A Positron Emission Tomography Study of the Functional Neuroanatomy of Closed Head Injury

by

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ABSTRACT

Structural changes in the frontal and temporal lobes and in subcortical white matter tracts often occur following closed head injury (CHI). In contrast to this well delineated structural pathology, the post-traumatic cognitively-related *functional* changes in these and other brain regions have not been adequately described.

To characterize the long-term functional neuroanatomy of CHI, the present study compared regional cerebral blood flow (rCBF) patterns in 13 severely-injured, well-recovered, unmedicated patients to those from 13 well-matched healthy controls. rCBF was measured using oxygen-15 water intravenous bolus positron emission tomography (PET) while subjects performed the Wisconsin Card Sorting Test (WCST), an indicator of prefrontal lobe functioning that involves matching stimuli to a changing sorting principle based on external feedback, and a Cued Recall Memory Test (CRMT), which involves remembering semantically-related word pairs. The neuropsychological tasks were used to provoke specific neural systems believed to be important in task performance (the prefrontal cortex in the former, the hippocampus in the latter). Subjects also performed two specially designed sensorimotor control tasks to provide measures of baseline rCBF.

Given the controversy regarding the statistical analysis of PET data, a two-pronged method was utilized: 1) Statistical Parametric Mapping, the state-of-the-art technique that examines rCBF throughout the entire brain, and 2) region of interest

analysis, an anatomically-based method for examining rCBF in a limited set of brain regions. Between-group rCBF differences were tested in the four tasks separately and also in the two neuropsychological tasks after subtracting baseline rCBF (i.e., rCBF activation). To characterize the relationship between cerebral perfusion and behavior, correlations were performed between performance and rCBF activation (i.e., task-control) for each group separately, and between rCBF activation and an index of current neuropsychological functioning for the CHI patients.

Analyses of each task separately revealed that, compared to controls, CHI patients showed *lower* rCBF in anterior cingulate cortex (ACC) and subcortical areas. Analyses of rCBF activation data revealed: 1) *increases* in left inferior frontal gyrus (including Broca's area) and left hippocampus of CHI patients relative to control subjects during the WCST, 2) a *negative* correlation between task performance and the right hippocampus during the WCST in CHI patients, and 3) correlations between the hippocampus and performance during the CRMT in the CHI patients that were in the *opposite* direction to those found in the control subjects.

These neurofunctional changes are compatible with the structural and cognitive sequelae of CHI. First, given a hypothesized role of the ACC in attentional processes, reduced rCBF in this region of CHI patients may relate to the persistent and often subtle difficulties in attention after CHI, whereas rCBF diminutions in subcortical regions may relate to diffuse damage to or deafferentation of subcortical regions in this CHI sample. Second, given similar (although slightly, but not significantly, poorer) performance on the WCST by the CHI patients, increased left prefrontal

cortical activity may partially reflect behavioral compensation (e.g., subvocalization to aid memory during the task) and also physiological compensation for inefficiencies in other brain areas (e.g., subcortical regions). Finally, in light of the relatively poorer task performance of CHI patients (non-significant tendency in the WCST but highly significant in the CRMT), differences between the groups in the direction of the correlations between performance/cognition and hippocampal activation may suggest disorganization of hippocampal functioning in CHI patients.

This exploratory and descriptive investigation identifies brain structures with post-traumatic changes that may be important to cognition. These results may provide evidence of both behavioral and neurophysiological compensation in patients with severe CHI.

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INTRODUCTION

HEAD TRAUMA

Head trauma is defined as a blow to the head or laceration of the scalp or forehead that results in altered consciousness, regardless of brevity (Jennett, Murray, MacMillian, MacFarlane, Bentley, & Hawthorne, 1977). According to the 1985 Status Report published by the U.S. National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) the annual incidence of head trauma in the United States is 0.2 percent with the peak incidence found for young adults between 15 and 24 years of age (Frankowski, Annegers, & Whitman, 1985). In this age group, the male to female incidence of head trauma is highest with males at three times the risk of females. Motor vehicle accidents are the principal cause of head trauma, accounting for one-third to one-half of all cases. Head trauma can be classified as closed head injury (CHI) or open head injury depending on whether skull penetration results. In non-war times, cases of the former far exceed the latter and are the focus of this investigation.

The most common sequelae of CHI are alterations in cognition and behaviour, which have been extensively described. Few investigations, however, have examined the neurophysiological basis of these changes. The following is an investigation of the long-term neurophysiological sequelae of CHI during neuropsychological performance using a functional brain imaging technique.

Pathophysiology of CHI

Following non-missile brain trauma, focal injuries (e.g., hematomas) often occur at the site of impact (the coup) and to the part of the brain opposite the coup (the contrecoup). In conjunction with focal injury, widespread cerebral damage frequently results from stretching of axons during high velocity impact, known as diffuse axonal injury (DAI), which is characteristically associated with punctate white matter lesions and enlarged ventricles. Effects of brain trauma occurring beyond the initial impact can further damage the brain. These secondary physiological events include hypoxia, hypotension, and edema, the latter of which can cause increased intracranial pressure (ICP) as well as ischemia and/or hemorrhage.

Although substantial heterogeneity exists in the location of lesions among CHI patients, data from neuropathological and neuroradiological examinations have provided compelling evidence of predominant frontal and temporal pole damage. In post-mortem histopathological investigations of large cohorts of CHI patients who sustained fatal injuries, Adams and colleagues found that, after taking into account the size and depth of contusions, damage was greatest in the frontal and temporal lobes, respectively (Adams, Graham, Scott, Parker, & Doyle, 1980; Adams et al., 1985). Similarly, in two studies of mild to moderate CHI patients within one week post-trauma, Levin and coworkers reported a predominance of frontal and temporal lesions visualized by magnetic resonance imaging (MRI) scans (Levin et al., 1987; Levin, Williams, Eisenberg, High, & Guinto, 1992).

The hippocampus, a structure of the temporal lobes, is particularly susceptible to damage following brain trauma. Examination of 112 brains from fatally-injured CHI patients revealed lesions in the hippocampus in 84% (Kotapka, Graham, Adams & Gennarelli, 1992). Of those cases, 74% showed hippocampal pathology bilaterally. In the minority of cases in which hypoxia, high ICP, and hypotension were ruled out, it was thought that pathological neuronal excitation via glutamate or other excitatory amino acid neurotransmitters caused the hippocampal damage (Kotapka, Graham, Adams, & Gennarelli, 1994). Because clinical evidence suggests that bilateral and not unilateral lesions to the hippocampus cause impairment in memory (Scoville & Milner, 1957), bilateral cell loss in the hippocampus was thought to be a possible mechanism underlying the persistent memory impairment frequently observed in CHI patients (Smith, Lowenstein, Gennarelli, & McIntosh, 1994).

Assessing Severity

Two methods of assessing severity of CHI are commonly employed (Appendix A): a) depth of coma measured by the Glasgow Coma Scale (GCS), an index rating motor, ocular, and verbal responses immediately following injury (Teasdale & Jennett, 1974), and b) length of post-traumatic amnesia (PTA), i.e., the length of time post-injury that a patient is unable to form continuous memories of ongoing events (Russell, 1932). Because determining depth of coma is more objective than assessing length of PTA, the former has become a more widely accepted tool for measuring severity of brain injury. However, because extracranial factors such as alcohol

intoxication and hypotension can decrease consciousness independently of brain injury, the GCS may overestimate injury severity. When medical records are either unavailable or lack sufficient detail regarding coma depth, the assessment of PTA length through interview with the patient or family member becomes the method of choice for documenting injury severity. Although the correlation between length of PTA and depth of coma is typically high (Bishara, Partridge, Godfrey, & Knight, 1992), short or no coma can be associated with lengthy PTA (Wilson, Teasdale, Hadley, Wiedmann, & Lang, 1993), suggesting that the two severity measures reflect different underlying neuropathology.

Predicting Outcome

The relationship of neurological, behavioral, and neuropsychological functioning immediately following injury to subsequent outcome has been extensively studied. Comparison of results across studies has been hampered by differences in: a) the measures employed to assess outcome, b) the accuracy of assessing the initial manifestation of injury, c) the nature of the subject sample (e.g., severity of injury, age of population), d) the interval between injury and assessment of outcome, and e) the statistical approach. Despite the procedural variations across studies, several neurological indices have been consistently identified as important predictors of outcome. These include initial GCS score, duration of coma or unconsciousness, length of PTA, and the presence and evacuation of hematoma (Haslan, Batchelor, Fearnside, Haslam, Hawkins, & Kenway, 1994).

Neuropsychological and Neurobehavioral Sequelae

The most common acute and chronic cognitive sequelae of CHI are disturbances of memory functions (Brooks, 1975; Oddy, Coughlan, Tyerman, & Jenkins, 1985; Levin et al., 1990). Neuropsychological studies indicate that memory for verbal information is disproportionately affected by CHI (Brooks, McKinlay, Symington, Beattie, & Campsie, 1987) and is independent of changes in intellect (Levin, Goldstein, High, & Eisenberg, 1988). Problems with attention following CHI have been reported by a number of investigators and frequently by patients themselves (e.g., Levin et al., 1988). Despite the claim that intellectual functions are more resilient to CHI than other abilities (Levin, High, Goldstein, & Williams, 1988), results from studies of patients with moderate to severe CHI have revealed consistently lower scores, relative to normal controls, on tests of intelligence (Correll, Brodginski, & Rokosz, 1993) and abstract reasoning (Scherzer, Charbonneau, Soloman, & Lepore, 1993). In general, perceptual abilities (Levin et al., 1990) and language skills, with the exceptions of word retrieval (Levin, Grossman, & Kelly, 1976; Menon, Ravichandran, & Tan, 1993) and verbal fluency (Perret, 1974), appear to be relatively preserved following CHI.

The cognitive and behavioral changes following CHI have been hypothesized to relate primarily to prefrontal dysfunction, which can result not only from direct lesions to the frontal lobes but also from the disruptive effects of DAI on prefrontal afferents and efferents. Evidence for this comes from the fact that executive functions (e.g., planning, initiation, and regulation of behaviour), which depend primarily on the

integrity of the prefrontal cortex (Lezak, 1983; Stuss & Benson, 1984), are frequently compromised following CHI. Stuss and colleagues (1985) found that the two neuropsychological tasks that best discriminated a group of CHI patients with good recovery of premorbid functional capacity from a group of well-matched normal subjects were tests sensitive to frontal lobe function: CHI patients were significantly impaired on the Brown-Peterson interference memory task (Brown, 1958; Stuss, Kaplan, Benson, Weir, Chiulli, & Sarazin, 1982) and displayed significantly more perseverative errors on the Wisconsin Card Sorting Test (Grant & Berg, 1948), a test of the ability to abstract and to shift mental set based on examiner feedback (Milner, 1963; Robinson, Heaton, Lehman, & Stilson, 1980).

FUNCTIONAL NEUROIMAGING

Functional neuroimaging techniques such as single photon emission computerized tomography (SPECT) and positron emission tomography (PET) provide a method to map brain activity in vivo (see Herscovitch, 1993 for a review). Brain function can be measured in terms of regional cerebral blood flow (rCBF) or the regional cerebral metabolic rate of glucose utilization. Although glucose is the principal substrate of neuronal metabolism, rCBF is closely coupled with and directly proportional to glucose utilization under most circumstances (Raichle, Grubb, Gado, Eichling, & Ter-Pogossian, 1976). Because rCBF PET measurements have substantially better temporal resolution (i.e., the minimum length of time necessary to record a particular physiological event) than glucose metabolism measurements (less

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than 5 minutes compared to approximately 30 minutes, respectively), the former techniques have become the methods of choice for mapping the regional physiological correlates of mental activity.

rCBF Measurement Principles

rCBF techniques involve administration, usually by inhalation or intravenous injection, of a small quantity of a radioactive substance that serves as a tracer of rCBF. The most commonly used radiotracer for rCBF PET studies of cognition is oxygen-15 water ($H_2{}^{15}O$). The popularity of this tracer derives from its physiologically inert nature (i.e., it has the same in vivo behavior as its nonradioactive counterpart H_2O) and its relatively short half life (approximately two minutes), which permits repeated scans in the same person within the same experimental session. The tracer is carried in the blood to the brain, where its passage through the brain is monitored and interpreted using mathematical models that describe the kinetics of the tracer.

The ability to monitor the passage of the tracer through the brain depends on emission by the radioactive tracer of positrons, which, after traveling a short distance, each form an annihilation pair with an electron, thereby producing a pair of photons (gamma rays) that travel at the speed of light approximately 180° to each other. The pair of photons can then be simultaneously detected by the PET detectors that surround the head, and the annihilation event can thus be localized to somewhere along a line connecting the two points of detection. The emission of paired photons

also allows for quantification of the loss of detectable annihilations by the absorption and attenuation of annihilated photons in brain tissue. When the distribution of radioactivity in the brain is measured over time and accompanied by a measurement of radioactivity in arterial blood over time, rCBF in units of ml/min/100g tissue can be calculated. Without sampling of radioactivity in arterial blood during the emission scan, the number of radioactive disintegrations (i.e., counts) detected in the brain cannot be converted to absolute blood flow and are not considered to be fully quantitative. The values, either in units of rCBF or counts of radioactivity per unit tissue (nCi/cc), can be linked to a color scale and represented as two-dimensional images reflecting a continuum of brain activity.

PET versus SPECT

The major difference between PET and SPECT lies in the type of radiotracer used to map brain activity. In contrast to PET radiotracers described above, SPECT uses isotopes that emit only one photon with each disintegration. As a result, localization of the emission and correction for photon attenuation by tissue and skull are less precise than with PET. Because photons originating from superficial brain areas have less tissue to travel through and therefore are less attenuated than photons originating in deeper brain structures, a bias toward higher activity in cortical than subcortical regions results. Although this bias can be partially corrected for by using an assumed value for the attenuation properties of tissue with a given isotope, the data from SPECT techniques remain semi-quantitative. With PET, on the other hand,

attenuation can be measured directly with transmission scans (see Methods). Although substantially more expensive and less widely available, PET produces the most quantitative data and has the highest spatial resolution (i.e., the minimum distance two point sources of radioactivity must be separated to be perceived as distinct) of any method available for mapping brain function.

Cognitive Activation Paradigms

Theoretically, functional brain scans conducted during a cognitive task (known as a cognitive activation paradigm) allow for mapping of the essential neural circuitry involved in a particular cognitive function. Functional brain mapping relies on the assumption that brain regions participating in a cognitive operation become more metabolically active. This is demonstrated in Figure 1, which shows that rCBF changes accompanying sequential finger movement can be seen in primary motor cortex even in the raw (unprocessed) data of a single subject (data from Ramsey et al., in press).

The most widely used approach for isolating the physiological concomitants of a complex cognitive act has been to employ a control task that is similar to the experimental task in all but the cognitive component of interest. The rCBF values derived from the control task are then subtracted from those from the experimental task to yield rCBF activation values associated with the cognitive function of interest (Fox, Mintun, Reiman, & Raichle, 1988). The subtraction method, which attempts to increase the signal-to-noise ratio in PET data, is demonstrated in Figure 1, which

Figure 1: Positron emission tomography (PET) scans of a single subject in a motor activation paradigm. The top 4.6 cm of the brain in axial orientation are presented ranging from inferior most at the left to superior most at the right. The left side of the brain is at the left of each slice. *Upper panel.* A PET scan acquired while a single subject performed a sequential finger tapping task with his right hand shows increases in activity in contralateral primary motor cortex (PMC) (denoted by an asterisk in slice #7), as well as many other brain areas. *Middle panel.* A PET scan acquired while the same subject was resting reveals brain activity in many of the same areas outside of PMC, but none in PMC. *Lower panel.* After subtraction of the resting scan from the motor scan, activations *within* PMC remain (denoted by an asterisk in slice #7), whereas increases in activity *outside* of PMC, which were seen in the original motor scan, disappear.


Single Subject in Motor Activation Paradigm
Scan during sequential finger tapping (right hand)
1
2
3
4
5
6
7
Scan during resting
1
2
3
4
5
6
7
Resting scan subtracted from sequential finger tapping scan
1
2
3
4
5
6
7

shows that, after subtraction of the resting scan from the motor scan of a single subject, increases in primary motor cortex seen in the original motor scan remain, whereas other, possibly less relevant, areas of activation are no longer present in the subtraction image (data from Ramsey et al., in press).

The validity of the "subtraction" approach for neural localization of cognition with PET has been challenged on the basis that the brain might not, and probably does not, process complex mental activities in a linear, decomposable fashion (Sergent, 1994). In other words, performing two activities at once, such as reading and speaking, might involve a qualitatively unique pattern of neural activity rather than an arithmetic summation of the two isolated activities. The subtraction method has also been criticized on the basis that the specific nature of the task selected as the control or "subtraction" task might affect the experimental results (Sergent, 1994). For studies attempting to delineate the physiological correlates of mental activity, these issues are paramount and have yet to be satisfactorily resolved. In contrast, for studies that use a cognitive task as a means to "stress" the circuitry involved in performing a particular action (without attempting to define the brain regions involved in that task per se), subtraction methods employing sensorimotor control tasks allow comparison of rCBF in the experimental condition to a baseline physiological measurement that takes into account sensory inputs and motor outputs. In this latter case, concerns about the subtraction method appear to be less critical.

Findings from Previous Functional Neuroimaging Studies of CHI

Relationship between outcome and global CBF

Previous functional neuroimaging studies of CHI patients, which mainly utilized SPECT to measure brain activity, have investigated the relationship between outcome and cerebral blood flow and/or metabolism across the entire brain (i.e., global activity) in the acute stage following injury (Uzzell, Obrist, Dolinskas, & Langfitt, 1986; Jaggi, Obrist, Gennarelli, & Langfitt, 1990). In general, results from these studies, which were initially confounded by the fact that blood flow and metabolism can uncouple (i.e., elevated rCBF levels associated with decreased metabolism) during the acute phase following CHI (Obrist, Langfitt, Jaggi, Cruz, & Gennarelli, 1984), showed that diminished global activity was associated with poor outcome (Barclay, Zemcov, Reichert, & Blass, 1985). A study by Terayama, Meyer, and Kawamura (1991) demonstrated that the relationship between perfusion deficits and cognitive outcome existed even a decade after injury. When global cerebral blood flow measured by SPECT was compared between patients with different cognitive outcomes, the investigators reported that persistent cerebral perfusion abnormalities predicted long-term cognitive impairment, whereas normalization of cerebral perfusion predicted cognitive improvement.

Sensitivity of functional neuroimaging in detecting cerebral abnormalities

More recently, the sensitivity of functional compared with structural neuroimaging techniques in detecting cerebral abnormalities has been investigated. By comparing the number of abnormalities revealed by each imaging modality, these

studies have found that SPECT and PET identified areas of abnormalities extending beyond those delineated by MRI (Newton et al., 1992; Wiedmann, Wilson, Wyper, Hadley, Teasdale, & Brooks, 1989; Ichise, Chung, Wang, Wortzman, Gray, & Franks, 1993) or CT (Grey, Ichise, Chung, Kirsh, Franks, 1992; Nedd et al., 1993). Both PET and SPECT, however, failed to reveal a substantial number of lesion sites confirmed by MRI, which demonstrates the need for both structural and functional imaging techniques in adequately identifying cerebral pathology following CHI.

Resting rCBF abnormalities and cognition

The relationship between rCBF abnormalities observed while subjects were simply resting in the scanner and neuropsychological dysfunction assessed at another time outside the SPECT scanner ("extra-scan") has been most recently studied. Wiedmann et al. (1989) demonstrated a consistent relationship between the location of rCBF abnormalities and extra-scan neuropsychological performance in a small group of CHI patients. These investigators found that poor performance on nonverbal tasks related to decreased rCBF in the right anterior temporal area. Goldenberg, Oder, and Podreka (1991), on the other hand, failed to demonstrate a reliable relationship between rCBF values in the temporal lobes and neuropsychological performance. Instead, they found that blood flow in the frontal lobes positively correlated with performance on tests of executive function. The correlations between executive functions and thalamic flow, however, were more robust, which the authors suggested reflected the effects of DAI (i.e., disruption of pathways from the frontal lobe to the thalamus).

Limitations of Previous Functional Neuroimaging Studies of CHI

The above mentioned investigations suffer from several important limitations. First, all of the studies measured rCBF during the resting state. Resting PET scans are poorly controlled for cognitive state and have been shown to produce more variable data than those scans collected when subjects have prescribed sensory inputs, motor outputs, and cognitive tasks to perform (Duara et al., 1987). Consequently, any differences in neurophysiology between two groups or between conditions in the same subject during rest may reflect differences in subjective experiences of the PET procedure rather than in primary differences in cerebral physiology. In contrast, in addition to helping control for behavioral state, performance of a task during PET is believed to stress the underlying neural systems involved in performing the task and thereby reveal subtle neurophysiological anomalies that would not be detected during rest (Berman & Weinberger, 1986). Given these facts, it is not surprising that studies attempting to relate brain physiology during rest with extra-scan cognitive performance have yielded inconsistent results.

Second, previous investigators have not required their patient samples to be unmedicated. Studies with both normal and neuropsychiatric populations have suggested that medications that alter central nervous system functioning (e.g., amphetamine) can affect rCBF measurements (Wolkin et al., 1987; Daniel et al., 1991). Third, none of the aforementioned studies employed PET, the functional neuroimaging technique with the highest spatial resolution, but rather used SPECT. As mentioned earlier, because of the nature of the radiotracers utilized, SPECT suffers

from the inability to quantify absolute levels of brain activity (Haxby, Grady, Ungerleider, & Horwitz, 1991). Data must therefore be expressed as a percentage of a reference brain activity value to obtain relative (normalized) data. If activity in the structure chosen for the normalization process has been pathologically affected, then artificially elevated or depressed values might result. Finally, these studies identified brain regions on the functional scans by visual inspection rather than by an objective method of anatomical localization (e.g., using an MRI as a structural map). In sum, to date there have been no published studies, with the exception of the investigation described below, of the functional neuroanatomy of CHI patients during cognitive activation using the high spatial resolution of PET to measure rCBF.

PILOT DATA FOR THE PRESENT STUDY

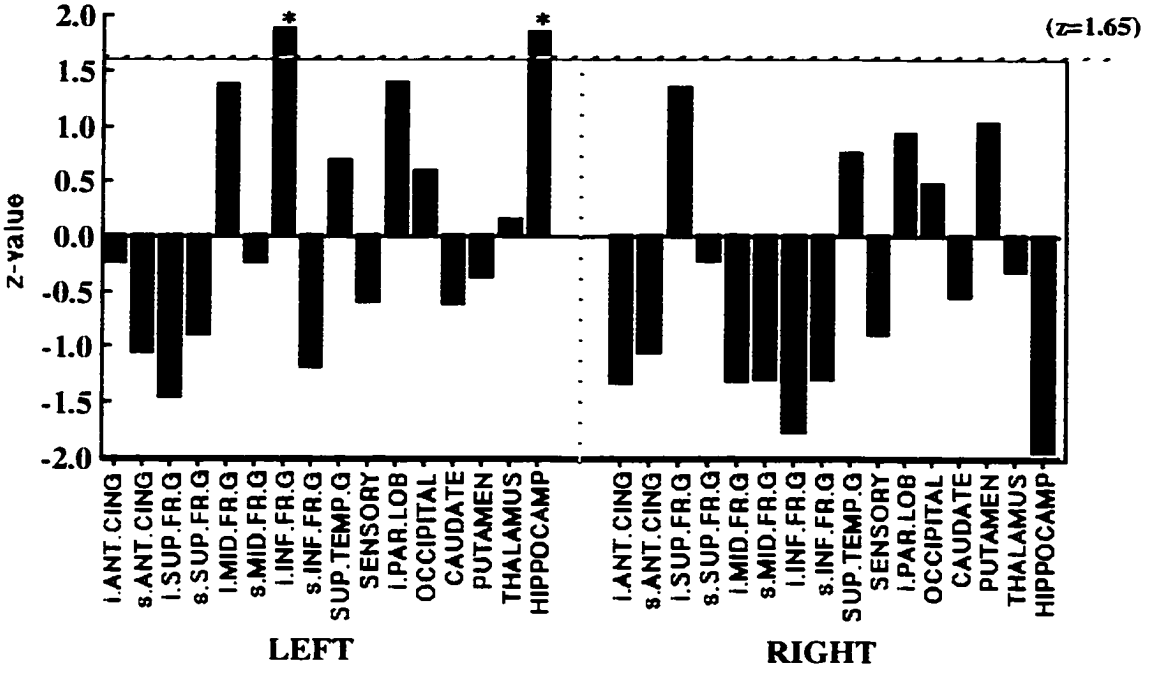
A recent case study, which served as pilot data for the present investigation and therefore is described in detail, measured rCBF using a cognitive activation PET paradigm in an unmedicated CHI patient (Kirkby, Van Horn, Ostrem, Weinberger & Berman, in press). The rCBF pattern of a 28-year-old male with predominant frontal lobe white matter lesions was assessed during performance of the Wisconsin Card Sorting Test (WCST) and a sensorimotor control task. His rCBF pattern was compared to his monozygotic (MZ) co-twin, who was in the same automobile accident but did not incur brain injury, and was assessed against the background of typical variability that existed between 10 normal pairs of similarly aged and educated, uninjured MZ twins. This was accomplished by comparing differences in rCBF

activation (WCST relative to its control task) between the two index twins to within-pair differences in the control group using a one-tailed z-score analysis (one-tailed because only z-scores in the positive direction reflect greater differences between the index twin pair compared with controls). Anatomical localization was determined with reference to the coplanar MRI scan of each subject.

Differences in rCBF between the co-twins discordant for CHI fell within the normal range defined by the 10 control MZ twin pairs in all regions examined but two: the inferior portion of the left inferior frontal gyrus ($Z=1.87$, $p< 0.04$) and the left hippocampus ($Z=1.83$, $p< 0.04$) (Figure 2). Qualitative inspection of the direction of these differences between the index twins revealed that, compared to his healthy co-twin, the CHI twin showed *less* rCBF activation in the left inferior frontal gyrus and *greater* rCBF activation in the left hippocampal region (Figure 2). Although both index twins performed poorly on the task, z-score analyses of the differences in performance between the index twins compared to those between co-twins of the MZ controls did not exceed chance.

The finding of lower rCBF in the left frontal lobe of the CHI twin possibly reflected deafferentation or neuronal loss and hence diminished vascularization in that region. The finding of elevated rCBF in the hippocampus, on the other hand, was surprising, not only because this region is often damaged by CHI, but also because the hippocampus is not typically activated, and in fact, if anything, tends to be significantly deactivated (i.e., rCBF greater in the control task than the WCST) during performance of the WCST. Rather, activation has been found to predominate in the

Figure 2: Z-scores for regional cerebral blood flow (rCBF) activation (task-control) differences in the Wisconsin Card Sorting Test between a pair of monozygotic (MZ) twins discordant for closed head injury (CHI). *Top.* Based on normative data obtained from 10 control MZ twin pairs, differences in normalized rCBF activation between the discordant MZ co-twins that exceeded typical rCBF variability between MZ co-twins of the control group were found in the inferior portion of the left inferior frontal gyrus and in the left hippocampus. The dashed line indicates the cutoff for significant z-scores ($z=1.65$, one-tailed). *$p<0.05$. i=inferior portion, s=superior portion, INF=inferior, MID=middle, SUP=superior, FR=frontal, ANT=anterior, CING=cingulate, G=gyrus, TEMP=temporal, PAR=parietal, LOB=lobule, HIPPOCAMP=hippocampus. *Bottom.* Normalized rCBF activation values in the left inferior frontal gyrus and the left hippocampus of the index twins are presented. The CHI twin showed *less* activation in the left inferior frontal gyrus and *greater* activation in the left hippocampus than his uninjured co-twin.


2.0
1.5
1.0
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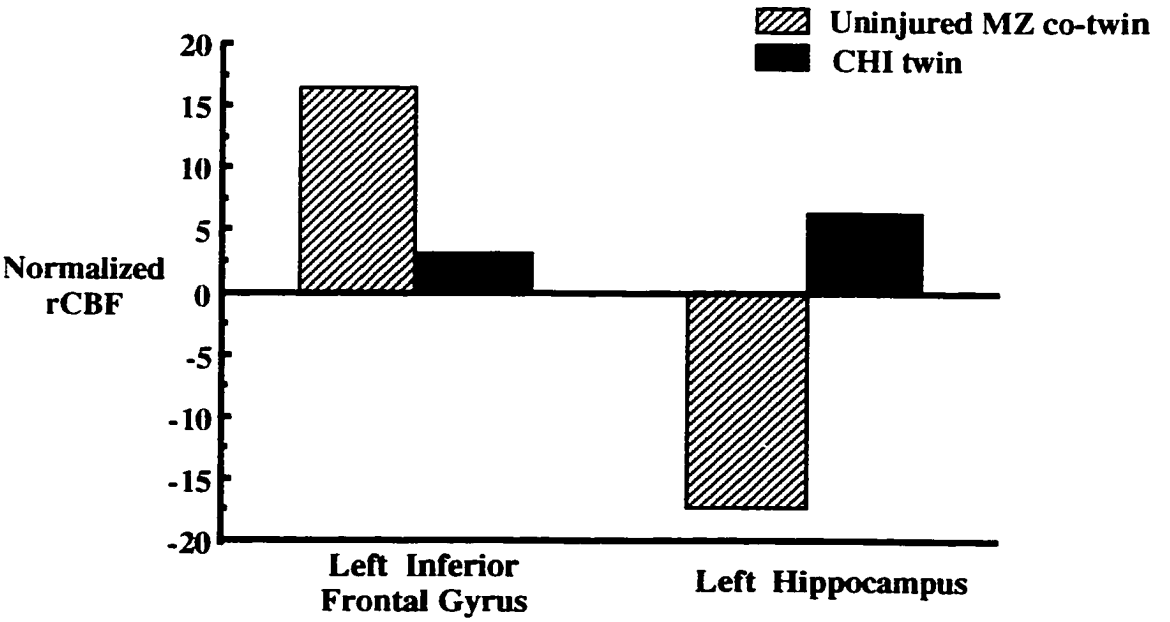
s.ANT.CING
l.SUP.FR.G
s.SUP.FR.G
l.MID.FR.G
s.MID.FR.G
l.INF.FR.G
s.INF.FR.G
SUP.TEMP.G
SENSORY
l.PAR.LOB
OCCIPITAL
CAUDATE
PUTAMEN
THALAMUS
HIPPOCAMP
LEFT
RIGHT


Uninjured MZ co-twin
CHI twin
20
15
10
5
0
-5
-10
-15
-20
Normalized rCBF
Left Inferior Frontal Gyrus
Left Hippocampus

prefrontal cortex during this task (Berman et al., 1995), which was the pattern demonstrated by the healthy index twin but opposite to the one found in the CHI co-twin. The equally poor performance of the normal twin on the WCST despite demonstrating the typical pattern of physiological activation in these two regions was surprising and possibly suggested subclinical neuropsychological sequelae of the accident. However, extensive evaluation of his history, current neuropsychological status, and MRI films failed to reveal any indication of head trauma.

The rCBF differences in the hippocampus and the prefrontal cortex between the index twins were speculated to reflect the utilization of different neural systems to perform a task thought to depend upon intact frontal lobe functioning, at similar levels of proficiency. Given that the healthy twin -- an ideal genetic and environmental control for his co-twin -- provided the best estimate of the neurophysiological pattern of his co-twin prior to his injury, the rCBF changes were considered attributable to the brain trauma incurred by the injured twin. Because there is evidence for both anatomical and functional connections between the dorsolateral prefrontal cortex and the hippocampal area in non-human primates (Goldman-Rakic, Selemon, & Schwartz, 1984), the "overactivation" of the hippocampus in the injured twin was speculated to represent an attempt at compensation for the compromised frontal lobes. It could not be ruled out, however, that the results merely reflected disinhibition of the hippocampus due to loss of frontal input or represented differences between the index twins in anxiety, motivation, or strategy. Despite the limited generalizability of these findings (not only across patients but within this patient across different tasks), the

results provided preliminary evidence for rCBF changes related to traumatic brain injury.

THE PRESENT STUDY

The present study attempted to expand on these preliminary findings by comparing rCBF in a group of unmedicated patients with severe CHI with that of a group of normal healthy volunteers using a PET cognitive activation paradigm. rCBF measurements were made while subjects performed two cognitive tasks that differentially involved functional activity of the hippocampus. rCBF was also measured during control tasks that served as a baseline against which to compare changes in rCBF during the cognitive tasks of interest.

The following two tasks were used in this study: 1) The Wisconsin Card Sorting Test (WCST), a classic test of prefrontal lobe functioning (Milner, 1963) and 2) an adaptation of the verbal paired associates test developed by Blaxton and colleagues (Blaxton, Bookheimer, Zeffiro, Figlozzi, Gaillard, & Theodore, submitted) for administration during PET, which in this study is called the Cued Recall Memory Test (CRMT). The WCST has been shown to produce reliable rCBF elevations (i.e., "activations") in the dorsolateral prefrontal cortex, the inferior parietal lobule, and the inferior portion of the posterior temporal cortex in a large group of normal control subjects (Berman et al., 1995). Depending on the control cohort studied, these activations have been found unilaterally (either hemisphere) or bilaterally. Furthermore, rCBF in the hippocampus has been found to be not activated, and if

anything, lower during the WCST than during the baseline control task (i.e., "deactivated") (Berman et al., 1995). Although not as widely studied as the WCST, the CRMT has been shown in normal subjects to produce rCBF elevations in the frontal cortex and hippocampus of the right hemisphere relative to a baseline word association control task.

Additional cognitive measures were obtained from each of the CHI patients outside of the PET scanner during a neuropsychological assessment to provide a description of the general level of cognitive functioning of this sample of severe CHI patients. Furthermore, these data were combined to produce a single index of overall cognitive functioning to correlate with perfusion data.

Purpose

The purpose of the present study was to characterize the functional neuroanatomy of patients with severe CHI with an emphasis on rCBF changes in the brain areas most susceptible to damage following CHI, the frontal and temporal lobes, particularly the hippocampus, during the performance of tasks that place a selective physiological load on these regions. Given the exploratory and descriptive nature of this study, specific hypotheses were not made. Instead, focus was placed on identifying and characterizing structures with functional changes in CHI patients. The results were viewed with the following issues in mind: First, to test whether there were functional changes following CHI, cerebral blood flow values, both in discrete regions and across the entire brain, was compared between the CHI patients and

controls. Second, the relationship between rCBF and PET task performance in CHI patients was quantitatively examined and then qualitatively contrasted to that of the control subjects. Finally, to investigate whether current cognitive functioning related to perfusion patterns in the CHI patients, rCBF data were correlated with indices of cognitive impairment determined by neuropsychological testing in the CHI patients.

Statistical Analyses

Because of three idiosyncratic features of PET, conventional statistical methods of data analysis are not utilized. First, due to the high cost of PET (as much as $3,000 per subject) the sample sizes of PET studies are typically small (e.g., often fewer than 10 subjects) (Pardo, Pardo, Janer, & Raichle, 1990). Second, thousands of dependent variables are produced per subject per emission scan. Third, changes in rCBF produced by cognition are small, as low as two to five percent of baseline) (Raichle, 1990). Because of the exceptionally low subject to dependent variable ratio in conjunction with a small effect size, significant results rarely emerge from multivariate statistical analyses or even from univariate analyses when traditional correction to the alpha level is made for the increased experiment-wise error associated with multiple comparisons. Because the most appropriate method for analyzing PET data remains controversial (Ford, McColl, McCormack, & McCrory, 1991), many studies present results from uncorrected univariate procedures.

