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Modulation of prefrontal-cingulate connectivity in affective processing of children with experiences of ostracism

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Background: The anterior cingulate cortex (ACC) has been shown to be involved in emotional distress induced by social exclusion and the ventrolateral prefrontal cortex (VLPFC) in the regulation or inhibition of the distress. Here, we examined modulation of effective connectivity between the regions in response to emotional feedback in children with experiences of ostracism in their everyday life. **Methods:** In functional magnetic resonance imaging experiments, 10 ostracized children and 11 control children were provided emotional feedback inducing negative or positive affective states. We employed effective connectivity analysis to explore connectivity models comprising the VLPFC and ACC, and to estimate connectivity parameters over the models. **Results:** In spite of psychological impacts on the ostracized children, behavioral data showed that their emotional responses did not deviate from the control children in response to the emotional feedback. The VLPFC to ACC connectivity was modulated only in the ostracized children, such that the modulation may help them regulate their emotional responses. **Conclusions:** The findings suggest that the effects of ostracism experiences on affective processing can be revealed in terms of modulation of prefrontal-cingulate connectivity.

Key Practitioner Message

- Effects of social exclusion on affective processing can be seen in children with experiences of ostracism in their real life.
- In spite of psychological impacts of ostracism, responses to emotional feedback do not deviate from the healthy children.
- Prefrontal-cingulate connectivity is modulated in affective processing under experiences of ostracism.

Keywords: Ostracism; social exclusion; functional magnetic resonance imaging; effective connectivity; dynamic causal modeling

Introduction

Ostracism is a salient manifestation of social exclusion in which an ostracized individual is being ignored and excluded from participating in social activity. Although the devastating effects of ostracism on psychological well-being have been demonstrated, little is known about brain mechanisms underlying the impacts of ostracism.

As the seminal article of neural correlates of social exclusion (Eisenberger, Lieberman, & Williams, 2003), the anterior cingulate cortex (ACC), and ventrolateral prefrontal cortex (VLPFC) have been shown to be key regions related to social exclusion; the ACC is associated with emotional distress induced by social exclusion and the VLPFC is involved in the regulation or inhibition of the distress. However, there seems to be less coherence in the subregions of the ACC and dorsolateral prefrontal cortex (DLPFC); especially in the ACC, dorsal, ventral, and subgenual parts were referred to in different studies (Bolling et al., 2011b; Gunther Moor et al., 2012; Karremans, Heslenfeld, van Dillen, & Van Lange, 2011).

Having acknowledged that the ACC and DLPFC are involved in the brain processing under social exclusion, connectivity between the two regions could shed light on a deeper understanding about the functional architecture of the brain in the face of social exclusion. In particular, a causal model of interactions, that is, effective connectivity (Stephan & Friston, 2010) would provide much more informative aspects of functional integration between the two regions, compared to only describing statistical dependencies. To our knowledge, only one study examined effective connectivity between the VLPFC and ACC by using psychophysiological interac-

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tion analysis to search for changes in the connection with age during social exclusion (Bolling et al., 2011a).

We examined the functional architecture of the brain under social exclusion by using different approaches from previous studies. First, we recruited children with experiences of ostracism in their real-life relationship to look at the effects of social exclusion, whereas most of the neuroimaging studies thus far have employed experimental manipulations such as a Cyberball task (Williams & Jarvis, 2006) as being a computerized ball-tossing game during which subjects are excluded from the game. Furthermore, we employed a novel experimental paradigm using criticizing or approving face stimuli that convey potential real-life emotional distress.

Second, we used functional magnetic resonance imaging (fMRI) data to examine modulation of effective connectivity between the VLPFC and ACC. We employed dynamic causal modeling (DCM) as a tool for the analysis of effective connectivity (Friston, Harrison, & Penny, 2003). DCM posits a causal model in which activation in a given region is directly altered by driving inputs or indirectly altered via modulation of interregional connections manipulated by contextual inputs. In DCM for fMRI data, the resulting model of neurodynamics, in combination with a model of hemodynamics, gives rise to fMRI time series. Effective connectivity is inferred using Bayesian inference on model parameters in a way that minimize the discrepancy between predicted and observed fMRI time series. As applications of DCM, abnormal interregional interactions deviating from the healthy children could be characterized in patients with various neuropsychiatric diseases [see (Seghier, Zeidman, Neufeld, Leff, & Price, 2010) for a review].

