Abnormal Hippocampal Shape in Offenders with Psychopathy

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Abstract: Posterior hippocampal volumes correlate negatively with the severity of psychopathy, but local morphological features are unknown. The aim of this study was to investigate hippocampal morphology in habitually violent offenders having psychopathy. Manual tracings of hippocampi from magnetic resonance images of 26 offenders (age: 32.5 ± 8.4), with different degrees of psychopathy (12 high, 14 medium psychopathy based on the Psychopathy Checklist Revised), and 25 healthy controls (age: 34.6 ± 10.8) were used for statistical modelling of local changes with a surface-based radial distance mapping method. Both offenders and controls had similar hippocampal volume and asymmetry ratios. Local analysis showed that the high psychopathy group had a significant depression along the longitudinal hippocampal axis, on both the dorsal and ventral aspects, when compared with the healthy controls and the medium psychopathy group. The opposite comparison revealed abnormal enlargement of the lateral borders in both the right and left hippocampi of both high and medium psychopathy groups versus controls, throughout CA1, CA2-3 and the subicular regions. These enlargement and reduction effects survived statistical correction for multiple comparisons in the main contrast (26 offenders vs. 25 controls) and in most subgroup comparisons. A statistical check excluded a possible confounding effect from amphetamine and polysubstance abuse. These results indicate that

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habitually violent offenders exhibit a specific abnormal hippocampal morphology, in the absence of total gray matter volume changes, that may relate to different autonomic modulation and abnormal fear-conditioning. *Hum Brain Mapp* 31:438–447, 2010. © 2009 Wiley-Liss, Inc.

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INTRODUCTION

Psychopathy is a severe alteration of emotional life that features a profound lack of empathy for other people's feelings, violation of social norms to obtain short term gains, and a failure to capitalize on experience, particularly punishment, to correct one's own behavior and thus benefit in the long run [Hare, 2006; Sommer et al., 2006]. The syndrome becomes apparent in early childhood development, and is frequently observed in people who are guilty of violent behavior, accompanied by substance abuse, and refractory to treatment [Hare, 2006]. Psychopathy overlaps partially with the DSM-IV-R diagnosis of antisocial personality disorder (ASPD). However, this only defines the phenotype of aberrant social behavior, and not only applies to offenders with psychopathy but also to persons with reversible, treatment-responsive aberrant behavior that may be due to a particular social context or situation. Deficits in classical conditioning, particularly fear conditioning [Birbaumer et al., 2005], in the processing of emotional (mainly negative) stimuli [Sommer et al., 2006], and in response inhibition tasks may be considered as central components of the clinical syndrome [Pridmore et al., 2005]. Together, these features lead to the core features of impulsive conduct and an inability to take into account the long-term consequences of one's actions. Results from functional MRI have consistently identified abnormalities in the limbic system of such cases, and offenders exhibit abnormally low affect-related activity in regions that are crucially involved in emotion processing, such as the amygdala, hippocampus, striatum, and cingulate gyrus [Birbaumer et al., 2005; Kiehl et al., 2001].

Among brain structures, the relevance of the hippocampus for emotional and adaptive behavior is underestimated. The hippocampus is involved in the acquisition and retrieval of fear conditioning [Burman et al., 2006; Giovannini, 2006; Tsetsenis et al., 2007], and in the nociceptive aspects of behavior and memory. The hippocampus belongs, among others, to the serotonergic system, a key circuit regulating fear conditioning and impulsive behavior [Cardinal, 2006; Deakin, 2003; van Goozen and Fairchild, 2006]. Despite a decreased activation in functional imaging studies [Kiehl et al., 2001], global hippocampal volumes among antisocial or psychopathic subjects do not seem to differ significantly from controls [Barkataki et al., 2006; Laakso et al., 2001; Raine et al., 2004].

Nonetheless, a more detailed morphological investigation denoted a negative correlation between the posterior hippocampal volume and severity of psychopathy in a sample of offenders [Laakso et al., 2001]. Consistent with a possible posterior hippocampal involvement, deficits in spatial performance have been detected in individuals with ASPD [Raine et al., 2003] and, at a very young age, also in conduct disorder [Raine et al., 2002].

