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Abnormal degree centrality of functional hubs associated with negative coping in older Chinese adults who lost their only child

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ABSTRACT

The loss of an only child is a negative life event and may potentially increase the risk of psychiatric disorders. However, the psychological consequences of the loss of an only child and the associated neural mechanisms remain largely unexplored. Degree centrality (DC), derived from resting-state functional magnetic resonance imaging (fMRI), was used to examine network communication in 22 older adults who lost their only child and 23 matched controls. The older adults who lost their only child exhibited an ineffective coping style. They also showed decreased distant and local DC in the precuneus and left inferior parietal lobule and decreased distant DC in the bilateral dorsolateral prefrontal cortex (DLPFC). Furthermore, the decreased local and distant DC of these regions and the decreased DLPFC-precuneus connectivity strength were negatively correlated with negative coping scores in the loss group but not in the controls. Overall, the results suggested a model that the impaired neural network communication of brain hubs within the default mode network (DMN) and central executive network (CEN) were associated with a negative coping style in older adults who lost their only child. The decreased connectivity of the hubs can be identified as a neural risk factor that is related to future psychopathology.

1. Introduction

The one-child only policy, where only one child is allowed in each family, has been in place for more than 30 years in China (see Supplemental materials for history of the policy). While this policy has successfully controlled the rapid population growth rate in China, its associated problems and challenges for the Chinese government and citizens have also appeared. For example, parents with one child often become highly psychologically dependent on their only children, which is a unique parent–child attachment phenomenon. As a consequence, when a couple has lost their only child unexpectedly, it would have serious consequences for the entire family. The advent and expansion of "childless" older adults in China have become a significant burden to Chinese society. According to the Minster of Health in China, the number of families who lost their only child has risen to more than 1 million by 2011 (Health, 2010) and this figure is estimated to be 10 million by 2035 (J, 2012). The death of the only child can cause pronounced psychological consequences to their parents including long-term grief, depression, and anxiety (Li & Wu, 2013). Thus, it may become a significant and widespread public mental health problem with the increase in the number of the parents dealing with this type of life event.

There is abundant evidence in the literature supporting an association between the death of the loved one and a range of psychiatric disorders (e.g., depression, PTSD and substance use) (Brown, Stout, & Mueller, 1999; Bruce, Kim, Leaf, & Jacobs, 1990; Keyes et al., 2014; Zisook, Chentsova-Dutton, & Shuchter, 1998; Zisook & Shuchter, 1991). The couples who lost their only child at an older age are often devastated because of their inability to have another child. Therefore, they are at an extremely high risk of developing psychiatry disorders. Experiencing the death of a loved one may influence the risk of psychiatric disorders via a variety of cognitive, affective and neurobiological pathways (McEwen, 2012). Among them, individual differences in the stress response are a vital factor. Coping style, the behavioral pattern humans adopt when facing stress, is a psychological trait that can strongly affect how a stressful event is perceived and whether it can be effectively

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managed (Folkman, 1984). Evidence suggests that personal coping style is related to individual differences in stress-induced psychopathology (Billings & Moos, 1984; Folkman & Lazarus, 1980). However, the individuals' coping style after a particular major negative life event has not been studied in a highly homogeneous group. Data from older adults in China who have lost the only child is unique and valuable in this sense. We hypothesized that those who have lost an only child at an older age would exhibit an ineffective coping style.

Abnormal anatomical and functional connectivity of the brain hubs have been related to behavioral and cognitive impairment in neurological and psychiatric disorders (Crossley et al., 2014; van den Heuvel & Sporns, 2013). These brain regions are intensively connected with other nodes (Buckner et al., 2009; Tomasi, Shokri-Kojori, & Volkow, 2015; Tomasi & Volkow, 2010, 2011) and the functional hubs are largely overlapped with subregions of the default-mode network (DMN), a network related to self-related processes such as self-reference (Sheline et al., 2009), autobiographical memory (Spreng & Grady, 2010) and rumination (Hamilton et al., 2011). Impairments in these hubs have been found in previous studies as they are highly susceptible to disconnection and dysfunction caused by psychiatric disorders due to their high level of centrality. For example, the precuneus is implicated in depression (Bluhm et al., 2009a; Zhu et al., 2012), schizophrenia (Paulus et al., 2002; Whitfield-Gabrieli et al., 2009), post-traumatic stress disorder (PTSD) (Geuze, Vermetten, de Kloet, & Westenberg, 2007; Yan et al., 2013) and Alzheimer's disease (AD) (Ikonomovic et al., 2011; Karas et al., 2007). The inferior parietal lobule (IPL), another hub within the DMN, shows abnormal DC in depression (Zhang et al., 2011) and an abnormal structure after stress exposure (Hanson et al., 2010). However, there are few studies that directly explore the functional connectivity of these brain hubs in individuals who are at a high risk for developing psychiatric disorders. The impairments may have happened before the onset of the clinical disorders and serve as the neural risk factors that contribute to future psychopathology. Therefore, we hypothesized that the older adults who lost their only child would exhibit reduced functional connectivity of these functional hubs,such as the precuneus and IPL or other brain regions, which, although not usually identified as brain hubs in previous studies, play a fundamental role in network communication. Additionally, these abnormalities may be associated with alterations of psychological variables.

In this preliminary study, every voxel was treated as an independent node and DC (Buckner et al., 2009; Sepulcre et al., 2010) was computed from this high-resolution functional brain network to map hubs in functional brain network and to identify the potential altered efficiency of any particular brain region after the death of an only child. We used DC to map the neural abnormality for two reasons. Firstly, the DC used in this study has been applied to mental disorders including the major depression disorder (Wang et al., 2014, 2015) schizophrenia (Tomasi & Volkow, 2014; Zhuo et al., 2014) and social anxiety disorder (Liu et al., 2015) and our major purpose is to investigate the risk for mental disorders. Secondly, DC is physiologically meaningful (Liang, Zou, He, & Yang, 2013; Tomasi, Wang, & Volkow, 2013) and can allow us to map the brain hubs with high sensitivity, specificity, and reproducibility (Tomasi et al., 2015). Therefore, DC is a better network parameters when compared to other measurements. Furthermore, we adopted an approach to capture the distant and local DC, respectively, using anatomical distance as a cutoff (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006; He, Chen, & Evans, 2008; Sepulcre et al., 2010). This method can allow us to investigate the local and distant brain interactions separately, which can explore the potential difference in the local and distant connectivity as a result of only child loss. Investigating the brain network abnormalities in older adults who lost their only child provides us an opportunity to test the hypothesis that people who experienced severe life events may exhibit impaired connectivity of the brain hubs, and, therefore, they are at a high risk of developing psychiatric disorders. This situation may also allow us to identify the neural alterations in these individuals that precede the onset of mental illnesses.

