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Title Page

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Functional connectivity bias in the prefrontal cortex of psychopaths

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Abstract

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 could not explain why psychopaths can regularly benefit from emotional information when placed on their focus of attention, and why they are more resistant to interference from non-affective contextual cues. The present study aimed to identify abnormal or distinctive functional links between and within emotional and cognitive brain systems in the psychopath brain to further characterize the neural bases of psychopathy. **Methods:** Twenty-two psychopaths and 22 control subjects were assessed using high-resolution anatomical MRI and a functional sequence acquired in the resting state. Anatomical and functional connectivity alterations were firstly investigated using a whole-brain analysis. Brain regions showing overlapping anatomical and functional changes were further examined using seed-based functional connectivity mapping. **Results:** Psychopaths showed gray matter reduction involving prefrontal cortex, paralimbic and limbic structures. Anatomical changes overlapped with areas showing increased functional connectivity degree 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 psychopaths. **Conclusions:** Our results suggest that a weakened link between emotional and cognitive domains in the psychopath brain may combine with enhanced functional connections within frontal executive areas. The

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identified functional alterations are discussed in the context of potential contributors to the inflexible behavior displayed by the psychopathic individuals.

Introduction

Psychopathy is characterized by a distinctive interpersonal style that includes callous-unemotional traits and antisocial features (1,2). Traditional emotional-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 a 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 psychopaths normally benefit from emotional information when it falls within the focus of attention (16). In addition, psychopaths may show abnormal interference effects during interference tasks using neutral (non-emotional) 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 colleagues have suggested that early deficits in selective attention may also characterize psychopathic individuals (21). Psychopaths exhibit a diminished aptitude to process contextual (peripheral) information when involved in goal-directed behavior. They 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).

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These above notions become additionally complicated when considering the inconsistent evidence regarding the function of dorsal executive brain networks in neuroimaging studies of psychopaths. Across such studies, psychopaths have 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 anatomical integrity of such networks in psychopaths, some studies report volumetric changes (26,27) while others do not (28,29) in addition to other studies reporting decreased cortical thickness (27,29,30). Relevantly, other recent imaging work suggests that psychopaths 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 psychopaths (14). Related to this idea, it is worth noting a recent study of anatomical connectivity which suggested that regions with strongest inter-connectivity, or "hubs", were more dorsally located in frontal cortex in psychopaths compared with control subjects (32).

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The present study aimed to comprehensively examine potential functional connectivity changes in relevant emotional and cognitive systems in psychopathic individuals with a combined anatomical and functional imaging approach. Anatomical and functional connectivity alterations were initially investigated with a whole-brain analysis approach. Brain regions showing overlapping anatomical and functional alterations were further examined via region-of-interest functional connectivity mapping. We hypothesized that

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psychopaths 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

Twenty-two male psychopaths (2) with a documented history of severe criminal offense were assessed and compared with 22 non-offender control subjects. Characteristics of both samples are fully described in Table 1 and in previous reports (6, 14). Psychopaths were selected from a larger sample if showing a total Psychopathy Checklist- Revised (PCL-R) score (2) greater than 20 *or* PCL-R Factor 1 score greater than 10. Mean total PCL-R for the included sample was 27.8 points. Additional sample characteristics are described in Supplementary material (S1).

Image acquisition

A 1.5 T Signa Excite system (General Electric, Milwaukee, WI, USA) equipped with an eight-channel phased-array head coil and single-shot echoplanar imaging (EPI) software was used.

Anatomical sequence. High-resolution axial T1-weighted anatomical images were acquired for each subject using a 3-dimensional fast spoiled gradient inversion-recovery prepared sequence (T1 3D fSPGR IR-prep) sequence. Acquisition parameters were 134

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contiguous slices (repetition time [TR], 11.8 ms; echo time [TE], 4.2 ms; flip angle, 15°; field of view, 30 cm; 256 x 256 pixel matrix; slice thickness, 1.2 mm).

