questionnaire was described: the Empathy Questionnaire for children and adolescents (EmQue-CA), which was validated in over a thousand children and adolescents aged 10–15 years old. The EmQue-CA contains three scales: 1) Affective Empathy (which measures the ability to share feelings of others), 2) Cognitive Empathy (which measures the ability to understand the emotional state of others), and 3) Support (which measures the tendency to act prosocially towards others). Factor analyses confirmed that the scales of the EmQue-CA measure three concepts that have found to be important for social cognitive development. High scores on the scales were related positively to high friendship quality, and negatively to bullying behavior. Although the EmQue-CA has proven to be a valid and reliable empathy measurement, this was not the first measurement on empathic abilities (Baron-Cohen & Wheelwright, 2004; Davis, 1980; Jolliffe & Farrington, 2006). The concepts affective and cognitive empathy have been measured before, therefore the EmQue-CA differentiates itself particularly by the inclusion of a scale measuring the tendency to act prosocial (Support).

In Chapter 5, prosocial acts were examined using an experimental approach, that is, by using a bargaining game. The behavioral study described in Chapter 5 examined fairness considerations by using a hidden version of the Ultimatum Game (UG) with varying amounts of coins in children aged 8–13 and adults aged 18–25. The hidden UG game consisted of two conditions: 1) a complete condition, in which all coins were visible to both players (participant is the proposer), 2) a hidden condition, in which one part of the coins was only visible to the proposer (participant) but not to the responder. The hidden condition allowed investigating strategic versus altruistic behavior, i.e. making a truly fair split (altruistic) by offering the hidden coins as well or making a seemingly fair split (strategic) by only offering coins that are visible to the other.

The results described in Chapter 5 showed that already the youngest children (8/9 years old) showed strategic behavior, as they offered fewer coins to the other player in case of a hidden condition compared to the complete condition. Furthermore, there was a general age related increase in offering coins to the other player. However, an age x condition interaction showed that in the complete condition relative to the hidden condition, adults offered more coins than young children (strategic altruistic behavior). These findings are interpreted as a strategic decrease in self-interest during late childhood and into adolescence and adulthood.

This finding could be explained by the development of cognitive empathic abilities. A correlation analysis with self-report empathy showed that perspective taking was related to the amount of coins divided to the other player in the hidden condition, and this cognitive empathy skill mediated the relationship between age and strategic behavior in the hidden condition trials. A prior developmental study also showed that during adolescence individuals become strategically altruistic rather than general altruistic with increasing age, (Meuwese, Crone, Güroğlu, in press), which is consistent with the current findings.

The increase with age in strategic acts toward the other player, could also be explained or at least strengthened by the relationship between the participant and the other player. Previous studies demonstrated that empathy for a stranger is significantly lower than for a friend, which could enhance the strategic acts in the hidden UG described in Chapter 5 as the other player is no acquaintance, friend or family of the participant (Cheng, Chen, Lin, Chou, & Decety, 2010; Meyer et al., 2013). This emphasizes the importance of including

the role of context, especially the relationships with the person(s) in that context as this could be of influence on individuals and their behavior (Güroğlu, Van den Bos, & Crone, 2014).

In Chapter 6, several measurements were combined in a newly developed empathy-dictator game (EDG). This new task had the function to measure the willingness of adolescents to help victims by allocating coins to them at their own expense. The EDG was combined with neural measurements and self-report empathy using the newly developed EmQue-CA.

In the EDG, adolescents (12–19 year olds) were instructed to observe social pictures. In each picture, a social situation was presented: a positive situation containing happy people or a negative situation containing a victim and an offender in which the offender inflicted pain intentionally to the victim. Besides a picture of the situation, a sentence was added for clarification, and an arrow was pointed to one of the persons in the pictures (either a happy person, a victim or an offender). Subsequently, adolescents were asked to divide coins between themselves and the other person (a happy person, a victim or an offender). Adolescents had four options to choose from: 1) a prosocial option (6 for the other person and 4 for the participant), 2) a fair option (fair split), 3) a slightly unfair option (4 for the other person and 6 for the participant), and 4) an unfair option (2 for the other person and 8 for the participant).

The EDG was intended to measure whether the division adolescents selected based on the condition (victim, offender or happy), was dependent on individual differences (i.e. self-reported empathic abilities). As expected, participants offered fair splits (5/5 divisions) to happy people, unfair divisions (2/8) to offenders, and prosocial divisions (6/4) to the victims. However, the results also showed that adolescents did not show variation in their choices, as all adolescents acted prosocially toward victims (6/4 or 5/5 division), fair toward happy people (5/5 division), and punishing toward offenders (4/6 or 2/8 division). This seems to indicate that they were treating each trial within the same condition similarly. All pictures in the negative situations (victim and offender conditions) showed physical pain inflicting situations, though each picture contained different people (adolescents in the same age range as the participants). A possible explanation for the high consistency in chosen divisions for the negative situations could be morality. Morality can be explained as the ability to indicate if something/someone is (acting) fair, justified and in

correspondence to universal social rules. By complying with moral codes, decision-making becomes influenced, as rules about how to behave in social groups become the norm (Decety & Cowell, 2014). The negative social situations could be judged on being morally right or wrong, and depending on the condition (victim or offender) the adolescent could select the most socially accepted division (mostly 6/4 for the victim and 2/8 for the offender). It will be interesting in future research to examine these divisions in adolescents who have difficulty to applying to social norms, such as in adolescents with oppositional behavior or conduct disorder (White, Brislin, Meffert, Sinclair, & Blair, 2013).

