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ORIGINAL PAPER

Neurogenetic Mechanisms of Self-Compassionate Mindfulness: the Role of Oxytocin-Receptor Genes

Yuyin Wang[1] · Linlin Fan[1] · Yiyi Zhu[1] · Junkai Yang[1] · Cong Wang[1] · Li Gu[1] · Shengqi Zhong[1] · Yingyu Huang[1] · Xiaolin Xie[1] · Hui Zhou[1] · Siyang Luo[1] · Xiang Wu[1]

Abstract

Objectives Self-compassionate mindfulness is an important component of self-compassion and has been viewed as an essential factor contributing to well-being. With current advances in social neuroscience highlighting the neurogenetic basis of human behaviors, the present study aimed to investigate the neurogenetic foundation of self-compassionate mindfulness. Of particular interest is OXTR rs53576, which is responsible for affiliation and has been suggested as the potential genetic mechanism underlying self-compassionate mindfulness.

Methods We performed a resting-state fMRI and used a graph theory-based analysis in a sample of genotyped healthy college students. The Self-Compassion Scale-Short Form (SCS-SF) was used to assess the trait of self-compassion.

Results G allele carriers of OXTR rs53576 displayed higher self-compassionate mindfulness than did A/A carriers ($p = 0.034$, $\eta_p^2 = 0.086$). Moreover, the graphic metric of the degree in regions in the empathy network (i.e., the right angular gyrus, medial prefrontal cortex, and anterior cingulate cortex) mediated the association between OXTR rs53576 and self-compassionate mindfulness (95% CI [0.1716, 1.2929]). The graphic metric of the local efficiency in regions of the executive control network (i.e., the right dorsal lateral prefrontal cortex and inferior parietal cortex) also mediated the relationship between OXTR rs53576 and self-compassionate mindfulness (95% CI [0.1792, 1.2866]).

Conclusions These findings advance our understanding of how self-compassionate mindfulness affects mental health improvements, which is conducive to preventions and interventions aiming to enhance well-being.

Keywords Self-compassion · Mindfulness · OXTR rs53576 · Network topological property

Self-compassion is regarded as a healthy attitude about oneself in the face of adversity, including being open to one's own experience, expressing love and mercy to one's own suffering, and recognizing difficulties as a part of every human being (Neff 2003a, b) Over the past decade, numerous studies have demonstrated robust associations of self-compassion with reduced psychopathology (MacBeth and Gumley 2012) and well-being (Zessin et al. 2015), and have shown significant improvements in mental health following self-compassion-based intervention (Albertson et al. 2015; Neff and Germer 2013). These findings have enhanced our understanding of how to foster mental health.

Self-compassion encompasses six components that represent opposing attitudes in three aspects: self-kindness vs. self-judgment, which indicates being caring and accepting one's failure or mistakes instead of blaming and judging; common humanity vs. isolation, which refers to feeling connected with all human beings rather than feeling isolated, since everyone experiences suffering at some point; mindfulness vs. over-identification, which entails staying open and objective to suffering instead of exaggerating or avoiding it (Neff 2003a, b). In particular, the mindfulness component of self-compassion (self-compassionate mindfulness) has been suggested as an essential element for cultivating compassionate self-attitudes (Davis-Siegel et al. 2015; Neff and Dahm 2015), and higher

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✉ Siyang Luo
Luosy6@mail.sysu.edu.cn

[1] Department of Psychology, Guangdong Provincial Key Laboratory of Social Cognitive Neuroscience and Mental Health, and Guangdong Provincial Key Laboratory of Brain Function and Disease, Sun Yat-sen University, Guangzhou 510006, China

levels of self-compassionate mindfulness have been associated with lower levels of depression and stress and higher levels of life satisfaction (Hall et al. 2013; Neff et al. 2008). Whereas mindfulness reflects a general condition of being objective (Bishop et al. 2004; Kabat-Zinn 1990), self-compassionate mindfulness focuses more on assessing the instance of suffering (Germer 2009; Neff and Germer 2013). Such differences between the self-compassionate mindfulness and general mindfulness have been indicated by their differing correlations with other components of self-compassion (Van Dam et al. 2011).

While self-compassion and general mindfulness have been extensively studied (Albertson et al. 2015; Hall et al. 2013; MacBeth and Gumley 2012; Neff and Germer 2013; Neff et al. 2008; Zessin et al. 2015), little research has been conducted on the mechanisms, especially the biological substrates of self-compassionate mindfulness. Current advances in social neuroscience have emphasized the importance of understanding social behaviors from a neurogenetic perspective, with a growing number of studies identifying genetic and neural mechanisms that contribute to complex human behaviors (Biswal et al. 2010; Cole et al. 2010; Tost et al. 2010). According to the culture-brain-behavior (CBB) loop model, psychological traits can be mapped onto corresponding brain activity patterns, suggesting that behavior and the brain interact with each other. Moreover, genes are proposed to lay the foundation for such an interaction (Han and Ma 2015). For example, genetic variation in the oxytocin-receptor gene (OXTR) rs53576 explained individual differences in social functioning, and this relationship was linked to brain alterations in the hypothalamus and amygdala (Tost et al. 2010).