Resting-state sequence. This functional sequence consisted of gradient recalled acquisition in the steady state ([TR], 2000 ms; [TE], 50 ms; flip angle, 90º; field of view; 24 cm; 64 x 64 pixel matrix; slice thickness, 4 mm; inter-slice gap, 1.5 mm). Twenty-two interleaved slices, parallel to the anterior-posterior commissure (AC-PC) line, were acquired to cover the whole-brain. The sequence first included four additional dummy volumes to allow the magnetization to reach equilibrium. A four-minute continuous resting-state scan was acquired for each subject. Subjects were instructed to relax, stay awake and to lie still with their eyes closed. The scan generated 120 whole-brain EPI volumes.

Preprocessing and analysis of imaging data

Anatomical and functional imaging data were processed using MATLAB version R2008b (The MathWorks Inc, Natick, Mass) and Statistical Parametric software (SPM8; The Welcome Department of Imaging Neuroscience, London). We excluded data from one psychopathic individual and one control from the larger original samples of 23 subjects, because of technical problems during imaging acquisition.

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Anatomical analyses. The 'VBM8 toolbox' default parameters were used (http://dbm.neuro.unijena.de/vbm.html).

We firstly obtained total intracranial and gray matter volumes from the original non-normalized images and compared them separately between groups with independent samples t test in SPSS 15.0 (SPSS Inc., Chicago IL).

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For voxel-wise analysis, standard preprocessing steps involved (i) bias-correction, (ii) optimally tissue classification using non-linear deformation fields to obtain tissue probability maps of gray matter based on the ICBM Tissue Probabilistic Atlas (http://www.Ioni.ucle.edu/ICBM_TissueProb.html) that best overlay the individual subjects' images (rather than assuming a stationary prior probabilities), (iii) and image registration using linear (12-parameter affine) and non-linear 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 half maximum (FWHM).

The individual voxel-wise gray matter concentration and volume images were then 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. In order to avoid possible edge effects between different tissue types, we excluded all voxels with values of less than 0.2 (absolute masking threshold).

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Global functional connectivity degree mapping. Preprocessing steps involved motion correction, spatial normalization and smoothing using a Gaussian filter (FWHM 8 mm). Data were normalized to the standard SPM-EPI template and resliced to a 6.3 x 7.6 x 9.2 mm resolution in Montreal Neurological Institute (MNI) space. We compared both

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study groups as for potential differences in movement for translations, rotations and mean inter-scan 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). Each voxel's fMRI signal time series was correlated with every other voxel's time series, resulting in a Pearson correlation coefficient r-matrix (2938 voxels x 2938 correlations each voxel). This connection matrix was then binarized at a threshold of r>0.3. 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 > 0.30. Connectivity degree was finally expressed in relative values as the ratio of total supra-threshold connections over all the possible connections. In the analysis, we also derived estimates of white matter, CSF, and global brain signal fluctuations to be included as confounding ("nuisance") variables. The individual connectivity maps were then 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 Montreal Neurological Institute (MNI) space. We used both anatomical and functional data to guide the placement of seed in accordance with two criteria : (i) that regions demonstrate a peak difference in the between-group anatomical

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comparison and (ii) 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 approximately 25 voxels) using MarsBaR region-of-interest toolbox in MNI stereotaxic 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 (CSF, 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 seconds was used to remove low-frequency drifts of less than approximately 0.008 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 then included in group (second-level) random-effects analyses to assess for within 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 anatomical (concentration and volume), global functional connectivity degree and seed functional connectivity analyses in the psychopathic group.

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 toolbox (46). The input parameters to AlphaSim

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included an individual voxel threshold probability of 0.005, a cluster connection radius of 5 mm, 12 mm FWHM smoothness, incorporating a gray matter mask volume of 167,265 voxels (2x2x2mm) voxels. The minimum cluster size was determined to be 1,000 mm3 (corresponding to 125 voxels for the anatomical and functional connectivity seed analyses and 3 voxels for the connectivity degree analysis) to satisfy a family-wise error rate correction of PFWE< 0.05.