We hypothesized that experiences of ostracism could alter the brain processing involving the VLPFC and ACC in the states of emotional distress, so that the modulation of effective connectivity between the two regions in response to emotional stimuli could be seen differently in children with experiences of ostracism.

Methods

Participants

Children between 10 and 12 years old who were recruited through advertisement completed the ostracism scale. The ostracism scale that measures the frequency of 12 different types of ostracism using five-point scale from 'none (1)' to 'almost every day (5)' over the last year (Shin, Kwon, Shin, & Cho, 2000) was used to divide the children into ostracized and healthy control groups. Ten children (11.30 ± 0.67 years; seven females) who reported experiences of ostracism within the last 1 year and scored over 28 points (above two standard deviations) on the ostracism scale, participated as the ostracized group. The control group consisted of 11 age- and gender-matched healthy children (11.00 ± 0.89 years; seven females) who scored less than 18 points (below two standard deviations) on the ostracism scale. All participants had no history of neurological illness, head trauma, or psychiatric disorder. The study was conducted with the understanding and full written consent of each child and their parents according to the Declaration of Helsinki. The Institutional Review Board of Uijeongbu St. Mary's Hospital, The Catholic University of Korea approved the study.

Behavioral measures

All children completed self-rating questionnaires including the social anxiety scale (SAS; Moon & Oh, 2002), Korean form of the Kovacs' Children's Depression Inventory (CDI; Cho & Lee, 1990), and Korean form of the State-Trait Anxiety Inventory for Children (STAI-C; Cho & Choi, 1989). The SAS was employed to measure social anxiety based on SAS for Children-Revised (LaGreca & Stone, 1993) and Social Phobia and Anxiety Inventory for Children (Beidel, Turner, & Morris, 1995). The CDI was used to evaluate the severity of depression. The STAI-C originated from Spielberger's STAI-C (Spielberger, 1972) was employed to evaluate state and trait anxiety. Furthermore, to compare the intellectual functioning between the two groups, the degree of academic achievement (high, middle, or low achievement) was examined based on the reports of the children' parents.

Experimental paradigm

During the fMRI scanning, the children attempted to solve geometric puzzles that had no solution. After the children selected an answer to each puzzle, they were shown prerecorded video clips of facial expressions depicting positive, negative, and neutral feedback in a pseudorandom order. This emotional feedback provided an opportunity for the children to feel as though the feedback was directed at them and their performance. For interpersonal feedback that the children received, they were asked to rate their subjective reaction. Timing of a single trial of the experiment is presented in Figure S1 (available online as Supporting information). Emotional feedback was preceded by a period of anticipation and followed by a period of fixation. The whole experiment included 60 trials; each trial lasted a total of 24 s on average and a fixation of 4 s was placed between two consecutive trials.

Imaging data acquisition

Magnetic resonance images were acquired using a 1.5T Avanto system (Siemens AG, Erlangen, Germany). A total of 307 functional images were acquired as T2*-weighted echo planar images with the blood-oxygen-level-dependent contrast (repetition time = 2000 ms, echo time = 24 ms, number of slices = 29, slice thickness = 4 mm, matrix size = 64×64, in-plane resolution = 3.59×3.59 mm). A structural image was also acquired as a T1-weighted image for coregistration to the functional images (number of slices = 160, slice thickness = 1 mm, matrix size = 512×512, in-plane resolution = 0.45×0.45 mm).

Imaging data analysis

Preprocessing and statistical analysis of the functional images were performed by using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing steps included spatial realignment of a series of volumes, spatial normalization into the same coordinate frame as the template brain conforming to the Montreal Neurological Institute (MNI) space, and smoothing using a Gaussian filter of 8 mm full width at half maximum. Transformation parameters for the spatial normalization were derived from segmentation of the high resolution structural image coregistered to the mean functional image.

