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Heritability of neural reactions to social exclusion and prosocial compensation in middle childhood

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ABSTRACT

Experiencing and observing social exclusion and inclusion, as well as prosocial behavior, are important aspects of social relationships in childhood. However, it is currently unknown to what extent these processes and their neural correlates differ in heritability. We investigated influences of genetics and environment on experiencing social exclusion and compensating for social exclusion of others with the Prosocial Cyberball Game using fMRI in a twin sample (aged 7–9; N = 500). Neuroimaging analyses (N = 283) revealed that experiencing possible self-exclusion resulted in activity in inferior frontal gyrus and medial prefrontal cortex, which was influenced by genetics and unique environment. Experiencing self-inclusion was associated with activity in anterior cingulate cortex, insula and striatum, but this was not significantly explained by genetics or shared environment. We found that children show prosocial compensating behavior when observing social exclusion. Prosocial compensating behavior was associated with activity in posterior cingulate cortex/precuneus, and showed unique environmental effects or measurement error at both behavioral and neural level. Together, these findings show that in children neural activation for experiencing possible self-exclusion and self-inclusion, and for displaying prosocial compensating behavior, is accounted for by unique environmental factors and measurement error, with a small genetic effect on possible self-exclusion.

1. Introduction

Social exclusion is a common event for school-aged children: in day-to-day interactions they either experience exclusion themselves, or they observe someone else being excluded. Experience of exclusion can lead to personal distress (Saylor et al., 2013), whereas the observation of someone else's exclusion often leads to prosocial compensating behavior (Masten et al., 2011), although in some cases individuals may also join in exclusion to follow group norms, possibly in order to prevent self-exclusion (Over and Carpenter, 2009). However, research to date remained inconclusive with respect to how experiencing exclusion and acting prosocially upon observed exclusion can be distinguished from each other in school-aged children, and whether these processes are differentially influenced by genetic and environmental factors. Earlier studies have indicated that sensitivity to experiencing social exclusion is influenced by personal experiences (Masten et al., 2012), whereas prosocial compensating behavior is both influenced by genetics (Knafo-Noam et al., 2015; Knafo and Plomin, 2006) and by the environment (Menting et al., 2013; Newton et al., 2014). A better understanding of heritability of social exclusion sensitivity and prosocial compensating behavior in middle childhood might help us explain the underlying mechanisms and provides insights for future development of (school-based) interventions.

Both social exclusion and subsequent prosocial compensating behavior have previously been studied with the Cyberball Game (Masten et al., 2011; Will et al., 2013; Williams et al., 2000). A four-player adaptation of this paradigm was used to study the experience of social exclusion and prosocial compensating behavior in a situation of observed social exclusion (Tousignant et al., 2017; van der Meulen et al., 2017, 2016). After an initial round of fair play, one player (not the participant) is excluded by the two other players. This manipulation allows the participant to either join in the exclusion or compensate for the exclusion by tossing more balls to the excluded player than to either of the two excluding players (i.e. prosocial compensating). In addition, the participant does not receive the ball for short periods of time from the two excluding players, which might lead to alternating feelings of

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worry about possible self-exclusion and relief about self-inclusion. Neural activation analyses in prior research revealed that experiencing alternating social exclusion was associated with increased activity in left inferior frontal gyrus (IFG) in children (van der Meulen et al., 2017). This finding reflects meta-analyses in adolescents and adults showing that the lateral orbitofrontal cortex (overlapping with the IFG) and subgenual anterior cingulate cortex (sgACC) are more active when experiencing social exclusion (Cacioppo et al., 2013; Rotge et al., 2015; Vijayakumar et al., 2017), as is the amygdala (Eisenberger et al., 2007). Interestingly, studies in which participants experienced exclusion during short intervals showed comparable results to studies examining social exclusion in more prolonged social rejection contexts. For example, it was found that the medial prefrontal cortex (mPFC) was activated during an extended period of exclusion in a classic Cyberball Game (Gunther Moor et al., 2012) as well as during short intervals of rejection in a social judgment task (Gunther Moor et al., 2010a,b). Moreover, studies also report that effects of social exclusion and rejection are sensitive to social experiences, such as a long-term history of social exclusion (Will et al., 2016) or childhood maltreatment (van Harmelen et al., 2014). Social inclusion, in contrast, was previously associated with activity in dorsal ACC (dACC) and the striatum (Davey et al., 2010; van der Meulen et al., 2017), which possibly signals the saliency and reward of this event (Menon and Uddin, 2010; Seeley et al., 2007).

A critical element of the four-player Prosocial Cyberball game is that it also allows for the study of prosocial compensating behavior towards an excluded player. Prior studies using the Prosocial Cyberball Game showed that both adults and children indeed engage in prosocial compensating behavior after observing prolonged social exclusion of a different player (Riem et al., 2013; Tousignant et al., 2017; van der Meulen et al., 2017, 2016; Vrijhof et al., 2016). Interestingly, in adults, but not in children, prosocial compensating behavior was associated with increased activity in the temporo-parietal junction (TPJ; Tousignant et al., 2017; van der Meulen et al., 2016; Will et al., 2015), which is considered to be part of the social brain network (Blakemore, 2008; Frith and Frith, 2007). Moreover, in studies using social dilemma paradigms, it was also found that prosocial behavior was associated with increasing activity in the TPJ over the course of adolescence (Güroğlu et al., 2009, 2014; Güroğlu et al., 2011; Tousignant et al., 2017). Finally, prior studies also showed consistent involvement of the ACC-insula network when participants acted against their own social norms, which was independent of age (Güroğlu et al., 2011). These findings warrant further investigation of the neural regions and motives that children use when acting prosocially towards others.

An important, but understudied question concerns to what extent neural activity in these regions is sensitive to genetic and environmental influences. Earlier studies have focused on heritability of brain volume (Teeuw et al., 2018), brain connectivity (for review see Richmond et al., 2016) and brain activity during cognitive tasks (for review see Jansen et al., 2015), and found significant influences of genetics. A prior study on heritability effects on neural correlates of social rejection showed small influences of genetics in middle childhood (Achterberg et al., 2018b), but to our knowledge there are currently no studies that have directly investigated heritability effects on neural correlates of social inclusion and prosocial behavior. Therefore it remains an important question whether these processes are more sensitive to genetic or environmental influences.

This study therefore had two goals: I) To test the main contrasts and the brain-behavior relations of possible social exclusion, inclusion, and prosocial compensating. II) To examine the heritability of social processes in brain regions that are involved in possible self-exclusion, self-inclusion, and prosocial compensating. Therefore we investigated the genetic versus environmental influences on brain activity in middle childhood using a twin design. First, we expected that experiencing self-exclusion would be associated with activation in IFG and sgACC (Cacioppo et al., 2013; Vijayakumar et al., 2017), as well as mPFC (Gunther Moor et al., 2012) and amygdala (Eisenberger et al., 2007), whereas experiencing inclusion was expected to lead to activation in bilateral insula/ACC (Menon and Uddin, 2010; Seeley et al., 2007) and the striatum (Van der Meulen et al., 2016). Second, we expected that children would show prosocial behavior in situations of observed exclusion (Masten et al., 2011). Third, we expected that social brain areas (mPFC, precuneus, TPJ and STS) would be activated when acting prosocially (Guroglu et al., 2014; van der Meulen et al., 2016). Finally, we tested the different influences of genetics, shared environment and unique environment on social exclusion sensitivity and prosocial behavior in these brain regions. Given that this is a first study examining heritability of fMRI signals in young children, it is important to validate the approach with measures that are more established in genetic designs. Therefore, we also tested the effects of genetics, shared environment and unique environment on total brain volume, a brain measure that has shown consistent heritability in adults (for reviews see Batouli et al., 2014; Peper et al., 2007) and children (Teeuw et al., 2018). We therefore expected to observe mainly genetic influences on total brain volume in the current sample (see Teeuw et al., 2018, including 9-year-old children).

