Neural bases of antisocial behavior: a voxel-based meta-analysis

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Individuals with antisocial behavior place a great physical and economic burden on society. Deficits in emotional processing have been recognized as a fundamental cause of antisocial behavior. Emerging evidence also highlights a significant contribution of attention allocation deficits to such behavior. A comprehensive literature search identified 12 studies that were eligible for inclusion in the meta-analysis, which compared 291 individuals with antisocial problems and 247 controls. Signed Differential Mapping revealed that compared with controls, gray matter volume (GMV) in subjects with antisocial behavior was reduced in the right lentiform nucleus ($P < 0.0001$), left insula ($P = 0.0002$) and left frontopolar cortex (FPC) ($P = 0.0006$), and was increased in the right fusiform gyrus ($P < 0.0001$), right inferior parietal lobule ($P = 0.0003$), right superior parietal lobule ($P = 0.0004$), right cingulate gyrus ($P = 0.0004$) and the right postcentral gyrus ($P = 0.0004$). Given the well-known contributions of limbic and paralimbic areas to emotional processing, the observed reductions in GMV in these regions might represent neural correlates of disturbance in emotional processing underlying antisocial behavior. Previous studies have suggested an FPC role in attention allocation during emotional processing. Therefore, GMV deviations in this area may constitute a neural basis of deficits in attention allocation linked with antisocial behavior.

Keywords: antisocial personality disorder; Brodmann area (BA) 9; conduct disorder; frontal pole; psychopathy

INTRODUCTION

Individuals with antisocial behavior, such as conduct disorder (CD), antisocial personality disorder (ASPD) and callous-unemotional traits or psychopathy, place a great physical and economic burden on society (Moffitt, 1993; Kratzer and Hodgins, 1997; Loeb and Stouthamer-Loeb, 1998). People with such disorders have symptoms of emotional detachment and a propensity for disinhibited, impulsive behavior combined with a general callousness and lack of insight for the impact that such behavior has on others (Cleckley, 1941; Anderson and Kiehl, 2012). Though not all children with CD have life-course persistent symptoms, genetic studies have suggested that continuous antisocial behavior is heritable (Moffitt, 2005) and children with CD or callous-unemotional traits frequently develop an ASPD or psychopathy in adulthood (Frick and Viding, 2009). Neurodevelopmental theories also suggest that brain abnormalities in early life are associated with lifelong antisocial behavior (Frick and Viding, 2009; Gao et al., 2009), indicating that individuals with CD, callous-unemotional traits, ASPD and psychopathy share a common neural basis.

Whether antisocial behavior is characterized by fundamental deficits in attention or emotion is a long-standing debate (Sadeh and Verona, 2012). Although numerous studies have confirmed that deficits in emotional processing are involved in the pathophysiology of antisocial behavior (Blair et al., 2006; Yang et al., 2009), abnormalities in these regions in people with antisocial behavior (Frick et al., 2002; Blair, 2003). Thus, the pathophysiology model of abnormal emotional processing cannot fully account for such deficits in emotionally neutral information processing. Based on psychological experiments in which appropriate emotional responses were reported when attention was focused on emotional stimuli (Glass and Newman, 2006; Newman et al., 2010; Baskin-Sommers et al., 2011), it is hypothesized that it is not only emotional processing deficits but also attention deficits, especially attention allocation and maintenance during emotional processing, that contributes to the pathophysiology of antisocial behavior (Sadeh and Verona, 2012).