As a genetic mechanism of self-compassionate mindfulness, the oxytocinergic system is of particular interest: it is responsible for various affiliative behaviors, including trust (Kosfeld et al. 2005), empathy (Hurlemann et al. 2010), and secure attachment styles (Tops et al. 2007). A recent study reported a negative correlation between plasma oxytocin level and fear of compassion (also a trend for fear of self-compassion) in individuals with borderline personality disorder (Ebert et al. 2018). This system is also particularly beneficial for helping individuals cope with stress to maintain a relatively calm and objective state (Ditzen et al. 2009; Heinrichs et al. 2003; Rodrigues et al. 2009). Therefore, these findings suggest a soothing and comforting role of the oxytocinergic system in the face of suffering, which is similar to a self-compassionate attitude.

One of the most frequently investigated genes associated with oxytocin is OXTR (responsible for encoding the oxytocin receptor). Previous research has indicated that GG carriers of OXTR rs53576 are more resilient than AG/AA carriers, because they are more likely to seek emotional support (Kim et al. 2010), display lower reactivity to stress (Rodrigues et al. 2009), and have a lower cortisol level after stressful events (Chen et al. 2011). Based on these findings, it is likely that individuals with the G allele of OXTR rs53576 would display higher self-compassionate mindfulness than A/A carriers.

The oxytocinergic system is closely associated with brain regions involved in empathy, especially theory of mind (ToM), since numerous studies have demonstrated that oxytocin facilitated the ability to infer the mental states of others (Domes et al. 2007; Wu and Su 2015). These regions include the temporal-parietal junction (TPJ), medial prefrontal cortex (MPFC), precuneus, anterior insula, and rostral anterior cingulate cortex (ACC) (Engen and Singer 2013; Fan et al. 2011; Singer et al. 2004). Previous research showed that plasma oxytocin was correlated with TPJ activation when performing a social cognition task (Lancaster et al. 2015) and that intranasal oxytocin could decrease TPJ activation when encountering negative social evaluation (Gozzi et al. 2017). Intranasal oxytocin also attenuated social deficits by increasing brain activity in the MPFC in individuals with autism (Watanabe et al. 2014) and reduced the heightened activity in the MPFC and ACC when viewing negative emotional cues in people suffering from anxiety disorders (Labuschagne et al. 2012).

Furthermore, the definition of self-compassionate mindfulness (an objective awareness of our suffering that helps cultivate a sense of compassion toward ourselves) indicates the involvement of the empathy network. Such a notion has gained some support from empirical research. For example, a mindfulness-based stress reduction (MBSR) intervention increased participants' gray matter density in the TPJ (Hölzel et al. 2011).

Taken together, these findings imply that regions related to empathy may mediate the relationship between the oxytocinergic system and self-compassionate mindfulness. However, this mediation path has not been tested based on empirical data. Recently, it was suggested that brain networks could be viewed as "intermediate phenotypes" between genetics and behavior (Bassett and Sporns 2017; Fornito and Bullmore 2012).

To explore the intermediate phenotypes (i.e., the empathy network) between the oxytocinergic system and self-compassionate mindfulness, a resting-state fMRI (R-fMRI) is an effective tool for delineating the fundamental organization of the brain without being constrained by certain tasks (Biswal et al. 2010; Cole et al. 2010). Using the temporal dependence of neural activity patterns among regions, R-fMRI enables us to unfold the general communication pattern (e.g., information integration) in the brain and investigate how such a pattern contributes to human behaviors (Bullmore and Sporns 2009). This advantage has given rise to a plethora of research exploring the network architecture underlying human behaviors over the past decade (Biswal et al. 2010; Cole et al. 2010; Wang et al. 2014).

Closely related to R-fMRI is graph theory analysis, which provides a novel and valid approach to the quantification of the interactions among elements within the human brain system rather than focusing on certain local regions (Bullmore and Sporns 2009). In graph theory, nodes refer to brain regions and edges refer to the relationship (i.e., connectivity) between nodes. Previous studies have demonstrated the small-world principle in functional brain networks (van den Heuvel and Hulshoff Pol 2010) and noted the application of graph theory metrics as biomarkers for understanding both clinical diseases and normal human functions (Bullmore and Sporns 2009; van den Heuvel and Hulshoff Pol 2010).

Accordingly, based on R-fMRI data and graph theory analysis, the present study aimed to investigate the neurogenetic basis of self-compassionate mindfulness by testing whether OXTR rs53576 impacts self-compassionate mindfulness via brain networks. The following questions were specifically addressed: (1) Are individual differences in self-compassionate mindfulness related to individual differences in OXTR rs53576? (2) Is the relationship between OXTR rs53576 and self-compassionate mindfulness mediated by brain network properties? The corresponding prediction is that individuals with the G allele of OXTR rs53576 would show a higher level of self-compassionate mindfulness than their counterparts would, and such a relationship would be mediated by brain topological properties.