2. Methods

2.1. Participants

Participants were recruited for the longitudinal twin study of the Leiden Consortium on Individual Development (L-CID). We sent invitations to families with twin children born between 2006 and 2008 in municipalities in the Western region of the Netherlands after obtaining address information from the municipal registries. We included same-sex twin pairs that were 7–9 years old at the time of data collection, had normal (or corrected to normal) vision, were fluent in Dutch or English, and did not suffer from psychological or physical conditions that could hinder their performance on the tasks. The study was approved by the Dutch Central Committee on Research Involving Human Subjects (CCMO).

The initial sample for the L-CID study consisted of 512 participants (256 twin pairs). Since our aim was to study a population sample, participants with a psychiatric disorder were included. In the initial sample, 11 participants were diagnosed with an Axis-I disorder (nine with attention deficit hyperactivity disorder (ADHD) and/or attention deficit disorder (ADD); one with generalized anxiety disorder (GAD), and one with pervasive developmental disorder-not otherwise specified (PDD-NOS). An estimate of IQ was obtained via two subscales (Similarities and Block Design of the Wechsler Intelligence Scale for Children, 3rd version (WISC-III); Wechsler, 1991). Estimated IQ was within the normal range (range = 72.5–137.5).

Twelve participants did not have complete data of the Prosocial Cyberball Game and were therefore excluded from further analyses on prosocial behavior, resulting in a *behavioral sample* of 500 participants (including 244 complete twin pairs in the behavioral twin sample). Of the initial 512 participants, 33 did not perform the Prosocial Cyberball Game in the MRI scanner; 17 due to anxiety, four due to lack of parental consent for the MRI scan, seven due to contra-indications for the MRI scan, and five due to technical errors. Five other participants were excluded from neuroimaging analyses due to anomalous findings, and an additional 191 participants were excluded due to excessive movement (defined as >3 mm in any volume). This resulted in a *MRI sample* for the neuroimaging analyses of 283 participants, including 89 complete twin pairs in the MRI twin sample (see Table 1 for demographic characteristics of the different samples). A non-response analysis indicated that the participants included in the MRI sample were older ($t(510) = -2.38$, $p = 0.02$), had a higher estimated IQ ($t(510) = -2.24$, $p = 0.03$), and were more often female (X^2 (1) = 9.34, $p = .004$) than the participants excluded from the MRI sample. There were no significant differences between the monozygotic (MZ) and dizygotic (DZ) twins in

Table 1
Demographic characteristics of the samples that were included at various stages of the study.

	Behavioral sample	MRI sample
N	500	283
Complete twinpairs	244	89
Male	48%	42.8%
Left handed	12.6%	12.4%
AXIS-I disorder	11 (2.2%)[a]	7 (2.5%)[b]
Age (SD)	7.94 (.67)	8.01 (.67)
Mean IQ (SD)	103.73 (11.72)	104.57 (12.01)

[a] 9 ADHD and/or ADD; 1 PDD-NOS; 1 GAD.
[b] 5 ADHD and/or ADD; 1 PDD-NOS; 1 GAD.

the behavioral and MRI twin samples for demographic measures (see Table A1 in supplementary material for demographic information).

2.2. Measures

2.2.1. Prosocial Cyberball Game

To measure behavioral and neural responses to observed social exclusion we used an adapted version of the Prosocial Cyberball Game (PCG; see also Riem et al., 2013; van der Meulen et al., 2017). Participants were instructed to participate in a virtual ball tossing game with three other players, placed at the left (Player 1), the top (Player 2), and the right (Player 3) of the screen. The participant was represented by the figure at the bottom of the screen (see also Fig. 1B). Participants were asked to imagine the social setting of the game, such as imaging what the other players and the settings of the game would look like. Previous studies have indicated that imagining playing a game with others is a strong manipulation in gaming research (Konijn et al., 2007), and that exclusion by virtual players leads to reduced feelings of self-esteem (Zadro et al., 2004). We validated this paradigm in earlier studies in children and adults (van der Meulen et al., 2017, 2016).

The PCG was administered in two rounds: a Fair Game and an Unfair Game. In the Fair Game (120 trials), which was administered on a laptop, all four players received the ball an equal number of times (25% of the trials). In the Unfair Game (168 trials), which was administered in the MRI scanner, player 2 was excluded by players 1 and 3 (referred to as the excluding players). The task was programmed in such a way that in case the excluding players were tossing, the participant received the ball on 50% of the trials from the excluding players (they tossed either to the other excluding player (resulting in short intervals of feelings of possible self-exclusion for the participant), or to the participant). In case the excluded player was tossing, the participant received the ball on 33% of the trials (i.e., the excluded participant tossed the ball to the three other players an equal number of times). The Unfair Game was played in two identical blocks, with a short rest period provided between the blocks. Responses during the Unfair Game were recorded through a button box attached to the participant's right leg. Throughout the PCG each trial consisted of one ball toss with a duration of 2000 ms, followed by a jitter with a duration ranging from 1000 to 2000 ms. When the participant had received the ball, the jitter consisted of the actual response time of the participant.

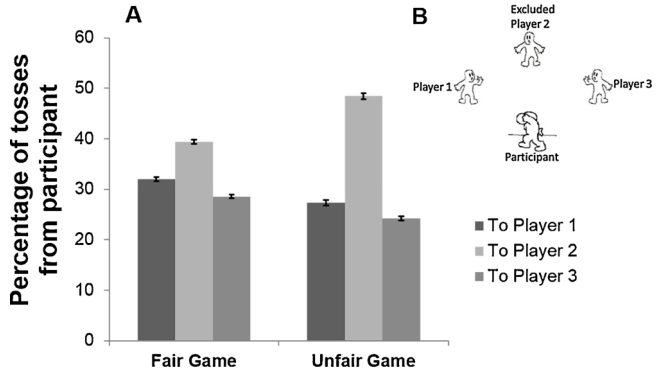

Fig. 1. (A) Percentage of tosses from the participant to the other three players during the Prosocial Cyberball Game. (B) Screenshot of play situation and players in Prosocial Cyberball Game.

After completion of the PCG, all participants answered a set of exit-questions to measure their feelings towards the other players in the game. For each of the three players, we asked how much the participants liked that specific player (e.g. "How much did you like player 1?"), indicated by answers on a 6-point Likert scale (1 = not at all, 6 = very much). In addition, we asked participants to whom of the three players they would prefer to donate a sticker (i.e. "If you could donate a sticker to any of the three players, which one would you choose?").