Neuroimaging studies have investigated the neural bases of the pathophysiology of antisocial behavior. The amygdala, one of the centers of emotional processing (Phelps and LeDoux, 2005), is the region most commonly implicated in functional and structural abnormalities of the brain in individuals who display antisocial behavior (Blair et al., 2006; Yang et al., 2009). In addition to the amygdala, the paralimbic system is also recognized as a center of emotional processing and has often been investigated in antisocial behavior research (Blair et al., 2006; Blair, 2007; Raine et al., 2010; Finger et al., 2012; Ly et al., 2012). Among the paralimbic regions, the orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC) are those most commonly studied in the field of antisocial behavior, and a number of structural magnetic resonance imaging (MRI) studies have reported abnormalities in these regions in people with antisocial behavior (Boccacci et al., 2011; Hyatt et al., 2012). Functional MRI (fMRI) studies have consistently revealed abnormal activity in the OFC/vmPFC in individuals with antisocial problems during tasks related to emotional processing in value-oriented or social situation, such as making judgments about legal actions (Marsh et al., 2011), social cooperation tasks (Rilling et al., 2002, 2007) and gambling tasks (Mitchell et al., 2002; Blair, 2003). Thus, dysfunction of the amygdala and paralimbic regions has been proposed as fundamental to the pathophysiology of abnormal emotional processing in people with antisocial behavior (Koenigs, 2012).
Neuroimaging studies with healthy volunteers indicate that the FPC is associated with allocating and maintaining attention on emotional stimuli (Koechlin et al., 1999; Burgess et al., 2007; Tsujimoto et al., 2011). Given that the FPC is a potential neural correlate of attention allocation deficits during emotional processing in individuals with antisocial behavior, we hypothesized that structural abnormalities would be observed in the FPC of such individuals.

A number of whole-brain voxel-based morphometry (VBM) studies of people with antisocial problems have reported various regional gray matter volume (GMV) abnormalities. Some have reported abnormalities in the FPC but results are inconsistent (Tiihonen et al., 2008; Gregory et al., 2012). A contributing factor to the inconsistency of results may be each study’s insufficient sample size. Therefore, integration of these results with a statistically conservative threshold would address our hypothesis. To clarify whether VBM studies demonstrate abnormality in the areas related to attention allocation deficit, we conducted a systematic review and meta-analysis of unbiased VBM studies.

METHOD
Study selection
A comprehensive literature search of VBM studies published in peer-reviewed journals between 2001 (the date of the first VBM study in subjects with antisocial behavior) and April 2013 that compared individuals with ASPD, CD, callous-unemotional trait, disruptive behavior disorder and psychopathy with healthy subjects was conducted using the MEDLINE, Embase and Web of Knowledge databases. The search keywords were ‘antisocial’, ‘conduct’, ‘disruptive’, ‘oppositional defiant’, ‘callous-unemotional’, ‘psychopathy’ or ‘psychopath’, plus ‘morphometry’, ‘voxel-based’, ‘VBM’ or ‘voxel-wise’. The titles and abstracts of the studies were examined to determine whether or not they should be included. The reference lists of the included articles were also examined to search for additional relevant studies to be included. We defined the individuals with ASPD, CD, disruptive behavior disorder, callous-unemotional trait and psychopathy as individuals with antisocial behavior.

Selection of studies
Studies were included in our database if (i) they reported a voxel-wise comparison between patients with antisocial behavior and controls for GMV; and similar to previous studies (Radua and Mataix-Cols, 2009; Radua et al., 2010), (ii) they reported whole-brain results in stereotactic coordinates and used thresholds for significance corrected for multiple comparisons, or uncorrected with spatial extent thresholds. The literature search was performed without language restriction. If the study did not provide sufficient data, we emailed the corresponding author to obtain more data. In cases where the author did not respond, we excluded the study. Two of the authors (Y.A. and R.I.) independently screened the studies.

Comparison of regional GMVs
For coordinate-based meta-analysis, we used Signed Differential Mapping (SDM) software (www.sdmproject.com/software/) (Radua and Mataix-Cols, 2009; Radua et al., 2010, 2011; Bora et al., 2011; Nakao et al., 2011) to analyze GM abnormalities in patients with antisocial behavior. Briefly, a map of GMV differences, comprising the reported stereotactic coordinates for each significant group difference, was generated for each study. In SDM, unlike in other coordinate-based, meta-analytic methods, both positive and negative differences are reconstructed in the same map, which prevents a particular voxel from appearing significant in opposite directions. Importantly, when using SDM, the effects of negative studies are also included in the meta-analysis. Meta-analytic statistical maps were subsequently obtained by calculating the corresponding statistics from the study maps, weighted by the square root of the sample size of each study, to enable studies with large sample sizes to contribute proportionally more. A random effect model is applied to integrate the effect sizes of the studies (Radua et al., 2012). The statistical significance of each voxel was determined using randomization tests ($P < 0.001$) as in previous studies (Radua and Mataix-Cols, 2009; Radua et al., 2010; Bora et al., 2011).

