Feeling left out or just surprised? Neural correlates of social exclusion and overinclusion in adolescence

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Abstract

Social belonging is an important human drive that influences mood and behavior. Neural responses to social exclusion are well-characterized, but the specificity of these responses to processing rejection-related affective distress is unknown. The present study compares neural responses to exclusion and overinclusion, a condition that similarly violates fairness expectations but does not involve rejection, with a focus on implications for models of dorsal anterior cingulate cortex (dACC) and anterior insula (AI) function. In an fMRI adaptation of the Cyberball paradigm with adolescents aged 11.1–17.7 years ($N = 69$), we employed parametric modulators to examine scaling of neural signal with cumulative exclusion and inclusion events, an approach that overcomes arbitrary definitions of condition onsets/offsets imposed on fluid, continuous gameplay. We identified positive scaling of dACC and posterior insula response with cumulative exclusion events, but these same regions exhibited trending signal *decreases* with cumulative inclusion events. Furthermore, areas within the dACC and insula also responded to context incongruity (throws to the participant in the exclusion run; throws between computer players in the overinclusion run). These findings caution against interpretations that responses in these regions uniquely reflect the affective distress of exclusion within social interaction paradigms. We further identified that the left ventrolateral PFC, rostromedial PFC, and left intraparietal sulcus responded similarly to cumulative exclusion and inclusion. These findings shed light on which neural regions exhibit patterns of differential sensitivity to exclusion or overinclusion, as well as those that are more broadly engaged by both types of social interaction.

Keywords Cyberball · Social exclusion · Functional MRI · Anterior cingulate cortex · Anterior insula

Introduction

From the earliest fMRI studies on social rejection, it has been proposed that the dorsal anterior cingulate cortex (dACC) and anterior insula (AI) process the affective distress underlying

both physical and social pain (Eisenberger, Lieberman, & Williams, 2003; Eisenberger, Jarcho, Lieberman, & Naliboff, 2006). This hypothesis suggests that neural resources dedicated to pain processing were co-opted over the course of evolution to make the experience of social rejection particularly salient, motivating the maintenance of close social ties and ultimately promoting evolutionary fitness (Baumeister & Leary, 1995; Eisenberger, 2012). While recent studies suggest that pain and social rejection have distinct representations in the dACC and AI (Woo et al., 2014; Kragel et al., 2018), many perspectives maintain a role for these regions in processing rejection-related affective distress.

This hypothesis can be evaluated by considering whether a brain region's responses are specific to social rejection compared with social overinclusion. Cyberball (Williams, Cheung, & Choi, 2000) is a virtual ball-tossing game commonly used to simulate social exclusion in neuroimaging studies (for review and meta-analysis, see Vijayakumar, Cheng, & Pfeifer, 2017). Such studies often compare social exclusion to a condition referred to as “social inclusion” that resembles fair play (i.e.,

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roughly equal participation by all players). However, this comparison forms a weak basis for claiming that a region is involved in processing affective distress, because exclusion differs from fair play by defying widely held baseline expectations of approximate fairness (Gunther Moor et al., 2010; Rodman et al., 2017), thereby inducing expectancy violations. Overinclusion may be a more appropriate comparison for determining the specificity of neural responses to the affective distress of exclusion, because its psychological experience may be better matched in the degree to which participant's expectations are violated (Kawamoto et al., 2012). Overinclusion also may be more similar to exclusion than fair play on other dimensions, such as the intensity of the affective experience. However, few human neuroimaging studies compare social exclusion to overinclusion.

Existing studies that compare social exclusion with overinclusion and/or acceptance do not paint a consistent picture of dACC and AI involvement. One such study with Cyberball in young adults found that the dACC exhibited greater responses to exclusion than overinclusion, but that the AI did not (Kawamoto et al., 2012). In contrast, a social judgment study in late adolescents/young adults found that the dACC and left AI responded to both positive and negative social feedback (Dalglish et al., 2017). Using a similar paradigm, a study in young adults found that the ventral (v)ACC responded to positive social feedback, whereas the dACC responded to expectancy violations across positive and negative feedback conditions (Somerville et al., 2006).

Moreover, inconsistencies in the role of the ACC and insula are evident in quantitative meta-analyses examining neural responses to social exclusion across different paradigms. Of the three meta-analyses, only one identified involvement of the dACC during social exclusion (Rotge et al., 2015). In comparison, more ventral regions of ACC were more reliably recruited across the meta-analyses, including (1) rostral perigenual ACC bordering on mPFC (Cacioppo et al., 2013), (2) perigenual and subgenual ACC (Vijayakumar et al., 2017), and (3) vACC (Rotge et al., 2015). Of the two whole-brain meta-analyses, the AI was identified by one (Cacioppo et al., 2013), but not the other (Vijayakumar et al., 2017). In contrast, both of these studies suggest more reliable engagement of the ventromedial PFC and ventrolateral PFC/lateral OFC. Whether the involvement of these other regions reflects processes unique to social rejection or whether they would also be identified during overinclusion remains unknown.

Therefore, the present study compares social exclusion to overinclusion. We employed an fMRI adaptation of Cyberball containing periods of overinclusion and exclusion interspersed with periods of fair play. This strategy was employed by Kawamoto et al. (2012), although they were constrained by arbitrary operationalization of inclusion and exclusion on continuous gameplay (e.g., the N^{th} throw between computer players marks the onset of exclusion). We reduce such

constraints by using parametric modulators to analyze changes in BOLD signal associated with cumulative exclusion and inclusion events. Given considerable interest in the role of the dACC and evidence from meta-analyses that the broader extent of the ACC is relevant to these processes, we interrogated eight parcels along the ACC as regions-of-interest (ROIs). We examined five additional ROIs reflecting both regions of similar theoretical interest (left and right AI) and regions that have been reliably recruited in Cyberball paradigms in a previous meta-analysis (left inferior frontal gyrus, posterior cingulate cortex, and ventral striatum [VS]; Vijayakumar et al., 2017).

Patterns of signal in the dACC and AI are evaluated for consistency with potential roles in processing affective distress and expectancy violation. Based on the assumption that exclusion, but not overinclusion, is associated with affective distress, we interpreted affective distress models to suggest that the dACC and AI will exhibit greater signal scaling with cumulative exclusion events than inclusion events and that this difference will be driven by signal increases to cumulative exclusion only. Based on the assumption that both exclusion and overinclusion similarly violate fairness expectations, we interpreted expectancy violation accounts to suggest that signal will scale similarly across both conditions. We take another modeling approach to explore neural responses to short-term expectancy violations, i.e., when a ball toss including or excluding the participant is incongruent with the broader inclusionary or exclusionary context established by the run.

Finally, we examined age-related differences in our sample of 11- to 17-year-olds. Developing the capacity to navigate complex social relationships is a critical aspect of adolescence (Blakemore & Mills, 2014). Social evaluation becomes a dominant concern (Somerville, 2013), with adolescents spending a significant amount of time with peers both on and offline (Csikszentmihalyi & Larson, 1984; Anderson & Jiang, 2018). Accordingly, adolescents experience stronger affective responses to negative social feedback than adults (Sebastian, Viding, Williams, & Blakemore, 2010). The VS plays a role in affective reactivity (Knutson, Westdorp, Kaiser, & Hommer, 2000; Sescousse, Caldu, Segura, & Dreher, 2013; Jensen et al., 2003; Levita et al., 2009), and its responses to social stimuli are negatively associated with peer susceptibility in adolescence (Pfeifer et al., 2011). Based on a previous meta-analysis that identified this region as more reliably recruited in Cyberball for adolescents than adults (Vijayakumar et al., 2017), we hypothesized that there would be an age-related decrease in VS response.