2.2.2. DNA collection

Twin zygosity was determined using information from DNA samples. To this end, buccal cell samples were collected via mouthswab (Whatman Sterile Omni Swab). Samples were collected halfway through the lab visit, to ensure that the children did not eat or drink anything for at least one hour prior to DNA collection. Results of the DNA analyses indicated that 54.9% of the twin pairs in the behavioral twin sample was MZ, whereas 45.1% of the twin pairs in the MRI twin sample was DZ (see Table A1 in Supplementary material for further demographics of the twin samples).

2.3. Procedure

Participants received an extensive explanation on the procedure of the MRI scan, as well as a practice session in a mock scanner to further familiarize them with the procedure. All participants performed the Fair Game of the Prosocial Cyberball Game before the scanning session. Participants also performed several behavioral measures as part of the larger L-CID program. Co-twins were randomly assigned to either start with the scanning session or to start with other behavioral measures. During the scanning session, participants first completed performed a social network task (Social Network Aggression Task; Achterberg et al., 2016), and then performed the PCG. After the fMRI tasks, a high resolution structural scan, DTI scans, and a resting state scan were collected. After completing the scanning session, participants answered exit questions about the PCG. After completion of the experimental session, participants received a small goodie bag and parents received financial compensation (€80) for their time, as part of a larger study.

2.4. MRI data acquisition

MRI scans were made with a Philips Ingenia MR 3.0 T scanner, using a standard 32-channel whole-head coil. The functional scans were acquired using a T2*-weighted echo-planar imaging (EPI). The first two volumes were discarded to allow for equilibration of T1 saturation effects (TR = 2.2 s; TE = 30 ms; sequential acquisition, 37 slices; voxel size = 2.75 × 2.75 x 2.75 mm; Field of View = 220 × 220 x 112 mm). After the functional runs, a high resolution 3D T1-weighted anatomical image was collected (TR = 9.8 ms, TE = 4.6 ms, 140 slices; voxel size = 1.17 × 1.17 × 1.2 mm, and FOV = 224 × 177 × 168 mm). Foam inserts were used within the head coil to restrict head movement. Stimuli were projected on a screen, visible via a mirror attached to the head coil.

2.5. fMRI data analyses

All data were analyzed with SPM8 (Wellcome Department of Cognitive Neurology, London). Images were corrected for slice timing acquisition and differences in rigid body motion. Functional volumes were spatially normalized to T1 templates. The normalization algorithm used a 12-parameter affine transform together with a nonlinear

transformation involving cosine basis functions and resampled the volumes to 3 mm cubic voxels. Templates were based on the MNI305 stereotaxic space (Cocosco et al., 1997). Functional volumes were spatially smoothed with a 6 mm full width at half maximum (FWHM) isotropic Gaussian kernel.

The different events in the PCG-Unfair Game were determined by the tossing of the ball, with the start of each ball toss modeled separately with a zero duration event. To study participants' neural reactions to possible self-exclusion we compared the events of the participant receiving tosses from the excluding players ("Inclusion"; approx. 50% of total tosses from excluding players) to the participant not receiving tosses from these players ("Exclusion; approx. 50% of total tosses from excluding players), and the reversed contrast to examine self-inclusion. To study neural correlates of prosocial behavior we compared the events of the participant compensating for the observed exclusion by tossing the ball to excluded player 2 ("Compensating"; on average 48.1% of total tosses from the participant) to the participant tossing the ball to players 1 and 3 ("Tossing to excluders"; on average 51.9% of total tosses from the participant). We chose these specific contrasts to control for possible confounding factors such as motor preparation or action (i.e. when tossing to one of the other players).

The trial functions were used as covariates 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 HRF for each condition were used in pair-wise contrasts. Six motion regressors were included in the first level analysis. The resulting contrast images were computed on a subject-by-subject basis and then submitted to group analyses.

2.5.1. Whole brain analyses

To investigate neural reactions to being excluded from the ball tossing game by the two excluding players, we tested the contrast *Exclusion > Inclusion* and the reversed contrast *Inclusion > Exclusion*. To investigate neural reactions to prosocial compensating, we tested the contrast *Compensating > Tossing to excluders* and the reversed contrast *Tossing to excluders > Compensating.*

To test for relations with prosocial behavior, both analyses were followed up with whole brain regression analyses with the behavioral index of prosocial compensating (tossing to player 2 in the Unfair Game – tossing to player 2 in the Fair Game). Condition-related responses were considered significant when they exceeded a FWE-corrected threshold ($p < .05$), or a cluster-corrected threshold of $p < .05$ FWE-corrected, with a primary threshold of $p < .001$ (Woo et al., 2014).

2.5.2. ROI analyses

To select ROIs, we extracted clusters of activation from the whole brain contrasts (Exclusion > Inclusion (and reversed) and Compensating > Tossing to excluders), using the MarsBar toolbox (Brett et al., 2002). To limit the number of regions for further analyses, we used a hypothesis-driven approach to select the final ROIs. Based on prior research, for the *Exclusion > Inclusion* contrast, we were primarily interested in the IFG, sgACC, and amygdala (associated with the experience of social exclusion; Cacioppo et al., 2013; Eisenberger et al., 2007; Vijayakumar et al., 2017), and mPFC (associated with perspective taking and social reasoning; Gunther Moor et al., 2012; Masten et al., 2011). For the reversed *Inclusion > Exclusion* contrast, we were interested in the striatum (associated with reward; Delgado, 2007), the bilateral insula, and the ACC (associated with saliency of events; Menon and Uddin, 2010; Seeley et al., 2007). For the contrast *Compensating > Tossing to excluders*, we were mainly interested in social brain regions such as the mPFC, precuneus, TPJ and STS (Moor et al., 2012; Will et al., 2015). After extracting the activation clusters from the whole brain contrasts, we used the MarsBar-AAL (Tzourio-Mazoyer et al., 2002) to mask the a-priori ROIs in the larger activation clusters. Parameter estimates were extracted from the resulting masked ROIs for the conditions "Exclusion" and "Inclusion", and the conditions "Compensating" and "Tossing to excluders". Outliers (z-value <-3.29 or >3.29) were winsorized (Tabachnick and Fidell, 2013).

2.6. Structural MRI data analysis

For the control analysis on total brain volume, we pre-processed T1-scans in FreeSurfer (v5.3.0). Anatomical labeling and tissue classification was performed on the basis of the T1- weighted MR image using the well- validated and well-documented FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/). In short, this software includes tools for non-brain tissue removal, cortical surface reconstruction, subcortical segmentation, cortical parcellation, and estimation of various measures of brain morphometry. Technical details of the automated reconstruction scheme are described elsewhere (Dale et al., 1999; Fischl et al., 1999). After pre-processing, each scan was manually checked to assess quality by three trained raters. Each scan was rated as 1 = 'Excellent', 2 = 'Good', 3 = 'Poor', or 4 = 'Failed', based on a set of specific criteria (e.g., affection by movement, missing brain areas in reconstruction, inclusion of dura or skull in reconstruction). After quality assessment, 53 scans (11.2%) were rated as 'Failed' and therefore excluded from further analyses. To check reliability of the three raters, 40 scans were checked by all three raters, resulting in an intra-class correlation of .60.

Total brain volume measures were included for complete twin pairs who also had fMRI data of sufficient quality (N = 166 participants). This sample included 43 MZ twin pairs (44.2% male) and 40 DZ twin pairs (37.5% male). For these participants, we used automatic subcortical segmentation (Fischl et al., 2002) to extract measures of total gray matter volume ("TotalGray" label, sum of left and right cortical volume, subcortical gray matter volume and cerebellum gray matter) for each participant.