Data extraction
We extracted the number of participants of both groups, and the coordinates and effect sizes of peak voxels. When different types of statistical values were reported, such as $z$-values, they were converted to $t$-values, accounting for the number of participants in both groups and the number of covariates. In addition, we extracted the mean age of participants.

In one study, which reported peak coordinates and threshold without statistical values of the coordinates, we determined the threshold value as the effect size of the coordinates (Fahim et al., 2011). The uncorrected statistical thresholds were set at $P < 0.001$ based on previous literature (Radua and Mataix-Cols, 2009; Radua et al., 2010; Bora et al., 2011).

RESULTS
Study selection for database
The literature search produced 23 potential candidates for the meta-analysis. Three studies were excluded because they did not involve healthy control comparisons (Ermer et al., 2012, 2013; Cope et al., 2012). Four studies were discarded because they did not adopt voxel-wise comparison or did not report peak coordinate (Yang et al., 2005; McAlonan et al., 2007; Schiffer et al., 2011; Sato et al., 2011). One study was discarded because it did not ensure any diagnosis of antisocial behavior we defined above in all the participants (Dalwani et al., 2011). One study was excluded because it did not directly compare individuals with antisocial behavior and healthy individuals (Sasayama et al., 2010). One study was discarded because it focused on only white matter (Wu et al., 2011). One study was not included because it was a review article with unpublished data (Vloet et al., 2008) (Figure 1).

Demographic characteristics
A comprehensive literature search identified 12 independent studies which were eligible for inclusion in the meta-analysis (Sterzer et al., 2007; de Oliveira-Souza et al., 2008; Huebner et al., 2008; Müller et al., 2008; Tiihonen et al., 2008; De Brito et al., 2009; Fahim et al., 2011; Fairchild et al., 2011, 2013; Gregory et al., 2012; Stevens and Haney-Carom, 2012; Bertsch et al., in press) (Table 1). In total, these 12 studies compared 291 individuals with antisocial problems and 247 control subjects. Nine studies included only male subjects (Sterzer et al., 2007; Huebner et al., 2008; Müller et al., 2008; Tiihonen et al., 2008; De Brito et al., 2009; Fahim et al., 2011; Fairchild et al., 2011, 2013; Gregory et al., 2012; Bertsch et al., in press), while one study recruited only female subjects (Fairchild et al., 2013). Seven reports involved children with antisocial problems; among these seven, five studied children with CD (Sterzer et al., 2007; Huebner et al., 2008; Fairchild et al., 2011, 2013; Stevens and Haney-Carom, 2012), one studied conduct problems (De Brito et al., 2009) and one studied disruptive behavioral disorder (Fahim et al., 2011). Five studies recruited adults, two included individuals with ASPD with psychopathy (Tiihonen et al., 2008; Gregory et al., 2012), one involved psychopathy (de Oliveira-Souza et al., 2008) and two recruited individuals with ASPD (Müller et al., 2008; Bertsch...
et al., in press). All the studies in the meta-analysis had excluded individuals with mental retardation.

Regional differences in GMV

A meta-analysis revealed that individuals with antisocial behavior had significantly smaller-than-normal GMV in the left superior frontal gyrus in its frontopolar portion (Talairach coordinates: x = −10, y = 62, z = 26; SDM value = −2.261, P = 0.0006; 16 voxels) (Table 2 and Figure 2a), in the left anterior insula (Talairach coordinates: x = −40, y = 8, z = 10; SDM value = −2.389, P = 0.0002; 53 voxels) (Table 2 and Figure 2b) and in the right lentiform nucleus (Talairach coordinates: x = 18, y = 6, z = −4; SDM value = −2.541, P < 0.0001; 110 voxels) (Table 2 and Figure 2c). Although the meta-analysis demonstrated a tendency of smaller-than-normal GMV in the amygdala in individuals with antisocial behavior, it did not reach statistical significance (Talairach coordinates: x = −28, y = 2, z = −16; SDM value = −1.957, P = 0.0049).

