ARCHIVAL REPORT

Functional Connectivity Bias in the Prefrontal Cortex of Psychopaths

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Background: Psychopathy is characterized by a distinctive interpersonal style that combines callous-unemotional traits with inflexible and antisocial behavior. Traditional emotion-based perspectives link emotional impairment mostly to alterations in amygdala-ventromedial frontal circuits. However, these models alone cannot explain why individuals with psychopathy can regularly benefit from emotional information when placed on their focus of attention and why they are more resistant to interference from nonaffective contextual cues. The present study aimed to identify abnormal or distinctive functional links between and within emotional and cognitive brain systems in the psychopathic brain to characterize further the neural bases of psychopathy.

Methods: High-resolution anatomic magnetic resonance imaging with a functional sequence acquired in the resting state was used to assess 22 subjects with psychopathy and 22 control subjects. Anatomic and functional connectivity alterations were investigated first using a whole-brain analysis. Brain regions showing overlapping anatomic and functional changes were examined further using seed-based functional connectivity mapping.

Results: Subjects with psychopathy showed gray matter reduction involving prefrontal cortex, paralimbic, and limbic structures. Anatomic changes overlapped with areas showing increased degree of functional connectivity at the medial-dorsal frontal cortex. Subsequent functional seed-based connectivity mapping revealed a pattern of reduced functional connectivity of prefrontal areas with limbic-paralimbic structures and enhanced connectivity within the dorsal frontal lobe in subjects with psychopathy.

Conclusions: Our results suggest that a weakened link between emotional and cognitive domains in the psychopathic brain may combine with enhanced functional connections within frontal executive areas. The identified functional alterations are discussed in the context of potential contributors to the inflexible behavior displayed by individuals with psychopathy.

Key Words: Amygdala, dorsal executive network, flexible self-regulation, functional magnetic resonance imaging, psychopathy, resting-state functional connectivity

Psychopathy is characterized by a distinctive interpersonal style that includes callous-unemotional traits and antisocial features (1,2). Traditional emotion-based perspectives have linked emotional impairment in psychopathy to alterations in amygdala-ventromedial frontal circuits (3) and other "limbic" (i.e., limbic/paralimbic) regions such as the cingulate cortex (4). Accumulating evidence for dysfunction of these brain systems comes from task-related functional neuroimaging studies of emotional face recognition (5–7), aversive conditioning (8,9), response modulation according to contingency change (10,11) and moral decision making (12–15). However, emotion-based models alone cannot explain why individuals with psychopathy normally benefit from emotional information when it falls within the focus of attention (16). In addition, individuals with psychopathy may show abnormal interference effects during interference tasks using neutral (nonemotional) contextual cues, which suggests that alterations in information processing are not limited to the emotional brain domain (17–20).

Notwithstanding evidence for a primary emotional processing alteration in psychopathy, Newman and Baskin-Sommers (21) suggested that early deficits in selective attention may also characterize individuals with psychopathy. People with psychopathy exhibit a diminished aptitude to process contextual (peripheral) information when involved in goal-directed behavior. These individuals show reduced ability in shifting attention from the leading response to perceive situational cues and alter behavior appropriately, which may significantly interfere with passive avoidance learning (16,22).

The aforementioned notions become further complicated when considering the inconsistent evidence regarding the function of dorsal executive brain networks in neuroimaging studies of people with psychopathy. Individuals with psychopathy in such studies demonstrated reduced medial-dorsal frontal cortex activation during cognitive tasks with an emotional component (8,14,23,24) but the use of lateral frontal compensatory mechanisms during emotional tasks (13,24,25). Regarding the anatomic integrity of such networks in individuals with psychopathy, some studies report volumetric changes (26,27), whereas others do not (28,29), in addition to other studies reporting decreased cortical

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Received Dec 12, 2013; revised Feb 18, 2014; accepted Mar 7, 2014.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2014.03.007

thickness (27,29,30). Other, more recent imaging work suggests that individuals with psychopathy may be characterized by disturbances of large-scale brain networks that integrate emotional and cognitive neural processes (6,14,30–33). For instance, neural activity synchronization between areas processing cognitive operations (prefrontal and angular cortices) and areas relevant to emotional processes (cingulate cortices) within the so-called default network (34) may be altered in individuals with psychopathy (14). Related to this idea, a study of anatomic connectivity suggested that regions with strongest interconnectivity, or "hubs," were more dorsally located in frontal cortex in subjects with psychopathy compared with control subjects (32).