Method

Participants

Fifty-three healthy Chinese students (14 males, 39 females; age range 19–26, mean age 21.8 years) were recruited as paid volunteers. Three participants did not complete the questionnaires and were excluded from further analyses. All the participants were free of neurological or psychiatric disorders. All experimental procedures conformed to the Declaration of Helsinki and were approved by the local Research Ethics Committee of the Department of Psychology, Sun Yat-sen University. The participants provided written informed consent after the experimental procedures had been fully explained and were reminded of their right to withdraw at any time during the study. A proper sample size for the present study was estimated with G*Power software (Faul et al. 2007) prior to data collection. To detect a similar effect size with previous study about OXTR effect on social emotional sensitivity (Luo et al. 2015a, Cohen's $d = 0.81$, alpha = 0.05, power = 0.80), a sample of 52 participants was required to detect the effects using correlation analysis.

Procedure

OXTR rs53576 and rs1042778 were extracted from the subject's blood sample and genotyped by the Shanghai Generay Biotech Co., Ltd. (http://www.generay.com.cn/) using allele-specific ligase detection reactions. A 198-bp DNA containing the polymorphic site was amplified by PCR thermal cycler (Black KingKong EDC-810 Gene Amplifier, Eastwin, Beijing, China) using the forward primer 5′-GCCCACCATGCTCTCCACATC-3′ and 5′-TGGGTTCAGGGTGGTAGAAG-3′, and the reverse primer 5′-GCTGGACTCAGGAGGAATAGGGAC-3′ and 5′-AGGCTGTGCTGGCATAAGTG-3′ (Bakermans-Kranenburg and van Ijzendoorn 2008). The PCR was carried out in a total volume of 15 μl containing 1.5 μl 10× PCR buffer, 0.15 μl 10 pmol each primer, 0.3 μl dNTP, 0.3 μl Taq polymerase (MBI fermentas), 1 μl of genomic DNA, 1.5 ul $MgCl_2$, and 10.25 μl H_2O. The PCR cycling parameters were 35 cycles of 15 s at 94 °C, 55 °C for 15 s, and 72 °C for 30 s. Ligase detection reaction (LDR) was performed in a total volume of 10 μl containing 2 μl PCR product, 1 μl 10× Taq DNA ligase buffer, 0.125 μl 40 U/μl Taq DNA ligase (NEB), 1 μl 10 pmol probes (0.33 μl each of probe), and 5.875 μl H_2O. Subsequently, LDR products were analyzed by DNA sequencing (Model 3720XL, Applied Biosystems).

The genotype distributions were similar with those previous samples in the similar region (OXTR rs53576 $n = 20$ A/A, $n = 27$ A/G, $n = 6$ G/G; OXTR rs1042778 $n = 6$ T/G, $n = 47$ G/G) (Luo et al. 2015a, b). We compiled individual multilocus genetic composite (MGC, Stice et al. 2012) profile scores reflecting the number of risk allele across these two OXTR polymorphic loci. The combined effects of these two SNPs on self-compassionate mindfulness were examined.

Measures

The Self-Compassion Scale-Short Form (SCS-SF) is a 12-item scale used to assess the trait of self-compassion (Neff, 2003b; Raes et al. 2011). Responses were given on a seven-point Likert scale (1 = *Almost never*, 7 = *Almost always*). This scale also contains six subscales corresponding to the six factors of self-compassion, including self-kindness, self-judgment, common humanity, isolation, mindfulness, and over-identification. Cronbach's α for the mindfulness subscale was 0.564. Prior studies have validated the psychometric properties of the SCS-SF in multiple populations, including college students (Garcia-Campayo et al. 2014; Raes et al. 2011), and this scale has been extensively adopted in contemporary research (Hu et al., 2018; Neff and Germer 2013; Peters et al. 2017; Smeets et al. 2014). The reliability of the SCS-SF in the current study was sufficient (Cronbach's α = 0.781).Resting-state fMRI images of all the participants were acquired using a 3.0-T Siemens scanner (Siemens Medical

Systems, Erlangen, Germany) with a standard head coil. The participants were instructed to relax and keep their eyes closed but not to fall asleep during scanning. Functional images were acquired using T2-weighted, gradient-echo, echo-planar imaging (EPI) sequence sensitive to blood oxygenation level dependent (BOLD) contrast: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle (FA) = 90°. An axial plane was used with a field of view of 224×224 mm^2 (64×64 voxels). Thirty-two slices of 3.5-mm thickness were acquired. A high-resolution T1-weighted structural image ($256 \times 256 \times 176$ matrix with a spatial resolution of $1 \times 1 \times 1.0$ mm^3, TR = 2300 ms, TE = 3.42 ms, FA = 9°) was acquired.

Data Analyses

Data Preprocessing

The imaging data preprocessing was implemented using Data Processing Assistant for Resting-State fMRI (DPARSF) (Yan and Zang 2010), which is based on Statistical Parametric Mapping 8 (SPM 8, http://www.fil.ion.ucl.ac.uk/spm). The following steps were included: (1) removing the first five volumes, permitting signal equilibrium and the adaptation of the participants to the immediate environment, (2) correction for slice acquisition and head movement with rigid body translation and rotation parameters, (3) normalization into Montreal Neurological Institute (MNI) space using unified segmentation on T1-weighted images and reslicing into 3-mm isotropic voxels, (4) spatial smoothing with 4-mm full-width half-maximum Gaussian kernel, (5) bandpass (0.01–0.1 Hz) filtering to reduce physiological noise, and (6) regression of 24 head motion parameters and three potential nuisance signals, including the cerebrospinal fluid, white matter, and global signal, to further reduce non-neuronal contributions.