In statistical analysis, a design matrix was built specifically for application to DCM. Four conditions (visual, positive emotional feedback, negative emotional feedback, and neutral emotional feedback conditions) were included as covariates in the design matrix, of which the visual stimuli corresponded to a driving input, whereas the positive and negative emotional feedback corresponded to contextual inputs in DCM. Voxel-wise parameter estimates were acquired in the general linear model with the design matrix. Contrast images of the parameter estimates were collected for the visual stimuli and for the difference between the negative and positive emotional feedback.

Dynamic causal modeling

As regions of interest (ROIs) for DCM, we found the involvement of the visual cortex (VC) for the visual stimuli, and the VLPFC and ACC for the difference between the negative and positive emotional feedback. When considering controversies in the literature over subregions in the VLPFC and ACC, we exploratively determined the subregions form the results of the conventional univariate analysis: the ostracized children showed higher activation in the right ventral ACC and right VLPFC for the negative emotional feedback than for the positive emotional feedback. Figure 1a displays the location of the right VC (x = 24 mm, y = −98 mm, z = −2 mm at the peak on the MNI space among 1827 voxels), and Figure 1b and c exhibit the locations of the right ventral ACC (x = 4 mm, y = 36 mm, z = −8 mm at the peak on the MNI space among 28 voxels) and right VLPFC (z = 58 mm, y = 26 mm, z = −2 mm at the peak on the MNI space among 115 voxels), respectively.

For each subject, a representative time series of each ROI was extracted as the first eigenvariate of time series from the ROI following the conventional procedure in SPM8. The representative time series of the three ROIs corresponded to regional outputs, or measured responses, in DCM.

We employed classical DCM that embodied deterministic, one-state, bilinear models by using DCM10 as implemented in SPM8. A connectivity model in DCM is defined by the pattern of connectivity by specifying which regions are connected to which other regions (intrinsic connectivity), and which inputs can modulate which connections (modulation of intrinsic connectivity). We constructed 33 connectivity models based on the following assumptions: (a) all the ROIs have self-connections; (b) the VC affects either the ACC (model 1–11) or VLPFC (model 12–22), or both the VLPFC and ACC (model 23–33); (c) a driving input (visual stimuli) enters the VC and contextual inputs (emotional feedback) modulate the connections between the VLPFC and ACC. The model space consisting of the 33 models is shown in Figure S1.

Connectivity parameters to be estimated were three sets: (a) the influence of the visual stimuli on the VC; (b) intrinsic connections between the VC, VLPFC, and ACC; (c) modulation of the intrinsic connections between the VLPFC and ACC induced by the positive and negative emotional feedback. For each model, estimation of the parameters was made using the posterior density in Bayesian analysis.

As the posterior density of a parameter is conditional on a particular model that embodies specific assumptions regarding intrinsic and modulatory architecture, we first searched for the best model among the 33 models that best explains the fMRI data across all children. Because individuals with pathological conditions were included in this study, we assumed that the best model was in random-effects (RFX) in the population. By using an RFX Bayesian model selection that gives consideration to heterogeneity of connectivity structure across individuals, we selected the best model based on an exceedance probability that quantifies our belief that a particular model is more likely than any other model (Stephan, Penny, Daunizeau, Moran, & Friston, 2009).

Unless one model clearly outperformed other models, we considered the entire model space of the 33 models, and computed weighted averages of each connectivity parameter over the model space, in which the weighting was given by the posterior probability of each model (Penny et al., 2010). That is, we acquired connectivity parameters in each child, irrespective of the dependence of parameter inference on the particular model. We assumed that connectivity parameters were in RFX in the population, so that we adopted an RFX Bayesian model averaging.

In this study, DCM was used primarily to answer questions about effective connectivity modulated by contextual inputs of emotional feedback. To this end modulatory effects on the connections between the VLPFC and ACC, and moreover, a contrast for the modulatory effects were compared between the two groups using two sample t-tests. The statistical significance was determined at a p value of .05, Bonferroni corrected for multiple comparisons.