Furthermore, the analysis also showed a significant increase in GMV in the right fusiform gyrus (Talairach coordinates: x = 46, y = −22, z = −24; SDM value = 1.385, P < 0.0001; 60 voxels) (Table 2 and Figure 2d), in the right inferior parietal lobule (Talairach coordinates: x = 38, y = 30, z = 42; SDM value = 1.040, P = 0.0003; 39 voxels) (Table 2 and Figure 3a), in the left superior parietal lobule (Talairach coordinates: x = −36, y = −68, z = 44; SDM value = 1.002, P = 0.0004; 41 voxels) (Table 2 and Figure 3b), in the right cingulate gyrus (Talairach coordinates: x = 12, y = 8, z = 44; SDM value = 1.001, P = 0.0004; 41 voxels) (Table 2 and Figure 3c) and right postcentral gyrus (Talairach coordinates: x = 58, y = −20, z = 30; SDM value = 1.001, P = 0.0004; 43 voxels) (Table 2 and Figure 3d) in subjects with antisocial behavior, compared with control subjects. The statistical conclusions for differences in regional brain volumes were preserved after controlling for the effect of age.

DISCUSSION

To the best of our knowledge, this is the first meta-analysis of studies integrating VBM in individuals with antisocial behavior. The analysis identified a significant regional GMV reduction in the left FPC as well as in the paralimbic region, such as the anterior insula, in individuals with antisocial behaviors compared with healthy controls, supporting our hypothesis. The current analysis also found significantly increased GMV in the right fusiform gyrus and the right inferior parietal lobule.

Although the function of the FPC is yet to be elucidated (Tsujimoto et al., 2011), it is thought to be responsible for holding in mind a goal while exploring and processing secondary goals, a process generally required in planning and reasoning, which integrates working memory and attentional resource allocation (Koechlin et al., 1999; Burgess et al., 2007). The FPC is also recognized to be responsible for cognitive branching—the maintenance of pending information related to a previous behavioral episode during an ongoing behavioral episode for future use (Koechlin and Hyafil, 2007; Charron and Koechlin, 2010). Recently, Boorman et al. (2009, 2011) showed that the FPC not only represents pending information or intentions for future use but also encodes the reward-based evidence favoring the best counterfactual option for future decisions. These results indicate that the FPC is not simply involved in attention allocation but also plays an important role in complex social decision based on its fundamental role. This notion is supported by results of a number of fMRI studies that have reported that the FPC is responsible for guiding complex social decisions such as moral judgment (Greene et al., 2001; Moll et al., 2002) or charitable donation (Moll et al., 2006). In addition, one study with transcranial direct current stimulation (tDCS) showed that inhibiting the excitability of the FPC with cathodal tDCS did not lead to impairment, but rather to a significant within-subject improvement of deceptive behavior (Karim et al., 2007). These previous studies have strongly indicated the possibility that abnormality in the FPC results in antisocial behavior.

Previous studies in individuals with antisocial behavior have identified an association between the impulsive trait and working memory deficit (Carlson et al., 2009; Venables et al., 2011). It is also thought that the FPC is associated with keeping information in working memory (Koechlin et al., 1999; Charron and Koechlin, 2010). Therefore, a reduction in GMV in the FPC may relate to impulsivity. Interestingly, one study describing two case reports of individuals who sustained injury to the FPC reported that damage in this region resulted in impulsitive antisocial behavior (Anderson et al., 1999).

