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Reduced frontotemporal perfusion in psychopathic personality

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Abstract

Several brain-imaging studies have found associations between aberrant functioning in the frontal and temporal lobes and violent offending. We have previously reported decreased frontotemporal perfusion unrelated to psychosis, substance abuse, or current medication in 21 violent offenders. In the present study, we compared the regional cerebral blood flow (rCBF) in a new group of 32 violent offenders to scores on the Psychopathy Checklist-Revised (PCL-R), which rates two aspects of psychopathy: disturbed interpersonal attitudes (Factor 1) and impulsive antisocial behavior (Factor 2). A recently proposed model has split Factor 1 into a new Factor 1 (deceitful interpersonal style), a new Factor 2 (affective unresponsiveness), and a Factor 3, which approximately corresponds to the old Factor 2. The rCBF was assessed by single-photon emission computed tomography (SPECT) with technetium-99m-*d*,*l*-hexamethylpropyleneamine oxime (HMPAO) in regions of interest (ROIs) placed in accordance with fusioned magnetic resonance images (MRI) and SPECT scans. Significant negative correlations were found between interpersonal features of psychopathy (the old and especially the new Factor 1) and the frontal and temporal perfusion. The two most clearly associated ROIs were the head of the caudate nuclei and the hippocampi. These findings in a group of violent offenders living under the same conditions, which reduced the number of state-related confounders, add to the evidence indicating that aberrant frontotemporal activity may be a factor in violent behavior.

Keywords: Regional cerebral blood flow (rCBF); HMPAO single-photon emission computed tomography (HMPAO-SPECT); Violence; Psychopathy Checklist-Revised (PCL-R)

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1. Introduction

Numerous studies have reported aberrations in frontal and temporal regional brain electric activity, perfusion, metabolism, and distribution of receptors and transporter proteins in violent offenders compared to healthy control subjects (Volkow and Tancredi, 1987; Oder et al., 1992; Goyer et al., 1994; Raine et al., 1994, 1998, 2000; Wong et al., 1994, 1997a; Amen et al., 1996; Tiihonen et al., 1995, 1997; Seidenwurm et al., 1997; Pillman et al., 1999; Critchley et al., 2000; Soderstrom et al., 2000). The findings have generally been heterogeneous and difficult to compare between studies due to the use of different imaging methods and anatomical placements of regions of interest (ROIs). Research in this area is also complicated by methodological questions regarding representative index subjects, adequate assessment methods, and control subjects matched for a broad spectrum of possible confounding factors. A general reliance on forensic psychiatric inpatients or subjects of pre-trial forensic psychiatric examinations has rendered generalizations of findings to other groups doubtful. Despite these problems, the evidence is still strong for a relationship between changes in frontal and/or temporal cerebral functioning and increased risk of violent behavior.

When violent or antisocial offenders are compared to healthy control subjects, results may be confounded by substance abuse, toxic exposure, child abuse, nutritional deficits and head trauma. Attempting to uncover as unbiased associations as possible between violent propensities and aberrant brain-imaging findings, some studies have used clinical contrast groups in addition to healthy control subjects. Others have dealt with the problem by separate analyses of subgroups of specific offenders (for example, subjects who are negative for possible confounders, repetitive offenders, or perpetrators of affective vs. predatory crimes) (Goyer et al., 1994; Raine et al., 1994, 1998, 2000; Wong et al., 1994, 1997b; Amen et al., 1996; Soderstrom et al., 2000). To eliminate confounding impact from stratified group differences between index subjects and healthy control subjects, Laakso et al. (2001) compared hippocampal volumes to psychopathic personality traits within a group of 18 violent subjects with alcoholism. They found highly significant negative associations between psychopathy ratings and the volumes of the posterior hippocampi bilaterally, most prominent on the left side. The first imaging study in a community-based, non-clinical, non-correctional study group was recently reported by Raine et al. (2000), who described a relationship between antisocial personality traits and decreased volume of the frontal cortices. Functional MRI (fMRI) has recently emerged as a promising tool for the study of functional changes in specific psychological challenges (Kiehl et al., 2001; Raine et al., 2001).

We have previously compared SPECT scans from 21 violent offenders to those in 11 control subjects (Soderstrom et al., 2000) and found decreased regional cerebral blood flow (rCBF) in the temporal and frontal regions, even in non-psychotic, unmedicated subjects without a history of substance abuse or head trauma. An unexpected finding was that the rCBF in the parietal association cortices was increased in the violent offenders. The problem of matching the control subjects to the index cases for possible confounders beyond age and sex remained unsolved, however, and state-dependent as well as trait-related differences in regional brain functioning might be expected between healthy control subjects and incarcerated offenders. Since it is next to impossible to recruit and investigate control groups matched for all types of confounders and subjected to the same conditions as the offenders, alternative approaches have to be taken. We have chosen to relate neurobiological findings to traits associated with severe forms of violent behavior and high relapse rates within our study groups by comparing the rCBF in 32 violent offenders to the best available rating scale for such traits—the Psychopathy Checklist-Revised (PCL-R) (Hare et al., 1990).

According to the definition by Cleckley (1941), psychopathy is characterized by inconsistent, impulsive behavior and distorted perceptions of interpersonal and temporal processes, with a propensity to violate the rights of others to achieve dominance. The PCL-R is a 20-item clinical and actuarial rating scale developed to assess these features (Hare, 1991). Ratings yield a two-factor structure, where Factor 1 reflects interpersonal

callousness, domination-seeking and emotional detachment, while Factor 2 reflects impulsive, violent or antisocial behavior (Harpur et al., 1988, 1989). A new three-factor model has recently been presented (Cooke and Michie, 2001), in which items directly describing criminal activities have been omitted, and Factor 1 has been divided into deceitful interactive style (new Factor 1) and affective hypo-responsiveness (new Factor 2), while Factor 2 approximately corresponds to the new Factor 3. The total and factor PCL-R scores correlate linearly or semilinearly with criminal behavior (Hart, 1998; Hemphill et al., 1998). Since PCL-R ratings have been consistently related to instrumental violent behavior and violent recidivism, negative correlations between the rCBF in the areas of hypothetical interest in the frontal and temporal lobes and the PCL-R ratings would corroborate the earlier findings of group differences in the rCBF of these regions between violent offenders and healthy control subjects, and point to direct associations between aberrant functions in the frontal and temporal lobes and traits associated with violent behavior.

