Brain Abnormalities in Murderers Indicated by Positron Emission Tomography

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Murderers pleading not guilty by reason of insanity (NGRI) are thought to have brain dysfunction, but there have been no previous studies reporting direct measures of both cortical and subcortical brain functioning in this specific group. Positron emission tomography brain imaging using a continuous performance challenge task was conducted on 41 murderers pleading not guilty by reason of insanity and 41 age- and sex-matched controls. Murderers were characterized by reduced glucose metabolism in the prefrontal cortex, superior parietal gyrus, left angular gyrus, and the corpus callosum, while abnormal asymmetries of activity (left hemisphere lower than right) were also found in the amygdala, thalamus, and medial temporal lobe. These preliminary findings provide initial indications of a network of abnormal cortical and subcortical brain processes that may predispose to violence in murderers pleading NGRI. © *1997 Society of Biological Psychiatry*

Key Words: Violence, murder, positron emission tomography, prefrontal, amygdala, hippocampus, thalamus, corpus callosum, angular gyrus, parietal, occipital

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Introduction

It has long been suspected that generalized brain dysfunction may predispose to violent behavior. Studies using electroencephalographic (EEG), neurological, neuropsychological, and cognitive test techniques have repeatedly shown that violent offenders have poorer brain functioning than normal controls (Eichelman 1993; Eysenck and Gudjonsson 1989; Elliott 1987; Lewis et al 1988; Moffitt 1988; Raine 1993), but until recently it has not been possible to localize which brain areas in particular may be dysfunctional in violent offenders.

Clues do however exist with respect to the source of brain dysfunction predisposing to violence. It has long been thought that dysfunction of the prefrontal cortex may disrupt the regulation of aggression, and this notion has been supported by neurological studies of patients with damage to the prefrontal cortex (Damasio et al 1990; Weiger and Bear 1988). Some neuropsychological and psychophysiological studies on violent and forensic populations have shown abnormalities in hemispheric asymmetries of function (Convit et al 1991; Hare and McPherson 1984; Raine et al 1990a) and reduced EEG interhemispheric coherence (Flor-Henry et al 1991), which may be linked to dysfunction of the corpus callosum (Nachshon 1983; Yeudall 1977), but this hypothesis has

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not been tested using direct measures of callosal functioning. Recent event-related potential mapping techniques have implicated dysfunction in the left angular gyrus in violent offenders as indicated by reduced slow-wave amplitudes (Barratt et al in press). Experimental animal research together with neurological studies of patients have further implicated limbic structures such as the amygdala and hippocampus in modulating aggression (Bear 1991; Elliott 1992; Gorenstein and Newman 1980; Mirsky and Siegel 1994; Watson et al 1983a), while the thalamus also provides an important afferent source of the hypothalamic-induced attack in cats (Mirsky and Siegel 1994). Nevertheless, such research on animals and humans who have suffered brain insults, although of key importance, is one step removed from the question of whether severely violent offenders have brain dysfunction localized to specific brain areas.

The advent of brain imaging research has recently made it possible for the first time to directly assess brain functioning in violent individuals. Initial research in this area has again implicated frontal brain regions in addition to the temporal cortex (Goyer et al 1994; Volkow and Tancredi 1987). These important initial studies support the notion of localized brain dysfunction in aggressive patients, although inevitable limitations of such initial research include small sample sizes in hospitalized patients, and a focus on aggressive personality as opposed to seriously violent behavior.

One particularly important group of violent offenders in forensic psychiatry consists of those who commit murder and plead not guilty by reason of insanity (NGRI). Although it is thought that such individuals have localized brain impairments, there has been no previous brain imaging research on this important population to support or refute this notion. In a preliminary report on a pilot sample of 22 such offenders compared to 22 normals, we provided some initial support for the notion of prefrontal dysfunction in this group (Raine et al 1994). In the present study the sample size is extended to 41 murderers and 41 controls, and analysis of subcortical structures is now undertaken. To our knowledge, this is the largest sample of violent offenders assessed on functional brain imaging. It is hypothesized that these seriously violent individuals have relatively localized brain dysfunction in the prefrontal cortex, angular gyrus, amygdala, hippocampus, thalamus, and the corpus callosum, brain areas previously linked empirically or conceptually to violence. Conversely, no dysfunction is expected in other brain areas (caudate, putamen, globus pallidus, midbrain, cerebellum), which have been implicated in other psychiatric conditions but which have not been related to violence.

Methods

Subjects

MURDERERS. The experimental group consisted of 41 subjects tried in the state of California (39 men, 2 women) with a mean age of 34.3 years (SD = 10.1) who had been charged with either murder or manslaughter (labeled below as "murderers" for ease of reference). Subjects were referred to the University of California, Irvine (UCI) imaging center to obtain evidence relating to a NGRI defense or to capability of understanding the judicial process (incompetence to stand trial), while some who had been found guilty were referred to obtain information for diminished capacity as an ameliorating circumstance in the sentencing phase of the trial. Reasons for referral were very diverse and included schizophrenia (6 cases), history of head injury or organic brain damage (23), history of psychoactive substance abuse (3), affective disorder (2), epilepsy (2), history of hyperactivity and learning disability (3), and passive–aggressive or paranoid personality disorder (2). In 7 of the above cases, there were also unusual circumstances surrounding the crime that additionally lead to the suspicion of some mental impairment. Offenders were not receiving regulated psychoactive medication at the time of positron emission tomography (PET) scans, and were instructed to be medication-free for the 2-week period preceding brain scanning. All subjects were in custody during this period, and penal authorities agreed to refrain from administering medication. Urine screens at the time of PET scanning were negative for every murderer referred for study.

CONTROLS. A control group was formed by matching each murderer with a normal subject of the same sex and age who had been tested using identical PET imaging procedures in the same laboratory. Six murderers (all men) had been diagnosed as schizophrenic by psychiatrists. These 6 were individually matched on age and sex with 6 schizophrenics from a larger psychiatric sample tested under identical procedures at the Brain Imaging Center at the University of California, Irvine (Buchsbaum et al 1990). The resulting 41 controls (39 men, 2 women) had a mean age of 31.7 years (SD = 10.3), which did not differ from murderers ($p > .26$). Normal controls had been screened for health by physical exam, medical history, and a psychiatric interview. No subject was taking any medication, had a history of psychiatric illness in self or first-degree relatives, or had current significant medical illness. Subjects with a history of seizure disorder, head trauma, or substance abuse were excluded. Subjects participated under protocols and consent forms approved by the Human Subjects Committee of University of California, Irvine.