2.7. Genetic modeling

To investigate genetic and environmental influences on differences in prosocial behavior, neural reactions to social exclusion and prosocial behavior, and total brain volume, we first computed within-twin pair Pearson correlations for each outcome variable, separately for MZ and DZ twins. A higher correlation for MZ twins would indicate influence of genetic factors, whereas a DZ correlation higher than half the MZ correlation would indicate influence of shared environment. A correlation smaller than 1 indicates an additional effect of unique environment. To further inspect influences of genetic and environmental factors on differences in activity in specific ROIs, prosocial behavior, and total brain volume, we used a structural equation ACE model in the OpenMx package (version 2.7.4; Neale et al., 2016) in R (R version 3.3.2; R Core Team, 2015). With this model we examined the contribution of genetic (A) and shared (C) and unique (E) environmental factors. The E component of the model also included measurement error. For each outcome variable, four different models (ACE, AE (with C set to 0), CE (with A set to 0), and E (with A and E set to 0)) were estimated and a log likelihood was calculated. Each model was then compared to a more parsimonious model (e.g. ACE to AE) by subtracting the log likelihoods, resulting in an estimate of the Log-Likelihood Ratio Test (LRT). Given that the LRT follows the $\chi 2$-distribution, an LRT < 3.84 would indicate that the more parsimonious model is a better fit to the data. The Akaike Information Criterion (AIC; Akaike, 1974) was used to determine the best model for equally parsimonious non-nested models (i.e. AE and CE), with better model fit being indicated by a lower AIC.

Since we used a total of nine ACE models to investigate heritability of neural reactions, we were concerned about multiple comparisons and resulting false discovery rate. To counteract this, we performed a supplementary analysis across all ROIs to compute an average heritability estimate of neural activity. For this purpose, we used Falconer's equations (Falconer and Mackay, 1996), with heritability defined as $h^2 = 2 \times (r_{MZ} - r_{DZ})$ and shared environment defined as $c^2 = 2 \times r_{DZ} - r_{MZ}$. We used the within-twin correlations for the MZ and DZ twin pairs for each

ROI (also see Table 4). Next, we transformed the within-twin correlations coefficients to Fisher z-values, to stabilize variance. Then we computed an average Fisher z-value for all ROIs for the MZ and DZ twin pairs separately (by adding the Fisher z-values for all ROIs, and dividing that value by the total number of ROIs). Finally, we transformed the Fisher z-value back to correlation coefficients, and we used the resulting correlation coefficients for MZ and DZ twins as variables in the Falconer's equations.

3. Results

3.1. Behavioral results

3.1.1. Prosocial behavior

The main outcome measure of the PCG is prosocial compensating behavior to excluded Player 2. Since the participants already showed a preference for Player 2 in the Fair Game (see Fig. 1A), we defined our outcome measure as the difference in percentage of tosses to Player 2 in the Fair Game and the Unfair Game, to control for behavior in the Fair Game. The percentage of tosses to Player 2 was calculated by dividing the number of tosses to Player 2 by the total number of tosses to all players (van der Meulen et al., 2016). Using a paired sample *t*-test in the behavioral sample (N = 500), we found that the percentage of tosses from the participant to player 2 was significantly higher when this player was excluded (Unfair Game: M = 48.44, SD = 13.47, range 5.45–100), compared to the Fair Game (M = 39.42, SD = 10.01, range 13.33–80.0; $t(499) = -14.09$, $p < 0.001$, $d = 0.75$), indicating prosocial compensating behavior. This difference between the Fair Game and the Unfair Game was also significant in the MRI sample (N = 283; $t(278) = -10.27$, $p < 0.001$, $d = 0.78$), and these results were not affected by age, sex or IQ when these factors were included as covariates in the analyses. Next, we computed the difference score between the Fair Game and Unfair Game. The resulting prosocial compensating score was used as index of prosocial behavior in further analyses. Correlations between percentage of tosses from the participant to the other three players in both the Fair and Unfair Game can be found in Table A2 in Supplementary material.

As a validity check for the PCG, we inspected answers on the exit questions. We found that children significantly liked player 2 (M = 5.03, SD = 1.12) more than player 1 (M = 4.29, SD = 1.34; $t(496) = -9.23$, $p < .001$) and player 3 (M = 4.33, SD = 1.46; $t(494) = 8.57$, $p < .001$). There was no significant difference in likeability of player 1 and 3 ($t(494) = .1$, $p = .62$). Next, we computed correlation coefficients for the relationship between prosocial behavior and feelings towards excluded player 2. As expected, prosocial compensating behavior was positively correlated to likeability of player 2 ($r = .14$, $p < .005$), and negatively to likeability of the two excluding players ($r = -.14$, $p < .005$ for player 1 and $r = -.11$, $p < .05$ for player 3), indicating that children who liked player 2 most also showed more prosocial compensating behavior. We also found that the majority of the children chose to donate the sticker to player 2 (60.6%), compared to player 1 (18.9%) and player 3 (20.5%). In addition, we found that children who donated the sticker to player 2 showed more prosocial behavior (M = 11.94, SD = 12.79) than the children who donated the sticker to player 1 (M = 6.38, SD = 15.72) or player 3 (M = 3.37, SD = 13.98; $F(2, 494) = 17.38$, $p < .001$).

3.1.2. Heritability of prosocial behavior

To estimate contributions of genetics, shared environment and unique environment to differences in prosocial behavior after observed exclusion in the behavioral twin sample (N = 244 twin pairs, 46.3% MZ) we first computed within-twin correlations for tosses from the participant to player 2 in the Fair and Unfair Game separately. We found no significant associations for MZ or DZ twins (Fair Game $r_{MZ} = .08$ and $r_{DZ} = .18$; Unfair Game $r_{MZ} = -0.13$ and $r_{DZ} = -0.03$; all p's > .05), indicating no influence of genetics nor shared environment. When performing the same analysis for the difference scores (compensating in Unfair – Fair Game) there were again no positive correlations observed, if anything, the correlation for MZ was negative ($r_{MZ} = -0.22$, $p < .05$; $r_{DZ} = -0.02$, $p > .05$). Next, we used ACE models to further investigate heritability of prosocial behavior and found that prosocial behavior was best accounted for by unique environmental factors and/or measurement error, with no apparent influence of genetics or shared environment (see Table A3 in Supplementary material for full statistics).

3.2. Neural results

3.2.1. Whole brain results

The next question concerned the neural regions that were involved in experiencing social exclusion, inclusion and prosocial compensating behavior in the MRI sample (N = 283). Since there was a significant difference in age, sex, and IQ between the children included in the MRI sample and the children excluded from the MRI sample, we added the variables age, sex, and IQ as covariates in all whole brain regressions. We first examined neural activity for the experience of possible self-exclusion by conducting a whole brain analysis on the contrast "Exclusion > Inclusion", defined as not receiving the ball from players 1 and 3 ("Exclusion") > receiving the ball from players 1 and 3 ("Inclusion"). This contrast resulted in five clusters, including a large cluster spanning the frontal to the occipital cortex, and clusters including mPFC/IFG, and sgACC (see Fig. 2A and Table 2 for an overview of all clusters).

