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Heightened neural sensitivity to social exclusion in boys with a history of low peer preference during primary school

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ABSTRACT

Peer preference among classmates is a highly influential factor in children's social development and not being preferred by peers has long-term consequences for children's developmental outcomes. However, little is known about how a history of low peer preference during primary school is associated with neural responses to a new social exclusion experience in childhood. In this functional magnetic resonance imaging (fMRI) study, we examined self-reported social distress and neural responses to social exclusion using the Cyberball paradigm in primary school boys (M_{age} = 10.40 years) with a history of low (n = 27) versus high peer preference (n = 28). Boys were selected from a longitudinal classroom-based study in which children's peer social preferences were assessed in three consecutive years prior to this study. Neuroimaging results showed that low peer preferred boys exhibited increased activation in the bilateral dorsolateral prefrontal cortex and right supramarginal gyrus during social exclusion as compared to high peer preferred boys. Increased neural activity was not accompanied by higher self-reported levels of social distress during social exclusion in low versus high peer preferred boys. Findings of this study may provide insight into the neural processes associated with real-life peer experiences in children attending primary school.

1. Introduction

Peer relationships during primary school are important for children's social and emotional development (Bukowski et al., 2018). However, some children are less preferred by their classmates in primary school (Gifford-Smith and Brownell, 2003). Classroom peer preference is the appraisal of a child by classroom peers and is typically assessed by asking classmates to nominate children they like and dislike (Cillessen and Bukowski, 2018). Children who are low preferred by classmates are aware that they are disliked in the peer group and do experience negative peer treatment (e.g., social exclusion), even if classmates do not provide immediate feedback to the child about the low preference (Buhs et al., 2006; Cillessen and Bellmore, 1999). Low preference among classmates may sensitize children to expect new negative peer treatment, a process referred to as rejection sensitivity (Downey and Feldman, 1996; London et al., 2007). Rejection sensitivity may be expressed as altered neural processing during new stressful social experiences, as found in adolescents (Burklund et al., 2007; Masten et al., 2009). Yet, little is known about how a history of low peer preference during primary school may translate into neural processing of a new, experimentally induced social exclusion experience in childhood. Hence, we studied 10-year-old children with a history of low versus high peer preference in early/mid primary school and examined their neural responses to social exclusion using Cyberball.

1.1. Neural responses to social exclusion

Being excluded or non-preferred is painful and distressing because it thwarts one's fundamental need to belong (Williams, 2007). Prior studies with adolescents and adults examined normative neural responses to a single episode of social exclusion and found that distress following exclusion is associated with activity in the anterior cingulate cortex (ACC), insula, and medial prefrontal cortex (mPFC) (Cacioppo et al., 2013; Masten et al., 2009; Vijayakumar et al., 2017). Recovery from

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social exclusion is achieved by regulation of the negative emotions, a process that is linked to the lateral PFC (Eisenberger et al., 2003). Recent studies have shown that neural processing of social stressors already occurs in children aged 7–10 years (Achterberg et al., 2018; van der Meulen et al., 2017, 2018). Moreover, as the regulatory function of the PFC improves, children's ability to regulate exclusion-related distress is thought to increase (Guyer et al., 2016). However, these prior studies focused on understanding the normative neural responses to social stressors during development. In this study, we examined how prior real-life social experiences during primary school may shape children's neural responses to social exclusion.

1.2. *Classroom peer experiences and the shaping of neural responses to social exclusion*

Being low preferred by peers in primary school may increase children's sensitivity to new negative peer treatment (London et al., 2007; McLachlan et al., 2012) by shaping neural responses to new exclusion experiences. Increased sensitivity may become expressed in the PFC as it still undergoes marked developmental changes until young adulthood (Achterberg et al., 2018; Gogtay et al., 2004; van der Meulen et al., 2018). Empirical work indeed found heightened dorsal ACC (dACC) activation in adolescents with negative social experiences such as a history of low peer preference or victimization during primary school (de Water et al., 2017; Masten et al., 2012; Rudolph et al., 2016; Will et al., 2016). In some studies, this difference in neural reactivity coincided with differences in self-reported social distress, although this was not found consistently (Rudolph et al., 2016; Will et al., 2016).

Previous studies thus have shown that prior social experiences may shape neural responses to social exclusion. However, these studies were conducted among adolescents during the secondary school period. It is uncertain how the results of these studies translate to childhood. For example, the dACC has been commonly found as a neural correlate of social exclusion in adolescents and adults (Cacioppo et al., 2013; Rotge et al., 2014; however see Vijayakumar et al., 2017) but not in children aged 7–10 years (van der Meulen et al., 2017, 2018). In addition, puberty may influence the neural reactivity to social exclusion (Silk et al., 2014). Importantly, later childhood may be a key period for studying the shaping of neural sensitivity to social exclusion. During primary school, children are for the first time exposed to prolonged experiences of low peer preference, which may result in the development of rejection sensitivity already during childhood (McLachlan et al., 2012). Moreover, especially at the end of primary school, experiences of low peer preference are linked to the development of negative outcomes such as internalizing symptoms (Ladd, 2006).