Results

Behavioral data

Demographic and clinical characteristics of the children are presented in Table 1. According to the distinction between the two groups, the mean score on the ostracism scale was higher for the ostracized group than for the control group (p value < .0001). The ostracized group exhibited higher social anxiety (p value < .05) as measured by the SAS, greater depression as measured by the CDI (p value < .0001), and higher state (p value < .01) and trait (p value < .01) anxiety as measured by the STAI-C, compared to the control group. There was no significant difference in the degree of academic achievement between the two groups.

In the experimental paradigm, the children in both groups rated their subjective responses congruently to the type of emotional feedback they received. There was no significant difference in subjective emotional responses to each type of emotional feedback between the two groups (Table 1).

Bayesian model selection

Among the 33 connectivity models considered, the model in Figure 2 (the model 4 in Figure S1) was selected to be the best by the RFX Bayesian model selection. The model comprised a unidirectional connection from the VC to the ACC and bidirectional connections between the VLPFC and ACC as intrinsic connections, and contextual inputs to the connection from the VLPFC to the ACC. As shown in Figure S2, however, the exceedance probability of the model was not clearly superior to other models.

Comparison of connectivity parameters between groups

Connectivity parameters for the influence of the driving input, intrinsic connections, and modulation of the intrinsic connections were acquired as weighted averages across the model space of 33 models (Table 2).

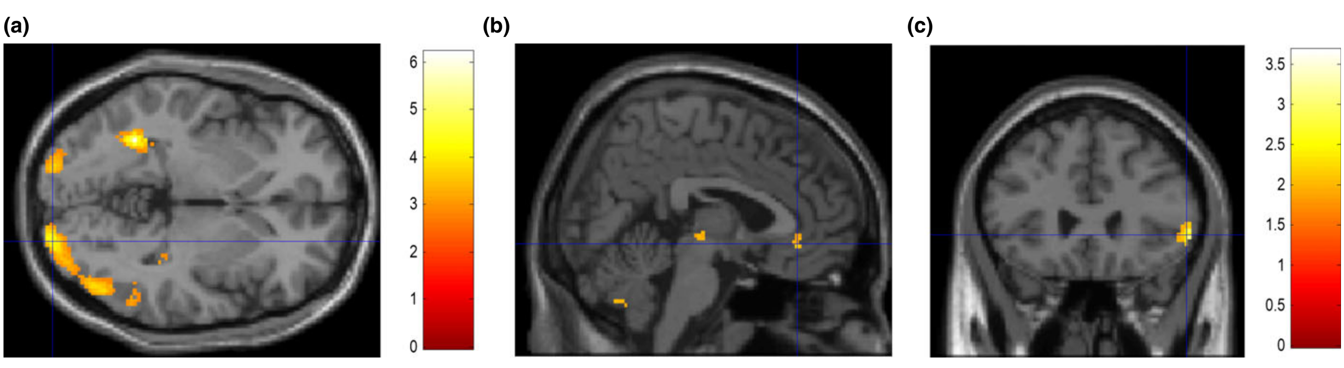

Figure 1. The locations of (a) the visual cortex, (b) anterior cingulate cortex, and (c) ventrolateral prefrontal cortex as regions of interest for dynamic causal modeling. The crosses indicate the peaks on the Montreal Neurological Institute space

Table 1. Demographic characteristics and behavioral states of children. Statistic values and *p* values were derived from statistical inference on the difference between ostracized and control groups

Variable	Ostracized group	Control group	Statistic	*p* Value
Age	11.30 ± 0.67	11.00 ± 0.89	0.8604	.4003
Sex (male: female)	3:7	4:7	0.7500	1.0000
Ostracism	38.90 ± 7.95	13.64 ± 2.20	10.1429	<.0001
Social anxiety	107.30 ± 37.08	70.73 ± 22.91	2.7485	.0128
Depression	24.40 ± 8.22	8.27 ± 4.94	5.5101	<.0001
State anxiety	37.80 ± 5.22	30.09 ± 6.88	2.8691	.0098
Trait anxiety	35.00 ± 6.96	27.00 ± 5.29	2.9826	.0077
Subjective emotional response to				
Positive emotional feedback	6.74 ± 0.71	7.16 ± 0.67	−1.3876	.1813
Negative emotional feedback	3.14 ± 0.74	2.99 ± 0.92	.4010	.6929
Neutral emotional feedback	4.87 ± 0.16	4.88 ± 0.34	−.1704	.8665

