Psychopathy as a disorder of the moral brain: Fronto-temporo-limbic grey matter reductions demonstrated by voxel-based morphometry

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Received 6 September 2007; revised 14 November 2007; accepted 28 December 2007
Available online 11 January 2008

Major advances have been made in the understanding of the neurobiology of psychopathy in the past years, yet the distribution and extent of neuroanatomical abnormalities underlying the disorder are still poorly known. It is also unclear if different dimensions of the construct of psychopathy (e.g., emotional callousness, antisocial behavior) correspond to structural abnormalities in distinct regions of the brain. We tested the following hypotheses: (1) psychopathy is related to grey matter reductions in regions of the brain that underlie moral conduct and (2) the severity of psychopathy is related to the degree of structural abnormalities. Optimized voxel-based morphometry and the screening version of the Psychopathy Checklist (PCL: SV) were employed to investigate a matched sample of 15 community psychiatric patients with high PCL: SV scores, and 15 healthy normal volunteers. The analyses controlled for total grey matter, white matter and cerebrospinal fluid volumes. Grey matter reductions were observed in the frontopolar, orbitofrontal and anterior temporal cortices, superior temporal sulcus region, and insula of the patients. The degree of structural abnormalities was significantly related to the interpersonal/affective dimension of psychopathy. The pattern of grey matter reductions in patients with high psychopathy scores comprised a distributed fronto-temporal network which plays a critical role in moral sensibility and behavior.

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Keywords: Moral; Limbic; Prefrontal cortex; Orbitofrontal; Psychopathy; Community psychiatric patients; Antisocial behavior; Brain morphometry

Introduction

Psychopathy is a personality disorder defined by a constellation of interpersonal, affective, and behavioral/lifestyle features, including manipulation and deception, grandiosity, shallow emotions, lack of empathy and remorse, an impulsive, irresponsible lifestyle, and the persistent violation of social norms and expectations (Cleckley, 1976; Hare, 2003). The international standard for the assessment of the disorder is the Psychopathy Checklist-Revised (PCL-R) (Book et al., 2006; Hare, 2003). Evidence for the reliability and validity of the PCL-R is extensive (Hare and Neumann, 2005). Antisocial behavior by itself is a nonspecific symptom common to many conditions, so psychopathy and antisocial personality disorder (ASPD, American Psychiatric Association, 1994) are not analogous constructs — while most cases of ASPD do not fulfill the interpersonal and affective criteria for psychopathy (Hare, 2003; Ogloff, 2006) the behavioral features observed in these individuals are best explained by their level of psychopathy (Forth et al., 1996). The profound physical, psychological and financial implications of psychopathy for society are well-documented (Patrick, 2006). The roots of the disorder are unclear, but there is growing evidence that genetic factors are important, that the precursors of adult psychopathy can be observed in early childhood, and that psychopathy is associated with a range of neurobiological abnormalities (Patrick, 2006; Viding et al., 2005).

The first clue that moral conduct can be impaired while leaving general cognition intact came from occasional reports of acquired brain damage causing morally improper behaviors in formerly normal (i.e., productive and socially adjusted) individuals (Macmillan, 2000). Interest in this matter was reawakened by systematic studies of acquired personality changes due to injury mostly, but not exclusively, of the frontal lobes (Eslinger and Damasio, 1985; Saver and Damasio, 1991). By analogy with
developmental psychopathy, such behavioral changes were sub-
subsumed under the label of “acquired sociopathy” (Blair and
Cipolotti, 2000; Eslinger and Damasio, 1985). A review of lesion
studies showed that inferences of social behavior based on
acquired sociopathy have emphasized the prefrontal cortex (PFC)
at the expense of other potential candidates (Moll et al., 2003).
The characterization of a distributed neural basis for psychopathy has
also been hindered because anatomical studies have focused on
relatively large anatomical structures, such as PFC, which harbors
a number of distinct subregions. Furthermore, the full clinical
picture of developmental psychopathy (Cleckley, 1976; Hare,
2003) is seldom reproduced by acquired brain lesions (Raine and
Yang, 2006; Rogers, 2006). In all, the complex manifestations
of psychopathy and the evidence that several brain regions may be
implicated suggest that psychopathy may have a more distributed
neuroanatomical basis than so far believed (Moll et al., 2005;
Raine and Yang, 2006). Consequently, the initial expectations that
acquired sociopathy would provide an encompassing neuroana-
tomical framework for psychopathy may only in part have been
fulfilled. The realization of this fact has redirected the interest of
researchers to the study of psychopathy without a priori assump-
tions on morphological equivalence between acquired sociopathy
and psychopathy proper.

The first carefully controlled investigation on the neuroana-
tomic underpinnings of psychopathy found an 11% reduction of
the volume of the PFC in high psychopathy males living in the
community, most of whom had committed violent crimes, such as
rape and homicide (Raine et al., 2000). An increase in the white
matter (WM) of the corpus callosum and corona radiata was also
related to psychopathy (Raine et al., 2003). Further analyses found
that PFC volume was reduced only in those high psychopathy
males who were arrested for their crimes (Yang et al., 2005). This
subset of individuals also showed volumetric decreases in the
anterior hippocampus (Raine et al., 2004). These authors also
reported an inverse association between PCL-R scores and total
PFC grey matter (GM) volume. Laakso et al. (Laakso et al., 2001)
did not find statistical differences in the volume of prefrontal GM
and WM of incarcerated alcoholic men as compared to normal
controls on MRI, but again their PCL-R scores were inversely
related to the volume of the posterior hippocampus. Dolan et al.
(Dolan et al., 2002b) found a volumetric decrease of the right
temporal lobe in incarcerated men diagnosed by the Antisocial
Personality Questionnaire. Although not specifically sought for,
these volumetric reductions possibly also affected those parts of
the posterior right temporal lobe which are involved in Theory of
Mind mechanisms (Decety and Lamm, 2007). However, another
study by the same authors did not find significant differences in
frontal or temporal lobe volumes in 22 incarcerated individuals
with personality disorders (18 high in psychopathy) compared to
controls (Dolan et al., 2002a).