Materials & methods

Participants

Ninety-seven adolescents aged 11 to 17 years were recruited from Lane County, Oregon. These participants form the

community control group in a study that included additional samples from the child welfare and juvenile justice systems. Anticipating that mental health diagnoses might be prevalent in these additional samples, we did not exclude for reported current or prior diagnoses of common psychiatric disorders in order to improve comparability across samples. These disorders included anxiety, depression, attention deficit disorder/attention deficit hyperactivity disorder, oppositional defiant disorder, or conduct disorder. However, no participants from the child welfare and juvenile justice system samples are included in any analyses presented in this paper. Of the 97 participants recruited from the community sample only, 9 dropped out of the study, 7 elected not to participate in the MRI portion, 8 completed an alternate (pilot) version of the Cyberball task, 1 failed to complete the Cyberball task, and 1 participant's data were not collected due to technical errors. Additionally, two participants were excluded when visual quality inspection of the imaging data revealed extreme motion and/or orbitofrontal signal dropout.

The analyses presented here were conducted with the remaining 69 participants (36 females) from the community sample aged 11 to 17 years (mean [M] = 14.2, standard deviation [SD] = 1.5, range = 11.1–17.7). The sample size was based on *a priori* power calculations for a different research question and statistical approach (group comparisons with the child welfare and juvenile justice system samples). Post-hoc analyses suggest that we have sufficient power (>0.8) to detect effect sizes of 0.31 or greater in two-tailed one-sample *t*-tests (e.g., Increasing Exclusion = 0) and effect sizes of 0.35 or greater in one-tailed one-sample *t*-tests of the difference between two dependent means (e.g., Increasing Exclusion $>$ Increasing Inclusion).

Our final sample included four subjects that had disclosed psychiatric diagnoses, including two with anxiety disorders and two with attention-related disorders. Six participants reported taking medication for behavioral issues (4 subjects reported taking antidepressant medications, 1 reported taking a mood stabilizer, and 1 reported taking stimulants typically prescribed for attention disorders). In total, eight participants reported either receiving psychiatric diagnoses or taking psychotropic medications. We conducted sensitivity analyses by re-running ROI and whole-brain analyses with the parametric modulators in a sample that excluded these eight participants ($N = 61$).

Procedures

Study procedure

Written informed consent was obtained from the parent/guardian, while written assent was obtained from the adolescent. At the first visit, the adolescent was screened for MRI eligibility as per procedures determined by the University of Oregon's

Lewis Center for Neuroimaging. The second visit was typically scheduled within one month of the first visit ($M = 14.8$ days, $SD = 16.5$, range = 1–106). Eligible participants then completed the MRI portion of the study as well as additional questionnaires and behavioral tasks, including the vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence, second edition (Wechsler, 1999). Participants were compensated for their time, and all materials and procedures were approved by the Institutional Review Board at the University of Oregon.

The Cyberball task

Developed by Williams, Cheung, and Choi (2000), Cyberball is an animated interactive ball-tossing computer game used virtually to simulate the experience of social exclusion. In our study, participants were informed that they were playing Cyberball with two adolescent peers at partner sites in real time via the Internet. However, the other players' throws were computer-automated. Similar adaptations of Cyberball have successfully simulated peer rejection in adolescents by leading them to believe that computer players were real peers (Bolling et al., 2011a; Masten et al., 2009). Participants also made short video profiles to introduce themselves to the other players and viewed the other players' profiles, further lending credibility to the cover story; to our knowledge, this has not been done in prior studies. Participants were instructed on how to play Cyberball in a mock scan session immediately before their MRI session.

Participants played an overinclusion and exclusion run of Cyberball. Each run contained a total of 44 ball throws. They were instructed to use a button box to indicate which of the two players they wanted to throw to, and if they did not make a decision within 5 s, the ball would be automatically thrown to another player at random. Traditional Cyberball paradigms seek to induce strong feelings of rejection and thus consist of extended periods of exclusion, sometimes taking up close to the entirety of the run. We instead employed periods of exclusion or overinclusion interspersed with periods of fair play to reflect more fluid interactions. In the inclusion run, participants experienced periods of overinclusion in which computer players repeatedly threw the ball to the participant rather than to one another. Periods of overinclusion were interspersed with periods of fair play such that, overall, 17 of the 27 throws by the other players were to the participant (63%). In the exclusion run, participants experienced periods in which the computer players only threw the ball to one another and not to the participant. These were interspersed with periods of fair play such that, overall, six of the other players' total combined 38 throws were to the participant (16%). In social judgment and evaluation tasks, adolescents' (aged 11–17 years) mean expectations of being liked are between 40–55%, and on average, such ratings are lower in mid-adolescence, i.e., between

the ages of 12–14 years (Gunther Moor et al., 2010; Rodman et al., 2017). Although our choice of paradigm differs, we suggest that the proportion of throws to the participant (63% in overinclusion and 16% in exclusion) was extreme enough to elicit the intended social manipulation in each case. (Note that these percentages are true of the overall run, and within each run participants experienced even more extreme periods of overinclusion or exclusion interspersed with periods of fair play). As other computer players still both received the ball some of the time and at approximately even rates, it is generally the case that neither computer player was explicitly excluded by greater participant inclusion. The time elapsed between each computer player catching and throwing the ball was a random number between 0 and 3 s ($M = 1.5$, $SD = 0.9$), and the ball took approximately 1.4 s to travel through the air. Therefore, the timing of events, including participant button presses, varied from trial to trial and did not systematically align with the TRs. See Fig. 1 for a schedule of throws in both runs.

In the protocol for this study, participants first played two rounds of the Yellow Light Game (YLG), a driving simulation adapted from the Stoplight Task (Gardner & Steinberg, 2005) outside of the scanner. Afterward, within the scanner, participants (a) played two rounds of the YLG, (b) played the Cyberball inclusion run, (c) were introduced to virtual peers and observed them playing the YLG, (d) played two peer-observed runs of YLG, (e) played the Cyberball exclusion

run, and (f) played two final peer-observed runs of YLG. The total length of the scan protocol was 1 hr 15 min. The inclusion run always preceded the exclusion run; Cyberball conditions were not counterbalanced due to concern about carryover of negative affect following exclusion (see Section 4.5 for a discussion of order effects). Participants were led to believe that peers from the YLG observations were the same as those in the Cyberball game. More details about this task and the overall protocol can be found in work by Op de Macks et al. (2018).