To examine neural activity for the experience of self-inclusion, we performed a whole brain analysis on the reversed contrast "Inclusion > Exclusion". This resulted in eight clusters, including one large cluster spanning the ACC, supplementary motor area, bilateral insula, and bilateral putamen (see Fig. 2B and Table 2 for an overview of all clusters).

We then examined neural activity for prosocial compensating behavior by performing a whole brain analyses on the contrast "Compensating > Tossing to excluders", defined as the participant tossing the ball to the excluded players ("Compensating") versus the participant tossing the ball to the other two players ("Tossing to excluders"). This contrast resulted in one cluster in the posterior cingulate cortex (PCC)/ precuneus (see Fig. 2C and Table 3 for an overview of all clusters). The reversed contrast "Tossing to excluders > Compensating" resulted in two clusters, including a large cluster in the visual cortex (see Table 3 for an overview of all clusters).

3.2.2. Whole brain regression with prosocial behavior

To test the relation between prosocial behavior and brain activation during prosocial behavior, we conducted a whole brain regression analysis on the contrast "Compensating > "Tossing" with the prosocial compensating score as a regressor. The analysis showed that more activity in the left and right insula when tossing to the excluded player was associated with less prosocial compensating behavior (see also Fig. 3). The reversed contrast (a positive relationship between prosocial behavior and the contrast "Compensating > Tossing") did not result in significant activity.

For completeness, we also tested the relation between brain activation during possible self-exclusion versus self-inclusion and subsequent prosocial behavior, using a whole brain regression analysis on the contrasts "Exclusion > Inclusion" and "Inclusion > Exclusion". No significant activity was observed in either of the two contrasts.

3.2.3. Heritability of brain activity for social exclusion/inclusion and prosocial behavior

To test the contributions of genetics, shared environment, and unique environment to differences in brain activity for the experience of possible self-exclusion and inclusion in the MRI twin sample (N = 89 twin pairs, 40.4% MZ), we performed follow up analyses on the five

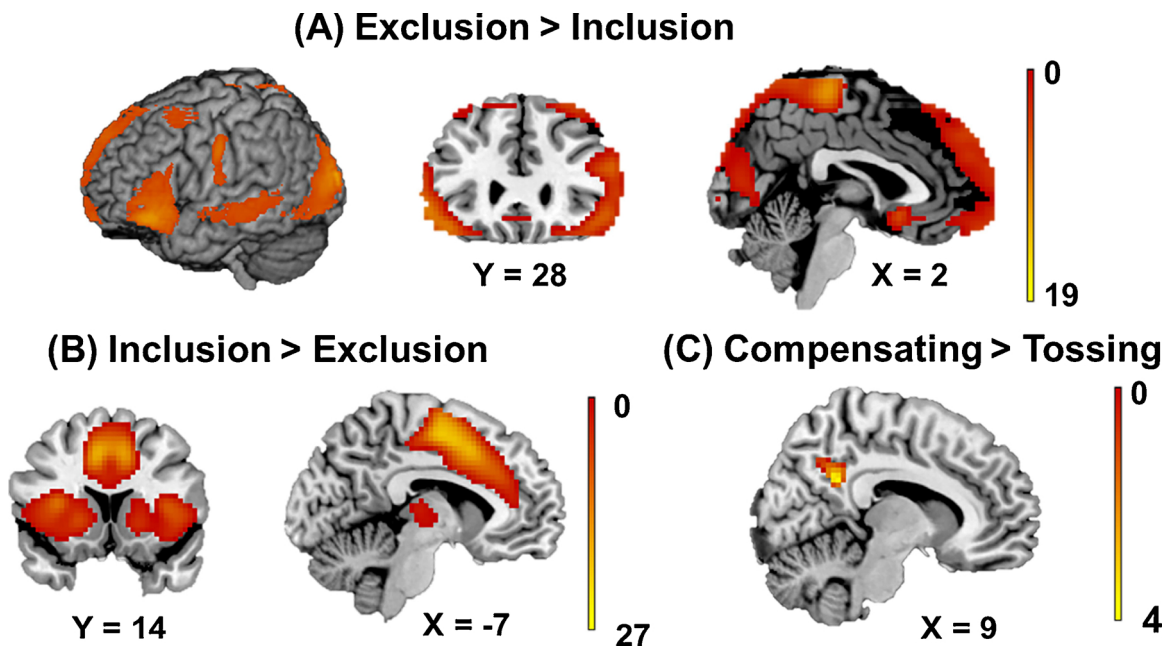

Fig. 2. Whole brain contrasts for (A) Exclusion > Inclusion and (B) Inclusion > Exclusion. Results are reported FWE corrected p < .05, clusters are only reported in case k > 10. (C) Whole brain contrast for Compensating > Tossing to excluders, results are reported at a cluster-corrected threshold of $p < .05$ FWE-corrected, with a primary threshold of $p < .001$.

Table 2
Whole brain table for the social exclusion contrasts: Exclusion > Inclusion and Inclusion > Exclusion. All results are reported FWE corrected p < .05, clusters are only reported in case k > 10.

			MNI Coordinates		
Name	Voxels	T-Value	X	Y	Z
Exclusion > Inclusion					
L Middle Occipital Gyrus	6521	18.92	−15	−94	−2
		16.64	−21	−94	10
R Superior Occipital Gyrus		16.46	24	−91	13
R Middle Orbital Gyrus	3167	13.3	39	41	−14
R Inferior Frontal Gyrus		12.4	48	41	−14
		10.32	57	35	16
R Insula	19	7.12	39	−16	22
R Hippocampus	37	6.03	21	−22	−11
		4.9	18	−22	−23
L Parahippocampal Gyrus	97	5.4	−21	−19	−20
L Amygdala		5.35	−21	2	−23
L Hippocampus		4.89	−27	−10	−23
L Caudate	15	5.09	−18	5	25
		4.92	−18	−7	28
L Fusiform Gyrus	14	5.03	−33	−34	−23
		4.86	−36	−25	−26
Inclusion > Exclusion					
L Precentral Gyrus	6592	27.36	−39	−25	58
L SMA		22.59	−6	−7	55
L SMA		20.5	−6	11	46
R Cerebellum	36	9.48	21	−55	−20
R Postcentral Gyrus	141	8.87	51	−25	49
R Precentral Gyrus	47	8.58	36	−13	61
L Middle Frontal Gyrus	206	6.89	−39	38	31
R Middle Frontal Gyrus	33	5.88	33	44	31
R Supramarginal Gyrus	16	5.85	54	−22	25
L Precuneus	28	5.46	−15	−64	31

Table 3
Whole brain table for the prosocial contrasts: Compensating > Tossing to excluders, Tossing to excluders > Compensating, and the whole brain regression for Compensating > Tossing to excluders. All results are reported at a cluster-corrected threshold of $p < .05$ FWE-corrected, with a primary threshold of $p < .001$.