Regardless of the advances in our understanding of the neuro-
anatomy of psychopathy, we still lack a comprehensive picture of
how the brains of psychopaths differ morphologically from those
of normal people, or from the brains of individuals with other
neuropsychiatric disorders. Although there is some anatomic
evidence of volumetric reductions of PFC (Raine et al., 2000)
and hippocampus (Raine et al., 2004) in psychopathic individuals,
an important characteristic of the studies mentioned above is that
they relied on a subjective delineation of a given anatomical
structure (e.g., PFC), which was then assessed post hoc assuming
intra-regional anatomic uniformity. While the relevance of such

studies is clear when they lead to positive results, they may
underestimate the role of additional brain regions, as well as of
sub-regions within regions of interest. Conclusions from these
studies may be incomplete in view of the possibility that the
cerebral abnormalities underlying psychopathy are distributed
across distant regions, and that their boundaries do not coincide
with traditional anatomical landmarks or discrete cytoarchitectonic
areas.

In an attempt to make sense of the plethora of experimental data,
Kiehl suggested that psychopathy is a disorder of the paralimbic
system (Kiehl, 2006). His suggestion was inspired by observations
that a large set of abnormal behavioral and laboratory results could
be traced to malfunction of a belt of cortex made up of less than six
cell layers (the “mesocortex” of classical anatomists), which
encircles the upper brain stem as it enters the cerebral hemispheres.
Notwithstanding the merits of Kiehl’s proposal, the concept of
psychopathy as a paralimbic, or mesocortical, disorder is at one time
too broad and too restrictive. On the one hand, it fails to specify
which limbic structures are critical for psychopathy. On the other
hand, certain brain regions which may play important roles in the
regulation of social conduct, such as the frontopolar cortex (FPC)
and the superior temporal sulcus region (STS), are not included in
the model because they fall outside the anatomical boundaries of
the paralimbic system.

This brief review indicates that a coherent neuroanatomical
account of psychopathy should draw on behaviorally meaningful
anatomical data without ignoring anatomical abnormalities of the
disorder, as well as those that are already known to give rise to
acquired sociopathy. Achievement of this goal requires the use of
quantitative and statistical anatomical techniques that minimize
observer bias and allow the formulation of hypotheses based on
plausible theoretical models. For this reason we used optimized
voxel-based morphometry (VBM) to test specific hypotheses con-
cerning psychopathy inspired by a recently formulated model of the
neural basis of moral behavior (Moll et al., 2005). Optimized VBM
is an in vivo method of regional volumetric analysis that reduces
biases involved in arbitrary definitions of anatomical boundaries
through the assessment of quantitative differences on a voxel-wise
basis (Good et al., 2001). We hypothesized that (i) patients high in
psychopathy display volumetric reductions in a set of brain re-
gions that underpin moral behavior (Moll et al., 2005), which
includes the basal forebrain-hypothalamus, frontal and temporal
poles, STS region and orbitofrontal cortex (OFC), and (ii) the
degree of volumetric reductions in these regions reflects the severity
of psychopathy, particularly its interpersonal/affective dimension.
The latter hypothesis is in line with recent evidence that both
the PCL-R (Guay et al., 2007) and the PCL: SV (Walters et al., 2007)
and their components are underpinned by a dimensional construct.
To minimize the confounding effects of institutionalization only
patients who had never been convicted were included. Because our
focus is anatomic, the large body of knowledge on functional
neuroimaging and electrophysiology on psychopaths will be
mentioned only if they substantially add to the understanding of the
morphological findings.

Methods

Subjects and materials

Patients were part of a larger group of 50 patients (De Oliveira-
Souza et al., in press) with a range of neurological and neuro-
psychiatric disorders who were brought to consultation by relatives and acquaintances in search of a diagnosis, treatment, or counseling for a variety of emotional and behavioral problems. These problems were generally characterized by chronic and recurrent antisocial behaviors and attitudes not necessarily criminal in nature. Each satisfied DSM-IV adult criteria for ASPD and was assessed with a derivative of the PCL-R, the PCL: SV (Hart et al., 1995). Fifteen of these patients (8 men, 7 women) volunteered for the present study. Most came from stable middle-class backgrounds. Many held, at one time or another, skilled or professional positions, but their occupational history was erratic and unstable. They lived in the community and eventually became a focus of medical attention due to chronic and recurrent misbehaviors which, although extremely upsetting to those with whom they lived, did not result in criminal prosecution. None of these patients exhibited clinical evidence of neurological impairment. The control group included 15 normal volunteers (NV; 8 men, 7 women) without a history of neurological or psychiatric disorders, or serious misconduct. Patients and NV were carefully matched on gender, age, and education (Table 1). None of them had a history of head trauma with loss of consciousness, chronic systemic diseases (in particular, kidney, respiratory, hepatic, cardiac or thyroid diseases), and past or current illness associated with psychosis. No participant fulfilled formal diagnostic criteria for a major depressive episode or for a generalized anxiety or panic disorder (APA 1994). The research project was approved by the LABS-D’Or Institutional Review Board. Participants provided written informed consent before entering the study. They were not paid for their participation, but were given digital or hardcopy prints of their structural brain scans free of charge.