Behavioral measures

Following the MRI scan (and typically within 30 min of the end of the scan), adolescents completed the Need-Threat Scale (NTS) to assess their subjective experience of distress during Cyberball. We used the 12-item version (Zadro et al., 2004), which has been validated as an overall measure of need-threat (Gerber et al., 2017). The 12 items on the NTS included ratings of belongingness, control, meaningfulness, and self-esteem on a scale from 1 (“not at all”) to 5 (“very much so”), with higher scores reflecting more threat. The overall scale exhibited good reliability in our sample (standardized Cronbach’s $\alpha = 0.81$). We assessed the believability of the deception by asking participants, “Did you think the peers could actually see you playing [the driving game]?” This question was part of a task experience survey administered at the very end of the session, just before participant debriefing. From this self-report, we inferred whether or not participants believed they were interacting with real peers during Cyberball.

fMRI data acquisition

Data were acquired on a 3T Siemens Skyra MRI scanner at the Lewis Center for Neuroimaging at the University of Oregon. High-resolution, T1-weighted structural images were collected with the MP-RAGE sequence ($TE = 3.41$ ms, $TR = 2,500$ ms, flip angle = 7° , 1.0-mm slice thickness, matrix size = 256×256 , $FOV = 256$ mm, 176 slices, bandwidth = 190 Hz/pixel). Two functional runs of T2*-weighted BOLD-EPI images were acquired with a gradient echo sequence ($TE = 27$ ms, $TR = 2,000$ ms, flip angle = 90° , 2.0-mm slice thickness, matrix size = 100×100 , $FOV = 200$ mm, 72 slices, bandwidth = 1,786 Hz/pixel). There were 60 to 87 images per run; run length varied with participants’ response times during Cyberball. To correct for local magnetic field inhomogeneities, a field map also was collected ($TE = 4.37$ ms, $TR = 639.0$ ms, flip angle = 60° , 2.0-mm slice thickness, matrix size = 100×100 , $FOV = 200$ mm, 72 slices, bandwidth = 1,515 Hz/pixel).

Fig. 1. Partial schedules of throws for a representative computer player in both runs are displayed. Each rectangle represents one throw by the computer player. The color of the rectangle indicates the recipient of the ball. The complete schedules extend the pattern displayed to the total number of computer-programmed throws per run, and both of the computer players followed the same schedule within a run.

fMRI processing

Raw DICOM image files were converted to the NIfTI format with MRIConvert (Smith, 2011). Data were preprocessed using Statistical Parametric Mapping software (SPM12, Wellcome Department of Cognitive Neurology, London, UK). Participants' anatomical images were coregistered to the 152 Montreal Neurological Institute stereotaxic template, segmented into six tissue types, and used to create a group anatomical template using DARTEL. Next, functional images were unwarped using field maps and corrected for head motion via image realignment. A group averaged field map was created and used as a substitute for two participants: one who did not have a field map, and another whose fieldmap was not well-aligned with their functional volumes. Unwarped and realigned mean functional images were coregistered to the anatomical image (that had in turn been coregistered to the MNI template). Transformations were applied to warp the functional data to the DARTEL group template, and these normalized images were smoothed using a 6-mm FWHM Gaussian kernel. Preprocessing scripts used for this analysis are available on GitHub at https://github.com/dsnlab/TDS_scripts/tree/cheng_cyb_main/fMRI/ppc/spm/tds2 (SPM scripts) and https://github.com/dsnlab/TDS_scripts/tree/cheng_cyb_main/fMRI/ppc/shell/schedule_spm_jobs/tds2 (shell scripts).

Motion artifacts were identified using an in-house automated script that evaluates changes in image intensity relative to the mean across all subjects, as well as volume-to-volume changes in Euclidean distance. This script for this is publicly available (Cosme et al., 2018). We refer interested readers to the most recent version (<https://github.com/dsnlab/auto-motion>), as well as the branch used in this analysis (https://github.com/dsnlab/TDS_scripts/tree/cheng_cyb_main/fMRI/fx/motion/auto-motion). A regressor of no interest was constructed by marking volumes of the following types: (a) volumes with greater than 0.3 mm of motion in Euclidean distance relative to the previous volume, (b) volumes for which the *mean intensity across voxels* was extreme (3 SDs above or 1.5 SDs below) relative to the mean intensity across subjects and runs, and (c) volumes for which the *standard deviation across voxels* was extreme (3 SDs above or below) relative to the mean standard deviation across subjects and runs. The mean intensity and standard deviation scores were calculated across all runs for all subjects, including volumes collected during the YLG and while participants observed others playing the YLG. Volumes immediately preceding and following marked volumes were also flagged. This script identified volumes exceeding these thresholds in 36 out of 138 total Cyberball runs across 69 participants. Of the volumes marked for motion, the script flagged an average of 3.94 (5.7%) volumes per run (SD = 3.58, range = 1–17, or up to 23.3%). Additionally, our models included four motion

parameters (absolute distance, absolute rotation, and the first derivatives of each of these values) as regressors of no interest. As mentioned previously, two participants were excluded on the basis of head motion/signal dropout. The first was identified for exclusion based on visual inspection of pre-processed images that revealed extreme signal dropout in the orbitofrontal gyrus. The second participant was identified for exclusion based on initial visual inspection of contrasts from their single-subject models, which revealed a clear and severe pattern of motion-related striping that indicated that their data was contaminated. No participants were excluded for exceeding an *a priori* threshold of >25% of marked motion volumes within a single run.

Experimental design and statistical analysis

Cyberball was modeled as an event-related design. For each participant's fixed-effects analysis, a general linear model was created with two regressors of interest modeled as zero-duration events: the computer-generated throws were each modeled as either inclusion (i.e., throws to the participant) or exclusion (i.e., throws to the computer players) events. These events occurred within an inclusionary or exclusionary context/run. An additional zero-duration event regressor of no interest marked when participants' computer avatar "caught" the ball, signaling the participant's turn to throw the ball. This regressor was included to control for neural responses related to participants' decision-making and subsequent button-press, as has been used in previous studies with event related designs (Bolling et al., 2011b). This regressor focused on the participant avatar's "catch" action and did not differentiate between cases when the participant pressed the button in time, or when the computer automated the throw due to no response or an untimely response (not modeled separately because this was only <0.2% of all throws across participants and runs). There was also a "wait" period at the start of each run, consisting of 6 s where the screen displayed the words "Connecting to other players..." along with a progress bar, plus additional time until the first throw of the game (on average 8 s in total).

Parametric modulators were created to track consecutive inclusion throws within the inclusion round (referred to as Increasing Inclusion) and consecutive exclusion throws in the exclusion round (referred to as Increasing Exclusion). Parametric modulators were not created for exclusion throws in the inclusion round or vice versa due to an insufficient number of such events in respective runs. Each parametric modulator was mean-centered relative to the average number of continuous throws of that type (for Increasing Inclusion: $M = 2.73$, $SD = 1.82$; for Increasing Exclusion: $M = 5.97$, $SD = 3.89$). The model was convolved with the canonical hemodynamic response function, and parameter estimates from the GLM were used to create six linear contrast images: one for each of the four types of events (*i.* inclusion throw in the

inclusion round, *ii.* exclusion throw in the inclusion round, *iii.* inclusion throw in the exclusion round, and *iv.* exclusion throw in the exclusion round) relative to wait periods (collapsed across both runs), and one for each of two parametric modulators (Increasing Inclusion and Increasing Exclusion).