			MNI Coordinates		
Name	Voxels	T-Value	X	Y	Z
Compensating > Tossing to excluders					
R Posterior Cingulate Cortex	143	3.97	6	−52	31
L Posterior Cingulate Cortex		3.76	−9	−52	28
R Precuneus		3.3	6	−61	40
Tossing to excluders > Compensating					
R Calcarine Gyrus	1121	18.23	12	−85	−2
L Lingual Gyrus		16.44	−9	−85	−5
R Middle Occipital Gyrus		8.13	24	−94	4
L Precentral Gyrus	175	5.5	−30	−10	61
Whole Brain regression: Negative relationship prosocial behavior with contrast Compensating > Tossing to Excluders					
R Insula	266	4.59	42	20	−2
		4.54	39	11	−11
		4.16	36	−4	14
L Insula	160	4.25	−36	20	−5
L Inferior Frontal Gyrus		3.99	−36	38	1
		3.82	−45	17	1

ROIs from the contrast "Exclusion > Inclusion" and four ROIs from the contrast "Inclusion > Exclusion". To test for heritability in neural correlates of prosocial behavior, we selected the cluster in the PCC from the contrast "Compensating > Tossing" (see Fig. 2C), as well as the activated clusters from the whole brain regression (left and right insula, see Fig. 3A). Since parameter estimates in bilateral ROIs (i.e. IFG and insula) were highly correlated (all $r > 0.73$), results were collapsed across left and right hemispheres. This resulted in four ROIs for the contrast "Exclusion > Inclusion" (sgACC, smPFC, bilateral IFG, and amygdala), three ROIs for the contrast "Inclusion > Exclusion" (ACC, bilateral insula, and striatum; see Fig. 4 for an overview), one ROI for the contrast "Compensating > Tossing" (PCC), and one ROI for the whole brain regression on the contrast "Compensating > Tossing" (bilateral insula).

ACE modelling indicated that differences in activity (in the contrast Exclusion > Inclusion) were partly explained by genetics. Specifically, 33% of variance in smPFC (95% CI: 0–53%) was explained by genetics,

Table 4
Within-twin correlations for MZ and DZ twins and full ACE model estimates with 95% confidence intervals for prosocial behavior and the ROIs associated with the possible experience of self-exclusion and prosocial behavior.

Outcome variable	r_{MZ}	r_{DZ}		A^2	C^2	E^2
Behavior PCG	**−.22***	−0	*95% CI*	*† - 0.05*	*† - 0.05*	*0.95 - †*
			ACE	0	0	1
Exclusion > Inclusion						
left amygdala	.11	−.14	*95% CI*	*† - 0.27*	*† - 0.19*	*0.73 - †*
			ACE	0.02	0	0.97
IFG	**.37***	.19	*95% CI*	*0 - 0.54*	*† - 0.45*	*0.46 - 0.89*
			ACE	0.29	0.05	0.66
smPFC	**.36***	.12	*95% CI*	*0 - 0.53*	*† - 0.40*	*0.46 - 0.91*
			ACE	0.33	0	0.67
sgACC	.02	.26	*95% CI*	*† - 0.29*	*† - 0.30*	*0.70 - †*
			ACE	0	0.1	0.9
Inclusion > Exclusion						
ACC	−.08	.07	*95% CI*	*† - 0.21*	*† - 0.20*	*0.79 - †*
			ACE	0	0	1
Striatum	−.08	.20	*95% CI*	† - 0.28	† - 0.27	0.73 - †
			ACE	0	0.07	0.93
Bilateral insula	.03	**.31***	*95% CI*	† - 0.38	0 - 0.38	0.62 - 1
			ACE	0	0.19	0.81
Compensating > Tossing						
PCC	.09	−.13	*95% CI*	*† - 0.27*	*NA - 0.19*	*0.73 - †*
			ACE	0.02	0	0.98
Whole brain regression						
Bilateral Insula	−.13	−.06	*95% CI*	*† - 0.15*	*0.82 - †*	*0.82 - †*
			ACE	0	1	1
Control analysis						
Total brain volume	**.87***	**.57***	*95% CI*	*0.00-0.58*	*0.09-0.23*	*0.09-0.23*
			ACE	0.26	0.14	0.14

r_{MZ} = within-twin correlation for monozygotic twins, r_{DZ} = within-twin correlation for dizygotic twins. Significant correlations and models are indicated by an asterisk (*) and bold font. † Due to relatively weak correlations, in combination with the sample size, the estimated likelihood function was too flat to accurately estimate 95% confidence interval bounds.

whereas in IFG 29% of variance (95% CI: 0–54%) was explained by genetics and 5% (95% CI: 0–45%) was explained by shared environment. All residual variance was best accounted for by the E component (unique environment and measurement error, also see Table 4). Model statistics indicated that an AE model was best fitting for neural activity in these two ROIs (see Table A3 in Supplementary material for full model statistics). Activity in other ROIs from the Exclusion > Inclusion contrast showed minimal to small influences of genetics (amygdala: 2%; 95% CI: 0–27%) and shared environment (sgACC: 10%; 95 CI: 0–30%, also see Table 4).

For the contrast Inclusion > Exclusion, we found small to moderate influences of shared environment for striatum (7%; 95% CI: 0–27%) and bilateral insula (19%; 95% CI: 0–38%). Finally, we found minimal influence of genetics on PCC activity (2%; 95% CI: 0–27%) in the contrast Compensating > Tossing. For these seven ROIs, differences in activity were best accounted for by an E model (see Table A3 in Supplementary material). In our supplementary analysis across all ROIs, the results of Falconer's equations show negligible estimates for both genetic influence (h^2 = 0.01) and shared environmental influence (c^2 = 0.08). Together these findings indicate an overall large contribution of unique environmental influence and measurement error on differences in activity in the selected ROIs.

3.2.4. Control analysis for heritability

We conducted an additional analysis on total brain volume, a structural brain measure, to test genetic contributions. In this analysis we used the residuals of total brain volume, accounted for age, sex, and IQ. We found a high within-twin correlation for MZ twins (r_{MZ} = .87, p < .001) and a moderate within-twin correlation for DZ twins (r_{DZ} = .57, p < .001). These within-twin correlations were used to compute Falconer's estimates of heritability, and we found a strong contribution of genetics (h^2 = 0.59) and a moderate contribution of shared environmental influence (c^2 = 0.28). The more sophisticated ACE modelling also showed a strong genetic component (60%, 95% CI: 26–90%) as well as a contribution of shared environment (26%, 95% CI: 0–58%). Model statistics showed that differences in total brain volume were best accounted for by an AE model (see table A3 in Supplementary material).

4. Discussion

The goal of this study was to examine genetic and environmental (shared and unique) influences on experiencing possible self-exclusion and inclusion, and subsequent prosocial compensating behavior when observing exclusion, in 7–9-year-old children. We found that children show prosocial compensating behavior after observing social exclusion by others, which fits well with prior studies in children and adults (Tousignant et al., 2017; van der Meulen et al., 2017, 2016; Vrijhof et al., 2016). Behavioral correlation analyses further showed that participants who demonstrated more prosocial compensating behavior, afterwards liked the excluded player more, and were also more inclined to donate a sticker to the excluded player. These findings suggest that compensation behavior was not solely provoked by inequity aversion or a preference to toss forward (Fehr et al., 2008). The behavior shown during the Prosocial Cyberball Game could also be motivated by a willingness to punish the bullies (i.e. tossing less often to the other two players). However, it seems likely that this motivation would result in overall significantly fewer tosses to the bullies, whereas our participants mainly compensated for exclusion but did not show over-inclusion of the excluded player. Taken together, the overall tendency to toss more