**PCL: SV, cognitive, drug dependence and socio-occupational assessments**

The PCL: SV is widely used in non-forensic contexts, both as a screen for psychopathy and as a reliable and valid “stand-alone” instrument. It consists of 12 items (scored 0, 1, or 2) grouped into two correlated (around .5) sets or factors of six items each. Factor 1 measures Interpersonal and Affective traits (superficial, grandiose, deceitful; lacks remorse, lacks empathy, doesn’t accept responsibility), whereas Factor 2 measures Lifestyle and Antisocial features (impulsive, lacks goals, irresponsible; poor behavioral controls, adolescent antisocial behavior, adult antisocial behavior). PCL: SV assessments were based on detailed interviews and information provided by at least one collateral source acquainted with the patient, usually a spouse or a close relative. In the sample from which the patients in this study were taken, the intraclass correlation (average measure reliability) was .92, .86, and .96 respectively for Total, Factor 1, and Factor 2 scores. The mean PCL: SV score for each group is presented in Table 1. The patient scores generally were high, with many approaching or exceeding the PCL: SV cut-score (18) commonly used for psychopathy in a research context. The Mini-Mental State Exam (MMSE) and the Wisconsin Cart Sorting Test (WCST) were used as measures of global cognitive status and of executive performance, respectively. Three WCST scores were computed: number of completed categories (a measure of overall success on the test), number of perseverative errors (a measure of the ability to shift attention across perceptual dimensions) and number of failures to maintain set (a measure of the ability to shift attention within perceptual dimensions). The WCST main scores have a fair to good correlation with standard measures of IQ (Heaton et al., 1993) and were used as surrogates for general intelligence in our subjects. Alcohol and substance abuse were diagnosed according to DSM-IV criteria. For ethical reasons, NV were not asked about substance use or abuse. Overall psychological, social, and occupational functioning was assessed with the Global Assessment of Functioning (GAF) (Spitzer et al., 2000).

### Neuroimaging procedures

#### Acquisition protocol

MRI scans were obtained at the Department of Radiology at Barra D’or Hospital, using a 1.5 Tesla MR scanner (Siemens Medical Systems, Erlangen, Germany), with a standard quadrature head coil. High-resolution T1-weighted three-dimensional structural MRI scan was acquired using a MPRAGE pulse sequence (TR=9.7 ms, TE=4 ms, TI=300 ms, flip angle=12°, field of view=256 mm, slice thickness=1.25 mm, matrix size=256×256) yielding 128 sagittal slices with a in-plane pixel size resolution of 1 mm×1 mm.
**Image processing**

Data pre-processing and statistical analysis of structural T1 images were performed with SPM2 (Wellcome Department of Imaging Neuroscience, London, UK; [http://www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)). The VBM toolbox was used to implement the optimized voxel-based morphometry protocol, which was performed in two stages. First, customized templates were created according to the following steps: segmentation in native space, linear normalization of the GM partitions to the MNI GM template, application of the ensuing deformation parameters to native T1 images, segmentation and creation of whole-brain T1, GM, WM, and cerebrospinal fluid (CSF) mean images, and Gaussian smoothing with FWHM=8 mm. In the second stage, images were segmented in native space and the GM partitions were non-linearly normalized to the customized GM template, with (total volume preservation) and without (concentration or density preservation) modulation. Following the application of the obtained deformation parameters to native T1 images, images were segmented to obtain GM partitions and smoothed (FWHM=12 mm). Group differences in GM concentration (GMC) and in absolute amount (volume) of GM (GMV) were assessed subsequently (see Appendix for details).

**Statistical analyses**

Statistical group analysis was performed on a voxel-by-voxel basis using the General Linear Model. Regionally-specific differences in GMC and GMV between NV and patients were then assessed using analysis of covariance. For each contrast, SPMs were computed on a voxel-by-voxel basis to test for morphological differences between groups. Results were initially thresholded at \( p<0.005 \), uncorrected for multiple comparisons, using a threshold of 5 contiguous voxels to protect against type I errors. In addition to the whole-brain results, uncorrected effects for *a priori* regions

![Fig. 1. Brain regions showing grey matter reductions in patients with high psychopathy scores compared to normal healthy volunteers. Results are displayed at \( p<.005 \) (uncorrected) for the whole-brain, with a cluster threshold of 5 voxels. *A priori* regions of interest that additionally survived Small Volume Correction for multiple comparisons are highlighted, and included the anterior temporal cortex (aTC), medial orbitofrontal cortex (mOFC), lateral orbitofrontal cortex (latOFC), frontopolar cortex (FPC) and the superior temporal sulcus region (STS).](image-url)
Table 3

<table>
<thead>
<tr>
<th>Anatomical region</th>
<th>Cluster (k)</th>
<th>p (FDR-corr), indiv ROI</th>
<th>p (FDR-corr), all ROI</th>
<th>T</th>
<th>Z</th>
<th>p (unc)</th>
<th>Talairach (x, y, z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial OFC (BA10/11)</td>
<td>76</td>
<td>0.007</td>
<td>0.055</td>
<td>4.11</td>
<td>3.59</td>
<td>0.001</td>
<td>−8</td>
</tr>
<tr>
<td>FPC (BA10/11)</td>
<td>89</td>
<td>0.001</td>
<td>0.003</td>
<td>4.38</td>
<td>3.77</td>
<td>0.001</td>
<td>−32</td>
</tr>
<tr>
<td>aTC (BA20)</td>
<td>20</td>
<td>0.025</td>
<td>0.104</td>
<td>3.08</td>
<td>2.82</td>
<td>0.002</td>
<td>−50</td>
</tr>
<tr>
<td>STS (BA21/22)</td>
<td>101</td>
<td>0.002</td>
<td>0.022</td>
<td>4.52</td>
<td>3.87</td>
<td>0.001</td>
<td>51</td>
</tr>
<tr>
<td>STS (BA21/22)</td>
<td>122</td>
<td>0.002</td>
<td>0.019</td>
<td>4.40</td>
<td>3.79</td>
<td>0.001</td>
<td>−53</td>
</tr>
<tr>
<td>Insula</td>
<td>80</td>
<td>0.007</td>
<td>0.050</td>
<td>3.53</td>
<td>3.17</td>
<td>0.001</td>
<td>32</td>
</tr>
<tr>
<td>Insula</td>
<td>75</td>
<td>0.008</td>
<td>0.063</td>
<td>3.42</td>
<td>3.09</td>
<td>0.001</td>
<td>−36</td>
</tr>
</tbody>
</table>

Uncorrected p values [p(unc)], corrected p values (SVC-FDR correction, voxel level) for individual ROIs [p(FDR-corr), indiv ROI], and corrected p values (SVC-FDR, voxel level) for the total volume of all 18 individual ROIs [p(FDR-corr), all ROI] are provided. The Talairach coordinates and the T and Z values of the local maxima, as well as the cluster sizes [Cluster (k)], are also provided. SVC, Small Volume Correction; FDR, false discovery rate; OFC, orbitofrontal cortex; aTC, anterior temporal cortex; FPC, frontopolar cortex; STS, superior temporal sulcus region; BA, Brodmann areas.

of interest (ROIs), defined on the basis of the brain regions previously implicated in moral behavior (Moll et al., 2005), are reported. Correction for multiple comparisons was additionally performed within each a priori ROI using Small Volume Correction (SVC), using the false discovery rate method (FDR). A priori defined ROIs included the FPC, supracingulate dorsomedial PFC, anterior cingulate cortex, medial and lateral OFC, subgenual/posterior OFC, anterior temporal cortex, STS, basal forebrain/hypothalamus, amygdala and anterior insula.