The present study aimed to examine comprehensively potential functional connectivity changes in relevant emotional and cognitive systems in individuals with psychopathy with a combined anatomic and functional imaging approach. Anatomic and functional connectivity alterations were initially investigated with a whole-brain analysis approach. Brain regions showing overlapping anatomic and functional alterations were examined further via region of interest functional connectivity mapping. We hypothesized that individuals with psychopathy would demonstrate altered functional connectivity between putative emotional and cognitive brain systems as previously indicated, but that functional connectivity changes would also be prominent within the cognitive system involving dorsal prefrontal regions.

Methods and Materials

Participants

We assessed and compared 22 male subjects with psychopathy (2) with a documented history of severe criminal offense with 22 nonoffender control subjects. Characteristics of both samples are presented in Table 1 and fully described in previous reports (6,14). Subjects with psychopathy were selected from a larger sample if showing a total Psychopathy Checklist–Revised (PCL-R) score (2) >20 or PCL-R Factor 1 score >10. Mean total PCL-R score for the included sample was 27.8 points. Additional sample characteristics are described in Supplement 1.

Image Acquisition

A 1.5-Tesla Signa Excite system (GE Healthcare, Milwaukee, Wisconsin) equipped with an eight-channel phased-array head coil and single-shot echo planar imaging software was used.

Anatomic Sequence. High-resolution axial T1-weighted anatomic images were acquired for each subject using a three-dimensional fast spoiled gradient inversion recovery prepared sequence sequence. Acquisition parameters were 134 contiguous slices (repetition time = 11.8 msec, echo time = 4.2 msec, flip angle = 15°, field of view = 30 cm, 256 × 256 pixel matrix, slice thickness = 1.2 mm).

Resting-State Sequence. The functional resting-state sequence consisted of gradient recalled acquisition in the steady state (repetition time = 2000 msec, echo time = 50 msec, flip angle = 90°, field of view = 24 cm, 64 × 64 pixel matrix, slice thickness = 4 mm, interslice gap = 1.5 mm). We acquired 22 interleaved slices, parallel to the anterior commissure–posterior commissure line, to cover the whole brain. The sequence first included four additional dummy volumes to allow the magnetization to reach equilibrium. A 4-min continuous resting-state scan was acquired for each subject. Subjects were instructed to relax, to stay awake, and to lie still with their eyes closed. The scan generated 120 whole-brain echo planar imaging volumes.

Preprocessing and Analysis of Imaging Data

Anatomic and functional imaging data were processed using MATLAB version R2008b (The MathWorks, Inc, Natick, Massachusetts) and statistical parametric mapping software (SPM8; Wellcome Trust Centre for Neuroimaging, UCL, London, United Kingdom). We excluded data from one subject with psychopathy and one control subject from the larger original samples of 23 subjects because of technical problems during imaging acquisition.

Table 1. Characteristics of Study Groups

	Control Subjects	Psychopathic Subjects
Age (Years), Mean ± SD (Range)	40.6 ± 9.5 (28–61)	39.8 ± 9.2 (28–64)
Gender	22 men	22 men
Vocabulary WAIS-III	10.3 ± 2.3 (6–14)	10.9 ± 3.0 (4–18)
Education (Years), Mean ± SD (Range)	10.5 ± 2.3 (8–16)	9.0 ± 2.7 (4–14)
Handedness (Left/Right)	2/20	1/21
PCL-R Total, Mean ± SD (Range)	.8 ± 1.9 (0–8.4)	27.8 ± 4.5[a] (15.8–34.4)
PCL-R Factor 1, Mean ± SD (Range)	.4 ± 1.1 (0–5)	12.5 ± 2.2[a] (8–16)
PCL-R Factor 2, Mean ± SD (Range)	.3 ± 0.6 (0–2)	13.2 ± 4.7[a] (4.4–20)
Comorbidities		
DSM-IV-R Axis I diagnosis[b]	None	None
Hamilton Depression Rating Scale score, mean ± SD (range)	.4 ± 1.0 (0–4)	1.9 ± 2.1[a] (0–8)
Hamilton Anxiety Rating Scale score, mean ± SD (range)	.8 ± 1.1 (0–4)	1.8 ± 3.2 (0–10)
Y-BOCS total score, mean ± SD (range)	0 ± 0 (0)	.5 ± 2.2 (0–10)
Current substance abuse	None	None
DSM-IV-R Axis II diagnosis (except APD)	None	None
Barratt Impulsiveness Scale, total score	34 ± 15 (16–72)	53 ± 23[a] (16–103)
Torrubia's Sensitivity to Punishment[c]	5.8 ± 4.9 (0–17)	8.1 ± 5.5 (0–19)
Torrubia's Sensitivity to Reward[c]	7.1 ± 4.6 (0–20)	11.9 ± 5.5[a] (5–22)

APD, antisocial personality disorder; PCL-R, Psychopathy Checklist–Revised; WAIS-III, Wechsler Adult Intelligence Scale (third edition); Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

[a] $p < .01$.