2. Methods

2.1. Index subjects

All subjects of pre-trial forensic psychiatric investigations in Göteborg during 1997 ($n=113$) were screened for participation in a research project (approved by the Research Ethics Committee at Göteborg University) aimed at evaluating neuropsychiatric functioning in violent offenders. Inclusion required that the subject had been charged with a severe crime (homicide, attempted homicide, aggravated assault, arson, rape or sexual abuse of minors), that he or she had no history of treatment for major mental disorder (MMD), and that no current clinical signs suggested the onset of such a disorder. A total of 49 subjects (46 men, three women), aged 17–67 (median 30) years, met the inclusion criteria, and 32 (29 men, three women, aged 17–67, median 31.5 years) consented to participate in MRI and SPECT examinations. According to χ^2 tests or Mann–Whitney nonparametric comparisons, participating subjects did not differ from the whole sample regarding: gender (too few women for statistical comparison); age ($P=0.644$); immigrant status ($P=0.311$); psychiatric morbidity (any Axis I diagnosis, $P=0.746$; any Axis II diagnosis, $P=1.00$); PCL-R median split ($P=0.760$); Factor 1 ($P=0.752$); Factor 2 ($P=1.00$); or type and severity of crime (violent features of the crime, $P=0.386$).

2.2. Clinical examinations

Psychiatric diagnoses according to strict operational DSM-IV criteria were made by a forensic psychiatric specialist in consensus with a clinical psychologist, a psychiatric social worker and ward staff on the basis of clinical interviews, neuropsychological tests, personality and psychiatric assessments, physical and neurological examinations, extensive file reviews and close observation on the ward. Special efforts were made to ascertain the true extent of all kinds of substance abuse in the lifetime history by means of collateral interviews and registered information. All diagnoses were subsequently reviewed and accommodated to the entire diagnostic work-up, file information and personal examinations made in all cases by one of the authors (HS or AF).

The following comprehensive Axis I diagnoses were registered at the conclusion of the forensic investigations: alcohol abuse in nine subjects (combined with major depression in one, with social phobia in two, and with a psychotic disorder NOS in one); alcohol dependence in one; mixed substance abuse in four (in one subject combined with social phobia and major depression); and mixed substance dependence in three (combined with generalized anxiety and post-traumatic stress disorder in one). One subject had a psychotic disorder NOS without concomitant substance abuse. Axis II disorders were diagnosed in 14 subjects (borderline personality disorder in two, antisocial personality disorder in two, dependent personality disorder in one, and personality disorder NOS with mixed Cluster B symptomatology in nine. None had a Cluster A personality disorder with psychotic features.). The total diagnostic pattern thus included 18 subjects with and 14 without Axis I disorders, and 14 with an Axis II disorder.

Eight subjects had both an Axis I and an Axis II disorder, and eight had no diagnosis on either axis.

All subjects with substance abuse or dependence had been detoxified in jail several weeks before admission to the study department and showed no signs of withdrawal when included in the study; 18 subjects were not receiving any medication, four were taking antidepressants and 10 were taking minor tranquilizers. None were taking a major tranquilizer.

Seven subjects were charged with murder, seven with attempted murder, nine with aggravated assault, one with kidnapping and aggravated rape, four with aggravated rape, one with aggravated sexual child abuse and three with arson. All were convicted in their subsequent trials.

Each subject was rated on the PCL-R by specially trained social workers who were blind to neuropsychological test results and laboratory findings, including SPECT scans, but had access to all other information. As suggested by the author of the instrument (Hare, 1991), the mean score of the total number of rated items could be applied to up to three missing items. Ratings ranged from 2 to 31.5 points (median 11.35) on the whole PCL-R and from 0 to 14 (median 4) on Factor 1 and from 0 to 14.1 (median 7.2) on Factor 2. The Factor 2 rating declined significantly with age (Spearman's rho $= -0.42$, $P = 0.017$) while the Factor 1 ratings were unaffected by age (Spearman's rho $= -0.04$, $P = 0.844$). The three women had slightly lower scores than the men (total score, range 5–10.20, median 9.4; Factor 1 score, range 0–5, median 1; Factor 2 score, range 0–7.9, median 7.7).

A subgroup ($n = 24$) had a computerized neuropsychological test evaluation according to a battery by Levander (1987), which, among other tests, included the following: finger tapping; reaction time; digit span; associative learning; long-term memory; maze exits; and specialized tests for perceptual organization and strategy flexibility.

2.3. MRI

The examinations were performed on either a 0.5-T (Gyroscan NT5) or a 1.5-T (Gyroscan ACS II) magnet. The protocol for all examinations included an initial T1-weighted spin-echo sequence (scout sequence including all three main projections: transverse, sagittal, and coronal) followed by transverse proton density- and T2-weighted sequences of the entire brain. Further sequences and projections were added when necessary. A written assessment was in each case issued by a specialist in neuroradiology. At the end of the study, all 32 scans were scrutinized by a professor of neuroradiology (SE).

2.4. rCBF measurements

The rCBF measurements were made with a SPECT gamma camera system (General Electric, Neurocam) equipped with high-resolution collimators. A standard dose of 1000 MBq [^{99m}Tc]-d, I-HMPAO was administered intravenously to the relaxed, pain-free subject who was resting with closed eyes. Tomographic acquisition was started 15 min after the injection. A total of 64 30-s projections were acquired in a 128×128 matrix with a 20% energy discrimination window centered at 140 keV. The projection data were pre-filtered with a two-dimensional Hanning filter and a cut-off frequency of 0.9 cm^{-1}. Conventional attenuation correction with an effective attenuation coefficient of 0.12 cm^{-1} was used. Transaxial slices were reconstructed with a zoom factor of 2, giving a pixel size of 0.16×0.16 cm^2 in 0.32-cm-thick slices (128×128 matrix). The spatial resolution in reconstructed slices was approximately 1.2 cm (full-width at half-maximum; FWHM). The tilt angle of the transaxial slices was corrected to the infra-orbitomeatal line.

Methods for visualization, segmentation, image matching and quantification were developed in IDL™ (Research System, Inc.) for Windows NT™. The surface of the brain was automatically segmented and visually corrected in T2-weighted MRI and rCBF images. An iterative Marquard algorithm was used to adjust the rCBF volume to minimize the distance between the surfaces of the two modalities.

