

## ORIGINAL ARTICLE

## Neural mediator of the schizotypy–antisocial behavior relationship

BYH Lam<sup>1</sup>, Y Yang<sup>2</sup>, A Raine<sup>3,4,5</sup> and TMC Lee<sup>1,6,7,8</sup>

Prior studies have established that schizotypal personality traits (schizotypy) were associated with antisocial behavior (crime), but it is unclear what neural factors mediate this relationship. This study assessed the mediating effect that sub-regional prefrontal gray, specifically the orbitofrontal gray matter volume, has on the schizotypy–antisocial behavior relationship. Five prefrontal sub-regional (superior, middle, inferior, orbitofrontal and rectal gyral) gray matter volumes were assessed using structural magnetic resonance imaging in 90 adults from the community, together with schizotypy and antisocial behavior. Among all five prefrontal sub-regions, the orbitofrontal cortex (OFC) was the major region-of-interest in the present study. Mediation analyses showed that orbitofrontal gray fully mediated the association between schizotypy and antisocial behavior. After having controlled the sex, age, socio-economic statuses, whole brain volumes and substance abuse/dependence of test subjects, the orbitofrontal gray still significantly mediated the effect of schizotypy on antisocial behavior by 53.5%. These findings are the first that document a neural mediator of the schizotypy–antisocial behavior relationship. Findings also suggest that functions subserved by the OFC, including impulse control and inhibition, emotion processing and decision-making, may contribute to the above comorbidity.

*Translational Psychiatry* (2015) 5, e669; doi:10.1038/tp.2015.162; published online 3 November 2015

## INTRODUCTION

Prior studies have established a linkage between schizophrenia and antisocial behavior.<sup>1</sup> In view of the fact that schizotypal personality traits (schizotypy) share similar genetic and neurobiological basis with schizophrenia,<sup>2</sup> it is crucial to investigate whether people with schizotypy are more prone to exhibiting antisocial behavior. Yet, previous studies that relate schizotypy to antisocial behavior are scarce. Furthermore, if schizotypy is associated with antisocial behavior, what could be the underlying factors of such a relationship? This question has rarely been addressed in research studies pertaining to schizophrenia and even more rarely in those of schizotypy.<sup>3</sup> Previously, it has been found that schizotypy was related to antisocial behavior of college students<sup>4</sup> and that of adolescents.<sup>5</sup> The present study elaborated on prior literature by examining adult schizotypy and taking a broader view of antisocial behavior by examining general crimes committed by people with schizotypy.

Apart from substance abuse that has been found to mediate antisocial behavior in schizophrenia,<sup>6</sup> a more recent study has shown that peer victimization also mediated the schizotypy–antisocial behavior relationship among adolescents.<sup>5</sup> However, neither substance abuse nor peer victimization can fully account for the schizotypy–antisocial behavior relationship. Hence, there may be other underlying factors. To understand this comorbidity better, the present study examined the neural mediator that may be a common correlate of these two conditions.

The orbitofrontal cortex (OFC) is regarded as a potential candidate for the neural substrate of the schizotypy–antisocial

behavior comorbidity. The primary reason is that neuroimaging studies have shown that abnormal gray matter volumes in the prefrontal cortex (PFC), particularly the OFC were related to both schizophrenia<sup>7–9</sup> and antisocial behavior<sup>10–14</sup> in various studies including lesion and longitudinal studies. For instance, Raine *et al.*<sup>9</sup> found that a reduction in PFC gray corresponds to the occurrence of schizotypal personality disorder, when compared with the healthy and psychiatric controls. Similarly, Pantelis *et al.*<sup>8</sup> found that OFC gray was reduced after the onset of psychosis. Furthermore, OFC lesion led to antisocial behavior, whereas increased OFC activity led to low levels of antisocial behavior.<sup>11–14</sup> Along those lines, Raine *et al.*<sup>10</sup> found that OFC gray was negatively associated with antisocial behavior. These findings suggest that the PFC sub-region, particularly the OFC, might have played a crucial role in the relationship between schizophrenia and antisocial behavior. However, prior studies that investigated the relationship between PFC abnormality and antisocial behavior have treated the PFC as one unitary structure, and studies pertaining to the PFC sub-regions are scarce.<sup>10,15</sup> Therefore, the present study attempted to examine structural gray matter abnormality in the PFC sub-regions, including OFC, middle frontal cortex (MFC), superior frontal cortex (SFC), inferior frontal cortex (IFC) and rectal gyri (RG). On the basis of previous findings, the OFC would be the major region-of-interest among these five PFC sub-regions in the present study.

Taking the above findings together, prior findings have suggested that antisocial behavior due to schizophrenia might owe to the impairment in the PFC sub-regions, specifically the OFC.<sup>16</sup> However, previous findings on patients of schizophrenia

<sup>1</sup>Laboratory of Neuropsychology, The University of Hong Kong, Hong Kong, China; <sup>2</sup>Department of Pediatrics, Children's Hospitals Los Angeles, Keck School of Medicine, The University of Southern California, Los Angeles, CA, USA; <sup>3</sup>Department of Criminology, University of Pennsylvania, Philadelphia, PA, USA; <sup>4</sup>Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA; <sup>5</sup>Department of Psychology, University of Pennsylvania, Philadelphia, PA, USA; <sup>6</sup>The State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong, China; <sup>7</sup>Institute of Clinical Neuropsychology, The University of Hong Kong, Hong Kong, China and <sup>8</sup>Laboratory of Cognitive Affective Neuroscience, The University of Hong Kong, Hong Kong, China. Correspondence: Professor Dr TMC Lee, Laboratory of Neuropsychology, The Jockey Club Tower, The University of Hong Kong, Pokfulam Road, Hong Kong, China.