PET data are conventionally analyzed using one of two main approaches: 1) a region of interest (ROI) method that involves testing for rCBF differences in a limited

set of brain areas determined a priori and defined on high resolution MRI scans, or 2) a voxel-by-voxel (i.e., each element of a volume) method called Statistical Parametric Mapping (SPM) (Friston, Frith, Liddle, & Frackowiak, 1991), the state-of-the-art method of image analysis, that involves testing for rCBF differences (either between tasks, groups or both) throughout the entire brain using t-tests. Because of the problems inherent in both procedures (see Discussion), data were analyzed in the present study using both approaches. Because the voxel-by-voxel approach is more standardized than the regional method, emphasis was placed on the results produced by SPM; results from the ROI analysis were used as confirmatory data, when possible[1]. In light of the unresolved controversy regarding an appropriate method of correcting the alpha level for multiple comparisons, a very conservative alpha level for the voxel-wise approach was used ($p \leq 0.001$). Because of the diminished likelihood of obtaining significance in the regional compared to the voxel-wise approach due to the relatively larger spatial extent of the dependent measures (see Discussion), a conventional alpha level of $p \leq 0.05$ was used in the confirmatory ROI analyses.

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[1]Because the ROI method does not examine rCBF in every brain area, significant results from a SPM analysis that lie in brain regions not examined using the ROI method cannot be confirmed.

METHODS

SUBJECTS

CHI Patients

Thirteen patients (10 males, three females) with severe CHI were recruited from outpatient cognitive rehabilitation facilities in the Washington, D.C. and Bethesda and Baltimore, Maryland areas and from solicitations via local advertisements to participate in this study conducted under NIH protocol #90-M-14 by the Unit on PET of the Clinical Brain Disorders Branch of the National Institute of Mental Health. Another patient participated in the study but was excluded from analyses because of technical difficulties during the PET scan. The demographics of the CHI patients are presented in Table 1 (see Appendix B for case histories). All patients sustained their injury from motor vehicle accidents with the exception of one who was injured from physical assault. To help obtain as homogeneous as possible a sample of patients, subjects were required to be/have:

1) *a severe CHI*: Because of the lack of availability from medical records or from patient self-report of a consistent measure of severity across subjects, a severe injury was operationalized in the present study to be an injury that produced either coma *or* PTA for more than 24 hours. Loss of consciousness was determined from patient disclosure and confirmed by medical records.

2) *native-English speakers between the ages of 18 and 50*: The lower limit was chosen because Food and Drug Administration and NIH regulations limit radiation exposure to minors to 1/10 the adult guidelines. Based on results of a recent PET

Table 1. Group demographics.

	Closed Head Injury Patients (n=13)	Normal Controls (n=13)
Age (years)	30.2 ± 6.6 (range: 23-45)	31.2 ± 6.9 (range: 24-45)
Gender	10 males, 3 females	10 males, 3 females
Handedness: **preferred hand** **laterality index***	8 right, 5 left 31.0 ± 77.0 (range: -90 to 100)	9 right, 4 left 37.4 ± 67.7 (range: -70 to 100)
Education (years)	15.23 ± 1.83 (range: 12-18)	16.7 ± 2.5 (range: 13-21)
Socioeconomic status:** **mother** **father**	2.8 ± 1.1 1.8 ± 0.93	2.5 ± 1.1 2.2 ± 1.4
Age at injury (years)	23.5 ± 6.5 (range: 16.4-41.6)	N/A
Length of coma or post-traumatic amnesia (days)	17.6 ± 16.9 (range: 2-30)	N/A
Length of time since injury (years)	7.1 ± 5.7 (range: 0.5-17.7)	N/A

N/A=Not applicable

*based on the Edinbergh Inventory.

**based on the Hollingshead Index.

study suggesting significant decrements in rCBF in the frontal lobe with normal aging beginning around age 50 (Esposito, Kirkby, Van Horn, Ostrem, Weinberger, & Berman, 1994), the upper age limit was chosen.

3) *incurred the CHI as an adult*: To control for the possible differential effects of age of injury on recovery (Kennard, 1938), this study examined people who sustained injury as an adult. The age of 16 was chosen to help maximize the chances that subjects were all post-pubertal at the time of their injury.

4) *at least six month post-injury*: Given the purpose of the present study to examine long-term changes in rCBF following CHI, this criterion was chosen to help ensure that the rCBF findings were not attributable to transient changes related to acute physiological effects of brain trauma (e.g., edema, chemical imbalances), which might spontaneously resolve with time.

5) *no past or present history of substance abuse*: Because chronic use of drugs affecting the central nervous system (CNS) (e.g., alcohol) has been reported to have long-term effects on rCBF (Erbas et al., 1992), patients were excluded who had histories of substance abuse.

6) *no premorbid history of major medical conditions, including neurological and psychiatric illness*: Because of the high prevalence of mood disorders following CHI, patients with the onset of psychiatric illness after, and relating to, their injury were not necessarily excluded from the study. Subjects that had sustained more than one head injury, however, were eliminated from the study.

7) *medication-free from psychotropic drugs*: Because psychotropic medications have been shown to modulate rCBF during the performance of cognitive tasks (Friston et al., 1992), a wash-out period of two weeks before participation in the PET scan was required to help ensure that blood and tissue drug levels had disappeared. Although permanent effects at the neuronal level may result from use of psychotropic drugs (Sutton, Hovda, & Feeney, 1989), the larger acute effects are diminished after several days. In addition, subjects were also asked to refrain from use of over-the-counter medications for 24 hours prior to the scan.

Medication status was ascertained by phone interview with each subject. A nuclear medicine physician determined, based on prior research, whether the medication had known or presumed effects on CNS functioning. At the time of screening, only one subject in this study was medicated[2]. The patient, after consultation with his physician, electively chose to terminate pharmacotherapy for two weeks prior to his PET scan.

8) *no metallic objects in their body*: This restriction was implemented to ensure the safety of patients when undergoing the MRI scan. Although the exposure to a magnetic field involved in an MRI procedure ordinarily poses few known health risks, injury can result to people with implanted metal objects (e.g., pacemaker, aneurysm clip), which may shift or malfunction in a magnetic field.

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[2]One patient had been medicated on dexedrine (a stimulant) and doxepin (an antidepressant).

9) *demonstrated the ability to give informed consent*: The ability of a subject to comprehend the procedures and risks involved in this study was evaluated informally via phone interview.

If the preceding criteria were met, written informed consent was obtained from each subject in accordance with the NIH Review Board Guidelines and the Radiation Safety Committee Requirements. Written permission was also obtained from each patient to request medical records from the hospital in which he/she was initially admitted for CHI. The records regarding all but one patient were successfully obtained.

Normal Controls

Thirteen age, sex, handedness, and education-matched healthy subjects (10 males, 3 females), whose demographics are presented in Table 1, were recruited as controls through the Normal Volunteers Program at the NIH and through community advertisements. Subjects were screened for a history of medical illness, including psychiatric, neurological, and substance abuse problems, and for use of medications. Subjects were paid $270.00 in accordance with NIH guidelines for completing a PET scan and an MRI scan. Given the available normative data for the neuropsychological tests administered to the CHI patients, normal controls in the present study did not undergo a neuropsychological assessment.

APPARATUS & STIMULI

Cognitive Conditions During PET

All tasks were presented on a 20 inch colour monitor suspended from a gantry, which was centred in front of the subject and tilted at an approximately 75° angle for adequate viewing. An experimental task and its sensorimotor control task were presented consecutively[3] but in a counterbalanced order. The order that the two pairs of tasks was presented was also counterbalanced. The control tasks were designed to be similar to its respective experimental task in visual stimulation, motor response requirements, and basic cognitive operations but not to require the more complex problem solving involved in the experimental task. The purpose of the control task was to serve as a baseline to compare rCBF changes during the higher cognitive operations of interest involved in the experimental task. The instructions for each of the four tasks are presented in Appendix C.

WCST: A computerized version of the WCST, which was specifically tailored for use with PET, was administered. Subjects were shown stimuli differing in colour, shape, and number of elements and asked to match each central target stimulus to one of four surrounding answer stimuli (top, bottom, left, or right) (Figure 3). Subjects determined the principle for matching (i.e., by colour, shape, or number) on the basis of feedback indicating whether each response was correct or incorrect. After 10

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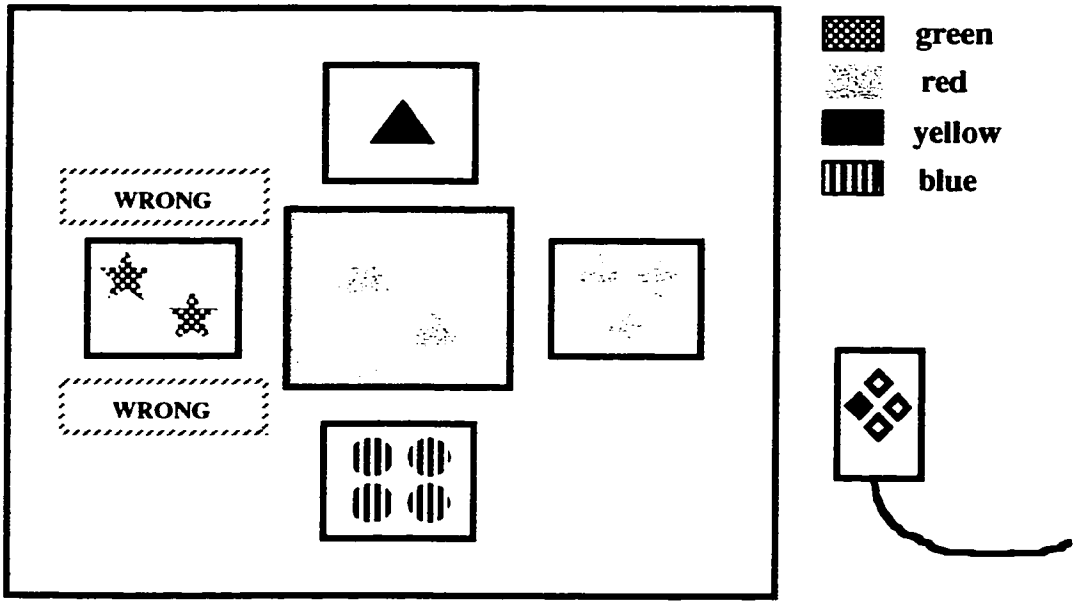
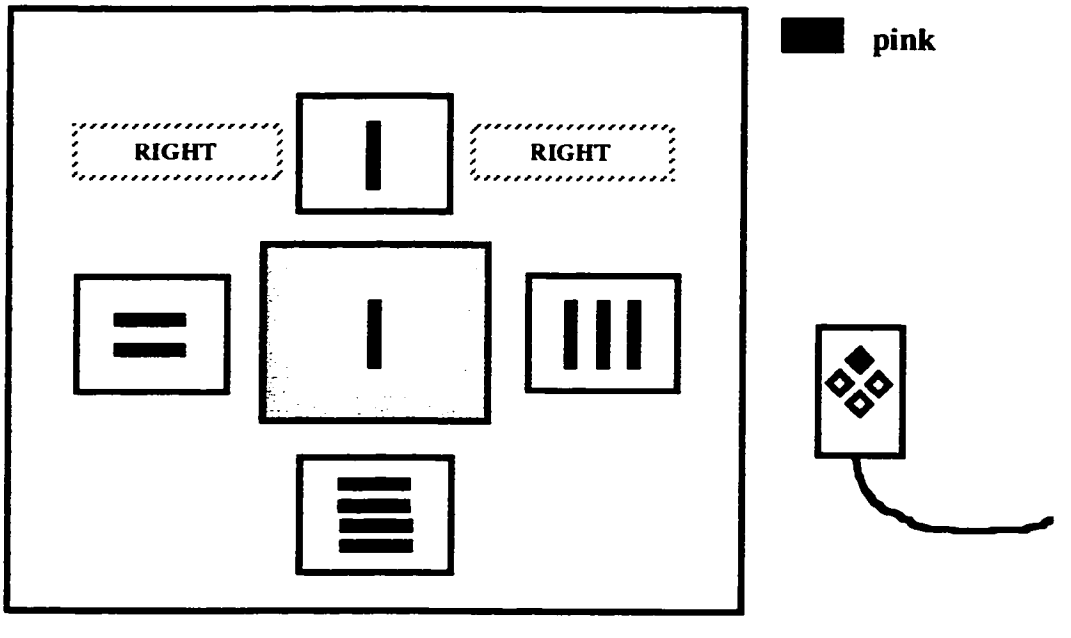
[3]Consecutive administration of the experimental task and its sensorimotor control task served to minimize state variables (e.g., anxiety) and thus to maximize similarities between the two tasks in most sensorimotor aspects.

Figure 3: The Wisconsin Card Sorting Test (WCST) paradigm. *Top.* In the WCST, subjects matched the centrally-presented target stimulus to one of four surrounding answer stimuli. Feedback regarding accuracy was given after every trial, and the correct sorting principle (i.e., either color, shape, or number of elements) changed after 10 consecutive correct responses. Subjects responded using a hand-held response device with buttons corresponding to the positions of answer stimuli. An example is presented of an incorrect response (left button press), one indicating a match by the number of elements rather than by the current correct matching principle of color (i.e., right button press). *Bottom.* In the WCST control task (WCSTc), subjects matched the centrally-presented target stimulus to one of four surrounding answer stimuli that was identical to it. Feedback regarding accuracy was given after every trial. Subjects responded using the same device described above. An example is presented of a correct response (top button press).

WCST



WCSTc



consecutive correct responses, the matching principle changed without warning, and the subject tried to determine the new correct solution for the match.

Subjects indicated their choice by pressing with their right thumb one of four buttons on a 2 x 3 x ½" hand-held device. The response buttons were arranged in a cross-shaped array corresponding to the configuration of possible answer stimuli. Immediately following a response, the computer briefly flashed "right" or "wrong" above the chosen answer. No time limit was imposed for each response. Prior to the PET scan, subjects practiced the response method while performing the control task (see below) until responses were judged automatic by the examiner.

WCST Control (WCSTc): The control task for the WCST involved no-delay matching-to-sample of stimuli that were visually similar to the ones employed during the WCST. Using the same response device as for the WCST, subjects matched a centrally-presented target stimulus to the one of four peripherally-presented answer stimuli that was identical to the target (Figure 3). Similar to the procedures for the WCST, there was no time limit for responding, and the computer displayed feedback following each response.

CRMT:

Study Phase: Approximately six minutes prior to commencement of the emission scan, subjects were shown a study list of 21 pairs of semantically-related words, one pair at a time. A row of three asterisks, which was presented for 750 msec in the center of the screen, preceded each word pair as a warning to the subject that the next word pair was about to appear. After 250 msec during which the screen

appeared blank, a word pair appeared for five seconds and was followed by an intertrial interval of 500 msec. Two consecutive presentations of the word-pair list were given for the CHI patients, whereas only one was given for the normal controls. This methodological difference was imposed to help equate performance between the two groups[4].

Recall Phase: This phase was carried out during the PET emission scan. Approximately two minutes following the Study Phase, subjects were shown a test list comprised of the first words of the word pairs from the study list (targets) and words that were not on the study list (distractors). Prior to the presentation of the subsequent word in the test list, which was signalled by the appearance of a row of asterisks, subjects either verbalized the word that was paired with the target stimulus or the word "pass" for distractor words and for unrecalled target words (Figure 4). In this manner, the number of verbal responses was held constant across scans and subjects, regardless of task performance. The time exposure of stimuli was the same as in the Study Phase except that the words were presented for four rather than five seconds. This reduction was implemented to allow two full repetitions of the recall list during the 5 1/2 minute scanning procedure.

CRMT Control (READ): The control task involved a similar presentation format as for the CRMT but used a different test list without prior presentation of a

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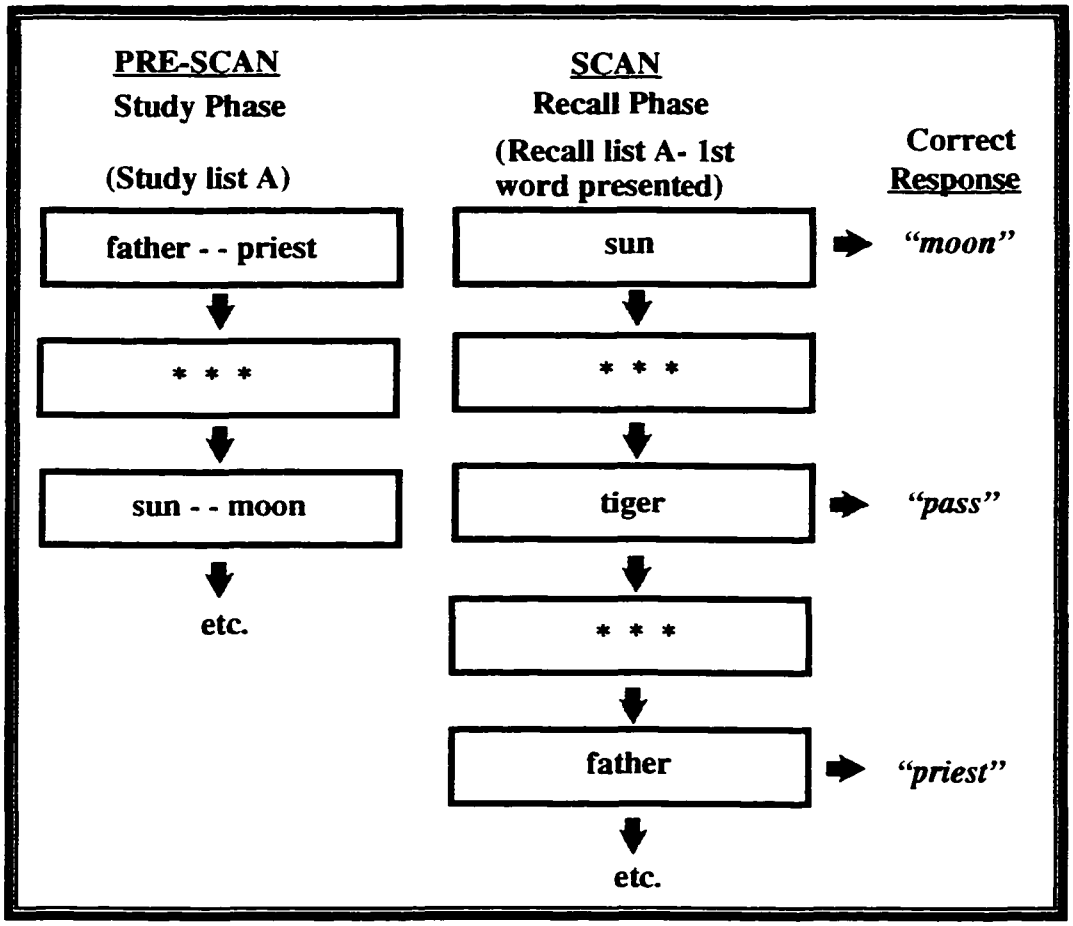
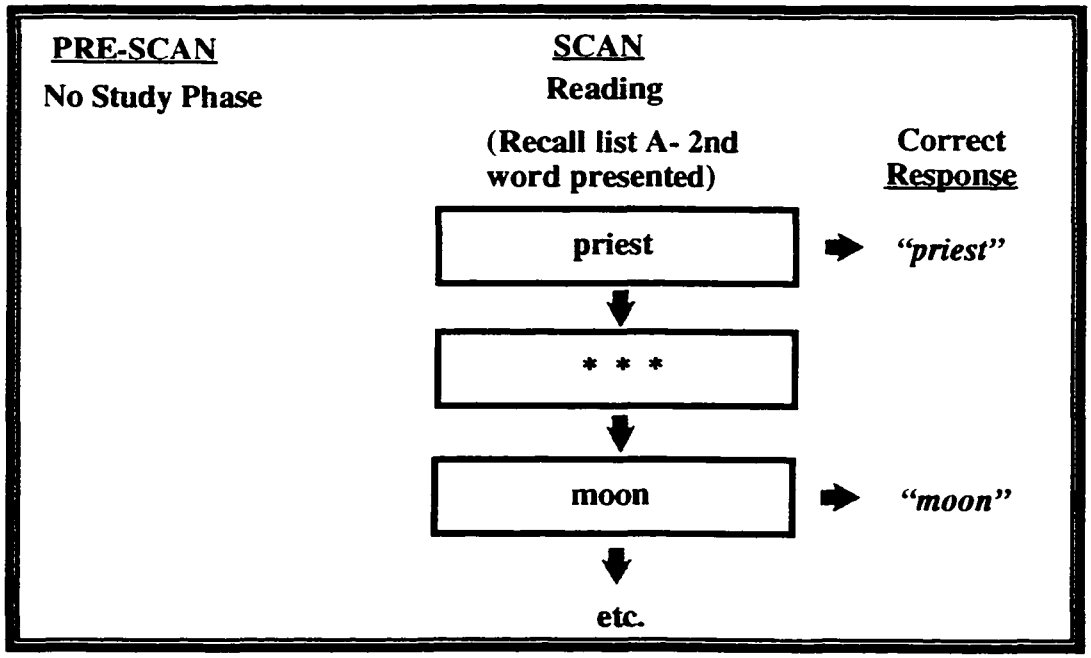
[4]Based on pilot data from patients with schizophrenia who performed the task outside of the PET scanner, two repetitions of the study list tended to improve performance to levels near that of normal subjects who received one repetition of the study list.

Figure 4: The Cued Recall Memory Test (CRMT) paradigm. Sequence of events is illustrated when list A was used in the CRMT for one subject (top) and when the same list was used in the CRMT control task for a different subject (bottom). In all conditions, each word stimulus presentation was interceded by a row of asterisks to signal the onset of the next trial. *Top.* In the CRMT, a subject was shown a list of semantically related word pairs, one at a time, prior to the scan (study list A). During the scan, the subject was presented with either the first word of a studied pair (target) or an unstudied item (distractor). The subject spoke aloud either the associated word for targets or "pass" for distractors and for forgotten targets. *Bottom.* When list A was used in the control condition (READ) for a different subject, pre-scan exposure to study list A was not given. During the scan, a list comprising the *second* word of pairs from study list A was presented, and the subject merely read each word aloud.

CRMT


PRE-SCAN
Study Phase
(Study list A)
father - - priest
* * *
sun - - moon
etc.
SCAN
Recall Phase
(Recall list A- 1st word presented)
sun
* * *
tiger
* * *
father
etc.
Correct Response
"moon"
"pass"
"priest"

READ


PRE-SCAN
No Study Phase
SCAN
Reading
(Recall list A- 2nd word presented)
priest
* * *
moon
etc.
Correct Response
"priest"
"moon"

study list (Figure 4). Because in the CRMT Recall Phase the second word of the word pair from a given test list was verbally spoken by the subject, the second word of the word pair from the test list in this control condition was presented to the subject to read aloud. In this manner, the similarity in the words spoken between and across conditions was maximized.

Because a second control task was administered but not reported in the present study, three rather than two different test lists were used for each subject and are presented in Appendix D. The test lists were counterbalanced across conditions using the Latin Square method. For example, if "jungle--tiger" was a word pair from the study list associated with Test List A, then in the CRMT condition, a subject would be shown the word "jungle" and verbally generate its associate. If Test List A was used in the READ condition, then the subject would be presented with the word "tiger", without prior presentation of the study list, and read the word aloud. The three word lists were used in each condition an approximately equivalent number of times across the 13 subjects.

A test list comprised 30 words (21 target words and 9 distractors). Details about how the word lists were constructed are presented in Appendix D. To create a task that endured the length of the scanning period (i.e., 5 1/2 minutes), the word list was repeated during the scan in a pseudorandom order that maintained the ratio and positioning of target to distractor words described in Appendix D.

Scoring of Cognitive Tasks Administered During PET

Performance on each of the tasks was based on the data acquired in 5½ minutes (i.e., 1 minute prior to and during the ensuing 4½ minute PET scan). Performances on the relatively simple control tasks were expected at ceiling levels and therefore were not statistically analyzed. The following performance variables for the experimental tasks were calculated and compared between the two groups using unpaired t-tests:

1) **WCST**: Although the WCST produces several measures of interest, including the number of categories, correct responses, perseverative errors, and failures to maintain set (FMS) (Heaton, 1981) (Appendix E), only the percent correct and the percent of perseverative errors were examined in order to reduce the number of statistical comparisons. Based on a factor analysis, the former variable, which accounted for 77% of the variance, was chosen (Appendix F). The latter variable was selected because of the theoretical interest in perseverative errors and frontal lobe dysfunction.

2) **CRMT**: The percentage of correctly recalled word pairs was used as the dependent measure. To control for the facilitating effects on performance of repetition (Challis & Sidhu, 1993), only responses from the first presentation of the list (i.e., 30 trials comprising 21 targets and 9 distractors) within a scan were used.

PROCEDURE

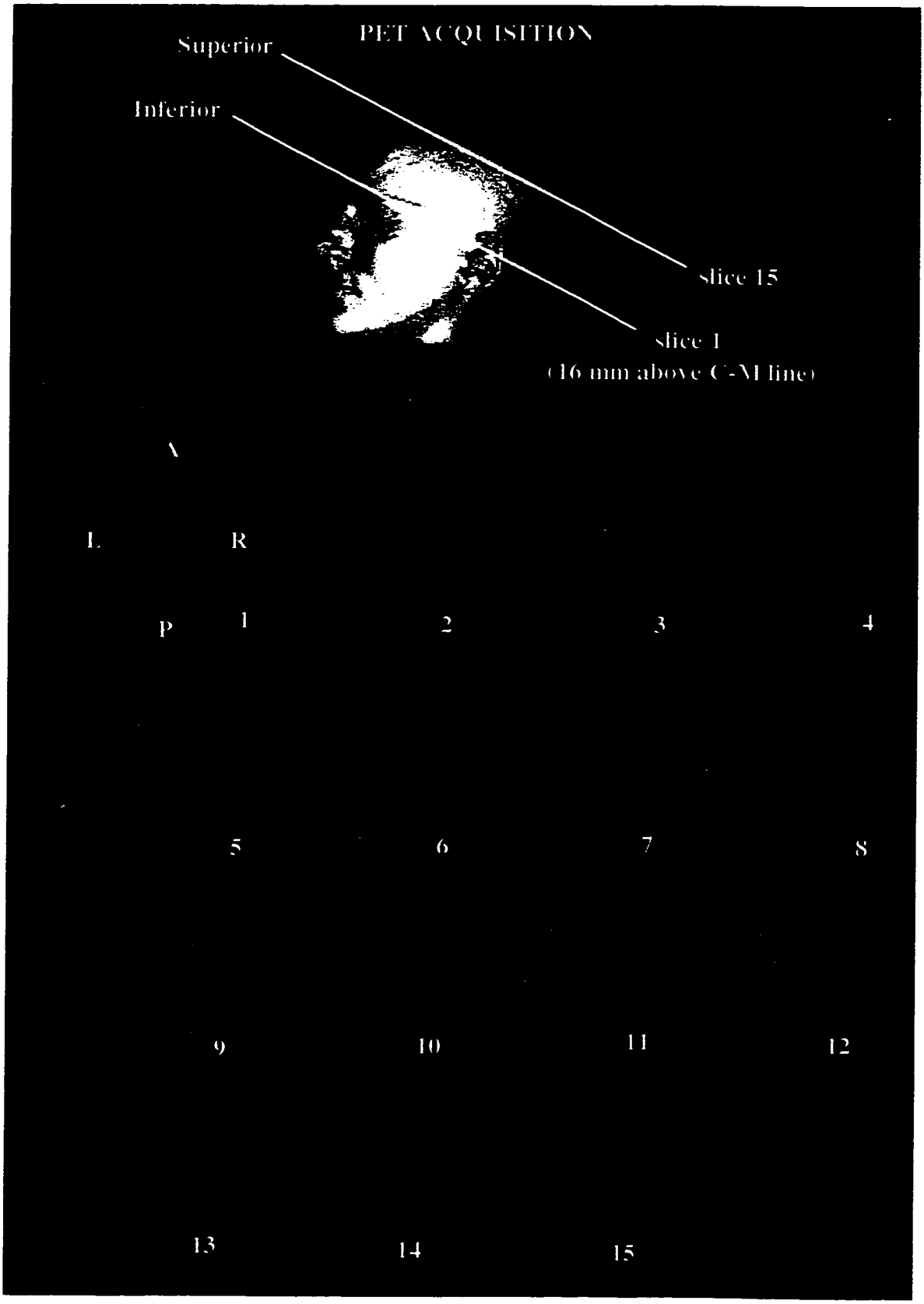
Neurofunctional Assessment

Each subject received an oral and a written explanation of the purposes, procedures, and risks involved in the study. Subjects were instructed to abstain from nicotine and caffeine ingestion for 4 hours prior to the PET scan. On the day of the PET scan, subjects were verbally queried about their compliance to this restriction, and none of the subjects admitted violating it.

Approximately one hour prior to the PET scan, an anesthesiologist placed a plastic catheter in the radial artery of the subject's left wrist, which was used for arterial blood sampling during the emission scans. A local anesthetic, lidocaine, was injected under the skin around the impending puncture site prior to insertion of the catheter. In addition, a catheter through which the isotope was subsequently administered was placed in the antecubital vein of the subject's right arm.

Subjects were studied in a supine position using a Scanditronix PC2048-15B PET scanner. Images were obtained parallel to the canthomeatal line (i.e., the axis between the canthus of the eye and the external auditory meatus) with the lowest of 15 slices collected 16 mm above this landmark (Figure 5). To help insure accurate positioning and immobility during the procedure, the head of the subject was secured with a thermoplastic mask, which was molded to the face and attached to the scanner bed. A transmission scan was then performed to measure the attenuation of radiation by the skull, scalp, and intracranial tissues. This was done by rotating a photon-emitting pin source around the field of view of the scanner and collecting tomographic

Figure 5: Positron emission tomography (PET). *Top.* The orientation of image acquisition during PET is illustrated. Fifteen slices, approximately 6.5 mm thick, were obtained parallel to and beginning 16 mm above the canthomeatal (C-M) line. *Bottom.* PET images of a single subject are presented from the most inferior to the most superior aspect of the brain. Images reflect a continuum of regional cerebral blood flow values (in ml/min/100g tissue) with red, yellow, green, and blue colours mapping to areas of highest and lowest activity, respectively. A=anterior, P=posterior, L=left, R=right.


PET ACQUISITION
Superior
Inferior
slice 15
slice 1
(16 mm above C-M line)
A
L
R
P
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15

scans of the radioactivity with and without the head of the subject in place. The ratio of the two measurements, which allows the amount of photon attenuation by each voxel of the brain and surrounding tissue to be determined, was used as a correction factor for the emission scans. Emission data were also reconstructed with correction for random coincidence, scatter and deadtime[5].

Ambient lighting was kept low and constant across all scans. For each emission scan, subjects received an intravenous bolus of approximately 42 millicuries of $H_2{}^{15}O$ one minute after initiation of the cognitive task. Following arrival of the tracer in the brain, the time course of regional cerebral radioactivity concentration was determined simultaneously for the 15 slices with a total of 16 scan frames (12x10 sec, 4x30 sec). Beginning at the time of injection and continuing throughout the scan, arterial blood was continuously sampled at a rate of 3.8 ml/min by an automatic blood sampler. These data were used to determine the time course of arterial blood $H_2{}^{15}O$, which was used in the subsequent reconstruction of PET images.

Approximately twelve minutes (about six half-lives of the isotope) interceded each injection to insure that less than one percent of the radioisotope remained in the subject prior to the subsequent injection. At the end of each scan, arterial blood samples were assessed for the pressure of carbon dioxide ($pC0_2$), a physiological

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[5]A random coincidence, which occurs when two photons from two *different* positron annihilations are sensed by a detector pair, results in the collection of a false count. Scatter, which occurs when the direction of an annihilation photon travelling in tissue is altered by collision with an electron, results in incorrect localization of the photon pair. Deadtime, which refers to the time during which the scanner cannot register further counts due to processing of a current count, reduces the total number of counts recorded.

parameter believed to affect global blood flow. When the series of PET scans was completed, a physician removed the venous and arterial catheters from the subject and applied appropriate medical care to the puncture sites.

Image reconstruction was performed by the PET technologists of the Nuclear Medicine Department at the NIH. The arterial time-activity curve was used in conjunction with a least-squares adaptation of the Kety (1951) model to calculate absolute rCBF in units of ml/min/100g tissue on a voxel-by-voxel basis[6] (Koeppe, Holden, & Ip, 1985). For each scan, 15 contiguous slices of the brain were produced with an in-plane and axial resolution of 6 to 6.5 mm after reconstruction (Figure 5).

Neurostructural Assessment

A set of 124 contiguous T-1 weighted sagittal MRI slices 1.5 mm thick was obtained from each subject using a 1.5 Tesla scanner (SIGNA, General Electric). All subjects except one underwent an MRI scan within six weeks of the his/her PET scan. Due to scheduling difficulties, one patient was scanned almost four months following his PET scan. Each MRI scan was interpreted by two NIH neuroradiologists who were not blinded to the diagnosis of the subject. The MRIs were used: 1) for qualitative lesion localization in the patients, 2) to rule out pathology in the normal subjects, and 3) to provide an anatomical map for evaluation of the PET scans in the ROI analysis.

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[6]A single voxel from a PET image in this study is a rectangular cube that has the dimensions 2mm (x-plane) by 2mm (y-plane) by 6.5mm (z-plane or slice thickness). An entire PET scan comprises a matrix of 128x128x15 voxels.

Neuropsychological Assessment

A neuropsychological assessment was conducted on each of the CHI patients within 15 days of his/her PET scan, with the exception of one patient who was tested almost three months after his PET scan. Results were reported in this study from the following tests, which were selected from a larger battery of administered tests based on the standardization and available normative data, objective scoring criteria, and emphasis on functions typically affected by CHI (Table 2):

Intellect

Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981): An abbreviated version on the WAIS-R, which included Similarities (a test of verbal concept formation), Arithmetic (a test involving the solution of orally-presented arithmetic problems and used as a measure of attention), Picture Completion (a nonverbal reasoning test requiring the perception of missing elements of a picture), and Digit Symbol (a test involving speeded coding of numbers with their associated symbols), was used to obtain a crude estimate of current intelligence (Kaufman, 1990). The abbreviated battery was chosen because of its short administration time and high correlation with the verbal (VIQ), performance (PIQ), and full scale (FSIQ) intelligent quotients calculated from the complete administration of the WAIS-R (r's=0.82, 0.68, 0.95 for VIQ, PIQ, and FSIQ, respectively).

Table 2. Neuropsychological test battery.

Function	Test	Dependent Measure
Intellect	Wechsler Adult Intelligence Scale-Revised (abbreviated version)	Full Scale Intelligence Quotient (estimated)*
Memory	California Verbal Learning Test	total correct across trials 1-5*
	Logical Memory I	total elements recalled after immediate delay*
Attention	Trail Making Test	time for Trail B*
	Continuous Performance Test	number correct*
Language	Boston Naming Test	number correct*
	Verbal Fluency Test	total across F, A, and S*
Mood	Beck Depression Inventory	total score
Outcome	Glasgow Outcome Scale	descriptive outcome (1-4)
	Wide Range Achievement Test (Revised): Reading Subtest	number correct

*dependent measure was used in a factor analysis.