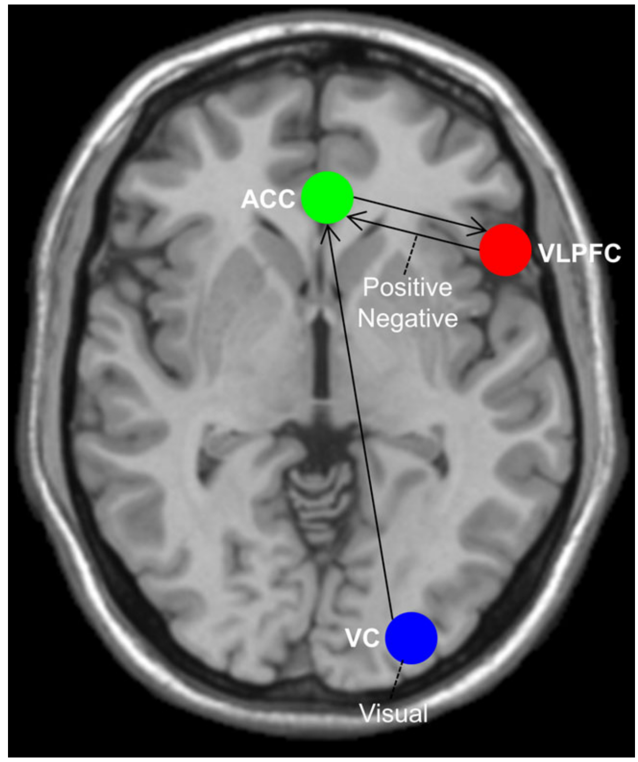

Figure 2. The best model determined by a random-effects Bayesian model selection. 'Visual' indicating visual stimuli is a driving input entering the visual cortex (VC), and 'Positive' and 'Negative' indicating positive and negative emotional feedback, respectively, are contextual inputs modulating the ventrolateral prefrontal cortex (VLPFC) to the anterior cingulate cortex (ACC) connection

In the ostracized group, the VLPFC to ACC connection was modulated for the negative emotional feedback (p value = .0054). Moreover, the modulatory parameter of the VLPFC to ACC connection was different between the negative and positive emotional feedback (p value = .0076). In contrast, the VLPFC to ACC connection was not modulated for either emotional feedback in the control group.

Between the two groups, the modulatory parameters of the VLPFC to ACC connection were marginally different for the positive and negative emotional feedback (Figure 3b and c), and furthermore, the contrast of the modulatory parameters (negative emotional feedback − positive emotional feedback) was different p value = .0034; Figure 3a).

Discussion

Greater severity in social anxiety, depression, and state and trait anxiety in ostracized children compared to healthy children in this study reflects psychological impacts following experiences of ostracism in everyday life. However, ostracized children's emotional responses did not deviate from control children when faced with emotional feedback similar to their interpersonal experience possibly due to the modulation of prefrontal-cingulate connectivity.

The strength of this study is to have included children who had real-life experiences of ostracism, whereas most previous studies have used brief experimental exposure to social exclusion. We demonstrated the effects of ostracism experiences on affective processing in response to criticizing or approving face stimuli that convey potential real-life emotional distress.

Modulation of effective connectivity

In this study, we searched for the modulation of effective connectivity, in the context of affective processing for different types of emotional feedback, in children with experiences of ostracism. Based on the anatomical model including the VLPFC and ACC (Figure 1), a set of connectivity models composing a model space (Figure S1) was proposed. Because model selection is considered as an essential step of a DCM study (Stephan et al., 2010), we first found the best model among the model space. Although the model selected to be the best appears not to show exceedingly clearer evidence than other models (Figure S2), it enables us to suppose a probable connectivity architecture between the VLPFC and ACC (Figure 2): the modulatory effects on the VLPFC to ACC connection suggest the pivotal role of this connection in affective processing with regard to emotional interpersonal feedback (Chiu, Holmes, & Pizzagalli, 2008; Guyer, Choate, Pine, & Nelson, 2012; Ochsner et al., 2006; Pavuluri, O'Connor, Harral, & Sweeney, 2007).