[b] Except past history of substance abuse.

[c] Sensitivity to Punishment and Sensitivity to Reward Questionnaire.

Anatomic Analyses. The VBM8 Toolbox default parameters were used (http://dbm.neuro.uni-jena.de/vbm.html). First, we obtained total intracranial and gray matter volumes from the original nonnormalized images and compared them separately between groups with independent samples *t* test in SPSS (SPSS Version 15.0; SPSS Inc, Chicago, Illinois).

For voxel-wise analysis, standard preprocessing steps involved 1) bias correction, 2) optimally tissue classification using nonlinear deformation fields to obtain tissue probability maps of gray matter based on the ICBM Tissue Probabilistic Atlas (http://www.bmap.ucla.edu/portfolio/atlases/ICBM_Probabilistic_Atlases/) that best overlay the images of the individual subjects (rather than assuming stationary prior probabilities), 3) and image registration using linear (12-parameter affine) and nonlinear transformations (warping) within a unified model (35). For the volumetric analyses, the normalized gray matter images were modulated with the Jacobian determinants (derived from the spatial normalization step) to restore volumetric information (36,37). Finally, both gray matter concentration and volumetric images were smoothed with Gaussian kernel of 8 mm full width at half maximum.

The individual voxel-wise gray matter concentration and volume images were included in a group (second-level) random-effects analysis to assess for between-group differences. The analyses were performed both with and without including total intracranial volume as a covariate. To avoid possible edge effects between different tissue types, we excluded all voxels with values of $<.2$ (absolute masking threshold).

Global Functional Connectivity Degree Mapping. Preprocessing steps involved motion correction, spatial normalization, and smoothing using a Gaussian filter (full width at half maximum 8 mm). Data were normalized to the standard SPM–echo planar imaging template and resliced to a 6.3 mm $\times$ 7.6 mm $\times$ 9.2 mm resolution in Montreal Neurological Institute (MNI) space. We compared both study groups for potential differences in movement for translations, rotations, and mean interscan motion and found no significant differences.

To obtain a quantitative measure of the extent each voxel is connected to every other voxel in the brain, we used a global brain connectivity degree measurement approach (38–42). The analysis was restricted to gray matter voxels (>40% gray matter tissue probability in SPM8 MNI templates). The functional magnetic resonance imaging signal time series of each voxel was correlated with the time series of every other voxel, resulting in a Pearson correlation coefficient *r*-matrix (2938 voxels $\times$ 2938 correlations each voxel). This connection matrix was binarized at a threshold of $r > .3$. From the connection matrix, connectivity degree of each voxel was computed by counting the number of correlations that a given voxel had above threshold $r > .30$. Connectivity degree was finally expressed in relative values as the ratio of total suprathreshold connections over all the possible connections. In the analysis, we also derived estimates of white matter, cerebrospinal fluid, and global brain signal fluctuations to be included as confounding ("nuisance") variables. The individual connectivity maps were included in a group (second-level) random-effects analysis to assess for between-group differences.

Seed-Based Functional Connectivity Analyses. Resting-state functional connectivity analyses were conducted using a region of interest ("seed")–based approach as detailed in previous studies (14,43). Preprocessing involved the same steps used for the global functional connectivity degree analysis except that the data were resliced to 2-mm isotropic resolution in MNI space. We used both anatomic and functional data to guide the placement of seed in accordance with two criteria: 1) that regions demonstrate a peak difference in the between-group anatomic comparison and 2) that these anatomically defined regions show clear overlap with significant between-group differences in the mapping of global functional connectivity.

The time course of each seed region was used as a regressor to be correlated with the time course of all brain voxels. Each seed was defined as 3.5-mm radial spheres (sampling $\sim$25 voxels) using the MarsBaR region of interest toolbox in MNI stereotactic space (44), and its signal value was calculated as the average signal of all the included voxels at each data point. Functional connectivity maps were estimated for each selected seed by including our signal of interest (seed) together with the same nuisance signals used in the connectivity degree analysis (cerebrospinal fluid, white matter, and global brain signal) as predictors of interest or no interest, respectively, in whole-brain linear regression analyses in SPM8. A high-pass filter set at 128 sec was used to remove low-frequency drifts of $<\sim$.008 Hz. Contrast images were generated for each subject by estimating the regression coefficient between the seed time series and each brain voxel signal. Resulting images were included in group (second-level) random-effects analyses to assess for within-group and between-group effects.