2. Materials and methods

2.1. Participants

This study was approved by the Research Ethics Committee of the Brain Imaging Center of Southwest University. Informed consent was obtained from each subject before they participated in the study. We recruited 26 subjects reported the only child losing and finished the MRI scanning and the essential psychological measurements. Four subjects did not be included in this study because they also lost their spouse. All of the participants volunteered to complete the MRI scans, questionnaires, and interviews. Older adults who lost their only child (referred as the loss group below) were recruited from a local, government-supported organization in the Beibei district of Chongqing that aims to provide assistance to "the loss families". It is notable that no subjects had another child after the death of their only child. Controls were age, sex, educational attainment, and handedness matched parents who do not experience the loss of their only child or any other recent significant life events, including the death or severe illness of their spouse, close relatives or friends. All of the subjects in the control group are also the parents of the single child. A face-to-face interview was conducted to obtain the subjects' major life events (especially the information about the death of their only child) and current or lifetime diagnoses of psychiatric disorders was conducted using the semi-structured Traumatic Antecedents Interview (TAI) and the Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID-I and SCID-II) (First, Spitzer, Gibbon, & Williams, 2012). Before the experiment, we ruled out the individuals who are not suitable for scanning by face-to-face communication and the self-reported checklist. The MRI related exclusion criteria include claustrophobia, metallic implants, Meniere's Syndrome and history of faint within half of the year. Exclusion criteria for both groups were as follows: current psychiatric disorders and neurological disorders; use of any psychiatric drugs within the three months before scanning; substance abuse; and stroke or serious encephala trophy. Based on the exclusion criteria, 22 older adults in the loss group and 23 matched controls were included in this study. Only one subject in the loss group had a history of major depression disorder (10 months) and had recovered from it three years ago. Except for this subject, no one in the loss or control group had a history of any psychiatric disorders. Detailed demographic information is presented in Table 1.

2.2. Measures

Each participant was evaluated on their level of cognition, anxiety, depression, and stress coping skills using the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), Self-rating Anxiety Scale (SAS) (Zung, 1976), Self-Rating Depression Scale (SDS) (Zung, 1965), UCLA Loneliness Scale (Russell, 1996), Subjective Happiness Scale (SHS) (Lyubomirsky & Lepper, 1999), Social Support Rating Scale (SSRS) (Xiao and Yang, 1987) and Simplified Coping Style Questionnaire (SCSQ) (Xie, 1999). The MMSE was used to screen subjects with potential dementia; the SAS, SDS, SHS, SSRS, and the UCLA Loneliness Scale were used to measure the anxiety, depression, subjective happiness, social support, and the loneliness level of participants respectively. SCSQ is a tool for

Table 1
Demographic and psychological profiles of the participants.

Characteristic	Loss	Control	*P* Value[a]
Age, mean (SD), y	61.00 (6.07)	61.84 (7.03)	.70
Sex (male/female), no. (% female)	9/8 (52/48)	9/10 (47/53)	.73
Education years, mean (SD), y	11.00 (3.53)	11.63 (2.96)	.56
Years after death, mean (SD), y	9.52 (6.31)	NA	
Death age of child, mean (SD), y [b]	23.43 (7.97)	NA	
Parents' age when child died, mean (SD), y	51.47 (5.94)	NA	
Past psychiatry disorder, no. (%)			
Major depression disorder	1 (5)	NA	
MMSE, mean (SD)	39.00 (4.62)	39.63 (3.18)	.63
SAS, mean (SD)	30.59 (5.30)	27.53 (7.22)	.16
SDS, mean (SD)	34.88 (7.45)	29.10 (7.78)	**.03**
Loneliness, mean (SD)	35.47 (8.33)	33.84 (8.12)	.55
SCSQ, mean (SD)			
Positive coping[c]	18.13 (5.38)	22.47 (2.89)	**.01**
Negative coping[d]	10.19 (4.02)	7.16 (3.79)	**.03**
SSRS, mean(SD)			
Subjective support[e]	24.31 (3.00)	25.19 (4.13)	.49
Objective support	9.53 (3.46)	9.68 (3.26)	.89
Support use	7.06 (2.56)	9.16 (2.16)	**.01**
SHS, mean (SD)	19.71 (2.82)	18.16 (4.10)	.19
Mean FD, mean (SD), mm	0.09 (0.05)	0.09 (0.03)	.83
Remaining time points, mean (SD)	217.00 (20.14)	215.26 (16.79)	.55

[a] *p*-Values were determined using $\chi 2$ analyses (sex), Mann–Whitney *U* test (remaining time points) or independent-samples *t*-tests (all other comparisons).
[b] Data were available for 16 participants in the loss group.
[c] Data were available for 15 participants in the loss group and 19 participants in the control group.
[d] Data were available for 16 participants in the loss group and 19 participants in the control group.
[e] Data were available for 16 participants in the loss group and 16 participants in the control group.

assessing individuals' coping style, which is simplified and modified based on Folkman's way of coping questionnaire (WAYS) (Folkman & Lazarus, 1988). It has been proven to have high internal consistency in Chinese samples, with a Cronbach's value of 0.90 (Xie, 1999). This questionnaire contains 20 items that measure two aspects of coping style: positive coping and negative coping. Subjects with a high score in positive coping tend to respond positively to stress events, adopting strategies such as seeking help from others or changing their personal value system, while individuals with a high score in negative coping are more likely to use strategies such as avoidance or substance use (alcohol, cigarette, food).

2.3. MRI data acquisition

All of the data were collected in the Southwest University Center for Brain Imaging using a 3.0-T Siemens Trio MRI scanner (Siemens Medical, Erlangen, Germany). During resting-state MRI scanning, the subjects were instructed to lie down, close their eyes, and rest without thinking about a particular thing, but do not fall asleep. The 8-min scan of 242 contiguous whole-brain resting-state functional images was obtained using gradient-echo echo planar imaging (EPI) sequences with the following parameters: slices = 32, repetition time (TR)/echo time (TE) = 2000/30 ms, flip angle = 90, field of view (FOV) = 220 mm × 220 mm, and thickness/slice gap = 3/1 mm, voxel size 3.4 × 3.4 × 4 mm^3. Meanwhile, a high-resolution T1-weighted anatomical image was also acquired using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR/TE/TI = 1900 ms/2.52 ms/900 ms; flip angle = 9°; slices = 176; slice thickness = 1.0 mm; resolution matrix = 256 × 256; voxel size = 1 × 1 × 1 mm^3).