The basal, medial and lateral frontal cortices (red, yellow and green demarcations in Fig. 1) were manually outlined on the MR images, and a total of 28 ellipsoidal ROIs (26 in the cerebrum

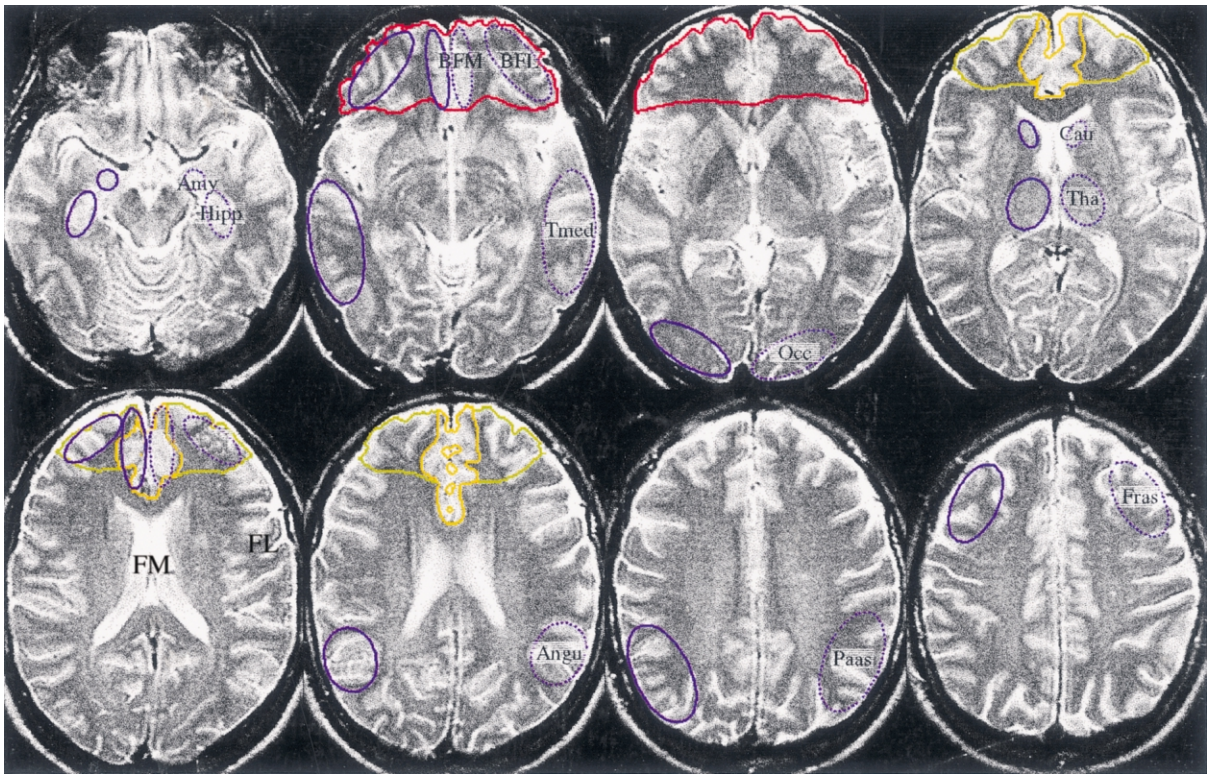

Fig. 1. MRI scans showing the anatomical placement of ROIs. The basal frontal cortex is outlined in red, the medial frontal cortex in yellow, the lateral frontal cortex in green, and the 13 paired ROIs of the cerebrum in blue. The pair of cerebellar ROIs is not included in the picture.

and two in the cerebellum, listed in Table 2 and outlined in blue in Fig. 1) were placed according to anatomical information obtained from the MR images. The size and rotation of the ROIs were adjusted to fit the anatomical structures. The ROIs were transposed to the matched rCBF images, and the relative quantification of the rCBF was conducted according to the Min–Max method (Arlig et al., 1994) and as mean uptake per pixel within the ROI. With the Min–Max method, the minimum and maximum counts per pixel (c/p) are registered in white and gray matter regions, respectively. The rCBF is subsequently calculated as the ratio between the max c/p in gray matter ROIs and max c/p in the cerebellar ROI, and between the min c/p in white matter ROIs and max c/p in the cerebellar ROI. The rCBFs quantified in all temporal ROIs (the hippocampi, the temporal gyri, the heads of the caudates and the angular gyri) and all prefrontal ROIs (the lateral basal frontal cortices, the medial basal frontal cortices, the lateral frontal cortices, the medial frontal cortices and the manually outlined frontal cortex ROIs) were added up to form a frontal and a temporal sum of the rCBF calculated for each side and bilaterally. The amygdala data were not included in the temporal sum, since the anatomical demarcation of the ROI could not be consistently transferred from the MRI to the lower resolution of the SPECT.

2.5. Statistical analyses

Since the statistical techniques employed in this study are included in the SPSS PC v. 10.0 software, further references are omitted. As normal distri-

butions could not be ascertained for the PCL-R ratings or for the relative uptake in all ROIs, nonparametric statistics were used; for correlations, Spearman's rank correlations, and for group comparisons, the Mann–Whitney *U* test in independent samples. A model with all ROIs compared to the PCL-R ratings yields a high number of comparisons, and a strict correction for multiple comparisons would reduce the power to detect correlations. To reduce the number of comparisons, rCBF indices in frontal and temporal ROIs (corresponding to the areas where we found differences in our previous study and that are indicated by the literature in the field) were collapsed on the right and left side separately and on average to be included in a predefined statistical protocol and compared to the PCL-R total and factor scores. As these analyses are based on previously published data and predefined hypotheses, corrections for multiple comparisons were not deemed necessary and one-tailed *P* values were used in this step of the analyses. All correlations were recalculated for subgroups without various possible confounders (such as gender, mental disorder, substance abuse, or current medication). To corroborate possible findings of significant correlations, the sample was subsequently split by the median of the PCL-R total and factor ratings to yield two groups between which the rCBF of the targeted areas could be compared. Finally, to explore the whole sample and to provide preliminary specific information on the ROIs included in the indices, the rCBF in all ROIs was compared to the PCL-R ratings using two-tailed *P* values.

3. Results

3.1. MRI

The clinical assessment of the MRI scans revealed no neurological disease or damage that might influence the SPECT scans. The MRI reassessments showed 20 normal scans, five with some focal gliosis or signs of old parenchymal injury, two with discrete signs of atrophy, four with high-signal changes in the deep white matter, and one with a smaller than normal right hippocampus. These changes affected the following anatomical localizations: the frontal lobes in three cases; the callosal body in three cases; the temporal lobe in two cases; the white matter in four cases; the hippocampus in one case; the internal capsule in one case; and the general cortex expressed as diffuse enlargement of sulci in three cases. This indicates an over-representation of minor pathological signs among subjects as young as ours, but no consistent pathology that could affect the risk of violent behavior or explain the SPECT findings.