The neural activation patterns showed that viewing negative (i.e., harm inflicting) situations was associated with increased activation in the STS and IPL, regions previously associated with detection of important social information. In contrast, viewing positive (i.e., happy) situations was associated with increased activation in the medial PFC and TPJ, regions previously associated with spontaneous mentalizing and perspective taking. Prior studies also reported activation in this same network when individuals were asked to observe or judge a social situation (Van der Heiden et al., 2013). In addition, the findings are also consistent with previous studies investigating moral development (Decety, Michalska, & Akitsuki, 2008), and with studies on mentalizing (Gunther Moor et al., 2012, see also Chapter 2). Considering that the conditions were quite clear as being morally right, neutral or wrong, it is likely that judging whether a social situation is morally right or wrong activates the detection node of the brain, including the bilateral STS and bilateral IPL.

A further goal of this study was to relate these neural patterns to individual differences in self-reported empathy. Therefore, all participants filled in the three subscales of the Empathy Questionnaire for children and adolescents (EmQue-CA): affective empathy (Contagion), cognitive empathy (Understanding), and the tendency to act prosocial (Support) described in Chapter 4. Scores on the EmQue-CA were examined in relation to neural activation in response to negative social situations (bilateral IPL and bilateral STS) and neural activation in response to positive social situations (TPJ and mPFC). The results showed that individual differences in cognitive empathy and tendency to act prosocial were negatively related to activation in the left STS when viewing negative situations. These findings suggest that individuals with high empathy show less activation in the detection node of the brain when

viewing negative social situations. There were no other regions that showed a positive relation with self-report empathy. In a prior study, Molenberghs and colleagues (2014) described a positive relationship between perspective taking and activation in the right STS when punishing in- and out-group members in adults. Therefore, the role of empathic abilities in social interactions should be further investigated in order to understand how individual differences could play a role in social situations. Possibly, the role of empathy is different depending on age; future research should examine individual differences in empathy across different stages of development using various social information processing paradigms.

7.4 CONCLUSIONS, IMPLICATIONS, AND FUTURE DIRECTIONS

In general, this dissertation contributes to a better understanding of stability and change in social reorientation during adolescence with a specific focus on individual differences in empathy. The following section will discuss the future directions based on the strengths and the limitations of the studies in order to further improve our understanding of developmental changes and individual differences in social reorientation and empathic concern and their relation with social behavior from a brain and behavioral perspective.

The first strength of this thesis is the use of longitudinal designs in Chapters 2 and 3. Longitudinal research is an effective method to test for subtle changes in development. By tracking individuals over a longer period of time, the development of social and cognitive abilities can be investigated. This eliminates the possibility that developmental differences that are observed are due to cohort differences, because the same individuals participate at different time points, and it allows for the possibility to test for traits (i.e., behavior and brain responses showing high stability over time) versus states (i.e., behavior and brain responses showing high variability over time). Finally, longitudinal studies allow for the possibility to predict outcomes in behavior based on brain assessment earlier in time (Telzer, Fuligni, Lieberman, & Galván, 2014). However, it should be noted that the studies presented in this thesis are parts of the first set of longitudinal studies using fMRI, the sample sizes are relatively limited and the number of repetitions is limited to two sessions. Future studies

should apply this method in larger samples and follow individuals over longer periods. The studies presented here show feasibility of this approach.

The second strength of this study is the use of multi-method assessments of the same construct. By the combination of experimental tasks, neural measures, and self-report indices it is possible to get a more detailed view of the development of social reorientation. For example, in Chapter 6 a new experimental paradigm was presented, which was developed based on behavioral research (Chapter 5) and a thorough validation of a new questionnaire (Chapter 4). This combination of measurements is expected to provide more insight in commonalities and unique contributions of different measurement methods.

This approach was applied in a relatively restricted age group (12–19 year olds). In future research, it will be important to use these multi-method perspectives in larger samples of various ages. In addition, Future research will benefit from making use of latent class analyses, which can be used to create groups based on specific characteristics that allow us to make predictions. This is especially relevant for an individually varying ability like empathy such as oppositional disorders or conduct disorder (White et al., 2013).