The current analysis showed GMV reduction in the anterior insula that consists of the paralimbic regions. The anterior insula has a strong connection with the amygdala (Naqvi and Bechara, 2009; Meyer-Lindenberg and Tost, 2012; Sesoues et al., 2013) and is involved in emotional processing and empathy (Vogt, 2005; de Vignemont and Singer, 2006; Fan et al., 2011; Morita et al., in press; Ponz et al., in press). The previous studies demonstrated abnormal activation of the anterior insula during empathy or emotional processing tasks in individuals with antisocial behavior (Herpertz et al., 2008; Saddeh et al., 2013). In addition, the previous study reported a thinner-than-normal cortex in the anterior insula in individuals with psychopathy (Ly et al., 2013).
<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>No. of ASB</th>
<th>No. of CTRL</th>
<th>Male (%)</th>
<th>FIQ</th>
<th>FWHM (mm)</th>
<th>ICV, GMV</th>
<th>Study Diagnosis</th>
<th>No. of ASB</th>
<th>No. of CTRL</th>
<th>Male (%)</th>
<th>FIQ</th>
<th>FWHM (mm)</th>
<th>ICV, GMV</th>
</tr>
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<tbody>
<tr>
<td>Bertsch et al. (2011)</td>
<td>12 (12)</td>
<td>27.3</td>
<td>97.6</td>
<td>58%</td>
<td>No</td>
<td>8</td>
<td>&lt; 0.01</td>
<td>ADHD, MDD</td>
<td>10 (10)</td>
<td>25 (25)</td>
<td>All right</td>
<td>NA</td>
<td>&lt; 0.05</td>
<td>corrected</td>
</tr>
<tr>
<td>Fahim et al. (2011)</td>
<td>22 (22)</td>
<td>8.39</td>
<td>NA</td>
<td>25 (25)</td>
<td>8.36</td>
<td>NA</td>
<td>&lt; 0.005</td>
<td>GMV increase in the fusiform gyrus</td>
<td>10 (10)</td>
<td>25 (25)</td>
<td>All right</td>
<td>NA</td>
<td>&lt; 0.05</td>
<td>corrected</td>
</tr>
<tr>
<td>Gregory et al. (2011)</td>
<td>63 (63)</td>
<td>17.78</td>
<td>99.1</td>
<td>27 (27)</td>
<td>18.5</td>
<td>101</td>
<td>&lt; 0.001</td>
<td>GMV increase in the fusiform gyrus</td>
<td>10 (10)</td>
<td>25 (25)</td>
<td>All right</td>
<td>NA</td>
<td>&lt; 0.05</td>
<td>corrected</td>
</tr>
<tr>
<td>Mullen et al. (2008)</td>
<td>16 (16)</td>
<td>NA</td>
<td>NA</td>
<td>16 (16)</td>
<td>16</td>
<td>NA</td>
<td>&lt; 0.05</td>
<td>GMV increase in the fusiform gyrus</td>
<td>10 (10)</td>
<td>25 (25)</td>
<td>All right</td>
<td>NA</td>
<td>&lt; 0.05</td>
<td>corrected</td>
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</table>

Although we have predicted abnormality in the amygdala as a potential neural correlate of abnormal emotional processing in individuals with antisocial behavior, the current meta-analysis suggested that abnormality in the anterior insula may also be responsible for abnormal emotional processing among them.

The analysis identified significantly smaller-than-normal GMV in the lentiform nucleus, mainly the putamen. Neuroimaging studies have repeatedly reported that the putamen is involved in reward-based learning (O’Doherty et al., 2004, 2006; Samejima et al., 2005; Liu et al., 2011, Wunderlich et al., 2012). Furthermore, it was also demonstrated that the putamen, along with the insula, is involved in judgment of distribution of justice (Hsu et al., 2008). As reward-based learning is disturbed in individuals with antisocial behavior (Finger et al., 2011), abnormality in these structures is suggested to be a potential pathophysiology of antisocial behavior (Glenn and Yang, 2012). However, the current finding should be interpreted with caution, because of comorbid attention deficit personality disorder (ADHD). ADHD is a frequent comorbidity in individuals with antisocial behavior clinically and sub-clinically, and some of the included studies in the current meta-analysis recruited individuals with comorbid diagnosis of ADHD (Sterzer et al., 2007; Fairchild et al., 2013). As it has been shown that there is a smaller-than-normal GMV in the right lentiform nucleus in individuals with ADHD (Nakao et al., 2011), comorbid ADHD may have influenced the results.