Results

Anatomical analyses

Global volumes. Mean±SD was similar between psychopaths and control subjects for total intracranial volume (1396±95 and 1419±95 mL, respectively; t_{42}= -0.8; P= 0.43) and gray matter volume (642±39 and 633±43 mL, respectively; t_{42}= 0.72; P= 0.47).

Gray matter concentration voxel-wise analysis. In the direct between-group comparison, differences were evident for absolute measurements (without total intracranial volume as covariate). Psychopaths showed significant gray matter concentration decrease 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 and dorsolateral prefrontal cortex, amygdala-hippocampus and insula-operculum complexes, right fusiform gyrus and left temporal cortex (Table S1, Figure 1).

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Gray matter volume voxel-wise analysis. In contrast to tissue concentration, psychopaths showed significant but mild gray matter volume decreases, 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, Figure 1).

Functional connectivity degree mapping

In the direct between-group comparison, psychopaths showed greater functional connectivity degree in a region of the medial-dorsal prefrontal cortex (MNI peak coordinates x, y, z: 4, 30, 40, t= 3.9; P<0.005, 4,845 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 anatomical 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).

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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). 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 the amygdala. The amygdala involvement was bilateral in the psychopath group and extended to the hippocampus (Figure 2, Table S2). In the direct between-group comparison, psychopaths 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).

Complementary functional connectivity seed analyses

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

Lateral prefrontal seed maps. In both the right and 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

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included bilateral operculo-insular regions (Figure 3, Table S2). 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, psychopaths 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 2 scores were associated with anatomical changes in psychopaths, although the correlations showed opposite signs. Specifically, Factor 1 showed negative correlations with gray matter concentration and volume measurements in several regions, including frontal cortex and amygdalae among others. Factor 2 in turn showed a pattern dominated by positive correlations involving several isocortical areas (Table S4).

In the global functional connectivity degree map, PCL-R Factor 1 showed positive correlations involving medial and lateral frontal areas (Table S4). 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 showing similar correlation strengths. This indicates that the severity of psychopathy, as opposed to incarceration time, is significantly associated with anatomical and functional brain anomalies.

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Discussion

We used a combined anatomical and functional imaging approach to explore potential brain connectivity changes in putative emotional and cognitive brain systems in criminal psychopaths. Psychopaths 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, the insula-operculum, amygdala-hippocampus and the fusiform gyrus. Changes in the degree of functional connectivity overlapped with such anatomical 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 psychopaths.

Relevantly, the functional and anatomical anomalies showed significant correlations with the severity trait psychopathy. PCL-R Factor 1 showed a negative correlation with anatomical measurements, whereas Factor 2 demonstrated a positive correlation with connectivity measurements. Figure S1 schematically summarizes the main correlation findings. It is worth noting that the negative correlation between anatomical measurements and Factor 1 scores largely involved the amygdala, thus 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.

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The distributed pattern of anatomical 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). Interestingly in one of these studies, antisocial offenders with high psychopathic traits showed anatomical alterations specifically involving the medial-dorsal prefrontal region that demonstrated significant anatomical and functional alterations here (49). The discrepancy that exits in our study as to 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 morphological changes with subtle volume changes and no global brain volume reduction further suggests a contribution of neurodevelopmental anomalies in psychopathy (50). The association of morphological 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 isocortex dorsally (51). This region participates both in the integration of affectively salient signals into cognitive control processes mediated by the prefrontal cortex (52-54) as well as in conflict monitoring (55,56). It is suspected that alterations in this region and adjacent prefrontal areas in psychopaths may be associated with their affective and self-regulatory deficits (21,57). Task-related fMRI studies using cognitive/emotional challenge have indeed demonstrated reduced response in this brain area (8,14,23,24). Nevertheless, only one study has explored the integrity of its functional connectivity in

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psychopaths, 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; namely, 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 psychopaths, 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 psychopathic individuals successfully performing on a variety tasks (16,59-61). In fact, prior functional imaging studies using attention-focused emotional tasks showed frontal hyperactivity in psychopaths, interpreted as reflecting a compensatory neural mechanism (13,24-26). However, the pattern of enhanced intra-cortical 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 was positively associated in psychopaths with global connectivity increases in the prefrontal cortex.