Correlation Analyses. Voxel-wise correlation analyses were performed in SPM8 between psychopathy severity scores (Factor 1 and Factor 2 as regressors) with the anatomic (concentration and volume), global functional connectivity degree, and seed functional connectivity analyses in the subjects with psychopathy.

Thresholding Criteria. Spatial extent thresholds for all statistical comparisons and correlation analyses were determined by 1000 Monte Carlo simulations using AlphaSim (45) as implemented in the SPM REST (Resting-State fMRI Data Analysis Toolkit) toolbox (46). The input parameters to AlphaSim included an individual voxel threshold probability of .005, a cluster connection radius of 5 mm, 12-mm full width at half maximum smoothness, incorporating a gray matter mask volume of 167,265 voxels (2 mm $\times$ 2 mm $\times$ 2 mm). The minimum cluster size was determined to be 1000 mm^3 (corresponding to 125 voxels for the anatomic and functional connectivity seed analyses and 3 voxels for the connectivity degree analysis) to satisfy a family-wise error rate correction of $p_{FWE} < .05$.

Results

Anatomic Analyses

Global Volumes. Mean $\pm$ SD values were similar between subjects with psychopathy and control subjects for total intracranial volume (1396 $\pm$ 95 mL and 1419 $\pm$ 95 mL, respectively; $t_{42} = -.8$; $p = .43$) and gray matter volume (642 $\pm$ 39 mL and 633 $\pm$ 43 mL, respectively; $t_{42} = .72$; $p = .47$).

Gray Matter Concentration Voxel-Wise Analysis. In the direct between-group comparison, differences were evident for absolute measurements (without total intracranial volume as covariate). Subjects with psychopathy showed significant decrease in gray matter concentration in several brain areas. These changes were notable in the brain medial wall involving part of the cingulate sulcus, extending to both anterior and posterior cingulate gyrus, precuneus, and medial frontal cortex. The medial frontal changes involved both dorsal and ventral areas and encompassed most of Brodmann area 12 (47) but spared the subgenual anterior cingulate region. Other brain regions with significant changes were located in the ventrolateral

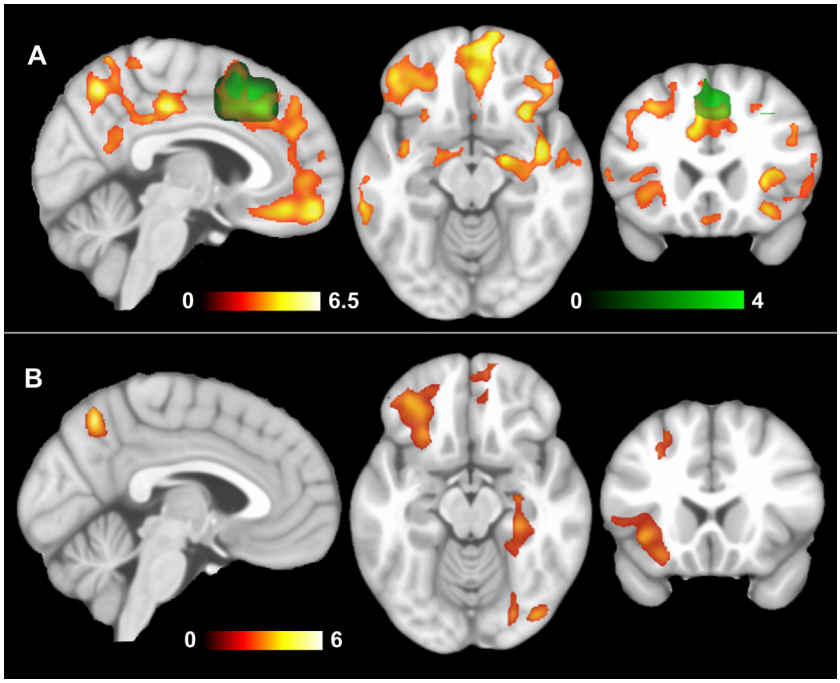

Figure 1. Anatomic and overlapping functional connectivity changes in subjects with psychopathy. **(A)** Concentration and **(B)** volumetric anatomic reductions in subjects with psychopathy compared with control subjects. Greater functional connectivity degree in medial-dorsal prefrontal cortex in subjects with psychopathy is displayed in green **(A)**. The right hemisphere corresponds to the right side of axial and coronal views.

and dorsolateral prefrontal cortex, amygdala-hippocampus and insula-operculum complexes, right fusiform gyrus, and left temporal cortex (Table S1 in Supplement 1, Figure 1).

Gray Matter Volume Voxel-Wise Analysis. Subjects with psychopathy showed significant but mild gray matter volume decreases, in contrast to tissue concentration, and only in the model including total intracranial volume as a covariate. Relative between-group differences involved ventral and lateral prefrontal cortices, the precuneus, right amygdala-hippocampus, left insula-operculum, and the fusiform gyrus (Table S1 in Supplement 1, Figure 1).