2.4. Preprocessing and quality control

Preprocessing of the resting-state and structural images was performed using the toolbox for Data Processing & Analysis of Brain Imaging (DPABI) (http://rfmri.org/dpabi). Most of the functions are based on the Statistical Parametric Mapping (SPM8) (http://www.fil.ion.ucl.ac.uk/spm). Firstly, the structural abnormality checking and the image quality checking was finished. Then we removed the first ten time points of the 242 time points. In sequence, slice timing, head motion correction were conducted for the remaining time points. Covariates were regressed out from the time series of every voxel. The covariates include total 26 variables including the white matter signal, cerebrospinal fluid signal, and the Friston 24-parameter (Friston, Williams, Howard, Frackowiak, & Turner, 1996). The Friston-24-parameter model of head motion includes the 6 standard head motion parameters, the derivative of the standard motion parameters to account for a one-frame delay in the effect of motion on the BOLD signal (Satterthwaite et al., 2013) and the 12 corresponding squared items. After filtering with a band-pass filter (0.01–0.1 Hz), the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) was used to compute transformations from the native space to the MNI space (Ashburner, 2007). The normalized images were smoothed using a 4-mm full-width-at-half-maximum Gaussian kernel. The scrubbing procedure was conducted according to the method of Power et al. (2012), excluding any volume with a framewise-dependent value exceeding 0.5, together with the two subsequent volumes and one preceding volume. Participants were excluded from subsequent analyzes if more than 33% of the volumes were removed. scrubbing and quality checking of the normalization (details in Supplementary materials). Five subjects (3 in the loss group and 2 in the control group) were excluded because the extensive mean framewise displacement (FD) (Jenkinson, Bannister, Brady, & Smith, 2002) in these subjects was more than 2.5 standard deviations of the pooled subjects. Three subjects did not pass the scrubbing step (1 in the loss group and 2 in the control group) because more than 33% of the total volumes were removed. Finally, normalization quality was monitored by checking the normalization image subject by subject. No subjects were excluded because of poor normalization (more details in the Supplemental materials).

2.5. Network degree centrality computation

To include only gray matter voxels, a study-specific gray matter mask was created by averaging each subject's mask of gray

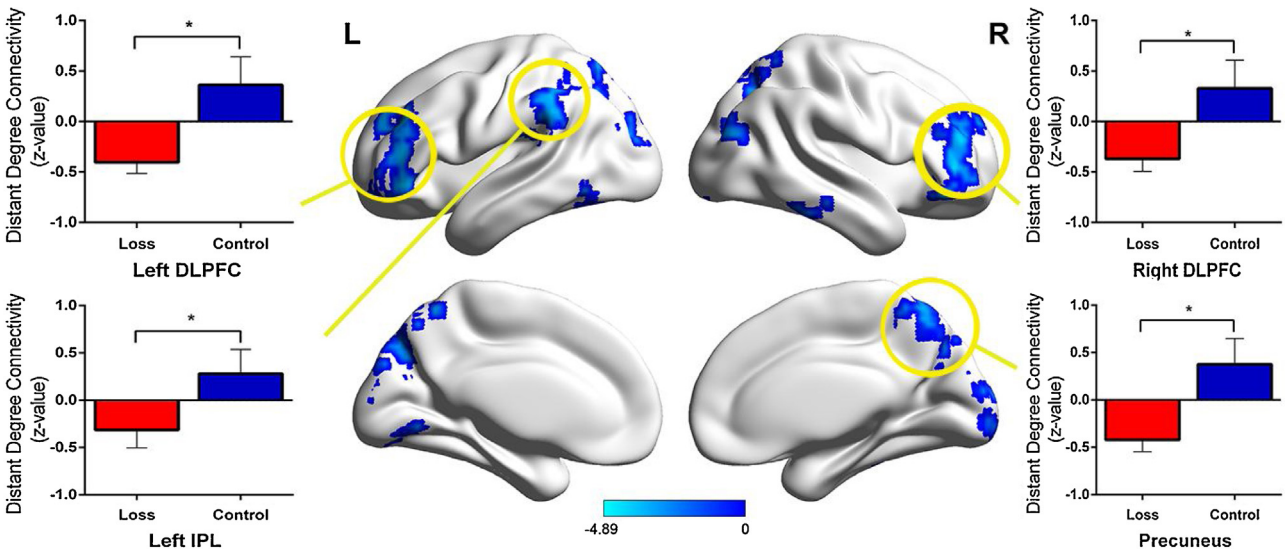

Fig. 1. Decreased distant degree centrality in the loss group compared to controls.

matter, resulting in a mask of 52,616 voxels. Pearson's correlation coefficients were computed between all pairs of brain voxels in the defined mask so that the whole-brain functional connectivity matrix for each participant was constructed. Three different types of degree centrality maps were computed using 0.3 as the threshold for deciding edge: (1) whole-brain maps, derived by counting the number of voxels where the correlation between a voxel with other voxels' in the BOLD time series exceeded the threshold (i.e.,0.3) in a whole-brain weighted graph; (2) local maps, computed by the same procedure but only considering voxels inside a sphere (radius = 12 mm) around a voxel; (3) and distant maps, also derived by the similar procedure but exclusively counting voxels outside the 12-mm sphere.

2.6. Seed-based whole-brain functional connectivity (FC)

Although the DC analysis can identify voxels that showed altered or decreased functional connectivity with other voxels, it cannot provide detailed information regarding the connectivity between a voxel and the particular regions that were changed. Therefore, we further conducted functional connectivity using the regions that showed significant alterations in the DC analysis. Specifically, the peak voxels of the brain regions that showed abnormally distant DC and were significantly correlated with neuropsychological measures were chosen as the centers of seeds. Specifically, the average blood–oxygen-level-dependent (BOLD) signal time courses within created spherical ROIs (radius = 6 mm) based on the coordinates of peak voxel were correlated to every voxel in the whole brain for each subject using Pearson's correlation coefficient (details in Supplemental materials).