Attention

Trail Making Test- B (TMT) (Army Individual Test Battery, 1944): This paper and pencil test of attentional processes requires the alternate connection of numbers and letters in chronological and alphabetic order, respectively.

Continuous Performance Test (CPT) (Gordon & Mettelman, 1988): The CPT, a test of sustained attention, involves selective responses to a series of visually-presented numbers vis-a-vis irrelevant, distractor stimuli during a six-minute trial period.

Memory

California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987): The CVLT involves learning of an orally-presented word list over a series of five trials with both immediate and delayed (after 20 minutes) tests of recall.

Logical Memory I (LM I) (Wechsler, 1987): LM I, a subtest from the Wechsler Memory Scale- Revised that assesses short-term verbal memory, requires subjects to remember elements of two orally-presented short stories immediately after presentation.

Language

Verbal Fluency (VF) (Spreen & Benton, 1969): This test, which has been found to be sensitive to prefrontal lobe function (Miceli, Caltagirone, Gainotti, Masullo, & Silveri, 1981) requires subjects to orally generate as many different words beginning with a specified letter (F, A, and S), each on separate trials.

Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 1983): The BNT. a test of word retrieval, involves confrontational naming of pictured objects.

Outcome

Reading Subtest from the Wide Range Achievement Test- Revised (WRAT-R) (Jastak & Wilkinson, 1984): Performance on the WRAT-R reading subtest, which involves self-paced reading of individual words, was used as an estimate of premorbid intelligence (Wiens, Bryan, & Crossen, 1993; Johnstone, Hexum, & Ashkanazi, 1995).

Glasgow Outcome Scale (GOS) (Jennett & Bond, 1975): The GOS, a frequently used classification system for rating outcome from brain injury, was completed by the examiner based on information obtained during interview and used as a measure of outcome. The GOS provides criteria for four levels of outcome ranging from Vegetative State to Good Recovery (Appendix G).

Mood

Beck Depression Inventory (BDI) (Beck, 1987): The BDI, a 21-item scale that assesses the affective and cognitive components of depression, requires a subject to indicate the presence and severity of each symptom on a scale from 0 to 3. Based on the sum of the values corresponding to the symptom severity endorsed, the level of depression for each subject was rated as either normal (0-9), minimal (10-15), mild to moderate (16-19), moderate to severe (20-29) or severe (30-63).

Handedness

Edinburgh Handedness Inventory (EHI) (Oldfield, 1971): The EHI comprises 10 questions concerning the preferred hand for performing various manual activities.

Hand preference was rated as either strong (two points for that hand), preferred (one point for that hand), or indifferent (one point for each hand). The handedness quotient was calculated by subtracting the sum of the points of the left hand from that for the right hand and dividing by the total number of points. Subjects with positive laterality scores were considered right handed; those with negative scores were considered left-handed.

Socioeconomic status (SES)

Hollingshead Index (HHI) (Hollingshead & Redlich, 1958): The HHI was used to determine the SES of the parents of all subjects. After ranking education and occupation on a seven point scale, the HHI score was calculated[7]. Each person was then assigned to one of five social classes based on their index score: I= (11-17), II= (18-31), III (32-47), IV (48-63), V=(64-77).

Indices of cognitive disability

Two measures of cognitive disability were calculated for the CHI patients and used in subsequent correlative analyses with rCBF data. First, the difference between pre- and post-injury intelligence, which was estimated using the difference in performance on the WRAT-R reading subtest (pre-injury estimate) and the abbreviated form of the WAIS-R (post-injury estimate), was used to indicate loss of intellectual functioning. Second, the dependent measure from each test of intellect, attention, memory, and language that was thought by the examiner to best characterize performance was selected and analyzed using a factor analysis (Table 2). For each

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[7]HHI= (occupational scale score * 7) + (educational scale score *4).

subject, the score on the Factor accounting for the most variance was calculated and considered to represent the construct of current overall cognitive functioning.

IMAGE PROCESSING

Voxel-by-Voxel Approach

PET images were analyzed using the 1995 version of Statistical Parametric Mapping (SPM) (Friston, Holmes, Worsley, Poline, Frith, & Frackowiak, 1995). SPM involved standardizing brains for size and shape, smoothing the image to account for individual variations in global anatomy[8], statistically removing the confounding effect of global flow on regional CBF between scans and across subjects, and analyzing rCBF changes throughout the brain, either within or between groups, on a voxel-by-voxel basis (Friston et al., 1991). The following standard procedures were performed in an automated fashion by the SPM software package (Hammersmith, London, 1995) on a SUN workstation (SUN Microsystems, Europe, Surrey, UK):

1) **PET Preproccesing:** All scans were corrected for deviations in the x (pitch), y (yaw), and z (roll) axes from the standard image acquisition position (i.e., subject in supine position with the nose pointing upward) using unpublished NIH software. The original 15-slice emission scans were then interpolated to 43 slices to create approximately cubic voxels (i.e., dimensions of equal size in the x, y and z planes). All scans for a given subject were realigned to one another using an

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[8]Smoothing (blurring), which involves passing a Gaussian filter through the image data, is a process that removes high spatial frequencies. The purpose of smoothing is to reduce individual anatomical differences.

algorithm to correct for head movement between scans (Woods, Cherry, & Mazziotta, 1992).

2) **Spatial Normalization**: Images for all subjects were placed into the same three dimensional space by determining sets of orthogonal basis functions and stretching or compressing these principle axes to fit a standardized image template having the same spatial dimensions as the stereotactic atlas of Talairach and Tournoux (1988)[9] (Figure 6).

3) **Smoothing**: A Gaussian filter (20 mm in the x and y planes and 12 mm in the z plane) was then applied to the image data to reduce the effect of individual differences in gyral anatomy (Figure 6).

4) **Normalization to Global Flow**: Each scan was normalized to an average value of 50 ml/100ml/min using an analysis of covariance to control for global differences in blood flow between scans of an individual and between subjects (Friston, Frith, Liddle, Dolan, Lammertsma, & Frackowiak, 1990).

5) **Statistical Analysis**: Statistical comparisons were made on a voxel-by-voxel basis for voxels common to all subjects. In this study, approximately 50,000 voxels spanning the planes from 28 mm below to 44 mm above the intercommissural line were examined. Two types of analyses were performed: a) between-group rCBF differences were tested on the average rCBF map derived for each group using the t-statistic, and b) the relationship between rCBF and performance was assessed within

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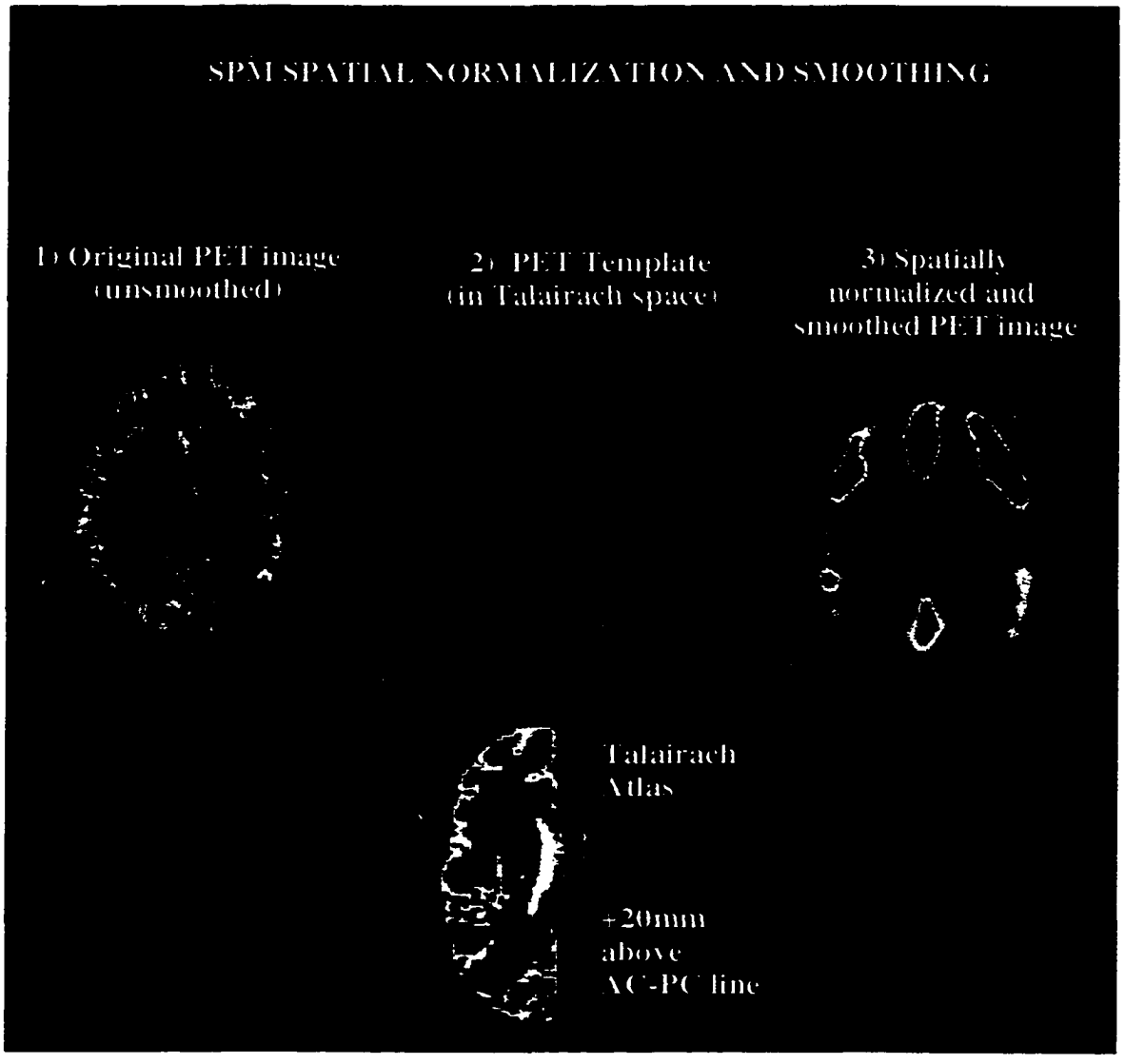
[9]This atlas is henceforth referred to as the Talairach atlas.

Figure 6: Spatial normalization and smoothing. For analyses using Statistical Parametric Mapping (SPM), each positron emission tomography (PET) scan was placed into the same three dimensional space by determining sets of orthogonal axes and stretching or compressing them to fit a standardized image template having the same spatial dimensions as the Talairach atlas. Data were then smoothed using a Gaussian filter (20x20x12mm) to account for individual variations in brain anatomy.


SPM SPATIAL NORMALIZATION AND SMOOTHING
1) Original PET image (unsmoothed)
2) PET Template (in Talairach space)
3) Spatially normalized and smoothed PET image
Talairach Atlas
+20mm above AC-PC line

each group separately with Pearson Product Moment correlations (unpublished program of Horwitz, National Institute on Aging, NIH).

The value of the statistic (either t or r) for each voxel was calculated, transformed to a normal standard distribution if a t-test analysis, and represented as an image (i.e., a statistical map). The critical value for alpha for all comparisons was set at $p \leq 0.001$. The stereotactic coordinates of the maxima (i.e., voxels with the most significant differences or correlations) in a cluster of significantly different voxels were produced and tabulated. Voxels that met or exceeded the statistical threshold were mapped onto a representative MRI scan for visual assessment.

Regional Approach

The ROI method, which was used to confirm, when possible, the results from the SPM analyses, involved coregistering (i.e., placing in the same three dimensional space) the MRI of each subject with his/her PET scan, drawing ROIs on the coregistered MRIs and superimposing the MRI-based ROI template on the emission

scans to determine average rCBF values for each region. Unless otherwise specified[10], the following procedures were performed on an individual basis using an image analysis computer software package MIRAGe (Medical Imaging Retrieval, Analysis, and Graphics) developed by the Department of Nuclear Medicine at the NIH on a VAX workstation:

1) **Creation of an Averaged PET Scan:** All PET scans for a given subject were averaged on a voxel-by-voxel basis to create an averaged 15-slice PET scan. This procedure was used to produce a scan unbiased by cognitive state with more anatomically precise borders than a single PET scan. The averaged 15-slice PET scan was used as a template for drawing whole brain ROIs and for the process of image coregistration described below.

2) **Calculation of Global Flow**: Regions were drawn around each of the 15 slices of the averaged PET scan (i.e., whole brain ROIs). The ROI template was then superimposed on each of the individual emission scans. Mean global CBF for each

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[10]One CHI patient had the four PET scans performed during two sessions approximately eight months apart. The WCST and WCSTc were administered during the first session, whereas the CRMT and READ were administered during the second session. Prior to steps 1 through 3, the four PET scans were first aligned to each other using the automated reslicing algorithm of Woods et al. (1992). Following this procedure, the first and last slice of each of the 15-slice emission scans were incomplete (i.e., partial slices) and were therefore omitted from further analysis. Global CBF was thus calculated based on CBF in the 13 brain slices that were common to all four scans. This contrasts with the procedure outlined above that used all 15 slices to determine global CBF. The calculation of regional CBF described in steps 4 through 8 was not affected by the omission of slices 1 and 15 of the emission scans since these slices did not contain regions of interest.

task was determined by summing the values of the voxels that fell within the whole brain ROIs and dividing by the total number of voxels within the ROIs.

3) **rCBF Normalization**: To account for whole brain blood flow differences between subjects and between separate scans of an individual, the data for each scan were normalized to the global mean (i.e., expressed as a percentage of global flow). This was done by dividing, on a voxel-by-voxel basis, the 15 slices of each individual emission scan by the global mean for that scan.

4) **Region Drawing**: To identify anatomical structures on the PET scan, the MRI scan of each subject was resliced to be in the same three-dimensional space as the averaged PET scan using the computer software package ANALYZE (Biodynamic Research Unit, Mayo Clinic, Rochester, MN, USA) on a SUN workstation (Figure 7). To realign the two sets of data, the program uses a surface matching algorithm that minimizes the average distance between points on the two surfaces (Jiang, Holton, & Robb, 1992). Using as a reference an atlas of human brain anatomy (Matsui & Hirano, 1978), seventy-two predetermined ROIs were manually drawn on the coplanar MRI of each subject around specific cortical and subcortical areas bilaterally with an emphasis on the prefrontal cortex and its connections. The ROI template of each subject was checked for accuracy by a nuclear medicine physician. Cortical ROIs included the: 1) inferior, middle, and superior frontal gyri, 2) superior temporal, parietal, and occipital cortices, and 3) anterior cingulate gyrus. Subcortical ROIs included the thalamus, caudate nucleus, and putamen.

Figure 7: Image coregistration. For the regions of interest (ROI) analysis, the magnetic resonance imaging (MRI) scan of each subject was resliced to match the size and orientation of his/her positron emission tomography (PET) scan using a surface-matching algorithm: A) sagittally-acquired MRI scan, B) transversely-acquired PET scan, C) PET scan superimposed on coregistered MRI scan, D) coregistered MRI scan used for anatomical localization.

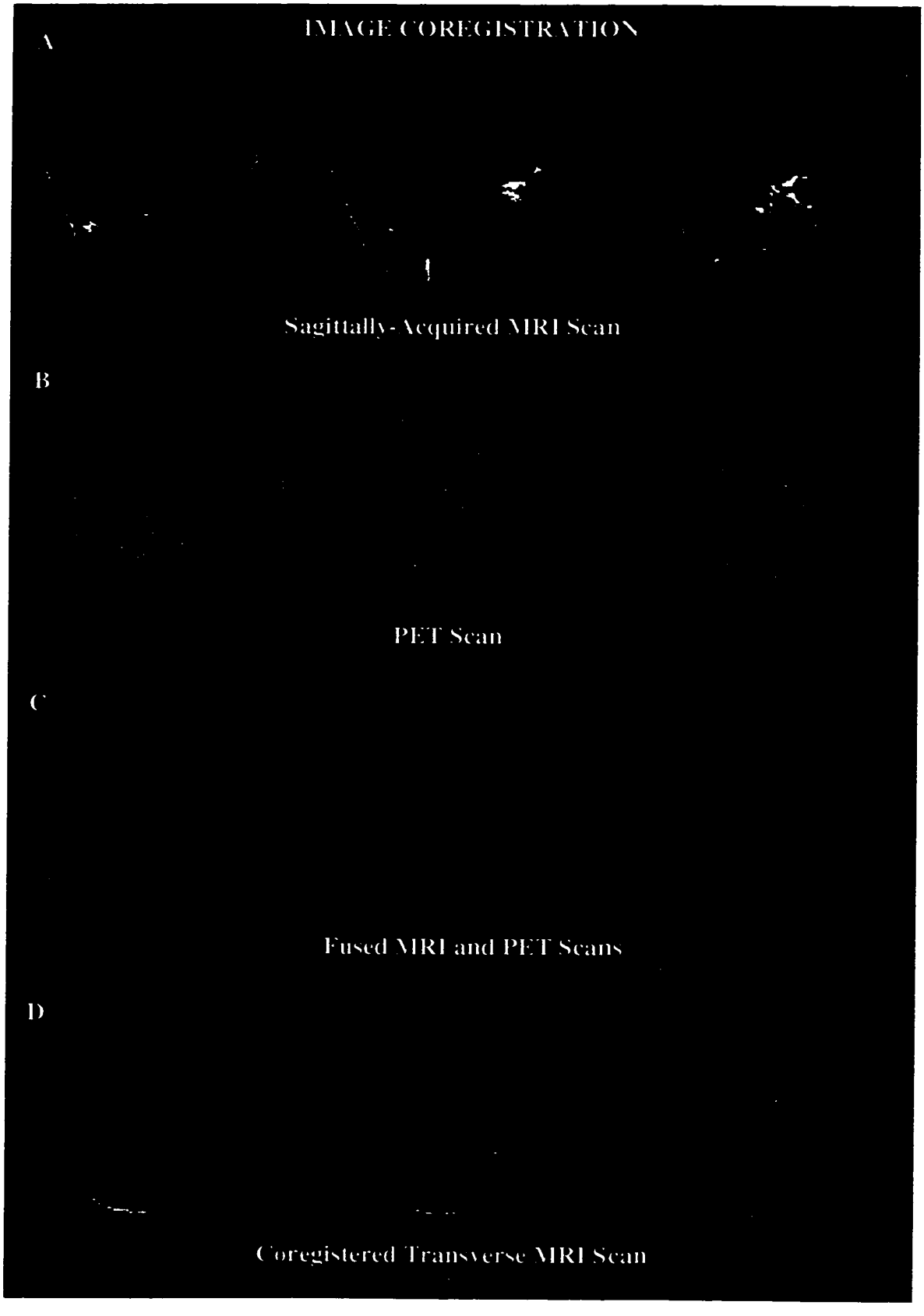
IMAGE COREGISTRATION
A
Sagittally-Acquired MRI Scan
B
PET Scan
C
Fused MRI and PET Scans
D
Coregistered Transverse MRI Scan

5) **Area-Weighted ROIs:** To reduce the number of statistical comparisons, rCBF area-weighted values for the same structure across several slices were averaged. In doing so, the differing sizes of the contributing ROI were taken into account by an area-weighting procedure[11]. As illustrated in Figure 8, 31 area-weighted mean rCBF values (15 per hemisphere) were determined as follows: Separate averages were determined for each frontal cortical region across slices B, C, and D and across slices E and F; other cortical regions were averaged separately across slices G, H, and I. For caudate, putamen, and thalamus ROIs, area-weighted mean rCBF values were computed across all slices on which the structure was originally drawn (3, 3, and 2 slices, respectively).

6) **Hippocampus:** Because the hippocampus was poorly visualized on the transversely-oriented MRI scans used above, additional steps were taken to optimally view the structure. First, the sagittally-acquired MRI for each subject was resliced along an axis parallel to the white matter tract of the temporal lobe using ANALYZE software (Figure 9). Second, each of the PET scans of an individual were resliced to match the resliced MRI scan. Third, on the slice in which the structure was best visualized, a ROI was drawn around the hippocampus in each hemisphere. Finally, each hippocampal ROI was split into an anterior and a posterior portion at the juncture of the pes hippocampi (Figure 9).

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[11]The number of voxels in each contributing ROI was multiplied by the rCBF value for that ROI. The resulting products for like structures were summed, and the sum was divided by the total number of contributing voxels.

Figure 8: Regions of interest. *Top.* An example of an individualized region of interest (ROI) template is presented. The ROI template was drawn on the magnetic resonance imaging (MRI) scan of each subject and then transferred onto the emission scans. 1) anterior cingulate gyrus, 2) superior frontal gyrus, 3) middle frontal gyrus, 4) inferior frontal gyrus, 5) superior temporal gyrus, 6) parietal cortex (included somatosensory cortex only in slices E and F), 7) occipital cortex, 8) caudate nucleus, 9) putamen, and 10) thalamus. For statistical analyses, area-weighted ROI averages were calculated across several slices as follows: superior, temporal, middle and inferior frontal gyri in slices B, C, and D (inferior portion) and in slices E and F (superior portion); superior temporal gyrus in slices E and F; occipital cortex in slices E and F; parietal cortex in slices E and F (somatosensory cortex) and in slices G, H, and I (inferior parietal lobule); caudate and putamen in slices B, C, and D; and thalamus in slices C and D. *Bottom.* Approximate locations of the centres of each slice with respect to the lateral view of a brain, which has been reconstructed as a three dimensional rendering from the MRI scan.

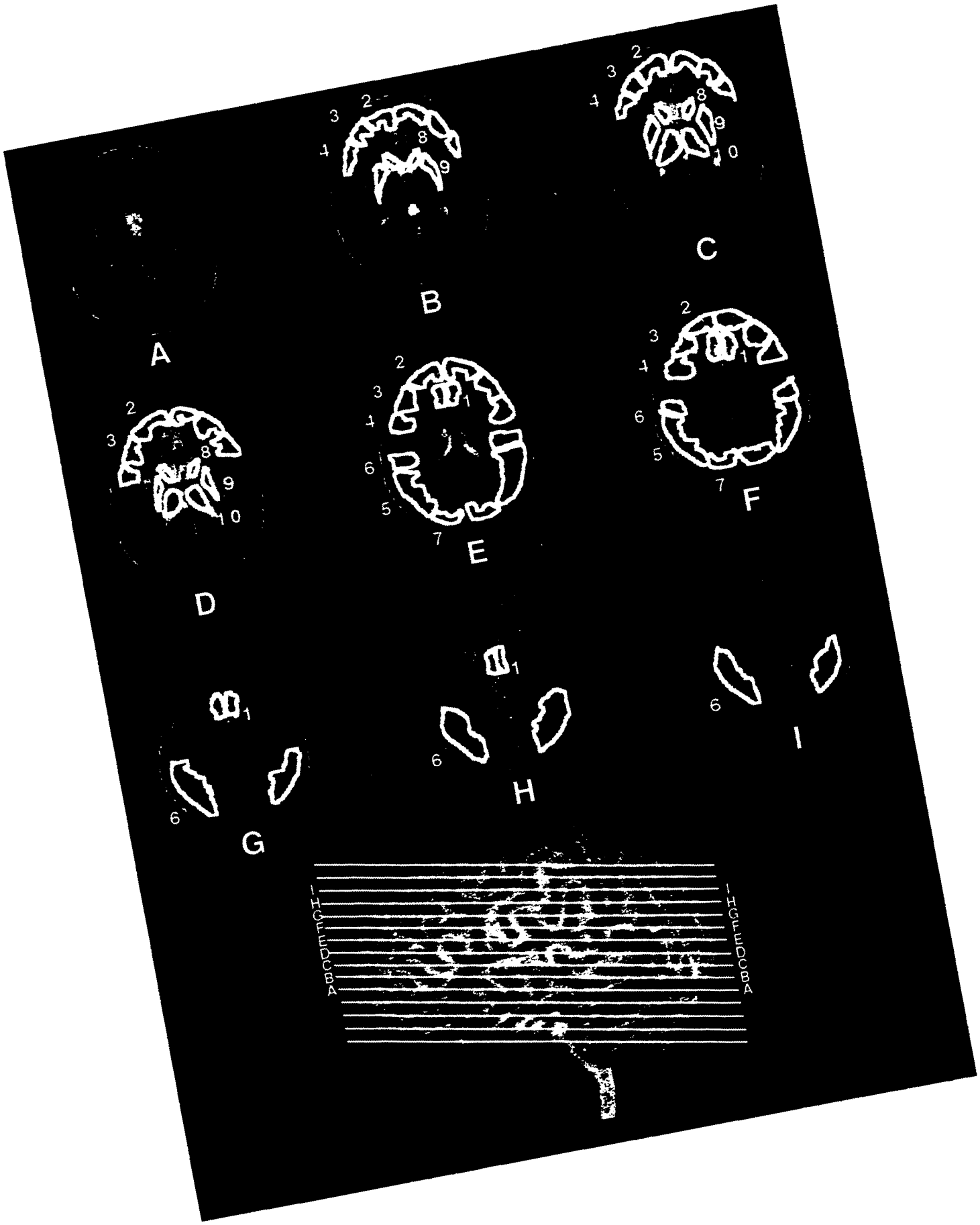
A
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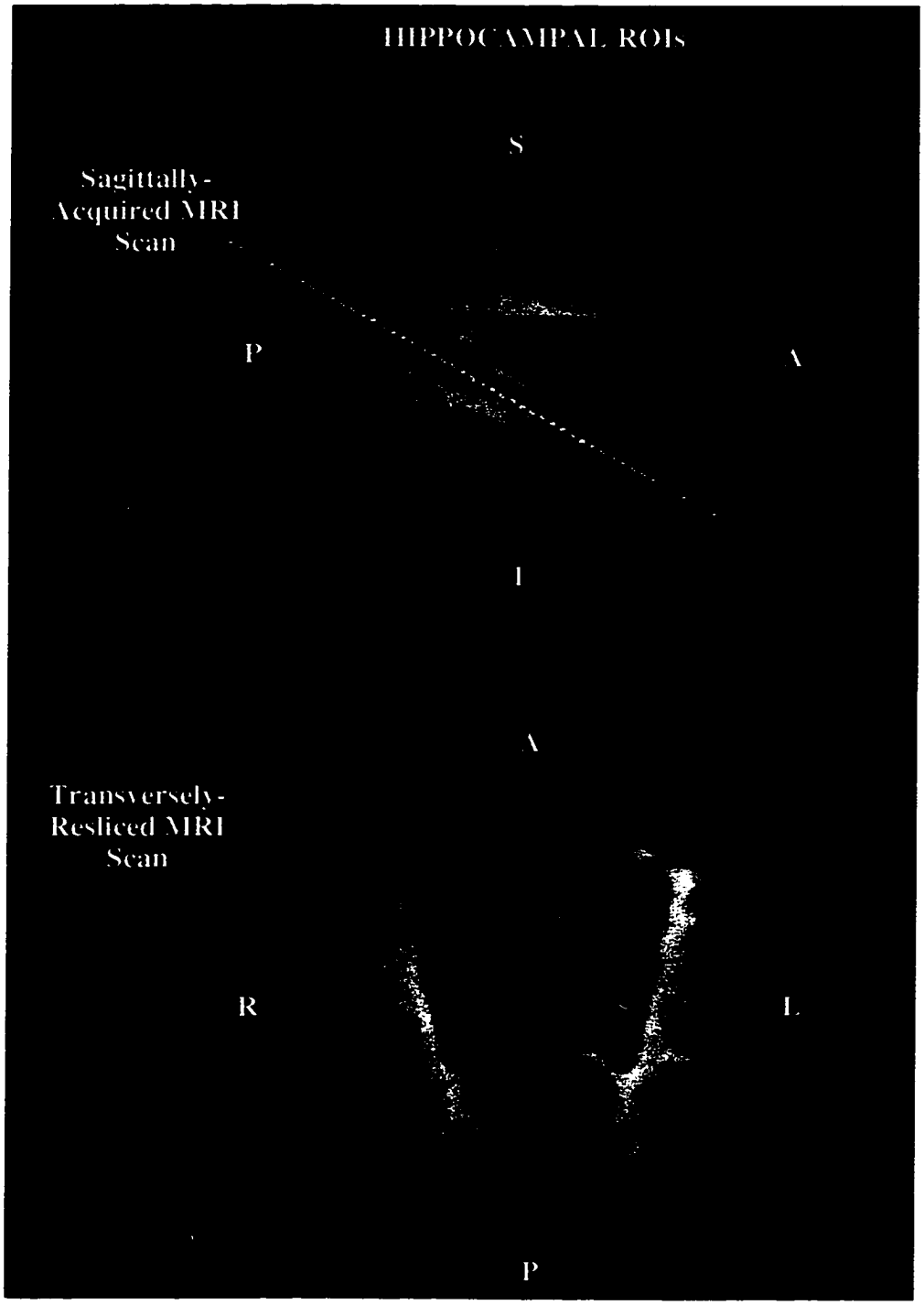
Figure 9: Region of interest (ROI) template for the hippocampus. *Top*. The sagittally-acquired magnetic resonance imaging (MRI) scan of each subject was resliced parallel to the axis of the white matter tract of the temporal lobe (indicated by dashed line). *Bottom*. ROIs were drawn on the anterior and posterior hippocampi of both hemispheres. S=superior, I=inferior, P=posterior, A=anterior, L=left, R=right.


HIPPOCAMPAL ROIs
S
Sagittally-Acquired MRI Scan
P
A
I
A
Transversely-Resliced MRI Scan
R
L
P

7) **ROI Application:** The MRI-based ROI template was then superimposed on each of the individual normalized PET scans, and the mean rCBF value for each ROI was calculated for each cognitive condition (Figure 10).

8) **Statistical Analyses:** The area-weighted mean rCBF values for normalized data were analyzed using Statistical Analysis System software (SAS Institute, 1994) programs. Unpaired t-tests were used to test for group differences in rCBF. Pearson Product Moment correlations were calculated to examine the relationship between rCBF data and performance. The critical level of alpha for both sets of exploratory analyses was set at $p \leq 0.05$.

rCBF Statistical Comparisons

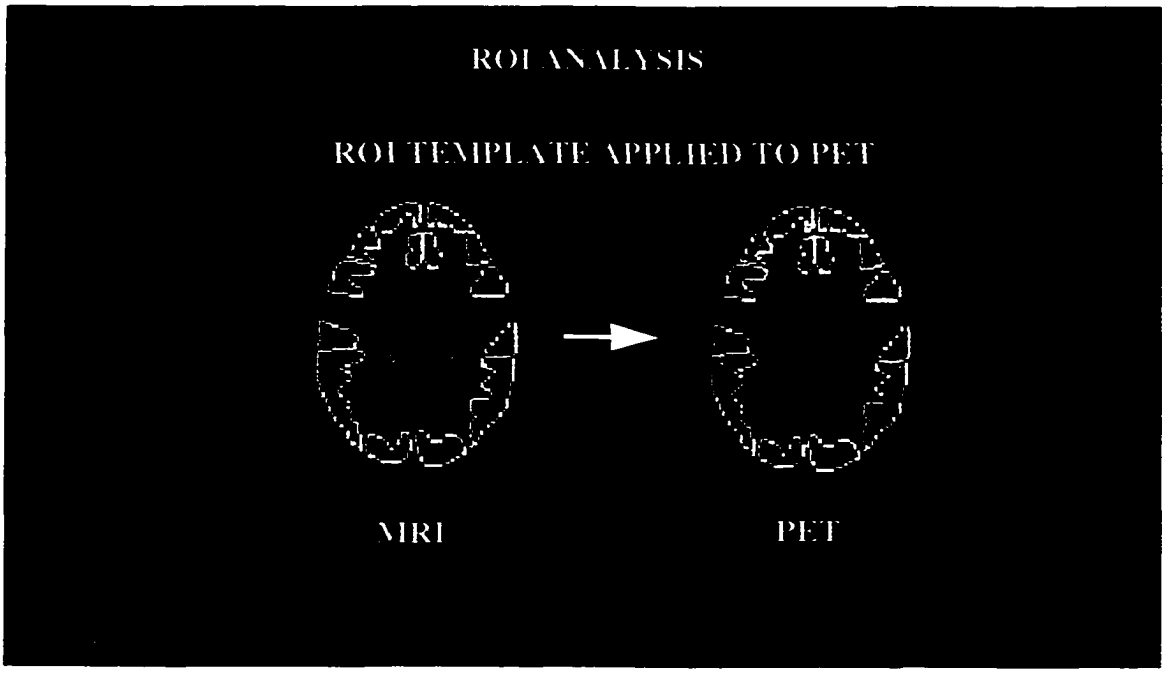
For both the SPM and ROI methods, the following comparisons, which involved examining both increases and decreases in rCBF, were made:

Between-group rCBF differences

a) To investigate rCBF differences that may exist regardless of cognitive state (and therefore would be eliminated by the subtraction method), between group comparisons were made for the four tasks separately (i.e., WCST, WCSTc, CRMT, READ).

b) To examine rCBF differences between the CHI patients and controls that were specific to the higher cognitive actions involved in performing the experimental tasks, the rCBF values for the control task were subtracted from those of its respective

Figure 10: Region of interest (ROI) analysis. Region of interest (ROI) analysis. *Top.* The application of a structurally-based ROI template to a positron emission tomography (PET) scan is illustrated. The individually drawn ROI template was transferred to the corresponding slice on the coregistered PET scans for anatomical localization to calculate mean regional cerebral blood flow values.


ROI ANALYSIS
ROI TEMPLATE APPLIED TO PET
MRI
PET

experimental task to produce cognitive "activation" values. Two between-group comparisons were then made: a) WCST-WCSTc and b) CRMT-READ.

Within-group rCBF and PET performance correlations

Within group correlations were made between: a) WCST rCBF activation (i.e., WCST-WCSTc) and performance (percent correct and percent perseverative errors, separately) and b) CRMT rCBF activation (i.e., CRMT-READ) and performance (percent correct).

Correlations between rCBF and cognitive functioning in CHI patients

For the CHI patients, additional correlations were made between measures of cognitive functioning (i.e., loss of cognitive function and current overall cognitive function) and rCBF activation for the WCST and CRMT, separately.

RESULTS

DEMOGRAPHICS

There were no significant differences between the control group and the CHI patients in age, gender, handedness, years of education, or SES (Table 1, Appendix H). Ten of the 13 patients received in-patient cognitive rehabilitation, although one of them did not undergo remediation until 11 years after injury. All patients attained either moderate (five patients) or good (eight patients) recovery as assessed by ratings on the GOS. All but two patients were either employed or attending school at the time of the study.

NEUROSTRUCTURAL ASSESSMENT

A summary of the lesion sites revealed by CT in the CHI patients immediately following their injuries is presented in Table 3. MRI scans obtained at the time of the present study were read as normal on all control subjects, whereas all but one of the CHI patients showed gross pathological changes (Table 4).

NEUROPSYCHOLOGICAL ASSESSMENT

General Performance

Based on age corrected normative data, CHI subjects, as a group, performed within the average range on measures of intelligence and attention. Scores on memory tasks were more variable: Patients performed better on short-term verbal memory tasks when information was presented in a contextual framework (e.g., a story) rather

Table 3. Lesion sites identified by computerized tomography immediately following closed head injury.