1.3. *Study overview*

In this study we examined how neural and subjective responses to a new social exclusion experience differed between boys with a history of low peer preference and boys with a history of high peer preference in primary school. We focused on boys because only a limited number of children could be included per classroom (see methods), and boys may be more oriented towards status in the peer group and more affected by low peer acceptance than girls, who are more focused on close friendships (Rose and Rudolph, 2006; Rudolph, 2002). We hypothesized that prior experiences of low peer preference would sensitize children to new social exclusion experiences resulting in higher levels of social distress following social exclusion compared to children with a history of high peer preference. Moreover, based on prior studies suggesting large environmental influences on PFC functioning in children (Achterberg et al., 2018; van der Meulen et al., 2018) and studies showing increased dACC activation during social exclusion for adolescents with adverse peer experiences (Rudolph et al., 2016; Will et al., 2016), we further hypothesized that this sensitivity would be reflected in increased activation in PFC regions implicated in social exclusion such as the dACC, medial PFC and lateral PFC for boys with a history of low peer preference compared to boys with a history of high peer preference in primary school.

2. Methods

2.1. *Participants*

Neural responses to social exclusion of 55 primary school boys (mean age = 10.40 years, *SD* = 0.74, median = 10.54, range = 8.32–11.66 years) were collected in June 2016 – May 2017 during a functional magnetic resonance imaging (fMRI) session. The participants were selected from a longitudinal classroom-based study on the social, emotional and cognitive development of children during primary school (Behnsen et al., 2018; de Wilde et al., 2016; Tieskens et al., 2018). Only boys were selected for the following reasons. First, children were selected from 30 classrooms across eight schools. Therefore, participants who completed the fMRI study could share information with their classmates on the social exclusion deception used in this study (although participants were asked not to share this information with classmates). To minimize this risk, we decided to approach no more than six children per classroom with an anticipated inclusion rate of two to three children per classroom. Second, sex differences in responses to low peer preferences are likely. Boys are more status-oriented toward the broader peer group than girls (Rose and Rudolph, 2006; Rudolph, 2002). As the present study addressed the influence of classroom peer preference on neural responses to social exclusion we decided to only include boys. To address this potential sex effect, we would have needed to include twice as many participants, resulting in too many children per classroom.

Participant selection was based on children's classroom social preference scores, which were assessed across three annual waves (2013–2015; see measures), prior to selection for the fMRI study (Fig. 1). Correlations between social preference scores of adjacent years were respectively .71 and .70 (*p's* < .001). These correlations are comparable to stability levels found in a meta-analysis by Jiang and Cillessen (2005), and suggest high stability of social preference across years. The social preference scores of each child in the longitudinal study were averaged across the three waves. Boys with an average social preference across three years falling in the 35% lowest percentile were classified as having a history of below average social preference (henceforth referred to as 'low peer preferred'). Boys falling in the 35%

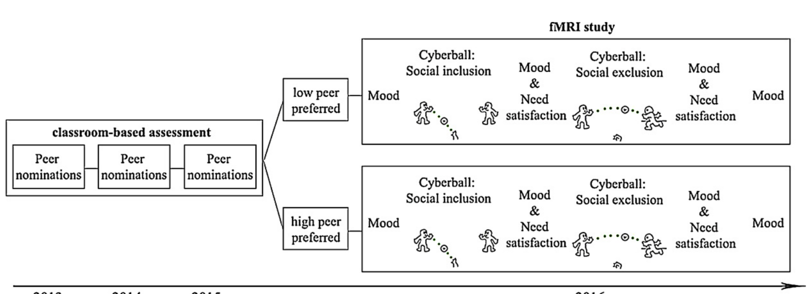

Fig. 1. Overview of study design. Participants were selected for the fMRI study based on their average social preference scores over three years (2013–2015) that were assessed using peer nominations during the classroom-based assessment. Children who were in the 35% lowest percentile of the average social preference score were classified as low peer preferred and children in the 35% highest percentile were classified as high peer preferred. During the fMRI study participants played a social inclusion and social exclusion round of the Cyberball and were assessed at multiple time points on their mood and need satisfaction levels using self-reports.

highest percentile were classified as having a history of above average social preference (henceforth referred to as 'high peer preferred'). None of the low peer preferred children scored one standard deviation above the mean of social preference on any of the three waves. Likewise, none of the high peer preferred children scored one standard deviation below the mean of social preference score on any of the three waves.

Based on the selection criteria 169 boys were eligible for participation in the fMRI study. Valid contact information of 30 boys was missing. Parents of the remaining 139 boys were contacted. Of these 139 boys, 70 boys or their parents did not give consent. Five boys had braces, one boy reported hypoxia during birth, and one boy moved to a school for children with special needs. These boys were therefore excluded from participation. Sixty-two boys (32 low peer preferred, 30 high peer preferred) agreed to participate in this study. Participants were slightly older (M = 10.95, SD = 0.77) than non-participants (M = 10.69, SD = 0.82, $F(1, 165) = 3.24$, p = .05), and had lower social preference scores (M = -0.25, SD = 1.09) compared to non-participants (M = -0.15, SD = 1.07, $F(1, 165) = 6.44$, p = .012), but this difference in age and social preference for participants and non-participants was similar for low and high peer preferred boys, respectively p = .24 and p = .93.

Of the 62 boys who participated in the MRI data collection, data of seven boys were excluded because of a brain anomaly (one high peer preferred boy) or head movements exceeding more than 3 mm (1 voxel) in at least one direction (one high peer preferred and five low peer preferred boys). All participants reported not to have MRI contra-indications such as claustrophobia, head injuries, disorders related to degeneration of the nervous system (e.g., multiple sclerosis), or a history of head injury resulting in loss of consciousness for more than 10 min. Parents of six low peer preferred boys reported that their child was diagnosed with an Axis-I disorder (attention deficit-hyperactivity disorder (ADHD), n = 5; autism, n = 1). Of the three participants diagnosed with ADHD who were on methylphenidate, two continued their use of methylphenidate during the day of testing. The majority of the participants (80%) of the present study were from a Dutch ethnical background, 15% of the children were from a mixed ethnical background, and information on ethnical background was missing for five percent of the children.