2.7. Statistical analysis

At the voxel level, individual centrality maps and seed-based FC maps were transformed to Z score maps for group-level analyzes. To test the group difference in the DC, we performed independent two-sample t- tests using the gray matter mask. We controlled the influence of sex, age, depression symptoms, and head motion using sex, age, SDS and mean FD as nuisance covariates. Given our interests in the relationship between neuroimaging measurements (i.e., DC and seed-based FC) with copying styles, voxel-based multiple regression analysis was conducted in the loss group on the regions that showed significant group differences in the DC and seed-based FC (voxel-wise: $Z > 2.3$). The scores on SCSQ (i.e., positive coping and negative coping) were used as covariates of interest. Gaussian random field (GRF) theory was used to control multiple comparisons errors in the voxel-wise group comparisons (minimum $Z = 2.3$; cluster significance: $p \leq .05$) and multiple regression(minimum $Z = 2.3$; cluster significance: $p \leq .001$). Meantime, the non-voxel wise correlation was also performed (see Supplementary materials). Any significant clusters within the cerebellum were not reported.

2.8. Addressing potential confounds

When computing degree centrality, the correlation coefficient threshold (0.3 in this study) was used to eliminate possible spurious connectivity. However, the choice of this threshold is arbitrary. Therefore, we also reanalyzed the data using two different correlation thresholds (i.e., 0.2, and 0.4) to examine whether our primary results were dependent on the chosen threshold.

One of the participants in the loss group once experienced an episode of major depression disorder, which may affect his intrinsic functional connectivity. Although we included him in our primary

Table 2
Distant degree centrality: regions that showed decreased connectivity in the older adults who lost their only child compared to the controls.

					Mean Z-score Within the cluster, mean (SD)	
Brain regions	BA	X,Y,Z	t	Number of voxels	Loss	Control
Precuneus	7/18/19	33 −66 33	-4.88	714	−.42(.51)	.37(1.18)
Right DLPFC	10/46	36 39 18	-4.28	281	−.36(.52)	.32(1.20)
Left DLPFC	10/46	−33 33 27	-4.21	298	−.40(.44)	.36(1.21)
Left IPL	40	-57-39 36	-3.89	241	−.31(.77)	.28(1.11)

DLPFC, dorsolateral prefrontal cortex; IPL, inferior parietal lobule.

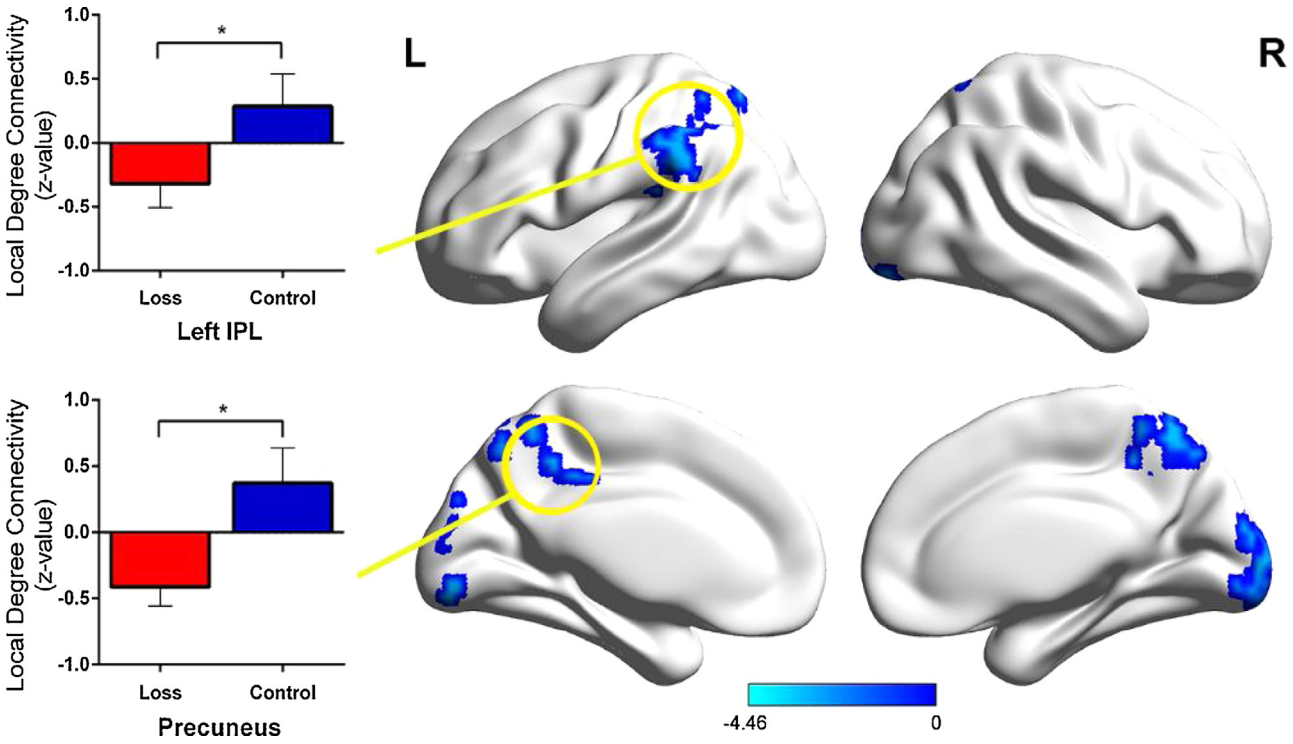

Fig. 2. Decreased local degree centrality in the loss group compared to control.

analysis, additional analysis without this subject was performed to avoid potential effects of the depression episode on group comparisons.

The intensity of spontaneous brain activity and brain structure could account for the DC findings in this study (Schaefer et al., 2014). We computed the power of the resting-state signal using a metric called amplitude of low-frequency fluctuations (ALFF) (Yu-Feng et al., 2007) and voxel-wise gray matter volume (GMV). Group comparisons were conducted to investigate potential significant ALFF or GMV difference between the two groups on the regions that showed significant findings in our primary DC analyzes using small volume correction (SVC).