E-mail: tmcleee@hku.hk

Received 28 March 2015; revised 8 August 2015; accepted 12 August 2015

with records of violence are inconsistent. Some studies<sup>17</sup> have revealed a reduction in OFC gray in people with schizophrenia who were violent, while other studies<sup>18</sup> have reported findings that are contradictory. These inconsistencies might have been due to the differences in the definition of violence<sup>3</sup> or the sampled populations used in each study. As of yet, the mediating effect of the PFC sub-regions on the schizotypy-antisocial behavior relationship has remained an unanswered question.

Previous findings have shown that people with schizophrenia and antisocial behavior share some common structural and functional abnormalities in the PFC, specifically the OFC. Hence, in this study, it was hypothesized that the OFC played a significant role in the schizotypy-antisocial behavior relationship. Furthermore, to go beyond prior findings where schizotypy and antisocial behavior were found to be related and reduced prefrontal gray was associated with schizotypal personality disorder;<sup>9</sup> this study examined (1) the relationship between schizotypy and antisocial behavior, particularly in general crimes, and (2) the mediating effect of sub-regional prefrontal gray matter volume on this relationship. We hypothesized that schizotypy would be associated with antisocial behavior positively, and the reduction in prefrontal gray, specifically orbitofrontal gray, would mediate the schizotypy-antisocial behavior relationship.

**MATERIALS AND METHODS**

**Participants**

The study was approved by the institutional review board of the University of Southern California and the Human Research Ethics Committee for Non-Clinical Faculties of the University of Hong Kong. This sample consisted of 90 subjects (78 males (87%) and 12 females (13%)) drawn from 5 temporary employment agencies in Los Angeles. This is because pilot data showed that samples from this community had higher rates of crime perpetration (Raine)<sup>19</sup> compared with other regions. Their mean age was 31.48 years, ranging from 21 to 46 (s.d.=6.84 years) years. The average whole brain volume was 110.51 × 10 000 cm<sup>3</sup> (s.d.=10.91 × 10 000 cm<sup>3</sup>). Written informed consents were obtained from all subjects.

**Measures**

*Diagnostic and criminal assessments.* Schizotypy were assessed according to the criteria set down in the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> Edition (DSM-IV).<sup>20,21</sup> The dimensional score was computed by the summation of the ratings (1 = absent, 2 = sub-threshold, 3 = threshold) on the nine schizotypal personality traits: (1) cognitive perceptual (magical thinking, unusual perceptual experiences, ideas of reference and paranoid ideation), (2) interpersonal (no close friends, constructed affect, undue social anxiety and paranoid ideation), and (3) disorganized features (odd/eccentric behavior and odd speech). The measure of antisocial behavior was based on the 27 criminal offences recorded by the court over a lifespan (for example, murder, manslaughter, rape, robbery, theft, fraud and embezzlement). Antisocial behavior was treated as a dichotomized variable, coded as 0, for those who had never been charged with committing any one of the listed criminal offences. Antisocial behavior was coded as 1 for those who had been charged of one or more criminal offences that are listed above throughout their lifetime. The reason for treating antisocial behavior as a dichotomous variable was that the distribution of this continuous variable was highly skewed and irregular (skewness = 4.05; mean = 3.30; median = 0.00; s.d. = 8.66; range = 0.00–52.0). Moreover, over half of the sample (66.7%) had never committed any crimes listed above. Hence, it was recommended to dichotomize this variable that had an irregular distribution.<sup>22</sup>

*Magnetic resonance imaging*

**Imaging protocol:** A Philips S15/ACS (Selton, CT, USA) magnetic resonance imaging scanner with a magnet of 1.5T field strength was used to assess brain structure. After an initial alignment sequence of one midsagittal and four parasagittal scans (spin-echo T1-weighted image acquisition, repetition time = 600 ms, echo time = 20 ms) to identify the anterior commissure/posterior commissure plane, 128 three-dimensional T1-weighted gradient-echo coronal images (repetition time = 34 ms, echo time = 12.4 ms, flip angle = 351, 1.7 mm over-contiguous slices, 256 × 256

**Table 1.** Association of potential covariates with gray matter volumes in PFC and its sub-regions, schizotypy and antisocial behavior

