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Hippocampal Structural Asymmetry in Unsuccessful Psychopaths

Adrian Raine, Sharon S. Ishikawa, Estibaliz Arce, Todd Lencz, Kevin H. Knuth, Susan Bihrle, Lori LaCasse, and Patrick Colletti

Background: Structural and functional hippocampal abnormalities have been previously reported in institutionalized psychopathic and aggressive populations. This study assessed whether prior findings of a right greater than left (R   L) functional asymmetry in caught violent offenders generalize to the structural domain in unsuccessful, caught **psychopaths**.

Methods: Left and right hippocampal volumes were assessed using structural magnetic resonance imaging (MRI) in 23 control subjects, 16 unsuccessful **psychopaths**, and 12 successful (uncaught) community **psychopaths** and transformed into standardized space.

Results: Unsuccessful **psychopaths** showed an exaggerated structural hippocampal asymmetry (R   L) relative both to successful **psychopaths** and control subjects (p   .007) that was localized to the anterior region. This effect could not be explained by environmental and diagnostic confounds and constitutes the first brain imaging analysis of successful and unsuccessful **psychopaths**.

Conclusions: Atypical anterior hippocampal asymmetries in unsuccessful **psychopaths** may reflect an underlying neurodevelopmental abnormality that disrupts hippocampal-prefrontal circuitry, resulting in affect dysregulation, poor contextual fear conditioning, and insensitivity to cues predicting capture.

Key Words: Hippocampus, psychopathy, MRI, trauma, neurodevelopment, asymmetry

Structural and functional brain imaging research is beginning to uncover significant neurobiological impairments in antisocial, violent, and psychopathic groups. Although the majority of these studies have implicated the prefrontal cortex (Henry and Moffitt 1997; Raine 2002), there is increasing interest in the role of temporolimbic structures such as the hippocampus in mediating antisocial and psychopathic behavior. At the general level of the temporal cortex, abnormal functioning has been found in antisocial, violent, and psychopathic groups using functional magnetic resonance imaging (fMRI; Raine et al 2001), single photon emission computerized tomography (SPECT; Amen et al 1996; Hirono et al 2000; Intrator et al 1997; Soderstrom et al 2002), and positron emission tomography (PET; Juhasz et al 2001; Seidenwurm et al 1997; Wong et al 1997).

Mesial temporal cortical abnormalities have been observed in antisocial and violent groups using PET (Volkow et al 1995). More specifically, abnormalities in the hippocampus have been reported in antisocial groups using PET (Raine et al 1997), SPECT (Soderstrom et al 2002), and fMRI (Kiehl et al 2001), whereas abnormal metabolism in the anterior amygdala-hippocampal complex has also been reported in repetitively violent offenders using magnetic resonance spectroscopy (MRS; Critchley et al 2000). In addition to these functional impairments, structural hippocampal impairments have also been reported in two studies of psychopathic individuals (Laakso et al 2000, 2001). This evidence for temporal and hippocampal impairments from brain

imaging studies is broadly consistent with the larger body of evidence from electroencephalographic (EEG) and neuropsychologic studies implicating temporal lobe abnormalities in violent and antisocial groups (Raine 1993; Volavka 1995). Because the hippocampus is involved in the regulation of aggression (Gregg and Siegel 2001) and contextual fear conditioning (LeDoux 1996), abnormalities in the hippocampus and disruption of prefrontal-hippocampal circuitry could contribute to affect dysregulation and impulsive, disinhibited behavior of the type observed in psychopaths.

Asymmetries in hippocampal structure and function have also been reported. In structural terms, one study found that 6 of 10 violent forensic patients with a diagnosis of antisocial personality disorder had unilateral hippocampal atrophy with twice as many lateralized to the left than right hemisphere (Chesterman et al 1994). In functional terms, one PET study showed a significant asymmetry of hippocampal functioning in violent offenders, with 41 murderers showing reduced left but increased right hippocampal functioning compared with 41 matched control subjects (Raine et al 1997). This effect was a specific asymmetry, that is, left hippocampal activity was relatively smaller than the right rather than group differences occurring in either the left or right hippocampus. This asymmetry could not be accounted for by a history of head injury. Similarly, Soderstrom et al (2002) using SPECT found an association between reduced left (but not right) hippocampal activation and high psychopathy scores in violent offenders. On the other hand, no structural imaging study has tested the hypothesis that psychopaths have an unusual R   L hippocampal asymmetry.