Taken together, this thesis demonstrates that a multi-method approach combining self-report, behavior and neural activation gives new insight in social reorientation in adolescence and the different aspects of empathy. Future research can benefit from the presented studies by applying it to a more detailed analysis of individual differences in this important period in life, which may help to explain why some adolescents are successful in developing social competencies and relationships, whereas others experience difficulties. Eventually, this may lead to the development of interventions for youth who do not cope well with the social requirements from the environments, and help to improve their lives and the lives of the individuals around them.

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Nederlandse samenvatting

Inleiding De adolescentie is een van de belangrijkste overgangsfases in ons leven en wordt gekenmerkt door de vele veranderingen die plaatsvinden op neurale-, hormonaal- en sociaal-emotioneel vlak (Blakemore, 2008; Blakemore, Burnett, & Dahl, 2010). Sociale heroriëntatie is een essentieel onderdeel van deze veranderingen en houdt in dat er een verschuiving plaatsvindt wat betreft de sociale omgeving. Bij de transitie naar de adolescentie nemen leeftijdsgenoten namelijk een steeds prominentere plaats in en verdwijnt de invloed van ouders steeds verder naar de achtergrond (Blakemore & Mills, 2014; Steinberg et al., 2008). Relaties met leeftijdsgenoten worden steeds hechter en er worden vaak nieuwe vriendschappen gevormd, zowel op platonisch als op romantisch vlak (Selman, 1980). Het aangaan van relaties kan zorgen voor een toename in risicogedrag om zo aan de normen van een groep te voldoen, maar het kan ook zorgen voor een toename in zelfvertrouwen door de emotionele wederkerigheid die er ontstaat (Taylor, Barker, Heavey, & McHale, 2013). Deze nieuwe ervaringen gaan hand in hand met de ontwikkeling van zelfbewustzijn, waardoor adolescenten zich steeds meer bewust worden van hun omgeving, hun eigen emoties en het besef dat hun gedrag door leeftijdsgenoten wordt beoordeeld (Somerville & Casey, 2010; Somerville et al., 2013). De transformatie die plaatsvindt tijdens deze roerige periode stelt de adolescent in staat om uit te groeien tot een onafhankelijk en zelfstandig individu (Brown, 2004).

Dit proefschrift heeft als doel om in kaart te brengen welke sociale vaardigheden nodig zijn om het proces van sociale heroriëntatie op een efficiënte wijze te kunnen doorlopen, waarbij de focus ligt op de neurale-, hormonale- en sociaal-emotionele ontwikkeling. Om dit proces te kunnen verklaren wordt in dit proefschrift getracht antwoord te geven op de volgende vragen: 1) hoe ontwikkelen hersengebieden die betrokken zijn bij sociale heroriëntatie gedurende de adolescentie, 2) wat is de rol van individuele verschillen en 3) wat is de rol van hormonale veranderingen.

Het **tweede hoofdstuk** beschrijft een longitudinale studie naar de neurale correlaten betrokken bij het verwerken van sociale informatie. Binnen deze studie is gebruik gemaakt van verschillende methodes waarmee subtiele veranderingen, stabiliteit en individuele verschillen op zowel gedragsmatig als neurale niveau zijn gemeten. De vaardigheid om intenties af te lezen op basis

van iemands emoties speelt een belangrijke rol bij sociale interacties. Op de vraag of dit vermogen al volledig is ontwikkeld tijdens de kindertijd of dat er nog subtiele veranderingen plaatsvinden tijdens de adolescentie kon tot nu toe nog geen antwoord worden gegeven. Met de studie beschreven in hoofdstuk 2 is onderzocht in hoeverre het aflezen van iemands emotie al is ontwikkeld op 10 jarige leeftijd en hoe deze vaardigheid zich ontwikkelt gedurende de adolescentie. Dit is onderzocht bij 32 adolescenten (10–19 jaar) aan de hand van de Reading the Mind in the Eyes taak (RMET). Deze taak liet foto's zien van emotionele gezichten van zowel mannen als vrouwen waarbij alleen de ogen zichtbaar waren. In de experimentele conditie (mentale staat conditie) werd onder de foto een viertal antwoordmogelijkheden gegeven in de vorm van emotioneel geladen woorden (bijvoorbeeld: blij, verrast, verbaasd en bang), waaruit deelnemers een antwoord moesten kiezen waarmee de af te lezen emotie het best kon worden omschreven. In de controle conditie (leeftijd/gender conditie) konden deelnemers kiezen uit de antwoordmogelijkheden: jongere man (jonger dan 60), jongere vrouw, oudere man (ouder dan 60 jaar) en oudere vrouw.

De gedragsresultaten voor de mentale staat conditie liet stabiliteit over tijd zien; een hoog percentage goede antwoorden op meting een hing samen met een hoog percentage goede antwoorden op meting twee. Hieruit kunnen we concluderen dat niet leeftijd, maar individuele verschillen tussen adolescenten van invloed zijn op het verwerken en op de juiste manier labelen van emoties.