The meta-analysis further identified a GMV increase in the fusiform gyrus as a potential neural basis of antisocial behavior. Although we could not statistically test relationship between symptoms of antisocial behavior and abnormality of GMV in the fusiform gyrus, previous fMRI studies suggest how abnormal GMV in the fusiform gyrus attributes to antisocial behavior. The fusiform gyrus is thought to be directly involved in the process of social categorization via top-down modulation of social and face perception (Sabatinielli et al., 2011; Schwarz et al., 2013; Shikuro, in press) and emotions of guilt and shame (Takahashi et al., 2004; Michl et al., in press). It is also thought that the right fusiform gyrus is a center of rapid learning regarding the moral status of others (Singer et al., 2004). In addition, individuals with Klinefelter syndrome, a chromosomal condition (XXY) whose phenotype is high risk for antisocial behavior, displayed less activation of the fusiform gyrus during judgment of faces with regard to trustworthiness (van Rijn et al., 2012). These evidence suggest that abnormal GMV in the fusiform gyrus is related to deviated face recognition (Dolan and Fullam, 2006) and sense of guilt and shame (Tangney et al., 2011) in individuals with antisocial behavior.

The analysis also identified an increase in GMV in the inferior parietal lobule as a potential neural correlate of antisocial behavior. This area has been suggested to contain mirror neurons (Molenberghs et al., 2012), indicating that disturbance in this region results in various social dysfunctions. For example, the inferior parietal lobule is involved in gaze processing (Pelphrey et al., 2003, 2004), action perception in understanding intentions (Gallese et al., 2004), comprehending impressions of others (Mende-Siedlecki et al., in press), predicting the actions of from their gaze (Ramsay et al., 2012) and risk-taking action (Tamura et al., 2012). Based on previous fMRI studies, increased GMV in the inferior parietal lobule may reflect inappropriate eye gazing of individuals with antisocial behavior (Dadds et al., 2008). The analysis also demonstrated larger-than-normal GMV in the left superior parietal lobule. The superior parietal lobule, which is often activated together with the inferior parietal lobule (Culham et al., 1998), is involved in spatial attention (Molenberghs et al., 2007) and is reported to be abnormally activated for fearful congruent in individuals with antisocial behavior (White et al., 2012). The current analysis also demonstrated larger-than-normal GMV in the postcentral gyrus of subjects with antisocial behavior. Recent studies suggested...
that the right postcentral gyrus was associated with emotional processing and empathy (Bernhardt and Singer, 2012; Morelli et al., in press; Sarkheil et al., in press). Thus, this abnormality may relate to a disturbance of emotional processing and empathy in individuals with antisocial behavior. The cingulate gyrus is also demonstrated to be larger-than-normal in individuals with antisocial behavior. As a number of previous fMRI studies reported abnormal activation of the BOLD signal during moral- or shame-related tasks (Raine and

### Table 2: Results of meta-analysis of VBM studies comparing individuals with antisocial behavior and controls

<table>
<thead>
<tr>
<th>Anatomical location</th>
<th>Maximum</th>
<th>Cluster</th>
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<tbody>
<tr>
<td></td>
<td>Talairach coordinate</td>
<td>SDM value</td>
</tr>
<tr>
<td>Smaller gray matter volume (individuals with antisocial behavior &lt; controls)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right lentiform nucleus</td>
<td>18, 6, −4</td>
<td>−2.541</td>
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<tr>
<td>Left insula</td>
<td>−40, 8, 10</td>
<td>−2.389</td>
</tr>
<tr>
<td>Left superior frontal gyrus</td>
<td>−10, 62, 26</td>
<td>−2.261</td>
</tr>
<tr>
<td>Larger gray matter volume (individuals with antisocial behavior &gt; controls)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right fusiform gyrus</td>
<td>46, −22, −24</td>
<td>1.385</td>
</tr>
<tr>
<td>Right inferior parietal lobule</td>
<td>38, −30, 42</td>
<td>1.040</td>
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<tr>
<td>Left superior parietal lobule</td>
<td>−36, −68, 44</td>
<td>1.002</td>
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<tr>
<td>Right cingulate gyrus</td>
<td>12, 8, 44</td>
<td>1.001</td>
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<td>Right postcentral gyrus</td>
<td>58, −20, 30</td>
<td>1.001</td>
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SDM, signed differential mapping.