To further investigate the effects of emotional feedback on interregional connections, we acquired connectivity parameters weightily averaged over the entire model space. In ostracized children, the VLPFC to ACC connection was modulated for the negative emotional feedback (Table 2), and the difference in the modulation between the negative and positive emotional feedback differed from that of healthy children (Figure 3).

In ostracized children, the VLPFC to ACC connection was modulated toward the inhibitory direction for the positive emotional feedback and toward the facilitatory direction for the negative emotional feedback. Previous

Table 2. Connectivity parameters estimated as weighted averages across 33 connectivity models

Connections	Group	Mean	Standard deviation	*t* Value	*p* Value
Driving input of visual stimuli					
VC	Control	−0.0075	0.0010	−24.8088	<.0001
	Ostracized	−0.0068	0.0009	−22.6944	<.0001
Intrinsic connectivity					
VC to ACC	Control	0.1922	0.0308	20.6664	<.0001
	Ostracized	0.2060	0.0386	16.8724	<.0001
VC to VLPFC	Control	0.1646	0.0374	14.5911	<.0001
	Ostracized	0.1753	0.0216	25.6900	<.0001
ACC to VLPFC	Control	0.0415	0.1950	7.0614	<.0001
	Ostracized	0.0629	0.0175	11.3416	<.0001
VLPFC to ACC	Control	0.0181	0.0192	3.1271	.0107
	Ostracized	0.0440	0.0268	5.1834	.0006
Modulation of intrinsic connectivity by positive emotional feedback					
ACC to VLPFC	Control	−0.0017	0.0062	−0.9378	.3705
	Ostracized	0.0034	0.0078	1.3849	.1994
VLPFC to ACC	Control	0.0009	0.0080	0.3587	.7273
	Ostracized	−0.0062	0.0074	−2.6189	.0279*
Modulation of intrinsic connectivity by negative emotional feedback					
ACC to VLPFC	Control	0.0010	0.0068	0.4823	.6400
	Ostracized	0.0048	0.0093	1.6238	.1389
VLPFC to ACC	Control	−0.0001	0.0074	−0.0234	.9818
	Ostracized	0.0073	0.0063	3.6460	.0054**
Difference in modulation of intrinsic connectivity between negative and positive emotional feedback					
ACC to VLPFC	Control	0.0027	0.0084	1.0753	.3075
	Ostracized	0.0013	0.0143	0.2914	.7773
VLPFC to ACC	Control	−0.0009	0.0078	−0.3910	.7040
	Ostracized	0.0134	0.0124	3.4237	.0076**

VC, visual cortex; ACC, anterior cingulate cortex; VLPFC, ventrolateral prefrontal cortex.
**significant nonzero at a Bonferroni corrected *p* value of .05; *significant nonzero at an uncorrected *p* value of .05.