	Frontal	Temporal	Parietal	Subcortical	Ventriculo-megaly
DA*			Bilateral		
JB*	L	L	L		L lateral ventricle (decreased)
RC	L	L	L		
VD*				R lateral to posterior limb of internal capsule	L posterior horn
EF	Bilateral		R		
PL	R		R		
WL	Normal MRI				
JN				L (posterior and adjacent to occipital horn)	clot in L 4th ventricle
BP	Bilateral (R > L)				Bilateral
TR	R				R frontal horn
GR*		L posterior	L posterior	L posterior limb of internal capsule	
KS					L (blood in posterior horn)
RW	L		Bilateral (L > R)	white matter shear	

NOTE: L=left, R=right

*Additional lesion sites: DA: left cerebellar contusions; JB: left mesial occipital lesion secondary to left posterior cerebral artery infarct; VD: right anterior occipital lobe; GR: left occipital lobe.

Table 4. Current lesion sites identified by magnetic resonance imaging (MRI).

	Frontal	Temporal	Parietal	Subcortical	Ventriculo-megaly
DA	Bilateral precentral (white matter)		Bilateral postcentral (white matter)	Bilateral peri-ventricular	
JB*	L (atrophy)		L posterior		L temporal & occipital horns
RC	R inferior	R anterior			
VD	R anterior (white matter)	R anterior	R	R periventricular R basal ganglia	R temporal horn
EF			R		
PL	L anterior R superior				
WL	**Normal MRI scan**				
JN		L (atrophy)		Bilateral periventricular	L temporal horn
BP	Bilateral (white matter)				Bilateral lateral & third ventricles
TR	L				
GR				L periventricular	
KS				R peri-ventricular	
RW				L white matter (adjacent to central sulcus)	

NOTE: L=left, R=right
*left occipital damage

than a word list. Most notably, CHI patients performed at the lower end of average to below average on language tests (Figure 11, Table 5, Appendix I).

Mood

Based on the BDI, four of the 13 patients (31%) were moderately or severely depressed (Table 6, Appendix I). Two of these patients had received drug treatment for depression during the six months preceding the study. However, the patients, as a group, were classified as only minimally depressed (average BDI score= 11.7).

Cognitive Disability Indices

a) Intellectual Loss: An unpaired t-test revealed that differences between estimated levels of pre-injury intelligence and current cognitive functioning, as determined by performance on the WRAT-R reading subtest and an abbreviated form of the WAIS-R respectively, were not significant (t= -0.59, p=0.57) (Table 7). However, two findings suggest that one or both of the estimates of cognitive functioning were invalid. First, nearly half the patients (6/13) scored *higher* on the test of current than premorbid intellectual abilities, which is contrary to the expectation, based on both theoretical and clinical evidence, of *lower* current than premorbid intellectual functioning in severe CHI patients. Second, as a group, CHI patients scored in the average range (i.e., 52nd percentile) on the WRAT-R reading test, suggesting that premorbid cognitive abilities fell in the average range. Given that about 60% (8/13) of the CHI patients had obtained at least a Bachelor's degree at the

Figure 11: Neuropsychological test battery results. Average percentile rankings of 13 closed head injury (CHI) patients on a neuropsychological test battery are presented. Scores between the 25th and 75th percentiles fall within the average range (demarcated by dashed lines). Error bars denote SEM. PRE= estimate of pre-injury cognitive level based on the reading subtest of the Wide Range Achievement Test-Revised; POST= current intellectual functioning based on an abbreviated version of the Wechsler Adult Intelligence Scale- Revised (estimated Full Scale Intelligence Quotient); LM1= Logical Memory I subtest of the Wechsler Memory Scale- Revised (number correct); CVLT= California Verbal Learning Test (sum of trials 1-5); TMT= Trail Making Test (time for Trail B); CPT= Continuous Performance Test (total correct); BNT= Boston Naming Test (total correct); FAS= Verbal Fluency (sum of trials F, A, S).

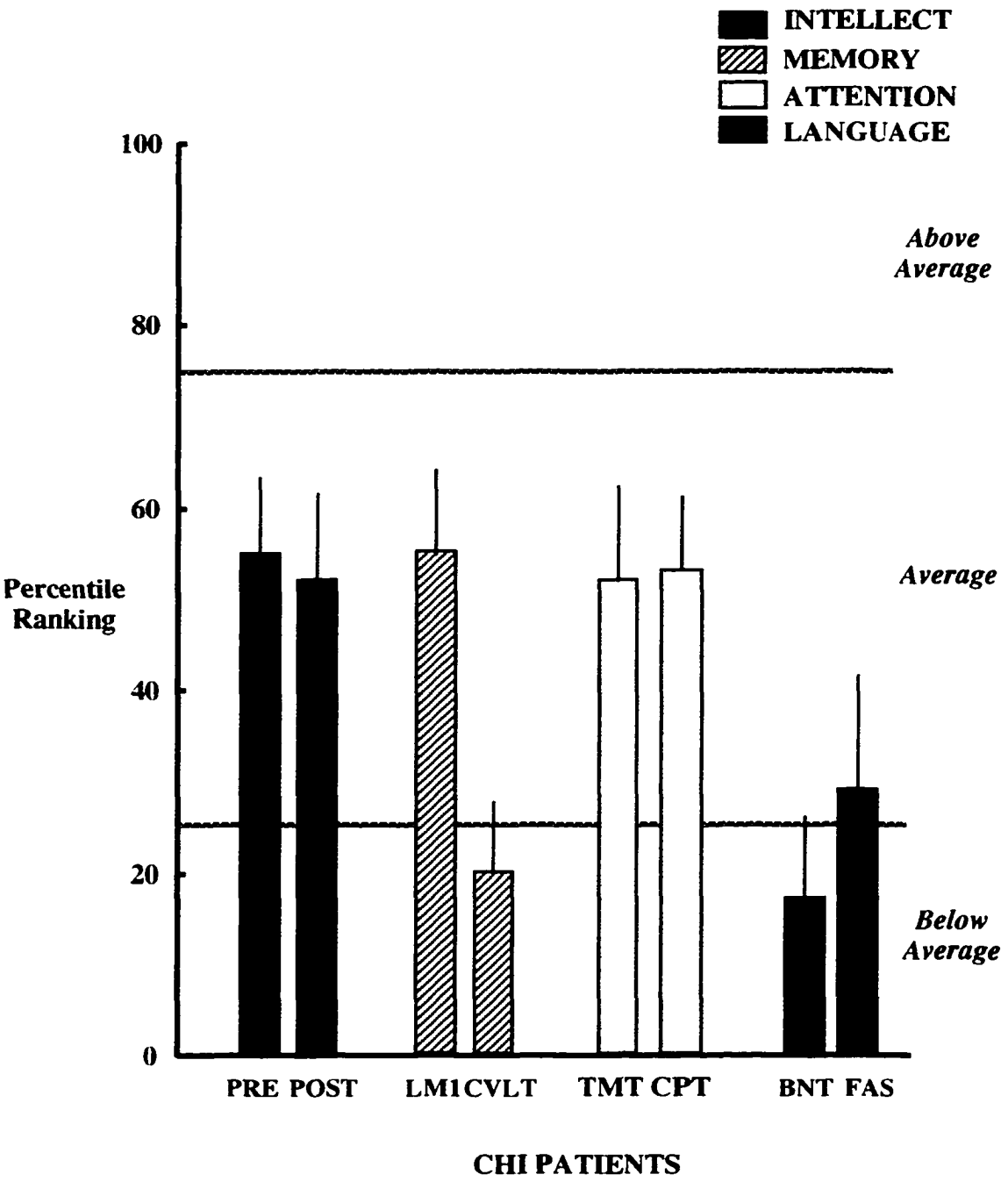

INTELLECT
MEMORY
ATTENTION
LANGUAGE
100
80
60
40
20
0
Above Average
Average
Below Average
Percentile Ranking
PRE POST
LM1 CVLT
TMT CPT
BNT FAS
CHI PATIENTS

Table 5. Neuropsychological performance of closed head injury patients.

Neuropsychological Test	Average Percentile Ranking (mean ±SD)	Range
Wechsler Adult Intelligence Scale-Revised (abbreviated version)	52 ±32	2-96
Logical Memory I	55 ±33	6-98
California Verbal Learning Test	20 ±27	0-73
Trails B	52 ±35	11-95
Continuous Performance Test	53 ±28	0-78
Boston Naming	17 ±31	0-93
Verbal Fluency Test	29 ±43	0-100
Reading subtest from the Wide Range Achievement- Revised	55 ±30	1-91

Table 6. Scores on the Beck Depression Inventory.

Level of Depression	Number of Closed Head Injury Patients (n=13)
Normal	7
Minimal	2
Mild to Moderate	0
Moderate to Severe	3
Severe	1

Table 7. Estimates of pre-injury and current levels of cognitive functioning.

CHI Patient	Current Intelligence[a]	Premorbid Intelligence[b]	Loss of Intellectual Ability (Current - Premorbid)
DA	2	6	-4
JB	55	58	-3
RC	77	75	2
VD	96	91	5
EF	25	25	0
PL	42	66	-24
WL	8	1	7
JN	81	77	4
BP	77	47	30
TR	37	77	-40
GR	19	32	-13
KS	86	77	9
RW	75	84	-9
Mean SD	52.3 32.0	55.1 30.2	-2.77 16.9

[a]based on percentile ranking on an abbreviated form of the Wechsler Adult Intelligence Scale- Revised
[b]based on percentile ranking on the reading subtest of the Wide Range Achievement Test- Revised
CHI= closed head injury

time of the present study, this finding is contrary to the expectation of high average to above average intellectual abilities in people with college educations. In light of these facts that raise questions about the validity of the cognitive disability index used in this study, correlations between this variable and rCBF data were not calculated.

b) Current Cognitive Functioning: The percentile rankings from each of the dependent measures listed in Table 2 were analyzed using a factor analysis. The analysis produced one factor that accounted for 73% of the variance with all subsequent factors accounting for only 27% of the variance. Therefore, only data for Factor 1 was used in further analyses (Appendix J).

NEUROFUNCTIONAL ASSESSMENT

Performance during PET

Unpaired t-tests of performance between CHI patients and controls during PET revealed: 1) no significant differences in percent correct or percent perseverative errors on the WCST ($p's \geq 0.20$), and 2) CHI patients remembered significantly fewer word pairs ($t = -2.84$, $p \leq 0.01$) than controls on the CRMT (Figure 12, Table 8, Appendix K).

Global CBF

Unpaired t-tests revealed no differences between CHI patients and controls in global flow for any of the four tasks ($p's > 0.30$) (Figure 13, Appendix L) or in pCO_2 values ($p's > 0.30$) (Appendix M).

Figure 12: Task performance during positron emission tomography (PET). Compared to controls, the closed head injury (CHI) patients did not perform significantly differently on the Wisconsin Card Sorting Test (WCST) based on percent correct and percent perseverative error measures ($p's>0.20$), but remembered significantly fewer word pairs on the Cued Recall Memory Task (CRMT). $*p<0.01$. Error bars denote SEM.

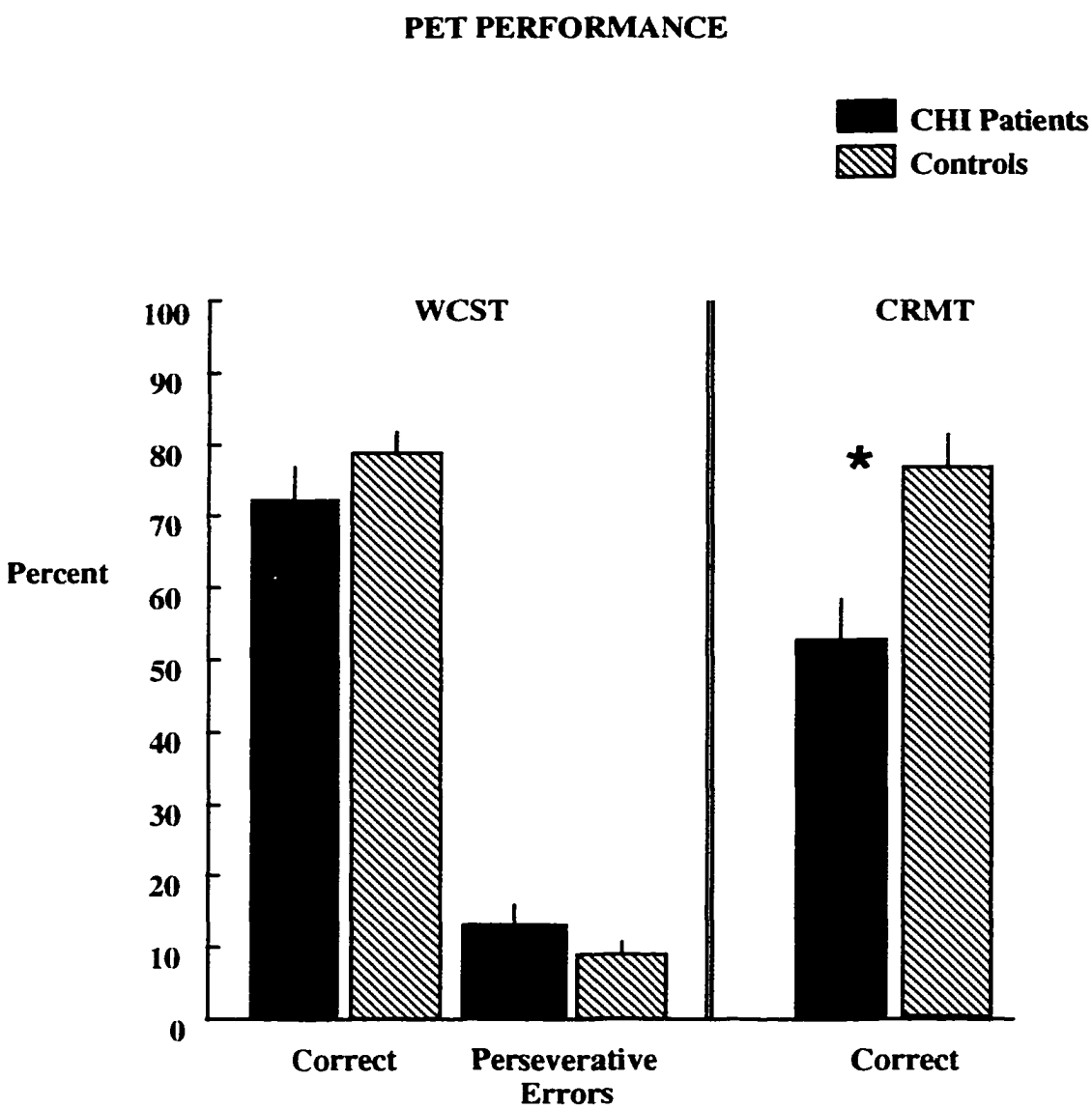
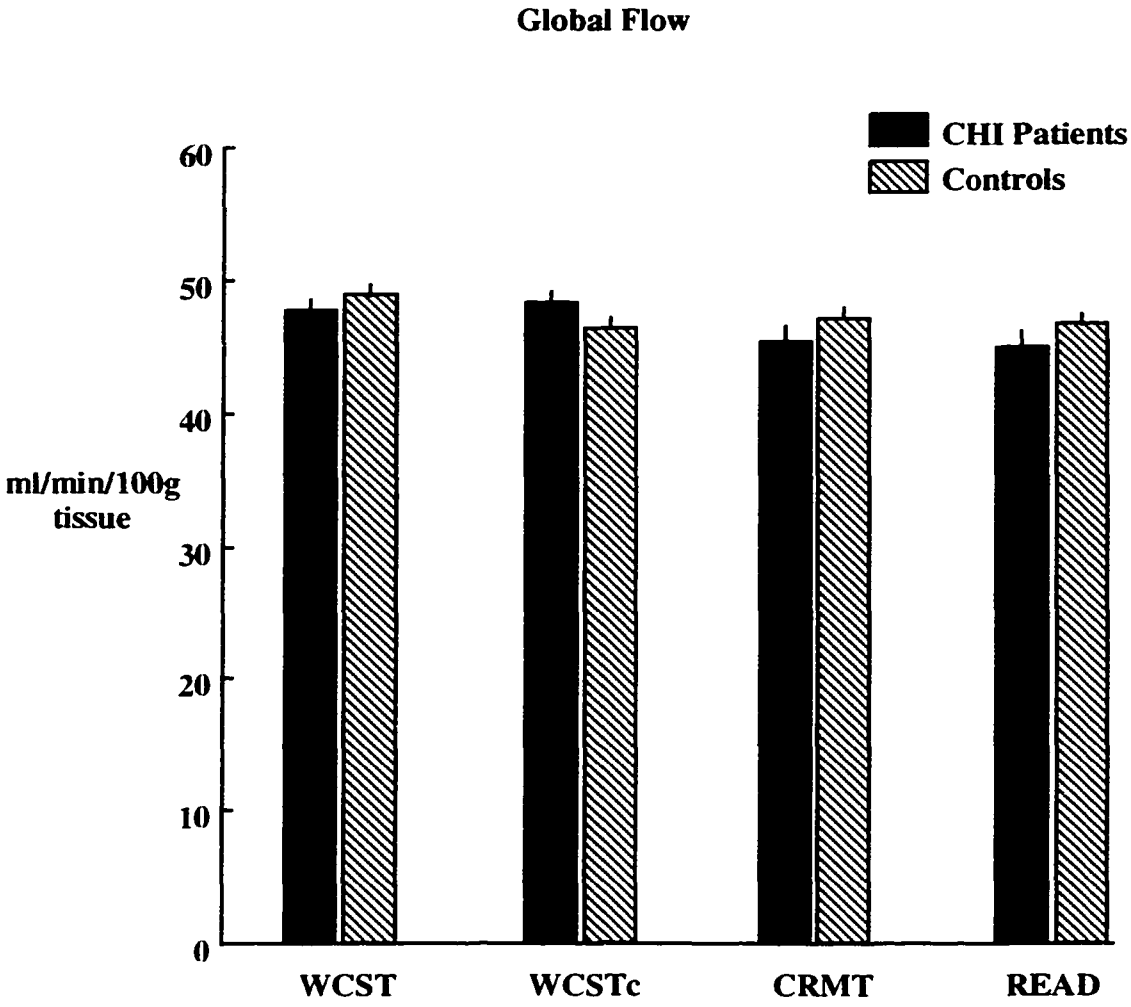

PET PERFORMANCE
CHI Patients
Controls
WCST
CRMT
100
90
80
70
60
50
40
30
20
10
0
Percent
*
Correct
Perseverative Errors
Correct

Table 8. Performance on tasks during positron emission tomography.

	Closed Head Injury Patients (mean ±SD)	**Controls (mean ±SD)**
Wisconsin Card Sorting Test:		
Percent Correct	71.61 ± 17.67	78.68 ± 11.23
Percent Perseverative Errors	14.17 ± 10.63	10.63 ± 5.59
Cued Recall Memory Test:		
*Percent Correct**	52.38 ± 21.73	76.18 ± 20.94

*$p<0.01$

Figure 13: Global cerebral blood flow. There were no significant group differences in global flow (ml/min/100g tissue) between controls and closed head injury (CHI) patients for either the Wisconsin Card Sorting Test (WCST), WCST control task (WCSTc), Cued Recall Memory Task (CRMT), or CRMT control task (READ) (p's>0.30). Error bars denote SEM.


Global Flow
CHI Patients
Controls
60
50
40
30
20
10
0
ml/min/100g tissue
WCST
WCSTc
CRMT
READ

Regional CBF: Voxel-Wise Approach

Results of each voxel-wise analysis have been presented in two ways. First, significant results were mapped onto a representative MRI scan. Slice numbers in each of the figures referred to below indicate the number of mm above (positive values) and below (negative values) the line passing through the anterior and posterior commissures (AC-PC) (slice 0). The slice numbers also correspond to the z coordinate of the Talairach atlas presented in corresponding tables. Second, the coordinates from the Talairach atlas of the location of maximum signal changes in a cluster of significant voxels (i.e., local maxima) have been presented in tabular form. The x coordinate refers to the number of mm either toward the left (negative values) or the right (positive values) away from the interhemispheric fissure. The y coordinate refers to the number of mm above (positive values) or below (negative values) the posterior margin of the anterior commissure. Finally, the z coordinate refers to the slice in mm above or below the AC-PC line.

Between-group rCBF differences

Voxel-by-voxel between-group analyses of normalized rCBF in CHI patients relative to controls revealed the following:

1) **WCST**

a) *Tasks Separately:* For both the WCST and WCSTc, greater rCBF in the CHI patients was found in many cortical regions bilaterally, including prefrontal cortex. In

contrast, less rCBF in the CHI patients was found in anterior cingulate cortex and subcortical regions, including the thalamus and caudate nucleus (Figure 14, Tables 9-10).

b) *Activation (WCST-WCSTc)*: When rCBF in the WCST was viewed against that for the WCSTc, CHI patients showed greater rCBF activation in the left inferior frontal gyrus (Brodmann's area 44) (Figure 15) and the left hippocampus than normal controls. In contrast, CHI patients showed less activation in a small portion of the left inferior parietal lobule (Figure 14, Table 11).

2) **CRMT**

a) *Tasks Separately*: As in the WCST paradigm, CHI patients generally showed hyperactivity in many cortical areas and showed hypoactivity in anterior cingulate cortex and in subcortical areas, including the thalamus and caudate nucleus. CHI patients also had diminished activity in the left hippocampus (Figure 16, Tables 12-13).

b) *Activation (CRMT-READ)*: When baseline rCBF was taken into account, the pattern of changes during the CRMT in the CHI patients differed from findings from the WCST paradigm. CHI patients showed greater activation in the left inferior parietal lobule, left primary motor cortex, and right visual association cortex. In contrast, CHI patients showed small areas of decreased rCBF activation in left cingulate cortex and right frontal cortex (Figure 16, Table 14).

Figure 14: Maps of between-group differences in regional cerebral blood flow (rCBF) in the Wisconsin Card Sorting Test (WCST) paradigm. The left side of the brain is at the left of the figure. Slice numbers correspond to the z coordinate (i.e., the number of mm above or below the intercommissural line) from the Talairach atlas presented for local maxima in Tables 9 through 11. Upper and middle panels show between-group rCBF differences for the WCST and the control task (WCSTc), separately. For both tasks, relative to controls, CHI patients showed hyperactivity in cortical regions and hypoactivity in subcortical regions and anterior cingulate cortex. The bottom panel, which shows rCBF differences for WCST activation (i.e., WCST-WCSTc), illustrates the hyperactivity in left inferior frontal cortex including Broca's area (slice +12), and in the left hippocampus (slice -8) found in CHI patients compared to controls ($p \leq 0.001$).

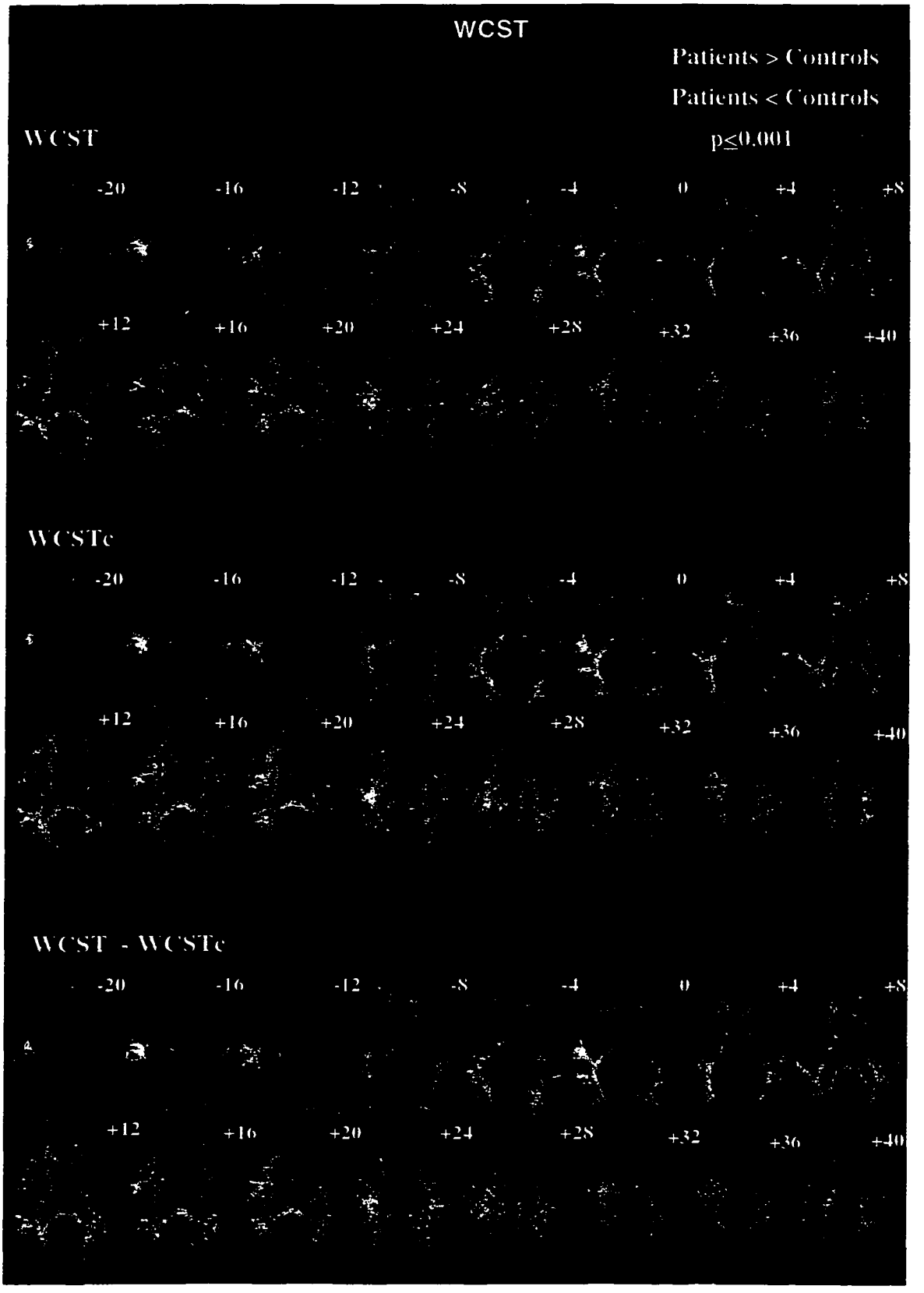

WCST
Patients > Controls
Patients < Controls
p≤0.001
WCST
-20
-16
-12
-8
-4
0
+4
+8
+12
+16
+20
+24
+28
+32
+36
+40
WCSTc
-20
-16
-12
-8
-4
0
+4
+8
+12
+16
+20
+24
+28
+32
+36
+40
WCST - WCSTc
-20
-16
-12
-8
-4
0
+4
+8
+12
+16
+20
+24
+28
+32
+36
+40

Table 9. Maxima from voxel-wise between group comparisons for the Wisconsin Card Sorting Test.

Greater rCBF in closed head injury (CHI) patients than control subjects		
Region (*Brodmann's area*)	**Z Score ($p \leq 0.001$)**	**Talairach coordinates (x, y, z)**
right inferior frontal gyrus (45/46/47)	6.08	46 40 8 44 -34 -4
right inferior occipital gyrus (17)	5.02	20 -94 -8
right precuneus (18)	4.69	18 -68 28
right inferior parietal lobule (39/40)	4.68	26 -42 32
left inferior frontal gyrus (45)	4.67	-48 24 12
right superior temporal gyrus (39)	3.35	34 -50 28
Less rCBF in CHI patients than control subjects		
right caudate nucleus	6.28	2 8 4
left cerebellum	6.15	-40 -82 -28
right cingulate gyrus (23/24)	5.79	4 -12 32
right superior frontal gyrus (10)	5.36	20 62 4
left thalamus	5.34	-8 -6 0
right cerebellum	4.84	44 -68 -28
left cingulate gyrus (32)	4.50	-8 20 32
left medial frontal gyrus (6/8)	4.22	-6 20 44
right thalamus	4.16	14 -2 12

Table 10. Maxima from voxel-wise between group comparisons for the control task of the Wisconsin Card Sorting Test paradigm.

Greater rCBF in closed head injury (CHI) patients than control subjects		
Region (*Brodmann's area*)	**Z Score ($p \leq 0.001$)**	**Talairach coordinates (x, y, z)**
R precuneus (18/19)	4.70	18 -70 28
L inferior parietal lobule (40)	4.32	-56 -30 32
R inferior frontal gyrus (45/46)	4.59	46 46 8
L middle temporal gyrus (21)	4.53	-58 -34 -8
R inferior occipital gyrus (18)	4.03	28 -94 -4
L middle frontal gyrus (9)	3.89	-50 12 36
Less rCBF in CHI patients than control subjects		
R caudate nucleus	6.52	2 8 4
R cingulate gyrus (23/34)	5.59	4 -12 32
L cerebellum	4.68	-44 -78 -24
R inferior frontal gyrus (47)	4.45	20 26 -12
R superior frontal gyrus (10)	4.38	18 60 4
R middle frontal gyrus (11)	4.14	16 34 -12
L medial frontal gyrus (8)	4.07	-6 20 44
R cerebellum	3.56	42 -66 -28
L cingulate gyrus (32)	3.30	-4 22 32

L=left, R=right

Figure 15: Activation (task-control) of Broca's area in the Wisconsin Card Sorting Test (WCST) paradigm. Significantly higher activation was found in Broca's area (Talairach coordinates -44 14 12) in the closed head injury (CHI) patients than the controls ($z=3.81$, $p \leq 0.001$). Horizontal black bars indicate the mean value for each group.

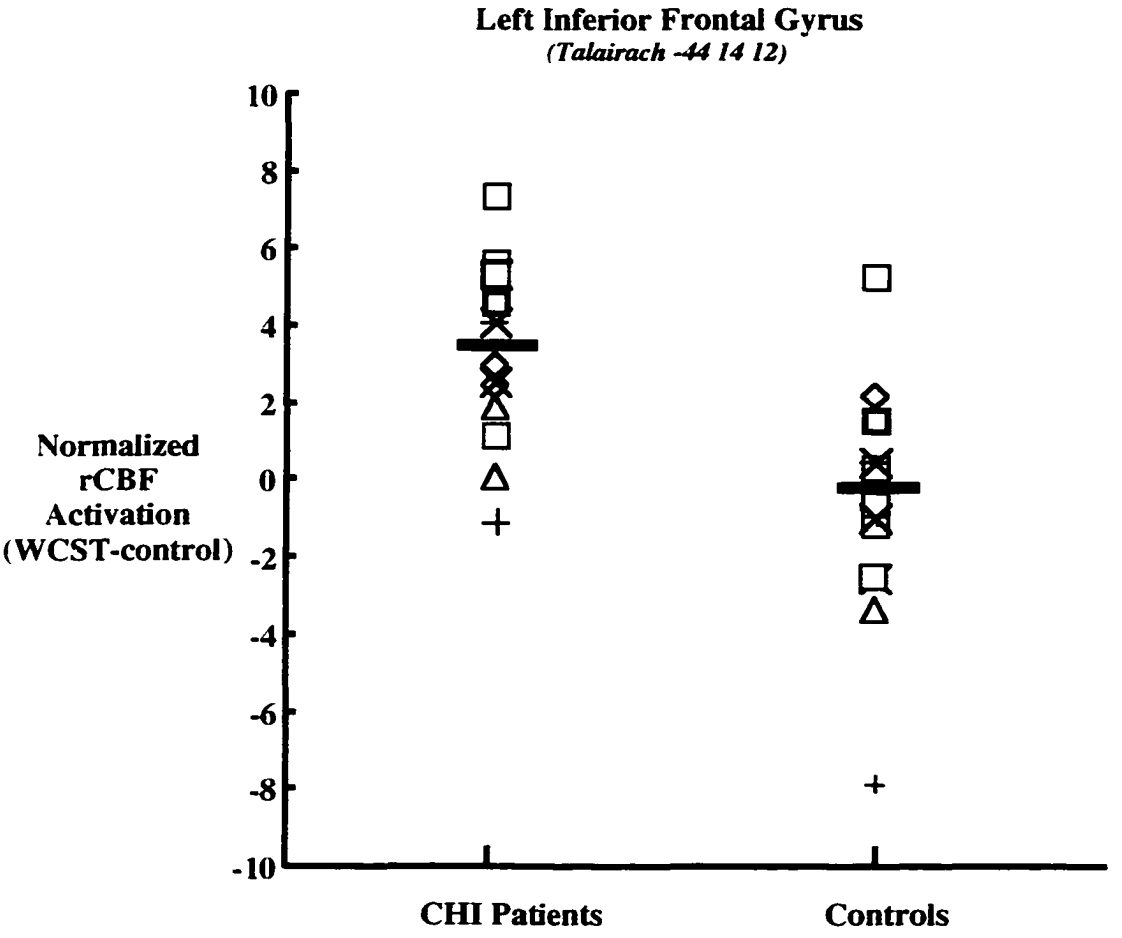

Left Inferior Frontal Gyrus
(Talairach -44 14 12)
Normalized rCBF Activation (WCST-control)
10
8
6
4
2
0
-2
-4
-6
-8
-10
CHI Patients
Controls

Table 11. Maxima from voxel-wise between group comparisons for activation (task-control) in the Wisconsin Card Sorting Test paradigm.

Greater rCBF in closed head injury (CHI) patients than control subjects		
Region (*Brodmann's area*)	**Z Score ($p \leq 0.001$)**	**Talairach coordinates (x, y, z)**
left inferior frontal gyrus (44)	3.81	-44 14 12
left hippocampal gyrus (36)	3.05	-24 -38 -8
Less rCBF in CHI patients than control subjects		
left inferior parietal lobule (40)	3.22	-56 -48 24

Figure 16: Maps of regional cerebral blood flow (rCBF) differences in the Cued Recall Memory Task (CRMT) paradigm. The left side of the brain is at the left of the figure. Slice numbers correspond to the z coordinate (i.e., the number of mm above or below the intercommissural line) from the Talairach atlas presented for local maxima in Tables 12 through 14. Upper and middle panels show rCBF differences for the CRMT and the control task (READ), separately. For both tasks, relative to controls, CHI patients show hyperactivity in cortical regions and hypoactivity in the left hippocampus, subcortical regions, and anterior cingulate cortex. The bottom panel, which shows rCBF differences for CRMT activation (i.e., CRMT-READ), illustrates the overactivity in left inferior parietal lobule (slice +28) and in right occipital cortex (slice -12) and the underactivity in left cingulate (slice +16) and right superior frontal cortex (slice -4) found in CHI patients compared to controls.