Informed consent for participation was obtained from parents according to the Declaration of Helsinki (World Medical Association, 2013). All study procedures were approved by the national ethics review board of the Netherlands (protocol no: NL53637.000.15). Children received two entry tickets, worth €38 in total, to a local zoo for their participation.

2.2. Procedures

2.2.1. Classroom-based assessment

During the three consecutive annual school visits prior to this study children completed the peer nominations measure (see measures) in their classroom. In addition, children reported on their pubertal development using the Pubertal Development Scale (Petersen et al., 1988, see supplementary material). Trained research assistants (master level or completed psychology education) instructed and supervised the children when completing the questionnaires. Children were seated in exam formation and were monitored for not sharing information with classmates. Children received a small gift for participation at the end of each annual school visit.

2.2.2. Lab-based assessment

The fMRI assessments were conducted at the Donders Institute for Brain, Cognition, and Behavior in Nijmegen, The Netherlands. After arriving at the lab, participants first completed the Social Experiences Questionnaire (Storch et al., 2005) to assess victimization levels and then completed a short Intelligence Quotient (IQ) task (i.e., WISC-III; Wechsler, 1991). Parents completed the Child Behavior Checklist (6–18 years) (Achenbach and Edelbrock, 1983) and Social Responsiveness Scale (Constantino and Gruber, 2012) to assess participants' behavioral and social problems, respectively (see supplementary materials). Before scanning, participants were familiarized with the scanning procedure in a practice session at the MRI scanner. After the practice session, participants were placed in the MRI scanner to acquire a resting-state scan and anatomical scan (15 min). Participants then left the MRI scanner for a short break. After the break participants completed a battery of cognitive tasks including the social exclusion task in the MRI scanner (30 min).

2.3. Measures

2.3.1. Classroom social preference

Classroom peer social preference was assessed in the spring of 2013 (T_1), 2014 (T_2) and 2015 (T_3). All children in the classroom whose parents granted their participation in the study completed a peer nomination form on an iPad. Children were asked to nominate an unlimited number of classmates who they liked and disliked. Like and dislike nominations were Z-standardized within each classroom. A social preference score was computed by subtracting the Z-standardized dislike from the Z-standardized like nomination score ($Z_{like} - Z_{dislike}$). This social preference score was then again Z-standardized within classrooms to allow for a comparison of social preference scores between children from different classroom sizes (Coie et al., 1982).

2.3.2. Social exclusion paradigm

The Cyberball computer game was used to assess neural correlates of social exclusion (Williams and Jarvis, 2006). As a cover story, participants were told that they would play two rounds of an on-line ball tossing game in the scanner together with two same-aged anonymous boys. Similar to other studies (van Beest and Williams, 2006; Will et al., 2016; Williams and Jarvis, 2006), participants were instructed to imagine the appearances of the other players and the location and weather conditions where they played the ball-tossing game. In reality the game was offline and the ball tosses were preprogrammed. The two other players were depicted as two cartoon images in the upper left and upper right corners of the screen. Participants were depicted by an image of a hand in the middle bottom part of the screen. Participants could toss a ball to the right or left player by pressing, respectively, a right or a left button of a MRI compatible button box. The right button was pressed using the index finger of their right hand and the left button was pressed using the middle finger of their right hand.

Similar to prior studies (e.g., Gunther Moor et al., 2012; Will et al., 2016), participants first played one social inclusion round followed by one social exclusion round of 30 tosses each. The inclusion and exclusion rounds were administered in two separate runs that lasted approximately 1.5 min each. In the social inclusion round each player received the ball an equal amount of times. That is, the participant received the ball in 10 of the 30 tosses. For the other tosses, the ball was either tossed from the participant to one of the other players (10 tosses) or between the two other players (10 tosses). In the social exclusion round the participant received the ball only once at the beginning of the game, followed by one toss from the participant to one of the other players. For the remaining 28 trials the ball was tossed between the two other players. The duration of each ball toss was two seconds. Ball tosses of the participant were self-paced. Ball tosses of the two other players were preceded by a pseudorandom jitter between 125–4000 ms. After participation, children were debriefed about the deception used in this task and were asked not to share this information with classmates.

2.3.3. Social distress

To assess exclusion-related social distress a shortened version of the mood (Gunther Moor et al., 2012; Will et al., 2016) and need satisfaction questionnaire (van Beest and Williams, 2006; Will et al., 2016) were used.

Mood was rated by the participant at four times, (1) at the start of the procedure, (2) directly after social inclusion, (3) directly after social exclusion, and (4) at the end of the procedure. Mood levels at time 1 and 4 were completed on an iPad outside the MRI room. Mood at time 2 and time 3 were completed inside the MRI scanner. Participants could indicate their answers using the MRI compatible button box. The mood questionnaire consisted of four items (*"I feel happy/sad/ relaxed/tense")* and could be answered on a five-point Likert scale, ranging from 1 (not at all) to 5 (very much). Similar to other studies (Gunther Moor et al., 2012; Will et al., 2016) responses on negative emotional items (*"I feel sad/tense"*) were reverse coded and the mean of the four items was calculated to create a measure of overall mood for each time point. Internal consistency of the mood questionnaire after social inclusion was low (Cronbach's $\alpha = .36$) and somewhat low for the other time points (α's between .62–.65). Lower mood levels after social exclusion indicated higher levels of exclusion-related social distress.