3. Results

3.1. Demographic data and psychological measurements

As shown in Table 1, the two groups did not differ significantly with regard to age ($t = -.38$, df = 34, $p = 0.70$), sex ($\chi^2 = .11$, df = 1,36, $p = 0.738$) or educational years ($t = -.58$, df = 34, $p = 0.56$). For head motion control, the two groups did not differ in mean FD ($t = .20$, df = 34, $p = 0.83$) or time points remaining after scrubbing ($p = .55$, Man–Whitney U test). Compared with the controls, the parents who lost their only child experienced higher depressive symptoms measured by SDS ($t = 2.26$, df = 34, $p = 0.03$) and showed ineffective coping strategies when facing life stress: a significantly lower score in positive coping ($t = -3.01$, df = 20.29, $p = 0.011$) and a higher score in negative coping ($t = 2.29$, df = 34, $p = 0.028$) in the SCSQ. We also found the death age of the child negatively correlated with the subjective well-being ($r = -0.696$, $p = 0.003$). For the social support rating scale (SSRS), two groups did not differ in the subjective ($t = -0.68$, $p = 0.49$) and objective support ($t = -0.13$, $p = 0.89$) score. However, the loss group showed the lower social support use score ($t = -2.66$, $p = 0.01$). We found that the loneness score measured by UCLA Loneness scale negatively correlates with the subjective social support score ($r = -0.646$, $p < 0.001$), objective social support score ($r = -0.388$, $p = 0.01$), and the support use score ($r = -0.526$, $p = 0.001$). Also, we found the significant negative correlation between the depression score and the support use score ($r = -0.339$, $p = 0.03$).

3.2. Decreased distant degree centrality in the loss group

Remarkably similar spatial distributions of the functional "hubs" (high degree centrality) were identified across the two groups (Fig. S1). However, the older adults who lost their only child exhibited a significantly decreased distant degree centrality in the precuneus, the bilateral dorsolateral prefrontal cortex (DLPFC) and the left inferior parietal lobule (IPL) (all $p < 0.05$ with GRF cluster-corrected) (Fig. 1, Table 2), which were the functional hubs in our data and several previous studies (Buckner et al., 2009; Tomasi & Volkow, 2011; van den Heuvel & Sporns, 2013). No regions showed enhanced distant functional connectivity under the same statistical threshold. The results of total maps comparison are presented in the supplementary materials (Table S1, Fig. S2). In fact, the total and distant degree connectivity maps were highly correlated (Sepulcre et al., 2010) and the group differences in the total maps were largely similar to the distant maps.

3.3. Decreased local degree centrality in the loss group

Significantly decreased local DC was also found in the precuneus and the left inferior parietal lobule (IPL) (all $p < 0.05$, cluster-corrected) (Fig. 2, Table 3). These results were similar to the significant clusters in the distant DC comparison, with the exception of the absence of the bilateral DLPFC clusters. No other regions showed increased local DC in the control group.

3.4. Brain–behavior association

The results from the voxel-wise correlational analyses between distant DC and the positive or negative coping scores revealed that,

Table 3
Local degree centrality: regions that showed decreased connectivity in the older adults who lost their only child compared to the controls.

					Mean *Z*-score Within the cluster, mean (SD)	
Brain regions	BA	*X,Y,Z*	*t*	Number of voxels	Loss	Control
Precuneus	7/31	0 −72 48	−4.08	247	−.41(.58)	.37(1.15)
Left IPL	40	−54 −36 39	−3.69	212	−.31(.77)	.28(1.10)

IPL, inferior parietal lobule.

in the loss group, those who had higher negative coping scores had lower distant DC in the left DLPFC ($MNI_{XYZ} = -45$, 48 and 9, $p = 0.001$, corrected) and left IPL ($MNI_{XYZ} = -54$, −42 and 42, $p < 0.001$, corrected) (Fig. 3, Table S2). No positive correlation was found for the negative coping scores. Post hoc partial correlations controlling for sex, age and mean FD (2-tailed in SPSS) revealed robust correlation relationships in both regions ($r = -.748$, $p = 0.003$ for the left DLPFC and $r = -.752$, $p = 0.003$ for the left IPL). There was no positive or negative correlation found for the positive coping scores.

Similar analyzes were performed with the local DC maps (Fig. 4, Table S2). Local DC in the left IPL ($MNI_{XYZ} = -39$, −48 and 48, $p < 0.001$, corrected), precuneus ($MNI_{XYZ} = 6$, −48 and 60, $p < 0.001$, corrected), left superior temporal gyrus ($MNI_{XYZ} = -60$, −21 and 3, $p < 0.001$, corrected), left cuneus/calcarine ($MNI_{XYZ} = 0$, −87 and 12, $p < 0.001$, corrected) and left precentral gyrus ($MNI_{XYZ} = -24$, −12 and 60, $p < 0.001$, corrected) were also negatively correlated with the negative coping scores ($r = -.788$, $p = 0.001$; $r = -.843$, $p < 0.001$; $r = -812.$, $p = 0.001$; $r = -.799.$, $p = 0.001$; $r = -.836.$, $p < 0.001$ respectively). There were no positive correlations of the local degree centrality maps with the negative coping scores. No regions showed any correlation of the DC with the positive coping scores.

Brain–behavior association *Z*-value within each mask generated by group comparisons to conduct a partial correlation. The correlation of the distant DC of the left DLPFC and left IPL, and the local connectivity of the left IPL and precuneus with the negative coping scores were preserved in these complementary analyzes (see Supplemental materials). Finally, we found no significant correlation between those regions and the negative coping scores in the control group (all $ps > 0.64$).

3.5. Addressing potential confounds in the DC analysis

To address the concern that an arbitrary connection threshold was chosen, we repeated the DC analyzes using the other two thresholds (0.2 and 0.4). Again, the analyzes yielded highly similar findings for all clusters (Figs. S3 and S4 and Tables S3 and S4).