To further investigate a putative hippocampal involvement in psychopathy, we used a technique that allows for the detection of local changes throughout the hippocampal surface in a group of well-characterized, habitually violent offenders that had different severities of psychopathy, and who were also free of other significant past or current major mental disorders.

METHODS

Subjects

A total of 26 violent offenders and 25 healthy Caucasian Finnish men were included, and have already been described in detail [Tiihonen et al., 2008]. Offenders were consecutively admitted to a forensic psychiatric hospital for pretrial assessment, and had no history or diagnosis of psychosis, Cluster A personality disorder, or brain damage. All offenders had been charged with violent offences, had a history of recurrent violent acts, and previous criminal convictions. Diagnoses were made by a senior forensic psychiatrist using multiple sources of information. All offenders fulfilled criteria for both DSM-IV ASPD and ICD-10 dissocial personality. All met the DSM-IV and ICD 10 criteria for alcohol abuse with early onset, corresponding to Cloninger Type 2 alcoholism [Cloninger, 1987], and had no access to alcohol for 3–6 months prior to the brain scan and no access to illicit drugs for 1–7 weeks prior to the brain scan. Fifteen offenders had used amphetamine at least once. Eleven of the offenders were free of psychotropic medication, and 15 were taking either a benzodiazepine, an antidepressant, or an antipsychotic medication (i.e., small doses used as an anxiolytic or hypnotic).

The Psychopathy Checklist Revised (PCL-R) ratings were used to assess psychopathy [Hare, 1991]. The pretrial psychiatric assessment consisted of thorough physical,

neuropsychological, and psychiatric evaluations, including the completion of the Wechsler Adult Intelligence Scale-Revised [Wechsler, 1981], and a structural MRI scan.

Controls were recruited among university students, hospital staff, and skilled workers, and were free of current or past substance abuse and mental disorders, which were determined on the basis of an unstructured interview. Psychological testing was not used to assess controls. All participants signed an informed consent, and additional data from the offenders were obtained retrospectively from hospital files, after approval by the ethical committee of the Kuopio University Hospital.

Magnetic Resonance Imaging

The participants were scanned with a 1.0 T Impact MRI scanner (Siemens; Erlangen, Germany) using a standard head coil and a tilted T1-weighted coronal 3D gradient echo sequence (magnetization prepared rapid acquisition gradient echo: TR 10 ms, TE 4 ms, TI 250 ms, flip angle 12°, FOV 250 mm, matrix 256 × 192, 1 acquisition). The three-dimensional spatial resolution was 2.0 mm × 1.3 mm × 0.97 mm.

Image Processing

MR images were registered to a customized template using the Statistical Parametric Mapping software (<http://www.fil.ion.ucl.ac.uk/spm/software/spm2/>), after manually setting the anterior commissure as the origin of the stereotactic space, reorienting along the AC-PC line, and removal of voxels below the cerebellum with the MRIcro software (www.psychology.nottingham.ac.uk/staff/cr1/micro.html). A 12-parameters affine transformation was used to register each image to a customized template created from the MRI of all the subjects included in the study. The images were resampled to an isotropic voxel of 1 mm. The hippocampi of offenders and controls were manually traced by a single tracer, who was blind to the diagnosis and followed a validated protocol (Pruessner et al., 2000). Tracings were carried out on contiguous coronal brain sections with the Segmentation software developed by the LONI (Laboratory of NeuroImaging) at the University of California at Los Angeles (http://www.loni.ucla.edu/ICBM/ICBM_ResSoftware.html#seg3). At the same time, the entire 3D MRI of the same subject was entered into the interactive segmentation software Display (Brain Imaging Center -Montreal Neurological Institute: <http://www.bic.mni.mcgill.ca/software>), to allow simultaneous orthogonal views, to assist in the identification of the hippocampal boundaries, especially for some slices where the coronal section does not provide optimal information. Reliability measures were previously obtained on an independent sample of 20 controls (intra-rater reliability: 0.94, inter-rater reliability: 0.89). Hippocampal volumes were obtained and corrected for brain size, and retained for subsequent statistical analyses [Thompson et al., 2004].

Figure 1.