ROI analyses

ROI selection and definition Due to considerable interest in these regions throughout the literature, we chose to examine the ACC and AI as ROIs. To define ACC ROIs, we used a parcellation scheme (Craddock, James, Holtzheimer, Hu, & Mayberg, 2012) derived from cluster analyses of resting state functional neuroimaging scans. We selected eight ACC parcels (6 regions, 2 were represented with separate parcels in each hemisphere) from the 250-parcel brain map (Fig. 2). The purpose of using multiple ACC ROIs was to contribute to ongoing discussion in the literature regarding the specificity of various ACC subregions for processing the affective distress of social exclusion (including but not limited to Eisenberger et al. 2003; Somerville et al. 2006; Kawamoto

et al. 2012; Bolling et al., 2011; Woo et al. 2014; Eisenberger, 2015; Lieberman & Eisenberger, 2015; Rotge et al., 2015). While we recognize that other ROIs in these analyses also may have functionally meaningful subregions, we sought *a priori* to answer outstanding questions in the literature regarding the ACC. Interested readers can explore additional ROIs and subdivisions by downloading the full statistical maps from NeuroVault.

We further examined left and right AI ROIs that were created from visual inspection of anatomical landmarks (also used in Morelli & Lieberman, 2013; Falk et al., 2014; post-hoc analyses described in section S6 of the *Supplementary Materials* also examined AI subdivisions). We also were interested in comparing signal between social exclusion and overinclusion in regions commonly associated with social exclusion in Cyberball. Therefore, we examined two ROIs identified from a prior meta-analysis as being reliably recruited across Cyberball studies (Vijayakumar et al., 2017). We extracted signal from the full clusters in the left inferior frontal gyrus extending into lateral orbitofrontal cortex (peak MNI coordinate: $-46, 32, -10$; volume = $1,992 \text{ mm}^3$) and posterior

Fig. 2. Regions-of-interest (ROIs). (A) Eight ROIs along the extent of the ACC and were identified using the Craddock et al. (2012) parcellation scheme with 250 parcels. (B) The left VS cluster ROI was identified from a meta-analysis by Vijayakumar et al. (2017) for being more reliably recruited in developmental than emerging adult samples across

Cyberball studies. (C) The posterior cingulate cortex cluster and (D) left inferior frontal gyrus cluster ROIs were identified from the same meta-analysis for being reliably recruited across Cyberball studies. The left and right AI ROIs are not pictured here but can be viewed in Fig. 3 of work by Falk et al. (2014).

cingulate cortex (peak MNI coordinate: $-8, -56, 12$; volume = $1,344 \text{ mm}^3$). We also examined a cluster in the VS (peak MNI coordinate: $8, 6, 2$; volume = 864 mm^3), which was more reliably recruited in developmental compared with emerging adult samples during Cyberball. We did not include ROIs that were unreliably recruited across Cyberball studies in nonclinical samples, and we did not include one large cluster that overlapped significantly with ACC ROIs from the Craddock parcellation. (See Vijayakumar et al., 2017 for details on how these ROIs were obtained.)

ROI extraction and statistical tests We used MarsBar (version 0.21) to extract parameter estimates of average signal associated with each of the parametric modulators within these parcels. For each parcel, we used a series of t -tests to examine whether signal scaled significantly with cumulative exclusion or inclusion events (null hypotheses: Increasing Inclusion = 0 and Increasing Exclusion = 0). We also examined whether signal scaled differently between cumulative exclusion and inclusion events (null hypothesis: Increasing Inclusion = Increasing Exclusion) via paired, two-tailed Student's t tests. We controlled the false discovery rate at .05 using the Benjamini-Hochberg procedure (Benjamini & Hochberg, 1995). We did not apply Bonferroni correction because the set of tests were not independent; adjacent parcels were spatially correlated both because parcels do not necessarily reflect strict signal boundaries and because of smoothing, and the results of different tests were correlated (i.e., if the difference between cumulative exclusion and cumulative inclusion is significantly different, it follows that at least one them is significantly different from zero).

Age-related changes in the VS ROI We used linear regression to examine the association between age and responses to cumulative events in the VS. We regressed parameter estimates averaged across the VS on age for each of three conditions: Increasing Inclusion, Increasing Exclusion, and their difference.

Whole-brain analyses

Using whole-brain analyses, we examined differences between social exclusion and overinclusion. In particular, smaller clusters may not have been identified from ROI analyses due to signal dilution when averaging over larger regions and/or nonoptimal parcel boundaries. Additionally, whole-brain analyses were used to identify regions outside of our ROIs that are significantly associated with conditions of interest, particularly for those that are less studied (e.g., Increasing Inclusion). Therefore, we conducted group-level analyses based on these fixed-effects (single subject) contrast images, modeling the subject variable as a random effect. We ran whole-brain conjunction and subtraction analyses with the

parametric modulators using paired samples t tests. We also used a repeated-measures flexible factorial ANOVA with a 2×2 design to examine the interaction between the event (inclusion and exclusion throws) and context (inclusion and exclusion round) factors. This enabled comparisons between Context Congruent (i.e., inclusion throw in the inclusion round and exclusion throw in the exclusion round) and Context Incongruent (i.e., inclusion throw in the exclusion round and exclusion throw in the inclusion round) events. The main effects of event and context are also reported in the Supplementary Materials (see Section S3). Whole-brain age effects are also reported in the *Supplementary Materials* (see Section S4), and controlling for age did not alter any of the results presented in Tables 3 and 4.

Unless otherwise specified, reported results exceeded the minimum cluster size threshold needed to control for false positives at a 0.05 family-wise error (FWE) rate given a voxel-wise threshold of $p = 0.001$ (bi-sided, $NN = 3$, $k = 68$). Cluster extent thresholds were identified using AFNI 3dClustSim, version AFNI_17.1.01 (Apr 12 2017; version update accounts for software bugs identified by Eklund et al. (2016)). Smoothness estimates entered into 3dClustSim were spatial autocorrelation function (acf) parameters averaged from each individual's first level model residuals as calculated by 3dFWHMx (acf parameters: 0.70986 4.667 8.5925).

Exploratory examination of functionally defined dACC

We used NTS scores to predict the degree of signal scaling to Increasing Exclusion within a functionally-defined dACC ROI. This ROI is a sphere with a radius of 4 mm constructed around the most ventral subpeak of a dACC-SMA cluster (MNI coordinates: $-8, 6, 38$) identified from the contrast of Increasing Exclusion > Increasing Inclusion (Fig. 3A). Among cluster sub-peaks, the most ventral peak was visually identified as most clearly within the dACC and thus least likely to include SMA signal. We were interested in whether responses in this region scaled with the affective distress of exclusion and therefore did not examine responses to Increasing Inclusion or the difference between the two conditions. Because only one statistical test was needed to answer this question, we did not correct for multiple comparisons. We additionally visualized the pattern of signal changes to Increasing Exclusion and Increasing Inclusion in this ROI (Fig. 3B).