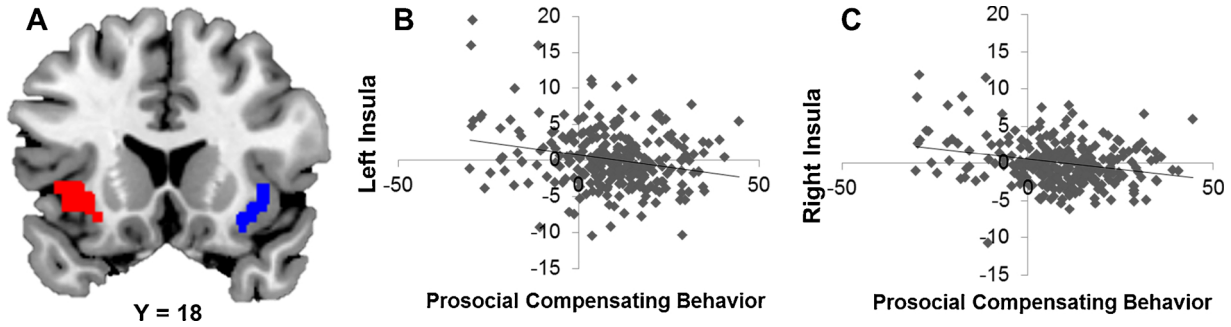

Fig. 3. (A) Activated clusters in whole brain regression with prosocial compensating behavior, with left (red) and right insula (blue). (B) Visualization of regression analysis of prosocial compensating behavior with activity in left insula. (C) Visualization of regression analysis of prosocial compensating behavior with activity in right insula.

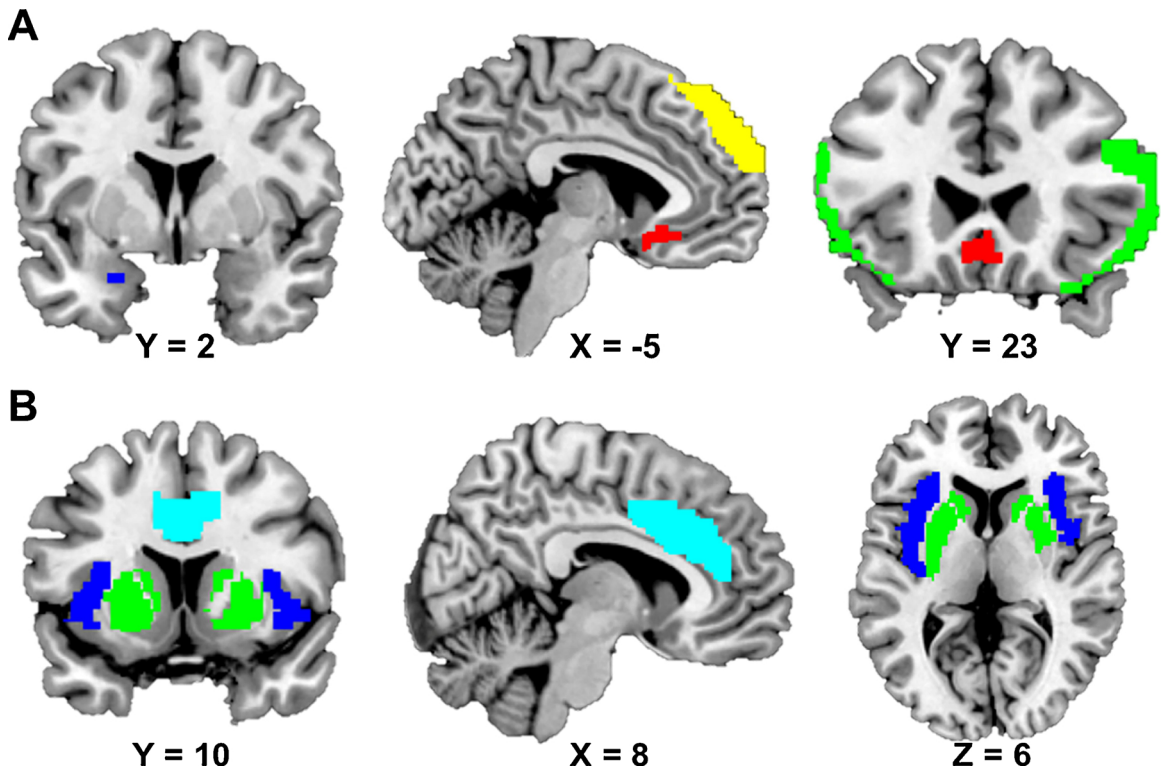

Fig. 4. (A) Overview of ROIs in the contrast Exclusion > Inclusion: amygdala (dark blue), smPFC (yellow), sgACC (red), and bilateral IFG (green). **(B)** Overview of ROIs in the contrast Inclusion > Exclusion: ACC (cyan), bilateral insula (dark blue), and striatum (green).

balls to the excluded player seems to indicate prosocial and helping motives from the participant.

An important question that we aimed to address was whether prosocial compensation behavior was related to genetic, shared environment, or unique environmental factors. Analyses of heritability revealed only unique environmental and/or measurement error influences on prosocial behavioral differences. Interestingly, previous research showed that parent-reported and self-reported prosocial behavior in children and adolescents was best accounted for by a combination of genetic and unique environmental influences (Gregory et al., 2009; Knafo-Noam et al., 2015; Knafo and Plomin, 2006). Possibly, questionnaires capture more trait-like prosocial behavior, which can partly be accounted for by genetic influences, whereas the Prosocial Cyberball Game elicits more state-like prosocial behavior that is specifically influenced by unique environment. Future research is necessary to examine the genetic contributions of different forms of prosocial behavior, such as based on self-report and in experimental settings.

The neural hypotheses were tested in two steps, first for the experiences of self-exclusion and self-inclusion, and second for subsequent prosocial compensating behavior after observing social exclusion of another player. First, experience of possible self-exclusion was associated with activity in an affective salience network including IFG, amygdala, and sgACC. Whereas the association between social exclusion and activity in IFG and sgACC has consistently been reported in both adolescents and adults (Cacioppo et al., 2013; Rotge et al., 2015; Vijayakumar et al., 2017), amygdala activity is less often associated with experience of social exclusion (Eisenberger et al., 2007). Together, these findings indicate that experience of possible social exclusion might be a meaningful event for children. Additionally, experience of inclusion was associated with activity in bilateral insula, ACC, and striatum. These regions have previously been associated with signaling appraisal of upcoming events (Shenhav et al., 2016) and reward processing (Bhanji and Delgado, 2014; Delgado, 2007), indicating the importance of being included in middle childhood. In interpreting these findings it should be noted that the experience of social exclusion and inclusion in the Prosocial Cyberball Game differs from experiencing social exclusion in the traditional Cyberball Game, as participants in our study were only excluded for short periods of time (3–5 trials) before being included again. Therefore, it is possible that the short intervals of social exclusion were only processed implicitly by the participants. In addition, the event of not receiving the ball from the other two players might have resulted in expectancy violation or disengagement from the task in the participant, thereby decreasing the experience of social exclusion. However, the alternating pattern of acceptance and rejection in the Prosocial Cyberball Game is comparable to other paradigms that have measured responses to social rejection by providing alternating positive and negative feedback to participants (Achterberg et al., 2016; Gunther Moor et al., 2010a,b; Silk et al., 2014; Somerville et al., 2006).