Stages of data processing; from the manual tracing of the hippocampus on coronal MRI images to the three-dimensional reconstruction of the hippocampal shape, where percent changes and statistical differences are mapped in color codes. Adapted from Apostolova et al., 2006 and Thompson et al., 2004 [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Radial Distance Mapping (RDM)

Three-dimensional parametric surface mesh models were generated from the manually segmented hippocampal tracings [Narr et al., 2004; Thompson et al., 2004] (see Fig. 1). Slices were resampled and resliced to the 150 uniformly spaced levels that were required for precisely matching the sequential points in the standard mesh model. Mathematical details for the interpolation of the hippocampal shape between image slices are presented elsewhere [Thompson et al., 1996]. Essentially, the surface was more highly sampled than the original images, as the hippocampus is found in different numbers of sections across subjects [Thompson et al., 1996]. Therefore, a standard sampling frequency of 150 sections was used. At the slice level, the points lying on the contour of the tracing were uniformly spaced into 100 homologous points. On

each resampled slice, the radial directions were defined as the shortest lines connecting each surface point to the centroid of the slice. The correspondence of the 3D parametric mesh models of each individual's hippocampi, therefore, was automatically obtained by matching, for each level, the homologous uniformly spaced points on the surface contour. This ensured a precise comparison of anatomy between subjects and groups at each hippocampal surface point.

The radial size of each hippocampus, at each boundary point, was assessed by measuring the length of the radial directions. Shorter and longer radial distances were used as an index of shrinkage and enlargement, respectively, and analyzed to estimate systematic differences in morphology between offenders and controls, which were finally mapped in color to the corresponding surface points [Thompson et al., 1996, 2004].

Statistical Maps and Permutation Testing

T-tests were used to evaluate local significant differences at each point in the radial mapping procedure, in comparison between the offenders and controls, and in subgroup comparisons (i.e., high psychopathy versus controls, medium psychopathy versus controls, medium psychopathy versus high psychopathy). PCL-R scores were used as covariates to generate 3D maps of Pearson's *R* and significant correlations with hippocampal morphology in the offenders. *P* values were computed for the maps at the surface level by setting a significance threshold of $P < 0.05$. Maps of systematic differences, corresponding to the uncorrected maps at $P < 0.05$ and subsequent percent changes were visualized in color codes on 3D models of the hippocampus, where its surface histological subregions were marked (see Fig. 2), as inferred from an atlas [Duvernoy, 1998]. Furthermore, a permutation method was applied to all of the experiments in this work, to provide an overall *P* value that was corrected for multiple comparisons [Thompson et al., 2003].

Permutation methods basically measure the probability that the observed distribution of a given feature (e.g., the number of vertices with statistics below $P < 0.05$ in the entire map) would occur by accident if the subjects were randomly assigned to groups. The effect observed in the random assignments was then compared to that observed in the true experiment. This calculation was made by computing the number of times that an effect with a similar or greater magnitude occurred in the random assignments compared to the true assignments, over the total number of "random" experiments run. This ratio represents the empirical probability that the observed pattern occurred by accident, and it provides an overall significance value for reliability of the map, corrected for multiple comparisons [Thompson et al., 2003]. In the RDM technique, $P = 0.01$ was set as the primary threshold for permutation testing. More specifically, 10,000 permutations of the assign-

Figure 2.

Regions with hippocampal gray matter changes in 26 offenders compared with 25 controls, expressed as percent changes (A; % values on the left of the color bar) and significant differences (B; *P* values on the right of the color bar). The surface cytoarchitectonic sectors (adapted from Frisoni et al., 2006) are derived from an atlas of the human hippocampus [Duvernoy, 1998]. Offenders exhibited a significant depression along the longitudinal midline, possibly reflecting a tissue reduction in the dentate gyrus. Larger lateral borders can be observed in the body and tail of the hippocampus, covering the subiculum, and the CA2-3 and CA1 regions. This figure illustrates regions significant at $P < 0.05$ uncorrected. The whole maps including both reduction and enlargement effects were significant, bilaterally, at the permutation test ($P < 0.002$).