Need Satisfaction was assessed twice while the participant was in the MRI scanner, directly after social inclusion and directly after social exclusion. Using the button box, participants could rate their levels of need satisfaction on each item on a 5-point Likert scale (1 = not at all; 5 = very much). The need satisfaction questionnaire consisted of one item for belongingness (*"I had the feeling that the other players thought it was nice that I was there")*, one item for control (*"I had the feeling I had control over the game")*, one item for self-esteem (*"I felt good about myself during the game")*, and one item for meaningful existence (*"I had the feeling that I was important during the game")*. A mean of these four items was computed at each time point as a measure of overall need satisfaction (van Beest and Williams, 2006; Will et al., 2016). Internal consistency of the need satisfaction questionnaire after social inclusion was low ($\alpha = .45$), but good after social exclusion ($\alpha = .85$). Lower scores for overall need satisfaction after social exclusion indicated higher levels of exclusion-related social distress.

2.4. Image acquisition

Scans were acquired using a 3.0 T MAGNETOM Prisma MRI scanner and a 32-channel head coil (Siemens Healthcare, Erlangen, Germany). Participants could view the screen through a mirror mounted on the head coil. Participants were slightly restrained by using foam inserts around their head and a tape placed across the forehead and head coil. Whole-brain multi-echo GRAPPA T2*-weighted imaging was used to acquire functional images during Cyberball (repetition time = 2240 ms, echo times = 9.0, 19.07, 29.14, 39.21, 49.28 ms, field of view (FOV) = 224 mm, voxel size = 3.5 × 3.5 × 3.0 mm, flip angle = 90°). For both sessions, 32 slices per volume were acquired in ascending interleaved order with a slice thickness of 3 mm. Before the first functional run we collected 30 volumes (prescans). For within-subject registration, a whole-brain T1-weighted anatomical scan was acquired (192 slices, TR = 2300 ms, TE = 3.03 ms, FOV = 256 mm, voxel size = 1.0 × 1.0 × 1.0 mm, flip angle = 8°).

2.5. Data analysis

2.5.1. Preprocessing

Functional images were preprocessed and analyzed using Statistical Parametric Mapping version 12 (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK). The 30 prescans were used to generate optimal weighting parameters for the five echo times to combine the functional data into one image per volume (Poser et al., 2006). Next, functional images were realigned, slice-time corrected, co-registered with the grey matter segmented T1-weighted anatomical image, and normalized to the MNI152 template using the unified segmentation approach with a resampling rate of 2.0 × 2.0 × 2.0 mm voxel size (Ashburner and Friston, 2005). Normalized images were smoothed with a Full Width Half Maximum kernel of 6 mm. Independent component analysis (ICA-AROMA) was used to identify and correct for motion-related noise (Pruim et al., 2015).

2.5.2. Neuroimaging analysis

A first-level general linear model was performed. Following previous studies (e.g., Gunther Moor et al., 2012; Will et al., 2016) the design matrix included four regressors of interest: receiving the ball (Receive), tossing the ball (Toss), tosses between the other players during the inclusion round (Others), and tosses between the other players during the exclusion round (Exclusion). Events were modelled as zero-duration events at the onset of the event. Events were convolved with a canonical hemodynamic response function to model the blood-oxygen-level dependent (BOLD) response. Finally, data were pre-whitened to remove any temporal autocorrelation in the data by using a first order autoregressive model. Data were high-pass filtered at a frequency of 128 Hz.

Contrast images were generated at the participant level. First, we examined which brain regions were sensitive to a social context in which participants were excluded. A contrast image was generated for the events in which the ball was tossed between the other players during the exclusion round versus events in which the two other players tossed the ball to each other during the inclusion round [Exclusion > Inclusion: Others]. In this contrast image both types of events were identical (i.e., a ball toss between the two other players). However, during the exclusion round participants had the continuous experience of being excluded from the game while during the inclusion round participants were included in the game.

Second, we examined which brain regions were more active during the experience of social exclusion relative to being included by the other players. We computed a second exclusion contrast and contrasted exclusion events in the exclusion round with events in which participants received the ball from one of the other players during the inclusion round [Exclusion > Inclusion: Receive].

Third, we examined which brain regions were more active during a single-trial exclusion experience in the social context of being overall included, henceforth referred to as incidental exclusion. We contrasted events in which the ball was tossed between the two other players during the inclusion round with trials in which the ball was tossed to the participant during the inclusion round [Inclusion: Others > Inclusion: Receive]. Participants were overall included in this round but these short single-trial exclusion events may have provided socially salient cues about the start of a social exclusion experience.

For the contrasts [Exclusion > Inclusion: Others] and [Exclusion > Inclusion: Receive] the number of events were imbalanced (i.e., 28 events > 10 events). Therefore, variance for the inclusion condition may have been larger than for the exclusion condition. However, the optimal number of exclusion trials for children younger than 12 to remain engaged is 20 trials (Zadro et al., 2013). Given that we had young children who were potentially very sensitive to social exclusion (i.e., low peer preferred boys) we decided to keep both the inclusion and exclusion round as short as possible. Moreover, prior studies used the same event-related design with 10 events for the [Inclusion: Others] and [Inclusion: Receive] conditions (Gunther Moor et al., 2012; Lelieveld et al., 2013; van Harmelen et al., 2014; Will et al., 2016, 2015) and found similar results to studies that used more trials (de Water et al., 2017; van der Meulen et al., 2018) or block designs (Masten et al., 2011, 2009; Masten et al., 2012; Puetz et al., 2014).