Measure	Whole brain volumes		Sex		Statistics	Substance abuse or dependent histories		Statistics
	SES	Age	Males (n = 78)	Females (n = 12)		Yes (n = 56)	No (n = 32)	
Schizotypy	r = -0.10	r = -0.15	16.09 (4.13)	15.33 (4.79)	t <sub>86</sub> = 0.58	16.56 (4.47)	15.03 (3.63)	t <sub>85</sub> = -1.65
Prefrontal gray	r = -0.54***	r = 0.67***	48.09 <sup>a</sup> (9.02)	45.65 <sup>a</sup> (9.82)	t <sub>88</sub> = 0.86	47.55 <sup>a</sup> (10.12)	47.80 <sup>a</sup> (7.38)	t <sub>86</sub> = 0.12
Orbitofrontal gray	r = -0.31**	r = 0.41***	23.98 <sup>a</sup> (3.52)	24.95 <sup>a</sup> (2.91)	t <sub>88</sub> = -0.90	23.84 <sup>a</sup> (3.58)	24.61 <sup>a</sup> (3.30)	t <sub>86</sub> = 1.00
Rectal gyri gray	r = -0.28**	r = 0.37***	5.86 <sup>a</sup> (1.31)	6.01 <sup>a</sup> (1.27)	t <sub>88</sub> = -0.37	5.92 <sup>a</sup> (1.27)	5.88 <sup>a</sup> (1.30)	t <sub>86</sub> = -0.14
Inferior frontal gray	r = -0.28**	r = 0.41***	16.34 <sup>a</sup> (3.60)	15.66 <sup>a</sup> (4.17)	t <sub>88</sub> = 0.60	16.33 <sup>a</sup> (3.79)	16.24 <sup>a</sup> (3.56)	t <sub>86</sub> = -0.11
Middle frontal gray	r = -0.16	r = 0.22*	24.66 <sup>a</sup> (4.80)	26.07 <sup>a</sup> (5.93)	t <sub>88</sub> = -0.92	24.19 <sup>a</sup> (4.95)	26.06 <sup>a</sup> (4.95)	t <sub>86</sub> = 1.71
Superior frontal gray	r = -0.37***	r = 0.32**	52.75 <sup>a</sup> (11.12)	47.10 <sup>a</sup> (12.63)	t <sub>88</sub> = 1.61	52.59 <sup>a</sup> (11.58)	50.54 <sup>a</sup> (11.34)	t <sub>86</sub> = -0.80
Antisocial behavior	t <sub>87</sub> = -3.34***	t <sub>88</sub> = 1.82	35.90 <sup>b</sup>	16.67 <sup>b</sup>	χ <sup>2</sup> <sub>1</sub> = 1.73	46.43 <sup>b</sup>	12.50 <sup>b</sup>	χ <sup>2</sup> <sub>1</sub> = 10.43***

Abbreviations: PFC, prefrontal cortex; SES, social-economic status. <sup>a</sup>Gray matter volumes (1000 cm<sup>3</sup>). <sup>b</sup>Percentage of the subjects in the group with antisocial behavior. \*\*\*P ≤ 0.001, \*\*P ≤ 0.01, \*P ≤ 0.05.

matrix, field-of-view=23 cm) were taken in the plane directly orthogonal to the anterior commissure/posterior commissure line.

**Image preprocessing:** LONI Pipeline Processing Environment (Los Angeles, CA, USA)<sup>23</sup> was used in processing the preparatory steps preceding manual delineation of prefrontal sub-regions for all the image data sets. The series of preparatory steps was as follows: (1) non-brain tissue and the cerebellum were removed from the brain images using BrainSuite,<sup>24</sup> with small errors corrected manually; (2) brain volumes were subjected to signal intensity inhomogeneity corrections<sup>25</sup> and a rigid body transformation was used to align and place the images into a stereotaxic coordinate system of the International Consortium for Brain Mapping,<sup>26,27</sup> without scaling the brain;<sup>28,29</sup> (3) a fully automated tissue segmentation algorithm and a validated partial volume correction method<sup>30</sup> were used, where brain voxels were automatically classified as the most representative of gray matter, white matter or cerebrospinal fluid; and (4) a three-dimensional active surface algorithm was used to help identify the anatomic boundaries for prefrontal sub-region delineation,<sup>31</sup> and a high-resolution shape representation of the cortex was extracted.

**Prefrontal region-of-interest delineation:** The PFC was divided into five sub-regions (SFC, MFC, IFC, OFC and RG) for both left and right hemispheres by using MNIDisplay, which is a visualization tool developed by McConnel Brain Imaging Center (<http://noodles.bic.mni.mcgill.ca/ServicesSoftware/HomePage>) employing methods described previously.<sup>32</sup> Each individual's three-dimensional cortical surface object and all three planes of their brain images were used to trace all anatomical delineations. This is to identify sulcal line markers for each sub-region. Furthermore, three human brain atlases<sup>33–35</sup> were used to verify the delineations. Raters who were blind to group membership and all other information of the participants were selected to perform the segmentation. For inter-rater reliability, 10 image data sets were chosen randomly for the delineation of all anatomical regions; intra-class correlation coefficients for gray matter and white matter ranged from 0.90 to 0.97 in all of the five frontal sub-regions.