ments for subjects to groups were computed, while keeping the total number of subjects in each group the same, to carry out 10,000 random experiments. In each of these experiments, instead of assigning 0 to cases and 1 to controls, as in the true experiment, the assignments of 0 and 1 to cases and controls was randomly scrambled (permuted). For each of these 10,000 permutations, the *P*-map of the differences for the "cases" (all individuals randomly assigned to Group 0) versus "controls" (all individuals randomly assigned to Group 1) was generated

TABLE I. Sociodemographic and clinical features of the healthy men and the violent offenders

	Controls (<i>N</i> = 25)	Violent offenders (<i>N</i> = 26)	<i>P</i> -value
Age, years	34.6 ± 10.8	32.5 ± 8.4	0.438
Alcohol dependence, %	0	100%	—
Age onset of alcohol abuse	—	13.6 ± 2.9	—
Polisubstance abuse, %	0	77%	—
Total intracranial volume (cm ³)	1,707 ± 117	1,654 ± 108	0.102
Hippocampus (mm ³)			
Right	3,258 ± 395	3,361 ± 316	0.306
Left	3,389 ± 378	3,460 ± 353	0.491
Hare's Factor 1	—	10.8 ± 3.5	—
Hare's Factor 2	—	16.6 ± 1.7	—
IQ	—	91.5 ± 9.0	—

Hippocampal volumes are normalized by total intracranial volumes. Values denote mean ± SD. *P* values refer to Student's *t* and Fisher's exact tests. Total hippocampal volumes are normalized and scaled to the ICBM (International Consortium Brain Mapping) standard space. Factor 1 is "Arrogant Deceitful Interpersonal Conduct and Deficient Affective Experience", and Factor 2 "Impulsive, Irresponsible Behavioral Style." The IQ of the offenders was assessed using the Wechsler Adult Intelligence Scale—Revised [Wechsler, 1981].

point by point along the whole 3D hippocampal mesh model, and a new *P*-map was obtained for each random experiment. Subsequently, the number of supra-threshold (i.e., significant) voxels was computed and compared between each random experiment and the true experiment. In the whole set of the 10,000 experiments, the total number of times that the supra-threshold count was equal or higher than that observed in the true experiment was divided by 10,000 (i.e., the number of random experiments carried out), and this estimated the probability that a map, with an amount of significant local differences greater than or equal to that observed in the true experiment, could be obtained by chance.

We note that this use of the supra-threshold volume of statistics is analogous to set-level inference in functional imaging [Frackowiak et al., 2003]. Other types of permutation tests are possible, examining the distribution of the size of the largest supra-threshold cluster, or the peak height (maximum statistic), etc. In general, we choose the supra-threshold volume statistic as it allows the detection of diffuse effects that occur weakly across the surface of a structure so long as they are present at larger number of voxels that would be expected by chance alone. This is very similar to analysis that control the false discovery rate [Hochberg and Benjamini, 1990; Genovese et al., 2002], where the supra-threshold counts are analyzed using a histogram.

RESULTS

Offenders and controls were of similar age. Alcohol dependence or other substance abuse was common among offenders (100%), and absent in controls (0%; *P* < 0.001). Besides alcohol, polysubstance abuse was present in 77%

of cases and 0% of controls (*P* < 0.001). IQ scores were not available for control subjects, but, in the offender group, they were typically on the lower range of normality (Table I).

Twelve of the 26 violent offenders obtained a score of 30 or higher on PCL-R featuring psychopathy [Hare, 1991], with a mean value of 34.6 and a standard deviation of 3.1. The other 14 had medium severity scores (25.9 ± 2.8). In comparison between the high and medium psychopathy groups, no significant differences were observed for age, duration of alcohol abuse, amphetamine use, or current use of psychotropic medication, but the prevalence of polysubstance abuse was higher in the subgroup with high psychopathy scores (Table II).

The hippocampal volumes, after correction for brain size, were similar between offenders and controls (Table I), and between the two subgroups of high and medium psychopathy. Paired *t*-tests between left and right hippocampi denoted a similar degree of significant difference in both offenders and controls (controls: *P* = 0.008, offenders: *P* = 0.007), consistently with the physiological volumetric asymmetry. When the asymmetry ratio (right/left) was computed and directly compared between offenders and controls, no significant differences were observed with the *t*-test (offenders: 0.97 ± 0.05; controls: 0.96 ± 0.07, *P* = 0.532).