Because results from GMV and GMC analyses were largely overlapping, only the GMC results will be reported. Multiple regression analyses were performed to test for parametric changes in GMC within the patient group. PCL: SV Factor 1 and 2 scores were entered as regressors, using total intracranial volumes as covariates of no interest. An explicit mask was employed to restrict the regression analyses to GM voxels surviving a p < .05 (uncorrected) in the categorical analysis (patients vs. NV). Correction for multiple comparisons (SVC) was additionally performed within each a priori ROI in which significant effects were detected, using the FDR method. Peak voxel values corresponding to suprathreshold local maxima for a priori ROIs were extracted, and regression analyses were performed again for further verification and generation of regression plots (SPSS Inc., Chicago, USA, http://www.spss.com). Coordinates of significant suprathreshold local maxima were converted from MNI to Talairach space (Talairach Daemon, http://ric.uthscsa.edu/projects/talairachdaemon.html). For both categorical and dimensional VBM analyses, statistical effects are also reported according to an additional, stricter correction for multiple comparisons procedure. This was done by adding the volumes of all 18 individual a priori spherical ROIs (Table 2), and estimating the radius of a sphere having this total volume (radius = 17.7 mm). The SVC procedure was performed again for each a priori ROI using this large radius, and the corresponding FDR-corrected values at the voxel level were derived.

Results

As intended, there were no significant differences between groups in gender, age, education, handedness, global cognitive status, and executive performance (Table 1). The difference between groups was significant for Total, Factor 1, and Factor 2 PCL: SV scores. Although 6 patients (3 men and 3 women) fulfilled diagnostic criteria for alcohol and marijuana abuse, they did not differ from the remaining cases in any of the variables of interest (p ≥ .17). The scores on the MMSE and on the WCST for each group were consistent with normal cognitive and executive functioning according to published norms for the Brazilian population (Nitrini et al., 2004). Scores on the GAF were in general abnormally low for patients (mean = 33), consistent with the severity of the disorders that brought them for consultation.

Direct group comparisons controlling for total intracranial volume with covariance analysis showed that GMC was decreased in patients in an array of brain regions that included the FPC (L>R), lateral OFC (R>L), left medial OFC, STS (L>R), mid-anterior insula (R>L), and left anterior temporal cortex (Fig. 1; Table 3; see also Table 5 in the Appendix for whole-brain, uncorrected results).

Discussion

The neuroanatomical correlates of psychopathy have eluded investigators until quite recently, when regional changes for the
first time demonstrated by in vivo anatomic techniques in the brains of psychopaths (Raine and Yang, 2006). These pioneering studies were constrained by the methods employed in the measurement of regional cerebral volumes and by the theoretical constructs used to account for their findings, which tend to stress the relevance of some brain structures (PFC, hippocampus, amygdala) at the expense of others that may also be relevant (e.g., STS). The present study attempted to circumvent some of these shortcomings by using a comprehensive framework for the neuroanatomical organization of moral cognition and behavior (Moll et al., 2005). Briefly, this model proposes that a set of related brain regions is preferentially dedicated to the binding of emotional, motivational and cognitive events into “event–feature–emotion complexes”, which are molded by situational context, agency and the current state of the organism, enabling the emergence of moral sentiments, values and long-term social goals. These brain regions include the basal forebrain–hypothalamus, frontal and temporal poles, STS and OFC. An additional methodological advantage was provided by using VBM as an investigative tool, as it avoids the need for arbitrary definitions of anatomical boundaries, thus minimizing subjective biases. The main findings of the study can be summarized as follows: (i) adult patients with high psychopathy scores living in the community showed a pattern of GM decreases in a set of paralimbic regions, as well as in the FPC and STS; viewed from a rostrocaudal direction, the abnormal structures included the FPC bilaterally, left medial OFC, postero-lateral OFC bilaterally, left anterior temporal cortex, anterior insula bilaterally, and the mid- and posterior STS region bilaterally; (ii) the GM decreases occurred against a background of normalized total grey and white matter, and CSF volumes; (iii) these results were not explained by gender, age, education, global cognitive status, and cannot be attributed to chronic institutionalization; (iv) The single best predictor of the regional GM decreases in the patients was their score on PCL: SV Factor 1; and (v) The magnitude of the GM decreases in several of these structures was inversely related to PCL: SV Factor 1, but not to PCL: SV Factor 2, scores.

The three FPC regions that showed GM decreases in psychopathy – the medial and lateral OFC, and the FPC – have been directly implicated in the regulation of social conduct. Abnormal OFC function has been inferred from studies showing that psychopathy is related to deficits in smell identification and behavioral control (e.g., GONO-GO, mazes) even in the absence of perseverative tendencies (Lapiere et al., 1995). Moreover, both psychopathy and OFC damage are related to defective electrodermal responding (Birbaumer et al., 2005). Patients with acquired sociopathy due to VMPFC damage and those with psychopathy likewise fare poorly on the earlier (Newman et al., 1987) and the more recent versions of gambling tasks (Bechara et al., 2000; Lösel and Schmucker, 2004; Schmitt et al., 1999), emphasizing their phenomenological and mechanistic relationships. These abnormalities may be traced further to discrete regions within the OFC (Mitchell et al., 2002; Price, 1999), as suggested by instances of acquired sociopathy in which the lesion is limited to the ventromedial OFC (VMPFC: BA 12, 25, and caudal 11). This raises the question of whether additional damage to the lateral OFC (BA 11/47) produces an entirely different pattern of character change or only increases the severity of ventromedial sociopathy (Mega et al., 1997).