PET Task Procedure

Full details of general PET scanning procedures and quantification may be found in Buchsbaum et al (1990). Briefly, the fluorodeoxyglucose (FDG) tracer was injected into the subject in the test room and taken up by the brain as a tracer of brain metabolic rate for a 32-min period during which the subject completed the continuous performance task (CPT; Nuechterlein et al 1983). A degraded stimulus version of the CPT was employed as the frontal challenge task because it has been shown to produce increases in relative glucose metabolic rates in the frontal lobes in normal controls, in addition to increases in right temporal and parietal lobes (Buchsbaum et al 1990). The key signal detection performance measure of d′ reflects target recognition accuracy across the 32-min period (Davies and Parasuraman 1982; Nuechterlein 1991). Split-half reliability for the task is high ($r = .843$, $p < .001$). Full procedural details are reported in Buchsbaum et al (1990).

Ten minutes before the FDG injection, subjects were given practice trials on the CPT. Thirty seconds before injection, the task was started so that initial task novelty would not be FDG labeled. After 32 min of FDG uptake, the subject was transferred to the adjacent PET scanner room. An individually molded, thermosetting plastic head holder was used to hold the head still during the scan. Ten slices at 10-mm intervals parallel to the canthomeatal line were obtained. Scans started at the level of 80% of head height above the canthomeatal line (vertex to canthomeatal line, usually 12–14 cm) and step downward at 10-mm intervals.

Brain regions were identified using two techniques as follows:

Cortical Peel Technique (lateral areas). Surface cortical regions of interest were measured using a modification of the original cortical peel technique (Buchsbaum et al 1990) with the four lobes and four anatomical subdivisions of each identified stereotactically (Buchsbaum et al 1989). This technique has been used by at least nine different PET groups, and a review of its advantages for facilitating intrasubject and intersubject differences may be found in Harris et al (1991). Absolute glucose values for each region of interest were expressed as a measure relative to all other regions contained in that slice. Relative rather than absolute metabolic rates were used because relative rates are more widely reported, have the advantages of removing whole brain metabolic rate, are more likely to be related to function in specific neuroanatomical systems (Fox and Mintum 1989), and show greater reliability within subjects over time (Bartlett et al 1991). The following three prefrontal values (averaged across slices) for each hemisphere were extracted: superior frontal gyrus, middle frontal gyrus, and inferior frontal gyrus (see Figure 1). Bilateral temporal (superior, middle, inferior, and posterior), parietal (postcentral, supramarginal, superior parietal lobule, and angular gyrus), and occipital (area 19, area 17 superior, area 17 inferior, and area 18) measures averaged across slices were also taken (see Figure 1).

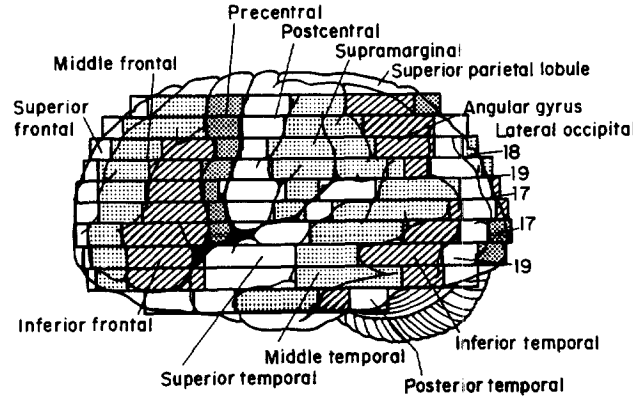


Figure 1. Lateral view of 10 stacked slices showing surface superior, middle, and inferior cortical prefrontal areas, precentral frontal cortex, and temporal, parietal, and occipital areas from cortical peel analysis. The top slice corresponds to slice #2, or 80% of head height in the brain atlas of Matsui and Hirano (1978).

Box Technique (medial areas). Medial cortical and subcortical regions of interest were located on PET slices by reference to stereotaxic coordinates as detailed in Buchsbaum et al (1989). A 3 × 3 pixel region of interest box was placed on cortical and subcortical structures at each level, according to a standard list (see Figure 2). As each pixel measured 2 × 2 mm, the size of the region of interest box was approximately one full-width half-maximum. Prefrontal measures extracted from each slice level (given as a percentage of the distance from the external auditory meatus to the top of the head) according to a brain atlas (Matsui and Hirano 1978) (see Figure 2) were as follows: superior frontal gyrus (average of 80%, 74%, 68%, and 61% slice levels as shown in Figure 2), anterior medial frontal gyrus (68% level), medial frontal gyrus (average of 61%, 54%, and 47% levels), and orbital gyrus (21% level).

To assess stereotaxic error due to individual differences in structure location within the plane, we evaluated the stereotaxic frame based on the brain outline. Stereotaxic error could place boxes in the caudate into the ventricle, thereby diluting metabolic rates with cerebrospinal zero rates, but confidence limits based on application of the