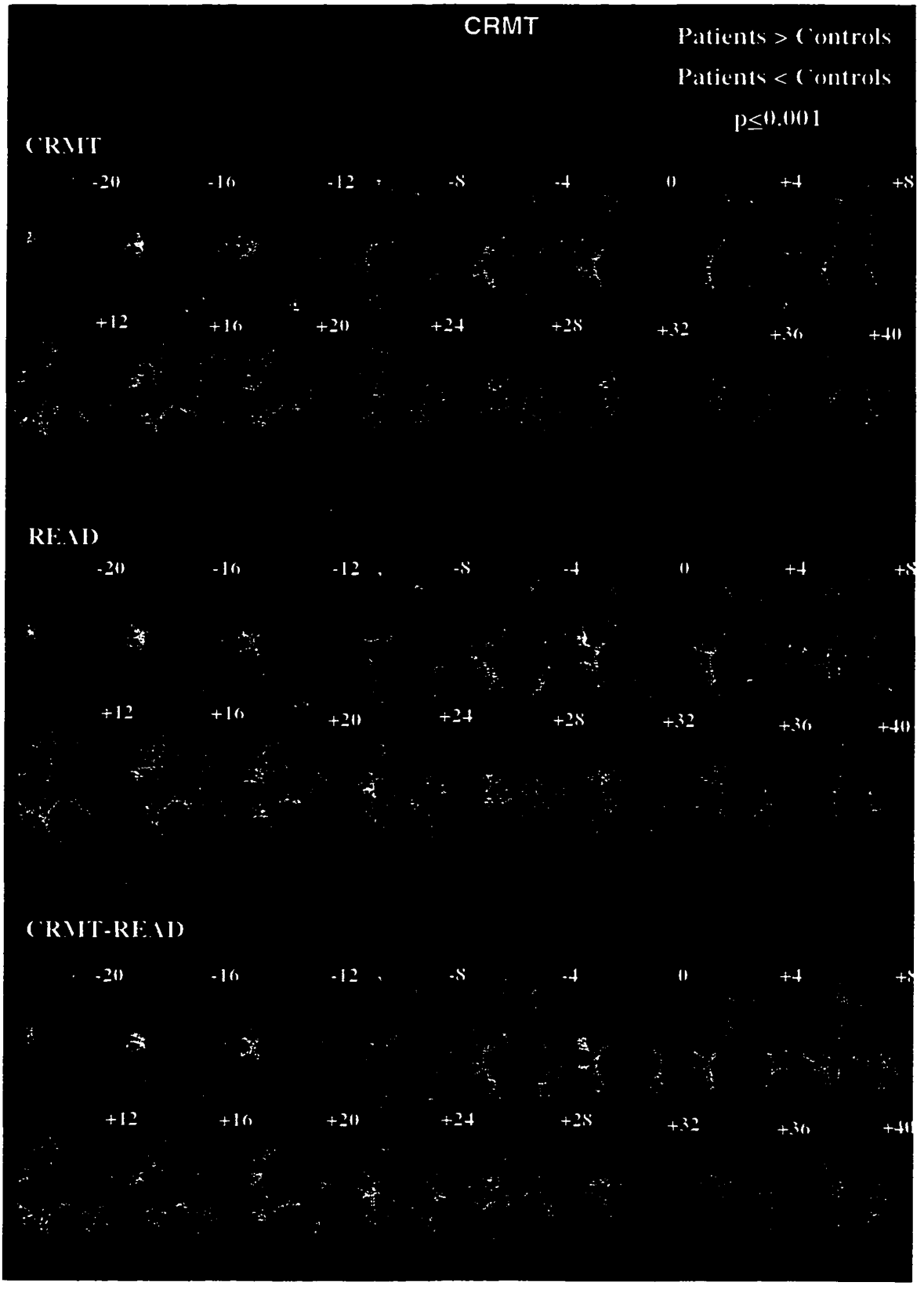

CRMT
Patients > Controls
Patients < Controls
p≤0.001
CRMT
-20
-16
-12
-8
-4
0
+4
+8
+12
+16
+20
+24
+28
+32
+36
+40
READ
-20
-16
-12
-8
-4
0
+4
+12
+16
+20
+24
+28
+32
+36
+40
CRMT-READ
-20
-16
-12
-8
-4
0
+4
+12
+16
+20
+24
+28
+32
+36

Table 12. Maxima from voxel-wise between group comparisons for the Cued Recall Memory Test.

Greater rCBF in closed head injury (CHI) patients than controls subjects		
Region (*Brodmann's area*)	**Z Score** ($p \leq 0.001$)	**Talairach coordinates** (x, y, z)
right lingual gyrus (17/18)	6.57	6 -86 -12
left precentral gyrus (4)	5.57	-52 -18 36
right middle temporal gyrus (21)	5.49	42 -56 0
right middle frontal gyrus (46)	5.44	34 42 16
left superior temporal gyrus (22)	5.26	-44 -40 16
right sylvian fissure	4.89	40 -34 20
Less rCBF in CHI patients than control subjects		
right thalamus	7.89	4 -4 8
left caudate nucleus	7.48	-4 6 4
cingulate gyrus (24): right left	 5.78 5.11	 4 -2 32 -6 -4 32
left hippocampal gyrus (28/36)	5.53	-24 -16 -20
right sylvian fissure	4.85	42 20 -12
right inferior frontal gyrus (47)	4.83	24 18 -16
right superior frontal gyrus (10)	4.60	18 60 0

Table 13. Maxima from voxel-wise between group comparisons for the control task of the Cued Recall Memory Test paradigm.

Greater rCBF in closed head injury (CHI) patients than control subjects		
Region (*Brodmann's area*)	**Z Score ($p \leq 0.001$)**	**Talairach coordinates (x, y, z)**
right middle frontal gyrus (46)	5.29	34 42 16
right lingual gyrus (17/18)	5.14	8 -82 -4
left superior temporal gyrus (22)	4.71	-44 -40 16
left precentral gyrus (6)	4.69	-54 -12 36
right inferior parietal lobule (40)	4.62	36 -28 24
right middle temporal gyrus (20/21)	4.49	46 -34 -8
left lingual gyrus (18/19)	4.45	-16 -68 -4
left supramarginal gyrus (39/40)	4.00	-56 -46 32
Less rCBF in CHI patients than control subjects		
right thalamus	7.76	4 -4 8
cingulate gyrus (24): right left	 5.97 5.07	 8 2 32 -8 4 32
left hippocampal gyrus (35)	4.62	-32 -20 -16
right inferior frontal gyrus (47)	4.17	26 18 -16
left cerebellum	3.96	-48 -72 -20
left medial frontal gyrus (11)	3.85	-2 32 -12

Table 14. Maxima from voxel-wise between group comparisons for activation (task-control) in the Cued Recall Memory Test paradigm.

Greater rCBF in closed head injury (CHI) patients than control subjects		
Region (*Brodmann's area*)	**Z Score** ($p \leq 0.001$)	**Talairach coordinates** (x, y, z)
left inferior parietal lobule (40)	4.08	-30 -24 28
left precentral gyrus (4)	3.68	-32 -8 40
right lingual gyrus (17)	3.42	6 -86 -12
Less rCBF in CHI patients than control subjects		
left cingulate gyrus (32)	3.60	-14 32 16
right superior frontal gyrus (10)	3.16	22 54 -4

Within-group rCBF and PET performance correlations

Voxel-wise within-group correlational analyses between normalized rCBF activation and task performance revealed the following:

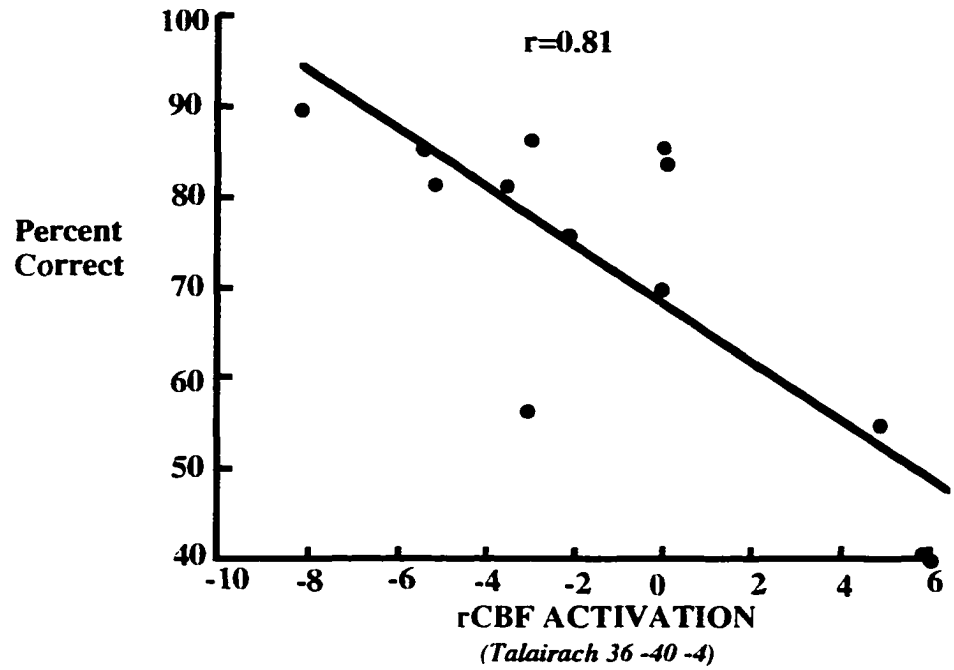
1) **WCST Activation**

a) *WCST-WCSTc and Percent Correct*: In the CHI group, percent correct was positively correlated with normalized rCBF activation in the right inferior frontal gyrus and left occipital cortex and negatively correlated with activation in the right hippocampus (Figure 17), right prefrontal cortex, and right temporal cortex. In the control group, percent correct was positively correlated with rCBF activation in the temporal cortex bilaterally and the left cerebellum, and negatively correlated with right prefrontal cortex, left visual association areas, and right temporal cortex (Figure 18, Table 15).

b) *WCST-WCSTc and Percent Perseverative Errors*: In the CHI group, percent perseverative errors was positively associated with normalized rCBF activation in the right hippocampus (Figure 17), right prefrontal cortex, left caudate nucleus, and left cerebellum, and negatively associated with activation in the right inferior frontal gyrus and left occipital cortex. In the control group, positive correlations were found in the cingulate cortex bilaterally and the right temporal lobe including the amygdala, whereas negative correlations were found in the left fusiform gyrus and the left cerebellum (Figure 19, Table 16).

Figure 17: Right hippocampal activation (task-control) and performance for the Wisconsin Card Sorting Test (WCST) in closed head injury (CHI) patients. *Top.* There was a significant negative correlation between regional cerebral blood flow (rCBF) activation in the right hippocampus (Talairach coordinates 36 -40 -4) and percent correct in the CHI patients ($r=0.81$, $p \leq 0.001$) during the WCST. *Bottom.* During the WCST, a positive correlation was found between right hippocampal rCBF activation (Talairach coordinates 32 -32 -12) and percent perseverative (PSV) errors in the CHI patients ($r=0.83$, $p \leq 0.001$).

Right Hippocampus & WCST Performance in CHI Patients



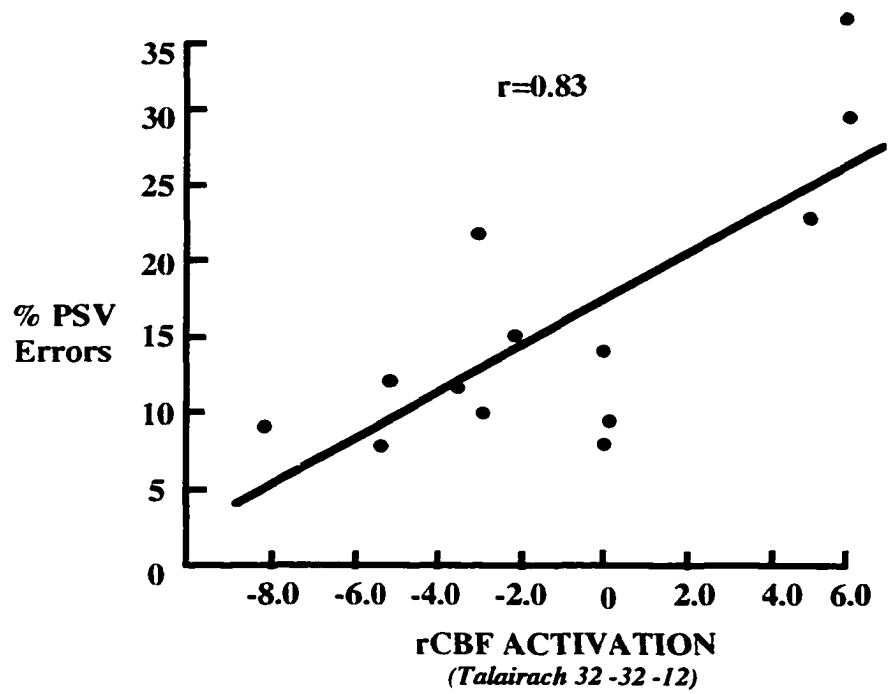


Figure 18: Maps of within-group correlations between activation (task-control) in the Wisconsin Card Sorting Test (WCST) and percent correct. The left side of the brain is at the left of the figure. Slice numbers correspond to the z coordinate (i.e., the number of mm above or below the intercommissural line) from the Talairach atlas presented for local maxima in Table 15. *Top.* A negative correlation between regional cerebral blood flow (rCBF) activation of the right hippocampus (slices -12 and -4) and percent correct was found in the closed head injury (CHI) patients ($r=-0.81$, $p \leq 0.001$). *(Also shown are positive correlations in the left cuneus [slice +20] and negative correlations in the right inferior frontal gyrus [slice +8]). Bottom.* A similar relationship between hippocampal activity and WCST performance was *not* found in the normal control subjects. *(Also shown are positive correlations in the left fusiform gyrus [slice -16] and negative correlations in the medial frontal cortex [slice +28]).*

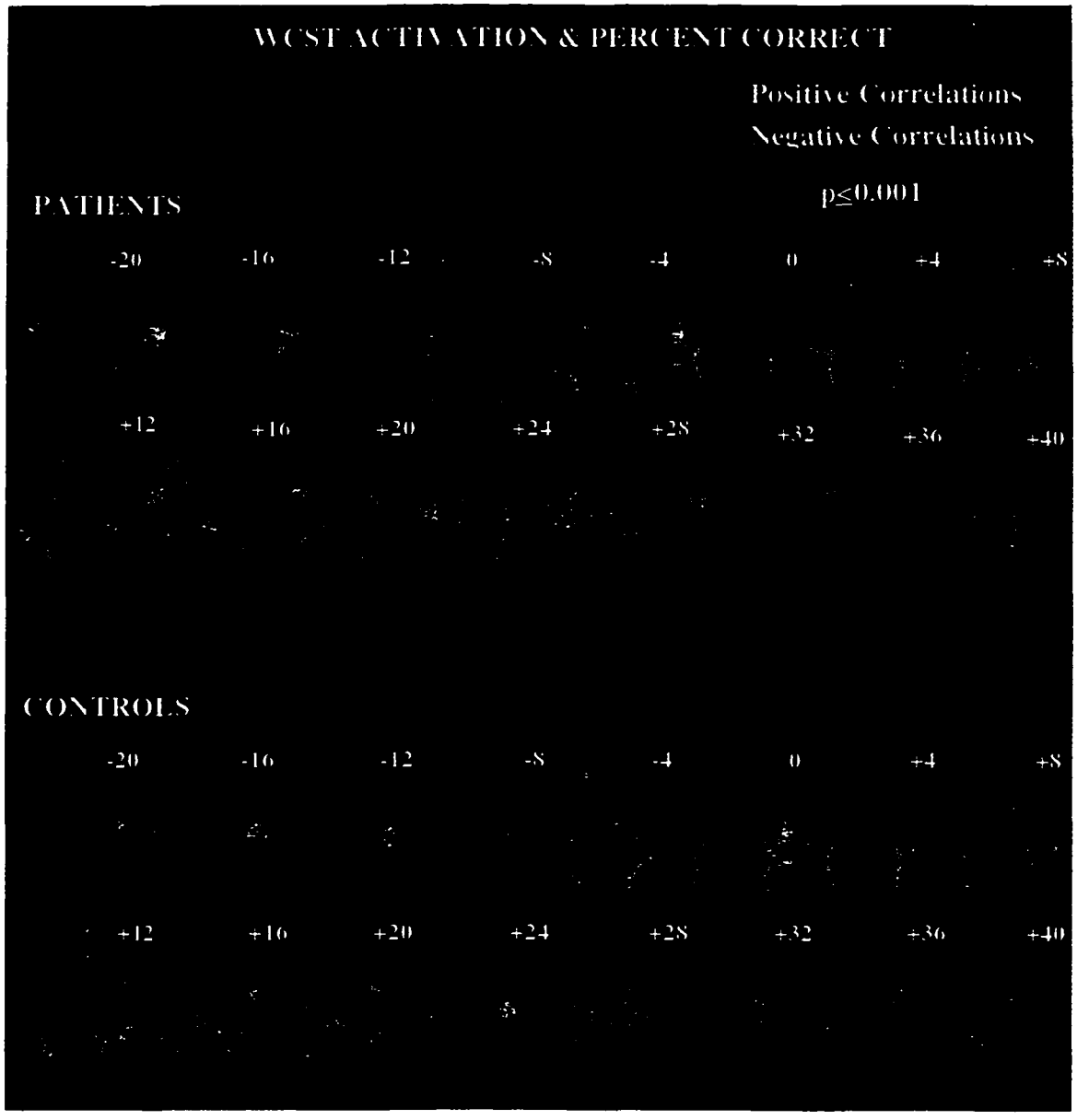

WCST ACTIVATION & PERCENT CORRECT
Positive Correlations
Negative Correlations
PATIENTS
p≤0.001
-20
-16
-12
-8
-4
0
+4
+8
+12
+16
+20
+24
+28
+32
+36
+40
CONTROLS
-20
-16
-12
-8
-4
0
+4
+8
+12
+16
+20
+24
+28
+32
+36
+40

Table 15. Maxima from voxel-wise correlations between Wisconsin Card Sorting Test activation (task-control) and percent correct ($p \leq 0.001$).

Closed Head Injury Patients				Control Subjects			
Positive	r	Negative	r	Positive	r	Negative	r
L cuneus *(BA 18)* *(-6 -70 20)*	0.89	**R inferior frontal gyrus** *(BA 46)* *(36 38 8)*	0.84	**L fusiform gyrus** *(BA 37)* *(-42 -52 -16)*	0.83	**R fusiform gyrus** *(BA 20)* *(40 -18 -24)*	0.87
R inferior frontal gyrus *(BA 45)* *(50 14 20)*	0.87	**R medial frontal gyrus** *(BA 10)* *(18 46 8)*	0.84	**L cerebellum** *(-42 -42 -24)* *(-44 -62 -20)*	0.81	**R medial frontal gyrus** *(BA 9)* *(2 54 28)*	0.83
L middle occipital gyrus *(BA 19)* *(-46 -80 4)*	0.83	**R hippocampal gyrus** *(BA 36/37)* *(32 -32 -12)* (36 -40 -4)	0.81	**R fusiform gyrus** *(BA 37)* *(42 -54 -12)*	0.81	**L precuneus** *(BA 7)* *(-14 -42 32)*	0.81
						R middle frontal gyrus *(BA 11)* *(26 38 -16)*	0.80
						R inferior temporal gyrus *(BA 20)* *(44 -8 -20)*	0.80

BA=Brodmann's area
L=left, R=right

Figure 19: Maps of within-group correlations between activation (task-control) in the Wisconsin Card Sorting Test (WCST) and percent perseverative errors. The left side of the brain is at the left of the figure. Slice numbers correspond to the z coordinate (i.e., the number of mm above or below the intercommissural line) from the Talairach atlas presented for local maxima in Table 16. *Top.* A positive correlation between right hippocampal activation (slice -12) and performance was found in the closed head injury (CHI) patients ($r=0.83$, $p \leq 0.001$). *(Also shown are positive correlations in the right inferior frontal gyrus [slices +4 and +8] and negative correlations in the left precuneus area [slice +20]). Bottom.* A similar relationship between hippocampal activation and WCST performance was *not* found in the normal control subjects. *(Also shown are positive correlations in the posterior cingulate gyri [slices +32 and +36] and the right amygdala [slice -16]).*

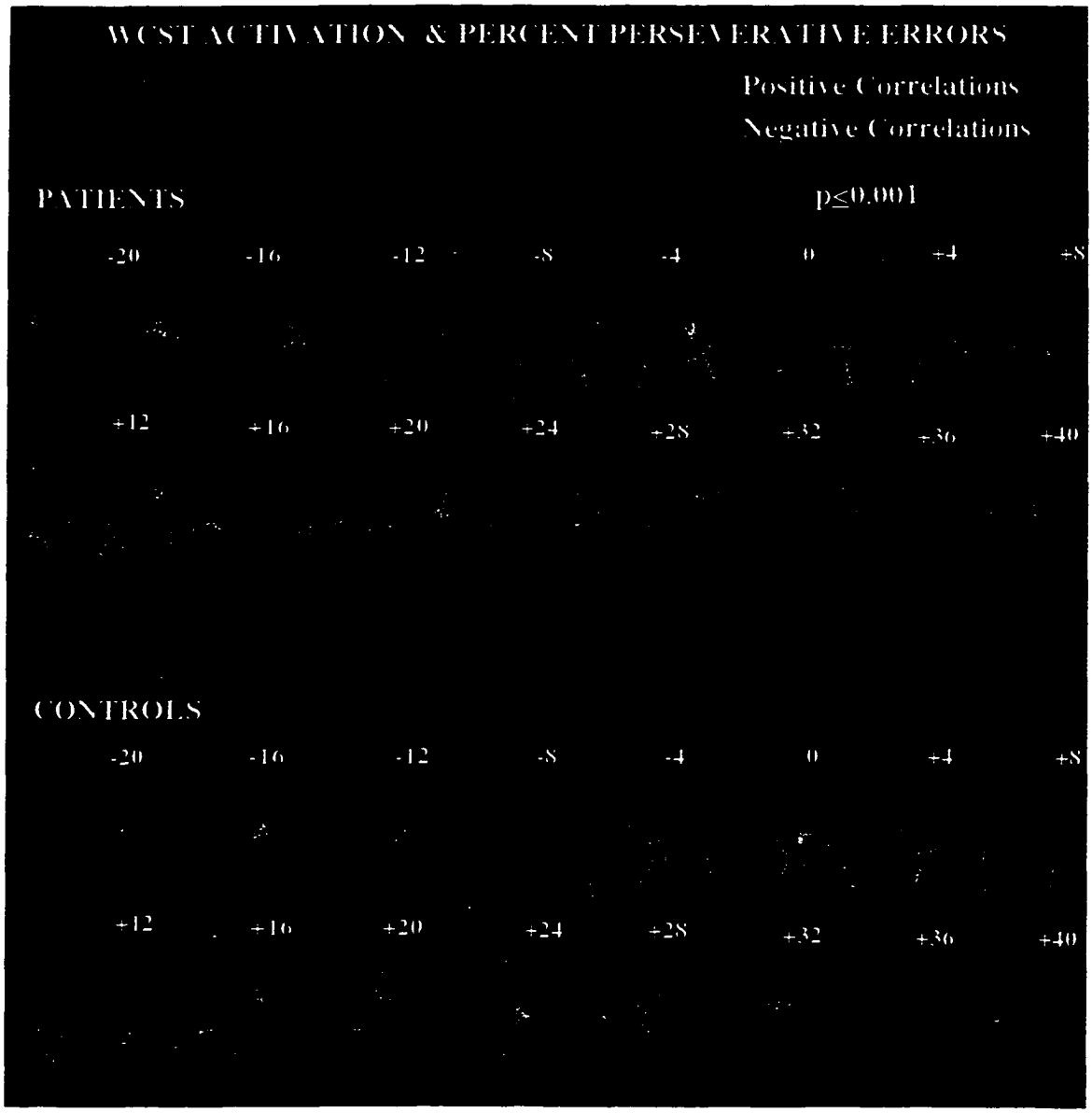

WCST ACTIVATION & PERCENT PERSEVERATIVE ERRORS
Positive Correlations
Negative Correlations
PATIENTS
p≤0.001
-20
-16
-12
-8
-4
0
+4
+8
+12
+16
+20
+24
+28
+32
+36
+40
CONTROLS
-20
-16
-12
-8
-4
0
+4
+8
+12
+16
+20
+24
+28
+32
+36
+40

Table 16. Maxima from voxel-wise correlations between Wisconsin Card Sorting Test activation (task-control) and percent perseverative errors ($p \leq 0.001$).

Closed Head Injury Patients				Control Subjects			
Positive	r	Negative	r	Positive	r	Negative	r
R hippocampal gyrus *(BA 36) (32 -32 -12)*	0.83	**L precuneus** *(BA 31) (-8 -68 20)*	0.88	**L cingulate gyrus** *(BA 31) (-12 -38 32) (-12 -46 28)*	0.84	**L fusiform gyrus** *(BA 37) (-46 -58 -16)*	0.84
L caudate nucleus *(-12 18 0)*	0.81	**R inferior frontal gyrus** *(BA 45) (50 14 20)*	0.83	**R fusiform gyrus** *(BA 20) (40 -18 -24)*	0.81	**L cerebellum** *(-44 -64 -20)*	0.84
L cerebellum *(-42 -82 -20)*	0.81	**L middle occipital gyrus** *(BA 19) (-46 -80 4)*	0.80	**R cingulate gyrus** *(BA 24) (2 -22 36)*	0.80		
R inferior frontal gyrus *(BA 45/46) (32 38 8) (48 36 4) (38 40 4)*	0.80			**R amygdala** *(24 -4 -16)*	0.79		

BA=Brodmann's area
L=left, R=right

2) **CRMT**

a) *CRMT-READ and Percent Correct*: In the CHI patients, only negative correlations between normalized CRMT activation and performance were found. They were localized to the temporal lobes bilaterally, including the right hippocampus (Figure 20), left mammillary body, left inferior parietal lobule, right cerebellum, and right precentral gyrus. In the control group, positive correlations with performance were found in the right hippocampus (Figure 20), bilateral occipital areas, right cingulate cortex, and left middle temporal cortex. Negative correlations, on the other hand were found in left temporal areas including the hippocampus (Figure 21), amygdala, and insular cortex, as well as in right superior frontal cortex, right anterior cingulate, and right midbrain areas (Figure 22, Table 17).

Correlations between rCBF and cognitive functioning in CHI patients

Voxel-by-voxel correlational analyses between normalized rCBF activation and current cognitive functioning in the CHI patients revealed the following:

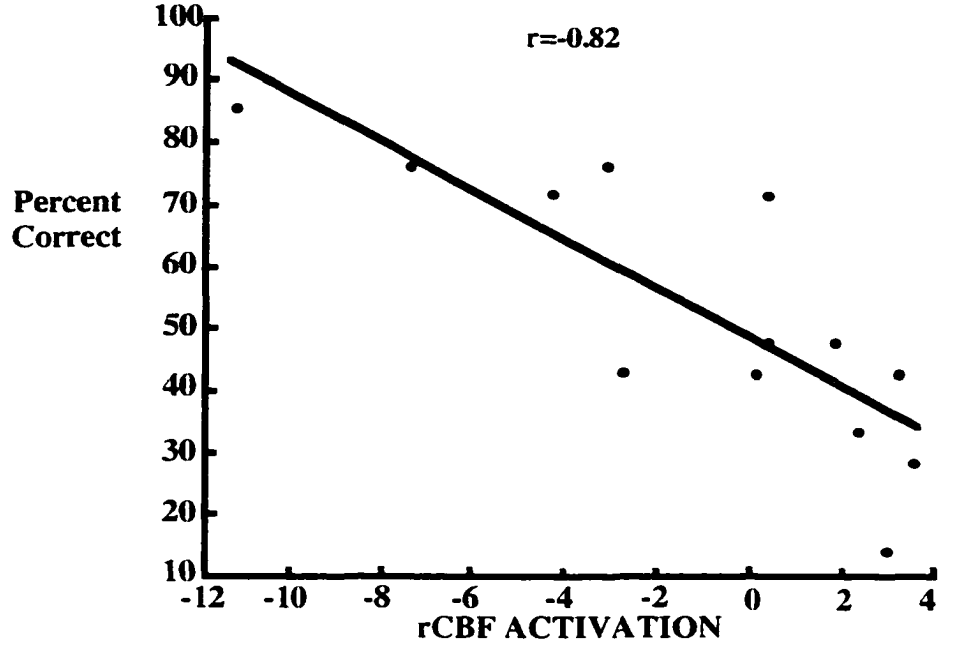
1) *WCST Activation and Current Cognitive Functioning*: No positive correlations between normalized WCST activation and current cognitive functioning in the CHI patients were found, whereas negative correlations were found in bilateral posterior cingulate cortex and right precentral gyrus (Figure 23, Table 18).

2) *CRMT Activation and Current Cognitive Functioning*: Positive correlations between CRMT activation and current cognitive functioning in the CHI patients were

Figure 20: Right hippocampal activation (task-control) in the Cued Recall Memory Test (CRMT) and performance. *Top.* In the closed head injury (CHI) patients, a significant negative correlation between regional cerebral blood flow (rCBF) activation in the right hippocampus (Talairach coordinates 26 -36 0) and CRMT performance (percent correct) was found ($r=-0.82$, $p \leq 0.001$). *Bottom.* In contrast, in the normal control group, a significant *positive* correlation was found between right hippocampal activation (Talairach coordinates 32 -26 -8) and CRMT performance ($r=0.79$, $p \leq 0.001$).

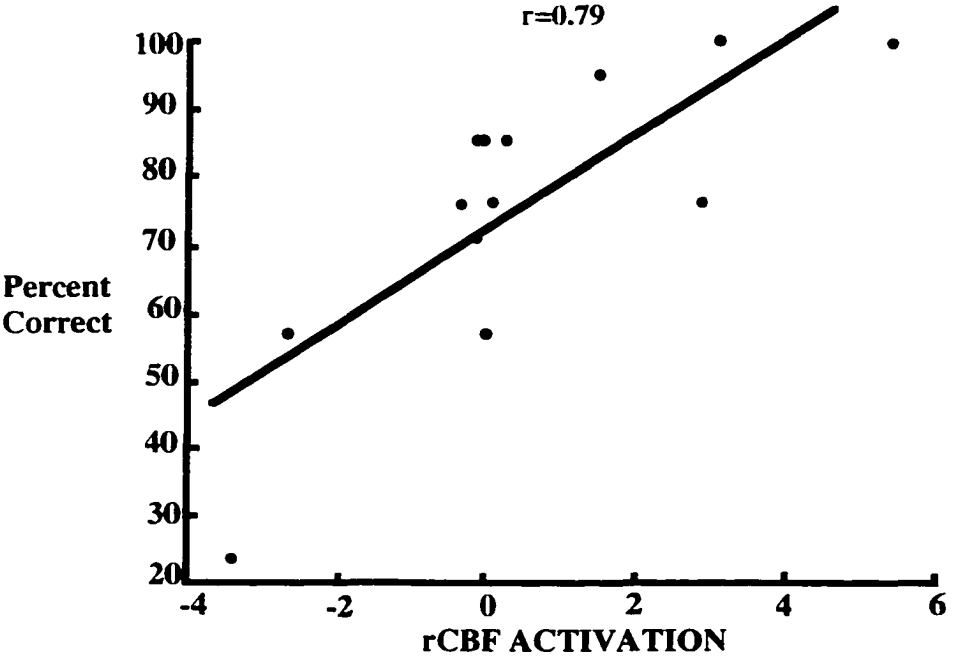
RIGHT HIPPOCAMPUS & CRMT PERFORMANCE

CHI PATIENTS



(Talairach 26 -36 0)

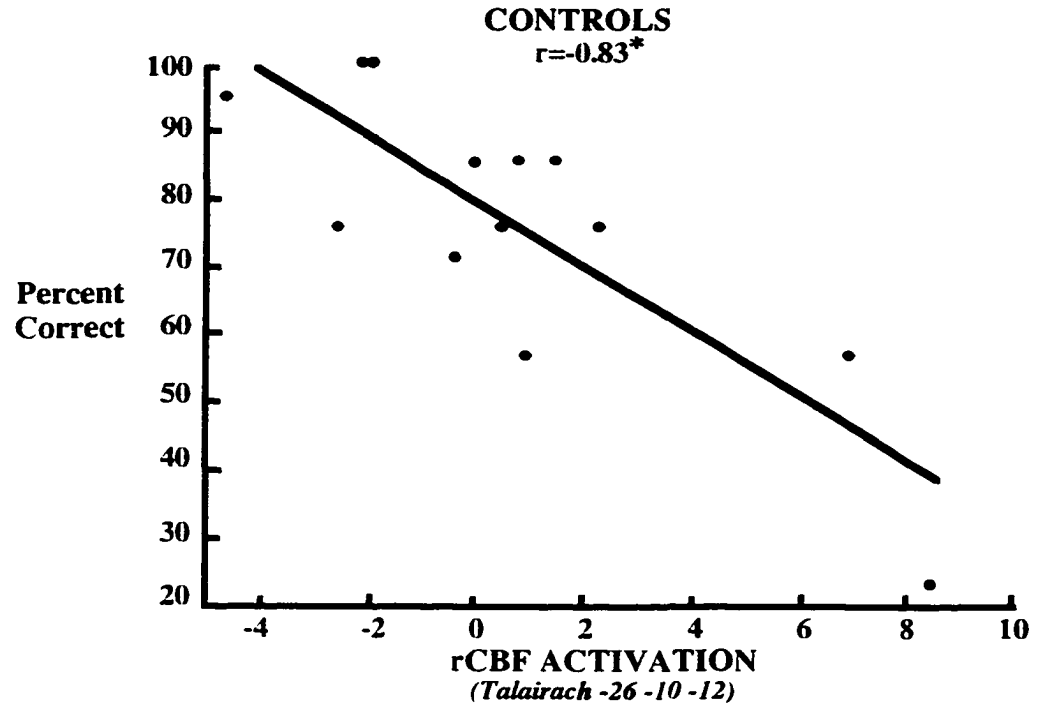
CONTROLS



(Talairach 32 -26 -8)

Figure 21: Left hippocampal activation (task-control) in the Cued Recall Memory Test (CRMT) and performance. *Top.* In the normal control group, a significant *negative* correlation was found between regional cerebral blood flow (rCBF) activation in the left hippocampus (Talairach coordinates -26 -10 -12) and CRMT performance (percent correct) ($r=-0.83$, $*p \leq 0.001$). *Bottom.* In the closed head injury (CHI) patients, no significant correlation was found between rCBF activation in the left hippocampus (Talairach coordinates -26 -10 -12) and CRMT performance ($r=0.06$, $p=0.85$).