Individual contrast images were submitted to whole-brain random-effect two-sample *t*-tests to assess differences in neural responses between boys with a history of low versus high peer preference. A Bonferroni correction accounted for the number of contrasts (n = 3) tested (i.e., alpha = .017). Therefore, results were considered significant using False Discovery Rate (FDR) cluster-correction at $p <$ .017, with an initial cluster-forming threshold of $p < .005$. To facilitate interpretation of significant findings beta weights of functional significant clusters were extracted using the MarsBar toolbox (Brett

Table 1
Sample Characteristics of Low Peer Preferred Boys and High Peer Preferred Boys.

	low peer preferred	high peer preferred	t-value
N	27	28	
Social preference (SD)	−1.17 (0.62)	0.78 (0.31)	14.95***
Age (SD)	10.32 (0.77)	10.44 (0.73)	0.57
Range	9.34 – 11.50	8.32 – 11.60	
Pubertal development (SD)	1.00 (1.14)	1.04 (1.09)	−0.13
Mean IQ (SD)	112.85 (17.97)	110.54 (14.75)	−0.52
Average head motion (SD)	0.52 (0.46)	0.42 (0.41)	−0.90
Mean SEQ score (SD)			
Relational victimization	1.76 (0.56)	1.44 (0.45)	−2.35*
Physical victimization	1.87 (0.77)	1.39 (0.44)	−2.86**
Mean CBCL t-score (SD)			
Affective problems	59.81 (11.00)	57.07 (7.48)	−1.08
Anxiety problems	58.00 (5.69)	56.89 (6.23)	−0.69
ADHD symptoms	58.37 (7.95)	54.64 (4.66)	−2.13*
ODD symptoms	58.30 (6.61)	54.35 (5.51)	−2.40*
CD symptoms	56.33 (6.77)	53.85 (5.18)	−1.53
Mean SRS t-score (SD)			
Social awareness	49.59 (9.93)	48.32 (6.23)	−0.57
Social cognition	50.04 (10.41)	47.71 (6.72)	−0.99
Social communication	51.66 (10.69)	45.18 (4.98)	−2.90**
N Axis-I disorder reported by parents	6[a]	0	

Note. SEQ = Social Experience Questionnaire (self-report), CBCL = Child Behavior CheckList (parent-report), SRS = Social Responsiveness Scale (parent-report), ADHD = attention deficit-hyperactivity disorder, ODD = oppositional deviant disorder, CD = conduct disorder.
[a] 5 ADHD, 1 autism.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

et al., 2002)

3. Results

3.1. Descriptive statistics

Sample characteristics are given in Table 1. Low peer preferred boys scored higher on self-reported relational and physical victimization and on parent-reported symptoms of ADHD and oppositional deviant disorder (ODD) than high peer preferred boys. Parent-reported social communication difficulties were higher for low peer preferred boys than for high peer preferred boys. Low and high peer preferred boys did not differ in age, pubertal development or IQ.

Fig. 2 shows the scores for mood and need satisfaction levels for low and high peer preferred boys. A repeated measures ANOVA showed no group differences in mood over time for low and high peer preferred boys, $F_{time*group}(3, 156) = 1.67$, $p = .175$, $\eta^2 = .03$ (Fig. 2A). Therefore, overall changes in mood over time were interpreted. Mood increased from the start of the procedure to inclusion, but dropped significantly after exclusion, and recovered at the end of the procedure, $F_{time}(3, 156) = 62.53$, $p < .001$, $\eta^2 = .55$. The individual mood items demonstrate similar results as the overall mood questionnaire (Supplementary Fig. S1).

A repeated measures ANOVA showed that need satisfaction decreased significantly from inclusion to exclusion, $F_{time}(1, 53) = 355.54$, $p < .001$, $\eta^2 = .87$, but changes in need satisfaction differed significantly between low and high peer preferred boys, $F_{time*group}(1, 53) = 4.27$, $p = .044$, $\eta^2 = .08$. As depicted in Fig. 2B, low peer preferred boys exhibited less need satisfaction after inclusion ($M = 2.64$, $SD = 0.67$) than high peer preferred boys ($M = 3.00$, $SD = 0.54$, $t(53) = 2.21$, $p = .032$). Inspection of the individual need satisfaction items show that the found group difference are driven by the items self-esteem and feelings of control (Supplementary Fig. S1).

3.2. Neuroimaging results

Before examining our hypothesis on differences in neural responses to social exclusion between low and high peer preferred boys, we first examined neural responses to social exclusion across the sample. When data were collapsed across low and high peer preferred boys, social exclusion relative to inclusion (Exclusion > Inclusion: Others) elicited activation in a cluster in the left rostral ACC (rACC) and middle cingulate cortex. Incidental exclusion elicited activation in the middle occipital cortex (results in Supplementary Table S1 and Supplementary Fig. S1).

Results of the comparisons between low versus high peer preferred boys are shown in Table 2 and Fig. 3. Compared to high peer preferred boys low peer preferred boys exhibited increased activation in the bilateral dorsolateral prefrontal cortex (dlPFC) and right supramarginal gyrus (SMG) during social exclusion relative to social inclusion (Exclusion > Inclusion: Others). As shown in Fig. 3, extracted beta weights of the functional significant clusters demonstrated that during social exclusion low peer preferred boys showed higher activation in these regions relative to high peer preferred boys. In contrast, during social inclusion low peer preferred boys showed lower activation in these functional clusters compared to high peer preferred boys. Adding parent-reported behavioral problems, social impairments often associated with autism, or victimization as measured with respectively the CBCL, SRS and SEQ as a covariate did not change the results (Supplementary Table S2). This confirms that the group differences in neural responsivity to social exclusion were not driven by psychopathology or victimization.