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A replicated finding in neuroimaging studies of psychopaths has been that they demonstrate decreased anatomical and functional connectivity between the amygdala and 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 psychopaths is responsive to emotional stimuli and that emotion-related brain activation may be even enhanced in sensory areas. However, functional connectivity analyses indicated that 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 psychopaths. The data are consistent with the notion that, despite the ability of psychopaths to capture emotional stimuli, emotional information is not properly processed in support of learning (67) and is not adequately utilized in the modulation of behavioral responses (21,68).

A limitation to this study is that psychopaths were convicted prisoners unlike the control participants. Therefore, the potential effect of incarceration on brain function was not

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controlled for. Nevertheless, the results from our correlation analysis may partly mitigate the limitation posed by the absence of an incarcerated non-psychopathic control group. Indeed, 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 would also mention a methodological issue that concerns to the potential effect of motion on functional connectivity measurements. Recognition of these effects has generated much concern as incorrect estimations of connectivity may lead to erroneous conclusions in studies comparing populations with different levels of head motion (69). In our study, psychopaths and control subjects did not differ as 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 functional connectivity increase within dorsal prefrontal cortex complements recent evidence by Yang et al (32) of prominent connectivity anomalies in the prefrontal cortex in psychopaths. Our study provides direct support for the hypothesis of functional disturbances within prefrontal networks in psychopathic individuals (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 psychopathic individuals.

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Figure Legends

Figure 1. Anatomical and overlapping functional connectivity changes in psychopaths. Top panel (A) shows concentration and bottom panel (B) volumetric anatomical reductions in psychopaths compared to controls. Greater functional connectivity degree in medial-dorsal prefrontal cortex in psychopaths is displayed in green (A). The right hemisphere corresponds to the right side of axial and coronal views.

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

Figure 3. Functional connectivity of the right amygdala, right lateral frontal and left lateral frontal seeds in controls (C) and psychopaths (P), and between-group differences (bottom panel). The right hemisphere corresponds to the right side of axial and coronal views.

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Table 1. Characteristics of study groups

	Controls	**Psychopaths**
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-handers/right-handers)	2/20	1/21
PCL-R Total, mean ± SD (range)	0.8 ± 1.9 (0-8.4)	*27.8 ± 4.5 (15.8-34.4)
PCL-R Factor 1, mean ± SD (range)	0.4 ± 1.1 (0-5)	*12.5 ± 2.2 (8-16)
PCL-R Factor 2, mean ± SD (range)	0.3 ± 0.6 (0-2)	*13.2 ± 4.7 (4.4-20)
Comorbidities:		
DSM-IV-R Axis I diagnosis#	None	None
Hamilton Depression score, mean ± SD (range)	0.4 ± 1.0 (0-4)	*1.9 ± 2.1 (0-8)
Hamilton Anxiety score, mean ± SD (range)	0.8 ± 1.1 (0-4)	1.8 ± 3.2 (0-10)
Y-BOCS total score, mean ± SD (range)	0 ± 0 (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 (16-103)
Torrubia's Sensitivity to Punishment^	5.8 ± 4.9 (0-17)	8.1 ± 5.5 (0-19)
Torrubia's Sensitivity to Reward^	7.1 ± 4.6 (0-20)	*11.9 ± 5.5 (5-22)

* indicates p< 0.01. #except past history of substance abuse. ^ Sensitivity to Punishment and Sensitivity Reward Questionnaire (SPSRQ). PCL-R, Psychopathy Checklist- Revised. Y-BOCS, Yale-Brown Obsessive-Compulsive Scale. APD, Antisocial Personality Disorder.