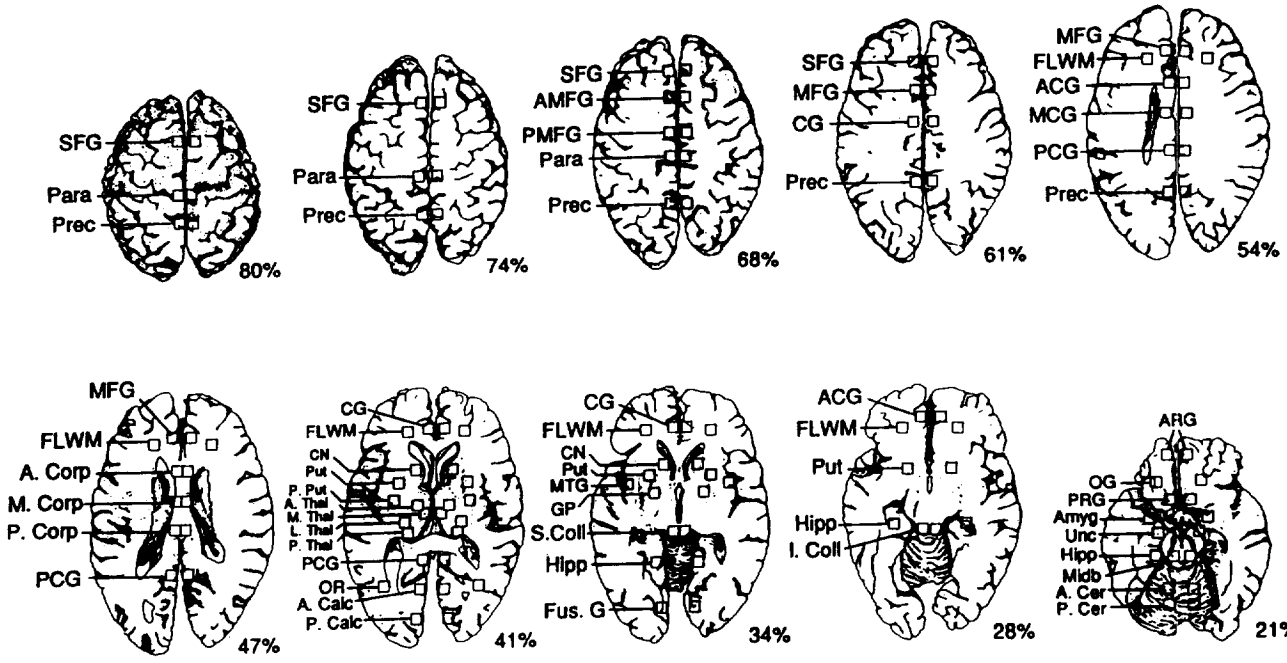


Figure 2. Transverse view of the 10 slices showing medial cortical prefrontal structures used in box analysis. Percentages refer to percent of head height above the canthomeatal line. Key to abbreviations: A. Calc = anterior calcarine gyrus, A. Cer = anterior cerebellum, ACG = anterior cingulate gyrus, A. Corp = anterior corpus callosum, AMFG = anterior medial frontal gyrus, Amyg = amygdala, ARG = anterior rectal gyrus, A. Thal = anterior thalamus, CG = cingulate gyrus, CN = caudate nucleus, FLWM = frontal lobe white matter, Fus. G = fuisform gyrus, GP = globus pallidus, Hipp = hippocampus, I. Coll = inferior colliculus, L. Thal = lateral thalamus, MCG = middle cingulate gyrus, M. Corp = middle corpus callosum, MFG = medial frontal gyrus, Midb = midbrain, MTG = medial temporal gyrus, M. Thal = medial thalmus, OG = orbital gyrus, OR = optic radiation, Para = paracentral lobule, P. Calc = posterior calcarine gyrus, P. Cer = posterior cerebellum, PCG = posterior cingulate gyrus, P. Corp = posterior corpus callosum, PMFG = posterior medial frontal gyrus, P. Put = posterior putamen, P. Thal = posterior thalamus, Prec = precuneus, PRG = posterior rectal gyrus, Put = putamen, S. Coll = superior colliculus, SFG = superior frontal gyrus, Unc = uncus.

current system to magnetic resonance images confirm 2-SD limits within the caudate (Buchsbaum et al 1992).

Subcortical regions theorized to relate to violence were as follows: corpus callosum (47% level, see Figure 2); medial temporal lobe, including the hippocampus (average of 34%, 28%, and 21%), amygdala (21%); thalamus (41%); and cingulate (61%, 54%, 41%, and 34%). Subcortical regions theorized not to be related to violence were extracted as follows: caudate (average of 41% and 34%), putamen (average of 41%, 34%, and 28%), globus pallidus (34%), midbrain (21%), and cerebellum (21%).

Results

For both cortical and subcortical analyses, values were averaged across slices and two-way group (murderers and controls) × hemisphere (left and right) repeated-measures multivariate analyses of variance using the MANOVA approach (Vasey and Thayer 1987) were conducted. For some brain areas gyrus was added as a third factor in a three-way MANOVA. All tests of significance for planned comparisons (t tests) are two tailed. Means and SDs for all brain areas are shown in Table 1.

Cortical Regions

PREFRONTAL. As anticipated on the basis of the previous pilot data, the expanded group of 41 murderers had lower glucose metabolism relative to controls in both lateral and medial prefrontal cortical areas (see Table 1 and Figure 3). We repeated exactly the same analyses that we had previously conducted on a smaller sample (Raine et al 1994) and found from two separate group × hemisphere MANOVAs a main effect for both lateral [$F(1,80) = 5.6$, $p < .02$] and medial [$F(1,80) = 6.2$, $p < .02$] prefrontal areas, with no interactions for hemisphere ($p > .75$).

A more detailed breakdown of prefrontal subregions indicated that murderers had significantly lower glucose metabolism for left and right medial superior frontal cortex ($t = 2.6$, $p < .02$), left anterior medial cortex ($t = 3.1$, $p < .003$), right orbitofrontal cortex ($t = 2.1$, $p < .04$),

Table 1. Group Means and Standard Deviations (in Parentheses) for Murderers and Controls for Cortical and Subcortical Relative Glucose Metabolism

	Left hemisphere		Right hemisphere	
	Control	Murderer	Control	Murderer
Cortical				
Lateral prefrontal[a]	1.12	1.09	1.14	1.11
	(0.05)	(0.06)	(0.05)	(0.06)
Medial prefrontal[a]	1.25	1.20	1.22	1.17
	(0.09)	(0.11)	(0.10)	(0.12)
Parietal[a]	1.15	1.10	1.17	1.13
	(0.10)	(0.11)	(0.10)	(0.11)
Occipital[a]	1.09	1.12	1.11	1.15
	(0.10)	(0.11)	(0.10)	(0.10)
Temporal	0.90	0.90	0.93	0.94
	(0.08)	(0.10)	(0.08)	(0.08)
Cingulate	0.99	0.96	0.94	0.92
	(0.12)	(0.17)	(0.12)	(0.14)
Subcortical				
Corpus callosum[a]	0.68	0.56	0.67	0.56
	(0.12)	(0.18)	(0.12)	(0.18)
Amygdala[b]	0.97	0.94	0.83	0.88
	(0.14)	(0.17)	(0.14)	(0.16)
Medial temporal lobe	0.95	0.91	0.93	0.96
and hippocampus[b]	(.10)	(0.10)	(0.11)	(0.09)
Thalamus[b]	1.09	1.09	1.09	1.15
	(0.14)	(0.12)	(0.16)	(0.14)
Caudate	1.19	1.18	1.27	1.27
	(0.16)	(0.15)	(0.13)	(0.12)
Putamen	1.22	1.21	1.26	1.28
	(0.12)	(0.13)	(0.11)	(0.10)
Globus pallidus	0.96	0.94	0.97	0.98
	(0.18)	(0.13)	(0.15)	(0.16)
Midbrain	0.74	0.75	0.76	0.80
	(0.12)	(0.13)	(0.11)	(0.12)
Cerebellum	1.01	1.05	1.03	1.10
	(0.17)	(0.16)	(0.16)	(0.17)