Op neuraal niveau liet deze studie zien dat de linker en rechter superior temporal sulcus (STS), de linker en rechter inferior frontal gyrus (IFG), de linker en rechter temporal pole en de dorsal medial prefrontal cortex (dmPFC) werden geactiveerd tijdens de mentale staat conditie (hoofdeffect mentale staat versus controle). Deze gebieden zijn onderdeel van de detectie 'node' (STS, temporal poles, IFG; belangrijk bij het detecteren en verwerken van emoties) en de cognitieve 'node' (dmPFC; belangrijk bij het redeneren over iemands emoties) van het sociale informatie verwerking model (SIPN-model; Nelson, Leibenluft, McClure, & Pine, 2005).

Van de gebieden die actief werden tijdens het aflezen van de mentale staat lieten alleen de rechter STS en de rechter IFG stabiliteit zien over tijd (op basis van ROIs). Uit deze resultaten kan worden geconcludeerd dat de rechter STS, een gebied belangrijk bij het detecteren van de emotionele staat

van anderen, en de rechter IFG, een gebied met meerdere functies waaronder taalverwerking en sociaal begrip, een rol spelen bij het aflezen van emoties en dat deze gebieden relatief stabiel zijn binnen de adolescentie. Deze bevinding komt overeen met de bevindingen op gedragsniveau waaruit bleek dat de prestaties op de RMET stabiel bleven over de tijd.

Hoewel de mogelijkheid om iemands emotie af te lezen al is ontwikkeld op 10-jarige leeftijd, kunnen subtiele veranderingen als gevolg van hormonale veranderingen, veranderingen in de structuur van het brein en omgevingsfactoren van invloed zijn op de sociale cognitie. De dmPFC liet zowel een kwadratisch als een lineair leeftijdseffect zien voor de mentale staat conditie, wat suggereert dat dit gebied een belangrijke rol speelt bij het aflezen van iemands mentale staat maar ook dat dit gebied een verandering laat zien over de tijd. De rijping van dit gebied in combinatie met het opdoen van ervaring met het aflezen van emoties zou mogelijk kunnen duiden op een strategie verschuiving gedurende de adolescentie, wat deze subtiele leeftijdsverandering zou kunnen verklaren. Toekomstig onderzoek is nodig om deze verklaring te ondersteunen.

In **hoofdstuk 3** worden een cross-sectionele (75 deelnemers, 10–25 jaar) en een longitudinale studie (31 deelnemers, 10–19 jaar) gecombineerd waarin de relatie tussen beloningsverwerking en puberteit van jongens en meisjes is onderzocht. Het doel van deze studies was om te onderzoeken of activatie in het ventrale striatum (VS; beloningsgebied; onderdeel van de affectieve ‘node’) in reactie op beloning toeneemt met leeftijd en of er individuele verschillen zijn wat betreft activatie in dit gebied op basis van sensatie zoekend gedrag (zelfrapportage).

De taak waarmee beloningsverwerking is gemeten is de ‘Jackpot taak’, een gok taak gepresenteerd als een fruitmachine. De taak bestond uit twee condities: 1) een ‘hoog-risico’ conditie (66% kans om te winnen) en 2) een ‘laag-risico’ conditie (33% kans om te winnen). Bij ieder nieuw spel (trial) kreeg de deelnemer de optie om te spelen met de kans om te winnen of te verliezen of om te ‘passen’ waarbij de deelnemer niks won of verloor. Op gedragsniveau namen alle deelnemers in zowel de cross-sectionele als in de longitudinale studie meer risico bij de ‘laag-risico’ conditie ten opzichte van de ‘hoog-risico’ conditie. Leeftijd, puberteit en scores op de BAS schalen (Drive, Fun-seeking, and Reward-responsiveness; Carver & White, 1994) lieten overigens geen relatie zien met risicogedrag gemeten aan de hand van de hoeveelheid gespeelde spellen.

Op neurale niveau lieten deelnemers, in zowel de cross-sectionele als in de longitudinale studie, activatie in de VS en de mPFC zien in reactie op beloning gemeten met de 'Jackpot taak' voor het contrast winst versus verlies. Activatie in de VS en mPFC was ook positief gerelateerd aan risicogedrag gemeten aan de hand van het aantal keuzes om te spelen in zowel high-risk als low-risk condities (winst versus verlies). Deze keuze om te spelen was ook gerelateerd aan de connectiviteit tussen de linker VS en de rechter anterior insula (AI). Behalve een relatie tussen gedrag op de taak en activatie in de beloningsgebieden, is er ook een positieve relatie gevonden tussen fun-seeking (zelfrapportage) en de VS, wat erop duidt dat er individuele verschillen zijn in het verwerking van beloning en verlies. Het omgekeerde contrast (verlies versus winst) liet overigens geen activatie zien in VS of mPFC.