Functional Connectivity Degree Mapping

In the direct between-group comparison, subjects with psychopathy showed greater degree of functional connectivity in a region of the medial-dorsal prefrontal cortex (MNI peak coordinates x, y, z: 4, 30, 40; $t = 3.9$; $p < .005$; 4845 mm^3; 11 voxels). This area overlapped in part with the area of significantly reduced gray matter concentration (Figure 1).

Functional Connectivity Seed Maps

A principal map was generated with the seed region placed on the area of overlap between anatomic and connectivity degree alterations in the medial-dorsal frontal cortex (MNI coordinates x, y, z: −6, 23, 38). To extend the analysis and explore the reciprocity of potential functional connectivity alterations, additional maps were generated placing seeds at peak between-group differences obtained in the principal functional connectivity (medial-dorsal frontal) seed map. Specifically, seeds were placed in the amygdalae (right, 18, −4, −12; left, −16, −2, −20) and lateral prefrontal cortex (right, 26, 14, 44; left, −30, 12, 42).

Medial-Dorsal Frontal Seed Map. Positive functional connectivity maps included medial and lateral frontal cortices and a region involving the left anterior insula, frontal operculum, and basal ganglia in both groups (Figure 2, Table S2 in Supplement 1). Control subjects additionally showed changes in the right anterior insula–frontal operculum region and thalamus. The anticorrelation maps included a region in the posterior insulae, anterior temporal cortex, ventral visual areas (extending to the mesencephalon), and amygdala. The amygdala involvement was bilateral in the subjects with psychopathy and extended to the hippocampus (Figure 2, Table S2 in Supplement 1). In the direct between-group comparison, subjects with psychopathy showed a significant increase of functional connectivity in dorsolateral prefrontal cortex bilaterally, a reduction of functional connectivity in the right anterior insula–frontal operculum, and increased anticorrelation in a region involving the amygdalae and hypothalamus bilaterally (Figure 2, Table S3 in Supplement 1).

Complementary Functional Connectivity Seed Analyses

Amygdala Seed Maps. For the sake of brevity, only results from the right amygdala seed maps are reported because results from both the left and the right seed maps were similar. Positive functional connectivity with the amygdala mostly involved brain ventral structures; whereas negative (anticorrelation) functional connectivity involved dorsal (frontoparietal) and ventral cortical areas (Figure 3, Table S2 in Supplement 1). In the between-group comparison, the most relevant finding was a significant increased anticorrelation in medial and left frontal cortical areas.

Lateral Prefrontal Seed Maps. In both the right and the left frontal seed maps, positive functional connectivity involved dorsal and medial prefrontal cortex, posterior cingulate cortex–precuneus, and bilateral inferior parietal cortex. The anticorrelation maps mostly included bilateral operculo-insular regions (Figure 3; Table S2 in Supplement 1). Between-group significant differences showed increased connectivity in an area of the medial frontal cortex in both right and left frontal seed maps. In the right frontal seed map, subjects with psychopathy additionally showed significant functional connectivity reduction in the precuneus and increased anticorrelation in the posterior cingulate cortex.

Correlation Analyses. Both PCL-R Factor 1 and Factor 2 scores were associated with anatomic changes in subjects with psychopathy, although the correlations showed opposite signs.