The FPC is the second brain region most often implicated in cases of acquired sociopathy that more closely resemble developmental psychopathy (Eslinger et al., 1992). Functional neuroimaging studies have shown that the FPC is involved in “branching”, a cognitive mechanism by which long-term goals are held in mind as nested subgoals are concurrently implemented (Koechlin et al., 1999). However, this may not be the exclusive, nor even the most relevant, contribution of the FPC to behavior. The strong engagement of the FPC by moral judgments (Heekeren et al., 2003; Moll et al., 2001) indicates that it also represents long-term social goals and values (Moll et al., 2006; Moll et al., 2005). One possible manifestation of FPC impairment in psychopathy is the recurrent violation of moral norms in favor of immediate consummatory behaviors (“gratification”). Further studies are needed to see whether this results from an impairment of the ability to mentally travel in time (Okuda et al., 2003) or to a primary difficulty in delaying gratification (Hare, 1966).

The temporal lobes have been less well studied than the frontal lobes in psychopathy. One study found reduced GM volumes of the right temporal lobe in conduct disordered adolescents (Kruesi et al., 2004), but the small sample size precluded inferences on how this abnormality related to the clinical features. We found significant changes in two behaviorally salient regions in the temporal lobe, the anterior temporal isocortex and the STS region. The anterior temporal isocortex stands among the most affected regions in cases of semantic dementia and has been directly implicated in the genesis of antisocial behaviors (Bozeat et al., 2000; Mendez et al., 2000). Supporting this notion, a recent functional imaging study showed that the anterior temporal cortex plays a specific role in representing social conceptual knowledge (Zahn et al., 2007). In our sample GM reductions were observed within the left anterior temporal isocortex. Further studies are needed to clarify whether these changes are related to the semantic and electrophysiological abnormalities described in psychopathy (Kiehl et al., 2004). Complementarily, there is a large body of evidence showing that the STS is critical for decoding social cues, including inferences on agency and intentionality, as part of an extended circuitry involved in “Theory of Mind” (Decety and Jackson, 2004), and subtle impairments of Theory of Mind abilities have in fact

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**Table 4**

<table>
<thead>
<tr>
<th>Cluster (k)</th>
<th>p (FDR-corr), indiv ROI</th>
<th>p(FDR-corr), all ROI</th>
<th>T</th>
<th>Z</th>
<th>p(unc)</th>
<th>Talairach (x, y, z)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior medial OFC/SGC (BA11/25)</td>
<td>76</td>
<td>0.008</td>
<td>0.035</td>
<td>3.56</td>
<td>2.88</td>
<td>0.002</td>
</tr>
<tr>
<td>FPC (BA10)</td>
<td>11</td>
<td>0.018</td>
<td>0.071</td>
<td>3.70</td>
<td>2.96</td>
<td>0.002</td>
</tr>
<tr>
<td>FPC (BA10)</td>
<td>5</td>
<td>0.022</td>
<td>0.115</td>
<td>3.08</td>
<td>2.59</td>
<td>0.005</td>
</tr>
<tr>
<td>STS (BA21/22)</td>
<td>128</td>
<td>0.003</td>
<td>0.025</td>
<td>4.80</td>
<td>3.52</td>
<td>0.001</td>
</tr>
<tr>
<td>STS (BA21/22)</td>
<td>93</td>
<td>0.005</td>
<td>0.021</td>
<td>5.01</td>
<td>3.61</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Uncorrected p values [p(unc)], corrected p values (SVC-FDR correction, voxel level) for individual ROIs [p(FDR-corr), indiv ROI], and corrected p values (SVC-FDR, voxel level) for the total volume of all 18 individual ROIs [p(FDR-corr), all ROI] are provided. The Talairach coordinates and the T and Z values of the local maxima, as well as the cluster sizes [Cluster (k)], are also provided. SVC, Small Volume Correction; FDR, false discovery rate; OFC, orbitofrontal cortex; SGC, subgenual cortex; FPC, frontopolar cortex; STS, superior temporal sulcus region; BA, Brodmann areas.
Fig. 3. Correlations of PCL: SV Factor 1 scores (interpersonal/affective dimension) and regional grey matter reductions in medial posterior orbitofrontal/subgenual cortex (MOFC), left frontopolar cortex (FPC), and left STS in patients with high psychopathy scores.
been demonstrated in psychopathic individuals (Dolan and Fullam, 2004). Future studies are also needed to clarify the relationships between specific “mind-reading” abilities and psychopathy.

The mid-insula, which was bilaterally affected in our cases, is responsible for re-mapping first-order somatic states primarily conveyed by the visceral nerves to the dorsal pons (Critchley et al., 2001). Peripheral autonomic denervation is associated with GM decreases in the anterior insula (Critchley et al., 2003), but, at least in adults, autonomic de-afferentation alone does not result in deficits in social and motivational functioning (Heims et al., 2004), suggesting that any role of the insular changes in the dissociative symptoms of psychopathy must be sought outside the sphere of insular modulation of visceral function. The affected insular region in our cases is a major convergence zone from cortical motor, somato-sensory and associative areas, which are channelled from the insula into basal forebrain structures (Mufson et al., 1981). Bilateral insular damage would be in a strategic position to disrupt the integration of higher-order visceral and associative processes with fundamental bodily states (Singer et al., 2004).