Abnormal neurodevelopment has been hypothesized as a basis for antisocial, psychopathic behavior, but evidence supporting this hypothesis is limited (Raine et al 1995). The finding of a hippocampal structural asymmetry in psychopaths in the same direction as the R   L functional hippocampal asymmetry found in violent offenders would be of interest because such asymmetries may reflect an early disruption to normal neurodevelopmental processes (Bilder et al 1999) as opposed to a later environmental process that would be more likely to reduce the hippocampus bilaterally, or reduce the volume in one hemisphere only. Alternatively, because posttraumatic stress disorder

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(PTSD) has been associated with reduced hippocampal volume

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(Bremner et al 1997), early stress has been associated with attenuated development of the left hippocampus (Teicher et al 2003), and psychopaths tend to be disproportionately exposed to traumatic events such as child abuse (Robins 1999), abnormal hippocampal structure could instead be accounted for by trauma exposure or history of head injury. At a psychiatric level, schizophrenia has been associated with R   L structural hippocampal asymmetries (Keshavan et al 2002), and because there is comorbidity between antisocial behavior and schizophrenia-spectrum disorders (Volavka et al 1997), this also could be a confound.

Although hippocampal structural abnormalities in psychopaths are greatly underresearched, an even larger gap in the literature is the almost complete lack of knowledge on an intriguing group of "successful" psychopaths who escape detection for their crimes, compared with "unsuccessful" psychopaths who are detected and convicted. One previous study has shown that successful psychopaths lack the autonomic and executive function deficits that have been traditionally shown by adult institutionalized psychopaths, whereas "unsuccessful" psychopaths show these intrinsic psychophysiologic and neuropsychologic impairments (Ishikawa et al 2001). Despite this provisional evidence for the differentiation of successful and unsuccessful psychopaths, there have been no prior brain imaging studies assessing whether brain abnormalities are similarly specific to unsuccessful psychopaths. Because the hippocampus is involved in contextual fear conditioning (LeDoux 1996), antisocial individuals with hippocampal impairments could become insensitive to cues that predict punishment and capture and consequently be more likely to be apprehended. Consequently, hippocampal impairments may be expected to characterize unsuccessful, caught psychopaths, but not psychopaths who successfully evade detection.

This study attempts to extend prior findings of a R   L functional asymmetry in hippocampal functioning in caught, violent offenders to the same asymmetry in hippocampal structure in a community-based sample of psychopaths. Because all prior hippocampal abnormalities in psychopaths have been observed in unsuccessful, caught offenders, and because the one prior study of successful versus unsuccessful psychopaths observed psychophysiologic and neuropsychologic impairments in the latter but not the former group, it was hypothesized that any lateralized structural hippocampal abnormality would be specific to unsuccessful psychopaths. Prior trauma exposure, head injury, schizophrenia-spectrum disorder, and demographic factors were also assessed to test whether any hippocampal abnormality was independent of possible confounds.

Methods and Materials

Participants

Adult men were recruited from five temporary employment agencies in the greater Los Angeles area (Raine et al 2000). Participants were excluded if they were under 21 or over 45 years of age, nonfluent in English, claustrophobic, or had a pacemaker, metal implants, or history of epilepsy. Qualified participants were informed of the nature of the study and of the study's potential risks and benefits and gave written, informed consent. Before beginning data collection, a certificate of confidentiality was obtained from the Secretary of Health pursuant to Section 303(a) of Public Health Act 42. Participants were assured that any information they might provide about uninvestigated crimes could not be subpoenaed by any United States court or law

enforcement agency. The study and all its procedures were approved by the Institutional Review Board at the University of Southern California.

We recruited 91 men into the study, of whom 84 received a structural MRI scan. Group classification was based on total scores from the Psychopathy Checklist—Revised (PCL-R; Hare 1991; described later), as well as history of criminal convictions derived from statewide court records and lifetime self-report (for full details, see Ishikawa et al 2001). Based on a neuroradiologic screen conducted blind to group membership and before image analysis, one participant was a priori excluded from the study because of major atrophy to the right superior temporal gyrus (Raine et al 2000). The final sample consisted of 12 successful psychopaths (i.e., top third of PCL-R scores [23 or more] with no convictions, mean PCL-R score   27.7, range 23–31), 16 unsuccessful psychopaths (i.e., top third of PCL-R scores with convictions, mean PCL-R score   31.5, range 23–40), and 23 control subjects (i.e., bottom third of PCL-R scores and no convictions, mean PCL-R score   10.9, range   2–14).