De resultaten van de studies beschreven in dit hoofdstuk dragen bij aan ons begrip van de mechanismen die de basis vormen voor beloningsverwerking en het nemen van risicovolle besluiten in de adolescentie. Toekomstige uitdagingen liggen in het uitzoeken hoe specifieke gebieden in het brein (inclusief connectiviteit tussen verschillende gebieden) gerelateerd zijn aan risicogedrag tijdens de adolescentie en in het creëren van taken die gevoelig zijn voor individuele en ontwikkelingsverschillen bij de neiging tot het nemen van risico's.

Hoofdstuk 4 beschrijft de evaluatie van een nieuw ontwikkelde vragenlijst naar empathie: de empathie vragenlijst voor kinderen en adolescenten (Empathy Questionnaire for Children and Adolescents; EmQue-CA). De validatie van deze vragenlijst is gedaan bij 1262 kinderen en adolescenten tussen de 10 en 15 jaar. De vragenlijst onderzoekt drie verschillende aspecten van empathie: affectieve empathie, cognitieve empathie en prosociale motivatie. Affectieve empathie houdt in dat je je kunt inleven in andermans emoties en dat je met een ander persoon kunt meevoelen. Met cognitieve empathie wordt het vermogen bedoeld om jezelf te verplaatsen in de ander, waarbij je de emoties van de ander begrijpt. Prosociale motivatie houdt de neiging in om een ander zonder eigenbelang van hulp te voorzien. Behalve de validatie van de EmQue-CA wordt in hoofdstuk 4 ook beschreven hoe empathische vaardigheden samenhangen met positieve en negatieve aspecten van sociale interacties.

Resultaten hebben aangetoond dat de nieuw ontwikkelde empathie vragenlijst voor kinderen en adolescenten een betrouwbare en valide zelf-

rapportage maat is om empathie te meten. Hoewel de EmQue-CA een goede maat is gebleken, is dit niet de eerste vragenlijst die empathische vaardigheden meet (Baron-Cohen & Wheelwright, 2004; Davis, 1980; Jolliffe & Farrington, 2006). Hetgeen waarin de EmQue-CA zich onderscheidt van eerdere vragenlijsten is de toevoeging van een derde schaal waarmee de neiging tot het vertonen van pro sociaal gedrag (pro sociale motivatie) kan worden gemeten. Daarnaast heeft de EmQue-CA als voordeel dat deze toegankelijk is voor jonge kinderen en klinische groepen vanwege het eenvoudige en op deze doelgroepen afgestemde taalgebruik.

Behalve dat de vragenlijst een goede maat is om de aspecten affectieve empathie, cognitieve empathie en pro sociale motivatie te meten, is ook gebleken dat de drie concepten samenhangen met maten voor sociaal cognitieve ontwikkeling. Het feit dat alle drie de schalen gerelateerd zijn aan een hogere vriendschap kwaliteit (Friendship Quality Scale; FSQ) en minder pestgedrag (Olweus Bully/Victimization Questionnaire; OBVQ), suggereert dat alle drie de aspecten van empathie elkaar aanvullen en evenredig van belang zijn bij het in stand houden van goede sociale relaties. Deze resultaten bevestigen de uitkomsten van eerdere studies waarin is gevonden dat empathie is gerelateerd aan betere sociale competenties en meer pro sociaal gedrag (Eisenberg, Miller, Shell, McNalley, & Shea, 1991; Güroğlu, van Lieshout, Haselager, & Scholte, 2007; McMahon, Wernsman, & Parnes, 2006; Oberle, Schonert-Reichl, & Thomson, 2010).

Met de studie beschreven in hoofdstuk 4 demonstreren we behalve een goed geëvalueerde vragenlijst ook sterke links tussen empathie en positieve en negatieve aspecten van sociale interacties. Dit is zeer relevant voor de leeftijdsgroep waar de EmQue-CA voor is bedoeld, aangezien interacties met leeftijdsgenoten cruciaal zijn bij de sociale en morele ontwikkeling. Behalve dat de EmQue-CA bijdraagt aan de bestaande literatuur, dient dit paper ook als voorbereiding op hoofdstuk 6 waarin externe maten aan de EmQue-CA worden gerelateerd.

In **hoofdstuk 5** wordt een gedragsstudie beschreven waarin is onderzocht wat de rol is van motivatie (strategisch versus altruïstisch) bij het onderhandelen over de verdeling van munten door middel van een Ultimatum Game (UG). Een Ultimatum Game is een munten-verdeelspel waarbij de verdeler een voorstel doet aan een ontvanger over de verdeling van een bepaald aantal munten (10 in dit onderzoek). De ontvanger kan het bod accepteren, waarbij de munten worden verdeeld zoals voorgesteld, of afwijzen, wat als gevolg heeft dat beide partijen geen munten ontvangen.