Results

Behavioral results

To infer whether or not participants believed they were interacting with real peers during the paradigm, participants

Fig. 3. Examination of a functionally defined dACC ROI. **(A)** The center of the 4-mm radius sphere was the most ventral sub-peak of a cluster encompassing the dACC identified from the contrast of Increasing Exclusion > Increasing Inclusion. **(B)** Parameters extracted from this sphere reflect expected signal change per continuous throw, and lines with those slopes are plotted. Mean beta parameter estimates suggest that

signal differences between the parametric modulators were driven by decreases with Increasing Inclusion (in blue, $M = -0.28$, $SE = 0.07$), as well as increases with Increasing Exclusion (in orange, $M = 0.08$, $SE = 0.02$). Faint lines represent individual estimates, while bold lines reflect the group averages

were asked in a post-task survey “Did you think the peers could actually see you playing [the driving game]?” Three participants (4%) did not respond, eight (12%) expressed disbelief, and the remaining majority (58 participants; 84%) believed that they were interacting with real peers. We did not exclude participants based on responses to this survey item because feelings of exclusion can be induced even when participants know they are playing with computer players (Zadro et al., 2004).

On average, participants reported a moderate level of subjective need threat during the Cyberball game as measured on the NTS ($M = 3.23$, $SD = 0.73$; higher scores reflect more threat), comparable to levels reported in other studies using Cyberball with adolescents (Masten et al., 2009; Bolling et al., 2011b). One subject did not complete the NTS, and was excluded from subsequent analyses with this scale.

fMRI results

Responses to increasing exclusion and increasing inclusion within ROIs

Table 1 shows the results of statistical comparisons across ROIs in the ACC, and Table 2 shows the results from all other ROIs. Regions-of-interest across the extent of the ACC (ROIs 3, 5, 7, 8), VS, left inferior frontal gyrus and left posterior cingulate cortex exhibited statistically significant increases with Increasing Exclusion after correction for multiple comparisons. Increasing Exclusion was associated with greater signal than Increasing Inclusion in the most superior and caudal dACC parcel only (ROI 1 in Fig. 2; $t(68) = 2.97$, $p = 0.004$). This dACC parcel appeared to exhibit both signal increases with Increasing Exclusion ($M = 0.06$, $SE = 0.02$,

Table 1. Evaluating parametric modulators within the ACC regions-of-interest

ROI	Increasing Exclusion M (SE)	H_0 : Increasing Exclusion = 0 t (p)	Increasing Inclusion M (SE)	H_0 : Increasing Inclusion = 0 t (p)	H_0 : Increasing Exclusion = Increasing Inclusion t (p)
1	0.06 (0.02)	3.02 (3.51e-3)**	-0.11 (0.05)	-2.06 (0.043)	2.97 (4.04e-3)**
2	0.05 (0.02)	3.09 (2.94e-3)**	-0.03 (0.06)	-0.53 (0.598)	1.40 (0.167)
3	0.08 (0.02)	3.69 (4.46e-4)***s	0.01 (0.08)	0.12 (0.906)	0.85 (0.396)
4	0.03 (0.02)	1.77 (.081)	0.07 (0.07)	1.05 (0.296)	-0.56 (0.579)
5	0.11 (0.02)	4.95 (5.17e-6)***s	0.13 (0.08)	1.66 (0.101)	-0.26 (0.792)
6	0.06 (0.02)	3.27 (1.70e-3)**s	-0.01 (0.06)	-0.15 (0.878)	1.16 (0.249)
7	0.07 (0.03)	2.89 (5.11e-3)**	0.11 (0.07)	1.42 (0.160)	-0.44 (0.664)
8	0.12 (0.03)	4.86 (7.12e-6)***s	0.22 (0.10)	2.19 (0.032)	-0.93 (0.358)

M = mean beta; SE = standard error; H_0 = null hypothesis; **raw $p < 0.01$; ***raw $p < 0.001$; ^s: Significant at FDR-adjusted $q = 0.05$.

Table 2. Evaluating parametric modulators within non-ACC regions-of-interest

ROI	Increasing Exclusion M (SE)	H ₀ : Increasing Exclusion = 0 <i>t</i> (<i>p</i>)	Increasing Inclusion M (SE)	H ₀ : Increasing Inclusion = 0 <i>t</i> (<i>p</i>)	H ₀ : Increasing Exclusion = Increasing Inclusion <i>t</i> (<i>p</i>)
Left inferior frontal gyrus	0.09 (0.02)	4.91 (6.07e-6) ^{***s}	0.18 (0.07)	2.71 (8.53e-3) ^{**}	-1.35 (0.181)
Left posterior cingulate cortex	0.13 (0.03)	4.93 (5.55e-6) ^{***s}	0.02 (0.09)	0.20 (0.839)	1.14 (0.259)
VS	0.08 (0.03)	3.20 (2.11e-3) ^{**s}	0.24 (0.11)	2.27 (0.026)	-1.50 (0.139)
Left AI	0.06 (0.02)	2.95 (4.34e-3) ^{**}	0.02 (0.05)	0.35 (0.730)	0.72 (0.474)
Right AI	0.05 (0.02)	2.69 (8.95e-3) ^{**}	0.01 (0.04)	0.25 (0.801)	0.97 (0.336)

M = mean beta; SE = standard error; H₀ = null hypothesis; ^{**}*p* < 0.01, ^{***}*p* < 0.001; ^s:Significant at FDR-adjusted *q* = 0.05.

t(68) = 3.02, *p* = 0.004) and decreases with Increasing Inclusion (M = -0.11, SE = 0.05, *t*(68) = -2.06, *p* = 0.043). However, none of the findings in this ROI were statistically significant after correction for multiple comparisons. The left inferior frontal gyrus also exhibited notable signal increases with Increasing Inclusion that were nonsignificant after correction for multiple comparisons. Additionally, the left and right anterior insula ROIs exhibited notable signal increases with Increasing Exclusion that were nonsignificant after correction for multiple comparisons. Post-hoc exploratory descriptive statistics suggest that this pattern may be driven by dorsal, rather than ventral aspects of the anterior insula (see *Supplementary Materials*, Section S6).

We conducted sensitivity analyses in two subsamples: 1) removing eight subjects taking that self-reported psychiatric diagnoses and/or taking psychotropic medications (N = 61), and 2) removing eight subjects that indicated disbelief in the manipulation (N = 61). The overall pattern of results in the caudal dACC parcel (ROI 1) in each of the subsamples was consistent with the pattern in the full sample (greater signal in Increasing Exclusion than Increasing Inclusion reflecting signal increases with Increasing Exclusion and decreases with Increasing Inclusion), although only signal increases with Increasing Exclusion were significant after correction for multiple comparisons. We note that *every* ROI except the most rostro-superior and rostro-inferior ACC parcels (ROIs 4 and 7) exhibited statistically significant increases with Increasing Exclusion across both subsamples. No ROIs exhibited significant differences between Increasing Exclusion and Increasing Inclusion across both subsamples, and this was generally due to either no responses or modest signal increases with Increasing Inclusion (and no notable decreases with Increasing Inclusion except for in the caudal dACC parcel). After excluding those with mental health disorders and/or medications, we also identified significant signal increases to Increasing Inclusion in the VS. Differences in the pattern of ROI results and whole-brain analyses are generally minor, and are reported in the *Supplementary Materials* (see Section S1).