LEFT HIPPOCAMPUS & CRMT PERFORMANCE



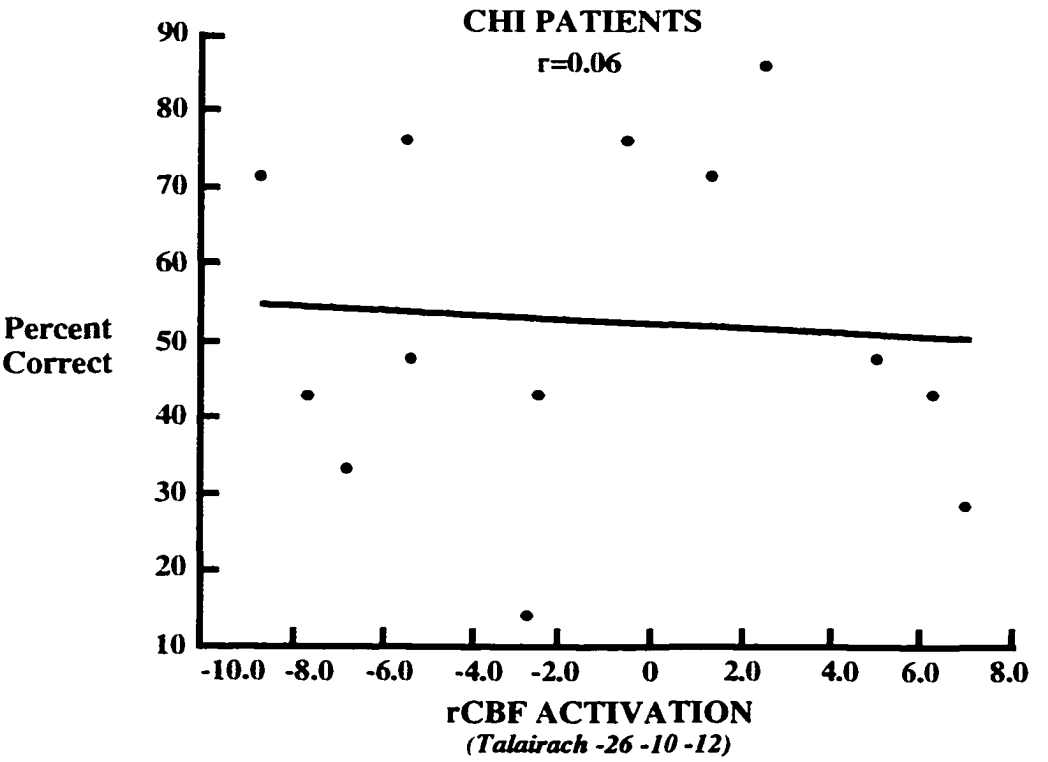


Figure 22: Maps of correlations between activation (task-control) in the Cued Recall Memory Test (CRMT) and percent correct. The left side of the brain is at the left of the figure. Slice numbers correspond to the z coordinate (i.e., the number of mm above or below the intercommissural line) from the Talairach atlas presented for local maxima in Table 17. *Top.* In the closed head injury (CHI) patients, a negative correlation between regional cerebral blood flow (rCBF) activation in the right hippocampus (slice 0) and CRMT performance was found ($r=-0.82$, $p \leq 0.001$). *(Negative correlations were also found in the left temporal cortex [slice -4], the right cerebellum [slice -8], and the left inferior parietal lobule [slice +24]). Bottom.* In contrast, a significant *positive* relationship between right hippocampal activation (slice -8) and CRMT performance was found in the control group ($r=0.79$, $p \leq 0.001$). Furthermore, a significant *negative* correlation between *left* hippocampal activation (slice -12) and CRMT performance was revealed in the control group. *(Also shown are positive correlations in left occipital cortex [slice +12] and negative correlations in cingulate cortex [slice +8]).*

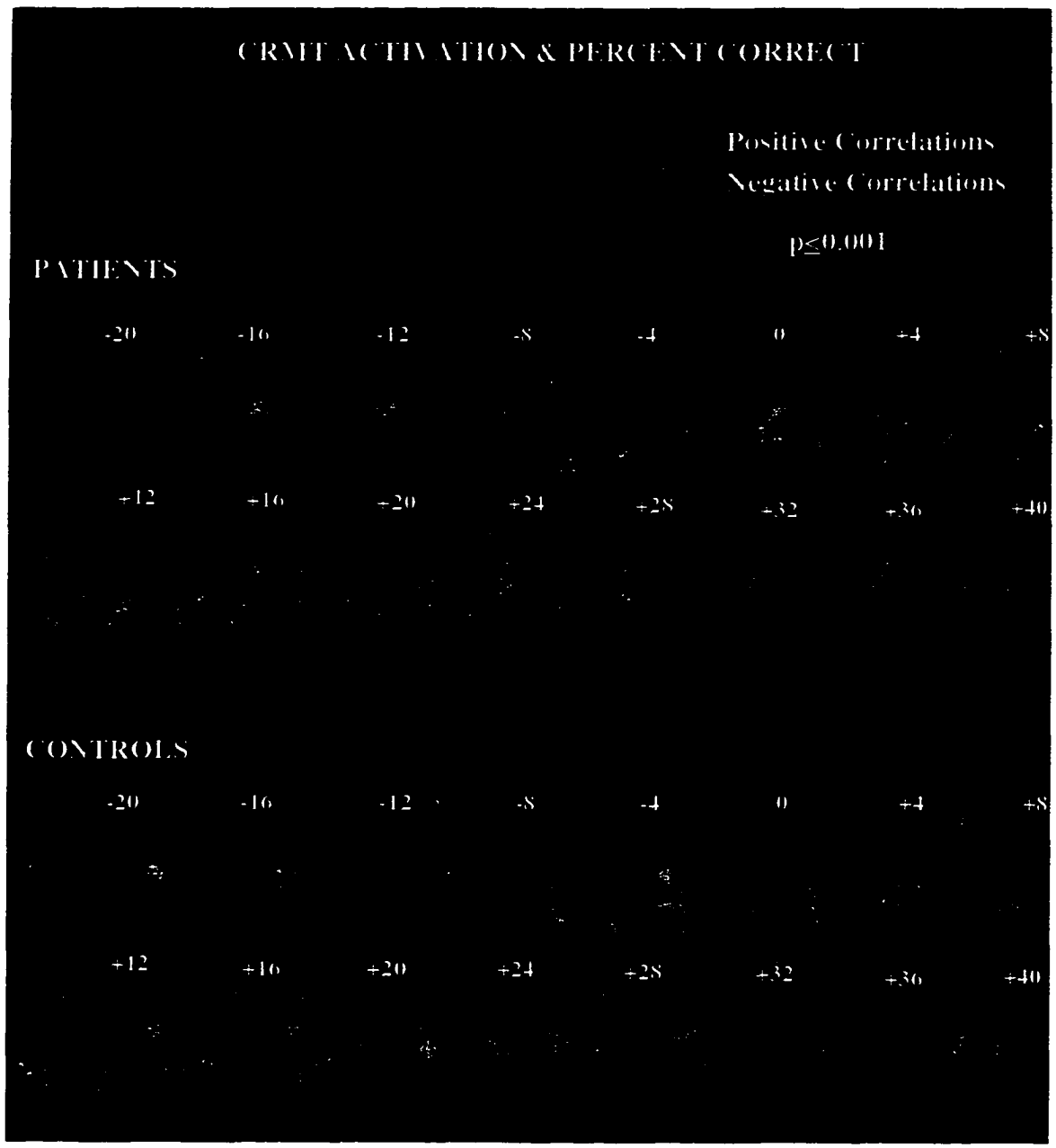

CRMT ACTIVATION & PERCENT CORRECT
Positive Correlations
Negative Correlations
p≤0.001
PATIENTS
-20
-16
-12
-8
-4
0
+4
+8
+12
+16
+20
+24
+28
+32
+36
+40
CONTROLS
-20
-16
-12
-8
-4
0
+4
+8
+12
+16
+20
+24
+28
+32
+36
+40

Table 17. Maxima from voxel-wise correlations between Cued Recall Memory Test activation (task-control) and percent correct ($p \leq 0.001$).

Closed Head Injury Patients			Control Subjects			
Positive	Negative	r	Positive	r	Negative	r
None significant at $p \leq 0.001$	**L superior temporal g.** *(BA 21/22)* *(-50 -4 -8)* *(-56 -58 4)*	0.92	**L middle occipital g.** *(BA 18/19)* *(-18 -94 16)*	0.89	**R cingulate g.** *(BA 32)* *(2 46 8)*	0.90
	L inferior parietal lobule *(BA 40)* *(-56 -32 24)*	0.91	**L middle temporal g.** *(BA 39)* *(-46 -74 28)*	0.85	**L hippocampus** *(BA 28)* *(-26 -10 -12)*	0.83
	R cerebellum *(12 -64 -8)* *(16 -54 -8)*	0.86	**R cingulate g.** *(BA 24/32)* *(24 -10 36)* *(20 -28 36)* *(22 -38 -10)*	0.85	**R midbrain** *(8 -18 -20)* *(16 -22 -20)*	0.82
	R superior temporal g. *(BA 22)* *(46 6 -4)* *(58 -40 8)*	0.85	**R cuneus** *(BA 19)* *(14 -84 36)*	0.85	**R superior frontal g.** *(BA 9)* *(12 50 32)*	0.81
	L mammillary body *(-6 -10 -8)*	0.84	**L cuneus** *(BA 19)* *(-26 -78 36)* *(-12 -78 36)* *(-30 -84 32)*	0.82	**L superior temporal g.** *(BA 22)* *(-52 -6 4)*	0.81
	R middle temporal g. *(BA 22)* *(40 -36 4)*	0.83	**R hippocampus** (BA 28) *(32 -26 -8)*	0.79	**L insular cortex** *(-42 -16 12)* *(-38 -10 12)*	0.80
	R precentral g. *(BA 6)* *(32 -2 36)* *(24 -4 36)*	0.82				
	R hippocampus *(BA 27)* *(26 -36 0)*	0.82				

BA=Brodmann's area; g.=gyrus; L=left, R=right

Figure 23: Maps of correlations between activation (task-control) and current cognitive functioning. The left side of the brain is at the left of the figure. Slice numbers correspond to the z coordinate (i.e., the number of mm above or below the intercommissural line) from the Talairach atlas presented for local maxima in Table 18. *Top.* Few robust correlations were found between current cognitive functioning in the closed head injury (CHI) patients and activation during the Wisconsin Card Sorting Test (WCST). *Bottom.* For the Cued Recall Memory Test (CRMT), a positive correlation between left hippocampal activation (slice -16) and current cognitive functioning was found in CHI patients ($r=0.80$, $p \leq 0.001$). *(Also shown are positive correlations in the left occipital cortex [slice +28] and negative correlations in left superior temporal cortex [slice +24]).*

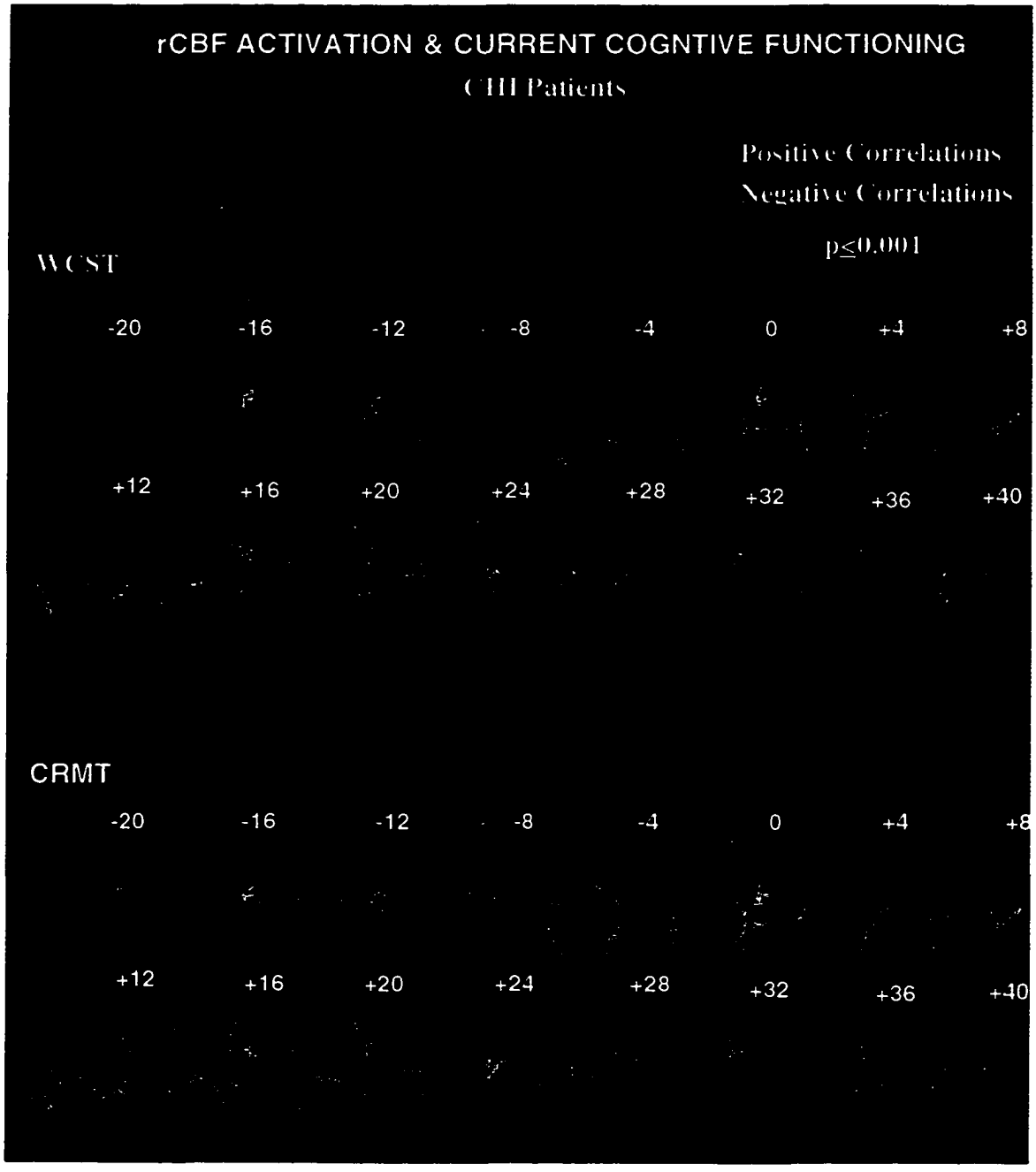

rCBF ACTIVATION & CURRENT COGNTIVE FUNCTIONING
CHI Patients
Positive Correlations
Negative Correlations
p≤0.001
WCST
-20
-16
-12
-8
-4
0
+4
+8
+12
+16
+20
+24
+28
+32
+36
+40
CRMT
-20
-16
-12
-8
-4
0
+4
+8
+12
+16
+20
+24
+28
+32
+36
+40

Table 18. Maxima from voxel-wise correlations between current cognitive functioning and activation (task-control) in closed head injury patients ($p \leq 0.001$).

Wisconsin Card Sorting Test Activation				Cued Recall Memory Test Activation			
Positive	r	Negative	r	Positive	r	Negative	r
None significant at $p \leq 0.001$		**R precentral gyrus** *(BA 6)* *(44 -2 36)*	0.86	**L cuneus** *(BA 18/19)* *(-10 -84 28)* *(-2 -80 20)*	0.87	**L superior temporal gyrus** *(BA 22)* *(-50 -36 20)*	0.90
		L cingulate gyrus *(BA 31)* *(-10 -36 36)*	0.83	**L orbital gyrus** *(BA 19)* *(-38 -80 24)*	0.86	**L inferior parietal lobule** *(BA 40)* *(-58 -32 24)*	0.89
		R cingulate gyrus *(BA 31)* *(20 -62 12)* *(24 -56 12)*	0.80	**L insular cortex** *(-24 -14 20)*	0.84	**L middle temporal gyrus** *(BA 21/37)* *(-54 -56 4)*	0.81
				L hippocampal gyrus *(BA 36)* *(-34 -22 -16)*	0.80	**R superior temporal gyrus** *(BA 22)* *(58 -38 8)*	0.79

L=left, R=right
BA=Brodmann's area

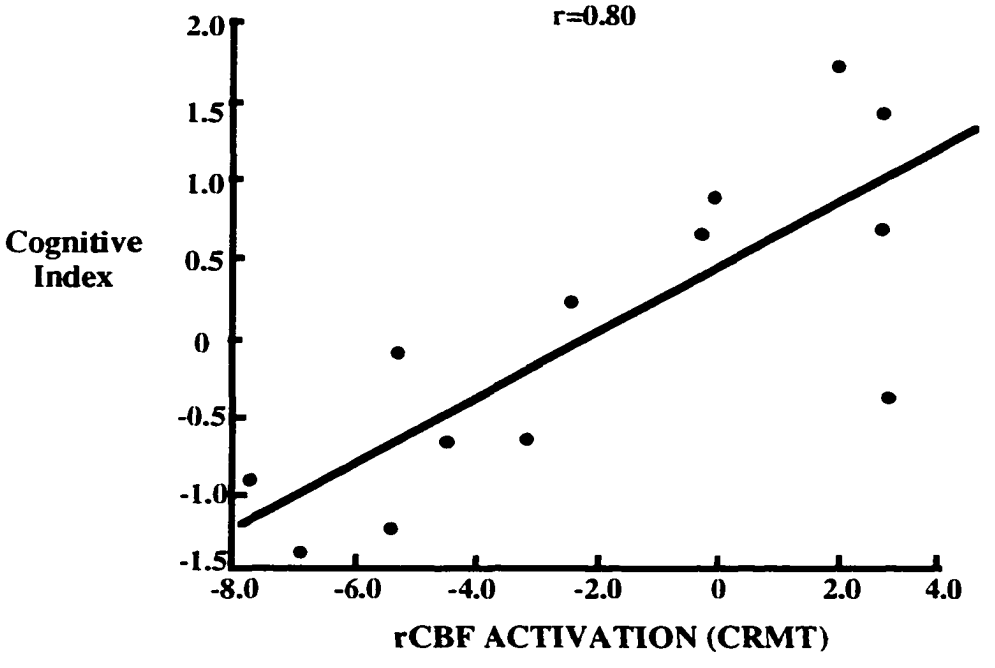
found in the left occipital areas and left temporal cortex including the hippocampus (Figure 24), whereas negative correlations were found in the temporal cortices bilaterally and the left inferior parietal lobule (Figure 23, Table 18).

Regional CBF: ROI Approach

The results of the ROI method were, for the most part, convergent with those of the voxel-wise analyses. It is important to point out, however, that many of the results were either non-significant trends ($1.0 \geq p \geq 0.05$) (Appendices N-S) and/or only found in the individual (i.e., not area weighted) ROIs (Appendices T-Y) (see Discussion).

Figure 24: Left hippocampal activation (task-control) in the Cued Recall Memory Test (CRMT) and current cognitive functioning. In the closed head injury (CHI) patients, a significant positive correlation between regional cerebral blood flow (rCBF) activation in the left hippocampus (Talairach Coordinates -34 -22 -16) during the CRMT and current cognitive functioning was found ($r=0.80$, $p \leq 0.001$).

LEFT HIPPOCAMPUS & CURRENT COGNITIVE FUNCTIONING IN CHI PATIENTS



(Talairach Coordinates -34 -22 -16)

DISCUSSION

This investigation constitutes the first study to use rCBF PET during neuropsychological tests to investigate cognitively-related neurofunctional differences in patients with severe CHI. Comparisons of rCBF patterns between the CHI patients and well-matched healthy controls revealed many robust between-group differences. Given the exploratory and descriptive nature of the study, interpretation of every result would be impractical and imprudent. Instead, emphasis is placed on describing and interpreting general rCBF *patterns*. However, given the importance of the frontal and temporal lobes in the pathophysiological and cognitive sequelae of CHI, more specific results from these structures are also discussed. From this vantage, normalized rCBF differences in the cortex, particularly left prefrontal areas, subcortical structures, anterior cingulate cortex, and the hippocampus[12] were revealed.

RESULTS FROM INDIVIDUAL TASKS

A number of significant differences emerged between the groups when each of the four tasks was viewed separately. Because the rCBF differences were found in both of the cognitive tasks of interest as well as in their sensorimotor control tasks, these results are not thought to relate to the particular cognitive actions involved in

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[12]In light of the limited spatial resolution of the PET data and the relatively small size of the hippocampus, it is difficult to localize blood flow changes in the hippocampus, per se (See page 136 for a discussion of this issue). Therefore, Talairach coordinates defining the "hippocampus" should be more conservatively considered the anterior medial temporal lobe. However, for the sake of brevity and clarity, the region will still be referred to as the hippocampus.

each task but rather are believed to represent general, non-specific sequelae of structural injury.

Relative Cortical Hyperactivity

In general, CHI patients showed relative *hyper*activity in cortical areas in all four tasks considered separately. Taken at face value, this surprising finding is potentially interesting and interpretable as an overactive cortex attempting functional compensation for inefficiencies elsewhere in the brain, particularly in subcortical structures (see below). However, while such overactivity has been described in other clinical populations with cerebral pathology (Weiller, Chollet, Friston, Wise, & Frackowiak, 1993; Cao, Vikingstad, Huttenlocker, Towle, & Levin, 1994; Sabatini et al., 1994; Weder et al., 1994), it was not seen in a study that specifically examined cortical activity following subcortical infarction. In that study, Demeurisse and colleagues (1991) found *decreased* cortical activity, but the fact that the patients in their study were elderly and acutely injured might have limited the expression of functional compensation and might account for these discrepant results. Thus, support from the literature for the possibility that the present finding of cortical hyperactivity reflects a long-term compensatory response to cerebral injury is equivocal. Moreover, an important methodological consideration (discussed next) suggests caution with this result in the present study.

In light of the rCBF decreases in other brain areas in this CHI sample (see below), increased cortical activity in the patients may be an artifact of the process of

rCBF normalization (i.e., expressing rCBF in a form that takes into account global CBF). As a result of a trend toward reduced global flow on the basis of true rCBF decreases in some brain regions, artificially *increased* rCBF can result in other brain areas when normalization is used. To help determine whether this was the case, absolute (i.e., raw) data were examined. These analyses revealed cortical increases in the CHI patients compared to controls in only one of the four tasks (i.e., the WCSTc), suggesting that the relative cortical hyperactivity may not reflect true elevations in rCBF. Given these technical and theoretical problems, the finding of cortical hyperactivity in this CHI sample remains equivocal and requires further study.

Areas of Relative Hypoactivity

Compared to controls, CHI patients generally showed diminished relative rCBF in subcortical structures and in anterior cingulate cortex in each task considered separately. In an analogous manner to the relative hyperactivity discussed above, it is possible that relative hypoactivity appeared in some structures after normalization for global flow because of increased metabolic demands in other brain areas rather than because of truly decreased metabolic demand in these structures. However, as noted above, the relative rCBF increases in the CHI sample were equivocal. Furthermore, unlike the rCBF increases, the relative rCBF decreases were confirmed by the absolute (i.e., unnormalized) data in all four tasks. This is strong evidence for a neurophysiological rather than an artifactual basis for diminished subcortical and anterior cingulate rCBF in CHI patients.

Subcortical regions

Hypoactivity in subcortical regions, including the basal ganglia and thalamus, was found in the CHI patients relative to controls in each of the four tasks considered separately. Given that these structures, particularly the thalamus, are major relay stations for cortical inputs and outputs, subcortical underactivity may reflect damage to or deafferentation/deefferentation of these regions. This interpretation is supported by the high incidence of white matter and periventricular injury in this CHI sample (Table 7). Furthermore, hypoactivity of the thalamus is consistent with findings from SPECT studies conducted during rest in severely injured CHI patients (Goldenberg et al., 1992; Prayer et al., 1993).

Anterior cingulate

Diminished activity in the CHI patients was also found in the anterior cingulate cortex during all tasks considered separately as well as during the CRMT when baseline physiology was taken into account. Previous PET studies have implicated a role for the anterior cingulate in tasks requiring attention, but the exact nature of the functional changes in relation to attentional processes has not been clearly established (i.e., whether attention relates to increases or decreases in cingulate activity) (Pardo et al., 1990; Deary et al., 1994). Although speculative, the consistently diminished activity of the anterior cingulate in this sample of CHI patients may relate to attentional impairments. Although performance on measures of attention during a brief neuropsychological evaluation was tremendously variable across these CHI patients, notable deficits in attention per se were not evident as a group (i.e., the

average scores on two tests of attention fell in the average range). However, given the pervasiveness of attentional deficits following CHI (Levin et al., 1988), it is believed that a more thorough examination of attentional processes in this severely-injured CHI sample would have revealed deficits in attention. That diminished activity in the anterior cingulate cortex relates to compromised attentional processes in these CHI patients is supported by the finding in the WCST paradigm that those patients who activated the anterior cingulate more tended to be more accurate and have fewer perseverative errors in the regional analyses (see Appendices P-Q).

RESULTS FROM ACTIVATION PAIRS

Since the above results were found in both the cognitive tasks and their sensorimotor control tasks, these findings were eliminated (i.e,. "subtracted out") when rCBF in the cognitive task of interest was viewed against rCBF in the control task (i.e., activation). However, a number of different findings emerged when the cognitive tasks were viewed in this manner. Significant between-group activation differences (i.e., rCBF in the task relative to its sensorimotor control) in both task paradigms consisted almost exclusively of *increases* in CHI patients compared to normal controls. Because pathophysiological alterations in the CHI patients existed above and beyond those found during the control task, these results were considered specifically linked to the cognitive task of interest. Moreover, unlike the results in the individual tasks described earlier, these increases in activation (i.e., task minus control) are unlikely to be an artifact of the normalization process. Because the same normalization process is

used on both tasks of the subtraction pair, any resulting artifacts would be consistent across task conditions and would be removed in direct linear contrasts performed between the two groups (see Fox et al., 1988).

Since structurally damaged areas typically show diminished vascularization due to tissue loss, the CHI patients in this study, a group with documented structural pathology, were expected to show many areas of decreased rCBF activation (i.e., activation deficits) compared to control subjects. The finding of *increased* rCBF activation in the CHI patients relative to controls was thus surprising. One explanation for the lack of activation deficits in the CHI patients as a group may relate to the anatomical heterogeneity of structural lesions across patients, which likely caused individual deficits to wash out in a group analysis. This may explain the apparent discrepancy between the results of the present group study, in which there was prefrontal *over*activation, and the single subject pilot data presented earlier (see Introduction), in which there was prefrontal *under*activation. The latter study (Kirkby et al., in press) offered a unique opportunity to investigate an *individual* (i.e., an injured monozygotic twin relative to his uninjured co-twin). This individual study revealed not only activation increases, which (as shall be seen below) were shared by the group, but also unique activation deficits in this CHI patient. In contrast to the lack of underactivations in the CHI group, a number of areas of overactivation were seen in the group analysis. The fact that these overactivations appeared in the group as a whole suggests that this pattern may represent a general response to brain compromise that was shared by the majority of patients in this study.

Prefrontal Cortex

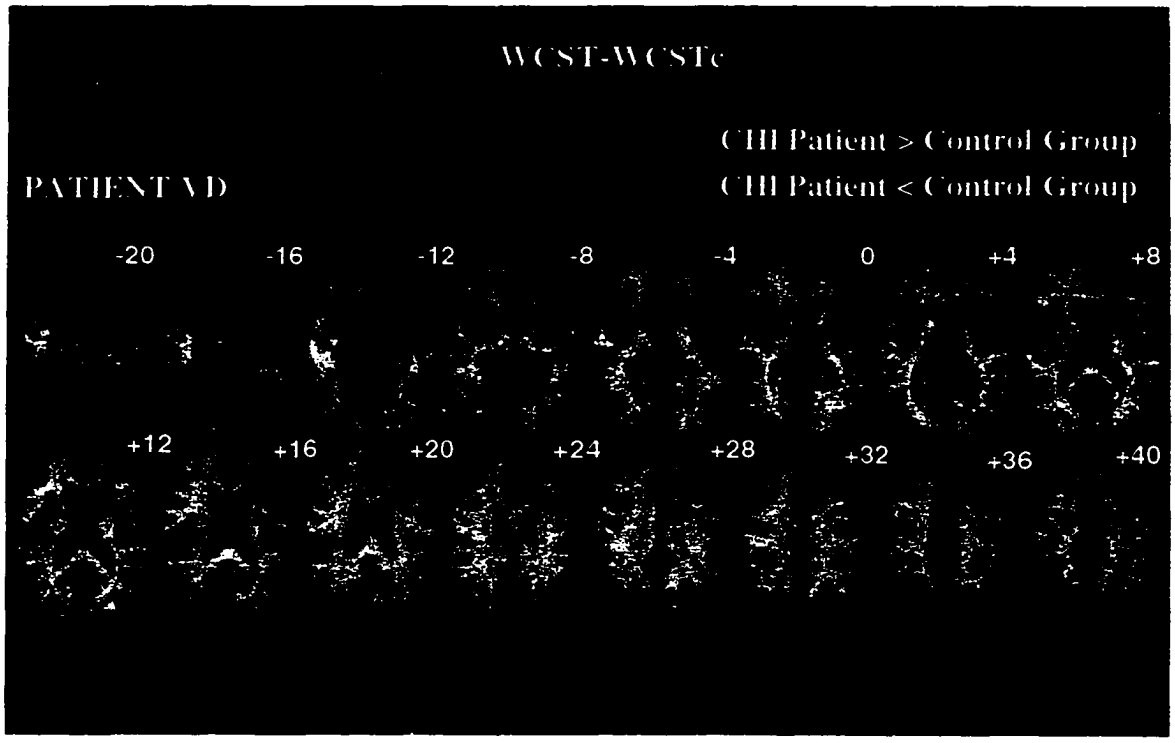
For WCST activation (i.e., task minus control), CHI patients showed hyperactivity in portions of the left dorsolateral prefrontal cortex. Because prefrontal dysfunction, either through direct injury to prefrontal cortex or through disruption of prefrontal afferent or efferents was thought to be likely in this sample of CHI patients, elevations in prefrontal cortical functioning were unexpected. Overactivation of parts of left prefrontal cortex during the WCST, a test of prefrontal lobe functioning, by the CHI patients relative to controls may reflect compensation (i.e., greater metabolic demand with greater functional output) for inefficiencies in other brain areas. Alternatively, these prefrontal cortical increases may merely represent metabolic inefficiency (i.e., greater metabolic demand with unchanged or even lessened functional output) possibly due to disrupted afferents and efferents from subcortical structures. Given that the CHI patients performed similarly (albeit slightly, but not significantly, lower) to controls on this test, the compensatory rather than inefficiency explanation may be more likely. The notion of compensatory rCBF changes is supported by functional brain imaging studies of patients with ischemic lesions (Weiller et al., 1993; Weder et al., 1994), tumor (Sabatini et al., 1994), and perinatal brain injury (Cao et al., 1994), in whom recovery of sensorimotor functions was associated with increased activation of ipsilateral pathways and recruitment of additional sensorimotor areas.

Increased activation in the prefrontal cortex, on the other hand, is inconsistent with the findings from the case study reported earlier (Kirkby et al., in press) in which

decreases in parts of left prefrontal cortex were found in the CHI co-twin. As suggested previously, this discrepancy may be accounted for by differences in group versus individual analyses. In group analyses, anatomically heterogeneous individual deficits may be obscured, whereas increases, which may represent a general response to brain compromise, can be seen. In contrast, single subject methodology allows both individual changes as well as some, but not all, of the group response to be revealed. In other words, it is likely that, in addition to the shared areas of prefrontal overactivation, many of the patients in this study had areas of prefrontal functional deficits as a direct result of structural injury that were not revealed by the group analysis because they occurred in different areas of the prefrontal cortex in different patients. This is illustrated in the preliminary single case analysis discussed below and shown in Figure 25.

Increases in left prefrontal cortical activation in CHI patients relative to controls included Broca's area, a structure involved in speech production (Broca, 1861). This was surprising given that overt speech was not required in either the WCST or the control task. However, a recent PET study has shown that subvocal speech was associated with increased activity in Broca's area in normal subjects (McGuire, Silbersweig, Murray, David, Frackowiak, & Frith, in press). Given that subjects in the present study had to remember a changing matching principle during the WCST, it is plausible that this sample of CHI patients, who have relatively impaired memory processes (see Figure 11), might have been subvocalizing the current matching principle to aid memory. Differences in cognitive strategy, therefore, may

Figure 25: Single subject analysis of a closed head injury patient. Using Statistical Parametric Mapping, normalized regional cerebral blood flow activation data (i.e., task-control) of a single subject (Patient VD) during the Wisconsin Card Sorting Test is compared to a control group of 13 healthy subjects. As in the group analysis and the monozygotic twin with CHI, areas of significant activation in Patient VD were found in the left hippocampus (slice -4). Other significant areas of increase were found in the left superior temporal cortex (slice -12) and the left middle frontal gyrus (slice 0). Large areas of significant rCBF deficit were also revealed. These were localized to the right temporal cortex (e.g., slice +16), the right medial frontal gyrus (slice -4), and the posterior cingulate cortex (+40).


WCST-WCSTc
CHI Patient > Control Group
CHI Patient < Control Group
PATIENT VD
-20
-16
-12
-8
-4
0
+4
+8
+12
+16
+20
+24
+28
+32
+36
+40

partially explain the increased left prefrontal activation in CHI patients, thereby raising the possibility that behavioral compensation plays a role in the long-term neurophysiological changes uncovered by this study.

Hippocampus

WCST activation

During the WCST, a task during which normal subjects (including those in this study) tend to suppress activity in the hippocampus, CHI patients showed greater activation in the left hippocampus than normal controls. This is consistent with the finding in the case study of the CHI co-twin reported earlier (Kirkby et al., in press) (see Introduction). Hyperactivation of the hippocampus has also been found in normal subjects with poor performance on the WCST and in patients with schizophrenia (Weinberger, Berman, Ostrem, Abi-Dargham, & Torrey, 1993), a group that, as a whole, performs poorly on this task. Furthermore, hyperactivation of the hippocampus during the WCST has been found in a cohort of normal aging subjects who performed poorly on the task (Esposito et al., 1994). Although the trend toward poorer task performance by this sample of CHI patients compared to controls did not reach significance, activation of the right hippocampus in the CHI patients was associated with fewer correct responses and a greater number of perseverative errors.

Given the role of the hippocampus in the maintenance and updating of long-term memory (Squire, 1992; Bechara, Tranel, Damasio, Adolphs, Rockland, & Damasio, 1995), these results suggest that the CHI patients may be using a less

effective memory mechanism (i.e., long-term) to solve a task better served by working (i.e., short-term) memory neural systems. Because left hippocampal increases during this task are not unique to CHI patients but also have been found in other populations with poor task performance, these results also suggest that overactivation in the hippocampus during the WCST may be an attempt at compensation for, or a general strategy in the face of, brain compromise. However, as in the case study reported earlier (Kirkby et al., in press), it cannot be ruled out that this result reflects disinhibition of the hippocampus due to loss of frontal input.

CRMT activation

In light of scant data in other cohorts of normal populations and no data in patients during the CRMT, the results from this task are more difficult to interpret. Recalling words in the CRMT has been found to activate the hippocampus relative to a baseline word association task in normal subjects (Blaxton et al., submitted). However, hippocampal functioning may be more involved in *learning* rather than *recalling* information. Since rCBF was measured during the recall rather than the learning phase of this task, important alterations in hippocampal functioning, therefore, might have been missed. Despite this methodological consideration, however, several interesting findings in the hippocampus were revealed in the CHI patients when recalling words in the CRMT compared to a reading control task. CHI patients showed less activation in the left hippocampus than control subjects. However, because a similar decrease in left hippocampal activity was also found in the control condition (reading), differences in left hippocampal activation (task minus control)

failed to emerge. Nevertheless, a number of behavioral/neurophysiological correlations were seen in the hippocampus. In the normal controls, left hippocampal activation was associated with *poor* CRMT performance. In contrast, in the CHI patients, left hippocampal activation during this task was associated with relatively *higher* general cognitive functioning (i.e., the correlation between CRMT rCBF activation and the cognitive index). Correlations in different directions in the two groups were also seen in the right hippocampus. In the control subjects, a positive correlation between right hippocampal activity and CRMT performance was found, whereas a negative correlation was found in CHI patients. Although the meaning of differences in right and left hippocampal activity within a group were not explored in this study, the consistently *opposite* correlation between cognition and hippocampal activity in CHI patients compared to controls suggests a disruption in hippocampal functioning in CHI patients.