In the hippocampal surface maps, the offender sample displayed a complex pattern of both enlargement and reduction, covering most cytoarchitectonic sectors of the hippocampus, as inferred from an atlas [Duvernoy, 1998; Fig. 2]. More specifically, a bilateral depression (Fig. 2, green-yellow color range) was observed along the longitudinal axis of the body and tail, in the dorsal and ventral aspects. On the anterior hippocampi, a grey matter

TABLE II. Comparisons of sociodemographic and clinical characteristics of the offenders with high and those with medium psychopathy

	High psychopathy (<i>N</i> = 12)	Medium psychopathy (<i>N</i> = 14)	<i>P</i> -value
Mean age (in years)	33.0 ± 8.6	32.1 ± 8.5	0.800
Duration of alcohol abuse (in years)	19.6 ± 10.0	18.3 ± 8.9	0.725
Amphetamine use	75%	43%	0.130
Polysubstance abuse	100%	57%	0.017
Mean global IQ score	94.7 ± 8.6	88.7 ± 8.8	0.095
Current psychotropic medication	67%	50%	0.453
Mean score PCL-R total	34.6 ± 3.1	25.9 ± 2.8	<0.001
Hare's Factor 1	14.0 ± 2.1	8.1 ± 1.5	<0.001
Hare's Factor 2	17.2 ± 1.8	16.0 ± 1.6	0.062
Cooke's Factor 1	6.03 ± 1.74	1.90 ± 1.12	<0.001
Cooke's Factor 2	7.83 ± 0.58	6.14 ± 1.10	<0.001
Cooke's Factor 3	9.67 ± 1.15	9.71 ± 0.47	0.889

Values denote mean ± SD or percent proportions. *P* values refer to Student's *t* and Fisher's exact tests. The IQ of the offenders was assessed using the Wechsler Adult Intelligence Scale—Revised [Wechsler, 1981]. Hare's Factor 1 is "Arrogant Deceitful Interpersonal Conduct and Deficient Affective Experience", and Hare's Factor 2 "Impulsive, Irresponsible Behavioral Style". Cooke's Factor 1 is "Arrogant and deceitful interpersonal style", Cooke's Factor 2 "Deficient affective experience" and Cooke's Factor 3 "Impulsive, irresponsible behavioral style" [Cooke and Michie, 2001].

reduction amounting to over 20% was observed, mapping to the CA1 sector of the offenders' hippocampi. When the medium and high PCL-R subgroups were directly compared to each other, or with controls separately, this finding was significant only for the medium PCL-R group, while the tissue reduction was more prominent in the group with high psychopathy along the longitudinal axis (Fig. 3B: green-yellow color range).

The opposite contrast showed an abnormal enlargement of the lateral borders (Fig. 2, red color range), in both lateral aspects throughout the right and left hippocampi of offenders, covering the CA1, CA2-3, and subicular regions. This feature distinguished both offender groups with medium and high PCL-R scores (Fig. 3A,B, red color range).

Mean differences between offenders and controls in regions with hippocampal gray matter changes that exceeded 15% were generally significant at $P < 0.05$ (Figs. 2B and 3). The corrected *P* value for the whole enlargement and reduction map of the main comparison, contrasting all offenders versus controls (see Fig. 2) was $P < 0.002$ for both the left and right hippocampi, as computed by permutation testing. The results of the comparisons of subgroups versus controls (see Fig. 3) also survived correction for multiple comparisons with the permutation test (Medium psychopathy: left hippocampus, $P < 0.008$; right, $P < 0.030$; high psychopathy: left, $P < 0.046$). However, the *P* map of the experiment "medium vs. high psychopathy" did not survive correction for multiple comparisons.

Overall, the hippocampal's deviation from the normal single convex morphology, observed in offenders, suggests a tendency to appear as a double convex structure in coronal sections, as illustrated by Figure 4.