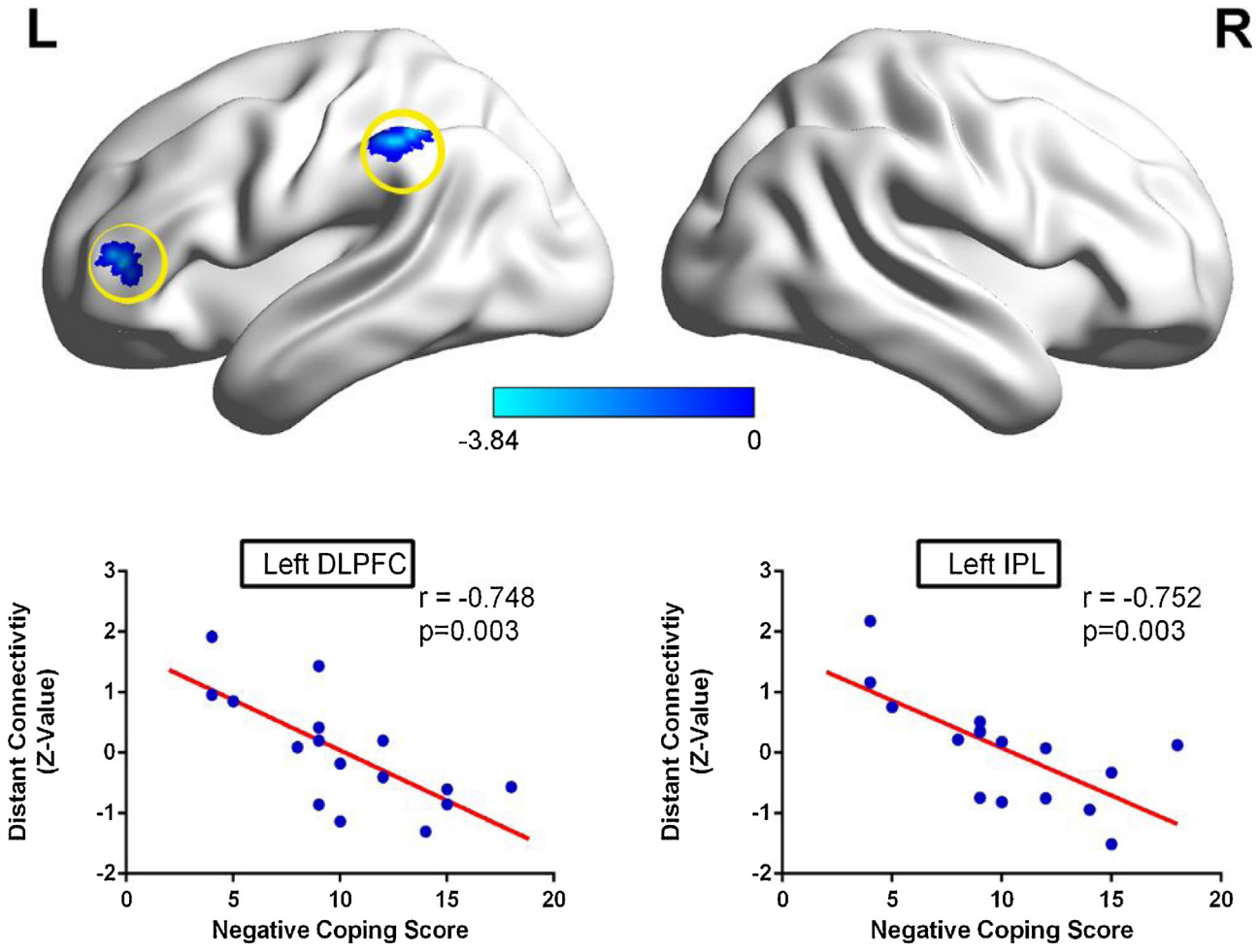

Fig. 3. Decreased distant degree centrality associated with negative coping.

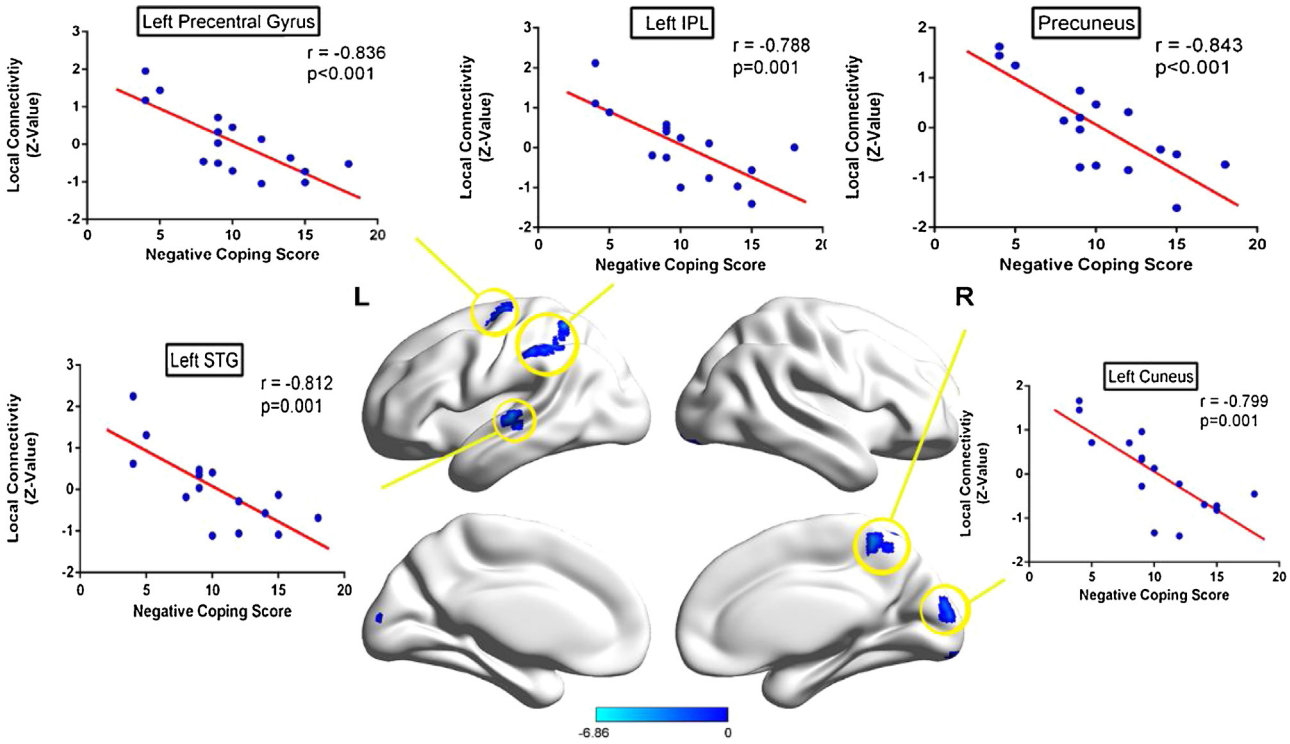

Fig. 4. Decreased local degree centrality associated with negative coping.