#### Statistical analyses

Pearson's correlations, two-sided independent *t*-tests and  $\chi^2$ -tests were initially conducted to examine the relationship between the gray matter volumes in the PFC and its sub-regions, schizotypy, antisocial behaviors, potential covariates (age, sex, socio-economic status,<sup>36</sup> whole brain volumes and substance abuse or dependence history) using SPSS (Chicago, IL, USA). Mediation analyses were then performed using SPSS PROCESS macro<sup>37</sup> by employing the bootstrapping method as outlined in the study by Shrout and Bolger.<sup>38</sup> Specifically, the mediation effect of the gray matter volumes of the PFC and its five sub-regions (SFC, MFC, IFC, OFC

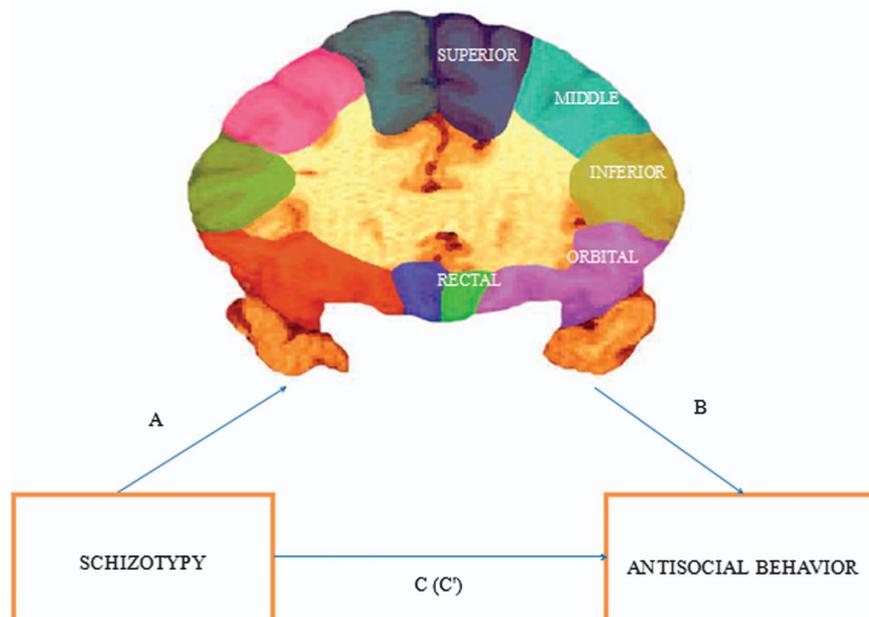
and RG) on the relationship between schizotypy and antisocial behavior was analyzed. Bootstrapping (95% bias-corrected confidence intervals) was used to estimate indirect effects using 1000 bootstrap samples, setting the effect size to 1. In the hypothesis, schizotypy was the independent variable, total gray matter volumes in the PFC and its sub-regions were the mediators, and antisocial behavior, as a dichotomized measure, was the dependent variable. Yet, it is a cross-sectional study and thus we cannot confirm causal relationship with the present data. To address this limitation and to further support the direction of causal effects in the predicted model, an alternative reverse mediation model was also analyzed to compare with the proposed mediation model. In the reverse mediation model, the prefrontal (SFC, MFC, IFC, OFC or RG) gray was the independent variable, schizotypy was the mediator and antisocial behavior was the dependent measure. It is suggested that the predicted mediation model would be more convincing if the reverse mediation model yields different pattern of or non-significant results.<sup>39</sup> A confidence interval that does not contain zero indicates significant mediation statistically ( $P < 0.05$ ).<sup>38</sup> According to the rule-of-thumb for adequate sample size ( $N \geq 50 + 8 \times \text{variables}$ ),<sup>40</sup> at least 74 subjects would be needed for the analysis in the present study and our sample size met this threshold.

## RESULTS

### Preliminary correlations and independent *t*-tests

Pearson's correlations, independent *t*- and  $\chi^2$ -tests (Table 1) were performed on subjects with varying sexes, ages, social-economic status, whole brain volumes, substance abuse or dependence histories, gray matter volumes in the PFC or its sub-regions, schizotypy and antisocial behavior. The results showed that ages of the subjects were associated with their antisocial behavior and the total gray matter volumes in their PFC, OFC, GR, IFC and SFC ( $P_s < 0.01$ ). Subjects with higher social-economic status were associated with decreased antisocial behavior ( $P = 0.042$ ), while those with substance abuse or dependence history were associated with more frequent antisocial behavior ( $P = 0.001$ ).

Schizotypy ( $t_{86} = -2.70$ ,  $P = 0.008$ ), as well as reduced prefrontal ( $t_{88} = 3.37$ ,  $P = 0.001$ ), orbitofrontal ( $t_{88} = 3.30$ ,  $P = 0.001$ ) and MFC gray ( $t_{88} = 3.68$ ,  $P < 0.001$ ) were associated with increased antisocial behavior. Furthermore, schizotypy was negatively associated with orbitofrontal gray ( $r = -0.29$ ,  $P = 0.006$ ). Such correlations were not significant to have contributed to the PFC and the other four PFC sub-regions ( $P_s > 0.05$ ).