Graph Theoretical Analyses

We first used the atlas of Automated Anatomical Labeling (Tzourio-Mazoyer et al. 2002) to segment the images into 90 regions/nodes. The Pearson correlation coefficients between the regional mean time series of all possible pairs of brain regions were calculated, resulting in a 90×90 correlation matrix for each subject. Whether negative RSFCs are biologically meaningful remains unclear; therefore, the diagonal and negative links were set to zero following convention (Power et al. 2011; Power et al. 2013; Rubinov and Sporns 2010). Individual correlation matrices were then converted into binary matrices according to the sparsity thresholds that we selected (*SM Method*). Since we have a total of 18 thresholds, we calculated the AUC of different graph metrics, included degree, global efficiency, local efficiency, clustering coefficient, shortest path, and small-worldness (*SM Method*). To ensure a better understanding of the nodal function among the measure's neighbors or its subgraph, we mainly focused on three measures in the nodal level analysis: degree, clustering coefficient, and local efficiency. To ensure analyses based on a small-world principle, we also calculated the small-worldness σ (*SM Method*) of the whole brain network in each threshold.

Statistical Methods

The graph theoretical network analysis toolkit (GRETNA) (http://www.nitrc.org/projects/gretna/) (Wang et al. 2015) was used to calculate functional connectivity matrices (r-score matrices and z-score matrices) and graphic metrics. The genotype intergroup differences in different metrics were evaluated by one-way ANOVA.

Hierarchical Regression Analysis

We first tested the association between genotype (A/A vs. A/G and G/G) and brain network property (graphic metrics including degree and local efficiency), and the association between brain network property and the self-compassionate mindfulness (SCM) measurement. Potential neural mediators between genotype and SCM were defined by the criterion that the association between genotype and brain network property and the associations between SCM and brain network property were both significant ($p < 0.05$). False discovery rate (FDR) was used to correct for type I error rates during multiple comparisons.

Furthermore, we tried to build a mediation model between genotype and SCM using brain network property as the mediator. Following the procedures from Aiken et al. (1991), we built three regression models for testing the mediation effect. In the first regression model, we used the independent variable (IV, genotype) to predict the mediator (brain network property). In the second model, we used the IV to predict the dependent variable (DV, SCM). Finally, IV and the mediator were entered simultaneously into a regression model to predict the DV. Bootstrap resampling analyses (10,000 iterations were taken) were used to estimate the mediation effect, and this process provided superior confidence intervals (CIs) that were bias-corrected and accelerated.

Results

Oxytocin-Receptor Gene and Self-Compassionate Mindfulness

We first test the relationship between the self-compassionate mindfulness subscale score and the MGC scores. The results revealed a significant negative association between MGC scores and self-compassion mindfulness ($r = -0.30$, $p =$

0.029), and individuals with more risk alleles in OXTR showed lower self-compassionate mindfulness (Table 1).

We then conducted ANOVA for the self-compassion mindfulness subscale score with the OXTR rs53576 genotype (A/A vs. G/G and A/G) and rs1042778 genotype (G/T vs. G/G) as a between-subjects variable. The results revealed a significant OXTR rs53576 genotype effect (F (1,52) = 4.77, $p = 0.034$, $\eta_p^2 = 0.086$) on self-compassion mindfulness. OXTR rs53576 G allele carriers showed higher self-compassionate mindfulness than did A/A homozygotes (Table 1).

Relationships Among the Gene, the Brain, and Self-Compassionate Mindfulness

Before assessing the association between nodal properties and the OXTR genotype and the association between nodal properties and self-compassionate mindfulness, we first examined the global properties to obtain a full picture of the whole brain network architecture. We first calculated the normalized clustering coefficient (i.e., γ, an indicator of the interconnectivity of the network, with higher scores indicating higher interconnectivity), the normalized characteristic path length (i.e., λ, an indicator of the communication efficiency of the network, with higher scores indicating low communication efficiency), and the small-worldness parameter (i.e., $\sigma = \gamma/\lambda$, with $\sigma > 1$ indicating that the network has a small-world characteristic) for each threshold to confirm that the graph metrics were calculated based on the principle of small-worldness. We discovered that the minimum σ was greater than 1 for each sparsity threshold.

Then, we conducted ANOVAs for the AUC of global network metrics with the OXTR rs53576 genotype (A/A vs. G/G and A/G) as a between-subjects variable. The results revealed a significant genotype effect on γ (F (1,52) = 9.18, $p = 0.004$, $\eta_p^2 = 0.153$), λ (F (1,52) = 6.91, $p = 0.011$, $\eta_p^2 = 0.119$), and σ (F (1,52) = 4.78, $p = 0.033$, $\eta_p^2 = 0.086$, Fig. S1). A/A carriers showed lower γ and higher λ and σ values than did G allele carriers.