3.2. Quantified rCBF

In the first step of the analyses, the bilaterally averaged frontal and temporal indices based on the rCBF calculated by the Min–Max method were analyzed for a possible relationship with the PCL-R ratings. There was no significant association between the rCBF indices and the total PCL-R scores, but the temporal and frontal rCBF indices showed significant negative correlations with PCL Factor 1, according to the two-factor model, and with the new Factor 1, according to the three-factor model. The correlations were strongest between the temporal blood flow (especially on the left side) and the new Factor 1 (Table 1). Both the averaged prefrontal and basal frontal rCBF indices were significantly correlated to each Factor 1 but, when analyzed separately for the left and right side, only the correlation on the right side remained significant. The correlations remained virtually unchanged when analyzed in subgroups of men ($n=29$), subjects with a normal MRI ($n=20$), subjects without current medication ($n=18$), subjects below 30 years of age ($n=16$), and in subjects without substance abuse ($n=15$), subjects without Axis I diagnoses ($n=14$), and subjects without a diagnosis on either Axis I or Axis II ($n=8$) (Table 2). When the mean uptake in each ROI was used as a measure of the rCBF in the analysis instead of the Min–Max measures, all results remained virtually unchanged.

Following the analysis of relationships between PCL-R and collapsed indices for the frontal and temporal areas of interest, all individual ROIs were analyzed for possible relationships with the PCL-R scores (Table 3; all *P* values are two-tailed). It is obvious that the features of psychopathy captured by Factor 1, especially in the new model, are most relevant for comparisons with resting

Table 1
Correlations (Spearman's rho) between frontotemporal rCBF and PCL-R scores in the whole study group ($n=32$) (one-tailed P values)

	PCL-R scores					
	Total	Factor 1	Factor 2	New Factor 1	New Factor 2	New Factor 3
Temporal lobe	−0.15	**−0.48**	0.04	**−0.51**	**−0.33**	−0.08
	(0.209)	(**0.003**)	(0.422)	(**0.001**)	(**0.031**)	(0.330)
Right side	−0.01	**−0.34**	0.17	**−0.35**	−0.17	0.06
	(0.484)	(**0.028**)	(0.173)	(**0.025**)	(0.171)	(0.374)
Left side	−0.23	**−0.49**	−0.09	**−0.55**	**−0.39**	−0.20
	(0.108)	(**0.002**)	(0.312)	(**0.001**)	(**0.013**)	(0.134)
Basal prefrontal cortex	−0.09	**−0.31**	−0.08	**−0.35**	−0.13	−0.12
	(0.316)	(**0.043**)	(0.342)	(**0.024**)	(0.237)	(0.251)
Right side	0.05	−0.20	0.10	**−0.37**	−0.05	0.09
	(0.387)	(0.142)	(0.302)	(**0.018**)	(0.390)	(0.310)
Left side	−0.07	−0.20	−0.09	−0.25	−0.11	−0.11
	(0.354)	(0.136)	(0.314)	(0.081)	(0.267)	(0.283)
Prefrontal cortex	−0.14	**−0.32**	−0.16	**−0.41**	−0.16	−0.20
	(0.215)	(**0.038**)	(0.194)	(**0.009**)	(0.189)	(0.135)
Right side	0.02	−0.17	0.02	**−0.40**	0.00	−0.02
	(0.458)	(0.174)	(0.464)	(0.012)	(0.496)	(0.463)
Left side	−0.06	−0.21	−0.10	−0.28	−0.11	−0.17
	(0.381)	(0.120)	(0.289)	(0.064)	(0.270)	(0.184)

Significant findings shown in bold-faced type.

regional perfusion as in the present study, and that frontal and temporal structures, including the caudate nucleus, hippocampus and amygdala, are of most interest for such analyses.

Median splits by total and factor scores yielded two groups: low-score subjects and high-score subjects, for each factor. The rCBF for each ROI was compared between these groups by repeated Mann–Whitney tests (two-tailed P values). The median split by total PCL-R scores showed no area with a significant difference in rCBF between high- and low-score subjects. Subjects with high scores on Factor 1 had significantly lower rCBF in the medial frontal ($P=0.030$) and lateral frontal ($P=0.018$) areas, in the head of the caudate nucleus ($P=0.024$), in the hippocampus ($P=0.037$), in the left thalamus ($P=0.013$), and in the amygdala ($P=0.049$). Those scoring higher than the median score of Factor 2 had significantly higher rCBF in the parietal association cortices on both the right ($P=0.012$) and the left ($P=0.026$) side than those with lower scores. Subjects scoring over the median on the new Factor 1 had decreased perfusion in the head of the right caudate nucleus ($P=0.026$); those with scores above the median on the new Factor 2 had decreased perfusion in the head of the caudate nucleus ($P=0.035$) and in the left hippocampus ($P=0.006$). Subjects scoring above the median in the new Factor 3 had significant hypoperfusion of the lateral prefrontal cortex ($P=0.036$).

The only significant correlation found between the neuropsychological tests and the rCBF was a negative relationship between the response time for the maze exit tests and the right-sided parietal and frontal rCBF (rho $=-0.46$, $P=0.021$ for the parietal association cortex; rho $=-0.45$, $P=0.023$ for the prefrontal cortex; and rho $=-0.40$, $P=0.048$ for the basal frontal cortex). There were no corresponding relationships with the psychopathy ratings.

4. Discussion

The temporal and frontal lobes have been indicated as sites for cerebral dysfunctions associated with an increased risk of violent behavior in a number of studies comparing violent offenders and

Table 2
Correlations (Spearman's rho) between rCBF and PCL-R scores in specified subgroups (one-tailed *P* values)