No significant differences in neural activation were found for the second social exclusion contrast (Exclusion > Inclusion: Receive) or the incidental exclusion contrast (Inclusion: Others > Inclusion: Receive).

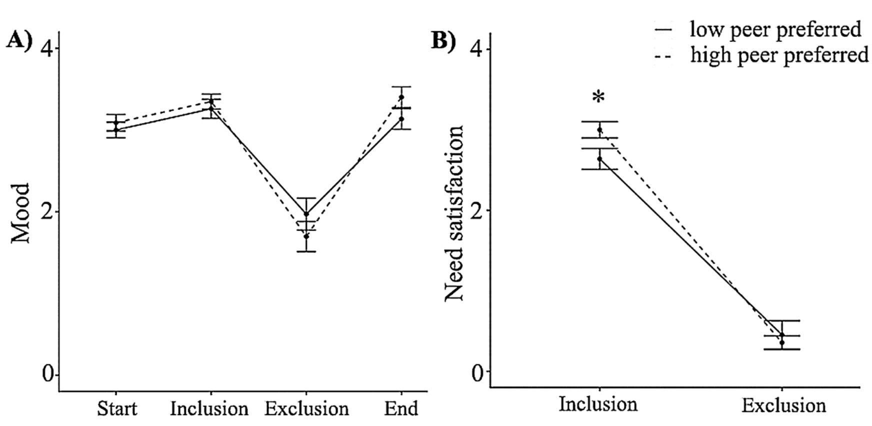

Fig. 2. Mood and need satisfaction levels for low and high peer preferred boys. (A) Mean levels of self-reported mood were assessed 30 minutes before social inclusion (start), after social inclusion, after social exclusion, and 30 minutes after social exclusion (end). (B) Mean levels of self-reported need satisfaction were assessed after social inclusion and after social exclusion. Error bars represent standard error of the mean. * $p < .05$.

Table 2
Significant Cluster Regions Revealed by Whole-brain Contrasts During the Cyberball Game Comparing Low Peer Preferred Boys to High Peer Preferred Boys.

				MNI coordinates		
Regions	Side	k	Z	x	y	z
Exclusion > Inclusion: Others						
Dorsolateral PFC (middle frontal gyrus)	R	821	4.95	40	36	40
			3.91	46	38	32
			3.76	24	32	32
Supramarginal Gyrus extending into Inferior Parietal Cortex	R	678	3.89	42	−34	48
			3.66	32	−52	34
			3.51	50	−40	34
Dorsolateral PFC (middle frontal gyrus)	L	770	3.91	−34	30	34
			3.74	−34	46	30
			3.56	−28	24	24
Exclusion > Inclusion: Receive						
No significant clusters found						
Inclusion: Others > Inclusion: Receive						
No significant clusters found						

Note. Side = left/ right hemisphere, k = number of voxels in cluster, Z = z-value reported at $p < .017$ FDR corrected, with an initial cluster-forming threshold of $p < .005$.

3.3. Region of interest (ROI) analyses

Results showed no group differences in dACC activation, a region found to be more active during social exclusion in adolescents with a history of negative social experiences in primary school (Rudolph et al., 2016; Will et al., 2016). To further examine the absence of dACC activation, we performed ROI analyses using SPM12's MarsBar toolbox (Brett et al., 2002). Beta weights for each event were extracted using the peak voxel coordinates of the dACC with a 6 mm sphere from the study by Will et al. (2016) (x = -3, y = 41, z = 16) and Rudolph et al. (2016) (x = 21, y = 32, z = 22). Beta weights of these ROIs showed that the dACC was active during both inclusion and exclusion conditions but activation during social exclusion (or during inclusion conditions) did not differ between low and high peer preferred boys (see Supplementary Table S3 and Supplementary Fig. S3).

4. Discussion

The aim of this study was to examine how prolonged experiences of low peer preference may shape neural responses to social exclusion in primary school boys. We found that social exclusion resulted in more self-reported social distress and increased neural activation in a cluster in the rostral ACC that extended into the medial PFC. This was in line with prior research with youths aged 13–17 years (Masten et al., 2009; Sebastian et al., 2011). However, we found that neural responsivity to social exclusion varied between boys with a history of low versus high preference by classroom peers in primary school. Low peer preferred boys showed more neural activation in the bilateral dorsolateral PFC (dlPFC) and right supramarginal gyrus (SMG) during social exclusion relative to social inclusion when compared to high peer preferred boys. We did not find significant group differences in subjective social distress after social exclusion.