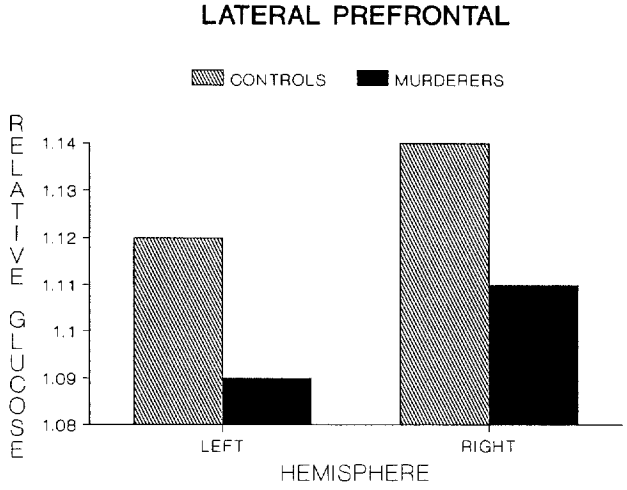
[a] Main group effect.
[b] Group × hemisphere interaction.

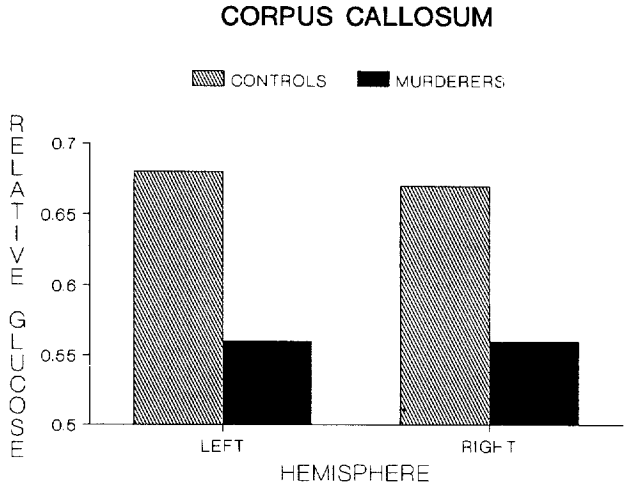
and lateral middle frontal gyri of both left ($t = 2.1$, $p < .04$) and right ($t = 2.8$, $p < .007$) hemispheres.

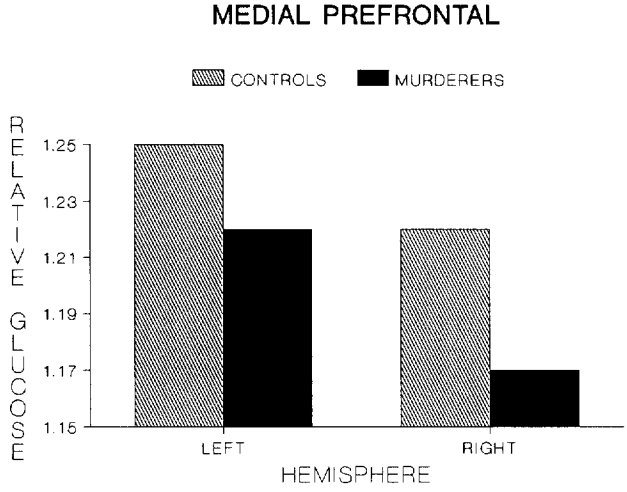
PARIETAL. Murderers had lower parietal glucose metabolism than controls, especially in the left angular gyrus and bilateral superior parietal regions. A three-way group × hemisphere × gyrus (angular, superior, supramarginal, and postcentral gyri) MANOVA indicated a marginal main effect for group, $F(1,80) = 3.7$, $p < .06$, but also a significant group × gyrus interaction, $F(3,78) = 3.9$, $p < .02$. As indicated in the lower half of Figure 4, murderers had significantly lower glucose specifically in both left ($t = 2.5$, $p < .02$) and right ($t = 2.0$, $p < .05$) superior parietal gyri, with an additional trend for the left angular gyrus ($t = 1.9$, $p < .06$). No other effects involving group were significant ($p > .33$).

TEMPORAL. Murderers were identical to controls on lateral temporal lobe glucose metabolism (see Table 1). A group × hemisphere × gyrus MANOVA revealed no significant main group effect ($p > .86$) or interaction involving group ($p > .20$).

OCCIPITAL. Murderers were found to show significantly *higher* occipital lobe glucose metabolism than normals (see Table 1). A group × hemisphere × area MANOVA revealed a main effect for group, $F(1,82) = 6.8$, $p < .02$, and a group × area interaction, $F(3,78) = 4.5$, $p < .006$. A breakdown of this interaction indicated that increased metabolism in murderers was especially marked bilaterally in areas 17 (inferior) ($t = 3.8$, $p < .0001$) and 18 ($t = 3.4$, $p < .001$). No other interactions with group were significant ($p > .11$).







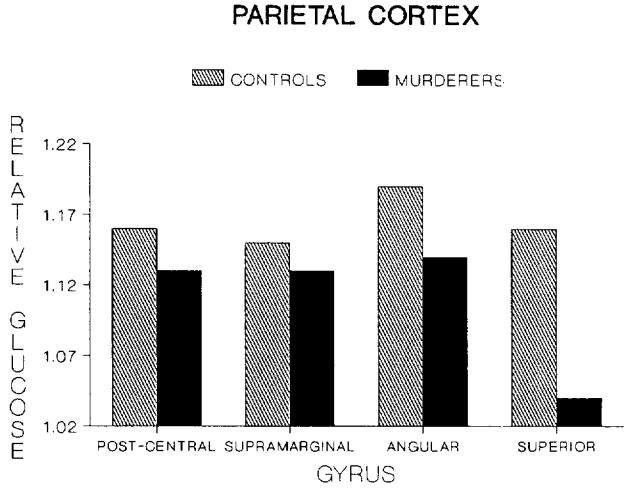


Figure 3. Relative glucose metabolic rates for murders and controls in lateral prefrontal cortex (above) and medial prefrontal cortex (below). Murderers have significantly lower lateral ($p < .02$) and medial ($p < .02$) prefrontal functioning in both hemispheres.