**Figure 1.** Hypothesized mediation model for the schizotypy–antisocial behavior relationship. The figure was adapted from the study by Raine *et al.*<sup>10</sup>

**Table 2.** Statistical tests for the neural gray mediation of schizotypal personality and antisocial behavior

Neural gray matter volumes	A	B	C	C'	Proportion of the effect C that is mediated	Indirect effect (lower limit 95% CI, upper limit 95% CI)
Prefrontal cortex	-0.304	-0.088*	0.147*	0.133*	18.2%	0.0268 (-0.0036, 0.0863)
	Controlling for all covariates (sex, age, SES, whole brain volumes and substance abuse/dependence history)					
Orbitofrontal cortex	-0.238**	-0.275**	0.147*	0.102	44.5%	0.0653 (0.0212, 0.1519)
Superior frontal cortex	-0.097	-0.004	0.147*	0.147*	0.3%	0.0004 (-0.0099, 0.0154)
Inferior frontal cortex	-0.067	-0.042	0.147*	0.146*	1.9%	0.0028 (-0.0081 - 0.0331)
Middle frontal cortex	-0.037	-0.231**	0.147*	0.173**	5.8	0.0086 (-0.0544, 0.0822)
Rectal gyri	-0.058	-0.343	0.147*	0.130*	13.5	0.0198 (-0.0006, 0.0694)
	-0.072	-0.109*	0.111	0.113	7.1%	0.0079 (-0.0464, 0.0727)
	-0.185*	-0.321*	0.111	0.069	53.5%	0.0594 (0.0010, 0.1524)
	-0.049	0.031	0.111	0.113	1.4%	-0.0015 (-0.0422, 0.0236)
	-0.019	0.035	0.111	0.111	0.6%	-0.0007 (-0.0363, 0.0203)
	0.023	-0.324**	0.111	0.182*	6.7	-0.0073 (-0.1250, 0.1055)
	-0.034	-0.220	0.111	0.104	6.7	0.0075 (-0.0115, 0.0611)

Abbreviations: CI, confidence interval; SES, social-economic status. \*\* $P < 0.01$ , \* $P < 0.05$  (A) Regression slope of schizotypy predicting neural gray; (B) regression slope of neural gray predicting antisocial behavior, controlling for schizotypy; (C) regression slope of schizotypy predicting antisocial behavior; (C') regression slope of schizotypy predicting antisocial behavior, controlling for neural gray. Bootstrapping was used to estimate indirect effects.<sup>38</sup>

### Mediation analyses

All covariates were taken into account in the mediation analyses. The relationship of the total gray matter volumes in the PFC and its five sub-regions (OFC, RG, IFC, MFC and SFC) with schizotypy and antisocial behavior was tested by mediation analyses. See Figure 1 for the hypothesized mediation model.

**Prefrontal cortex.** The PFC, as one unitary cortex gray, did not mediate the relationship between schizotypy and antisocial behavior before (mean indirect effect = 0.0268, 95% confidence interval (CI) = -0.0036–0.0863) and after controlling all covariates (mean indirect effect = 0.0079, 95% CI = -0.0464–0.0727) (Table 2).

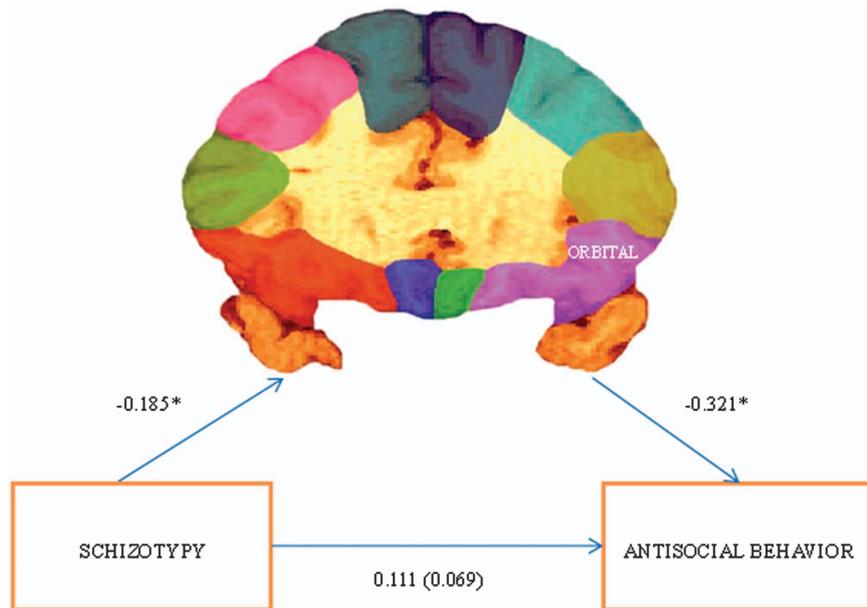
**Regional specificity: PFC sub-regions.** To test whether specific PFC sub-regions, in particular the OFC, mediated the relationship between schizotypy and antisocial behavior, mediation analyses were performed for the five PFC sub-regions. OFC gray was shown to have mediated the relation between schizotypy and antisocial behavior even after controlling all covariates (mean indirect effect = 0.0594, 95% CI = 0.0010–0.1524) (Table 2). To be specific, OFC gray significantly mediated the effect of schizotypy on antisocial behavior by 53.5% (after controlling the covariates) and 44.5% (before controlling the covariates). Schizotypy ( $\beta = -0.185$ ,  $P = 0.022$ ) and antisocial behavior ( $\beta = -0.321$ ,  $P = 0.018$ ) were associated with OFC gray negatively. The strength of the relationship between schizotypy and antisocial behavior was reduced from  $\beta = 0.111$  ( $P = 0.099$ ) to  $\beta = 0.069$  ( $P = 0.350$ ) after having controlled the OFC gray and all covariates (Figure 2). The mediation results were not significant for the other four sub-regions: SFC, MFC, IFC and RG (see Supplementary Figure 1).