The results of both of these pairs of tasks suggest that the functional state of the hippocampus has important implications for cognition in CHI patients. It is noteworthy that on the WCST, a frontal lobe task in which hippocampal activation has not been found necessary for successful performance (Berman et al., 1995), CHI patients performed similarly to controls despite atypical hippocampal increases but in the context of increased prefrontal cortical activity. In contrast, on the CRMT, a task in which the importance of hippocampal activity has been implicated, CHI patients performed dramatically worse than controls in the context of atypical functional changes in the hippocampus. The results suggest that the behavioral consequences of

functional disorganization of hippocampal functioning may be context-dependent. The finding of a high incidence of neuropathological changes in the hippocampus from post-mortem studies of CHI patients (Kotapka et al., 1992) suggests a plausible neuroanatomical substrate for the hippocampal neurofunctional alterations found in the present study.

LIMITATIONS

While functional brain imaging techniques have tremendous potential power for examining clinical populations, the results of any PET study must be viewed in light of the numerous confounding variables inherent in the technique and those specific to studies of patient populations. These variables, which may contribute to between-group differences, or the lack thereof, are addressed in the following sections.

Subject Attributes

Anxiety

Situational anxiety levels have been shown to influence rCBF levels (Naveteur, Roy, Ovelac, & Steinling, 1992). While the exact relationship between brain activity and anxiety remains unclear (Mathew & Wilson, 1990), the possibility therefore exists that rCBF differences between the two groups in this study were attributable to group differences in anxiety levels. However, physiological indicators of anxiety (i.e., decreased pCO_2 levels in arterial blood from hyperventilation) were not significantly different between patients and controls for any of the tasks (Appendix M) nor were

behavioral signs of anxiety informally judged to be different between the groups. Therefore, the effects of anxiety on between-group differences in rCBF patterns in this study, while impossible to conclusively rule out, were thought to be minimal.

Depression

PET studies have shown that severe depression can affect rCBF patterns (e.g., Dolan, Bench, Brown, Scott, Friston, & Frackowiak, 1992). Given the high prevalence of depression reported in CHI patients (Jorge, Robinson, Arndt, Starkstein, Forrester, & Geister, 1993), differences in mood between patients and controls might have contributed to between-group rCBF differences. However, in this sample of CHI patients, only a minority of the patients (33%) were significantly depressed based on objective measurement and none were undergoing pharmacological treatment for depression. Furthermore, patients appeared highly motivated (e.g., willingly endured arterial puncture and exposure to radioactivity, travelled from out-of-state to participate), a characteristic not generally found in severely depressed patients. Taken as a whole, these observations suggest that a major mood disturbance did not dominate the clinical picture of the patients at the time of the PET scan. Finally, the fact that the most commonly reported finding in patients with major depression is of *decreased* activity in frontal and temporal cortices suggests that depression was not responsible for, and in fact would serve to attenuate, the finding of *increased* rCBF activation in left prefrontal cortex during the WCST in patients compared to controls in this study.

Education

Although statistical significance was not reached, there was a tendency for the controls to be more educated than the CHI patients. Therefore, it is possible that educational differences rather than the impact of CHI on cognitive status could have accounted for between-group performance differences and thus for differences in rCBF patterns. However, when a group includes subjects afflicted with a disorder having clinical onset during or prior to formal schooling as in this study, the SES of one or both parents has been considered a more reliable indicator of general intellectual ability than education (Saykin et al., 1991). Based on the HHI, there were no differences in SES of either parent between the CHI patients and normal controls in this study. Therefore, differences in education did not appear to reflect innate differences in intellectual ability between the groups, and are, thus, unlikely to have been a direct cause of performance and rCBF group differences.

Patient heterogeneity

An important limitation of this investigation, as with most studies of CHI, is the heterogeneity of the patient sample, which may have caused the group findings to be lessened. Although patient heterogeneity in this study was thought to be minimized because of the stringent inclusion criteria employed (e.g., incurred injury as an adult, unmedicated, severe injury), lesion sites across patients were highly variable. Given this neuroanatomical heterogeneity, the group analysis might have obscured individual alterations, particularly rCBF deficits related to areas of injury. On the other hand, if rCBF increases represent a general response to brain compromise, the neuroanatomical

variability in the group might not have washed out individual rCBF increases. This is supported by the fact that comparison of rCBF activation data between the groups was largely dominated by areas of rCBF increase in the CHI patients with very few areas of rCBF deficit.

Control group characteristics

To rule out the possibility that the findings of this study were due to comparing the patients to an atypical control group, the performance and rCBF patterns of the control group were compared to those of a well-studied cohort of 40 normal subjects during performance of the WCST (Berman et al., 1995). The controls used in the present study performed similarly to the large cohort (79 versus 80 for percent correct and 11 versus 10 for percent perseverative errors, respectively) and showed significant increases in rCBF compared to baseline in the three brain regions shown by the large cohort and others to be reliably activated during performance of the WCST-- the dorsolateral prefrontal cortex, the inferior parietal lobule, and the posterior portion of the inferior temporal cortex (Berman et al., 1995). These results suggest, therefore, that the control sample employed in this study was adequately representative of the normal population.

Methodological Issues

Control tasks

Given the use of the paired task subtraction method (see Methods), it is important to note that the control tasks for the WCST and CRMT, although reasonably

well equated, were not ideally matched to their respective experimental task in all sensorimotor components or in difficulty and effort involved in performance of the task. However, the nature of the control tasks, and even the validity of the subtraction method per se, were not critical to the interpretation of the results of the between-group analyses in the present study because the purpose of the activation paradigm was *not* to define the neural systems that are normally involved in performing a task (in which case the nature of the control task *has* proven critical) (Bench et al., 1993). Rather, the activation paradigm was used to provoke the neural circuitry of interest, a tactic that has been thought to reveal subtle perfusion aberrations between groups that may not manifest in unprovoked circumstances (Berman & Weinberger, 1986). Given the latter purpose, the control task, therefore, served as a baseline upon which to compare rCBF changes in the condition of interest rather than as a way of isolating the neurophysiological components of performing the task. Regardless of the nature of the cognitive probes and control tasks utilized, significant differences in rCBF between the CHI patients and control subjects were found and therefore, in theory, reflect neurophysiological differences between the two groups.

Performance and methodological differences

Based on studies indicating significant memory difficulties in patients with severe CHI, a large discrepancy in performance on the CRMT between controls and patients was predicted. Because task proficiency has been associated with brain activity (Haier, Siegel, MacLachlan, Soderling, Lottenberg, & Buchsbaum, 1992), group differences in rCBF may relate to inferior performance per se rather than to a

fundamental neurophysiological change in one of the groups. One method of dealing with predicted performance discrepancies has been to artificially equate performance by methodological intervention (e.g., making the task easier for one group). However, any differences in rCBF between the two groups may then relate to the fact that they were not performing *exactly* the same task and not performing it the same way rather than to a fundamental neurophysiological difference between the two groups. Vis-a-vis an unresolved debate about which difference (i.e., performance or methodological) most hinders data interpretation, an attempt was made to equate potentially dramatic performance differences on the CRMT via a minor methodological manipulation (i.e., providing the CHI patients with an additional repetition of the study list). In spite of this methodological discrepancy, however, the CHI subjects performed significantly worse than the controls. Both the performance and the methodological differences limit the interpretation of activation differences between the groups on the CRMT.

Image Processing

Despite the fact that the methods used in this study are state-of-the-art and have become the standard world wide, there are several limitations. It is important to note that, with the exception of multiple comparisons (reviewed in the next section), all of the problems mentioned below would have lead to false negative, rather than false positive, results. Also, the fact that the voxel-wise and regional analyses are subject to different limitations as discussed below helps to explain any inconsistencies in the results between the two methods.

Voxel-wise approach

A limitation of the voxel-wise procedure involves the stereotaxic spatial transformation process used by SPM to configure all brains into a common shape and space. This process may not adequately correct for variability in brain shape or gyral patterns or in functional variability (i.e., differences in the location of the neurophysiological substrate subserving a particular function) between subjects. Voxel-by-voxel intersubject averaging may thus produce increased variance in the data that may obscure significant changes in within-group activation analyses (Steinmetz & Seitz, 1991). For between-group analyses of *normal* subjects, the issue has been controlled for because both groups, regardless of the inaccuracies in the spatial normalization process, have been treated equally. However, when one group is suspected to have more anatomical variability than another group, such as in the CHI sample in the present study, intersubject averaging following spatial normalization may result in more variable data in the anatomically-variable group and may thus account for the lack of between-group differences. To help minimize intersubject anatomical variability in this study, a large smoothing filter was passed over the rCBF data prior to the voxel-by-voxel analyses. Additionally, individually determined MRI-based ROI templates, which are based on the unique neuroanatomy of each subject, were used as a conjoint and confirmatory method.

Another limitation of the voxel-wise approach involves the stereotaxic atlas used by SPM to define brain neuroanatomy. Given that the Talairach atlas was based on a small standardization sample, the Talairach brain may not adequately represent

typical brain morphology. Therefore, anatomical localization of functional changes using SPM may be inaccurate. However, since the SPM results of focus in this study were largely confirmed by the ROI method, which utilized an independent method of anatomical localization, localization of blood flow changes in the present investigation was considered reasonably accurate.

An additional problem of the voxel-wise approach involves the limited spatial resolution of the images in the SPM analyses (12-20 mm after spatial filtering). When functional assessments are made of relatively small brain structures (i.e., those less than two times the spatial resolution of the images), partial voluming effects[13] can diminish the accuracy of brain activity measurements. For the results of the present study, the effect of partial voluming is particularly relevant for blood flow measurements in the hippocampus, a small region of the anterior medial temporal lobes. However, given that results for the hippocampus from the ROI method, an approach that used essentially unfiltered data (6-6.5 mm resolution), were largely convergent with those from SPM analyses, the functional measurements in the hippocampus were thought to be valid. In light of the problems of anatomical localization and partial voluming described above, however, the functional measurements in this structure may be more conservatively considered to reflect activity in the anterior medial temporal lobe rather than the hippocampus, per se.

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[13]Partial voluming refers to the fact that measurements from a structure smaller than the spatial resolution of the scanner will also contain radioactivity from surrounding structures. Depending on whether surrounding structures have high or low levels of radioactivity, measurements of radioactivity in the structure of interest will be overestimated or underestimated, respectively.

ROI approach

The main limitation of the ROI approach is the subjectivity of region drawing. Due to the difficulty in consistently and reliably identifying anatomy (across slices of the same individual or between two individuals), a particular brain area might not have been accurately and identically localized across all subjects. Another problem with the ROI approach involves the large spatial extent, as compared to a voxel-based approach, encompassed by a region. The inclusion of functionally heterogeneous brain areas, which becomes more probable the larger the region, might have obscured significance when there was functional change in only a portion of the structure. Averaging of rCBF values for a particular structure across several brain slices, which was performed to reduce the number of dependent variables, might have similarly obscured a significant result.

Statistical Analysis

Multiple comparisons

Given the nature of PET (i.e., relatively small sample and effect sizes, numerous dependent measures, high expense), data were analyzed using univariate statistics, rather than more conservative multivariate statistics in order to avoid false negative results (i.e., Type II errors). To help minimize false positive results (i.e., Type I errors) due to the number of univariate statistical comparisons made (i.e., 50,000 per SPM comparison), a stringent alpha level (i.e., $p \leq 0.001$) for the voxel-wise analyses was utilized. Furthermore, a second and more hypothesis-driven method of

image processing and analysis, ROIs, was performed for confirmation. That the results of the present study were not due to chance but rather reflected neurophysiological sequelae of CHI is suggested by the fact that these findings, which were based mostly on the voxel-wise analyses were: 1) for the most part, supported by either statistically significant results or non-significant tendencies in the ROI analyses, 2) consistent with a putative anatomical mechanism, and 3) consistent with findings in PET studies of other populations.

Sample size

Another possible limitation of this study is that the sample of 13 subjects per group was too small to detect reliable group differences. In a recent study, Ostrem and colleagues (Ostrem, Van Horn, Esposito, Gold, Weinberger, & Berman, 1994) concluded that a sample size of 12 subjects was sufficient to reliably detect signal changes in PET data of complex cognitive tasks using SPM. From a cohort of 48 normal subjects who underwent PET during performance of the WCST, four groups of 12 subjects were created. For each subgroup separately, regions of significant activation compared to baseline control were determined using SPM. In comparison to the results from the overall group analysis, the subgroups were found to have, on average, rates of 0% false positives (i.e., findings that were significant in the subgroups but not in the overall cohort), 28% false negatives (i.e., findings that were not significant in the subgroups but significant in the overall cohort), and 72% true positives (i.e., findings that were significant in the subgroups *and* the overall cohort). The sample size in the present study, which is comparable to if not greater than the

sample sizes of most PET studies, thus appears adequate to detect rCBF changes using SPM with a reasonable degree of reliability.

Correlational analyses

It is important to note that within-group correlations with performance were calculated on differences in rCBF between task and control. This subtraction procedure was used to control for rCBF changes occurring during a task that may relate to general visual, motor, or arousal functions, rather than to the higher cognitive act of interest. However, subtraction methodology may, in theory, obscure important brain-behavior relationships given that the brain probably does not function in an additive, modular manner (Sergeant, 1994). Analyses of performance correlations with rCBF in the task itself (i.e., without subtraction of sensorimotor control data), revealed, in general, *fewer* significant correlations than in the activation analyses. The fact that correlations emerged with the subtraction data suggests that this approach might have indeed served to reduce variability due to non-specific, non-task related brain activity and may be useful in detecting at least some signals specifically associated with the cognitive act of interest.

Aside from subtraction methodology, other factors might have obscured the relationship between rCBF and performance. First, a linear relationship may not exist between blood flow and performance (Sergent et al., 1994). Second, because performance of a complex cognitive task involves several different mental processes operating simultaneously (e.g., switching set *and* abstraction during the WCST), the signal detected from the mental action of interest might have been diluted. Finally,

differences in the time frames during which rCBF and performance were measured might have weakened rCBF performance correlations. Given the temporal resolution of PET, the rCBF signal detected during the first 30 seconds after tracer injection contributed the most to the overall PET data. In contrast, performance data were recorded during the entire 4½ minute scanning period, as well as one minute prior to tracer injection, which was done to stabilize rCBF prior to data acquisition. Overall performance, therefore, included data that did not contribute either at all or very little to the signal detected by PET.

In addition to these limitations, it is also important to note that interpretation of correlational analyses of PET data with performance, even when significance was found, is complicated by the inability to determine whether rCBF increases reflect excitatory or inhibitory neural processes. Therefore, a positive relationship between rCBF and performance might have indicated that either greater activity (i.e., neural excitation) *or* greater *inactivity* (i.e., neural inhibition) of the structure related to good performance.

Generalizability

Good recovery

In this study, a subgroup of CHI patients who showed relatively good recovery following a severe injury was chosen for investigation. This patient sample was recruited because they were believed to be more likely than more mildly-injured and poorly recovered individuals to have incurred permanent neurophysiological changes

post-injury and to exhibit cognitively-related compensatory neurofunctional changes, which were the focus of the present investigation. However, because this CHI sample is not likely representative of the general population of CHI patients, the results of this study may not generalize to CHI patients with different severity or outcome from injury.

Left-handedness

The higher incidence of left handedness in this sample of CHI patients than in the general population (38% versus 10%) (Annett, 1972) was not accounted for by a switch to the non-dominant hand following injury. The high rate of left handedness might have reflected merely chance factors that would have normalized with a larger sample size. On the other hand, it has been suggested that left-handers demonstrate better recovery from brain injury than right-handers as a result of greater bilateral representation of function (Luria, 1970). The high incidence of left-handed individuals in this sample, therefore, might have resulted from the recruitment of patients with a relatively good outcome. Although patients and controls were matched for handedness in this study, it is possible that the left-handed CHI patients responded differently to brain injury than right-handed patients and thus added variability to the data. If so, this sample of CHI patients with a disproportionately high number of left-handers may not adequately represent the general population of CHI patients, which limits the generalizability of the findings. The effect of handedness on rCBF patterns in CHI patients remains an issue for future studies to address.

FUTURE RESEARCH

Single Subject Studies

Although the focus of this study was on describing neurofunctional changes in CHI patients as a group, because of the heterogeneous nature of CHI lesions, it would be particularly important and informative to examine neurofunctional changes in *individual* patients or in subgroups of patients (e.g., those showing cognitive impairment based on an objective criteria). As stated earlier, a single subject approach may allow both the general and unique functional alterations of a patient to be viewed. Currently, single subject methodologies are under development but have not been completely worked out for PET data like that obtained in this study. Because of the relatively low signal-to-noise ratio in a single scan of a given condition, as well as the limited size of the normative sample, the rCBF data obtained in the present study are not ideally suited to single subject analysis.

With these limitations in mind, an SPM analysis ($p<0.01$) of normalized WCST activation (i.e., WCST-WCSTc) for a single subject (Patient VD) compared to the sample of 13 controls is presented in Figure 25. This method developed by Karl Friston and his colleagues (Wellcome Department of Cognitive Neurology, Institute of Neurology, University of London, Queen Square, London) uses the error variance from the control group to assess the statistical significance of functional changes in the individual. Consistent with the group analysis, significant increases were found in the left hippocampus. Significant increases were also found in the left superior temporal cortex and in the left middle frontal gyrus. Unlike the group analysis, large areas of

significant rCBF deficit were also revealed and were localized to bilateral visual association areas, right temporal lobes including the hippocampus, posterior cingulate cortex, and right medial frontal areas. These preliminary results demonstrate that at least some increases in rCBF activation may be seen at both the individual and the group level, whereas the unique rCBF deficits associated with the specific neuroanatomy of a patient's lesion may be best visualized at the individual level.

Group Studies

Issues not addressed by this study, but which are important in understanding these rCBF results, include the effects of age of injury, time after injury, severity of injury, lesion locale, and medication status on rCBF patterns following CHI. Future studies investigating these issues, either using group or single subject methodology, would benefit from the use of a three-dimensional PET camera, which acquires a greater number of brain slices and offers improved spatial resolution. Moreover, because this relatively new technical advance requires only one-fourth or one-fifth the radiation dose necessary with a two-dimensional PET camera as used in the present study, many more measurements can be made in each subject. These recent improvements in PET technology now allow the entire brain to be imaged, permit multiple scans of the same condition to be performed in order to improve group and single subject statistical assessment, and, given the reductions in radioactivity, may facilitate future PET scanning of children and adolescents with CHI.

SUMMARY AND CONCLUSIONS

In this exploratory and descriptive study of long-term neurofunctional changes in severe CHI patients, generalized rCBF diminutions in subcortical structures were found in the patients and were thought to relate to the high incidence of DAI in this CHI sample. Generalized decreases were also found in anterior cingulate cortex and were speculated to relate to impaired attentional processes in CHI patients. The generalized relative rCBF increases in cortical structures found in CHI patients compared to controls were interpreted with caution in light of the possible contribution to this finding by a procedural artifact.

When rCBF during the cognitive task was considered against the control task baseline, between-group differences were largely dominated by areas of *elevated* activations in CHI patients relative to controls. These unexpected activation increases, which may represent general responses to brain compromise that were shared by many of the patients, were found in the prefrontal cortex and in the hippocampus in the WCST paradigm and in the left inferior parietal lobule and right visual association cortex in the CRMT paradigm. These elevations were thought to reflect both behavioral compensation (e.g., the use of different cognitive strategies) and neurophysiological compensation (e.g., prefrontal cortical *over*activity in response to *under*activity/inefficiencies in other brain areas). The relative paucity of activation deficits may be due to the variability of lesion sites across CHI patients, which might have obscured the individual deficits in this group analysis. Finally, the results of within-group correlations between performance and hippocampal rCBF activation

during both the WCST and the CRMT paradigms suggest functional disorganization of this structure in CHI patients. It is concluded that further research into the rCBF patterns of CHI patients is warranted, particularly using single subject methodology to examine individual rCBF deficits, as it may yield valuable insights into the neuroanatomical and neurophysiological substrates of normal and abnormal cognition and behaviour.

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APPENDICES

APPENDIX A

Schemes of classifying severity of closed head injury.

Classification Scheme	Mild	Moderate	Severe
Glasgow Coma Scale	13-15	9-12	3-8
Post Traumatic Amnesia Length	less than 1 hour	between 1 and 24 hours	greater than 24 hours

APPENDIX B

Case histories of closed head injury patients.

Patient DA: A 27 year-old, high-school educated, right-handed female sustained CHI at age 26 during a MVA. She worked as a secretary both pre- and post-injury. Medical records indicated that she was comatose (GCS=7) at the accident scene and required intubation. An initial CT scan revealed biparietal contusions with left cerebellar shear. Currently, she shows deficits in most areas of neuropsychological functioning and complains of depression, immature behaviors, and hypersexuality.

Patient JB: A 27 year-old, right-handed, college-educated male sustained CHI at age 21 from physical assault. Medical records revealed that he was comatose and required intubation at the accident scene. An initial CT scan revealed an extensive subdural hematoma in the left frontal and parietal regions, which was evacuated during a frontal craniotomy. A left cerebral artery infarct secondary to uncal herniation was also found. Early in his recovery, he presented with a right paraparesis and right visual field defect, the latter of which persists to date. Current neuropsychological testing revealed a prominent anomia and deficits in verbal learning. Currently, he works as a civil engineer.

Patient RC: A 23 year-old, right-handed male sustained CHI at age 20 during a MVA. Medical records revealed that he was comatose (GCS=8) and required intubation at the accident scene. An initial CT scan revealed a right temporal contusion. Behaviorally, he was reported to be confused and aphasic (expressive and receptive). Current neuropsychological testing revealed weaknesses in language, including verbal fluency and naming. He was a student at the time of injury and since has obtained a Master's degree in industrial engineering.

Patient VD: A 24 year-old, right-handed Hispanic male sustained CHI at age 20 during a MVA. He, a full-time student in computer science, was hit from behind by a

car while riding a motorcycle. At the accident scene, he was comatose (GCS=7), required intubation and resuscitation, and incurred multiple physical injuries. An initial CT scan revealed encephalomalacia of the right frontal lobe and parenchymal hemorrhages of the right internal capsule. He received extensive rehabilitation and has since obtained a Bachelor's degree. He performed in the average to above average ranges on all tests administered during a current neuropsychological evaluation.

Patient EF: A 29 year-old, left-handed, high-school educated, black male sustained CHI at age 25 during a MVA. He worked as a police officer both before and after injury. At the accident scene, he was comatose (GCS=7) and intubated. Medical records revealed right hemiparesis, diplopia, and anomia. An initial CT scan indicated frontal and parietal subarachnoid hemorrhages. Current neuropsychological testing revealed prominent deficits in attention, memory, and language.

Patient PL: A 38 year-old, left-handed South American male with an architecture degree sustained CHI at age 22 when struck by an automobile while riding his motorcycle. The initial medical records of Patient PL were unavailable; therefore historical information is based on self report. He reported a hospital stay of two months with PTA lasting 3-4 weeks. Behaviorally, he reported loss of speech, initial left-sided paralysis, and memory problems. In 1982, a CT scan revealed a right frontal-parietal depressed fracture, and an electroencephalogram indicated "anterior slowing slightly greater on the right". Currently, he, employed as a banker, complains only of incoordination of the left hand. Current neuropsychological testing revealed prominent language deficits, although cultural factors may explain some of his poor performances on these tests.

Patient WL: A 30 year-old, left-handed black male with an Associates degree sustained CHI at age 29 during a MVA. Premorbidly, he worked in plumbing and construction; currently, he is unemployed. Medical reports indicated PTA for 48 hours, an inability to speak, and disorientation to person. Although his initial CT scan

and current MRI scan were negative for pathology, he currently demonstrates substantial deficits in attention, memory, and language and is depressed.

Patient JN: A 45 year-old, right-handed, college-educated Hispanic male who worked as a credentialed accountant sustained CHI at age 41 during a MVA. Following injury, he was comatose (GCS=7), incurred respiratory arrest, was intubated, and had a seizure. An initial CT scan revealed a clot in the left lateral ventricle, a subdural hematoma in the left 4th ventricle, and small left to right hemisphere shift. Although he has received extensive rehabilitation, he has never returned to work. Significant depression, a profound anomia, and verbosity characterize his neuropsychological profile.

Patient BP: A 31 year-old, left-handed male sustained CHI at age 22 during a MVA. Medical records revealed that he was comatose at the accident scene (GCS=4) with PTA lasting nearly a month. An initial CT scan revealed bilateral white matter lesions in the frontal lobes and ventriculomegaly. At the time of injury, he was attending his senior year of college, and following extensive rehabilitation, has since obtained a Master's degree. Currently, his neuropsychological profile is characterized by an anomia and a prominent weakness in verbal learning.

Patient TR: A 38 year-old, right-handed female sustained CHI at age 21 during a MVA. Medical records revealed that she was comatose for approximately one week. An initial CT scan showed a right frontal lobe lesion. Although prior to her injury she had been a high-achieving high school student, she has never been employed despite recently attaining her Bachelor's degree. Currently, she demonstrates deficits in sustained attention, verbal fluency, and verbal learning, complains of numerous physical ailments, and is depressed.

Patient GR: A 23 year-old, left-handed, high-school educated male sustained CHI at age 16 when he was hit by an automobile while riding his bicycle. Medical records

indicated that, at the accident scene, he was comatose (GCS=6), required intubation, and demonstrated decerebrate posturing. Upon resolution of coma, he exhibited an expressive aphasia and a right hemiparesis. An initial CT scan revealed a hemorrhage of the posterior horn of the left internal capsule. Current neuropsychological testing indicated weaknesses in language and verbal learning.

Patient KS: A 31 year-old, right-handed female sustained CHI at age 16 during a MVA. According to medical records, she was comatose at the accident scene and had a seizure. An initial CT scan showed a bleed in the posterior horn of the left lateral ventricle. She was a high-school student at the time of injury and has since obtained a Master's degree in audiology. Her current cognitive weaknesses involved language skills.

Patient RW: A 27 year-old, right-handed male sustained CHI at age 20 during a MVA. Medical records indicated a PTA length of approximately 10 days with a GCS score of 11. An initial CT scan revealed a left frontal lobe lesion and bilateral white matter damage in the parietal lobes, more severe in the left hemisphere. He was a student at the time of injury and has since obtained a Bachelor's degree in math and physics. A current neuropsychological evaluation revealed a notable weakness in verbal fluency.

APPENDIX C

Instructions for tasks administered during functional imaging.

During each of the 5 1/2 minute scans, it is important for you to be absolutely still and quiet except for that necessary to make your response. No matter how easy or hard the task may be for you, it's important that you concentrate on the task. I will inform you when the scan begins and ends. Do the best you can.

WCST: On the screen you see a design in the center box with four designs surrounding it. You have to figure out how to match the center design to one of the four outside designs. I can't tell you how to match it. You are to press the button that corresponds in position to the design you chose. After each response, the computer will briefly flash "right" or "wrong" above the answer you have chosen, and the next item will appear. You only get one response per item. The object of the task is to get as many correct as possible. There is no time limit for each response.

WCSTc: On the screen you see a design in the center box with four designs surrounding it. I want you to match the center design to one of the four outside designs that matches it *exactly*. You are to press the button that corresponds in position to the design you chose. After each response, the computer will briefly flash "right" or "wrong" above the answer you have chosen, and the next item will appear. You only get one response per item. The object of the task is to get as many correct as possible. There is no time limit for each response.

CRMT: **Prescan Study Phase:** On the screen you will see a list of word pairs on the screen, one pair at a time, each for about five seconds. For example, a word pair might be "jungle" and "tiger". There are many pairs in the list, but the words within a pair will always be related in meaning. I will show you the study list only once (for CHI subjects, "... you will see the list twice"). Then during the scan, you will see the first word of the word pair and you must tell me the word that was paired with it. So, if you saw the word "pizza" during the scan, you'd say "dough". Read the word pairs aloud. Try to concentrate on the relationship between the words within a word pair because it'll help you recall the word pair during the scan.

Recall Phase: During the scan, you will see the first word of each word pair, and you are to tell me the word that was paired with it. You will have about five seconds to respond. If you see the row of asterisks indicating that the next word is about to appear and you haven't thought of the word that was paired with it, then say "pass". Also, there will be words presented during the scan that were not on the study list. For example, the word "pizza" was not on the study list. When you see a word that was *not* on the study list, then say "pass". You only get one response per item. Try to get as many correct as you can.

READ: On the screen you will see a list of words, one at a time, each for about five seconds. I want you to read the word aloud. If you don't know a word, then say "pass". You only get one response per item. Try to get as many correct as you can.

APPENDIX D

Test lists for the Cued Recall Memory Test (CRMT).

In the CRMT, the first word of each word pair was presented, whereas the second word of each word pair was presented in the control task *(learned* word pairs presented in upper case letters; *unlearned* distractor word pairs presented in lower case letters).

LIST A	LIST B	LIST C
1) PLANT (*GARDEN*)	1) KITCHEN (*STOVE*)	1) GRASP (*HOLD*)
2) wings--eagle	2) tree--stem	2) mask--robber
3) GREY (*BLUE*)	3) GRIEF (*JOY*)	3) ROOM (*OFFICE*)
4) pants--leg	4) hour--curfew	4) cushion--pillow
5) clam--oyster	5) bulb--lamp	5) ceiling--floor
6) GOATS (*SHEEP*)	6) VACATION (*TOURIST*)	6) STAGE (*DRAMA*)
7) sheet--bed	7) pear--apple	7) gum--candy
8) STORE (*BUSINESS*)	8) COW (*LEATHER*)	8) TITLE (*AUTHOR*)
9) NOISY (*LOUD*)	9) PIANO (*MUSIC*)	9) BODY (*MIND*)
10) wet--cold	10) glove--hand	10) clear--foggy
11) won--lost	11) female--woman	11) seat--chair
12) HATE (*ANGER*)	12) MARKET (*GROCER*)	12) CURTAIN (*WINDOW*)
13) THIMBLE (*NEEDLE*)	13) IDEA (*BELIEF*)	13) NET (*WEB*)
14) LITTLE (*SHORT*)	14) GOLF (*TENNIS*)	14) BEER (*DRINK*)
15) BERRY (*FRUIT*)	15) KITTENS (*CATS*)	15) FIRE (*HEAT*)
16) EGGS (*BUTTER*)	16) HORN (*OBOE*)	16) WICK (*CANDLE*)
17) TOOL (*HAMMER*)	17) CROOK (*THIEF*)	17) RANK (*ORDER*)
18) LOW (*DEEP*)	18) FLAT (*SMOOTH*)	18) LEAF (*GRASS*)
19) STAMP (*LETTER*)	19) MUSCLE (*ARM*)	19) DANGER (*TROUBLE*)
20) CANVAS (BURLAP)	20) MEAL (*DINNER*)	20) CAVE (*HERMIT*)
21) FATHER (*PRIEST*)	21) GARAGE (*HOUSE*)	21) BLUNT (*SHARP*)
22) GRADE (*COURSE*)	22) TRAPEZE (*CIRCUS*)	22) TEA (*LEMON*)
23) TOUGH (*HARD*)	23) LANE (*STREET*)	23) TRAP (*DECOY*)
24) BEAR (*LION*)	24) NICE (*CLEAN*)	24) QUICK (*FAST*)
25) moon--sun	25) rapid--swift	25) spring--blossom
26) KID (*CHILD*)	26) SING (*WHISTLE*)	26) PETAL (*FLOWER*)
27) FAITH (*RELIGION*)	27) DOVE (*PEACE*)	27) NECK (*HEAD*)
28) PIPE (*TOBACCO*)	28) DAY (*MORNING*)	28) SALAD (*CABBAGE*)
29) officer--command	29) sky--earth	29) wish--dream
30) soft--quiet	30) honey--sugar	30) travel--road

The word lists were adapted from those of Blaxton et al. (submitted), which consisted of words and their third or fourth most frequently named associate. In their task, 50% of the words were distractors, whereas only 30% were distractors in this study. Furthermore, 67% of the distractor words in the present study were presented during the minute prior to the scan and during the last minute of the scan when the signal detected by PET contributed little to the overall data. These changes were implemented to help avoid measuring the effects of two different cognitive processes during the same scan (i.e., those involved in recalling the pair of a target versus those involved in recognizing a word as a distractor without an associate to be recalled). Distractor words were not entirely eliminated from the lists to maintain comparability between the results of the present study and those of Blaxton and colleagues.

APPENDIX E

Performance measures of the Wisconsin Card Sorting Test.

Performance Measure	Description
Correct Response	*A correct match to a sorting principle*
Category	*Ten consecutive correct matches*
Perseverative Error	*A match to a sorting principle that was correct prior to the most recent change in sorting principle*
Failure to Maintain Set	*An incorrect match after a series of five to nine consecutive correct responses*

APPENDIX F

Factor analysis of performance on the Wisconsin Card Sorting Test.

Dependent Measure	Factor 1	Factor 2
Number Correct	0.96684	-0.00942
Percent Correct*	0.97920	0.06536
Number of Categories	0.94477	-0.19908
Percent Perseverative Errors	-0.92334	-0.18010
Failures to Maintain Set	-0.03336	0.99236

*measure with the highest loading on Factor 1

Variance explained by each factor:

Factor 1 (eigenvalue = 3.639853): 77%

Factor 2 (eigenvalue = 1.061200): 33%

APPENDIX G

Levels of the Glasgow Outcome Scale.