Exploratory examination of a functionally-defined dACC ROI

Averaged signal from a dACC ROI (functionally defined for exhibiting greater signal with Increasing Exclusion than Increasing Inclusion) was positively associated with participant reports of need-threat (B = 0.06, SE = 0.03, *t*(66) = 1.83, *p* = 0.072). An examination of Cook's *d* statistic suggested the presence of three outliers (Cook's *d* greater than 4/N, or 0.059, where N = 68). Re-running model statistics without outliers strengthened the effect (*t*(63) = 2.51, *p* = 0.0146). See Fig. 3 for a visualization of this ROI and its parameter estimates.

Age associations in the VS ROI While signal in the VS exhibited significant increases with Increasing Exclusion, age was associated with reductions in the VS response to Increasing Exclusion only (B = -0.03, SE = 0.017, *t*(67) = -1.99, *p* = 0.050). An examination of Cook's *d* statistic suggested the presence of four outliers (Cook's *d* greater than 4/N, or 0.058, where N = 69). Re-running model statistics without outliers weakened the effect (*t*(63) = -1.80, *p* = 0.077).

Whole-brain responses to increasing inclusion and increasing exclusion

See Table 3 for a summary of whole-brain results involving parametric modulators. Statistical maps are also available on NeuroVault (<https://neurovault.org/collections/3794>). The conjunction of Increasing Inclusion and Increasing Exclusion identified shared signal decreases in the left intraparietal sulcus, as well as shared increases in the rostromedial PFC, as illustrated in Fig. 4. The conjunction of signal positively associated with Increasing Exclusion and negatively associated with Increasing Inclusion identified clusters in the left primary motor cortex, supplementary motor area, and left posterior insula. The contrast of Increasing Inclusion > Increasing Exclusion identified significant clusters in the supplementary motor area, right cuneus, and in a sub-gyral region ventral to the cingulate gyrus. The contrast of Increasing Exclusion > Increasing Inclusion identified the left motor cortex (encompassing pre-

Table 3. Whole-brain results with parametric modulators

Condition	Peak Region	BA	Extent	Peak t-statistic	x	y	z
II>IE	R cuneus		192	4.80	18	-100	16
	R sub-gyral region, inferior to cingulate gyrus		87	4.50	-18	-12	26
	R SMA	6	74	4.04	6	-22	66
IE>II	L postcentral gyrus extending into insula	3	3177	9.06	-42	-18	56
	Supplementary motor area/dACC		1055	7.30	0	-2	52
	L precentral gyrus	6	112	4.84	-58	6	30
	R posterior insula	13	101	4.48	48	-20	20
II+ & IE+	Rostromedial PFC	9	107	4.04	-4	58	22
II- & IE-	L intraparietal sulcus		94	4.50	-34	-48	38
II- & IE+	L postcentral gyrus extending into precentral gyrus	2, 3, 4	975	6.57	-42	-18	54
	Supplementary motor area	6	234	5.07	0	-2	48
	Left posterior insula	13	122	4.22	-42	-22	20

IE, Increasing Exclusion; II, Increasing Inclusion; –, negative association; +, positive association; PFC, prefrontal cortex; dACC, dorsal anterior cingulate cortex; BA, Brodmann's area. All clusters were present after controlling for age. No effects were identified in the conjunction of IE- and II+. No linear effects of age or interactions between age and our parametric modulators were identified. Results are FWE cluster corrected at $p < 0.05$ (voxel-wise $p < 0.001$, $k \geq 68$). Reporting of whole-brain findings associated with the parametric modulators alone (i.e., not in contrast/conjunction with one another) are available in the *Supplementary Materials* (see Section S2).

and postcentral gyri and extending into the insula), right posterior insula, and supplementary motor area extending into the dACC. There were no age effects, nor were there age interactions with the parametric modulators. Controlling for age did not alter whole-brain findings with the parametric modulators.

Whole-brain responses in the repeated measures 2x2 ANOVA

See Table 4 for comparisons of context congruence, and see section S3 in the *Supplementary Materials* for detailed whole-brain results from this 2x2 ANOVA. We further explore short-term

Fig. 4. Conjunction of Increasing Exclusion and Increasing Inclusion. The rostromedial prefrontal cortex is identified from the conjunction (white) of parametric modulators for Increasing Exclusion (red) and Increasing Inclusion (blue). Results are FWE cluster-corrected at $p < 0.05$ (voxel-wise $p < 0.001$, $k \geq 68$).

expectancy violations during Cyberball by examining the interaction between context and event type, which compares when events are congruent (i.e., inclusion throws in the inclusion round and exclusion throws in the exclusion round) versus incongruent (i.e., inclusion throws in the exclusion round and exclusion throws in the inclusion round). The contrast of Context Incongruent > Context Congruent events identified the bilateral putamen, bilateral inferior parietal lobule (extending into right posterior superior temporal sulcus and posterior insula), bilateral inferior frontal gyrus, left AI, left precentral gyrus, left precuneus, left posterior superior temporal sulcus, left middle frontal gyrus, right superior temporal gyrus, supplementary motor area, cerebellum, thalamus, and dACC (Fig. 5). Comparing Context Congruent > Context Incongruent events yielded no significant clusters.

Age effects and age interactions in the repeated measures 2x2 ANOVA did not reveal clusters in the ACC or insula, and these analyses are reported in the *Supplementary Materials* (see Section S4). Controlling for age did not substantively alter findings in the repeated measures 2x2 ANOVA.

Discussion

This study characterizes neural scaling to cumulative exclusionary and inclusionary events during Cyberball, with a focus on evaluating affective distress models as compared to alternate accounts of dACC and AI functioning. Interestingly, our results support diverse roles for the dACC and insula during Cyberball. Specifically, we found that (a) dACC responses to exclusion are correlated with affective distress, (b) the dACC and posterior

Table 4. Whole-brain results with 2x2 factorial ANOVA

Condition	Peak Region	BA	Extent	Peak t-statistic	x	y	z
Context Incongruent > Context Congruent	Bilateral putamen		176	5.51	-14	0	4
			89	4.36	22	8	4
	L precentral gyrus	9	188	5.46	-46	2	36
		6	254	4.49	-20	-10	58
	Bilateral inferior parietal lobule, R extends into posterior superior temporal sulcus and posterior insula	40	986	5.34	60	-30	30
		40	115	4.19	-46	-36	24
	Supplementary motor area	6	417	5.15	4	2	54
	L anterior insula		147	4.75	-30	22	-6
	R thalamus (medial dorsal nucleus)		104	4.73	10	-16	6
	Bilateral inferior frontal gyri	9	196	4.73	-56	6	22
			84	3.97	42	8	22
	R superior temporal gyrus		123	4.32	50	-10	-16
	L precuneus		85	4.13	-18	-76	40
	L posterior superior temporal sulcus		274	4.04	-40	-52	16
	L middle frontal gyrus	9	72	4.04	-26	34	22
	R cerebellum		184	4.02	28	-50	-12
	dACC	24	71	3.88	-8	6	38

dACC, dorsal anterior cingulate cortex; BA, Brodmann area; Context Congruent: events which match the context, i.e., inclusion throws in the inclusion round and exclusion throws in the exclusion round; Context Incongruent: events which do not match the context, i.e., inclusion throws in the exclusion round and exclusion throws in the inclusion round. All clusters were present after controlling for age. The comparison of Context Congruent > Context Incongruent yielded no clusters. Comparisons of each event and context type are reported in the *Supplementary Materials* (see Section S4). Results are FWE cluster corrected at $p < 0.05$ (voxel-wise $p < 0.001$, $k = 68$).

insula exhibit signal increases with exclusion as well as *decreases* with overinclusion, and (c) the dACC and AI respond to events that violate short-term expectancies established by the context of each run. Additionally, we used conjunction analyses to identify regions that respond to both types of social interactions, which notably include the left ventrolateral PFC and rostromedial PFC. Finally, we identified a trending negative association between age and responses to cumulative exclusion in the VS that is consistent with age effects in the literature.