**Alternative reverse mediation model.** Schizotypy did not mediate the relationship between the gray matter volumes (PFC and all five sub-regional cortexes) and antisocial behavior after controlling all covariates. Specifically, all confidence intervals for the alternative reverse mediation models contained zero, suggesting non-significant mediation. For instance, the mean direct effect was -0.0112 and the 95% confidence interval was -0.1035–0.0517 for the OFC–schizotypy–antisocial behavior mediation model.

### DISCUSSION

To the best of our knowledge, this is the first study that examines the neural mediator of the relationship between schizotypy and antisocial behavior. The key finding was that reduced gray matter volumes in the PFC sub-region, specifically the OFC, fully mediated the positive relationship between schizotypy and antisocial behavior before controlling the covariates. After controlling all covariates, OFC gray partially mediated such a relationship. However, the mediating effects of the other four PFC sub-regions (superior, middle, inferior and rectal gyral) and the PFC as one unitary structure were not significant before or after controlling the covariates. Our findings supported our priori hypothesis. Importantly, the functional specificity of the OFC may explain the comorbidity of schizotypy and antisocial behavior. The causal mediational relationship is yet to be established in future longitudinal studies since such a causality could not be confirmed with present cross-sectional data.

As with the hypothesis, the reduction in the volume of OFC gray mediated the association between schizotypy and antisocial behavior fully before controlling the covariates. After controlling the sexes, ages, socio-economic status, whole brain volumes, substance abuse or dependence histories of test subjects, OFC gray still partially mediated such a relationship.<sup>8,10</sup> Specifically, schizotypy was positively associated with antisocial behavior.<sup>4,5</sup> Both were associated with total gray matter volumes in the OFC negatively.<sup>8,10</sup> The strength of the relationship between schizotypy



**Figure 2.** Mediation model for the OFC (regression slopes in parenthesis indicate the full mediation estimate between schizotypy and antisocial behavior after controlling for the OFC gray matter volume) ( $P < 0.5$ ). The figure was adapted from the study by Raine *et al.*<sup>10</sup>

and antisocial behavior was significantly reduced once OFC gray was taken into account. Indeed, OFC gray mediated the effect of schizotypy on antisocial behavior by 53.5%. On the other hand, these associations were not significant for the other four PFC sub-regions. Moreover, the proportion of the schizotypal effect on antisocial behavior mediated by these 4 PFC sub-regional gray was minimal (0.6–6.7%) when compared with that by OFC gray (53.5%). All these findings suggested the specificity of the OFC in understanding the schizotypy–antisocial behavior relationship. Besides, the mediation was not significant for the PFC as one unitary structure, which might have been due to the fact that the PFC is a relatively large brain cortex comprised of sub-regional cortices. Taking these findings together, it was suggested that the reduction in the volume of gray matter in a specific PFC sub-region—the OFC—is the common denominator for the comorbidity of schizotypy and antisocial behavior.

Furthermore, to address the limitation of the present cross-sectional data and to rule out potential reverse causal effect, as well as the chance effect of the predicted casual direction, we also analyzed and compared the proposed mediation model (for example, schizotypy–OFC–antisocial behavior) with alternative reverse mediation model (for example, OFC–schizotypy–antisocial behavior). The mediation analyses in the alternative reverse model showed that schizotypy did not mediate the relationship between the gray matter volumes (PFC and all five sub-regional cortices) and antisocial behavior after controlling all covariates. These non-significant findings further supported that the proposed mediation model was more promising and valid than the reverse mediation model. All in all, based on the evidence supporting the schizotypy–OFC–antisocial behavior mediation with the present data, the causality of such a mediation is suggested to be tested in future longitudinal studies for confirmation.

In terms of the functional neuroanatomy of OFC, this PFC sub-region is involved in controlling and inhibiting impulsive actions,<sup>41</sup> emotion processing<sup>42</sup> and decision-making.<sup>43</sup> These functions subserved by the OFC are impaired among people with schizophrenia<sup>44,45</sup> and antisocial personality disorder.<sup>46–48</sup> In particular, individuals with schizophrenia<sup>45</sup> and antisocial personality disorder<sup>47</sup> lack the ability to control and inhibit impulsive

behavior. In addition, impairment regarding emotion processing is associated with schizophrenia<sup>44</sup> and antisocial personality disorder.<sup>46</sup> Similarly, the abilities to learn from punishment or mistakes and to make advantageous decisions are found to be impaired among individuals with schizophrenia<sup>49</sup> and antisocial behavior.<sup>48</sup> Such neurocognitive dysfunction may help understand the schizotypy–antisocial behavior comorbidity.

#### Limitations

The limitations of the study should be recognized. First, this study is cross-sectional and a causal relationship among OFC gray, schizotypy and antisocial behavior cannot be established. However, the causal model examined is a crucial factor in testing the way OFC gray mediates the relationship between schizotypy and antisocial behavior before a longitudinal study is applied. Second, although we have segmented and investigated the five PFC sub-regions, the specific OFC sub-region involved in schizotypy–antisocial behavior comorbidity is still unclear. The OFC is a relatively large brain area in humans, and its constituent parts serve different functions. For instance, the medial OFC is involved in monitoring, learning and memory of the reward value of reinforcers. On the other hand, the lateral region is involved in evaluating punishers.<sup>50</sup> Thus, future studies should be conducted to identify the specific OFC sub-region involved in schizotypy–antisocial behavior comorbidity. Finally, due to the fact that the present findings were based on a modest sample size, the findings may be inadequate in terms of representation. Thus, a larger sample size is desirable in future studies.