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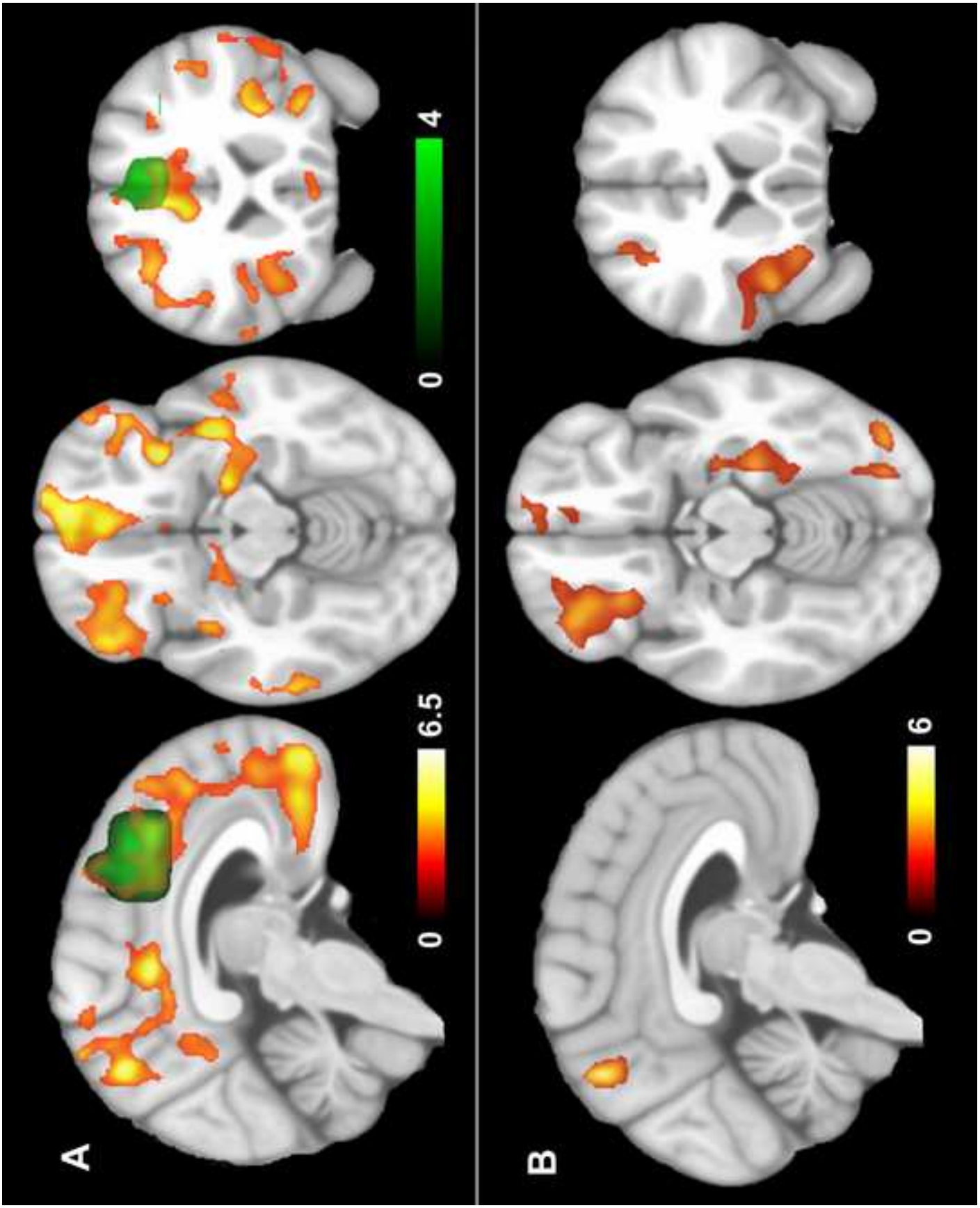