Remarkably, an even more restricted set of regions was related to a core feature of psychopathy, a proverbial “lack of empathy” (Cleckley, 1976). These structures comprised the VMPFC (posterior gyrus rectus and subgenual cortex), the FPC and the STS. In particular, this part of VMPFC is essential for the enactment of prosocial behaviors driven by feelings of empathy and altruism. In a recent fMRI study (Moll et al., 2006) in which volunteers were allowed to choose between retaining a given amount of real cash (self-rewarding choice) or donating it to a charitable institution (altruistic choice), keeping the money was associated with activation of several basal forebrain regions that belong to the reward system. These basal forebrain regions were equally activated when they gave away the money. However, in this case, the VMPFC was additionally engaged. The VMPFC region activated in this study was mainly represented by the subgenual cortex (Moll et al., 2006). Because the subgenual cortex is also damaged in patients with severe acquired sociopathy (who tend to adopt selfish modes of behavior in morally conflicting situations), we believe that the subgenual cortex is critical for attachment and interpersonal cooperation motivated by empathy and altruism. This hypothesis gains further support from the high receptor concentrations in this region for neuropeptides such as oxytocin (Freedman et al., 2000; Young and Wang, 2004), which are known to enhance trust and cooperation among humans (Zak et al., 2004).

Our findings naturally bring us back to the question of the extent to which the patterns of damage in acquired sociopathy may explain what is already known in psychopathy. They suggest that, from an anatomical point of view, acquired sociopathy and psychopathy do share some characteristics, an injury of the VMPFC. However, our results also indicate that the brain regions that are affected in psychopathy go far beyond the VMPFC. This discrepancy possibly explains why acquired sociopathy and psychopathy are not phenomenologically equivalent. Given the distributed organization of the neural structures which were found to be abnormal in acquired sociopathy and psychopathy, the patterns of damage in acquired sociopathy may explain variations in the phenomenology of psychopathy.

An even more pressing issue concerns the functional state of the regions showing volumetric decreases. Without confirmatory studies on the microscopic anatomy of regions showing abnormalities in optimized VBM images (Silani et al., 2005), interpretations concerning structure-function relationships based on volumetric decreases are, for the time being, informed guesses at best. Although we might suppose that regions showing anatomical changes are

<table>
<thead>
<tr>
<th>Anatomical region</th>
<th>Brodmann areas (BA)</th>
<th>Cluster (k)</th>
<th>T</th>
<th>Z</th>
<th>p(unc) vs. normal healthy volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPC/medial OFC</td>
<td>BA 10/11</td>
<td>527</td>
<td>5.31</td>
<td>4.36</td>
<td>0.001 −38 48 −12</td>
</tr>
<tr>
<td>Medial OFC</td>
<td>BA 11</td>
<td>74</td>
<td>3.64</td>
<td>3.26</td>
<td>0.001 16 52 −14</td>
</tr>
<tr>
<td>Lateral OFC</td>
<td>BA 47</td>
<td>160</td>
<td>3.95</td>
<td>4.48</td>
<td>0.001 22 13 −17</td>
</tr>
<tr>
<td>Ventral striatum (putamen)</td>
<td>−</td>
<td>(within cluster above)</td>
<td>3.14</td>
<td>2.88</td>
<td>0.002 18 9 −9</td>
</tr>
<tr>
<td>Lateral OFC</td>
<td>BA 47</td>
<td>78</td>
<td>3.8</td>
<td>3.37</td>
<td>0.001 −28 19 −16</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>BA 9</td>
<td>50</td>
<td>3.95</td>
<td>3.48</td>
<td>0.001 −20 40 33</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>BA 6</td>
<td>115</td>
<td>3.38</td>
<td>3.06</td>
<td>0.001 −10 14 55</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>BA 9</td>
<td>26</td>
<td>3.34</td>
<td>3.03</td>
<td>0.001 44 10 38</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>BA 6</td>
<td>137</td>
<td>3.48</td>
<td>3.14</td>
<td>0.001 −42 6 42</td>
</tr>
<tr>
<td>Ventral post-central gyrus</td>
<td>BA 43</td>
<td>97</td>
<td>3.63</td>
<td>3.24</td>
<td>0.001 −57 11 15</td>
</tr>
<tr>
<td>Caudate head</td>
<td>−</td>
<td>38</td>
<td>3.26</td>
<td>2.96</td>
<td>0.002 20 18 10</td>
</tr>
<tr>
<td>STS</td>
<td>BA 21/22</td>
<td>269</td>
<td>4.52</td>
<td>3.87</td>
<td>0.001 51 −20 −2</td>
</tr>
<tr>
<td>STS</td>
<td>BA 22</td>
<td>242</td>
<td>4.4</td>
<td>3.79</td>
<td>0.001 −53 25 0</td>
</tr>
<tr>
<td>Supramarginal/angular gyri</td>
<td>BA 7/39/40</td>
<td>227</td>
<td>4.68</td>
<td>3.97</td>
<td>0.001 −55 −41 33</td>
</tr>
<tr>
<td>Supramarginal/angular gyri</td>
<td>BA 39/40</td>
<td>799</td>
<td>4.95</td>
<td>4.14</td>
<td>0.001 55 −51 27</td>
</tr>
<tr>
<td>Insula</td>
<td>BA 13</td>
<td>572</td>
<td>5.31</td>
<td>4.36</td>
<td>0.001 −34 −20 18</td>
</tr>
<tr>
<td>Insula</td>
<td>BA 13</td>
<td>160</td>
<td>3.42</td>
<td>3.09</td>
<td>0.001 −36 2 9</td>
</tr>
<tr>
<td>Posterior cingulate gyrus/precuneus</td>
<td>BA 31</td>
<td>70</td>
<td>4.02</td>
<td>3.52</td>
<td>0.001 −10 −21 43</td>
</tr>
<tr>
<td>Inferior temporal gyrus (aTC)</td>
<td>BA 20/21</td>
<td>47</td>
<td>3.42</td>
<td>3.09</td>
<td>0.001 −55 −11 −20</td>
</tr>
<tr>
<td>Inferior temporal gyrus (aTC)</td>
<td>BA 20/21</td>
<td>21</td>
<td>3.08</td>
<td>2.82</td>
<td>0.002 −50 −2 −32</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>BA 37</td>
<td>23</td>
<td>3.58</td>
<td>3.21</td>
<td>0.001 −50 −62 7</td>
</tr>
<tr>
<td>Middle occipital gyrus</td>
<td>BA 19</td>
<td>148</td>
<td>5.03</td>
<td>4.19</td>
<td>0.001 −38 −79 11</td>
</tr>
</tbody>
</table>