Figure 4. Relative glucose metabolic rates for murderers and controls in the corpus callosum and parietal cortex. Murderers have lower activity in the corpus callosum bilaterally ($p < .001$), in the superior parietal gyri bilaterally ($p < .05$), and also in the left angular gyrus ($p < .06$).

Subcortical Regions

CORPUS CALLOSUM. Murderers had bilaterally lower glucose metabolism in the corpus callosum than controls (see upper half of Figure 4). A group × hemisphere MANOVA indicated a main effect for group, $F(1,80) = 11.6$, $p < .001$, with no interaction effect ($p > .10$).

AMYGDALA. Murderers had relatively reduced left and greater right amygdala activity relative to controls. A group × hemisphere MANOVA revealed no main group effect ($p > .83$), but instead showed a significant group × hemisphere interaction, $F(1,80) = 6.8$, $p < .02$. As indicated in Figure 5, murderers showed an abnormal asymmetry consisting of relatively reduced left amygdala activity, but relatively greater right amygdala activity. A laterality coefficient (computed using the formula left − right/left + right) indicated that murderers had relatively lower left than right amygdala activity (mean = 0.03, SD = .10) compared to controls (mean = 0.08, SD = .08) ($t = 2.5$, $p < .02$).

MEDIAL TEMPORAL LOBE INCLUDING THE HIPPOCAMPUS. Murderers had relatively reduced left and greater right activity. A group × hemisphere MANOVA revealed no main group effect ($p > .93$), but instead showed a significant group × hemisphere interaction, $F(1,80) = 8.4$, $p < .005$. As indicated in Figure 5, murderers showed an abnormal asymmetry consisting of relatively reduced

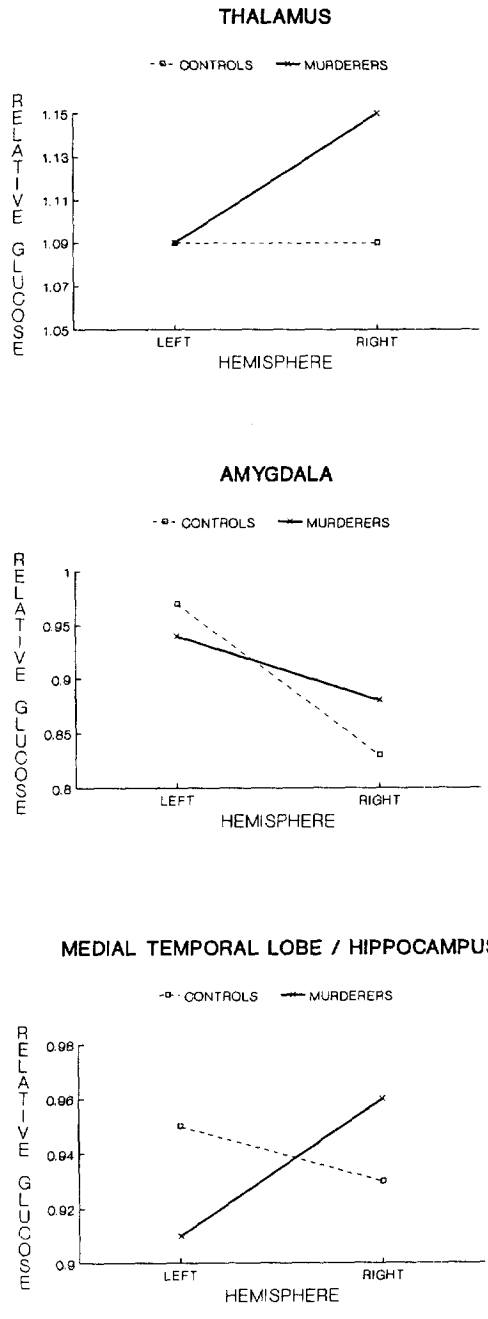


Figure 5. Significant group × hemisphere interactions for relative glucose metabolic rates for murderers and controls in the thalamus ($p < .04$), medial temporal lobe/hippocampus ($p < .005$), and amygdala ($p < .02$).

left medial temporal/hippocampal activity, but relatively greater right activity. A laterality coefficient indicated that murderers had relatively lower left than right activity (mean = −0.03, SD = 0.06) compared to controls (mean = 0.01, SD = 0.07) ($t = 2.8$, $p < .006$).

THALAMUS. Murderers had relatively greater right thalamic activity relative to controls. A group × hemisphere MANOVA revealed no main group effect ($p > .25$), but instead showed a significant group × hemisphere interaction, $F(1,80) = 4.4$, $p < .04$. As indicated in Figure 5, murderers showed an abnormal asymmetry consisting of relatively greater right thalamic activity. A laterality coefficient indicated that murderers had relatively lower left than right thalamic activity (mean = −0.03, SD = 0.07) compared to controls (mean = 0.0, SD = 0.06) ($t = 2.0$, $p < .05$).

CINGULATE. Murderers did not differ from controls on cingulate glucose metabolism (see Table 1). Both the group main effect and the group × hemisphere interaction were nonsignificant ($p > .29$).

CAUDATE, PUTAMEN, GLOBUS PALLIDUS, MIDBRAIN, AND CEREBELLUM. To assess specificity of subcortical findings, groups were compared on glucose metabolic activity in the above structures, which have characterized other mental disorders (see Discussion), but which have not been theorized to relate to violent crime. Means and SDs are given in Table 1. Group main effects for the caudate, putamen, globus pallidus, and midbrain were all nonsignificant ($p > .25$), as were all interactions involving group ($p > .17$). A trend was observed for murderers to have slightly higher (not lower) cerebellar glucose metabolic activity than normals ($t = 1.7$, $p < .10$). All interactions involving group were nonsignificant ($p > .30$).