	PCL-R scores					
	Total	Factor 1	Factor 2	New Factor 1	New Factor 2	New Factor 3
Temporal lobe						
Men only ($n=29$)	−0.23 (0.113)	**−0.50 (0.003)**	−0.06 (0.383)	**−0.51 (0.002)**	**−0.38 (0.021)**	−0.16 (0.209)
Normal MRI ($n=20$)	0.04 (0.432)	**−0.57 (0.004)**	0.15 (0.268)	**−0.52 (0.010)**	**−0.38 (0.049)**	0.10 (0.341)
No medication ($n=18$)	0.01 (0.492)	−0.43 (0.037)	0.17 (0.253)	**−0.51 (0.015)**	−0.21 (0.204)	0.10 (0.352)
≤30 years old ($n=16$)	−0.20 (0.227)	**−0.52 (0.020)**	−0.07 (0.398)	**−0.46 (0.036)**	**−0.50 (0.026)**	−0.07 (0.401)
No substance abuse ($n=15$)	−0.08 (0.395)	**−0.58 (0.012)**	0.22 (0.216)	**−0.52 (0.024)**	−0.27 (0.164)	−0.01 (0.486)
No substance abuse and no Axis I diagnosis ($n=14$)	−0.22 (0.225)	**−0.70 (0.003)**	0.10 (0.368)	**−0.62 (0.009)**	−0.37 (0.099)	0.01 (0.494)
No substance abuse and no Axis I or II diagnosis ($n=8$)	−0.59 (0.063)	**−0.83 (0.005)**	−0.42 (0.151)	**−0.69 (0.029)**	**−0.75 (0.017)**	**−0.69 (0.029)**
Right side						
Men only ($n=29$)	−0.06 (0.373)	**−0.37 (0.024)**	0.11 (0.292)	**−0.36 (0.027)**	−0.22 (0.129)	0.02 (0.462)
Normal MRI ($n=20$)	0.19 (0.207)	−0.36 (0.058)	0.29 (0.104)	−0.33 (0.080)	−0.12 (0.315)	0.23 (0.168)
No medication ($n=18$)	0.24 (0.166)	−0.18 (0.241)	**0.39 (0.056)**	−0.27 (0.136)	0.01 (0.488)	0.31 (0.102)
≤ 30 years old ($n=16$)	0.12 (0.324)	−0.29 (0.136)	0.27 (0.155)	−0.27 (0.155)	−0.21 (0.222)	0.19 (0.241)
No substance abuse ($n=15$)	0.13 (0.326)	−0.33 (0.113)	0.39 (0.075)	−0.30 (0.142)	0.02 (0.469)	0.17 (0.273)
No substance abuse and no Axis I diagnosis ($n=14$)	0.01 (0.488)	−0.42 (0.066)	0.29 (0.154)	−0.37 (0.099)	−0.05 (0.437)	0.21 (0.238)
No substance abuse and no Axis I or II diagnosis ($n=8$)	−0.55 (0.080)	**−0.64 (0.045)**	−0.52 (0.091)	−0.40 (0.166)	**−0.63 (0.048)**	−0.58 (0.067)
Left side						
Men only ($n=29$)	−0.30 (0.058)	**−0.47 (0.005)**	−0.18 (0.175)	**−0.52 (0.002)**	**−0.41 (0.013)**	−0.28 (0.068)
Normal MRI ($n=20$)	−0.10 (0.334)	**−0.62 (0.002)**	−0.04 (0.440)	**−0.55 (0.006)**	**−0.54 (0.007)**	−0.12 (0.308)
No medication ($n=18$)	0.16 (0.268)	**−0.58 (0.006)**	0.00 (0.493)	**−0.68 (0.001)**	−0.31 (0.102)	−0.13 (0.307)
≤30 years old ($n=16$)	**−0.45 (0.041)**	**−0.66 (0.003)**	−0.36 (0.085)	**−0.64 (0.004)**	**−0.64 (0.004)**	**−0.44 (0.045)**
No substance abuse ($n=15$)	−0.27 (0.163)	**−0.65 (0.004)**	0.01 (0.490)	**−0.62 (0.007)**	−0.41 (0.067)	−0.30 (0.138)
No substance abuse and no Axis I diagnosis ($n=14$)	−0.42 (0.068)	**−0.75 (0.001)**	−0.13 (0.325)	**−0.70 (0.003)**	**−0.50 (0.035)**	−0.34 (0.116)
No substance abuse and no Axis I or II disorder ($n=8$)	−0.48 (0.116)	**−0.71 (0.025)**	−0.21 (0.305)	**−0.72 (0.023)**	−0.58 (0.067)	−0.59 (0.062)
Basal prefrontal cortex						
Men only ($n=29$)	−0.11 (0.290)	−0.25 (0.099)	−0.11 (0.278)	−0.30 (0.057)	−0.07 (0.368)	−0.16 (0.203)
Normal MRI ($n=20$)	0.10 (0.341)	**−0.39 (0.046)**	0.01 (0.489)	−0.36 (0.058)	−0.23 (0.170)	−0.06 (0.406)