Psychopathy Assessment

Psychopathy was assessed with the PCL-R and supplemented by five sources of collateral data (Ishikawa et al 2001). The PCL-R consists of 20 items and reflects two factors: interpersonal and affective characteristics (Factor 1, e.g., glibness or superficial charm, pathologic lying, shallow affect) and antisocial behavior (Factor 2, e.g., need for impulsivity, stimulation seeking or proneness to boredom, juvenile delinquency). PCL-R ratings were made by a clinical Ph.D. student trained and supervised by the first author (AR). The five collateral sources for assessing psychopathy were 1) the Interpersonal Measure of Psychopathy (IM-P; Kosson et al 1997), which provides an interviewer's ratings of the participant's interpersonal behaviors and which has been validated for use with incarcerated and nonincarcerated samples; 2) self-reported crime as assessed by an adult extension (Raine et al 2000) of the National Youth Survey self-report delinquency measure (Elliott et al 1983); 3) official criminal records; and 4) data derived from, and behavioral observations made during, the Structured Clinical Interview for the DSM-IV mental disorders (SCID I; First et al 1995a) and (5) the SCID Axis II personality disorders (SCID II; First et al 1995b).

Diagnostic, Cognitive, and Demographic Assessments

The SCID I and II were administered by a clinical Ph.D. student who received systemized training in SCID assessment that included reliability checks with expert raters (Ventura et al 1998). Subjects also completed an alcohol use questionnaire to assess number of times alcohol was used in the past week and past month (Raine et al 2000). Because only 1 of 51 participants met full DSM-IV diagnostic criteria for PTSD, a dichotomous variable was created indicating whether the individual had ever been exposed to a life-threatening event that left him feeling fearful, helpless, or horrified (i.e., Criteria A of DSM-IV PTSD). Similarly, a dimensional measure of antisocial personality was created as a more sensitive indicator of antisocial tendency by summating SCID scores on individual DSM-IV APD symptoms.

Subtests of the WAIS-R (Wechsler 1981) were used to estimate verbal IQ (vocabulary, arithmetic, digit span), performance IQ (digit symbol, block design), and full scale IQ. Degree of right-versus left-hand preference was assessed using the abbreviated Oldfield Inventory (Bryden 1977), with high scores indicating a stronger preference for right-handedness. History of head injury was defined as head trauma resulting in hospitalization. Details

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of group scores on psychiatric, cognitive, and demographic measures together with group comparisons are given in Table 1.

MRI Acquisition

Structural imaging of the hippocampus was conducted using a 1.5-T Philips (S15/ACS) MRI scanner. Three-dimensional images were reconstructed on a SPARC workstation, and segmentation was performed using semiautomated software (CAMRA S200 ALLEGRO; Cedar Software Corp., Mississanga, Ontario, Canada). The anterior commissure–posterior commissure (AC-PC) plane was identified through one midsagittal and four parasagittal scans (spin echo T1-weighted; repetition time [TR], 600 msec; echo time [TE], 20 msec). In the plane directly orthogonal to the AC-PC line, 128 three-dimensional T1-weighted gradient-echo coronal images (TR, 34 msec; TE, 12.4 msec; flip angle, 35°; slice thickness, 1.7 mm; matrix, 256 $\times$ 256; field of vision, 23 cm) were obtained.

Image Analysis

Morphometric analyses of the hippocampus were conducted using CAMRA S200 ALLEGRO software. All measurements were obtained by manual tracings performed by raters who were blind to group membership. Bilaterally, the anterior border of hippocampus was defined as the first slice in which the pes hippocampus appeared just caudal to the amygdala (Altshuler et al 1990; McNeil et al 2000). The posterior border was defined as the slice just rostral to where the crus of the fornix appeared as a continuous tract or in which the lateral ventricle body joined with the temporal horn of the lateral ventricles (Bogerts et al 1990; Laakso et al 2000; also the posterior boundary of the thalamus). Measurement of the hippocampus included the hippocampal body, dentate gyrus, uncus, fimbria, alveus, entorhinal cortex, and subiculum. The borders were defined by the surrounding white matter and cerebrospinal fluid, and, when present superiorly, the amygdala, tail of the caudate, optic tract, and lateral geniculate. Reliability of hippocampal volume measurements computed by intraclass correlations on 10 randomly picked cases was .71. Whole brain volume was defined as all cerebral gray and white matter excluding the ventricles, pons, and cerebellum. The pons was excluded by drawing a straight line between the two innermost points that form the superior border. The colliculi were excluded when they were no longer attached to the cerebral hemispheres.