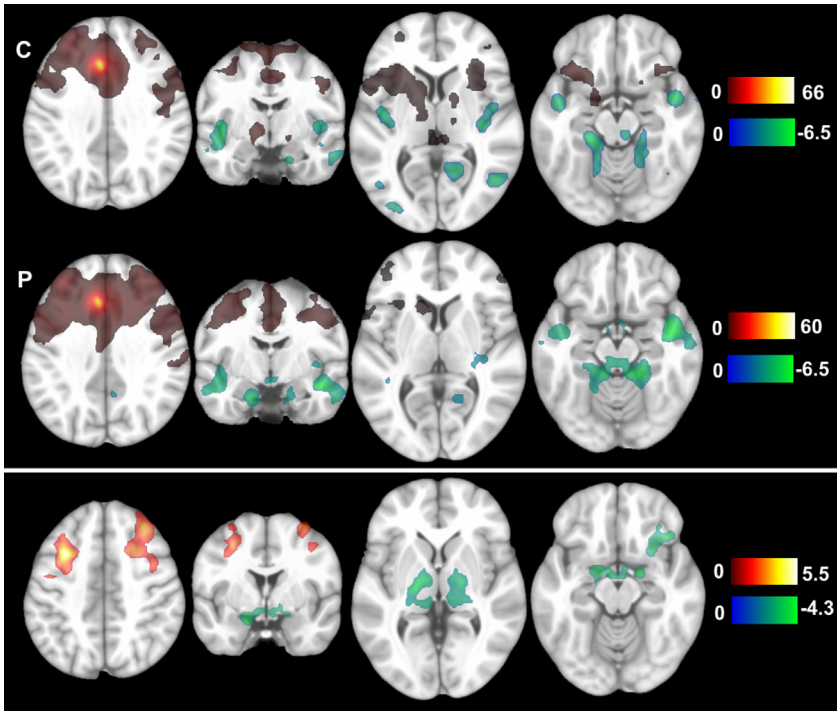

Figure 2. Functional connectivity of the medial-dorsal frontal seed in control subjects (C) and subjects with psychopathy (P) and between-group differences (bottom panel). The right hemisphere corresponds to the right side of axial and coronal views.

Specifically, Factor 1 score showed negative correlations with gray matter concentration and volume measurements in several regions, including frontal cortex and amygdalae among others. Factor 2 score showed a pattern dominated by positive correlations involving several isocortical areas (Table S4 in Supplement 1). In the global functional connectivity degree map, the PCL-R Factor 1 score showed positive correlations involving medial and lateral frontal areas (Table S4 in Supplement 1). No significant associations were found in the principal medial-dorsal frontal seed analysis.

The correlation analysis was repeated controlling for total months spent in prison, and results remained significant for each finding reported in Table S4 in Supplement 1 showing similar correlation strengths. This finding indicates that the severity of psychopathy, as opposed to incarceration time, is significantly associated with anatomic and functional brain anomalies.

Discussion

We used a combined anatomic and functional imaging approach to explore potential brain connectivity changes in putative emotional and cognitive brain systems in criminal subjects with psychopathy. Subjects with psychopathy showed significant gray matter decreases involving areas of the ventral, lateral, and medial aspects of the prefrontal cortex, anterior and posterior cingulate cortex at the cingulate sulcus, insula-operculum, amygdala-hippocampus, and fusiform gyrus. Changes in the degree of functional connectivity overlapped with such anatomic alterations specifically in the medial-dorsal frontal cortex. The area of overlap served to direct a region of interest analysis that revealed a pattern of reduced functional connectivity of prefrontal areas mostly with limbic-paralimbic structures (i.e., insula, amygdala, hypothalamus, and posterior cingulate cortex) and enhanced connectivity within the dorsolateral prefrontal cortex in subjects with psychopathy.

The functional and anatomic anomalies showed significant correlations with the severity trait psychopathy. The PCL-R Factor 1 score showed a negative correlation with anatomic measurements, whereas the Factor 2 score demonstrated a positive correlation with connectivity measurements. Figure S1 in Supplement 1 schematically summarizes the main correlation findings. The negative correlation between anatomic measurements and Factor 1 scores largely involved the amygdala, further supporting the proposal that this limbic structure has a relevant contribution to psychopathy (3), but the results also indicate that the association is not limited to limbic system structures.

The distributed pattern of anatomic alterations in our study is in agreement with previous reports in which psychopathy was also associated with changes mostly in frontal cortex, anterior temporal cortex, insula, and amygdala (12,27,29,30,48–50). In one of these studies, antisocial offenders with high psychopathic traits showed significant anatomic and functional alterations specifically involving the medial-dorsal prefrontal region (49). The discrepancy that exists in our study regarding the pattern of between-group differences in tissue concentration and volume likely reflects the fact that changes in cortical shape or cortical thickness (or both) may add to simple regional volume reductions. The combination of relevant morphologic changes with subtle volume changes and no global brain volume reduction further suggests a contribution of neurodevelopmental anomalies in psychopathy (50). The association of morphologic and volume changes in psychopathy was also observed in previous studies with similar involvement of the frontal cortex and amygdala (27,29).

Our imaging approach identified a medial-dorsal frontal brain area at the junction with the anterior cingulate cortex. Histologically, this area of the cingulate sulcus is considered transitional cortex, extending to both the limbic cortex ventrally and the isocortex dorsally (51). This region participates both in the integration of affectively salient signals into cognitive control processes mediated by the prefrontal cortex