Uncorrected p values (p(unc)) at the voxel level are provided. The Talairach coordinates and the T and Z values of the local maxima, as well as the cluster sizes [Cluster (k)], are also provided. OFC, orbitofrontal cortex; aTC, anterior temporal cortex; FPC, frontopolar cortex; STS, superior temporal sulcus region.
dysfunctional and that such impairment is causally related to at least some core symptoms of psychopathy, it is not yet possible to tell if that impairment interferes with all functions of these areas more or less equally, or if some degree of selectivity is in order. Our own unpublished data suggests that the latter hypothesis is closer to the truth. For example, a subset of our patients was tested for semantic access to words and pictures with the Pyramids and Palm Trees Test (PPTT) and showed no abnormalities (Howard and Patterson, 1992). The PPTT is typically abnormal in patients with semantic dementia, in whom the left superior temporal gyrus is usually affected earlier than other brain regions (Jefferies and Lambon Ralph, 2006). Incidentally, this was one of the regions that showed significant volumetric decreases in our patients.

Some additional caveats and limitations of our study deserve consideration. As stated in the preceding paragraph, discrete dimensions of psychopathy may bear more direct relationships with different sets of structures, a hypothesis that may directly be tested in future studies. Furthermore, there is evidence from normal human anatomy that most cortical areas found to be abnormal in psychopathy are heavily interconnected anatomically, an aspect that was not explored here but that needs to be addressed in future investigations using diffusion tensor imaging (DTI) and tractography. Although we did not find any clear effects of substance abuse in our patients, this remains an open issue. Lack of statistical power may have obscured any possible cerebral change due to drug addiction. In view of the complex interactions that are known to take place between psychopathy and chronic substance abuse (Kessler et al., 2005), we would expect that substance abuse exerted a modifying influence on the neuroanatomical changes that may be common to psychopathy. Another important point is to what degree intelligence might have influenced our findings. The lack of statistical differences between controls and patients on the MMSE and on the WCST herein reported should not discourage a more comprehensive assessment of intelligence in future studies. This issue assumes further relevance in view of recent VBM findings. The lack of statistical differences between controls and patients on the MMSE and on the WCST herein reported should not discourage a more comprehensive assessment of intelligence in future studies. This issue assumes further relevance in view of recent VBM findings. The lack of statistical differences between controls and patients on the MMSE and on the WCST herein reported should not discourage a more comprehensive assessment of intelligence in future studies. This issue assumes further relevance in view of recent VBM findings. The lack of statistical differences between controls and patients on the MMSE and on the WCST herein reported should not discourage a more comprehensive assessment of intelligence in future studies. This issue assumes further relevance in view of recent VBM findings.

Financial disclosure

Robert D. Hare, who co-authors the paper, receives royalties from the sale of the PCL: SV, the internationally established standard measure of psychopathy in community settings. Ricardo de Oliveira-Souza, Ivaneti E. Bramati, Fátima Azevedo Ignácio, Griselda J. Garrido, Fernanda Tovar-Moll and Jorge Moll reported no biomedical financial interests or potential conflicts of interest.

Acknowledgments

The authors are grateful to Mr. José Ricardo Pinheiro and Mr. Jorge Baçal (Osvaldo Cruz Institute Library) for providing invaluable help in the retrieval of the relevant bibliography, and to Drs. Pedro A. Andreiuolo, Paulo Bernandes, Ricardo Pinheiro, Ricardo Gattass, and Andrea S. de Souza for their help in various stages of this project. ROS is indebted to Professor Omar da Rosa Santos (Head of the Internal Medicine Department, Gaffrée e Guinle Hospital) for institutional support. This research was supported by the LABS-D’Or Hospital Network, by PRONEX-cnq (JM), and by FAPESP, project #03/11794-6 (GJG).

Appendix

Behavioral: PCS-SV

PCL: SV. This is a 12-item derivative of the PCL-R developed for use in the MacArthur Risk Assessment study (Steadman et al., 2000). It is conceptually and empirically related to the PCL-R and is widely used in non-forensic contexts, both as a screen for psychopathy (Guy and Douglas, 2006) and as a reliable and valid “stand-alone” instrument, particularly in countries outside of North America (Urbanik et al., 2007). Recent confirmatory factor analyses of the PCL: SV have yielded a correlated 4-factor solution (Neumann et al., 2006) consistent with the factor structure of the PCL-R. The factors are labeled as: Interpersonal (Superficial, Grandiose, Deceitful); Affective (Lacks remorse, Lacks empathy, Doesn’t accept responsibility for actions); Lifestyle (Impulsive, Lacks goals, Irresponsible); and Antisocial (Poor behavioral control, Adolescent antisocial behavior, Adult antisocial behavior). The Interpersonal and Affective factors and the Lifestyle and Antisocial factors comprise, respectively, the original Factors 1 and 2 described in the PCL: SV Manual. In the present sample, the correlation between Parts 1 and 2 was .57, similar to the values described in the Manual.

Using information provided by semi-structured interviews and available collateral sources, each item is scored on a 3-point scale, ranging from 2 (item is consistent with the individual’s behavior) through 1 (item applies in some respects) to 0 (item is not at all descriptive of the individual). In the present study, PCL: SV assessments were based on detailed interviews and information provided by at least one collateral source acquainted with the patient, usually a spouse or close relative.

The mean PCL: SV scores for each group are presented in the Table 1. The difference between groups was significant (p < .001) for Total, Factor 1, and Factor 2 scores. The mean Total score for the patients was 17.8. A score of 18 or higher was obtained by 9 of 15 patients (5 of 8 males; 4 of 7 females). To put these findings into perspective, they are higher than the mean scores of the criminal (13.0–16.4) and forensic psychiatric (13.7–16.6) samples described in the PCL: SV Manual, and much higher than the mean score of the community sample (2.7) used in the MacArthur study of mental disorder and violence (Monahan et al., 2001). Less than 1% of those in the MacArthur community sample had a PCL: SV score of 18 or higher.