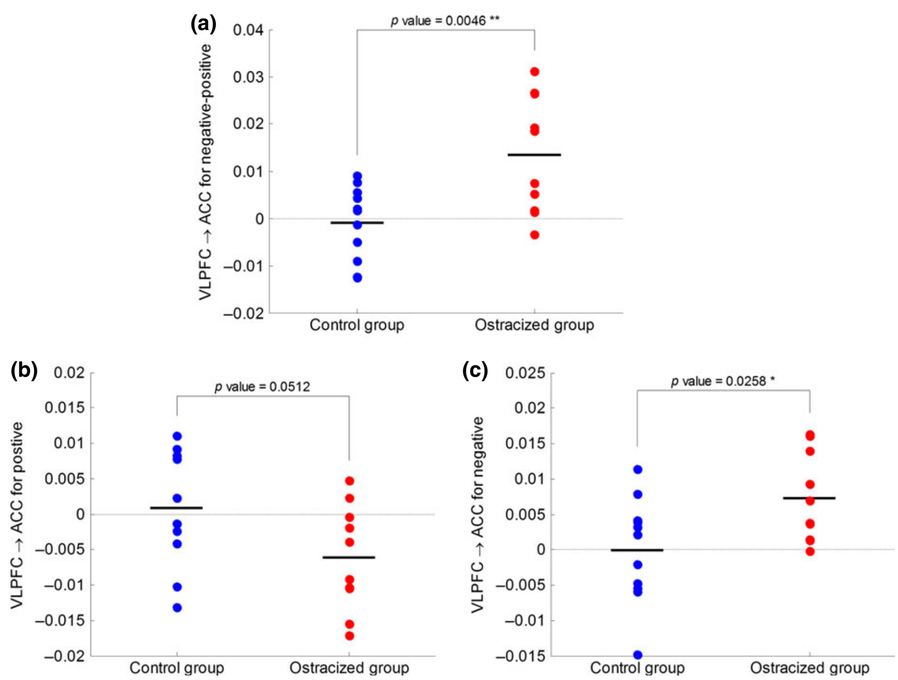

Figure 3. Comparisons of connectivity parameters between ostracized and control groups. (a) The difference in the modulation of the ventrolateral prefrontal cortex (VLPFC) to the anterior cingulate cortex (ACC) connection between positive and negative emotional feedback. (b) The modulation of the VLPFC to ACC connection for the positive emotional feedback. (c) The modulation of the VLPFC to ACC connection for the negative emotional feedback. **Significant difference at a Bonferroni corrected *p* value of .05; *significant difference at an uncorrected *p* value of .05

studies demonstrated that the VLPFC is in charge of top-down cognitive control, such as regulation of distress in social exclusion (Eisenberger et al., 2003) and inhibition to emotional stimuli in affective processing (Chiu et al., 2008). In a similar vein, the modulation of the VLPFC to ACC connection is thought to help regulate emotional responses. This modulation of effective connectivity in ostracized children may have induced no difference in their subjective emotional responses to emotional feedback compared to those in healthy children.

Implications for development

As the seriousness of ostracism is evident in the lower as well as in the upper grades of elementary schools (Wang, Iannotti, & Nansel, 2009), it is important to understand how experiences of ostracism affect the developing brain. Local activation and connectivity involving the VLPFC and ACC change with age in the face of social exclusion (Bolling et al., 2011a). Even though we have shown a possible link between the modulation of effective connectivity between the regions and affective processing in ostracized children, aspects of the relationship would change during their development. Considering that maturation of the regions subserving affective processing would be continued during development (Gogtay et al., 2004), proper psychiatric intervention such as emotion regulation training or emotional support to ostracized children may guide the functional architecture of the brain for attenuating atypical affective processing in them.

Limitations

In spite of novel approaches for finding alterations in effective connectivity in the context of affective processing under ostracism experiences, there are a few caveats in this study. First, the limited sample size may not provide definitive conclusion, so that further investigation on the relationship between clinical symptomatology and interregional connectivity could be performed with a larger number of children. In addition to the small sample size, potential heterogeneity among ostracized children should be noted: psychiatric effects following experiences of ostracism in everyday life may evolve in diverse ways depending on how long and how severely the ostracism experiences lasted and whether suitable treatment or care was provided after ostracism experiences. Second, we selected the ROIs by relying on the activation results from only the ostracized group, not from both groups. Such selected ROIs could have biased the comparisons of connectivity parameters between the two groups. Furthermore, even though we exploratively specified the locations of the ROIs, there have been controversies over the subregions among various studies with respect to social exclusion and affective processing. Further investigation is clearly warranted for a better understanding about the subregions.

Conclusions

In summary, we revealed an ostracism experience-induced difference in the modulation of effective connectivity in the context of different types of affective processing. Prefrontal-cingulate connectivity was modulated only in ostracized children, such that the modulation may help them regulate their emotional responses. Task context-dependent changes in interregional connectivity as well as local activation could offer a comprehensive understanding about brain mechanisms underlying social exclusion.

Acknowledgements

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. A single trial of the experiment of emotional feedback which was provided as a positive, negative, or neutral facial expression.

Figure S2. A model space comprising 33 connectivity models.

Figure S3. Comparisons of expected posterior model probabilities and exceedance probabilities between 33 connectivity models in the model space.

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