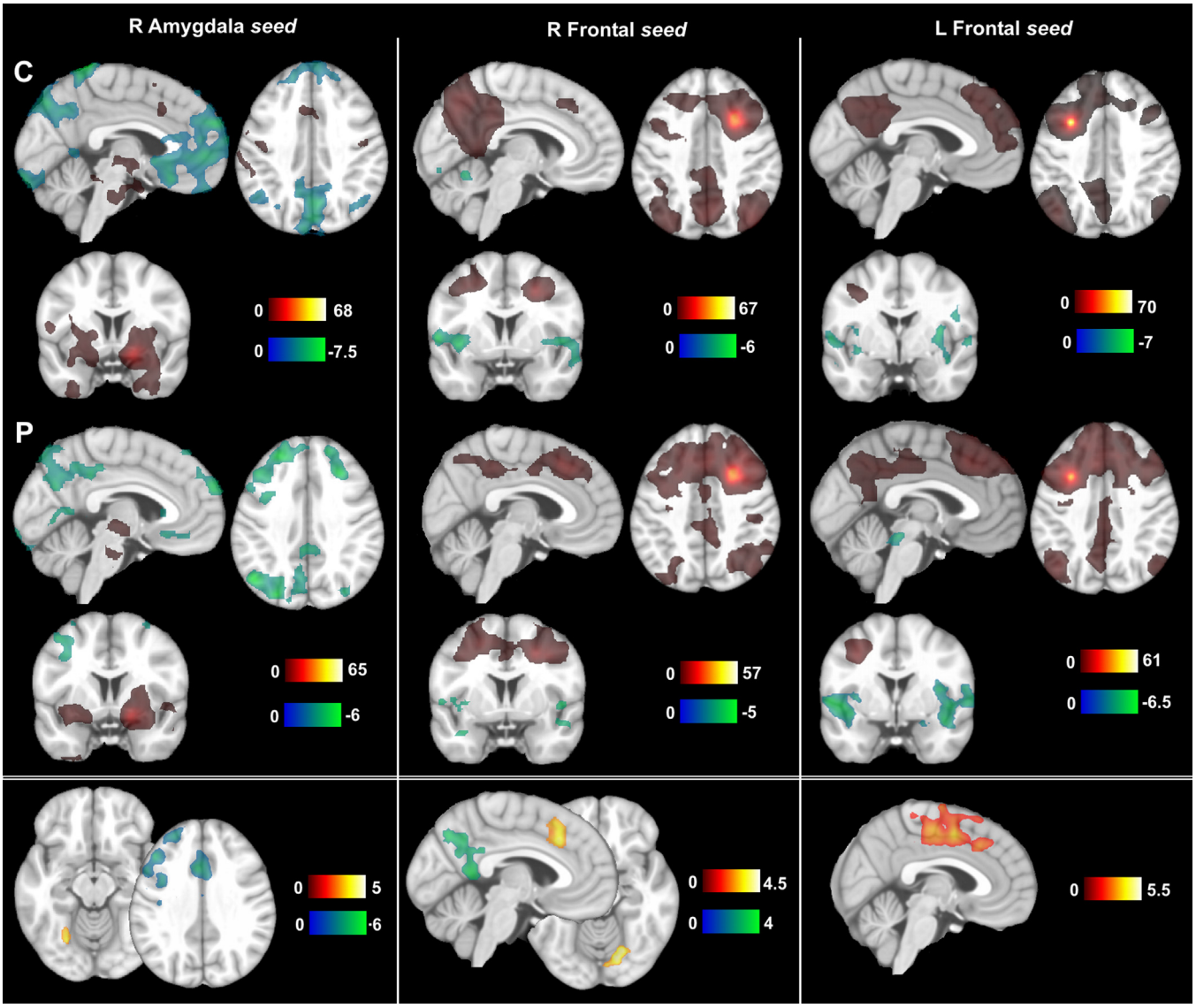

Figure 3. Functional connectivity of the right amygdala and right lateral frontal and left lateral frontal seeds in control subjects (C) and subjects with psychopathy (P) and between-group differences (bottom panel). The right hemisphere corresponds to the right side of axial and coronal views. L, left; R, right.

(52–54) and in conflict monitoring (55,56). It is suspected that alterations in this region and adjacent prefrontal areas in subjects with psychopathy may be associated with their affective and self-regulatory deficits (21,57). Task-related functional magnetic resonance imaging studies using cognitive/emotional challenge have demonstrated reduced response in this brain area (8,14,23,24). Nevertheless, only one study has explored the integrity of its functional connectivity in subjects with psychopathy, demonstrating reduced connectivity specifically between the dorsal anterior cingulate cortex and the insula (30). In the present study, this area emerged as a putative "hub" to which two distinct alterations converged—reduced connectivity with distant emotional systems and increased connectivity with neighboring prefrontal cortex. Globally, our results may suggest that activity in cortical areas supporting cognitive processes are accentuated in subjects with psychopathy, whereas their link with putative emotional brain structures is weakened.