#### CONCLUSIONS

This study has extended the scope of prior literature on schizophrenia to its sub-clinical construct, schizotypy. After controlling for substance abuse/dependence histories and other covariates, the mediating effect of the OFC gray was still significant in contributing to the comorbidity. This observation suggests that the neural mediator, the OFC, is a crucial factor in understanding the comorbidity. Our findings are important for

understanding the neural basis of the relationship between schizotypy and antisocial behavior.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGMENTS

This work was supported by the National Institute of Mental Health (Research Scientist Development Award K02 MH01114-01, Independent Scientist Award K02 MH01114-01 and 5 RO3 MH50940-02); the Research Grant Council Humanities and Social Sciences Prestigious Fellowship (HKU703-HSS-13); and the May Endowed Professorship of The University of Hong Kong.

## REFERENCES

- Fazel S, Gulati G, Linsell L, Geddes JR, Grann M. Schizophrenia and violence: systematic review and meta-analysis. *PLoS Med* 2009; **6**: e1000120.
- Siever LJ, Koeningsberg HW, Harvey P, Mitropoulou V, Laruelle M, Abi-Dargham A et al. Cognitive and brain function in schizotypal personality disorder. *Schizophr Res* 2002; **54**: 157–167.
- Serper MR. Aggression in schizophrenia. *Schizophrenia Bull* 2011; **37**: 897–898.
- Schaub M, Boesch L, Stohler R. Association between aggressiveness, schizotypal personality traits and cannabis use in Swiss psychology students. *Psychiat Res* 2006; **143**: 299–301.
- Raine A, Fung ALC, Lam BYH. Peer victimization partially mediates the schizotypy-aggression relationship in children and adolescents. *Schizophr Bull* 2011; **37**: 937–945.
- Fazel S, Långström N, Hjern A, Grann M, Lichtenstein P. Schizophrenia, substance abuse, and violent crime. *JAMA* 2009; **301**: 2016–2023.
- Kanahara N, Sekine Y, Haraguchi T, Uchida Y, Hashimoto K, Shimizu E et al. Orbitofrontal cortex abnormality and deficit schizophrenia. *Schizophr Res* 2013; **143**: 246–252.
- Pantelis C, Velakoulis D, McGorry PD, Wood SJ, Suckling J, Phillips LJ. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* 2003; **361**: 281–288.
- Raine A, Lencz T, Yarlalian P, Bihle S, LaCasse L, Ventura J et al. Prefrontal structural and functional deficits in schizotypal personality disorder. *Schizophr Bull* 2002; **28**: 501–513.
- Raine A, Yang Y, Narr KL, Toga AW. Sex differences in orbitofrontal gray as a partial explanation for sex differences in antisocial personality. *Mol Psychiatr* 2011; **16**: 227–236.
- Bufoin JL, Luttrell VR. Neuroimaging studies of aggressive and violent behavior: Current findings and implications for criminology and criminal justice. *Trauma Violence Abuse* 2005; **6**: 176–191.
- Damasio H, Grabowski T, Frank R, Galaburda AM, Damasio AR. The return of Phineas Gage: clues about the brain from the skull of a famous patient. *Science* 1994; **264**: 1102–1105.
- Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation—a possible prelude to violence. *Science* 2000; **289**: 591–594.
- Strüber D, Lück M, Roth G. Sex, aggression and impulse control: an integrative account. *Neurocase* 2008; **14**: 93–121.
- Giancola PR, Zeichner A. Neuropsychological performance on tests of frontal-lobe functioning and aggressive behavior in men. *J Abnorm Psychol* 1994; **103**: 832–835.
- Shurman B, Horan WP, Nuechterlein KH. Schizophrenia patients demonstrate a distinctive pattern of decision-making impairment on the Iowa Gambling Task. *Schizophr Res* 2005; **72**: 215–224.
- Kumari V, Barkataki I, Goswami S, Flora S, Das M, Taylor P. Dysfunctional, but not functional, impulsivity is associated with a history of seriously violent behaviour and reduced orbitofrontal and hippocampal volumes in schizophrenia. *Psychiat Res* 2009; **173**: 39–44.
- Hoptman MJ, Volavka J, Weiss EM, Czobor P, Szeszko PR, Gerig G et al. Quantitative MRI measures of orbitofrontal cortex in patients with chronic schizophrenia or schizoaffective disorder. *Psychiat Res* 2005; **140**: 133–145.
- Raine A. Structural and Functional Brain Imaging Correlates of Violence. *Proceedings of the Annual Meeting of the American College of Neuropsychopharmacology*; 8–12 December 1997; Walkoloa, HI, USA, 1997.
- First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for Axis I DSM-IV Disorders (SCID, Version 2.0)*. New York State Psychiatric Institute: New York, NY, USA, 1994.
- First MB, Spitzer RL, Gibbon M, Williams JBW, Benjamin L. *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II, Version 2.0)*. New York State Psychiatric Institute: New York, NY, USA, 1994.