Table 2 *(Continued)*

	PCL-R scores					
	Total	Factor 1	Factor 2	New Factor 1	New Factor 2	New Factor 3
No medication ($n=18$)	−0.18	**−0.52**	−0.10	**−0.53**	−0.33	−0.21
	(0.244)	(**0.014**)	(0.350)	(**0.012**)	(0.090)	(0.203)
≤30 years old ($n=16$)	−0.23	−0.38	−0.28	−0.27	−0.39	−0.31
	(0.193)	(0.072)	(0.151)	(0.153)	(0.067)	(0.120)
No substance abuse ($n=15$)	−0.07	−0.43	0.08	−0.34	−0.10	−0.28
	(0.398)	(0.056)	(0.396)	(0.107)	(0.356)	(0.153)
No substance abuse and	−0.20	**−0.51**	−0.04	−0.41	−0.17	−0.27
no Axis I diagnosis ($n=14$)	(0.251)	(**0.032**)	(0.452)	(0.072)	(0.286)	(0.171)
No substance abuse and no	**−0.71**	**−0.83**	−0.55	**−0.68**	**−0.90**	−0.61
Axis I or II diagnosis ($n=8$)	(**0.023**)	(**0.006**)	(0.080)	(**0.032**)	(**0.001**)	(0.053)
Right side						
Men only ($n=29$)	0.02	−0.13	0.07	**−0.33**	0.01	0.07
	(0.461)	(0.250)	(0.369)	(**0.040**)	(0.477)	(0.362)
Normal MRI ($n=20$)	0.29	−0.25	0.24	**−0.48**	−0.16	0.22
	(0.111)	(0.141)	(0.159)	(**0.016**)	(0.254)	(0.177)
No medication ($n=18$)	0.02	**−0.41**	0.18	**−0.53**	−0.19	0.06
	(0.476)	(**0.046**)	(0.238)	(**0.012**)	(0.231)	(0.409)
≤30 years old ($n=16$)	−0.18	**−0.43**	−0.16	−0.38	−0.42	−0.20
	(0.253)	(**0.048**)	(0.280)	(0.074)	(0.052)	(0.234)
No substance abuse ($n=15$)	0.24	−0.12	0.40	**−0.46**	0.11	0.12
	(0.195)	(0.330)	(0.068)	(**0.043**)	(0.346)	(0.338)
No substance abuse and	0.15	−0.20	0.32	**−0.54**	0.06	0.15
no Axis I diagnosis (n=14)	(0.305)	(0.247)	(0.132)	(**0.024**)	(0.422)	(0.305)
No substance abuse and no	−0.02	−0.12	0.07	−0.46	−0.20	0.09
Axis I or II diagnosis ($n=8$)	(0.478)	(0.389)	(0.433)	(0.127)	(0.321)	(0.420)
Left side						
Men only ($n=29$)	−0.06	−0.11	−0.08	−0.18	−0.02	−0.11
	(0.377)	(0.291)	(0.342)	(0.173)	(0.465)	(0.286)
Normal MRI ($n=20$)	0.08	−0.26	−0.05	−0.23	−0.23	−0.08
	(0.364)	(0.138)	(0.424)	(0.164)	(0.170)	(0.372)
No medication ($n=18$)	−0.06	−0.36	−0.01	−0.40	−0.24	−0.15
	(0.405)	(0.069)	(0.490)	(0.051)	(0.165)	(0.282)
≤30 years old ($n=16$)	−0.29	−0.31	**−0.44**	−0.30	−0.34	−0.41
	(0.142)	(0.120)	(**0.042**)	(0.133)	(0.102)	(0.058)
No substance abuse ($n=15$)	−0.29	−0.38	−0.19	−0.38	−0.14	**−0.52**
	(0.150)	(0.082)	(0.254)	(0.084)	(0.315)	(**0.025**)
No substance abuse and	−0.31	−0.39	−0.21	−0.39	−0.13	**−0.48**
no Axis I diagnosis ($n=14$)	(0.140)	(0.083)	(0.236)	(0.083)	(0.323)	(**0.041**)
No substance abuse and no	−0.43	**−0.68**	−0.21	**−0.64**	**−0.69**	−0.38
Axis I or II diagnosis ($n=8$)	(0.145)	(**0.031**)	(0.305)	(**0.043**)	(**0.030**)	(0.176)
Prefrontal cortex						
Men only ($n=29$)	−0.18	−0.30	−0.20	**−0.40**	−0.14	−0.23
	(0.173)	(0.060)	(0.152)	(**0.016**)	(0.227)	(0.116)
Normal MRI ($n=20$)	0.04	**−0.39**	−0.05	**−0.41**	−0.24	−0.08
	(0.439)	(**0.046**)	(0.415)	(**0.037**)	(0.151)	(0.366)
No medication ($n=18$)	−0.17	**−0.42**	−0.18	**−0.49**	−0.23	−0.28
	(0.255)	(**0.040**)	(0.237)	(**0.019**)	(0.175)	(0.129)
≤30 years old ($n=16$)	−0.29	−0.40	−0.41	−0.35	−0.40	−0.42
	(0.137)	(0.064)	(0.057)	(0.090)	(0.065)	(0.055)
No substance abuse ($n=15$)	−0.03	−0.29	0.02	−0.28	0.03	−0.36
	(0.465)	(0.146)	(0.469)	(0.153)	(0.454)	(0.092)

Table 2 *(Continued)*

	PCL-R scores					
	Total	Factor 1	Factor 2	New Factor 1	New Factor 2	New Factor 3
No substance abuse and no Axis I diagnosis ($n=14$)	−0.17 (0.281)	−0.37 (0.094)	−0.14 (0.314)	−0.35 (0.113)	−0.03 (0.467)	−0.39 (0.084)
No substance abuse and no Axis I or II diagnosis ($n=8$)	−0.57 (0.069)	−0.61 (0.054)	−0.45 (0.130)	−0.49 (0.107)	**−0.63 (0.048)**	−0.61 (0.053)
Right side						
Men only ($n=29$)	−0.02 (0.463)	−0.13 (0.253)	0.00 (0.495)	**−0.39 (0.018)**	0.07 (0.364)	−0.04 (0.427)
Normal MRI ($n=20$)	0.28 (0.117)	−0.20 (0.201)	0.20 (0.197)	**−0.45 (0.023)**	−0.05 (0.422)	0.14 (0.279)
No medication ($n=18$)	−0.03 (0.450)	−0.36 (0.072)	0.05 (0.429)	**−0.59 (0.005)**	−0.07 (0.391)	−0.14 (0.297)
$\leq$ 30 years old ($n=16$)	−0.12 (0.332)	−0.36 (0.086)	−0.17 (0.263)	**−0.47 (0.033)**	−0.27 (0.156)	−0.27 (0.152)
No substance abuse ($n=15$)	0.33 (0.115)	−0.04 (0.442)	0.43 (0.053)	**−0.54 (0.018)**	0.29 (0.151)	0.11 (0.348)
No substance abuse and no Axis I diagnosis ($n=14$)	0.25 (0.191)	−0.11 (0.356)	0.35 (0.109)	**−0.62 (0.009)**	0.26 (0.189)	0.14 (0.319)
No substance abuse and no Axis I or II diagnosis ($n=8$)	−0.02 (0.478)	−0.12 (0.389)	−0.02 (0.478)	−0.59 (0.061)	−0.12 (0.386)	−0.09 (0.420)
Left side						
Men only ($n=29$)	−0.06 (0.374)	−0.17 (0.190)	−0.09 (0.318)	−0.26 (0.091)	−0.05 (0.403)	−0.16 (0.199)
Normal MRI ($n=20$)	0.10 (0.345)	−0.26 (0.134)	−0.03 (0.453)	−0.25 (0.142)	−0.21 (0.184)	−0.13 (0.296)
No medication ($n=18$)	0.14 (0.296)	−0.39 (0.054)	−0.12 (0.323)	**−0.44 (0.032)**	−0.26 (0.151)	−0.30 (0.113)
$\leq$ 30 years old ($n=16$)	−0.32 (0.115)	−0.30 (0.131)	**−0.46 (0.036)**	−0.25 (0.174)	−0.37 (0.079)	**−0.51 (0.022)**
No substance abuse ($n=15$)	−0.09 (0.374)	−0.31 (0.130)	−0.02 (0.467)	−0.26 (0.172)	−0.03 (0.461)	**−0.45 (0.045)**
No substance abuse and No Axis I diagnosis ($n=14$)	−0.21 (0.232)	−0.39 (0.086)	−0.14 (0.315)	−0.33 (0.127)	−0.08 (0.398)	**−0.46 (0.050)**
No substance abuse and no Axis I or II diagnosis ($n=8$)	−0.48 (0.116)	**−0.73 (0.020)**	−0.26 (0.265)	−0.61 (0.056)	**−0.70 (0.027)**	−0.49 (0.108)

Significant findings shown in bold-faced type.

normal control subjects. Recent MRI studies have documented reduced volumes of the frontal lobes in antisocial personality disorder (Raine et al., 2001) and of the hippocampi in psychopathy (Laakso et al., 2001). The affective abnormalities noted in psychopathy have been linked to a deficient limbic activation in the processing of affective stimuli in a functional MRI study (Kiehl et al., 2001). Changes in the regional metabolism or perfusion have been detected by various functional imaging methods, but the etiology is uncertain. Hereditary factors, as well as injuries from child abuse, skull trauma, substance abuse or functional disorders, could be involved.