Hippocampal Interpolation Procedure

To assess whether group differences in volume are specific to estimated hippocampal subregions (i.e., anterior, posterior), the slice-by-slice hippocampal measurements were transformed into standardized space. Cubic spline interpolation (Press et al 1992) was applied to the original data so that the total hippocampal volume for each subject, regardless of the original number of slices, was reconfigured to fit into 30 slices. Interpolation was conducted separately for the left and right hippocampus. The volume of each interpolated slice was then calculated in two steps. First, the thickness for each standardized slice was computed using the following formula:

$$\text{(original slice thickness} \times 1.7 \text{ mm)}$$

$$\times \text{ (no. original slices)/(standardized no. slices} \times 30\text{)}$$

$$\text{standardized slice thickness}$$

The area of each standardized slice was then multiplied by the standardized slice thickness to obtain the volume for each interpolated slice. Each slice volume was divided by whole brain volume to correct for individual differences in brain volume.

Data Analysis

Initial hypothesis testing was carried out using a 3 $\times$ 2 $\times$ 30 repeated-measures multivariate analysis of variance (MANOVA) comparing groups (i.e., control subjects, successful psychopaths, unsuccessful psychopaths) on hemisphere (i.e., right, left hemisphere) and slice (i.e., 1–30). Analyses in which hippocampal slices were summed were carried out using a 3 (group) $\times$ 2 (hemisphere) repeated-measures MANOVA. Main effects for group and group interaction terms (i.e., group $\times$ hemisphere, group $\times$ hemisphere $\times$ slice) were evaluated using Wilks's lambda. Omnibus tests were two-tailed with alpha set at .05, and effect sizes were calculated using eta^2. To maximize power while protecting against type II error, the highest level significant effect was followed up using the adjusted Bonferroni procedure: (between group df $\times$ 2) $\times$ (family wise alpha $\times$ .05) / (no. pairwise tests $\times$ 3) (Keppel 1991). Thus, alpha for all pairwise comparisons was .033.

Results

Psychopathy Group Analysis

The 3 $\times$ 2 $\times$ 30 repeated-measures ANOVA revealed a significant main effect of hemisphere [$F(1,48)$ $\times$ 14.25, p $\times$ .0001] indicating increased right relative to left (R $\times$ L) hippocampal volumes across subjects. A group $\times$ hemisphere interaction [$F(2,48)$ $\times$ 3.97, p $\times$ .02] indicated the hemisphere asymmetry differed across groups, whereas a significant group $\times$ hemisphere $\times$ slice interaction [$F(58,40)$ $\times$ 2.12, p $\times$ .007] indicated that group differences in laterality were localized within the hippocampus. The main effect for group was not significant [$F(2,48)$ $\times$ .53, p $\times$ .59].

To better focus the follow-up analyses of the three-way interaction, a laterality index was computed by subtracting left volume from right volume and dividing by total slice volume at each slice. Laterality scores were then plotted by group. Visual inspection (see Figure 1) indicated that group differences were localized to the anterior region of the hippocampus. Consequently, estimates of anterior and posterior hippocampal volumes were computed by summing slices 1–15 and 16–30, respectively, within the right and left hemispheres (i.e., right and left anterior hippocampal volumes, right and left posterior hippocampal volumes).

Using 3 $\times$ 2 repeated-measures MANOVA, group differences in volume across hemispheres were then separately tested for the anterior and posterior hippocampus. The group $\times$ hemisphere interaction was significant for the anterior hippocampus [$F(2,48)$ $\times$ 4.44, p $\times$ .017, eta^2 $\times$ .16] and nonsignificant for the posterior hippocampus [$F(2,48)$ $\times$ 1.71, p $\times$ .19]. Bonferroni-corrected pairwise tests indicated that unsuccessful psychopaths, relative both to successful psychopaths and control subjects, had significantly increased laterality (R $\times$ L) in the anterior hippocampus [$F(1,26)$ $\times$ 7.80, p $\times$ .01 and $F(1,37)$ $\times$ 6.14, p $\times$ .018]; however, successful psychopaths and control subjects did not differ [$F(1,33)$ $\times$ .29, p $\times$ .60].