We were also interested in testing how children act upon observing social exclusion. Whereas earlier studies in adults showed that more prosocial behavior was related to increased activity in mPFC, we found that in children prosocial compensating was associated with increased activity in PCC/precuneus. This region has previously been associated with retrieval of social information (Pfeifer et al., 2007) and empathy (Masten et al., 2011), and is seen as part of the default mode network that specializes in mentalizing (Hyatt et al., 2015). Interestingly, in previous research in adults more prosocial behavior was related to activity in the TPJ (van der Meulen et al., 2016), which has also been associated with mentalizing and perspective taking (Carter and Huettel, 2013; Hyatt et al., 2015). We also found a negative association between prosocial behavior and activity in the bilateral insula, consistent with other studies towards insula activation during prosocial behavior in adolescence (Güroğlu et al., 2014; Schreuders et al., 2018). However, previous research in adults showed a positive association between activity in bilateral insula and prosocial compensating towards the excluded player (van der Meulen et al., 2016). Together, these findings suggest that the brain network involved in mentalizing and prosocial behavior continues to develop from childhood to adulthood. Possibly, the PCC holds the function of mentalizing during childhood, while the

TPJ holds this function in adulthood. The function of the bilateral insula possibly changes to accommodate this shift in function. Longitudinal studies are necessary to examine this in more detail.

When we investigated heritability of the neural reactions towards social exclusion, we found that across all ROIs differences in activity were best accounted for by unique environmental factors and measurement error. Although heritability of brain function has received little attention in earlier studies, our overall findings fit with a prior study on heritability of the neural correlates of social rejection in middle childhood (Achterberg et al., 2018b) that also reported large influences of unique environment and/or measurement error, and smaller influences of genetics (estimated between 10–14%). In the current study, ACE models showed significant genetic contributions in two out of our nine ROIs: We found that differences in activity in IFG and smPFC during the experience of possible self-exclusion were best accounted for by genetic (estimated 29–33%) and unique environmental factors/measurement error. These findings are partly consistent with earlier research showing that there is more similarity in activity during cognitive tasks in adult MZ twins than DZ twins, with estimated influences of genetics ranging from 40 to 65% (Jansen et al., 2015). It should be noted that earlier studies towards the heritability of brain function mostly studied well-defined and highly reliable processes (e.g. processing of visual stimuli; Polk et al., 2007). Possibly, genetic effects are less pronounced in brain activity for complex social situations (such as social exclusion) that encompass relatively more individual differences, due to a strong interplay of genetics and personal experiences (van Harmelen et al., 2014; van Schie et al., 2017). In the current study, we had no a-priori hypotheses for the selected ROIs and the outcomes of the ACE models were not corrected for multiple comparisons. Our sample size for heritability analyses was also relatively small (N = 168), but comparable to earlier studies in infants and children (Achterberg et al., 2018a, b; Bakermans-Kranenburg et al., 2004; van den Heuvel et al., 2013). Therefore, our findings should be regarded as exploratory and as a starting point for future studies towards heritability of neural activity for complex social situations.

Our control analysis on heritability of total brain volume showed that differences in total brain volume were accounted for by genetic (86%) and unique environmental factors. This finding fits well with earlier research on heritability of total brain volume in children, which indicated moderate to high heritability in children (Jansen et al., 2015; Teeuw et al., 2018). Possibly, the divergence in our findings for brain activity and brain structure can be explained by the fact that brain structure is a more stable measure, whereas brain activity for complex social stimuli shows more state-like characteristics. For example, it has been found that neural responses to social exclusion in a Cyberball Game change when participants feel emotionally supported (Onoda et al., 2009), whereas brain structure is less affected by these individual state differences. In addition, functional MRI has relatively lower signal to noise ratio than structural MRI, especially for social processes (Lieberman and Cunningham, 2009) such as social exclusion and prosocial behavior. The larger amount of noise in functional MRI could lead to an overestimation of unique environment and/or measurement error, compared to structural MRI. A direction for future studies would be to focus on disentangling influence of measurement error and unique environment in the E component (for example by using repeated measures to account for intra-subject fluctuations as described by Ge et al. (2017)), as this is currently not possible in ACE modelling. Nonetheless, the finding of heritability of total brain volume shows that the current sample size is sufficient to estimate heritability of if within-twin correlations are at least moderately strong.

4.1. Strengths and limitations

This study had several strengths. To our knowledge this is the first research conducted on neural correlates of experiencing self-exclusion, self-inclusion, and prosocial behavior, with a large sample size that allowed us to investigate individual differences. Moreover, the twin design allowed us to test for influences of genetics and shared and unique environment on differences in neural activity during social exclusion and prosocial behavior, which has not been investigated before.

Some limitations of this study should also be noted. First, we now focused on the Unfair Game to control for time effects and to allow for a clear comparison of tossing to excluded and excluding players. An adaptation of this design in future studies would provide further insight in prosocial compensating behavior by also examining brain activity during the Fair Game. Additionally, in the current design it is difficult to differentiate between different motives for engaging in prosocial behavior. Although it is an advantage that we now studied reactions to observed social exclusion in a relatively controlled environment, for future studies it would be interesting to also investigate a more diverse battery of prosocial tasks. Second, although our neural findings for the experience of possible self-exclusion are comparable to earlier studies on social rejection, we have no additional information on the participant's experience of being excluded. For future studies, exit questions about how participants felt when they did not receive the ball from excluding players 1 and 3 could lead to more insight in the participant's experience. Third, genetic contributions for fMRI were relatively low and were only observed for one contrast (possible self-exclusion). Therefore, not all brain areas that were selected as ROIs might be equally suitable for investigating influences of genetics and environment. For example, amygdala activity has shown low to moderate test-retest reliability in an earlier study (Sauder et al., 2013; van den Bulk et al., 2013), indicating that this might not be a very stable outcome measure (but see Lumian and McRae, 2017). In addition, the ROIs selected in the current study were based on clusters of whole brain activation, thereby decreasing individual variation in activation of these brain regions. Possibly, this has made the current selection of ROIs less suitable for discovering genetic and environmental influences on differences in brain activity. Final recommendations for future research would be to also include a control task (preferably not aimed at measuring social exclusion) to test whether the current heritability results on neural activation are specific for a social exclusion context, or whether these results are applicable for brain activity in various brain regions. In addition, it would be very interesting to study overlapping effects of genetics and environment on both behavior and brain activation, to find out whether similar heritability mechanisms are driving differences in behavior and brain activation.

4.2. Conclusion

The current study builds upon the existing literature by showing that children show prosocial compensating behavior when they observe social exclusion. Further, although we note that certain conclusions are based on reverse inference, our findings suggest that children experience possible social self-exclusion as a negative event (as indicated by activity in IFG, smPFC and amygdala), inclusion as a positive and salient event (as indicated by striatum and ACC-insula activity) and that prosocial compensating behavior is partly driven by mentalizing capacities (as indicated by activity in PCC). Heritability analyses showed that differences in both prosocial behavior and neural activity during possible self-exclusion and prosocial behavior are potentially driven by unique environmental factors, but since measurement error is relatively high in fMRI research due to higher signal-to-noise ratio's, at this point the role of unique environment versus measurement error remains inconclusive. In future research, it will be important to study the neural processes and heritability profiles across multiple stages of development, and to test for heritability estimates of activity in specific brain regions to further investigate sensitive periods in development.

Conflict of Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.dcn.2018.05.010

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