Figure1

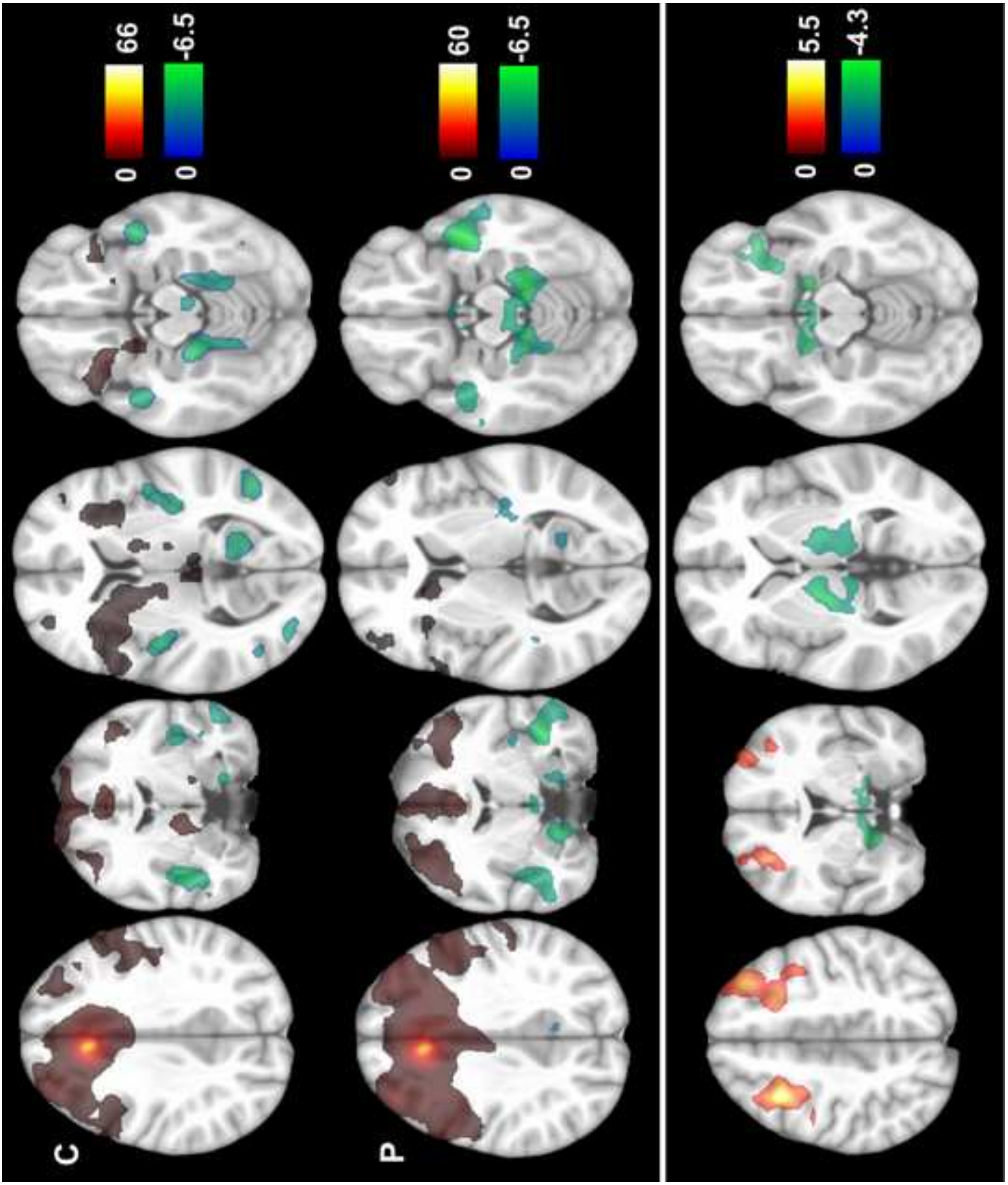


Figure2