**Fig. 2** Regions of decreases (blue) or increases (red) in regional gray matter volume in individuals with antisocial behavior, compared with controls voxel threshold \( P < 0.001 \). (a) Left frontopolar cortex; (b) left insula; (c) lentiform nucleus; (d) right fusiform.
Yang, 2006; Christensen et al., in press; Michl et al., in press), the structural abnormality may contribute to these dysfunctions. As a number of functional neuroimaging studies of individuals with antisocial behavior have repeatedly shown functional abnormality in the amygdala and OFC/vmPFC (Phelps and LeDoux, 2005; Blair, 2007; Yang et al., 2009; Hyatt et al., 2012), we have predicted GMV reduction in these regions. But contrary to the prediction, the analysis did not show significant GMV reduction in the amygdala and OFC/vmPFC. This dissociation between functional and structural alteration is surprising. A possible explanation for this negative result is the heterogeneity of the participants. We integrated people with several different disorders into the analysis, because all were at higher risk of antisocial behavior. Further, it is thought that people with these disorders share a common neural basis of antisocial behavior. However, some participants with CD and ASPD had a dual diagnosis of psychopathy. The diagnosis of CD and ASPD has also been criticized for over-emphasizing behavioral outcomes (such as criminality) and neglecting core psychological features (Blair, 2007). With this in mind, it is possible that we have integrated individuals with similar behavioral phenotypes but with partially different neural correlates. Another explanation is that functional abnormality derives from abnormality in the white matter instead of the gray matter. As abnormal connectivity between the amygdala and the OFC/vmPFC has been reported in individuals with antisocial behavior (Passamonti et al., 2012), white matter abnormality without GMV reduction may contribute to their well-established functional abnormality.

**Limitations**

There are some methodological considerations in the reported meta-analysis. First, although we have integrated only whole-brain VBM studies in individuals with antisocial behavior, there is considerable heterogeneity between studies, in terms of participants and methodologies. For example, as we discussed above, we may have included studies with individuals with similar phenotypes but different neural or psychological bases for their symptoms. In addition, there is significant diversity in the methodology of imaging between the studies we included, such as smoothing function used and strength of magnetic field. Further, the studies adopted different statistical analyses. Thus, although we used a conservative threshold in our analysis to minimize study heterogeneity, the results should nevertheless be treated with caution. Second, the majority of participants within the integrated studies had psychiatric comorbidity, such as substance abuse or subclinical features of other psychiatric disorders, including depression, anxiety disorder, autism, and attention deficit hyperactivity disorder. It is known that these comorbid conditions have an impact on structure of the frontotemporal cortex (Yamasue et al., 2003, 2004; Aoki et al., 2012a,b,c; Lucantonio et al., 2012). Therefore, it is possible that the abnormal GMV was an artifact of the comorbid psychiatric disorders. In addition, differences in the subjects' behavioral and emotional traits may also affect GMV (Takeuchi et al., 2011; Morishima et al., 2012; Takeuchi et al., in press). We could not conduct sensitivity analysis or meta-regression due to an insufficient number of studies, although our conservative meta-analysis of unbiased studies demonstrated significant abnormalities in GMV. Thus, although we robustly found GMV abnormalities, the functions of which may relate to a psychological trait of individuals with antisocial behavior, we could not directly address the relationship between abnormalities in brain structure and behavior. Third, as non-significant data have a higher possibility of not being published, there exists strong publication bias. In addition, although SDM reconstructs both positive and negative differences in the same map (signed map) (Radua and Mataix-Cols, 2009; Radua

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**Fig. 3** Regions of decreases (blue) or increases (red) in regional gray matter volume in individuals with antisocial behavior, compared with controls voxel threshold P < 0.001. (a) Right inferior parietal lobule; (b) left superior parietal lobule; (c) right cingulate gyrus; (d) right postcentral gyrus.

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et al., 2010), peak-based meta-analyses are based on highly significant data (i.e. $P<0.001$ uncorrected) rather than raw statistical brain maps, and this approach may result in less accurate results.

**CONCLUSION**

In conclusion, the meta-analysis of unbiased whole-brain VBM studies of individuals with antisocial behavior demonstrated significantly abnormal GMV reductions in the FPC and parahippocampal gyrus, including the amygdala, and GMV increases in the right fusiform gyrus and the right inferior parietal lobe. These abnormalities may correspond to deficits in keeping information in the working memory during allocation of attention, emotional processing and inappropriate face information processing in social context. The current analysis emphasized that attention deficit is also an important factor in the pathophysiology of individuals with antisocial behavior.

**Conflict of Interest**

None declared.

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