In addition, the rs53576 genotype effect on the networks' clustering coefficient, shortest path, global efficiency, local efficiency, and betweenness values was also significant (C_p F (1,52) = 8.41, $p = 0.006$, $\eta_p^2 = 0.141$; L_p F (1,52) = 5.66, $p = 0.021$, $\eta_p^2 = 0.100$; E_{global} F (1,52) = 6.13, $p = 0.017$, $\eta_p^2 = 0.107$; E_{local} F (1,52) = 10.44, $p = 0.002$, $\eta_p^2 = 0.170$; Bet F (1,52) = 6.25, $p = 0.016$, $\eta_p^2 = 0.109$). The AUCs of the clustering coefficient, shortest path, local efficiency, and betweenness were significantly lower among G allele carriers than they were among subjects in the A/A group, while A/A carriers showed lower global efficiency than did G allele carriers (Figure S2). The global network properties that showed a significant genotype effect were not correlated to self-compassionate mindfulness (r (53) = − 0.11~0.08, $p > 0.4$ for all analyses).

We then examined whether there were potential nodal metrics that showed significant associations with both the OXTR genotype and self-compassionate mindfulness. The results illustrated that the AUC values of the degree in the right MPFC (OXTR r (53) = − 0.29, $p = 0.036$; SCM r (53) = − 0.35, $p = 0.011$, Fig. 1), right anterior cingulate cortex (ACC) (OXTR r (53) = − 0.35, $p = 0.009$; SCM r (53) = − 0.36, $p = 0.009$), and right angular gyrus (OXTR r (53) = − 0.29, $p = 0.036$; SCM r (53) = − 0.41, $p = 0.002$) were significantly different among OXTR genotypes and were significantly correlated with self-compassionate mindfulness. A similar analysis for the AUC of nodal local metrics (local efficiency and clustering coefficient) revealed a significant genotype effect and significant correlation with self-compassionate mindfulness in the right dorsal lateral prefrontal cortex (C_p OXTR r (53) = − 0.51, $p < 0.001$; SCM r (53) = − 0.32, $p = 0.022$; E_{local} OXTR r (53) = − 0.44, $p = 0.001$; SCM r (53) = − 0.30, $p = 0.029$) and right inferior parietal cortex (C_p OXTR: r (53) = − 0.48, $p < 0.001$; SCM r (53) = − 0.45, $p = 0.001$; E_{local} OXTR r (53) = − 0.50, $p < 0.001$; SCM r (53) = − 0.39, $p = 0.004$).

We then built a mediation model using OXTR genotype as the independent variable, using the degree in the right MPFC, right ACC, and right angular gyrus (the mean values of the normalized degree of these regions) as the mediator, and using self-compassionate mindfulness as the DV (Figure S3A). A bootstrap analysis illustrated that A/A carriers were more likely to have a higher degree in these three regions ($B = - 0.63$, t (52) = − 3.29, $p = 0.002$) and lower scores on self-compassionate mindfulness ($B = 0.91$, t (52) = 2.18, $p = 0.034$) than were G allele carriers. In the further regression model, the degree in these three regions negatively predicted individuals' self-compassionate mindfulness scores ($B = - 1.03$, t (52) = − 4.11, $p < 0.001$). When genotype and the degree in the three regions were both used to predict self-compassionate mindfulness, the degree of the three regions still significantly predicted self-compassionate mindfulness ($B = - 0.94$, t (52) = − 3.40, $p = 0.001$), but the genotype alone did not yield a prediction of self-compassionate mindfulness ($B = 0.32$, t (52) = 0.76, $p = 0.453$). A bootstrap resampling analysis (10,000

Table 1 The OXTR effect on self-compassionate mindfulness

SCM scores	OXTR			r	p
	MGC scores			− 0.30*	0.03
SCM scores	OXTR rs53576				
	A/A	A/G and G/G	F	p	η_p^2
	10.15 ± 1.79	11.06 ± 1.25	4.77*	0.03	0.086
SCM scores	OXTR rs1042778				
	G/T	G/G	F	p	η_p^2
	10.50 ± 1.38	10.74 ± 1.55	0.14	0.72	0.003