In het onderzoek beschreven in hoofdstuk 5 speelden deelnemers tussen de 8 en 25 jaar twee soorten Ultimatum Games: 1) normale UG conditie: spellen waarbij alle munten zichtbaar waren voor zowel de verdeler (deelnemer) als de ontvanger en 2) verborgen UG conditie: spellen waarbij een deel van de munten alleen zichtbaar was voor de verdeler. De verborgen UG conditie bood deelnemers de mogelijkheid om een echt eerlijke (altruïstische) verdeling te maken door zowel de zichtbare als de onzichtbare munten met de andere speler (ontvanger) te delen of om een schijnbaar eerlijke verdeling (strategisch) te maken door alleen de voor beide partijen zichtbare munten te verdelen. De hoofdvraag van dit onderzoek was of deelnemers strategisch of altruïstisch zouden handelen wanneer een deel van de munten niet zichtbaar is voor de andere partij en hoe deze vaardigheden zich ontwikkelen met leeftijd.

Om te meten welke motivationele aspecten belangrijk zijn bij het maken van een verdeling, is gebruik gemaakt van een munten-verdeelspel. De motivationele aspecten die kunnen worden onderscheiden zijn: 1) handelen vanuit eigenbelang en 2) handelen vanuit het belang van de ander (Van Dijk & Vermunt, 2000). Om dit te kunnen meten is er in dit onderzoek een zelfrapportage maat voor cognitieve empathie (begrijpen van de emoties van een ander en je hierin kunnen verplaatsen) meegenomen (Interpersonal Reactivity Index; IRI; Davis, 1980). Er is namelijk aangetoond dat er individuele verschillen zijn in de mate waarin iemand het perspectief van de ander kan innemen en dat deze vaardigheden veranderen met leeftijd (Harbaugh et al., 2003; Takagishi et al., 2010). Om die reden wilden we testen of volwassenen hoger scoorden op cognitieve empathie dan kinderen en of volwassen meer altruïstische motieven hadden om te kiezen voor een eerlijke verdeling.

De resultaten beschreven in hoofdstuk 5 laten zien dat de jongste kinderen (8–9 jaar) al in staat zijn om te handelen vanuit een strategisch motivatie, aangezien ze minder munten aanboden aan de ontvanger in de verborgen UG conditie vergeleken met de normale UG conditie. Verder lieten de uitkomsten een interactie tussen leeftijd en conditie zien; volwassenen (18–25 jaar) boden meer munten in de normale UG conditie dan jonge kinderen (8–9 jaar). Deze bevindingen kunnen geïnterpreteerd worden als een toename in strategisch altruïstisch gedrag met leeftijd, aangezien het aantal voorgestelde munten alleen toenam met leeftijd bij de normale UG conditie en bij de verborgen UG conditie. Dit gedrag kunnen we verklaren vanuit de ontwikkeling van cognitieve empathie. Een correlatie analyse met zelf gerapporteerde cognitieve empathie

liet namelijk zien dat het nemen van perspectief samenhangt met het aantal voorgestelde munten in de verborgen UG conditie en dat cognitieve empathie een mediator is voor de relatie tussen leeftijd en strategisch handelen. Een uitkomst die aansluit bij eerder onderzoek waarin een positieve relatie werd gevonden tussen strategisch altruïstisch gedrag en leeftijd (Meuwese, Crone, De Rooij, & Güroğlu, 2014).

De bevindingen in dit onderzoek suggereren dat kinderen al vroeg in staat zijn om strategisch te handelen, maar dat oudere kinderen (10–12 jaar) en volwassenen (18–25 jaar) deze motieven meer laten gelden. Daarnaast wordt in dit onderzoek aangetoond dat individuele verschillen op het vlak van cognitieve empathie een rol spelen bij strategisch handelen (hogere score op cognitieve empathie = meer strategisch).

Hoewel strategisch handelen verklaard kan worden vanuit leeftijd en vanuit cognitieve empathie, zou ook de relatie tussen verdeler en ontvanger een rol kunnen spelen. Zo heeft eerder onderzoek aangetoond dat men minder empathie voelt voor een vreemde dan voor een vriend of een familielid (Cheng, Chen, Lin, Chou, & Decety, 2010; Meyer et al., 2013). Dit benadrukt dat essentiële rol van de omgeving, met name de relaties met de mensen die van invloed zouden kunnen zijn op het gedrag van de individu (Güroğlu, Van den Bos, & Crone, 2014). Toekomstig onderzoek zou dit verder uit moeten wijzen.