Neuroimaging procedures

MRI image acquisition

A localizer sequence (GRE-T1 weighted, TR=15 ms, TE=6 ms) with 4 slices on each orthogonal plane was obtained for correct
alignment according to the anterior-posterior commissural (AC-PC) plane. High-resolution T1-weighted three-dimensional structural MRI scans were acquired using a MPRAGE (Magnetization Prepared Rapid Acquisition Gradient Echo) pulse sequence (TR=9.7 ms, TE=4 ms, TI=300 ms, flip angle=12°, field of view=256 mm, slice thickness=1.25 mm, matrix size=256×256) yielding 128 sagittal slices with a slice thickness of 1 mm and a matrix size of 1 mm.

**Image processing**

The optimized voxel-based morphometry protocol (Good et al., 2001) was implemented using a semi-automated script (VBM2-v1.18, Christian Gaser, Department of Psychiatry, University of Jena, Jena, Germany; http://dbm.neuro.uni-jena.de/home/) within SPM2 (Statistical Parametric Mapping — Functional Imaging Laboratory, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm), running on Matlab 6.5, Release 13 (The MathWorks, Natick, MA, USA).

The optimized protocol consists of recursive spatial processing steps that improve image registration and segmentation by incorporating automated removal of nonbrain voxels; image registration to customized stereotactic study-specific templates; application of tissue-specific normalization parameters (which provides a better normalization for GM); and an optional modulation step to incorporate volume changes during normalization (consisting of a multiplication of GM/WM voxel values by the Jacobian determinants). This protocol is implemented in two stages: (1) creation of customized templates based on Montreal Neurological Institute (MNI) templates and (2) processing the native images using the newly created templates. Customized templates of whole-brain structural T1 images and the GM WM and CSF priors were derived from both control and patient groups to reduce bias in spatial normalization related to group differences. This is important because (1) the contrast of the MRI images might differ from the SPM templates, as each scanner can introduces specific non-uniformities in image intensity and inhomogeneities in T1 field, and (2) the demographics of the control population may differ from that used to generate the SPM templates. The optimized VBM approach here employed affords intergroup comparisons with greater biological plausibility than simply using the MNI templates and priors.

To generate the customized stereotactic templates, each structural T1 image was segmented in native space. The ensuing GM partition was linearly normalized to the MNI SPM GM template using trilinear interpolation. The obtained deformation parameters were then applied to the original images in native space, which were subsequently segmented using SPM priors. Mean images of GM, WM and CSF partitions, as well as whole-brain images, were created. Finally, smoothing with a 8 mm isotropic Gaussian kernel was applied to account for individual differences.

On a second stage, each image was segmented in native space using the customized templates as priors. Then, the GM partition was normalized to the customized GM template using affine and 7×7×7 non-linear basis functions. The obtained deformation parameters were applied to the original data in native space. The normalization step was implemented with and without modulation to assess differences in GM concentration (GMC) and volume (GMV), respectively. The modulation step accounts for volumetric brain changes that are a consequence of the expansion or reduction produced by non-linear spatial normalization, preserving the total amount of GM that was present before the deformation. The normalized images were segmented and the GM partitions smoothed with an isotropic Gaussian kernel with FWHM=12 mm for subsequent statistical analysis.

Because the GMC and GMV analyses led to largely overlapping results, GMC results were primarily reported for conciseness.

Global GM, WM, CSF and total intracranial volume (TIV) compartments (integrals) were calculated from the non-normalized segmented images in native space for each subject. Statistical group analysis was performed on a voxel-by-voxel basis using the General Linear Model. Regionally-specific differences in GMC and GMV between control and patient groups were then assessed using analysis of covariance, in which the TIV of each subject was included as a covariate of no interest. Contrasts were defined to detect differences between control and patient groups for unmodulated GMC and modulated GMV. To minimize the effect of false-negative results in VBM analysis due to multiple comparisons correction, statistical maps were initially thresholded at p<.005, uncorrected for multiple comparisons, using a threshold of 5 (equivalent to 40 mm³) contiguous voxels to protect against Type I errors. Uncorrected effects are reported for the whole-brain analysis (see Table 5), and for a priori regions of interest (ROIs), defined on the basis of the brain regions previously implicated in moral cognition and behavior in functional imaging and lesion studies (Moll et al., 2005). Correction for multiple comparisons was additionally performed using the SVC tool of the SPM2 package, based on spherical a priori ROIs with anatomically-based radieus and the False Discovery Rate (FDR) method (p<.05). A further multiple comparison correction procedure was performed, which corrected the statistical effects according to the total search volume of all 18 a priori spherical ROIs (see Methods). The a priori ROIs are reported in Table 2. In addition to the categorical comparison between groups, multiple regression analysis was performed to test for parametric changes in GMC within the patient group. For this aim, the two components Factor scores of the total PCL: SV (PCL: SV Total) were entered as variables of interest in a multiple regression analysis, using TIVs as covariates of no interest. Factor 1 comprises the interpersonal/affective dimension of psychopathy (e.g., callousness, lack of empathy), while Factor 2 embodies its lifestyle/antisocial dimension (e.g., impulsivity, poor behavioral control). An explicit mask was employed to restrict the regression analyses to GM voxels surviving a p<.05 (uncorrected) in the categorical analysis (patient vs. control groups). Correction for multiple comparisons was additionally performed within each a priori ROI in which significant effects were detected, using the SVC tool. Corrected results (FDR) are reported at a p<.05. Peak voxel GM values corresponding to suprathreshold local maxima for a priori ROIs were extracted, and regression analyses were again performed using SPSS (SPSS Inc., Chicago, USA, http://www.spss.com), for further verification and generation of plots. All coordinates of significant suprathreshold local maxima for each ROI were converted from MNI to Talairach space using Talairach Daemon application (http://ric.uthscsa.edu/projects/talairachdaemon.html).

**References**