To the extent that functional connectivity may relate to neural activity integration (58), increased functional connectivity within the dorsal prefrontal network fits well with reports of individuals with psychopathy performing successfully on a variety tasks (16,59–61). Prior functional imaging studies using attention-focused emotional tasks showed frontal hyperactivity in subjects with psychopathy, interpreted as reflecting a compensatory neural mechanism (13,24–26). However, the pattern of enhanced intracortical prefrontal processes combined with reduced long-distance influences could also reflect a bias in mental operations related to the impaired ability to use contextual information and the inflexible behavior displayed by the psychopathic individuals (61–64). This is consistent with the response modulation hypothesis, which has suggested inadequate use of contextual information despite notably preserved executive functioning (21,57). Supporting this viewpoint, affective-interpersonal traits have been related to an abnormal sensitivity to peripheral information, including emotional information (22,61,65), and we have

observed here that the PCL-R Factor 1 score was positively associated in subjects with psychopathy with global connectivity increases in the prefrontal cortex.

A replicated finding in neuroimaging studies of individuals with psychopathy has been that they demonstrate decreased anatomic and functional connectivity between the amygdala and the ventromedial prefrontal cortex (31,33,66). Our findings appear to complement such observations by also suggesting altered coupling between putative emotional-limbic and dorsal executive brain regions.

The current findings also complement our previous work in this cohort (6,14). In one study (6), we showed that the brain in subjects with psychopathy is responsive to emotional stimuli and that emotion-related brain activation may even be enhanced in sensory areas. However, functional connectivity analyses indicated that there was a deficient coupling of sensory evoked activity to the amygdala and, ultimately, the lateral frontal cortex. In the other study (14), we identified deficient activation and anomalous connectivity within the "default mode network," which largely overlaps the proposed network underlying moral judgment (34). This network demonstrated reduced long-distance connectivity between frontal isocortex and the limbic posterior cingulate gyrus. The results of the present study further emphasize a functional connectivity bias in the prefrontal cortex with enhanced local connectivity and anomalous coupling with distant brain systems. Although far from complete, these results together provide an overall picture of the brain functioning disturbances in people with psychopathy. The data are consistent with the notion that despite the ability of individuals with psychopathy to capture emotional stimuli, emotional information is not properly processed in support of learning (67) and is not adequately used in the modulation of behavioral responses (21,68).

A limitation to this study is that subjects with psychopathy were convicted prisoners and the control participants were not convicted prisoners. We did not control for the potential effect of incarceration on brain function. Nevertheless, the results from our correlation analysis may partly mitigate the limitation posed by the absence of an incarcerated nonpsychopathic control group. We found a similar pattern of results when the correlations between psychopathy scores and brain measurements were conducted with and without controlling for the length of the incarceration period, suggesting that the correlation findings were not merely an effect of subjects' confinement. We also acknowledge a methodologic issue related to the potential effect of motion on functional connectivity measurements. Recognition of these effects has generated much concern because incorrect estimations of connectivity may lead to erroneous conclusions in studies comparing populations with different levels of head motion (69). In our study, subjects with psychopathy and control subjects did not differ in regard to the measurements of head motion, which may be the optimal situation to avoid artifactual motion effects. Finally, although current substance use was controlled by urine screening, we cannot rule out the potential influence (i.e., group difference) of past substance use patterns on our observed findings.

In conclusion, the identified increase in functional connectivity within dorsal prefrontal cortex complements more recent evidence from Yang *et al.* (32) of prominent connectivity anomalies in the prefrontal cortex in people with psychopathy. Our study provides direct support for the hypothesis of functional disturbances within prefrontal networks in individuals with psychopathy (21,57). Disturbed local connectivity in such regions, together with a disrupted coupling between emotional and cognitive brain domains, further indicates a bias in the control of goal-directed attention that may contribute to the inflexible behavior displayed by individuals with psychopathy.

This work was supported by the Fondo de Investigaciones Sanitarias de la Seguridad Social of Spain Grant Nos. PI050884 and PI050884, the Ministerio de Ciencia e Innovación of Spain Grant No. SAF2010-19434, the Departament de Justícia de la Generalitat de Catalunya, a National Health and Medical Research Council of Australia Clinical Career Development Award (I.D. 628509; BJH), a "Miguel Servet" contract from the Carlos III Health Institute (CP10/00604; CS-M), and the Beatriu de Pinós-A postdoctoral fellowship (2010_BP_A_00136) of the Government of Catalunya (ML-S). JD and ML-S are part of the Research Group SGR1450 of the Catalonia Government. We thank the Secretaria de Serveis Penitenciaris Rehabilitació i Justícia Juvenil and the Centres Penitenciaris de Catalunya for their collaboration.

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

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2014.03.007.

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