To investigate the influence of a past depression episode of one subject in the loss group, we removed this subject and performed the group comparisons again. We found that our main findings were also reproducible, and only the number of voxels changed slightly (Fig. S5, Table S5).

In the analyzes of ALFF and GMV, we did not find any significant increased or decreased ALFF or GMV in the loss group compared to the controls in regions showing abnormal DC (SVC, $p < .05$).

3.6. Seed-based whole-brain functional connectivity

Because decreased distant connectivity of the left DLPFC and left IPL were correlated with abnormally high negative coping scores in the loss group, additional FC analyses using those two regions as seed regions were conducted to capture the details of connectome abnormality and its relationships with behavior. The areas significantly connected to each seed region were similar across the two groups (Figs. S6 and S7).

However, the FC strength was significantly reduced in the loss group compared to controls for the left DLPFC-seed in the precuneus, the IPL, the cuneus, the right ITG, the right STG, the right fusiform gyrus and the right precentral gyrus (all $p < 0.05$, corrected; Fig. S8, Table S6). The reduced strength of the left DLPFC-precuneus ($r = -.787$, $p = 0.001$) and left DLPFC-middle occipital gyrus/cuneus ($r = -.762$, $p = 0.002$) connectivity was significantly correlated with higher negative coping scores (Fig. 5).

Furthermore, there were several regions that showed impaired connectivity with the left IPL seed in the loss group, including the left parahippocampal gyrus/hippocampus/amygdala, the cuneus/precuneus, the precentral gyrus/STG/insular and the supplementary motor area (all $p < 0.05$, corrected; Fig. S8, Table S7). The connectivity strength of the left IPL-Cuneus ($r = -.796$, $p = 0.001$) and left IPL- superior occipital gyrus(SOG)/Cuneus ($r = -.816$, $p = 0.001$) was also negatively correlated with the negative coping scores (Fig. 5).

Because our primary analyses are restricted in the masks derived from the control group, we reanalyzed our data at the whole-brain level (see Supplementary materials for the detailed methods) and found no significant findings outside our masks. All of the observed regions remained at the whole-brain level comparisons. As for the uniqueness of brain–behavior relationship, all of the observed correlations did not exist in the control group (all $p > 0.32$).

4. Discussion

To the best of our knowledge, this is the first study to provide empirical evidence on the effects of losing an only child on the psychological characteristics and the connectivity of functional brain networks. Our study also evaluated the links between only child loss and neural network communications within an older adult sample with a high risk for developing psychiatric disorders. Psychologically, the loss group exhibited more depressive symptoms and an improper coping style compared to the controls. Neurally, our study demonstrated decreased distant and local DC, a network index in RS-fMR, in the precuneus and the left IPL, which are core hubs in the DMN. The loss group also showed decreased distant DC in the bilateral DLPFC, which are major hubs in the central executive network (CEN). Importantly, a higher negative coping score was correlated with decreased distant and local DC of multiple regions as well as the decreased DLPFC-precuneus connectivity strength. These findings suggested that the significant negative stressful life event had impaired the functional connectivity of the neural network hubs in the default-mode and executive control systems even when individuals were not experienced psychiatric disorders during the scanning period and that the abnormalities in the neural network were associated with an ineffective coping style.

In the present study, parents who lost their only child did not tend to respond positively (i.e., seeking help) and tended to respond negatively (i.e., avoidance and substance use) to stressful events. The current findings are similar to previous studies on coping style in stress-related psychiatric disorders such as MDD (Bruder-

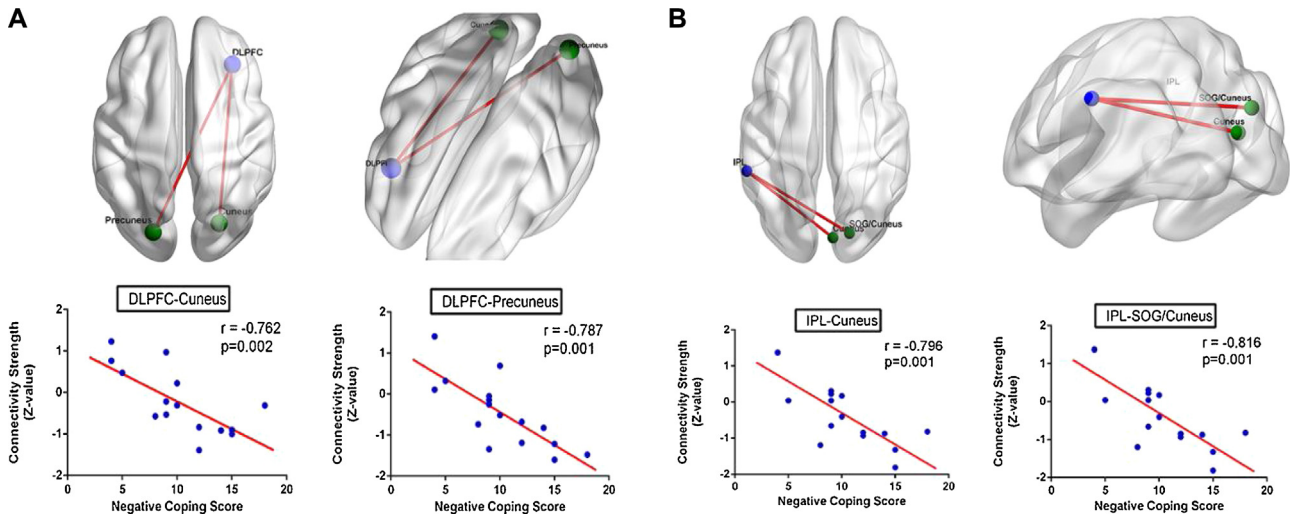

Fig. 5. Reduced seed-based functional connectivity and its correlation with negative coping.

Mattson & Hovanitz, 1990; Gan, Zhang, Wang, Wang, & Shen, 2006; Rohde, Lewinsohn, Tilson, & Seeley, 1990) and PTSD (Amir et al., 1997; Bryant & Harvey, 1995). Therefore, the improper coping style can be regarded as a psychological factor that may increase the risks for mental disorders after several life events (losing one's only child in this study).