4.1. Primary school social experiences and neural sensitivity to social exclusion

The heightened dlPFC activation during social exclusion for boys who were low preferred by peers may provide insight into their difficulties. The dlPFC is seen as an important area for top-down control of behavior such as emotion regulation (Goldin et al., 2008; MacDonald et al., 2000; Ochsner and Gross, 2005; Schmitz et al., 2004). Emotion regulation is the attempt to manage internal states (Eisenberg et al., 2004) and the regulatory function of dlPFC may directly lower social distress (Ochsner and Gross, 2005). Previous findings among children and adolescents using Cyberball support the idea of the dlPFC as a regulatory area during social exclusion (Nishiyama et al., 2015; Onoda et al., 2009; Puetz et al., 2014). Besides emotion regulation, dlPFC functioning also has been implicated in top-down attentional control (Corbetta and Shulman, 2002). Prior studies with young adults linked higher rejection sensitivity to increased vigilance to social rejection cues which was reflected in increased neural activation in top-down attentional control networks (Ehrlich et al., 2015; Kawamoto et al., 2015). Interestingly, high peer preferred boys showed greater dlPFC activity during social inclusion, whereas low peer preferred boys showed greater dlPFC activity during social exclusion. The opposite pattern of increased dlPFC activity between low and high preferred children suggests that low peer preferred boys may allocate more attention to new social exclusion experiences, and may need to regulate the social exclusion, whereas boys with a history of positive peer experiences allocate more attention to social inclusion. In other words, the increase in dlPFC activity during social exclusion in low peer preferred boys may indicate that these boys are more focused on social exclusion, whereas high peer preferred boys are more focused on social inclusion.

A second important insight of this study was the heightened activation in the right SMG during social exclusion for low peer preferred boys. Previous research has shown that the SMG is involved in the ability to infer mental states (Frith and Frith, 2007). Another study found associations between SMG activation and increased internal blame attribution (Seidel et al., 2010). Interestingly, adolescents who reported anxious expectations of new rejection experiences also reported more self-blame for negative social events than adolescents who do not have this anxious rejection sensitivity (Zimmer-Gembeck et al., 2016). The increased activation in the SMG may suggest that low peer preferred children blame themselves for a new exclusion experience while high peer preferred children do not. Future neuroimaging studies should address this.

A third important finding is that although previous studies found increased dACC activation for adolescents with a history of negative social experiences we did not find increased dACC activation in younger low peer preferred children (Rudolph et al., 2016; Will et al., 2016). The dACC has been linked to expectancy violation and conflict monitoring (Botvinick et al., 2004; Somerville et al., 2006), signaling salient events or information that is self-relevant (Dalgleish et al., 2017; Menon and Uddin, 2010; Perini et al., 2018), as well as processing both positive and negative social events (Achterberg et al., 2016). In line with this, our ROI results also showed that across groups the dACC was activated for both social inclusion and exclusion. However, against our hypothesis, low peer preferred boys did not show higher dACC activation during social exclusion compared to high peer preferred boys and thus deviates from the found group differences in prior adolescent studies (Rudolph et al., 2016; Will et al., 2016). One potential explanation for this difference may be that adolescents are more sensitive to negative social information (relative to positive social information) with the transition to secondary school, especially those with a history of adverse peer experiences (Crone and Dahl, 2012; Nelson et al., 2005). As mentioned earlier, later childhood may be an important period for studying associations between prior adverse social experiences and neural sensitivity to social exclusion (i.e., links with rejection sensitivity and psychopathology). The fact that our results were not comparable to the previous adolescent studies further emphasize the importance of studying social influences on neural correlates during childhood. Future studies are needed to assess at what age effects of low peer preference on neural responses to social exclusion emerge, whether the observed effects are reversible with changes in social preferences among peers, and whether neural responses to social exclusion change with the

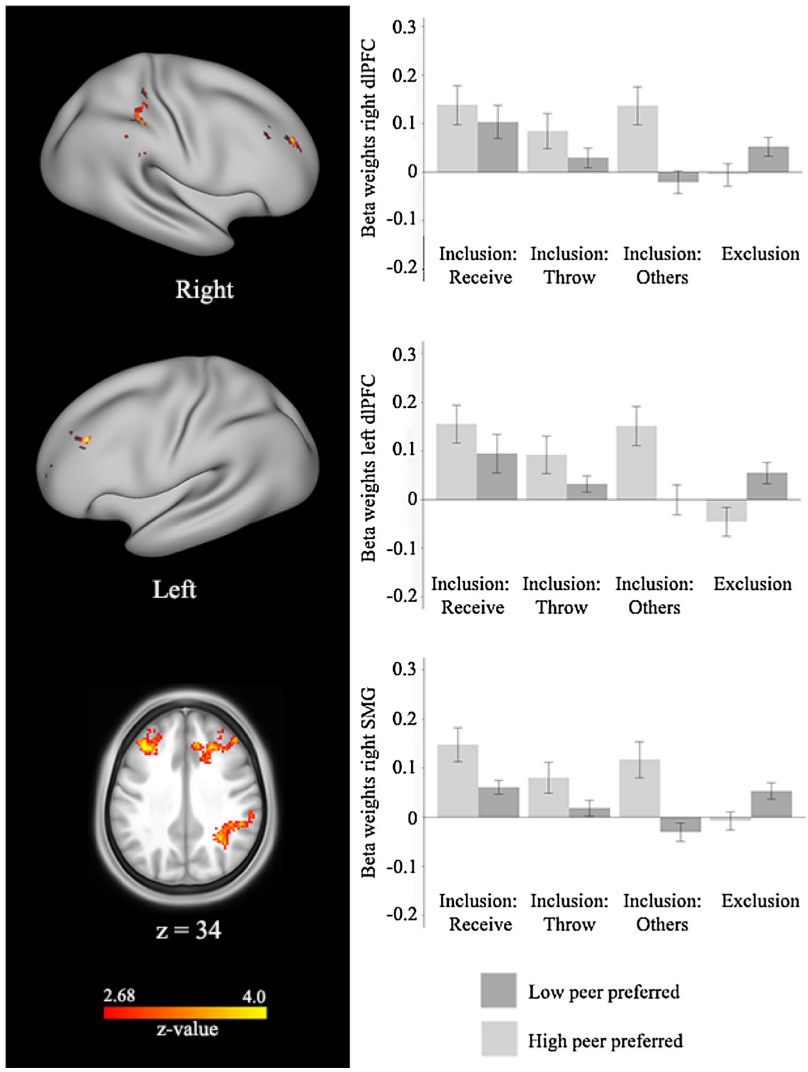

Fig. 3. Activation in clusters in bilateral dorsolateral prefrontal cortex and right supramarginal gyrus during social exclusion relative to social inclusion (Exclusion > Inclusion: Others) for low compared to high peer preferred boys. Results are reported at a cluster-level of $p < .017$ FDR corrected, with an initial cluster-forming threshold of $p < .005$. Beta weights from significant clusters were extracted to facilitate interpretation. Error bars represent standard error of the mean.

transition to secondary education.