Subjects were classified according to whether they showed a hippocampal asymmetry that was higher or lower than the mean of the control subjects. A chi-square analysis indicated a significant relationship between subject grouping and high–low laterality score, χ^2 $\times$ 10.76, df $\times$ 2, p $\times$ .005, eta $\times$ .46. Whereas 47.8% of control subjects and 41.7% of successful psychopaths

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showed a relatively high R   L hippocampal asymmetry, all but one of the unsuccessful psychopaths, or 93.8%, showed an exaggerated R   L asymmetry.

To determine whether the laterality differences were being accounted for by an overall significant reduction in estimated left volume or an overall significant increase in estimated right volume, a series of pairwise comparisons (Student's t test) with right or left anterior hippocampal volume as the dependent variable were conducted. All comparisons were nonsignificant (ps .18), indicating that the laterality difference resulted from a combination of slightly decreased left and slightly increased right hippocampal volume in the unsuccessful psychopaths relative to the other two groups.

Potential Confounds

As shown in Table 1, groups differed or tended to differ (p .10) on age, substance use, history of head injury, degree of antisocial personality, trauma exposure, and schizophrenia-spectrum disorder, with one or other psychopathy groups scoring higher on these measures. To assess whether any of these variables met criteria as a mediator of the psychopathy–anterior hippocampal relationship (Baron and Kenny 1986), relationships were assessed between these measures and anterior hippocampal asymmetry. Correlational analyses with anterior hippocampal laterality score were nonsignificant for age (p .55), SES (p .97), and antisocial score (p .25). Repeated-measures MANO-VAs on left and right anterior hippocampal volumes and grouping variables failed to reveal group   hemisphere interactions for schizophrenia-spectrum (p .62), trauma exposure (p .24), head injury (p .50), or substance use (p .47). Consequently, no measures on which groups differed passed criteria for mediator status. Furthermore, within the unsuccessful psychopathy group, anterior hippocampal asymmetry was not significantly correlated with the number of incarcerations (r .275, p .30), indicating that the structural asymmetry was not a consequence of degree of institutionalization.

Discussion

Unsuccessful psychopaths have an exaggerated structural asymmetry in the anterior hippocampus (R   L) relative to both successful psychopaths and normal control subjects. These structural hippocampal findings are consistent with and extend prior functional findings of the same R   L hippocampal asymmetry in caught violent offenders during a cognitive activation challenge (Raine et al 1997). This hippocampal abnormality cannot be accounted for by confounds such as trauma exposure, schizophrenia-spectrum disorders, head injury, substance use, and other demographic and behavioral confounds. Findings lend support to a neurodevelopmental model of unsuccessful psychopathy (Raine et al 1995) and represent the first brain imaging analysis of successful and unsuccessful psychopaths.

Atypical brain asymmetries are thought in part to reflect disrupted neurodevelopmental processes (Best 1988). Such disruption probably occurs early in life because brain asymmetries first emerge during fetal development (Best 1988), and the overall degree of structural change attributable to environmental influences is limited by early morphogenesis (Bilder et al 1999; Zaidel 1999). Developmentally, the R   L structural asymmetry decreases somewhat with age in normal children (Szabo et al 1999), and consequently the greater R   L asymmetry in unsuccessful psychopaths may reflect an interruption to this normal developmental process. Our findings of an exaggerated R   L hippocampal asymmetry suggest, but do not prove, that unsuc-

Figure 1. Right-left hippocampal laterality scores from interpolated slice volumes for the three groups. R, right; L, left.

cessful psychopathy may be associated with disruption to early morphogenesis or normal brain maturation. A neurodevelopmental perspective of psychopathy is consistent with the facts that it has its roots early in life (Moffitt 1993a, 1993b), unfolds relatively consistently over childhood and adolescence (Lynam 1996), is impervious to conventional treatments (Rice 1997; Seto and Barbaree 1999), and is in part genetically determined (Dolan 1994). The fact that the morphologic change in the hippocampus in unsuccessful psychopaths was a relatively complex R   L asymmetry alteration dictates against simple, nondevelopmental processes such as discrete trauma or degenerative disease processes.