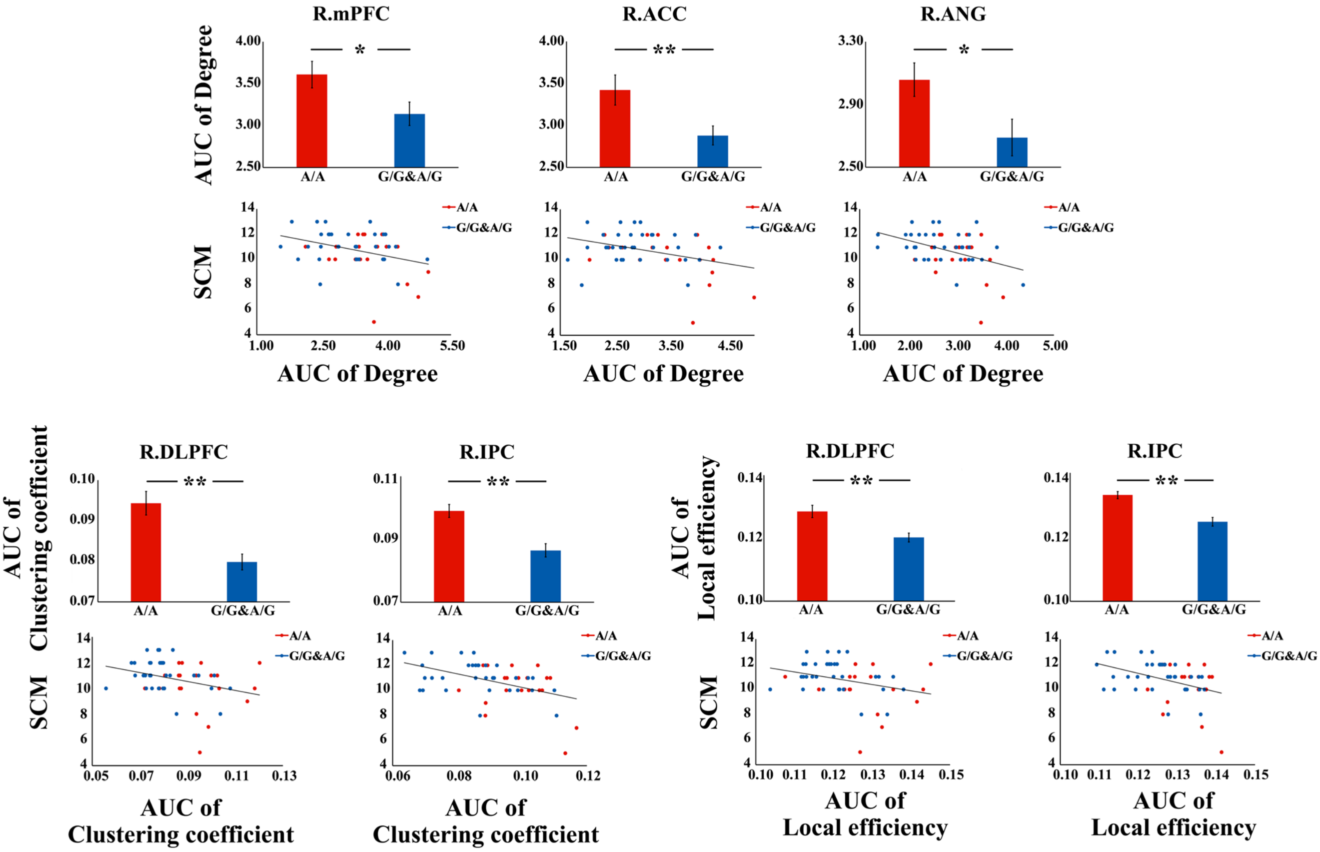

Fig. 1 The association of nodal metrics with OXTR rs53576 and SCM. The AUC values of the degree of right MPFC, right ACC, and right angular gyrus were significantly different between the two genotype groups and were negatively correlated with SCM. Moreover, the AUC values of the clustering coefficient and local efficiency of right DLPFC and right IPC exhibited significant genotype effects and showed negative correlations with SCM. SCM, self-compassionate mindfulness; R.MPFC, right MPFC; R.ACC, right anterior cingulate gyrus; R.ANG, right angular gyrus; R.DLPFC, right dorsal lateral prefrontal cortex; R.IPC, right inferior parietal gyrus

iterations) of the effect size indicated that this mediation effect was different from zero (95% CI [0.1716, 1.2929]).

A similar mediation analysis was conducted using the local property in the right dorsal lateral prefrontal cortex and right inferior parietal cortex (the mean values of normalized local efficiency and clustering coefficient) as the mediator and self-compassionate mindfulness as the DV (Figure S3B). The first regression model illustrated that A/A carriers were more likely to have a higher local efficiency of these two regions ($B = -0.99$, $t\ (52) = -4.70$, $p < 0.001$) than were G allele carriers. In the second regression model, the local efficiency of these four regions negatively predicted individuals' self-compassionate mindfulness ($B = -0.71$, $t\ (52) = -3.23$, $p = 0.002$). When genotype and the local property of two regions were used simultaneously to predict self-compassionate mindfulness, the local property of two regions significantly predicted self-compassionate mindfulness ($B = -0.62$, $t\ (52) = -2.34$, $p = 0.023$). A bootstrap analysis (10,000 iterations) of the effect size indicated that this mediation effect was different from zero (95% CI [0.1792, 1.2866]).

Finally, we conducted mediation analysis using degree and local property as mediators (Fig. 2). When genotype, degree, and local property were used simultaneously to predict self-compassionate mindfulness, the degree in the three regions significantly predicted self-compassionate mindfulness ($B = -0.82$, $t\ (52) = -2.93$, $p = 0.005$), and the local efficiency effect on self-compassionate mindfulness was marginally significant (local efficiency $B = -0.43$, $t\ (52) = -1.69$, $p = 0.097$). A bootstrap analysis (10,000 iterations) of the effect size indicated that the total mediation effect of degree and local efficiency was different from zero (95% CI total [0.3623, 1.7960]; degree [0.1304, 1.1279]; local efficiency [0.0249, 1.0448]).