4.2. Self-reported social distress

We did not find significant differences in self-reported social distress after social exclusion between low peer preferred boys and high peer preferred boys. However, previous findings on differences in subjective social distress in adolescents with and without negative peer experiences are mixed (Rudolph et al., 2016; Will et al., 2016). Apart from this, an additional explanation may be that children are less reliable in reporting behaviors and emotions than adolescents (Achenbach et al., 1987). The fairly low reliability of our mood and need satisfaction questionnaire may confirm this. Another explanation may be that the power to detect differences in subjective social distress between our two groups was low due to the low number of children tested. Last, responses to the mood and need satisfaction questions may have reached a floor effect after social exclusion and thus not allow us to find potential group differences after social exclusion. For these reasons, we are cautious in interpreting the absence in differences in subjective social distress between low and high peer preferred boys. Regardless of these limitations, the clear differences in *neural responses* suggest that already in primary school, low peer preferred children are more sensitive to a new social exclusion experience as is reflected in heightened neural activity in areas related to attention allocation, emotion regulation, and social cognition. Our results together with those from previous studies on adolescents provide evidence that negative peer experiences become biologically embedded. Our findings suggest that this process already begins in primary school.

4.3. Limitations

Some limitations should be acknowledged. First, the primary schools in the overarching longitudinal study from which participants were selected were situated in urban and rural regions in the eastern part of the Netherlands. As such, populations from the major cities in the western part were underrepresented. However, the percentage of children with a Dutch background in our sample (80%) was only slightly higher than in the national population (78.8%) (Statistics Netherlands, 2017). Moreover, we only included boys which may limit the generalizability of our results. Future studies are needed to determine whether findings extend to low peer preferred girls.

Second, the Cyberball paradigm had a fixed order of inclusion, followed by an exclusion round, with a relative low number of trials, especially for the inclusion round. This design was chosen to be comparable to prior studies on neural correlates of social exclusion in adolescents with a history of adverse social experiences (Rudolph et al., 2016; Will et al., 2016). Randomly changing the order of inclusion and exclusion would result in some children having the inclusion round after the exclusion round. This could change the meaning of the inclusion round (i.e., re-inclusion) and possibly in a different way for children with history of low peer preference than for children with a history of high peer preference. Regarding the number of trials, as this study included young and low peer preferred children who are potentially sensitive to exclusion experiences we wanted to keep the social exclusion experience short (Zadro et al., 2013). The low number of trials in the inclusion round may have resulted in more variance in the inclusion than the exclusion condition, which had more trials. However, prior studies showed that the Cyberball robustly evokes neural activity related to social exclusion throughout development (Eisenberger et al., 2003; Masten et al., 2009; van der Meulen et al., 2017, 2018; Vijayakumar et al., 2017). Additionally, results from studies using the same event-related design overlap with results from studies using a block design, more trials or alternating order of inclusion and exclusion trials (de Water et al., 2017; Masten et al., 2009; Rudolph et al., 2016; Sebastian et al., 2011; Will et al., 2016). This suggests that the chosen paradigm allows us to interpret how a history of low versus high peer preferences is associated with neural responses to social exclusion and how our findings relate to prior studies. Also, the Cyberball paradigm is a powerful measure to assess social exclusion with large effect sizes (Hartgerink et al., 2015). It is unclear how the impact of Cyberball exclusion experiences relate to the impact of potentially subtler every-day life adverse social experiences.

Third, participants were selected based on their average social preference score across three years. Low peer preference co-occurs with various difficulties, including peer victimization and problem behaviors (Buhs et al., 2006; Prinstein et al., 2018). Adding concurrent victimization or behavioral problems as covariates to our analysis yielded similar results (Supplementary Table S2), suggesting that peer preference is a robust predictor of differences in neural responses to social exclusion. However, other correlates of social preference were not accounted for, also due to limited sample size.

Finally, our results cannot be interpreted in terms of direction of effects. Low peer preferred boys may already have exhibited neural differences that may have predisposed them to show behaviors that resulted in low social preference among peers. Longitudinal studies are needed to disentangle the direction of effects.

4.4. Conclusion

Prior work has shown that low peer preference during primary school is linked to the development of rejection sensitivity in late childhood and that during this period links between social preference and internalizing problems become more profound (Ladd, 2006; London et al., 2007; McLachlan et al., 2012). Our results suggest that prolonged experiences of low peer preference become embodied in children's neurobiology during primary school. This embodiment of negative peer experiences may possibly explain their negative impact in development. Our findings emphasize that teachers, school psychologists and clinicians must be aware of the impact of low peer preference and exclusion on primary school children, and that schools should monitor and intervene in classroom peer rejection as early as possible.

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Appendix A. Supplementary data

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