The hippocampal laterality differences were not attributable to environmental influences such as trauma exposure, substance use, or head injury, factors that have previously been associated with hippocampal abnormalities (Agartz et al 1999; Tate and Bigler 2000). Environmental insults such as these would tend to result either in bilateral volumetric reductions of the hippocampus (DeBellis 2002) or in right hippocampal reductions (Agartz et al 1999; Laakso et al 2000). It could be argued that other stressful environmental conditions such as abuse could affect the hippocampus, but groups in this study experienced similar rates of childhood physical punishment and sexual abuse (Ishikawa et al 2001). Thus, it seems unlikely that environmental factors would produce the exaggerated asymmetry observed in the current study. This is instead suggestive of a more neurodevelopmental process underlying the structural asymmetry. Furthermore, although R   L structural asymmetries localized to the anterior region have been found in both schizophrenia subjects and the high-risk relatives of schizophrenia patients (Keshavan et al 2002; Pegues et al 2003), and although unsuccessful psychopaths had higher rates of schizophrenia-spectrum disorders than control subjects, such comorbidity could not account for the hippocampal finding.

An important question concerns how hippocampal impairments predispose to unsuccessful psychopathy in particular. At a general level, research in cats has shown that the hippocampus regulates aggression via projections to midbrain periaqueductal gray and the perifornical lateral hypothalamus, structures important in mediating both defensive rage and predatory attack (Gregg and Siegel 2001). Aggressive male mice show size reductions in intra- and infrapyramidal mossy fiber terminal fields in the hippocampus (Hensbroek et al 1995; Sluyter et al

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Table 1. Demographic and Psychiatric Measures of the Three Groups

	Unsuccessful Psychopaths (UP) (n 16)		Successful Psychopaths (SP) (n 12)		Controls (C) (n 23)		Statistics	Group Comparisons
Demographic/Cognitive	M	SD	M	SD	M	SD		
Age	33.81	6.62	29.5	6.39	28.35	6.63	$F_{(2,48)}$ 3.38, p .04	C UP
Socioeconomic status	31.81	7.40	30.67	10.65	37.36	10.54	$F_{(2,49)}$ 2.47, p .09	
IQ	96.44	14.69	97.25	13.18	105.09	16.93	$F_{(2,49)}$ 1.8, p .18	
Ethnicity	Caucasian	Other	Caucasian	Other	Caucasian	Other		
	5	11	6	6	14	9	$^2(2,51)$ 3.32, p .19	
	Present	Absent	Present	Absent	Present	Absent		
Head injury	6	10	8	4	6	16	$^2(2,50)$ 5.08, p .08	C SP
	Right	Left	Right	Left	Right	Left		
Handedness	13	3	11	0	17	6	$^2(2,51)$ 3.44, p .18	
Psychiatric/Criminal	Present	Absent	Present	Absent	Present	Absent		
Substance abuse/dependence	14	2	8	4	7	16	$^2(2,48)$ 23.0, p .0001	C SP, UP
APD	12	4	4	7	0	21	$^2(2,48)$ 23.0, p .0001	C UP, SP
Trauma exposure	7	9	0	12	6	17	$^2(2,51)$ 6.92, p .031	SP UP
Schizophrenia-spectrum disorder	5	11	3	8	1	21	$^2(2,49)$ 5.16, p .08	C UP
	M	SD	M	SD	M	SD		
No. drinks/month	4.31	5.30	7.67	8.05	3.95	6.54	$F_{(2,47)}$ 1.35, p .27	
APD score	10.43	2.92	7.73	2.53	2.65	1.69	$F_{(2,49)}$ 55.4, p .0001	C UP, SP SP UP
Criminal charges	11.06	12.40	.42	.79	.09	.42	$F_{(2,48)}$ 13.44, p .0001 C, SP UP	
Criminal convictions	4.06	5.09	.00	.00	.00	.00	$F_{(2,48)}$ 11.18, p .0001 C, SP UP	
Self-report crimes	26.50	17.00	19.27	8.39	8.68	4.34	$F_{(2,48)}$ 12.78, p .0001 C SP, UP	

All group comparisons are p .05.
APD, Antisocial Personality Disorder.