The correlation analysis of local hippocampal morphology with PCL-R scores carried out in the offenders showed both positive and negative correlation values (see Fig. 5), but did not survive the permutation test. The subgroup with polysubstance (i.e., alcohol plus any other substance) abuse ($n = 20$) exhibited a less strong, but qualitatively similar pattern of correlation values as nonusers ($n = 6$), and analogous findings were found in the correlation analyses in amphetamine users ($n = 15$) and nonusers ($n = 11$) (see Supporting Information Fig. 5Suppl: http://www.centroalzheimer.it/public/Figure5Suppl_CorrAmphetamine.doc). To further check for the possible effect of substance abuse, users and nonusers of polysubstances and of amphetamine were subsequently compared with controls separately (Fig. 6; Supporting Information Fig. 6Suppl at: http://www.centroalzheimer.it/public/Figure6-Suppl_pMaps-directComp-SubstAbuse.doc). These *P* maps, that resembled those observed in the main comparisons, also survived correction for multiple comparisons in the contrasts: "polysubstance users vs. controls" (left, $P < 0.002$, right, $P < 0.003$), "amphetamine users vs. controls" (left, $P < 0.003$, right, $P < 0.02$), "amphetamine nonusers vs. controls" (right, $P < 0.02$).

DISCUSSION

In this work, hippocampal volume and morphology of habitually violent offenders with different severities of psychopathy were compared to normal controls. Size comparisons denoted a similar overall volume and asymmetry pattern, but surface maps detected a peculiar distribution

Figure 3.

Regions with hippocampal gray matter changes in offenders with medium psychopathy (mean PCL-R = 25.9 ± 2.8 , $N = 14$) (A) and with high psychopathy (mean PCL-R = 34.6 ± 3.1 , $N = 12$) (B) compared to controls ($N = 25$), and in offenders with medium psychopathy compared to offenders with high psychopathy (C), expressed as percent differences (left panel; % values on the left of the colour bar) and P values (right panel; P values on the right of the color bar). The right panel illustrates regions sig-

nificant at $P < 0.05$ uncorrected. The permutation test, indicating significance corrected for multiple comparisons, was significant in the comparison "medium psychopathy versus controls" (A) (left hippocampus: $P = 0.008$; right hippocampus: $P = 0.030$) and in the comparison "high psychopathy versus controls" (B) (left hippocampus: $P = 0.046$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

of alterations in the offenders, consisting of an extensive enlargement of lateral borders in the hippocampal body and tail, with a depression along the midline longitudinal axis. In the coronal plane, the hippocampus tended to appear in a double convex shape. This structural pattern was similar on both right and left sides, was more pronounced in the subgroup with greater severity of psychopathy, and could not be attributed to any of the studied confounders (i.e., amphetamine or polysubstance abuse).

Our data on total hippocampal volume are consistent with previous findings that did not observe global volumetric differences in antisocial or psychopathy subjects [Barkataki et al., 2006; Laakso et al., 2001; Raine et al., 2004]. A negative correlation between tissue volumes in posterior sections and PCL-R scores [Laakso et al., 2001] was described in a sample of antisocial offenders. The correlation analysis with PCL-R scores in our offender group identified predominant negative correlations with the posterior hippocampal sectors in both the subgroups with and

without polysubstance abuse. Therefore, this finding should be interpreted in the context of changes relative to the normal morphology of controls, consisting of reduction but also of enlargement effects.

The RDM technique allows a fine reconstruction for the 3D shape of the hippocampus, but it is not possible to identify for sure which cytoarchitectonic regions are specifically involved. Atlas-based inferences are typically used to interpret such results [Fig. 2, top panel; Csernansky et al., 2005; Duvernoy, 1998; Frisoni et al., 2006] and thus formulate more precise experimental hypotheses for future studies. In this case, the depressed line in the hippocampi of the psychopathic offenders may reflect lesser tissue in the underlying dentate gyrus, which contains CA4 neurons, and is located along the midline of the hippocampal core [see also the cytoarchitectonic map in Csernansky et al., 2005]. The putative involvement of this anomaly is biologically plausible, as CA4 neurons are responsible for visceral sensory and autonomic response [Mollace et al., 2005], via different kinds of neurotransmission. Among

Figure 4.