We found strong negative correlations between the interpersonal, but not the behavioral, features of psychopathy and the frontal and temporal perfusion. Temporal structures are known to be involved in the affective coloring of interpersonal experiences and in the development of emotional behavior regulation, whereas the frontal lobes are thought to control executive functions, such as

Table 3
Correlations between all ROIs and the PCL-R scores ($n=32$) (two-tailed P values)

	PCL-R scores					
	Total	Factor 1	Factor 2	New Factor 1	New Factor 2	New Factor 3
Basal frontal lobe	−0.14	**−0.38**	−0.06	−0.27	−0.23	−0.15
	(0.463)	(**0.034**)	(0.755)	(0.132)	(0.215)	(0.417)
Medial frontal lobe	−0.15	−0.25	−0.19	−0.30	−0.17	−0.18
	(0.421)	(0.173)	(0.295)	(0.095)	(0.354)	(0.318)
Lateral frontal lobe	−0.24	−0.30	−0.25	−0.28	−0.21	−0.30
	(0.193)	(0.091)	(0.160)	(0.121)	(0.240)	(0.095)
Basal frontal lateral cortex	−0.08	**−0.37**	−0.02	**−0.36**	−0.24	−0.10
	(0.657)	(**0.038**)	(0.912)	(**0.040**)	(0.190)	(0.594)
Right side	−0.13	**−0.40**	−0.06	**−0.36**	−0.26	−0.12
	(0.487)	(**0.025**)	(0.734)	(**0.041**)	(0.154)	(0.514)
Left side	0.12	−0.15	0.16	−0.18	−0.08	0.03
	(0.532)	(0.422)	(0.391)	(0.328)	(0.650)	(0.863)
Basal frontal medial cortex	0.00	−0.10	−0.02	−0.29	−0.02	0.02
	(0.986)	(0.584)	(0.919)	(0.104)	(0.936)	(0.919)
Right side	0.13	−0.03	0.13	−0.26	0.10	0.17
	(0.471)	(0.889)	(0.487)	(0.151)	(0.579)	(0.368)
Left side	−0.15	−0.20	−0.18	−0.27	−0.14	−0.13
	(0.418)	(0.263)	(0.319)	(0.134)	(0.433)	(0.480)
Frontal association cortex	0.00	−0.19	0.08	**−0.42**	−0.02	−0.07
	(0.994)	(0.309)	(0.682)	(**0.016**)	(0.934)	(0.691)
Right side	0.01	−0.22	0.10	**−0.44**	−0.03	−0.05
	(0.979)	(0.233)	(0.572)	(**0.011**)	(0.869)	(0.778)
Left side	0.06	−0.06	0.10	−0.25	0.06	−0.02
	(0.759)	(0.730)	(0.593)	(0.167)	(0.734)	(0.919)
Frontal lateral cortex	0.03	−0.14	−0.02	−0.29	−0.03	−0.13
	(0.890)	(0.431)	(0.911)	(0.110)	(0.855)	(0.480)
Right side	0.01	−0.17	−0.01	−0.32	−0.01	−0.12
	(0.963)	(0.364)	(0.954)	(0.077)	(0.959)	(0.510)
Left side	0.05	−0.09	0.00	−0.24	−0.04	−0.12
	(0.779)	(0.615)	(0.998)	(0.185)	(0.810)	(0.508)
Frontal medial cortex	0.03	−0.13	−0.02	−0.32	0.01	−0.07
	(0.891)	(0.490)	(0.921)	(0.073)	(0.964)	(0.691)
Right side	0.05	−0.10	0.01	−0.32	0.05	−0.04
	(0.795)	(0.593)	(0.942)	(0.071)	(0.794)	(0.848)
Left side	−0.03	−0.20	−0.06	−0.30	−0.10	−0.12
	(0.885)	(0.271)	(0.740)	(0.102)	(0.586)	(0.517)
Head of caudate nucleus	−0.32	**−0.48**	−0.19	**−0.35**	**−0.42**	−0.16
	(0.073)	(**0.005**)	(0.298)	(**0.050**)	(**0.018**)	(0.394)
Right side	−0.32	**−0.44**	−0.19	**−0.37**	−0.30	−0.18
	(0.080)	(**0.012**)	(0.310)	(**0.039**)	(0.091)	(0.313)
Left side	−0.24	**−0.37**	−0.17	−0.31	**−0.37**	−0.05
	(0.192)	(**0.039**)	(0.357)	(0.080)	(**0.039**)	(0.804)
Angular gyrus	0.04	−0.29	0.25	**−0.38**	−0.19	0.02
	(0.847)	(0.102)	(0.170)	(**0.033**)	(0.305)	(0.896)
Right side	−0.01	−0.29	0.20	−0.29	−0.20	0.02
	(0.939)	(0.109)	(0.266)	(0.103)	(0.282)	(0.894)
Left side	0.06	−0.21	0.20	**−0.36**	−0.13	0.01
	(0.750)	(0.256)	(0.265)	(**0.044**)	(0.479)	(0.955)
Temporal gyrus	0.01	−0.29	0.16	**−0.43**	−0.16	0.05
	(0.976)	(0.106)	(0.375)	(**0.014**)	(0.397)	(0.785)
Right side	0.07	−0.17	0.17	−0.25	−0.07	0.13