Discussion

The present study used resting-state fMRI and graph theory-based analysis to examine the impact of OXTR rs53576 on self-compassionate mindfulness and the underlying mediating role of brain architecture. In sum, we found that compared with A/A homozygotes, G allele carriers of OXTR rs53576 showed more self-compassionate mindfulness, lower degree in the empathy network (i.e.,

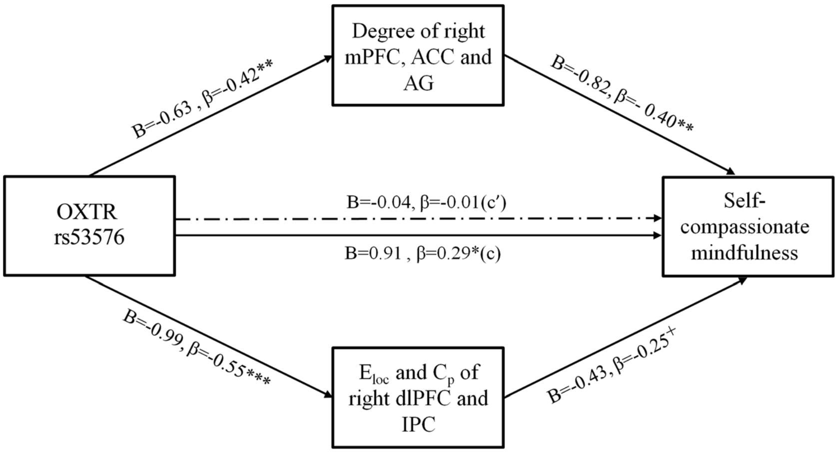

Fig. 2 Mediation analysis results (c). The total mediation effect of degree and local efficiency was different from zero (95% CI total [0.3623, 1.7960]; degree [0.1304, 1.1279]; local efficiency [0.0249, 1.0448]). $^{+}p < 0.10$; $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

right angular gyrus, MPFC, and ACC), and lower local efficiency in the executive control network (i.e., right dorsal lateral prefrontal cortex (DLPFC) and inferior parietal gyrus (IPC)). These brain network properties were negatively associated with self-compassionate mindfulness and further mediated the relationship between OXTR rs53576 and self-compassionate mindfulness.

Our findings provide initial empirical support linking self-compassionate mindfulness to the oxytocinergic system. According to the emotion regulation system (Gilbert and Irons 2005; Gilbert 2009), self-compassion is thought to originate from the self-soothing system, which is responsible for attachment, affiliation, and feelings such as peace, calm, and safety and is also closely related to certain hormones in the brain such as oxytocin. Animal studies also highlight the role oxytocin plays in the self-soothing system (Panksepp 2011). By deactivating the threat system (which is pertinent to stress reactions, feelings such as anxiety and anger, and hormones such as cortisol) and activating the soothing system, self-compassion manages to mitigate stress reactivity when encountering negative life events, as revealed in emerging empirical research (Leary et al. 2007; Sbarra et al. 2012). As a core component of self-compassion, self-compassionate mindfulness serves the function of sensing our internal states in a curious, balanced, and accepting manner when facing adversities.

In the current study, self-compassionate mindfulness was associated with the oxytocinergic system, suggesting that the self-soothing effect of self-compassion could be largely attributed to self-compassionate mindfulness. Indeed, Neff and Dahm (2015) have argued that only after acknowledging our painful internal experiences could individuals engender a sense of kindness and connectedness. Moreover, some researchers believe that the ultimate outcome of mindfulness is compassion toward oneself and others (Davis-Siegel et al. 2015). In line with previous results showing the association between self-soothing behaviors and oxytocin (Uvnäs-Moberg et al. 2015), the lower stress levels of GG carriers of OXTR rs53576 (Rodrigues et al. 2009) and the modification of gene expression processes by MBIs (Buric et al. 2017), our findings add direct evidence to the notion that the oxytocinergic system is the underlying neurogenetic basis of self-compassionate mindfulness.

Moreover, the oxytocinergic system demonstrated a close relationship with brain nodal metrics within the empathy network, suggesting that this may be one of the pathways through which OXTR rs53576 takes effect. This observation is consistent with a previous report showing that children with the GG genotype of OXTR rs53576 performed better on ToM tasks than did children with other genotypes (Wu and Su 2015). Moreover, our results are in line with those of numerous studies that found an association between the oxytocinergic system and brain regions related to empathy (Luo et al. 2015a, b; Luo et al. 2018). For instance, the TPJ has been widely validated for its role in social cognition (e.g., mentalizing and self-other distinction) (Van Overwalle 2009) and has been related to both plasma and intranasal oxytocin (Gozzi et al. 2017; Lancaster et al. 2015). Similarly, plasma oxytocin can also predict the activity of the MPFC, which is another critical region for social cognition (Lancaster et al. 2015).

Intriguingly, OXTR rs53576 was also associated with the executive control network in the present results, which is in agreement with a previous finding that plasma oxytocin enhanced DLPFC activation during social cognitive tasks (Lancaster et al. 2015). Given that research on the oxytocinergic system primarily focused on its function in emotional processing, our results suggest that this neural chemical may also exert influence on brain regions related to executive control. Future studies should explore how oxytocin works in this network.