Coronal view of the hippocampal head ($z = 117$), body ($z = 100$), and tail ($z = 90$) in a control (left) and an offender with high psychopathy (PCL-R score > 30) (right). In the body and tail, larger lateral borders, and a steeper dip in the middle of the upper border can be observed in the original coronal slices. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

these, the 5-HT system is associated with nociception [Echeverry et al., 2002], aggressive behavior [van Goozen and Fairchild, 2006], impulsivity [Cardinal, 2006; Masaki et al., 2006], drug addiction, and threat avoidance [Deakin, 2003] that are all key features in psychopathy [Birbaumer et al., 2005]. As to the lateral expansions in the body and tail of the hippocampus, it is known that the CA3 region is also involved in the processing of emotional and visceral input [Mollace et al., 2005], and in contextual fear-conditioning [Daumas et al., 2007]. Together with other evidence from animal research [Butkevich et al., 2003; Tsetsenis et al., 2007], these data are compatible with the clinical syndrome of psychopathy. However, these points should be kept more as a basis for further experimental hypotheses.

All offenders had both problems with alcohol or other forms of substance abuse, and most of them had used amphetamine, while these conditions were absent in controls. Our effort to isolate a pattern of hippocampal alterations that were independent of substance abuse eventually resulted in the analyses of subgroups for polysubstance or amphetamine abuse. In all of these analyses, the same hippocampal morphology was replicated, indicating that the observed anomalies in hippocampal morphology were associated with psychopathy, rather than with substance abuse. Nonetheless, this was a statistical check: further experiments are needed to investigate the effect of psychopathy in larger groups, stratified by kind and dosages of substances.

In spite of these positive findings, it should be acknowledged that sample size should be larger to ensure confidence, especially when analyzing subgroups, and in the

need to correct for multiple comparisons. Moreover, the RDM technique also has some acknowledged limitations. First, we can only indirectly infer observations about inner structures from the surface shape, as the hippocampal morphology is reconstructed from the tracings of the hippocampal contour in the coronal plane. Second, as in the voxel-based analyses, the RDM technique can detect a significant change only when most cases display a difference in exactly the same points, compared to controls. Therefore, even important changes, such as those observed along the midline longitudinal axis of the hippocampus, which we suppose to reflect the dentate gyrus' morphology, actually turn out to be significant only in those few points where the local change has exactly the same

Figure 5.

Correlation of local hippocampal gray matter with PCL-R scores, expressed as a map of Pearson's R values ranging from -1 to 1 (upper line) and of p values (lower line) in offenders with no substance abuse other than alcohol (**A**; $n = 6$) and in offenders with polysubstance abuse (**B**; $n = 20$). The subgroup with no polysubstance abuse exhibited a stronger but similar correlation map to that observed in the subgroup with polysubstance abuse. P maps relate to uncorrected P ; correlation experiments did not survive correction for multiple comparisons. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Figure 6.

Regions with hippocampal gray matter changes in subgroups of users (**A**; $n = 20$) and nonusers (**B**; $n = 6$) of polysubstances (i.e., any substance other than alcohol) and amphetamine (users, **C**; $n = 15$; nonusers **D**; $n = 11$), compared to controls ($n = 25$). Maps denote percent enlargement (red range) or reduction (light blue-green-yellow range) effects. Regions with tissue change greater than 20% were usually significant at $P < 0.05$ (see Fig. 6Suppl at http://www.centroalzheimer.it/public/Figure6_Suppl_pMaps-directComp-SubstAbuse.doc). The permutation test, indicating significance corrected for multiple comparisons, was significant in the comparisons “polysubstance users versus controls” (left: $P = 0.002$; right: $P = 0.003$), “amphetamine users versus controls” (left: $P = 0.003$; right: $P = 0.029$), “amphetamine nonusers versus controls” (right: $P = 0.02$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

location in most subjects. Regarding the potential confounding variables that we could not rule out by subject selection, such as substance abuse, the statistical analyses did show that their effect did not influence the pattern of anomalies associated with psychopathy. Nonetheless, we could estimate only the presence versus absence of abuse, and not the exact amounts used during the whole lifetime. Finally, autopsy information on the cytoarchitectonic hip-

pocampal regions involved in psychopathy is required to definitively elucidate the exact cellular correlates of these MR findings.

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