Across analyses, interpretations of our findings should be considered in light of several imbalances between our conditions, including that only inclusion throws required participants to respond with a button press, that the average number of exclusionary throws contributing to measuring Increasing Exclusion was greater than Increasing Inclusion, and that inclusion and exclusion rounds were not counterbalanced. The implications of these imbalances are discussed in more detail in the limitations section of this discussion.

Evaluating an affective distress model of dACC and insula functioning

We evaluated the hypothesis that dACC and AI responses to social exclusion during Cyberball reflect the affective distress of exclusion. To fully support an affective distress model,

these regions should exhibit greater signal scaling with Increasing Exclusion (cumulative exclusion events in the exclusion context) than Increasing Inclusion (cumulative inclusion events in the inclusion context), and this difference should be attributable to signal increases with Increasing Exclusion only. Whole-brain analyses revealed that the caudal dACC exhibited significantly greater signal in Increasing Exclusion than Increasing Inclusion (ROI analyses were consistent with this finding, but were not significant after correction for multiple comparisons). Exploratory analyses found that affective distress was positively associated with signal responses to Increasing Exclusion in a functionally defined caudal dACC ROI. However, greater signal in the dACC was driven not only by significant increases in signal with Increasing Exclusion, but also by nonsignificant but notable (in effect size) *decreases* in signal with Increasing Inclusion. Similarly, a cluster in the left *posterior* insula exhibited significant signal increases with Increasing Exclusion and significant decreases with Increasing Inclusion. These findings intriguingly suggest that the dACC and posterior insula are both involved in processing overinclusion. A previous study implicated both the dACC and AI in social acceptance in addition to rejection (Dalglish et al., 2017), although these regions responded similarly to both conditions, rather than in opposing directions. Nevertheless, our findings are not fully consistent with our affective distress model, as this model does not

Fig. 5. Context Incongruent > Context Congruent results of the event by context interaction. (A) Sagittal view displays the supplementary motor area and dACC. (B) Sagittal view displays the left premotor cortex,

posterior insula, and posterior superior temporal sulcus. (C) Coronal view displays the left AI cluster. Results are FWE cluster corrected at $p < 0.05$ (voxel-wise $p < 0.001$, $k \geq 68$)

predict signal decreases with overinclusion. Decreased signal with repeated stimulus presentation has been used as a tool for structure-function brain mapping, as it is thought that signal decreases reflect neuronal populations that represent and detect change in stimulus features (Barron, Garvert, & Behrens, 2016; Jenkins, Macrae, & Mitchell, 2008; Lau & Cikara, 2017 for implementations of these paradigms in the social cognitive domain). Due to the comparison with exclusion, we suggest that these signal patterns cannot be attributed to repeated social interactions in general and may be attributed to the affective or motoric experience of repeated inclusion in our paradigm.

However, one important consideration is that there may be individual differences in affective distress related to being in the scanner environment or social interactions in general. For adolescents experiencing such distress, signal decreases with Increasing Inclusion may reflect an attenuation of distress with inclusion over time (cumulative inclusion as “less negative affect”). While the tradition of examining affective distress within social exclusion only led us to focus on this type of interaction in our affective distress models, our results are also compatible with the possibility that social inclusion attenuates baseline levels of affective distress while performing this task in the scanner environment. It is also possible that signal decreases with Increasing Inclusion reflect relatively more positive compared to negative affect, although it is uncommon for regions to respond monotonically along a single valence dimension (Lindquist et al., 2016). Future research might clarify this possibility by measuring affective distress at the beginning and end of the inclusion run. However, beyond a certain extent, repeated assessments of affective state may draw attention to the manipulation and impact its ecological validity (although several published studies identify neural and behavioral Cyberball effects with 2–3 affective state assessments, such as Gunther Moor et al., 2012; Will et al., 2016; de Water et al., 2017).

Evaluating alternate models of the dACC and insula functioning

The most prominent alternate model of dACC and AI functioning emphasizes the role of these regions in processing expectancy violations (Bush, Luu, & Posner, 2000). We first examined support for this model using parametric modulators. As both exclusion and overinclusion might similarly violate fair play expectations, an expectancy violation model implies that signal would scale similarly to both types of events. This pattern was not observed in the dACC or AI. However, we also examined neural responses associated with violations of short-term expectancies developed through repeated events of one type establishing a context *within* a run (contrast of Context Incongruent > Context Congruent events). This contrast identified the dACC, left AI, and bilateral posterior insula as processing short-term expectancy violations. These are different regions than those associated with expectancy violations across longer time-scales (i.e. linear change in neural responses to consecutive events using parametric modulators). Interestingly, the dACC and posterior insula clusters associated with context incongruence partially overlapped with those that exhibited greater signal in Increasing Exclusion than Increasing Inclusion. As it seems unlikely that Context Incongruent events elicit distress across both contexts, the involvement of these regions is not necessarily associated with rejection-related processing in social rejection paradigms. Thus we caution against reverse inference of dACC and insula involvement as distress-related, unless otherwise corroborated. Considered together, our two analysis approaches (parametric modulators and unmodulated analysis of congruency between events and context) implicate overlapping regions of the dACC and posterior insula in different processes within the same paradigm.

Other interpretations remain plausible (e.g., participant response demands also scale in opposite directions for

cumulative exclusion and inclusion, with cumulative exclusion requiring fewer participant button responses), and our paradigm is unable to disentangle these competing explanations. Future studies with more detailed measures of participants' expectations of inclusion and degree of affective distress might adjudicate these theories.

Neural regions underlying both exclusion and overinclusion

The rostromedial and left ventrolateral PFC exhibited signal increases to *both* Increasing Exclusion and Increasing Inclusion. Prior meta-analyses have consistently implicated the anterior PFC in social exclusion (Cacioppo et al., 2013; Vijayakumar et al., 2017), with recent work indicating that this region processes negative affect (Kragel et al., 2018). Our whole-brain results suggest that this region processes unexpected and/or affectively charged social interaction more generally. Its involvement may reflect self-oriented processing, as the anterior PFC is implicated in perspective-taking (Ames et al., 2008), prospection (Addis et al., 2007) and self-reflection (Modinos et al., 2009). The left ventrolateral PFC ROI encompasses Brodmann area 47 and is distinct from areas of the ventrolateral PFC associated with the regulation of negative affect (Masten et al., 2009; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008) and rule violation (Bolling et al., 2011b). Instead, this region is primarily associated with language and semantic processing (Petrides, 2016; Ardila, Bernal, & Rosselli, 2017) and also has been implicated in processing others' intentions (Brunet, Sarfati, Hardy-Baylé, & Decety, 2000), social norm violations (Berthoz, Armony, Blair, & Dolan, 2002), and social punishments (Spitzer, Fischbacher, Herrnberger, Grön, Fehr, 2007). Future studies might explore whether anterior and left ventrolateral PFC indicate the extent to which cumulative exclusionary or inclusionary interactions are self-relevant and/or socially salient.