- DeCoster J, Iselin AMR, Gallucci M. A conceptual and empirical examination of justifications for dichotomization. *Psychol Methods* 2009; **14**: 349.
- Rex DE, Ma JQ, Toga AW. The LONI pipeline processing environment. *Neuroimage* 2003; **19**: 1033–1048.
- Shattuck DW, Leahy RM. BrainSuite: an automated cortical surface identification tool. *Med Image Anal* 2002; **6**: 129–142.
- Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE T Med Imaging* 1998; **17**: 87–97.
- Mazziotta JC. Brain mapping: its use in patients with neurological disorders. *Rev Neuro* 2001; **157**: 863–871.
- Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J. A probabilistic atlas of the human brain—theory and rationale for its development. *Neuroimage* 1995; **2**: 89–101.
- Woods RP, Grafton ST, Holmes CJ, Cherry SR, Mazziotta JC. Automated image registration: I. General methods and intrasubject, intramodality validation. *J Comput Assist Tomo* 1998; **22**: 139–152.
- Woods RP, Grafton ST, Watson JD, Sicotte NL, Mazziotta JC. Automated image registration: II. Intersubject validation of linear and nonlinear models. *J Comput Assist Tomo* 1998; **22**: 153–165.
- Shattuck DW, Sandor-Leahy SR, Schaper KA, Rottenberg DA, Leahy RM. Magnetic resonance image tissue classification using a partial volume model. *Neuroimage* 2001; **13**: 856–876.
- MacDonald D, Avis D, Evans A. Multiple surface identification and matching in magnetic resonance images. In: Robb RA (ed) . *Proceedings of the International Society for Optical Engineering (SPIE) Conference on Visualization in Biomedical Computing*. SPIE: New York, NY, USA, 1994, pp 160–169.
- Ballmaier M, Toga AW, Blanton RE, Sowell ER, Lavretsky H, Peterson J et al. Anterior cingulate, gyrus rectus, and orbitofrontal abnormalities in elderly depressed patients: an MRI-based parcellation of the prefrontal cortex. *Am J Psychiatry* 2004; **161**: 99–108.
- DeArmond J, Fusco MM, Dewey MM. *Structure of the Human Brain*. 3rd edn, Oxford University Press: New York, NY, USA, 1989.
- Duvernoy HM. *The Human Brain: Surface, Three-dimensional Sectional Anatomy with MRI, and Blood Supply*. 2nd edn., Springer: New York, NY, USA, 1999.
- Mai JK, Assheuer J, Paxinos G. *Atlas of the Human Brain*. Academic Press: San Diego, CA, USA, 1997.
- Hollingshead AB. Four factor index of social status. *Department of Sociology, Yale University*: New Haven, CT, USA, 1975.
- Hayes AF. *An Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-based Approach*. Guilford Press: New York, NY, USA, 2013.
- Shrout PE, Bolger N. Mediation in experimental and nonexperimental studies: New procedures and recommendations. *Psychol Methods* 2002; **7**: 422–445.
- Judd CM, Kenny DA. Data analysis in social psychology: recent and recurring issues. In: Fiske ST, Gilbert DT, Lindzey G (eds). *Handbook of Social Psychology*, 5th edn, vol. 1. John Wiley & Sons: Hoboken, NJ, USA, 2010, pp 115–142.
- Green SB. How many subjects does it take to do a regression analysis. *Multivar Behav Res* 1991; **26**: 499–510.
- Volavka J. *Neurobiology of Violence*. American Psychiatric Press: Washington DC, USA, 1995.
- Hornak J, Bramham J, Rolls ET, Morris RG, O'Doherty J, Bullock PR et al. Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain* 2003; **126**: 1671–1712.
- Wallis JD. Orbitofrontal cortex and its contribution to decision-making. *Annu Rev Neurosci* 2007; **30**: 31–56.
- Berenbaum H, Oltmanns TF. Emotional experience and expression in schizophrenia and depression. *J Abnorm Psychol* 1992; **101**: 37–44.
- Kaladjian R, Jeanningros JM, Azorin JL, Anton JM, Mazzola-Pomietto P. Impulsivity and neural correlates of response inhibition in schizophrenia. *Psychol Med* 2011; **41**: 291–299.
- Kropp JP, Haynes OM. Abusive and nonabusive mother's ability to identify general and specific emotion signals of infants. *Child Dev* 1987; **58**: 187–190.
- Swann AC, Lijffijt M, Lane SD, Steinberg JL, Moeller FG. Trait impulsivity and response inhibition in antisocial personality disorder. *J Psychiat Res* 2009; **43**: 1057–1063.
- Yechiam E, Kozl J, Bechara S, Stout J, Busemeyer JR, Altmeyer EM et al. Neurocognitive deficits related to poor decision making in people behind bars. *Psychon B Rev* 2008; **15**: 44–51.

- 49 Sevy S, Burdick KE, Visweswaraiah H, Abdelmessih S, Lukin M, Yechiam E *et al*. Iowa gambling task in schizophrenia: A review and new data in patients with schizophrenia and co-occurring cannabis use disorders. *Schizophr Res* 2007; **92**: 74–84.
- 50 Kringelbach ML, Rolls E. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Prog Neurobiol* 2004; **72**: 341–372.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

Supplementary Information accompanies the paper on the Translational Psychiatry website (<http://www.nature.com/tp>)