We also found an association between self-compassionate mindfulness and the empathy network. Notably, the empathy network found here includes the TPJ, MPFC, and ACC, which are structures pertinent to the ability to understand the mental states of others (Decety and Lamm, 2007; Fan et al. 2011). In fact, Davis-Siegel et al. (2015) stated that it is the ability to detect and relate to one's own thoughts and feelings (a similar process to empathy) that gives rise to compassion. There are also some commonalities between receiving and offering compassion and experiencing self-compassion (Longe et al. 2010; Neff and Pommier 2013). The relationship between self-compassionate mindfulness and the empathy network in our findings is in line with previous studies reporting altered brain properties in the TPJ following practices of cultivating self-compassionate mindfulness (Farb et al. 2007; Hölzel et al. 2011; Leung et al. 2013) and heightened activation in the pregenual ACC after compassion training (Klimecki et al. 2014). More importantly, these areas are also implicated in the mental process of the self and others (Ochsner et al. 2008; Van Overwalle 2009) and social connection (Hutcherson et al. 2015). This finding further suggests that being mindful and caring toward oneself is probably related to a broad view of the self and the others. This notion is consistent with the assumption that individuals with increased self-compassionate mindfulness will be more likely to view others as parts or extensions of the self rather than as separate beings (Davis-Siegel et al. 2015; Neff and Dahm 2015).

The current findings also imply a role of top-down executive control in self-compassionate mindfulness. Our results are consistent with previous research that found stronger activity in the IPC in long-term meditators participating in loving-kindness meditation (LKM) than that found in novices (Brewer et al. 2011), altered activity in the IPC and DLPFC, and changed connectivity between the DLPFC and other regions in the executive control network after compassion- and mindfulness-based trainings (Barnby et al. 2015; Taren et al. 2017; Weng et al. 2013). In fact, these findings could possibly be credited to the mindfulness element in self-compassionate mindfulness, since the detached observation and improved regulation of emotions cultivated by mindfulness practice has been linked to alterations in the executive network (Hölzel et al. 2011; Hinton et al. 2013; Teper et al. 2013). By separating the mental states (e.g., sensations, thoughts, feelings) from ourselves and observing the mental states, which is the intention of mindfulness, we create the "self-as-observer," which allows a space for disentangling complex emotional states and contributes to the mindful acceptance of the mental states (Hayes et al. 2006). Therefore, the final outcome of being mindful in the face of suffering will probably be successful emotion regulation. Indeed, the DLPFC and IPC are involved in emotional processing (Gallese et al. 2004; Longe et al. 2010). Based on these findings, our results further indicate that the executive control network may mirror the mindful process of self-compassionate mindfulness.

Both the degree and local efficiency were negatively associated with self-compassionate mindfulness in the present study. In graph theory, the degree is a measure of the connections of a given node, reflecting the importance of this node; the local efficiency and clustering coefficient measure the clustered connectivity centered at a given node, reflecting network segregation (Rubinov and Sporns 2010). Therefore, in contrast with emphasis of regional activation in task-fMRI, the graphic properties we used in this R-fMRI study can better capture the association between nodes in a general state. More importantly, the reduced degree of the empathy network and the local efficiency of the executive control network may imply the relatively isolated roles of these regions in individuals with a high level of self-compassionate mindfulness. This finding is compatible with that of a previous study reporting negative correlations between the degree, clustering coefficient, and local efficiency of the thalamus and trait mindfulness (Wang et al. 2014). Notably, connectivity is not equivalent to activity or function. As maintaining a relatively high degree often means higher wiring costs (Rubinov and Sporns 2010), individuals with high self-compassionate mindfulness may manage to minimize the energetic costs while maintaining the same or even superior function.

Limitations and Future Research Directions

Several limitations of this work should be considered. The first limitation lies in the weak correlation between self-compassionate mindfulness and OXTR rs53576. This limitation may be due to the relatively small sample size, which could also conceal potential associations between OXTR rs53576 and other dimensions of self-compassion. Future research is recommended to extend our results in a larger population. It deserves to be emphasized that the weak correlation between self-compassionate mindfulness and OXTR rs53576 did not interfere with the mediation analysis, which is suggested as a new method for testing the mediation effect (Zhao et al. 2010) and is the focus of the present study. Second, we measured OXTR rs53576 in the current study and the mediation mechanism may be found for other genes of the oxytocinergic system (e.g., CD38 rs3796863). Finally, while this work provides primitive support to the neurogenetic basis of self-compassionate mindfulness, further investigations are encouraged to examine the effects of intranasal oxytocin and the interaction between social environment and genotypes on self-compassionate mindfulness.

The present study provides initial empirical evidence supporting the notion that the oxytocinergic system is the neurogenetic foundation of self-compassionate mindfulness and that the brain architecture of the empathy network and executive control network serves as the intermediate phenotype. Our findings advance the understanding of how self-compassionate mindfulness exerts its effect on improving mental health, which could inspire preventions and interventions to enhance well-being.

Author Contributions WYY, LSY, and WX designed the research; YJK collected and analyzed the gene data; ZSQ, GL, YJK, and HYY collected the MRI data; FLL, XXL, and ZH collected the questionnaire data; FLL and ZSQ analyzed the questionnaire data; ZYY, WC, and LSY analyzed the fMRI data; and WYY, FLL, and LSY wrote the manuscript. All authors commented on the manuscript.

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Compliance with Ethical Standards

Ethical Approval All experimental procedures conformed to the Declaration of Helsinki and were approved by the local Research Ethics Committee of the Department of Psychology, Sun Yat-sen University.

Informed Consent The participants provided written informed consent after the experimental procedures had been fully explained and were reminded of their right to withdraw at any time during the study.

Conflict of Interest The authors declare that they have no conflict of interest.

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