In **hoofdstuk 6** wordt een cross-sectionele studie besproken waarin is onderzocht welke hersengebieden betrokken zijn bij het evalueren van sociale situaties. In deze studie hebben in totaal 32 deelnemers (12–19 jaar) de Empathy Dictator Game (EDG) in de scanner gedaan. Aan deelnemers werd van tevoren uitgelegd dat ze munten moesten verdelen met een persoon op de foto, aangeduid middels een pijl. Na het zien van de foto moest een keuze worden gemaakt uit een van de vier verdelingen (Dictator Game): prosociaal (6 munten voor de ander, 4 voor jezelf), eerlijk (5/5), beetje oneerlijk (4/6) en straffend (2/8). De keuze die de deelnemer maakte kon niet door de ontvanger worden beïnvloed, dus de munten werden altijd verdeeld zoals voorgesteld.

Tijdens de taak kregen deelnemers positieve en negatieve sociale situaties te zien. Op de foto's waar een negatieve sociale situatie te zien was, werden adolescenten getoond waarbij de een de ander fysiek pijn deed. De negatieve sociale situaties werden onderverdeeld in twee condities: 1) slachtoffer (pijl gericht op het slachtoffer, deelnemer werd gevraagd munten te

verdelen met het slachtoffer), 2) dader (pijl gericht op de dader, deelnemer werd gevraagd munten te verdelen met de dader). De positieve sociale situaties vormden de derde conditie, waarbij foto's van blijde gebeurtenissen (bijv. een verjaardag) werden getoond. Met deze taak kon inzicht worden verworven in verdeelgedrag van adolescenten na het observeren van positieve- en negatieve sociale situaties. De uitkomsten van de EDG op gedrags- en neurale niveau zijn gecombineerd met de EmQue-CA. Het doel van dit onderzoek was om te onderzoeken of specifieke sociale hersengebieden gevoelig zijn voor de perceptie van negatieve sociale situaties en positieve sociale situaties en of de mate van zelf gerapporteerde empathie van invloed is op het gedrag op de taak en/of op de neurale activatie tijdens het uitvoeren van de taak.

De gedragsresultaten lieten zien dat deelnemers meer munten weggaven aan de slachtoffers, minder munten aan de daders en overwegend voor een gelijke verdeling kozen na het observeren van een positieve sociale situatie. Er waren geen onderlinge verschillen tussen adolescenten. Een mogelijke verklaring voor deze consistentie zou moraliteit kunnen zijn, oftewel de mogelijkheid om in te schatten of iets goed of fout is op basis van universele sociale regels (Decety & Cowell, 2014). Door deze sociale morele regels te handhaven wordt keuzegedrag beïnvloedt, wat zou kunnen verklaren waarom er weinig tot geen variatie is tussen de verschillende trials binnen de condities.

De uitkomsten op neurale niveau lieten zien dat het observeren van negatieve sociale situaties een toename in activatie in de STS en inferior parietal lobule (ILP) veroorzaakt, gebieden die geassocieerd worden met het detecteren van belangrijke sociale informatie. Het observeren van positieve sociale situaties liet een toename in activatie in de mPFC en de temporal parietal junction (TPJ) zien, gebieden die geassocieerd worden met het redeneren over andermans mentale staat en het jezelf verplaatsen in de ander. Eerdere studies hebben hetzelfde netwerk gevonden wanneer aan individuen werd gevraagd om een sociale situatie te observeren of te beoordelen (Van der Heiden et al., 2013). Dit geldt ook voor studies naar morele ontwikkeling (Decety, Michalska, & Akitsuki, 2008) en voor studies naar het redeneren over iemands mentale staat (Gunther Moor et al., 2012, zie ook hoofdstuk 2).

Tot slot wordt in hoofdstuk 6 de relatie tussen neurale activiteit tijdens de taak en de zelfrapportage scores op de EmQue-CA (zie hoofdstuk 4) beschreven. Resultaten lieten zien dat er een negatief verband is tussen cognitieve empathie en de linker STS wanneer deelnemers negatieve situaties observeren. Ditzelfde verband werd gevonden voor prosociale motivatie en de linker STS. Deze uitkomsten suggereren dat deelnemers die hoog scoren op empathie, minder activatie laten zien in de detectie node van het brein wanneer ze negatieve sociale situaties observeren. Een uitkomst die tegenstrijdig is met eerder onderzoek naar volwassenen, waarbij een positieve relatie werd gevonden tussen perspectief nemen en activatie in de rechter STS wanneer in- en outgroup leden werden gestraft (Molenberghs et al. 2014).

De rol van empathie in sociale interacties moet nog verder worden onderzocht om beter te begrijpen hoe individuele verschillen een rol kunnen spelen in sociale situaties, waarbij de verandering van empathie met leeftijd zou kunnen worden meegenomen. Daarnaast zou het interessant zijn om de EDG af te nemen bij groepen die moeite hebben met het naleven van sociale regels, zoals adolescenten met oppositionele gedragsstoornissen (White, Brislin, Meffert, Sinclair, & Blair, 2013).