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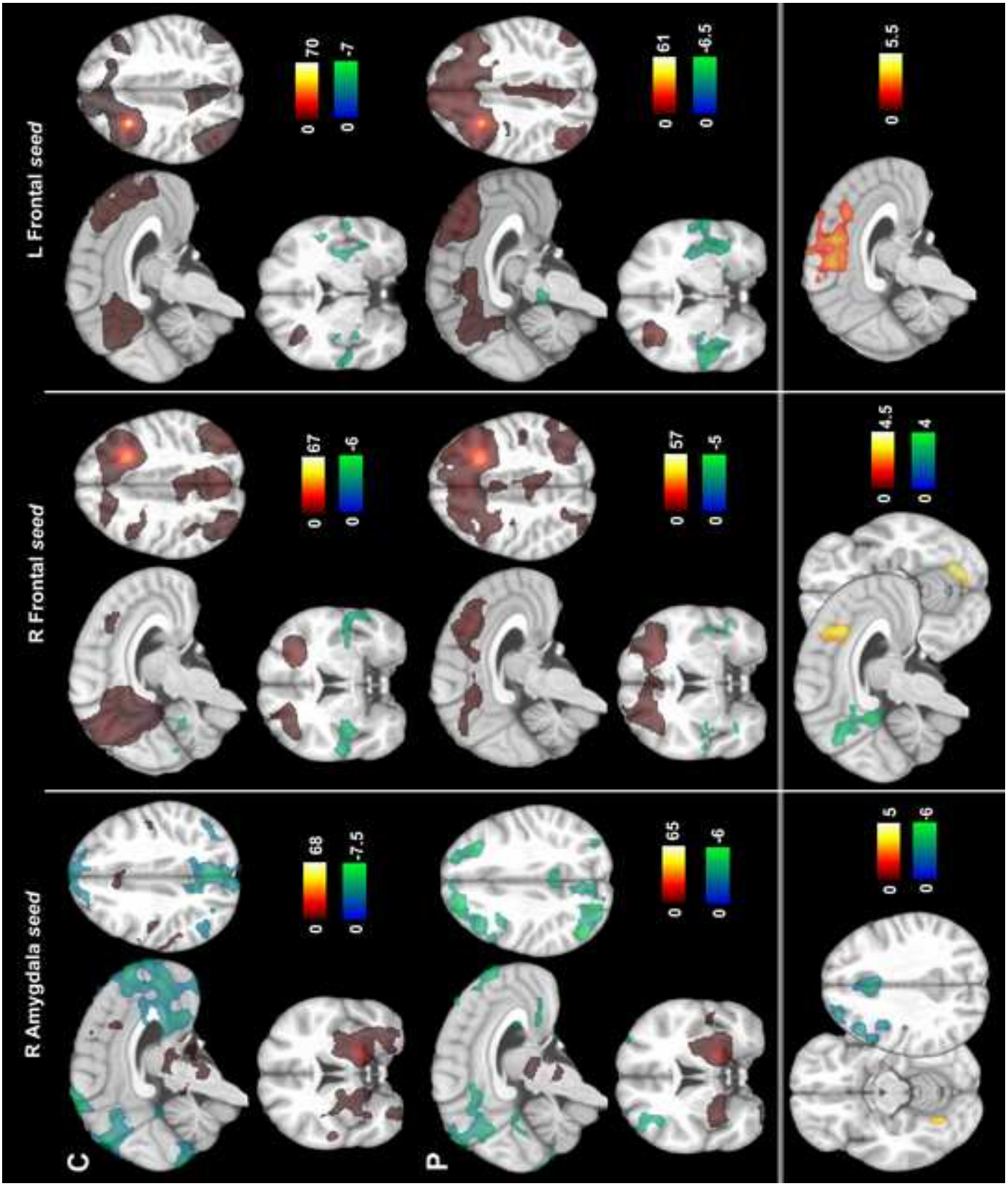


Figure3