Behavioral Performance on the CPT

Groups did not differ on any aspect of behavioral performance on the CPT. Averaged means and SDs (in parentheses) for the two groups (controls and murderers respectively) were as follows: d′: 3.63 (0.73), 3.55 (0.74), $t = 0.5$, $p > .64$; true positives (correct hits): 37.1 (5.6), 36.7 (4.5), $t = .79$, $p > .42$; false negatives (errors of omission): 3.6 (5.0), 3.3 (4.5), $t = .24$, $p > .80$; false positives (errors of commission): 4.5 (8.4), 2.3 (3.9), $t = 1.5$, $p > .15$; true negatives (correct misses): 114.8 (8.4), 117.7 (3.9), $t = 1.3$, $p > .20$.

Effects of Handedness, Head Injury, and Ethnicity

Although subjects were matched on gender, age, and schizophrenia, it was not possible to simultaneously match them on handedness, head injury, and ethnicity. Six of the murderers were left-handed. These were compared to right-handed murderers and the analyses described earlier for PET variables that produced significant group differences were repeated. All such analyses were nonsignifi-

cant, with the exception that left-handed murderers tended to have *higher* (not lower) medial prefrontal activity ($p < .08$), and had a significant *less* abnormal amygdala asymmetry ($p < .002$) than right-handed murderers. Results indicate therefore that greater rates of left-handedness in the murderer group relative to controls cannot account for reduced prefrontal activity and the abnormal amygdala asymmetry.

Fourteen of the murderers were nonwhite. Analyses comparing them to white murderers on PET measures were nonsignificant ($p > .14$) in all cases, indicating that ethnic status did not influence findings.

Twenty-three murderers had a history of head injury. They did not differ from murderers without a history of head injury on PET measures ($p > .27$), with the one exception of a trend for head-injured murderers to have lower activity in the corpus callosum ($p < .08$) than non–head-injured murderers. Although analyses suggest that history of head injury cannot account for most findings, the possibility that they account for group differences in the corpus callosum cannot be ruled out.

Discussion

Key Findings

The key findings from this preliminary study are that murderers pleading NGRI are characterized by a) reduced glucose metabolism in bilateral prefrontal cortex, the posterior parietal cortex (bilateral superior gyrus and left angular gyrus), and the corpus callosum, and b) abnormal asymmetries of activity (left hemisphere lower than right) in the amygdala, thalamus, and medial temporal gyrus including the hippocampus. These data both confirm deficits in the prefrontal cortex from our earlier pilot study, and also yield new findings. These in turn provide both some general support for preexisting biological theories of violence, and also suggest new perspectives for understanding the type of brain dysfunction that may predispose to violence in this specific group of offenders.

Biosocial Pathways from Brain Deficits to Violence

A key question concerns how these multisite deficits can translate into violence via neuropsychological, psychological, cognitive, social, and situational pathways. Regarding prefrontal deficits, damage to this brain region can result in impulsivity, loss of self-control, immaturity, altered emotionality, and the inability to modify behavior, which can all in turn facilitate aggressive acts (Damasio 1985; Damasio et al 1994; Moffitt and Henry 1991; Stuss and Benson 1986; Weiger and Bear 1988). Regarding limbic deficits, the amygdala has been repeatedly associated with aggressive behavior in both animals and humans (Bear 1989; Mirsky and Siegel 1994; Weiger and Bear 1988). The amygdala, hippocampus, and prefrontal cortex make up part of the limbic system governing the expression of emotion, while the thalamus relays inputs from subcortical limbic structures to the prefrontal cortex (Fuster 1989; Mirsky and Siegel 1994). The hippocampal formation is thought to modulate aggression in cats through its action on the lateral hypothalamus via the lateral septal area (Mirsky and Siegel 1994; Siegel and Flynn 1968), and together with the septal area and prefrontal cortex forms the neurobiological basis of the behavioral inhibition system of Gray (1982), which is theorized to be dysfunctional in violent and psychopathic individuals (Gorenstein and Newman 1980). The amygdala is believed to act on the medial hypothalamus through at least two pathways in the modulation of aggression in animals (Watson et al 1983b). The hippocampus, amygdala, and thalamus are also of critical importance to learning, memory, and attention; abnormalities in their functioning may relate to deficits in forming conditioned emotional responses and the failure to learn from experience displayed by criminal and violent offenders (Cleckley 1976; Raine 1993). The amygdala additionally plays a role in the recognition of affective and socially significant stimuli (Nishijo et al 1988), with destruction of the amygdala in animals resulting in a lack of fear (Bear 1991) and in man in a reduction in autonomic arousal (Lee et al 1988); thus, abnormalities in the amygdala could be relevant to a fearlessness theory of violence based on psychophysiological findings of reduced autonomic arousal in offenders (Raine et al 1990b; Raine 1993).

The posterior parietal cortex (including superior and angular gyri) is centrally involved in the integration of sensory input and the formation of abstract concepts (Kolb and Wishaw 1990), and in conjunction with its reciprocal connections with the dorsolateral prefrontal cortex (Goldman-Rakic et al 1983) may contribute to the cognitive and social information processing deficits observed in violent offenders (Dodge and Crick 1990; Moffitt and Silva 1988). Reductions in glucose metabolism in the left angular gyrus have been correlated with reduced verbal ability (Gur et al 1994), while damage to the left angular gyrus has been linked to deficits in reading and arithmetic. Such cognitive dysfunction could predispose to educational and occupational failure, which in turn predispose to crime and violence. Learning deficits have been found to be common in violent offenders who also have low verbal IQs (Quay 1987; Raine 1993). One caveat here is that the finding for the left angular gyrus was a trend using a two-tailed test ($p < .06$), although the effect is significant on a one-tailed test ($p < .03$) and was predicted on the basis of event-related brain potential data from Barratt et al in press. In contrast to these posterior parietal areas,

which are dysfunctional in murderers, the more anterior parietal regions are involved in more basic somatic sensations and perceptions and are unaffected in murderers, indicating some specificity of dysfunction within the parietal region.