In **hoofdstuk 7** worden de studies uit de voorgaande hoofdstukken bediscussieerd, waarbij aandacht wordt besteed aan de kwaliteiten en limitaties. Hoofdstukken twee en drie beschrijven longitudinale studies waarin adolescenten op meerdere tijdstippen (interval van +/- 2 jaar) meededen aan hetzelfde onderzoek. Longitudinaal onderzoek is een effectieve methode om subtiele veranderingen in de ontwikkeling te onderzoeken. Door individuen gedurende een langere periode te volgen is het mogelijk om de ontwikkeling van sociale en cognitieve vaardigheden in kaart te brengen. Hierdoor kan worden voorkomen dat ontwikkelingsverschillen worden opgemerkt als gevolg van verschillen binnen een cohort, aangezien dezelfde deelnemers op meerdere tijdstippen deelnemen. Daarnaast biedt longitudinaal onderzoek de mogelijkheid om te testen of bepaalde verschillen voortkomen uit een karaktertrek (stabiliteit over tijd) van een persoon of uit een tijdelijke staat van zijn (variabiliteit over tijd). Tot slot bieden longitudinale studies de mogelijkheid om gedrag te voorspellen op basis van eerder verzamelde gegevens over het brein (Telzer, Fuligni, Lieberman, & Galván, 2014). De studies gepresenteerd in dit proefschrift maken deel uit van de eerste serie longitudinale studies waarbij

fMRI is gebruikt. De groepsgroottes zijn daarom relatief klein en het aantal herhaalde metingen blijft beperkt tot twee. Het zou een goede vooruitgang zijn als toekomstige studies deze methode in grotere groepen zouden toepassen, waarbij individuen over een langere periode gevolgd worden.

Behalve een longitudinale component in een aantal studies, hebben de hoofdstukken uit dit proefschrift een multi-method benadering. Zo zijn experimentele taken, neurale maten en zelfrapportage indexen gebruikt om een meer gedetailleerd beeld te krijgen van de ontwikkeling van sociale heroriëntatie. De combinatie van verschillende meetinstrumenten biedt de mogelijkheid om meer inzicht te verwerven over een bepaald concept, waarbij de unieke bijdrage van elk afzonderlijk meetinstrument kan worden onderzocht. Deze benadering is binnen dit proefschrift toegepast in een relatief smalle leeftijdsgroep (12-19 jaar). Toekomstig onderzoek zou zich moeten richten op grotere groepen waarbij een brede leeftijdsrange wordt aangehouden en waarbij meerdere methoden worden toegepast. Daarnaast zou toekomstig onderzoek kunnen profiteren van het gebruik van latente klassen analyses, waarmee groepen kunnen worden gevormd op basis van specifieke kenmerken. Hiermee wordt het mogelijk om voorspellingen te doen op basis van iemands karaktereigenschap(en).

Toekomstig onderzoek kan profiteren van de gepresenteerde studies door individuele verschillen in deze belangrijke periode in het leven op een meer gedetailleerde wijze te analyseren. Dit kan helpen bij de verklaring waarom sommige adolescenten succesvol zijn in het ontwikkelen van sociale vaardigheden en relaties, terwijl anderen hier veel moeilijkheden in ervaren. Uiteindelijk kan dit leiden tot de ontwikkeling van interventies voor jongeren die niet goed kunnen omgaan met de sociale eisen vanuit de omgeving (bijvoorbeeld jongeren met een antisociale gedragsstoornis) wat hen kan helpen om de kwaliteit van leven voor henzelf maar ook de mensen om hen heen te vergroten (White et al., 2013).

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Curriculum Vitae

Sandy Overgaauw was born on the 10th of June in Schiedam, The Netherlands. In 2002 she obtained her HAVO (Higher General Secondary Education) diploma at SG Spieringshoek, Schiedam. In 2007 she obtained her Bachelor's degree of Social Work (B SW) at Rotterdam University of Applied Sciences (Hogeschool Rotterdam), The Netherlands. In 2011 Sandy received her Master's degree in Education and Child Studies at Leiden University, The Netherlands, with a specialization in Clinical Child and Adolescent Studies. From November 2007 until February 2011 Sandy worked as a social worker at the TriviumLindenhof foundation. During this time period she also did her research internship at the Brain & Development lab at Leiden University under supervision of prof. Eveline Crone. From March 2011 until December 2011 Sandy continued at the Brain & Development lab as a research assistant, and in January 2012 she started her PhD on the neurodevelopment of empathy under supervision of prof. Eveline Crone and dr. Berna GÜROĞLU. In addition to her PhD, Sandy coordinated a behavioral pilot study (Gravitation) to examine tests for prosocial and antisocial behavior to be used in future intervention studies and feasible for imaging, supervised by prof. Eveline Crone, prof. Marinus IJzendoorn, prof. Marian Bakermans-Kranenburg, and prof. Rutger Engels. From August 2014, Sandy is working as a postdoctoral researcher at the Brain and Development Lab at Leiden University.