Age effects

We identified a trending negative association between age and VS responses to Increasing Exclusion. The VS ROI was independently identified via meta-analysis for being more reliably recruited during social exclusion in developmental (ages 7–18 years) than emerging adult samples, and it is notable that a consistent negative effect was identified in our cross-sectional sample of 11- to 17-year-olds. Further developmental research would be beneficial to corroborate this effect, which suggests that changes in VS response with age may not be limited to reward processing (Silverman, Jedd, & Luciana, 2015). This region is known for processing both rewarding (Knutson et al., 2000; Sescousse et al., 2013) and aversive stimuli (Jensen et al., 2003; Levita et al., 2009), and increases in VS responses to social stimuli have been

associated with reduced susceptibility to peer influences (Pfeifer et al., 2011). We did not find further associations between age and neural responses to either Increasing Exclusion or Increasing Inclusion, despite prior research identifying age-related changes in medial and ventrolateral PFC, among other regions, during social exclusion as compared to fair play (Bolling et al., 2011a). However, these studies examine different age ranges than ours, and use less stringent thresholding methods for whole-brain analyses.

Strengths and limitations

The current study includes noteworthy methodological strengths. Parametric modulators model exclusion and overinclusion-related neural changes in gameplay without arbitrary definitions of when these conditions begin and end. In contrast, the literature widely employs block and event-related designs that model social experience assuming binary, static, and independent periods or occurrences. A parametric approach may better capture changes in neural signal when gameplay is more fluid, reflecting naturalistic social interactions that often involve greater ambiguity than typical laboratory tasks. An additional strength is the use of independent ROIs identified via meta-analysis for being reliably recruited in Cyberball paradigms (that use block and event-related designs). These ROIs exhibited signal increases with Increasing Exclusion, providing evidence in favor of the validity of this modeling approach.

Our study also faced several limitations. First, it did not account for possible order effects, as overinclusion always preceded exclusion. We did not counterbalance because exclusion paradigms can induce distress among adolescents (Masten et al., 2009; Peake, Dishion, Stormshak, Moore, & Pfeifer, 2013; Sebastian et al., 2010), and we sought to minimize the potential carryover of any such negative affect into the subsequent round of Cyberball. We also prioritized maintaining a consistent affective experience overall, because experiencing overinclusion after a period of exclusion reflects an affective experience that is distinct from the reverse; inclusion runs occurring before and after exclusion runs have been found to elicit different neural responses in Cyberball (White et al., 2013). Some differences between conditions might also be attributed to consistently viewing participant introduction videos and YLG game play in between the social inclusion and exclusion runs. Watching one another's videos and gameplay before exclusion provided a plausible basis for (computer) players to shift toward a negative evaluation of the participant, and was found to be a critical component for the believability of the manipulation during pilot testing.

Another limitation is that the intensity of overinclusion and exclusion was imbalanced, with a greater average number of cumulative events in Increasing Exclusion (5.97 cumulative exclusion throws in the exclusion context) than in Increasing

Inclusion (2.73 cumulative inclusion throws in the inclusion context). Relatedly, there were few incongruent throws in each context, and a particularly low number of inclusion throws in the exclusion context. We thus have relatively less precision in our estimates of some conditions, weakening certain inferences due to varying ability to detect effects. Furthermore, it is unlikely that the true modulation of neural signal driven by social interactions is linear, particularly as interactions become prolonged (i.e., as the number of events becomes large). Our results provide a valuable estimate of linear signal scaling with a low yet affectively meaningful (based on NTS responses) number of events, but do not elucidate the true shape of the trajectory—with an average of less than three consecutive inclusion throws, this was not feasible. Additional investigation is needed to describe the true response trajectories (including nonlinear and/or plateau effects) of exclusion and inclusion across longer timescales. Future studies might also require participants' button press response even when the ball is not thrown to them to minimize the influence of asymmetrical motor demands (as has been done in previous Cyberball studies, such as Sebastian et al., 2011), which would particularly serve to clarify whether findings are due to preparatory motor responses. We modeled the period during which participants would press the button as a regressor (as in Bolling et al., 2011a; Bolling et al., 2011b; Bolling, Pelphrey, & Wyk, 2016), but this may not have fully accounted for preparatory motor responses.

Finally, we take the positive association between dACC responses to increasing exclusion and subjective reports of need-threat to confirm that such neural responses to exclusion are indeed related to the affective distress of exclusion. However, our need-threat measure was limited in several ways. Participants completed the Need Threat Scale in reference to the Cyberball game in general (run unspecified), weakening the specificity of associations between this measure and neural responses to exclusion. However, the exclusion run took place at least ten minutes after the inclusion run, was the most recent run when participants were completing the scale, and participants report average levels of need-threat comparable to those in previous studies of exclusion, suggesting that the exclusion run was the reference point for most participants. While need-threat was assessed within 30 minutes of the end of the scan, retrospective reports of distress may be less reliable than immediate reports. Additionally, the absence of need-threat assessment before the scan does not control for individual differences at baseline.

Conclusions

We used parametric modulators to examine the specificity of neural responses to social exclusion as compared to overinclusion during Cyberball. We found BOLD signal increases with cumulative exclusion in the left and right AI (in

sensitivity analyses), left inferior frontal gyrus, left posterior cingulate cortex, VS, and across the extent of the ACC. While dACC signal was associated with reported affective distress, areas within the dACC and insula scaled negatively with cumulative inclusion events, and also responded to violations of short-term expectancies established by the context of each run. As such, our findings caution against interpreting involvement of the dACC and AI as necessarily reflecting aspects of the affective distress of exclusion in social rejection paradigms. The left ventrolateral PFC and rostromedial PFC exhibited similar signal increases in both Increasing Exclusion and Increasing Inclusion, suggesting that these regions play a role in processing events across conditions. Finally, a trending negative age association with cumulative exclusion events in the VS may reflect changes in emotional reactivity and/or regulation across adolescence.

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Open practices statement None of the analyses were pre-registered. Statistical maps are available on NeuroVault (<https://neurovault.org/collections/3794>). Preprocessing scripts used for this analysis are available on GitHub at https://github.com/dsnlab/TDS_scripts/tree/cheng_cyb_main/fMRI/ppc/spm/tds2 (SPM scripts) and https://github.com/dsnlab/TDS_scripts/tree/cheng_cyb_main/fMRI/ppc/shell/schedule_spm_jobs/tds2 (shell scripts). High motion volumes were identified using an in-house automated script that is publicly available (Cosme et al., 2018). We refer interested readers to the most recent version (<https://github.com/dsnlab/auto-motion>), and the branch used in this analysis is available at https://github.com/dsnlab/TDS_scripts/tree/cheng_cyb_main/fMRI/tx/motion/auto-motion.

Compliance with ethical standards

Conflict of interest The authors declare no competing financial interests.

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