Table 3 *(Continued)*

	PCL-R scores					
	Total	Factor 1	Factor 2	New Factor 1	New Factor 2	New Factor 3
	(0.710)	(0.352)	(0.349)	(0.173)	(0.720)	(0.463)
Left side	−0.11	**−0.40**	0.06	**−0.52**	−0.26	−0.10
	(0.567)	(**0.024**)	(0.735)	(**0.002**)	(0.159)	(0.581)
Hippocampus	−0.12	**−0.43**	−0.05	**−0.41**	−0.30	−0.08
	(0.509)	(**0.015**)	(0.803)	(**0.022**)	(0.095)	(0.660)
Right side	0.09	−0.21	0.20	−0.30	−0.09	0.16
	(0.624)	(0.244)	(0.281)	(0.100)	(0.625)	(0.375)
Left side	−0.29	**−0.54**	−0.24	**−0.49**	**−0.42**	−0.27
	(0.104)	(**0.001**)	(0.188)	(**0.005**)	(**0.016**)	(0.132)
Parietal association cortex	0.16	−0.22	0.32	−0.34	−0.08	0.17
	(0.392)	(0.231)	(0.072)	(0.060)	(0.661)	(0.364)
Right side	0.21	−0.17	**0.37**	−0.33	−0.02	0.23
	(0.247)	(0.341)	(**0.037**)	(0.069)	(0.933)	(0.213)
Left side	0.16	−0.16	0.32	−0.26	−0.07	0.14
	(0.382)	(0.379)	(0.078)	(0.154)	(0.714)	(0.446)
Thalamus	0.04	−0.21	0.10	−0.13	−0.15	−0.07
	(0.837)	(0.244)	(0.606)	(0.471)	(0.424)	(0.700)
Right side	0.15	−0.10	0.17	−0.07	−0.04	0.04
	(0.399)	(0.572)	(0.350)	(0.699)	(0.842)	(0.809)
Left side	−0.08	−0.32	0.02	−0.23	−0.26	−0.18
	(0.650)	(0.079)	(0.910)	(0.217)	(0.148)	(0.329)
Occipital lobe	−0.04	−0.04	0.05	−0.12	0.01	−0.05
	(0.822)	(0.836)	(0.774)	(0.507)	(0.955)	(0.793)
Right side	−0.10	−0.05	−0.05	−0.12	−0.01	−0.10
	(0.588)	(0.772)	(0.798)	(0.498)	(0.951)	(0.590)
Left side	0.08	0.05	0.19	−0.04	0.11	0.03
	(0.672)	(0.772)	(0.304)	(0.831)	(0.543)	(0.862)
Amygdala	−0.29	−0.30	−0.20	−0.33	−0.24	−0.26
	(0.103)	(0.100)	(0.280)	(0.069)	(0.192)	(0.144)
Right side	−0.10	−0.24	0.03	−0.21	−0.11	−0.08
	(0.605)	(0.178)	(0.891)	(0.244)	(0.534)	(0.646)
Left side	−0.33	−0.27	−0.25	−0.33	−0.25	−0.27
	(0.068)	(0.135)	(0.160)	(0.065)	(0.164)	(0.135)
Cerebellum	0.19	0.13	0.15	0.08	0.08	0.18
	(0.303)	(0.476)	(0.428)	(0.678)	(0.682)	(0.315)
Right side	−0.03	−0.01	−0.12	0.00	0.01	−0.10
	(0.865)	(0.947)	(0.527)	(0.993)	(0.970)	(0.572)
Left side	0.19	0.11	0.23	0.07	0.10	0.20
	(0.311)	(0.535)	(0.205)	(0.694)	(0.579)	(0.273)

Significant correlations shown in bold-faced type.

impulse control, planning and problem-solving strategies. It is not ascertained if the subjects with high psychopathy scores have abnormally low frontotemporal perfusion, or if the correlation rather reflects hyperperfusion in the subjects with low scores. On the basis of our previous results, we believe that the current findings represent absolute hypoperfusions, but another study design is required to explore this further.

The significant association between the interpersonal PCL-R Factor 1 scores and the left-sided hippocampal rCBF in our study conforms to the hippocampal volume decreases in interpersonal psychopathy described by Laakso et al. (2001).

This association was even stronger for the new model Factor 1, while the new Factor 2 showed a less pronounced association with the hippocampal rCBF, which matches the findings by the Tiihonen group (as cited in Cooke and Michie, 2001).

Visual assessments of regional perfusion in both our studies have suggested hypoperfusions of the frontal lobes in violent persons, and this has to some extent been supported by the quantitative analyses of these areas, even if these associations are not as strong as those for the temporal blood flow. The North American data have suggested both frontal and temporal involvement, but with more consistent evidence for a frontal dysfunction. There are, however, differences between Scandinavian and North American offender groups. The low crime base rate and drug availability in Scandinavia probably led to an over-representation of crimes committed on the grounds of mental disorders, impulsivity and strong affective states, whereas clearly antisocial and drug-related crimes would be under-represented. Our findings have remained virtually unchanged in subgroups without Axis I disorders (including substance abuse and major mental disorders) in both studies.

An unexpected finding in our first study was a significant hyperperfusion of the parietal association cortex bilaterally, but most pronounced on the right side. The same phenomenon was observed in the present study, where the behavioral aspects of psychopathy were positively correlated with the rCBF of the parietal association cortex, significantly on the right side and close to significantly on the left. This is most probably explained by a confounding impact of age, as both rCBF and PCL-R, especially Factor 2, tend to decline with age. This age effect renders most of our findings concerning negative correlations between rCBF and PCL-R scores more conservative, but might falsely indicate positive correlations between the PCL-R and unrelated areas.

Analyses of regional brain activity for possible covariance with personality traits that are linked to an increased risk of violent behavior may prove more fruitful than mere comparisons between index and control subjects, as differences in cognition, personality, affective state and life situation may have far stronger impact than the target behavior on the variables measured. All our subjects were on remand and lived under the same conditions, they were admitted to our department for the same period of time, and they were all facing trials for severe crimes.

The PCL-R is a robust instrument that reflects personality and behavioral factors on the basis of interviews, clinical judgement and actuarial data. This kind of instrument has a number of advantages when used in clinical settings for studies with high-technological methods and small numbers of subjects; they rely on multiple sources, ratings are corroborated by file data and the information may be modulated by clinical judgement. Self-rating instruments have obvious advantages in large-scale epidemiological research, but should be regarded as second-line tools in smaller clinical settings, where highly accurate and stable ratings are needed for comparison to laboratory results. With the introduction of instruments that enable us to depict the function in more specific brain areas, the development of instruments for phenotypic characterization in behavioral situations, as well as in resting phases, is of crucial importance. It will also be highly interesting to study violent persons in simulated violent situations, in resting conditions, in neuropsychological test situations and in follow-up studies, as we still do not know whether the aberrant functions reported from various studies reflect state or trait features.

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