Although there have been speculations for many years that dysfunction to the corpus callosum may be a neurobiological predisposition to violence (e.g., Nachshon 1983; Yeudall 1977), until now there has been no direct evidence to support such a contention. Although white matter metabolic values are only approximately 50% of grey matter values (thus biasing toward floor effects and nonsignificant results), we obtained our strongest group difference for this region. Callosal dysfunction and the consequent lack of interhemispheric integration could contribute to the abnormal asymmetries of function and reduced interhemispheric integration previously observed in antisocial and violent groups (Hare and McPherson 1984; Flor-Henry et al 1991; Raine et al 1990a). We have previously hypothesized that the reduced lateralization for processing linguistic information observed in violent groups may arise from a reduction in the normal neurodevelopmental processes of hemispheric specialization, a process that may in part be accounted for by dysfunction of the corpus callosum (Raine et al 1995).

Another potential implication of poor interhemispheric transfer is that the right hemisphere, which has been implicated in the generation of negative affect in humans (Davidson and Fox 1989), may experience less regulation and control by left hemisphere inhibitory processes (Cook 1986; Flor-Henry 1987), a factor that may contribute to the expression of violence in predisposed individuals. In animals, rats who are stressed early in life are right hemisphere dominant for mice-killing (Garbanati et al 1983). Severing the corpus callosum in these rats leads to an increase in muricide (Denenberg et al 1986), indicating that the left hemisphere acts to inhibit the right hemisphere mediated killing via an intact corpus callosum. The fact that both Sperry (1974) and Dimond (1979) commented on the inappropriate nature of emotional expression and the inability to grasp long-term implications of a situation in split-brain patients may also give pointers to the inappropriate emotional expression of violent offenders and their lack of long-term planning (Cleckley 1976). Nevertheless, findings from animal research cannot be directly extrapolated to humans. Furthermore, callosal dysfunction per se is unlikely to cause aggression; instead it may contribute to violence in those with concurrent limbic and cortical abnormalities.

Findings of group differences in glucose metabolism in the posterior parietal cortex, amygdala, and medial temporal lobe including the hippocampus may not be unrelated. The amygdala has been viewed as part of a system for processing socially relevant information (Brothers and Ring 1993), and functions in parallel with the object recognition system of the hippocampus and the spatial recognition system of the posterior parietal cortex (Kolb and Wishaw 1990). Disruption of such a system could in part relate to the socially inappropriate behavior shown by some violent individuals (Cleckley 1976) and the misrecognition and misappraisal of ambiguous stimuli in social situations that have potential for violent encounters (Dodge et al 1990; Nachshon and Rotenberg 1977).

Findings of this study suggest that the neural processes underlying violence are complex and cannot be simplistically reduced to single brain mechanisms causing violence in a direct causal fashion. Instead, violent behavior probably involves disruption of a network of multiply interacting brain mechanisms that predispose to violence in the presence of other social, environmental, and psychological predispositions (Eichelman 1992; Earls 1991; Lewis et al 1988). Nevertheless, attempts to "network" findings from the individual brain sites in this study must proceed cautiously, because there are brain mechanisms relevant to aggression (e.g., septum and hypothalamus) that could not be imaged in this study. For this reason, this study cannot provide a complete account of the neurophysiology of violence in this specific and selected subgroup of violent offenders, although it is felt both that it does provide preliminary evidence that murderers pleading NGRI have different brain functioning compared to normals, and also that it gives initial suggestions as to which specific neural processes may predispose to their violent behavior.

Potential Confounds

We do not believe that these results reflect merely chance findings for five reasons. First, the sample size (41 in each group) is not small for PET research, and is substantially larger than other imaging studies of violent populations. Second, the strength of effects were not trivial, with a mean effect size of 0.55 (range = 0.36–0.80), which is viewed as medium (Cohen 1988). Third, areas were selected for analysis on the basis of prior theorizing, and all but one of these produced significant effects. Fourth, to help limit the possibility of type I errors, overall MANOVAs were conducted and two-tailed tests used throughout. Fifth, brain areas that have not been theoretically linked to violence but that have been linked to other mental disorders (caudate, putamen, globus pallidus, midbrain, cerebellum) did *not* yield group differences; this double dissociation lends some support to the relatively differential nature of the brain deficits in terms of both anatomy and mental condition. Nevertheless, it should be emphasized that some effects were marginal (e.g., left angular gyrus), and results must be treated cautiously, particularly

those regarding subcortical laterality effects and increased occipital functioning, which were not predicted a priori.

It does not appear that the findings are a function of group differences in age, gender, schizophrenia, handedness, ethnicity, or history of head injury. Groups were matched on age, gender, and ethnicity. Analyses comparing left-handed with right-handed murderers, white versus nonwhite murderers, and murderers with and without a history of head injury do not support the view that the greater rates of left handedness, head injury, and nonwhites in the murderer group account for overall murderer versus control group differences. One caveat to this conclusion is that there was a trend ($p < .10$) for murderers with a history of head injury to have reduced glucose metabolism in the corpus callosum. This would be consistent with the notion that sheering of white nerve fibers during closed head injuries could contribute to damage to the corpus callosum (McAllister 1992). In addition, because we did not have more extensive neurological and medical data to assess history of head injury, we cannot definitively rule out prior head injury as a possible contribution toward reduced brain activity in the murderers.

The fact that groups did not differ in behavioral performance on the CPT suggests not only that difference in brain functioning is not easily accounted for by motivational or attentional deficits in the murderers, but also that the significantly *greater* occipital activity (visual areas 17 and 18) in murderers may possibly represent compensation for the reduced activity in the prefrontal cortex, an area which is critical for the execution of this challenge task (Buchsbaum et al 1990). Cognitive parity between groups cannot be claimed, because no IQ data were available on the subjects. Nevertheless, we do not believe that lower IQ in the murderer group can account for findings of reduced glucose metabolism, because low IQ has been associated with *higher,* not lower, cerebral glucose metabolism (Haier et al 1988).