1994). Furthermore, rats with hippocampal lesions applied at birth but not at 18 weeks show increased aggressive behavior (Becker et al 1999), again suggesting a neurodevelopmental link between hippocampal abnormalities and aggression. Normal hippocampal functioning is critical for the retrieval of emotional memories and contextual fear conditioning (i.e., remembering the situational context of previously experienced aversive events; Fanselow 2000; LeDoux 1996). Unsuccessful psychopaths have repeatedly been found to show poor fear conditioning (Patrick et al 1994), and hippocampal impairments that disrupt learning the social context of a previously punished response would make such offenders relatively insensitive to environmental cues signaling danger and capture. In contrast, successful psychopaths who lack hippocampal impairments may have relatively normal contextual fear conditioning, making them more sensitive to cues predicting capture. Similarly, LeDoux (1996) has suggested that uncoupling of the hippocampus from the amygdala could result in the expression of emotions that are inappropriate to the social context and also in poor insight into emotional states, a perspective consistent with clinical features of caught psychopaths. Interestingly, a PET study of humans indicates that unpleasant emotions activate the left but not right hippocampus (Lane et al 1997), a finding conceptually consistent with the notion that unsuccessful psychopaths have relatively reduced left hippocampal structure and also reduced autonomic reactivity to a social-emotional stressor (Ishikawa et al 2001).

The anterior hippocampal asymmetries may be associated with unsuccessful psychopathy by signaling disruption to frontal-subcortical neural circuitry. In humans, the orbitofrontal cortex likely exerts control over the anterior hippocampus through entorhinal-hippocampal projections (Pansky et al 1988; Stuss and Benson 1986), whereas afferent connections have been mapped between the subiculum and ventral, dorsolateral, and rostral regions of the prefrontal cortex in cats (Scannell et al 1995). Animal research has also found that lesions to the septal-hippocampal-frontal system result in behavioral disinhibition and a hypersensitivity to immediate reward (Gorenstein and Newman 1980). Disruption to circuits involving the prefrontal cortex and hippocampus have been implicated in both disrupted emotion regulation and antisocial–aggressive behavior (Davidson 2000; Davidson et al 2000; Hoptman et al 2002; Raine 2002; Raine et al 2000), whereas frontal and executive function deficits are frequently identified in institutionalized psychopathic and antisocial individuals (Moffitt 1993b; Raine et al 1998). Prior research with the present sample has found that unsuccessful psychopaths demonstrate executive dysfunction compared with successful psychopaths (Ishikawa et al 2001), and hippocampal abnormalities may be most likely to predispose to aggressive, inappropriate, and psychopathic behavior when combined with prefrontal impairments that decrease behavioral inhibition. Disruption to prefrontal-hippocampal circuitry could therefore result in impulsive, disinhibited, unregulated, and reward-driven antisocial behavior that is more prone to

legal detection in the unsuccessful psychopath, but further work is needed to verify such prefrontal involvement in unsuccessful psychopaths.

Although we found that environmental factors could not explain the hippocampal asymmetry, and although it is possible that the exaggerated R   L asymmetry in unsuccessful psychopaths may have a genetic basis, environmental influences on neurodevelopment cannot be ruled out. Specifically, neonatal exposure to new environments in the first 3 weeks of life results a shift in hippocampal asymmetry in the direction of greater right volume in rats (Verstynen et al 2001). It is therefore conceivable that very early environmental factors not measured in this study could have contributed to the exaggerated hippocampal asymmetry in unsuccessful psychopaths.

Despite support for the notion that unsuccessful psychopaths differ from both their successful psychopathic counterparts and normal control subjects on hippocampal asymmetries, several limitations should be noted. First, sample sizes were modest, thus raising the risk of type II error; however, we were still able to detect structural abnormalities in laterality that are directionally consistent with our prior findings on asymmetrical hippocampal functioning in another antisocial sample. Second, the findings cannot be extrapolated to women because only male subjects were included in this study. Third, there is only partial overlap between the constructs of psychopathy, violence, and antisocial personality disorder; consequently it remains to be seen whether these findings generalize to antisocial constructs other than unsuccessful psychopathy. Fourth, the question of what factors predispose to successful forms of psychopathy requires further clarification. Finally, the neurodevelopmental hypothesis suggested here could not be directly tested due to the use of an adult sample and the cross-sectional nature of the study. Nevertheless, our results provide further support for the notion that successful and unsuccessful psychopaths are distinct subgroups with different autonomic, cognitive, and neuroanatomic deficits, provide initial findings from brain imaging research on these two subgroups, and more broadly support prior imaging, EEG, and neurocognitive research implicating the hippocampus–mesial temporal cortex in antisocial groups.

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