The degree centrality (DC) in this study represents the overall connectivity between particular brain regions to other brain areas and which is relatively high in the hubs of the brain network (Buckner et al., 2009; van den Heuvel & Sporns, 2013; Zuo et al., 2012). In this study, we compared the DC between the two groups and found decreased DC of the brain hubs in the loss group. Reduced DC of the brain hubs indicated that fewer areas showed correlated activity during the resting state conditions and that the role of those hubs in facilitating neural network communication is impaired (Beucke et al., 2013). Yet, without the separate computation of distant and local DC separately, we cannot observe the potentially different effects of only child loss on the connectivity within the immediate regional neighborhood ($\leq$12 mm) and the connectivity over relatively long distances ($\geq$12 mm) (Beucke et al., 2013; Sepulcre et al., 2010).

The findings of a lower degree of both distant and local connectivity of the precuneus and the IPL in the DMN, are consistent with our knowledge of the importance of these hubs and DMN in psychiatric disorders. The precuneus was found to exhibit abnormal activity and connectivity patterns in both MDD (Bluhm et al., 2009a; Zhu et al., 2012) and PTSD (Geuze et al., 2007; Yan et al., 2013). The association between the precuneus and perceived social support, a key psychological factor in stress response after trauma, was detected in structural (Che et al., 2014a) and functional MRI (Che et al., 2014b) studies. Therefore, decreased connectivity in the precuneus may result from the sudden loss of social support, which is one of the mechanisms that link the death of a loved one to depression (Stice, Ragan, & Randall, 2004). As for the IPL, this region showed abnormal nodal centralities in depression (Zhang et al., 2011) and had smaller GMV after stress exposure (Hanson et al., 2010). Importantly, the local DC of the precuneus and both the local and distant DC of the IPL were associated with the negative coping score, suggesting a strong link between network changes and behavior changes. Negative coping (refuse seeking help, engage in self-focused emotion, and cigarette and alcohol use when facing stress) psychologically overlaps with the self-related processing (i.e., self-referential and rumination), which is the function of the DMN (Sheline et al., 2009; Zhu et al., 2012). In addition, in our study, the reduced connectivity between the IPL and SOG/cuneus was correlated with negative coping. Beyond the function of visual attention, the cuneus is also a center of inhibitory control (Cui et al., 2014; Haldane, Cunningham, Androutsos, & Frangou, 2008). Therefore, the abnormal negative coping could be related to the inhibitory control of the human brain.

The current data also showed reduced distant connectivity in the bilateral DLPFC, critical regions in the CEN (Seeley et al., 2007), indicating reduced long-term connectivity ($\geq$12 mm) via this region. Although the DLPFC was not usually identified as a functional hub in previous studies, it plays a critical role in executive function (Alvarez & Emory, 2006), the top–down control of emotional regulation (Frank et al., 2014) and the suppression of unwanted memories (Anderson et al., 2004). The importance of this region in MDD, PTSD and early life stress (ELS) was proven by structural MRI (Bora et al., 2012; De Bellis et al., 2002; Hanson et al., 2010), functional MRI (Rive et al., 2013; Zhong et al., 2014) and brain stimulation studies (Holtzheimer et al., 2000). Seed-based FC also revealed that the reduced connectivity of the DLPFC with precuneus and cuneus was negatively correlated with negative coping, suggesting week interaction between these regions associated with poor coping style. By analyzing the local and distant DC separately, we found that the DLPFC is the only region that showed decreased distant DC but not significant abnormalities in the local DC, which suggested that the most prominent disruptions of this area appear in the long-range functional connectivity. Moreover, local connectivity the DLPFC might remain intact in the current condition, while, in the precuneus and IPL, there were reductions of the both distant and local DC. The vulnerability of the distant DC may result from the greater demand for energy and metabolic supply to establish long-range connections when compared to short-range connections (Liang et al., 2013). Interestingly, we also found that a correlation between reduced DLPFC-precuneus connectivity strength and negative coping in our study. This finding is similar to the findings of stronger negative DLPFC-precuneus connectivity in individuals with ELS (Philip et al., 2014), which suggests that the interaction of the DLPFC and the precuneus is susceptible to stressful life events.

Notably, although our results indicate a strong link between a severe stressful life event with alterations in the network hubs within the DMN and the CEN as well as poor coping style, we cannot prove a causal relationship from this study. A possible causal model may be that only child loss impaired the connectivity of the network hubs, which is associated with negative coping. These psychological and neural changes serve as the risk factors for future

mental disorders. However, we cannot rule out the possibility that the abnormal DC and coping style already existed in the loss group before the experience of only child loss. Only longitudinal studies that examine the changes in behaviors and neuroimaging measures in individuals before and after the severe loss would confirm the causal relationship. In addition, this study is exploratory in nature because of the limited sample size and the number of similar studies. However, our results were largely consistent with the findings from the studies on other stressors (and stress in general) in the literature (Bluhm et al., 2009b; Hanson et al., 2010; Philip et al., 2014) and provided a reliable and valid stress model on behavior/brain effects. We believe this preliminary study of the relationship between this unique life event and the subsequent brain changes may more attention from researchers in the neuroimaging field to further investigate the effects of this life event. Furthermore, there is some debate in the field of resting-state MRI regarding the control of nuisance signals (mainly the head motion). In addition, different preprocessing procedures and computational approaches (threshold of the edge in this study) can affect the results. In this study, we used the most recent rigorous methods to remove the artifacts from head motion and reanalyzed the data considering the potential confounds. Our results are largely consistent and replicable among the potential confounds control analyzes. Finally, we lacked sufficient psychological assessments of the parents who lost their only child. For example, we can not explore the relationship between several psychological measurements including levels of bonding between the parents and their children, the gender and educational level of the child who passed away and the existence of other social support systems and clinical symptoms and brain measurements. By increasing the sample size, we aim to investigate those questions in our subsequent studies.

5. Conclusion

In conclusion, as the first study using neuroimaging to investigate the effects of only child loss on neural networks, we found disrupted connectivity in the hubs within the DMN and CEN networks. These changes were associated with coping style, which may contribute to the onset of mental illness. Theoretically, these findings support the hypothesis that decreased functional connectivity of the brain hubs may exist in individuals at a high risk for psychiatric disorders and is associated with coping style. The results of this study can guide psychological interventions targeting to coping style and neurological interventions targeting to the hub regions within the DMN and CEN in older adults who lost their only child and other individuals who are vulnerable to mental disorders.

Conflict of interest

The authors report no biomedical financial interests or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.biopsycho.2015.09.005.

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