Specificity of Findings

The question of whether comorbid psychiatric conditions in the murderers could account for PET findings needs to be considered. The most important psychiatric condition in murderers consists of schizophrenia. We controlled for this by matching 6 schizophrenic murderers with age- and sex-matched hospital schizophrenics. We do not believe that other forms of psychiatric comorbidity can easily account for our findings, because differences in brain functioning in murderers show a different pattern to that observed in other mental disorders. Psychiatric patients show abnormalities in brain structures not found in the murderers, while murderers have abnormalities not previously reported in psychiatric patients. For example, whereas altered functioning has been found in schizophrenics for the lateral temporal cortex (Buchsbaum et al 1990; DeLisi et al 1989), basal ganglia (Buchsbaum 1990; Early et al 1987; Gur and Pearlson 1993), cingulate gyrus (Siegel et al 1993), caudate (Siegel et al 1993), and cerebellum (Volkow et al 1992), these structures were unaffected in murderers. Similarly, there is a growing consensus that affective disorder involves dysfunction to both frontal and temporal lobes (Baxter et al 1989; Cummings 1993; George et al 1993). In contrast, although murderers have widespread bilateral reductions in prefrontal glucose utilization, they did not show the lateral temporal deficits that have been observed in schizophrenics using the same methodology (Buchsbaum et al 1990), while depressives tend to have dysfunction lateralized to the left hemisphere (Baxter et al 1989; Bench et al 1993; Drevets et al 1992) and to the left dorsolateral prefrontal region in particular (Baxter et al 1989; Bench et al 1993), in contrast to the bilateral prefrontal findings for murderers. Furthermore, depressives have been reported to show additional involvement of the caudate nucleus (Cummings 1993) and cingulate gyrus (George et al 1993), brain areas unaffected in murderers. Obsessive–compulsives show higher, not lower, glucose levels in orbitofrontal cortex (Baxter et al 1988; Benkelfat et al 1990), while symptom intensity in this group is associated with higher (not lower) functioning in the hippocampus and thalamus (McGuire et al 1994). With respect to substance abuse, acute cannabinol administration affects cerebellar functioning (Volkow et al 1991), whereas murderers showed normal cerebellar activity. Detoxified alcoholics show increased (not decreased) brain metabolism during detoxification, with persistent low metabolic levels being shown for the basal ganglia (Volkow et al 1994), a structure unaffected in murderers. Whereas cerebellar hypometabolism and degeneration has been observed in chronic alcoholics (Gilman et al 1990), murderers showed nonsignificantly higher, not lower, cerebellar activity.

Reduced prefrontal activity does not seem to be specific to severe violence, as this finding has been observed in a variety of psychiatric conditions. On the other hand, to the authors' knowledge there have been no previous reports in any psychiatric condition of left lower than right asymmetries in the amygdala, thalamus, and hippocampus coupled with dysfunction of the corpus callosum and left angular gyrus. For example, although there have been variable reports of either increased, decreased, or normal thalamic activity in schizophrenia (Buchsbaum et al 1987; Resnick et al 1988; Siegel et al 1993), the left lower than right asymmetries for these structures in murderers have not been previously reported. While prefrontal dysfunction may represent a deficit common to many forms of psy-

chopathology, additional dysfunction to these other brain structures may lead to a pathway toward violence as opposed to other conditions. In drawing comparisons across imaging studies, it must be borne in mind that some studies have used exactly the same imaging methodology employed in the present study (e.g., Buchsbaum et al 1990; Siegel et al 1993; DeLisi et al 1989), whereas others have employed different methodologies (e.g., Baxter et al 1989; Volkow et al 1992). As such, strict comparisons across studies are not possible.

Although coexisting psychopathology may contribute to violence and should not be discounted as unimportant, it does not seem that such pathology per se can account for the specific network of brain dysfunction observed in this violent group. Nevertheless, although subjects constituted a relatively specific subgroup of violent offenders (all had committed homicide and were pleading NGRI), it must be acknowledged that they do not constitute a homogenous clinical group. Specifically, heterogeneity would contribute to type II error and the failure to observe significant group differences in some brain regions of interest. As such, it must be emphasized that these initial findings must be viewed with caution and due circumspection.

Strengths, Limitations, and Conclusions

As with all initial findings, the current study has limitations, including relatively modest spatial resolution relative to the most advanced present-day PET techniques, the lack of standardized diagnostic and neuropsychological assessments, and the use of the canthomeatal line for slice placement, which has a variable orientation to brain landmarks, and which can lead to significant variability across subjects in the anatomical localization of regions of interest. Limitations such as the absence of psychiatric control groups have also characterized the first brain imaging studies of other conditions such as schizophrenia as well as some current studies. In addition, it must be reiterated that findings apply only to a select subgroup of severely violent offenders and cannot be generalized at this stage to violence per se. Furthermore, findings for subcortical asymmetries and the occipital cortex were not predicted a priori and need to be replicated in an independent study.

Balancing these limitations, it is felt that the study also has a number of strengths. These include by far the largest sample of seriously violent offenders ever imaged, matching for age, sex, and schizophrenia, ruling out confounds of handedness, ethnicity, and head injury, and establishing group equivalence on behavioral performance of the challenge task and psychopharmacologic control over medication and illegal drug use in weeks prior to scanning. Such strengths are not common in this field, which is hampered by multiple obstacles to research. Despite some limitations in the research, we nevertheless feel it appropriate to report these findings, because they constitute the first to document multiple but selective brain deficits assessed using PET in a group of severely violent offenders who are of particular importance in forensic psychiatry, and because they provide both theoretical directions and a critical empirical base upon which future brain imaging studies of violent offenders may build. At the same time, the need for caution in interpreting findings due to the preliminary nature of the findings and the need for independent replication must be reemphasized.

Although the study has strengths, it is critically important to document what this study does and does not indicate. First, these findings cannot be taken to demonstrate that violence is determined by biology alone; clearly, social, psychological, cultural, and situational factors also play important roles in predisposing to violence (Eichelman 1992; Elliott 1987, 1988). Second, these data do not demonstrate that murderers pleading NGRI are not responsible for their actions, nor do they demonstrate that PET can be used as a diagnostic technique. Third, our findings cannot speak to the issue of the cause (genetic or environmental) of the brain dysfunction, nor do they establish causal direction. Fourth, findings cannot be generalized at the present date from NGRI murder cases to other types of violent offenders. Fifth, specificity to violence as opposed to crime per se has not been established, as this requires the inclusion of a nonviolent criminal control group, which was not available. What these initial findings do document, however, is that as a group, murderers pleading NGRI have statistically significant differences in glucose metabolism in selected brain regions compared to normals. They also suggest, but do not conclusively demonstrate, that reduced activity in the prefrontal, parietal, and callosal regions of the brain, together with abnormal asymmetries of activity in the amygdala, thalamus, and medial temporal lobe including the hippocampus, may be one of many predispositions toward violence in this specific group. As with all initial findings in the field, future independent replication, refinement, and extension to less select populations of violent offenders are greatly needed.

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