Outcome	Behavioral Description
1) Persistent Vegetative State	*No meaningful response*
2) Severe Disability	*Conscious but dependent*
3) Moderate Disability	*Independent but disabled*
4) Good Recovery	*Capacity to resume normal occupational and social activities with only mild deficits*

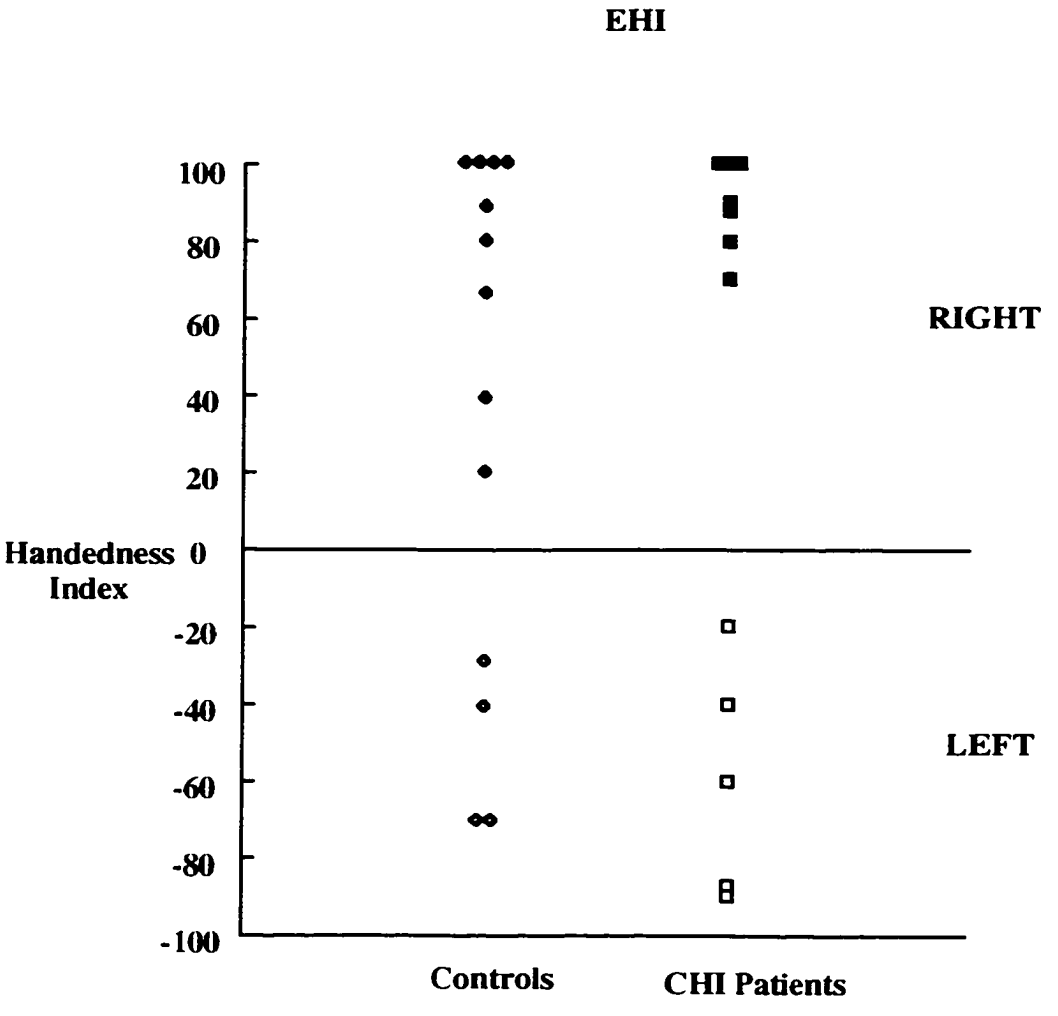
APPENDIX H

Subject demographics.

Subject	Handedness* R=right L=left	Gender M=male F=female	Age	Years of Education
Closed Head Injury Patients				
DA	R	F	27	13
JB	R	M	27	16
RC	R	M	23	17
VD	R	M	24	14
EF	L	M	29	13
PL	L	M	38	16
WL	L	M	30	14
JN	R	M	45	16
BP	L	M	31	17
TR	R	F	38	16
GR	L	M	23	12
KS	R	F	31	18
RW	R	M	26	16
Normal Control Subjects				
ED	R	F	25	16
JK	R	M	29	15
PA	R	M	24	18
JR	L	F	25	16
JY	R	M	32	21
SR	R	M	36	21
AJ	R	M	32	13
PT	R	M	48	18
SG	L	M	35	13
LB	R	F	37	16
DM	L	M	24	16
MB	L	F	32	16
JH	R	M	26	18

*The distribution of handedness scores for each group are presented in Figure 26.

Figure 26: Distribution of handedness scores. There was no significant difference between controls and closed head injury (CHI) patients in handedness based on the Edinburgh Handedness Inventory (EHI) ($p>0.80$). Positive index values indicate greater use of the right than left hand, whereas negative index values reflect greater use of the left than right hand.


EHI
100
80
60
40
20
Handedness 0
Index
-20
-40
-60
-80
-100
RIGHT
LEFT
Controls
CHI Patients

APPENDIX I

Neuropsychological performance data.

Percentile rankings, except where indicated, are presented for closed head injury patients. Full Scale Intelligence Quotient (FSIQ), Logical Memory I (LM1), Trail Making Test (TMT), Continuous Performance Test (CPT), Boston Naming Test (BNT), Verbal Fluency Test (FAS), California Verbal Learning Test (CVLT), Beck Depression Inventory (BDI)*.

		FSIQ	LM1	TMT	CPT	BNT	FAS	CVLT	BDI
1	DA	2	16	29	0	0	0	0	33
2	JB	55	55	19	78	4	69	0	10
3	RC	77	57	100	78	8	6	73	0
4	VD	96	94	94	78	77	100	43	6
5	EF	25	25	0	71	0	0	3	11
6	PL	42	75	11	63	0	1	5	3
7	WL	8	7	34	29	0	0	1	29
8	JN	81	70	80	78	0	96	14	22
9	BP	77	85	23	46	5	96	0	6
10	TR	37	49	33	0	28	0	4	20
11	GR	19	6	81	63	0	1	7	7
12	KS	86	81	90	63	10	0	31	3
13	RW	75	98	85	46	93	12	73	3
Mean		52.3	55.2	52.2	53.3	17.3	29.3	19.5	11.76
SD		32.0	32.6	36.2	28.0	31.2	43.0	27.1	10.73
SEM		8.9	9.0	10.1	7.8	8.7	11.9	7.5	3.0

*raw scores are presented

APPENDIX J

Factor analysis of neuropsychological measures of closed head injury patients.

Dependent Measure (in percentile ranking)	**Factor 1**	**Factor 2**
Full Scale Intelligence Quotient (*estimated*)	0.94020	0.23222
Logical Memory I: (*total correct*)	0.84965	0.17626
Trails B (*total time*)	0.72191	-0.38675
Continuous Performance Test (*total time*)	0.55455	0.44435
Boston Naming (*total correct*)	0.68375	-0.42194
Verbal Fluency Test (*total across F,A, S*)	0.51456	0.72287
California Verbal Learning Test (*trials 1-5*)	0.78277	-0.53498

Variance explained by each factor:

Factor 1 (eigenvalue = 3.779562): 73%
Factor 2 (eigenvalue = 1.418797): 27%

APPENDIX K

Raw performance data during functional imaging.

WCST= Wisconsin Card Sorting Test, CRMT= Cued Recall Memory Test. Variables are: CRMT percent correct, WCST number completed, WCST percent correct, WCST number of categories, WCST percent perseverative errors, WCST failures to maintain set, respectively.

Closed Head Injury Patients

DA) 14.29 31 56.36 1 20 0

JB) 47.62 82 81.19 7 9.9 0

RC) 76.19 52 54.74 3 21.05 1

VD) 71.43 86 89.58 8 7.29 0

EF) 42.86 63 86.3 5 8.22 0

PL) 28.57 31 40.79 1 34.21 0

WL) 42.86 26 40 1 27.69 0

JN) 47.62 70 85.37 5 6.1 2

BP) 71.43 71 81.61 6 10.34 0

TR) 33.33 63 75.9 3 13.25 1

GR) 42.86 51 69.86 4 12.33 0

KS) 85.71 83 85.57 6 6.19 1

RW) 76.19 87 83.65 7 7.69 1

Matched Normal Controls

ED) 57.14 81 85.26 6 5.26 0

JK) 85.71 50 60.98 1 13.41 1

PA) 85.71 98 89.09 9 10 0

JR) 100 81 84.38 7 7.29 0

JY) 76.19 65 83.33 6 8.97 0

SR) 76.19 56 75.68 3 8.11 2

AJ) 100 75 75.76 6 13.13 0

PT) 76.19 77 81.91 6 7.45 0

SG) 23.81 29 50 1 27.59 1

LB) 71.43 79 81.44 7 9.28 0

DM) 95.24 81 86.17 7 10.64 1

MB) 85.71 67 81.71 6 9.76 0

JH) 57.14 95 87.16 8 7.34 1

APPENDIX L

Individual global Means.

Raw data (in ml/min/100g tissue) are for the Wisconsin Card Sorting Test (WCST), the WCST control task, the Cued Recall Memory Test (CRMT) and the CRMT control task, respectively.

Closed Head Injury Patients	Matched Normal Controls
DA) 69.69 66.25 50.70 48.51	ED) 57.92 57.35 59.24 52.93
JB) 41.35 38.86 60.85 39.33	JK) 51.06 47.6 51.47 48.20
RC) 59.39 56.37 48.02 52.83	PA) 49.08 50.43 51.83 51.42
VD) 46.32 50.95 40.77 45.20	JR) 48.25 41.30 42.21 44.58
EF) 40.65 52.22 46.34 47.25	JY) 42.97 44.31 44.82 49.97
PL) 40.50 47.84 36.08 41.76	SR) 50.54 46.43 42.56 43.71
WL) 47.81 44.64 43.75 45.38	AJ) 38.53 42.84 43.00 43.93
JN) 32.64 44.61 32.30 34.16	PT) 45.84 45.87 39.75 41.72
BP) 35.97 32.41 44.01 43.06	SG) 50.74 49.31 39.83 45.59
TR) 54.92 55.04 52.97 45.58	LB) 53.88 51.99 51.09 49.93
GR) 41.21 41.52 37.70 37.92	DM) 56.43 46.02 59.56 50.27
KS) 61.09 48.34 51.52 53.10	MB) 45.26 41.36 44.18 47.87
RW) 48.49 47.23 44.37 48.87	JH) 42.43 34.94 42.41 36.53

APPENDIX M

Individual pCO_2 values.

Raw data (in mg of mercury) for the Wisconsin Card Sorting Test (WCST), the WCST control task, the Cued Recall Memory Test (CRMT) and the CRMT control task, respectively.

Closed Head Injury Patients	Matched Normal Controls
DA) 40 41 35 36	ED) 40 40 39 40
JB) 39 40 40 39	JK) 44 41 40 44
RC) 43 44 43 43	PA) 41 42 41 42
VD) 38 38 29 41	JR) 42 43 42 42
EF) 39 40 41 39	JY) 41 41 40 41
PL) 33 35 44 31	SR) 42 42 40 41
WL) 42 40 41 42	AJ) 40 41 40 40
JN) 36 36 33 37	PT) 36 36 35 36
BP) 34 38 36 34	SG) 38 38 35 35
TR) 40 40 39 39	LB) 35 36 37 37
GR) 37 37 41 42	DM) 36 39 37 34
KS) 39 39 40 25	MB) 36 34 36 36
RW) 39 40 38 39	JH) 41 42 42 41

APPENDIX N

Results from ROI between-group analyses of the WCST paradigm (L=left, R=right). P values are only presented for regions with p's≤0.10 except for the hippocampus in which nonsignificant p values are also reported.

Area-Weighted Regions of Interest	WCST	Control	WCST - Control
(<) = rCBF less in CHI patients than controls; (>) = rCBF greater in CHI patients than controls			
L anterior cingulate gyrus (inferior slice)	0.02 (<)	0.03 (<)	
R anterior cingulate gyrus (inferior slice)			
L superior frontal gyrus (superior slice)			
R superior frontal gyrus (superior slice)			
L inferior frontal gyrus (superior slice)			
R inferior frontal gyrus (superior slice)	0.08 (>)		
L middle frontal gyrus (superior slice)			
R middle frontal gyrus (superior slice)			
L parietal lobe			
R parietal lobe			
L temporal gyrus			
R temporal gyrus			
L occipital gyrus			
R occipital gyrus			
L caudate nucleus			
R caudate nucleus			
L putamen			
R putamen			
L thalamus	0.07 (<)	0.02 (<)	
R thalamus	0.07 (<)		
L superior frontal gyrus (inferior slice)			
R superior frontal gyrus (inferior slice)			
L middle frontal gyrus (inferior slice)			
R middle frontal gyrus (inferior slice)			
L inferior frontal gyrus (inferior slice)			
R inferior frontal gyrus (inferior slice)	0.05 (>)	0.07 (>)	
L inferior parietal lobule	0.08 (>)	0.04 (>)	
R inferior parietal lobule			
L anterior cingulate gyrus (superior slice)	0.03 (<)		
R anterior cingulate gyrus (superior slice)	0.03 (<)		
L hippocampus (whole)	*0.81 (>)*	*0.13 (<)*	*0.15 (>)*
R hippocampus (whole)	*0.97 (>)*	*0.43 (>)*	*0.28 (<)*
L hippocampus (anterior)	*0.29 (<)*	0.01 (<)	*0.28 (>)*
R hippocampus (anterior)	*0.61 (>)*	*0.75 (>)*	*0.83 (>)*
L hippocampus (posterior)	*0.61 (>)*	*0.73 (<)*	*0.48 (>)*
R hippocampus (posterior)	*0.64 (<)*	*0.34 (>)*	*0.12 (<)*

APPENDIX O

Results from ROI between-group analyses of the CRMT paradigm (L=left, R=right). P values are only presented for regions with p's≤0.10 except for the hippocampus in which nonsignificant p values are also reported.

Area-Weighted Regions of Interest	CRMT	Control	CRMT -Control
(<)=rCBF less in CHI patients than controls; (>)=rCBF greater in CHI patients than controls			
L anterior cingulate (inferior slice)			
R anterior cingulate (inferior slice)	0.01 (<)	0.07 (<)	
L superior frontal gyrus (superior slice)			
R superior frontal gyrus (superior slice)			
L inferior frontal gyrus (superior slice)	0.05 (>)		0.04 (>)
R inferior frontal gyrus (superior slice)			
L middle frontal gyrus (superior slice)			
R middle frontal gyrus (superior slice)			0.07 (>)
L parietal lobe			
R parietal lobe			
L temporal gyrus	0.05 (>)		
R temporal gyrus		0.04 (>)	
L occipital gyrus			
R occipital gyrus			
L caudate nucleus			
R caudate nucleus	0.02 (<)		
L putamen			
R putamen			
L thalamus	0.01 (<)		0.001 (<)
R thalamus	0.02 (<)		
L superior frontal gyrus (inferior slice)			
R superior frontal gyrus (inferior slice)			
L middle frontal gyrus (inferior slice)			
R middle frontal gyrus (inferior slice)			
L inferior frontal gyrus (inferior slice)			
R inferior frontal gyrus (inferior slice)			
L inferior parietal lobule	0.06 (>)	0.06 (>)	
R inferior parietal lobule			
L anterior cingulate gyrus (superior slice)			
R anterior cingulate gyrus (superior slice)			
L hippocampus (whole)	*0.22 (<)*	*0.45 (<)*	*0.37 (<)*
R hippocampus (whole)	*0.27 (<)*	*0.78 (>)*	*0.10 (<)*
L hippocampus (anterior)	*0.95 (<)*	*0.24 (<)*	*0.39 (>)*
R hippocampus (anterior)	*0.73 (<)*	*0.32 (>)*	*0.23 (<)*
L hippocampus (posterior)	0.10 (<)	*0.65 (>)*	0.05 (<)
R hippocampus (posterior)	0.73 (<)	*0.95 (=)*	0.10 (<)

APPENDIX P

Results from ROI correlations between normalized WCST activation (task-control) and percent correct (L=left, R=right). Values are only presented for regions with p's≤0.10 except for the hippocampus in which nonsignificant r values are also reported.

	Patients	Controls
Area-Weighted Regions of Interest	**Pearson's r**	**Pearson's r**
L anterior cingulate (inferior slice)		
R anterior cingulate (inferior slice)		
L superior frontal gyrus (superior slice)		
R superior frontal gyrus (superior slice)		
L inferior frontal gyrus (superior slice)		
R inferior frontal gyrus (superior	-0.77 (p=0.002)	
L middle frontal gyrus (superior slice)		
R middle frontal gyrus (superior slice)		
L parietal lobe		
R parietal lobe	0.60 (p=0.03)	
L temporal gyrus		0.53 (p=0.06)
R temporal gyrus		
L occipital gyrus		
R occipital gyrus		
L caudate nucleus	-0.64 (p=0.02)	
R caudate nucleus		-0.60 (p=0.03)
L putamen		-0.55 (p=0.05)
R putamen		
L thalamus		-0.56 (p=0.04)
R thalamus		
L superior frontal gyrus (inferior slice)		
R superior frontal gyrus (inferior slice)		
L middle frontal gyrus (inferior slice)		
R middle frontal gyrus (inferior slice)		
L inferior frontal gyrus (inferior slice)		
R inferior frontal gyrus (inferior slice)		
L inferior parietal lobule		
R inferior parietal lobule		
L anterior cingulate (superior slice)	0.40 (p=0.09)	0.52 (p=0.07)
R anterior cingulate (superior slice)		
L hippocampus (whole)	*-0.07*	-0.49 (p=0.09)
R hippocampus (whole)	*-0.02*	*-0.41*
L hippocampus (anterior)	*-0.21*	*-0.37*
R hippocampus (anterior)	*0.19*	*0.16*
L hippocampus (posterior)	*-0.02*	*-0.45*
R hippocampus (posterior)	*-0.27*	-0.55 (p=0.05)

APPENDIX Q

Results from ROI correlations between normalized WCST activation (task-control) and % perseverative errors (L= left, R=right). Values are presented for regions with p's≤ 0.10 except for the hippocampus in which nonsignificant r values are also reported.

	Patients	Controls
Area-Weighted Regions of Interest	**Pearson's r**	**Pearson's r**
L anterior cingulate (inferior slice)		
R anterior cingulate (inferior slice)		
L superior frontal gyrus (superior slice)		
R superior frontal gyrus (superior slice)		
L inferior frontal gyrus (superior slice)		
R inferior frontal gyrus (superior slice)	0.75 (p=0.003)	
L middle frontal gyrus (superior slice)		
R middle frontal gyrus (superior slice)		
L parietal lobe		0.49 (p=0.09)
R parietal lobe	-0.64 (p=0.02)	
L temporal gyrus		
R temporal gyrus		
L occipital gyrus		
R occipital gyrus		
L caudate nucleus	0.59 (p=0.03)	
R caudate nucleus		0.52 (p=0.07)
L putamen		0.72 (p=0.006)
R putamen		
L thalamus		0.52 (p=0.07)
R thalamus		
L superior frontal gyrus (inferior slice)		0.53 (p=0.06)
R superior frontal gyrus (inferior slice)		
L middle frontal gyrus (inferior slice)		
R middle frontal gyrus (inferior slice)		
L inferior frontal gyrus (inferior slice)		
R inferior frontal gyrus (inferior slice)		
L inferior parietal lobule		
R inferior parietal lobule		
L anterior cingulate (superior slice)	-0.51 (p=0.07)	-0.59 (p=0.03)
R anterior cingulate (superior slice)		
L hippocampus (whole)	*-0.04*	0.50 (p=0.08)
R hippocampus (whole)	*-0.01*	0.65 (p=0.02)
L hippocampus (anterior)	*0.20*	*0.39*
R hippocampus (anterior)	*-0.20*	*0.04*
L hippocampus (posterior)	*-0.07*	*0.40*
R hippocampus (posterior)	*0.26*	0.71 (p=0.007)

APPENDIX R

Results from ROI correlations between normalized CRMT activation (task-control) and percent correct (L= left, R=right). Values are only presented for regions with p's≤0.10 except for the hippocampus in which nonsignificant r values are also reported.

	Patients	Controls
Area-Weighted Regions of Interest	**Pearson's r**	**Pearson's r**
L anterior cingulate (inferior slice)		
R anterior cingulate (inferior slice)		-0.72 (p=0.006)
L superior frontal gyrus (superior slice)		
R superior frontal gyrus (superior slice)		
L inferior frontal gyrus (superior slice)	-0.62 (p=0.02)	
R inferior frontal gyrus (superior slice)		
L middle frontal gyrus (superior slice)		
R middle frontal gyrus (superior slice)		0.55 (p=0.05)
L parietal lobe		
R parietal lobe		
L temporal gyrus		
R temporal gyrus	-0.54 (p=0.06)	
L occipital gyrus		
R occipital gyrus		
L caudate nucleus		
R caudate nucleus		
L putamen		
R putamen		-0.52 (p=0.07)
L thalamus		0.51 (p=0.07)
R thalamus		
L superior frontal gyrus (inferior slice)		
R superior frontal gyrus (inferior slice)		
L middle frontal gyrus (inferior slice)	0.49 (p=0.09)	
R middle frontal gyrus (inferior slice)		
L inferior frontal gyrus (inferior slice)		
R inferior frontal gyrus (inferior slice)		
L inferior parietal lobule		0.60 (p=0.03)
R inferior parietal lobule		
L anterior cingulate (superior slice)		
R anterior cingulate (superior slice)		-0.64 (p=0.02)
L hippocampus (whole)	*-0.08*	*-0.41*
R hippocampus (whole)	*-0.03*	*0.36*
L hippocampus (anterior)	*-0.16*	*-0.40*
R hippocampus (anterior)	*0.19*	*0.28*
L hippocampus (posterior)	*0.12*	*-0.30*
R hippocampus (posterior)	*-0.38*	*0.31*

APPENDIX S

Results from ROI correlations between current cognitive functioning and normalized activation for CHI patients (L= left, R=right). Values are presented for regions with p's≤0.10 except the hippocampus in which all r values are reported.

	WCST Activation	CRMT Activation
Area-Weighted Regions of Interest	**Pearson's r**	**Pearson's r**
L anterior cingulate (inferior slice)		
R anterior cingulate (inferior slice)		-0.53 (p=0.06)
L superior frontal gyrus (superior slice)		
R superior frontal gyrus (superior slice)		
L inferior frontal gyrus (superior slice)		
R inferior frontal gyrus (superior slice)		
L middle frontal gyrus (superior slice)		
R middle frontal gyrus (superior slice)		
L parietal lobe		
R parietal lobe		
L temporal gyrus		
R temporal gyrus		-0.74 (p=0.004)
L occipital gyrus		
R occipital gyrus		
L caudate nucleus		
R caudate nucleus		
L putamen		
R putamen		
L thalamus		
R thalamus		
L superior frontal gyrus (inferior slice)		
R superior frontal gyrus (inferior slice)		
L middle frontal gyrus (inferior slice)		
R middle frontal gyrus (inferior slice)		
L inferior frontal gyrus (inferior slice)		
R inferior frontal gyrus (inferior slice)		
L inferior parietal lobule		
R inferior parietal lobule		
L anterior cingulate (superior slice)		
R anterior cingulate (superior slice)		
L hippocampus (whole)	*0.26*	*0.25*
R hippocampus (whole)	*0.09*	*0.01*
L hippocampus (anterior)	*-0.01*	*0.19*
R hippocampus (anterior)	*0.31*	*0.29*
L hippocampus (posterior)	*0.27*	*0.18*
R hippocampus (posterior)	*-0.47*	*-0.32*

APPENDIX T

Results from ROI between-group analyses of normalized rCBF in unweighted ROIs in the WCST paradigm: (>) rCBF greater in patients than controls; (<) rCBF less in patients than controls. P values are only presented for regions with p's≤0.10.

L=left, R=right; AC=anterior cingulate (inferior slice); ACING=anterior cingulate (superior slice); SFG=superior frontal gyrus (inferior slice); MFG=middle frontal gyrus (inferior slice); IFG=inferior frontal gyrus (inferior slice); SUPF=superior frontal gyrus (superior slice); MIDF=middle frontal gyrus (superior slice); INFF=inferior frontal gyrus (superior slice); P=parietal; PAR=inferior parietal lobule; T=temporal O=occipital; CAUD=caudate nucleus; PUT=putamen; THAL=thalamus.

	WCST	WCSTc	WCST-WCSTc		WCST	WCSTc	WCST-WCSTc
LAC1				LTHAL1	0.04(<)	0.09(<)	
RAC1	0.004(<)	0.07(<)		RTHAL1			
LSFG1				LCAUD3			
RSFG1				RCAUD3			
LMFG1				LPUT3			0.06(<)
RMFG1				RPUT3			
LIFG1				LTHAL2		0.07(<)	
RIFG1	0.05(>)			RTHAL2			
LP1				LSUPF2			
RP1				RSUPF2			
LT1				LMIDF2			
RT1	0.06(>)			RMIDF2			
LO1				LINFF2			
RO1				RINFF2			
LAC2			0.03(<)	LSUPF1	0.02(<)		
RAC2		0.03(<)	0.09(>)	RSUPF1			
LSFG2				LMIDF1			
RSFG2				RMIDF1			
LMFG2				LINFF1			
RMFG2				RINFF1			
LIFG2				LSUPF0			
RIFG2				RSUPF0			
LP2				LMIDF0			
RP2				RMIDF0			
LT2				LINFF0	0.009(>)		0.01(>)
RT2				RINFF0	0.09 (>)		
LO2				LACING3			
RO2				RACING3	0.07(<)		0.06(<)
LCAUD1				LPAR3			
RCAUD1				RPAR3			
LPUT1				LACING4	0.01(<)		0.04(<)
RPUT1	0.02(>)			RACING4			
LCAUD2				LPAR4	0.09(>)	0.01(>)	
RCAUD2				RPAR4			
LPUT2				LPAR5			
RPUT2				RPAR5			

APPENDIX U

Results from ROI between-group analyses of normalized rCBF in unweighted ROIs in the CRMT paradigm: (>) rCBF greater in patients than controls; (<) rCBF less in patients than controls. P values are only presented for regions with p's≤0.10.

L=left, R=right; AC=anterior cingulate (inferior slice); ACING=anterior cingulate (superior slice); SFG=superior frontal gyrus (inferior slice); MFG=middle frontal gyrus (inferior slice); IFG=inferior frontal gyrus (inferior slice); SUPF=superior frontal gyrus (superior slice); MIDF=middle frontal gyrus (superior slice); INFF=inferior frontal gyrus (superior slice); P=parietal; PAR=inferior parietal lobule; T=temporal O=occipital; CAUD=caudate nucleus; PUT=putamen; THAL=thalamus.

	CRMT	READ	CRMT-READ		CRMT	READ	CRMT-READ
LAC1				LTHAL1	0.05(<)		
RAC1	0.09(<)			RTHAL1			
LSFG1				LCAUD3			
RSFG1			0.05 (<)	RCAUD3			
LMFG1				LPUT3			
RMFG1				RPUT3			
LIFG1				LTHAL2	0.01(<)		0.002(<)
RIFG1		0.03(>)	0.07(<)	RTHAL2	0.00(<)	0.05(<)	
LP1				LSUPF2			
RP1				RSUPF2	0.02(<)	0.05(<)	
LT1	0.01(>)			LMIDF2			
RT1		0.05(>)		RMIDF2			
LO1	0.06(<)			LINFF2			
RO1	0.09(<)	0.06(<)		RINFF2			
LAC2				LSUPF1			
RAC2	0.03(<)	0.03(<)		RSUPF1			
LSFG2				LMIDF1			
RSFG2				RMIDF1			
LMFG2				LINFF1	0.06(>)	0.08(>)	
RMFG2			0.02(>)	RINFF1			
LIFG2			0.01(>)	LSUPF0			
RIFG2			0.02(>)	RSUPF0			
LP2				LMIDF0			
RP2				RMIDF0			
LT2				LINFF0	0.08(>)		
RT2				RINFF0			
LO2				LACING3			
RO2				RACING3			
LCAUD1				LPAR3			
RCAUD1				RPAR3			
LPUT1				LACING4			
RPUT1				RACING4			
LCAUD2				LPAR4	0.02(>)	0.02(>)	
RCAUD2	0.03(<)			RPAR4			
LPUT2		0.05(>)	0.01(<)	LPAR5			
RPUT2				RPAR5			

APPENDIX V

Results from ROI correlations between normalized activation (task-control) in unweighted ROIs and percent correct in the WCST paradigm. (+) positive correlation, (-) negative correlation. P values are only presented for regions with p's≤0.10.

L=left, R=right; AC=anterior cingulate (inferior slice); ACING=anterior cingulate (superior slice); SFG=superior frontal gyrus (inferior slice); MFG=middle frontal gyrus (inferior slice); IFG=inferior frontal gyrus (inferior slice); SUPF=superior frontal gyrus (superior slice); MIDF=middle frontal gyrus (superior slice); INFF=inferior frontal gyrus (superior slice); P=parietal; PAR=inferior parietal lobule; T=temporal O=occipital; CAUD=caudate nucleus; PUT=putamen; THAL=thalamus.

	PATIENTS	CONTROLS		PATIENTS	CONTROLS
LAC1			LTHAL1		
RAC1			RTHAL1		
LSFG1			LCAUD3		
RSFG1			RCAUD3		
LMFG1			LPUT3		0.02(-)
RMFG1			RPUT3	0.03(-)	
LIFG1			LTHAL2	0.06(-)	
RIFG1	0.06(-)		RTHAL2		
LP1		0.09(-)	LSUPF2		0.08(-)
RP1			RSUPF2		
LT1	0.07(+)		LMIDF2		
RT1		0.03(+)	RMIDF2		
LO1			LINFF2		
RO1			RINFF2		
LAC2			LSUPF1		
RAC2		0.05(-)	RSUPF1		
LSFG2		0.07(-)	LMIDF1		
RSFG2			RMIDF1		
LMFG2		0.04(-)	LINFF1		
RMFG2			RINFF1	0.06(-)	
LIFG2			LSUPF0		0.04(-)
RIFG2			RSUPF0		
LP2	0.006(+)		LMIDF0		
RP2	0.01(+)		RMIDF0		
LT2			LINFF0		
RT2	0.03(+)		RINFF0	0.03(+)	
LO2			LACING3		
RO2			RACING3		
LCAUD1	0.04(-)		LPAR3	0.04(+)	
RCAUD1	0.09(+)		RPAR3		
LPUT1			LACING4		0.05(+)
RPUT1		0.04(+)	RACING4		
LCAUD2		0.06(-)	LPAR4		
RCAUD2		0.05(-)	RPAR4		
LPUT2	0.07(-)		LPAR5		
RPUT2			RPAR5		

APPENDIX W

Results from ROI correlations between normalized activation (task-control) in unweighted ROIs and percent perseverative errors in the WCST paradigm. (+) positive correlation, (-) negative correlation. P values are only presented for regions with p's≤0.10.

L=left, R=right; AC=anterior cingulate (inferior slice); ACING=anterior cingulate (superior slice); SFG=superior frontal gyrus (inferior slice); MFG=middle frontal gyrus (inferior slice); IFG=inferior frontal gyrus (inferior slice); SUPF=superior frontal gyrus (superior slice); MIDF=middle frontal gyrus (superior slice); INFF=inferior frontal gyrus (superior slice); P=parietal; PAR=inferior parietal lobule; T=temporal O=occipital; CAUD=caudate nucleus; PUT=putamen; THAL=thalamus.

	PATIENTS	CONTROLS		PATIENTS	CONTROLS
LAC1			LTHAL1		
RAC1			RTHAL1		
LSFG1			LCAUD3		
RSFG1			RCAUD3		
LMFG1			LPUT3	0.09(+)	0.004(+)
RMFG1			RPUT3	0.06(+)	
LIFG1			LTHAL2		
RIFG1	0.04(+)		RTHAL2		
LP1		0.06(+)	LSUPF2		
RP1			RSUPF2		
LT1	0.06(-)		LMIDF2		
RT1		0.07(-)	RMIDF2		
LO1			LINFF2		
RO1			RINFF2	0.08(+)	
LAC2			LSUPF1		
RAC2		0.02(+)	RSUPF1		0.03(+)
LSFG2			LMIDF1		
RSFG2			RMIDF1		
LMFG2		0.06(+)	LINFF1		
RMFG2		0.04(+)	RINFF1		
LIFG2			LSUPF0		0.05(+)
RIFG2			RSUPF0		
LP2	0.006(-)		LMIDF0		
RP2	0.009(-)		RMIDF0		
LT2			LINFF0		
RT2	0.03(-)		RINFF0	0.04(-)	
LO2			LACING3		
RO2			RACING3		
LCAUD1	0.07(+)		LPAR3	0.05(-)	
RCAUD1	0.06(-)		RPAR3		
LPUT1			LACING4		0.02(-)
RPUT1			RACING4		
LCAUD2		0.08(+)	LPAR4		
RCAUD2		0.03(+)	RPAR4		
LPUT2	0.05(+)	0.03(+)	LPAR5		
RPUT2			RPAR5	0.07(+)	

APPENDIX X

Results from ROI correlations between normalized activation (task-control) in unweighted ROIs and percent correct in the CRMT paradigm. (+) positive correlation, (-) negative correlation. P values are only presented for regions with p's≤0.10.

L=left, R=right; AC=anterior cingulate (inferior slice); ACING=anterior cingulate (superior slice); SFG=superior frontal gyrus (inferior slice); MFG=middle frontal gyrus (inferior slice); IFG=inferior frontal gyrus (inferior slice); SUPF=superior frontal gyrus (superior slice); MIDF=middle frontal gyrus (superior slice); INFF=inferior frontal gyrus (superior slice); P=parietal; PAR=inferior parietal lobule; T=temporal O=occipital; CAUD=caudate nucleus; PUT=putamen; THAL=thalamus.

	PATIENTS	CONTROLS		PATIENTS	CONTROLS
LAC1			LTHAL1		0.05(+)
RAC1		0.002(-)	RTHAL1		
LSFG1			LCAUD3		
RSFG1			RCAUD3		
LMFG1			LPUT3		
RMFG1		0.06(+)	RPUT3		
LIFG1			LTHAL2		
RIFG1	0.05(-)		RTHAL2		
LP1			LSUPF2		
RP1			RSUPF2		
LT1			LMIDF2		
RT1			RMIDF2		
LO1			LINFF2		0.08(-)
RO1			RINFF2		
LAC2			LSUPF1		
RAC2			RSUPF1		
LSFG2			LMIDF1	0.9(+)	
RSFG2			RMIDF1		
LMFG2			LINFF1		
RMFG2			RINFF1		
LIFG2			LSUPF0		
RIFG2			RSUPF0		
LP2			LMIDF0	0.09(+)	
RP2			RMIDF0		0.04(-)
LT2			LINFF0		
RT2	0.04(-)		RINFF0		
LO2		0.004(+)	LACING3		
RO2			RACING3		0.02(-)
LCAUD1			LPAR3		
RCAUD1			RPAR3		
LPUT1			LACING4		
RPUT1			RACING4		
LCAUD2	0.06(+)		LPAR4		0.09(+)
RCAUD2			RPAR4		
LPUT2		0.007(-)	LPAR5		
RPUT2			RPAR5		

APPENDIX Y

Results from ROI correlations between current cognitive functioning and normalized activation (task-control) in unweighted ROIs in the CRMT and WCST paradigms in CHI patients. (+) positive correlation (-) negative correlation. P values are only presented for regions with p's≤0.10.

L=left, R=right; AC=anterior cingulate (inferior slice); ACING=anterior cingulate (superior slice); SFG=superior frontal gyrus (inferior slice); MFG=middle frontal gyrus (inferior slice); IFG=inferior frontal gyrus (inferior slice); SUPF=superior frontal gyrus (superior slice); MIDF=middle frontal gyrus (superior slice); INFF=inferior frontal gyrus (superior slice); P=parietal; PAR=inferior parietal lobule; T=temporal O=occipital; CAUD=caudate nucleus; PUT=putamen; THAL=thalamus.

	WCST	CRMT		WCST	CRMT
LAC1			LTHAL1		0.08(+)
RAC1			RTHAL1		
LSFG1			LCAUD3		
RSFG1			RCAUD3		
LMFG1			LPUT3		
RMFG1			RPUT3	0.03(-)	
LIFG1			LTHAL2	0.05(-)	
RIFG1			RTHAL2		
LP1			LSUPF2		
RP1			RSUPF2		
LT1			LMIDF2		
RT1	0.04(-)	0.09(-)	RMIDF2		
LO1			LINFF2		
RO1		0.09(-)	RINFF2		
LAC2			LSUPF1		
RAC2		0.08(-)	RSUPF1		
LSFG2			LMIDF1		0.03(+)
RSFG2	0.04(+)		RMIDF1		
LMFG2			LINFF1		
RMFG2			RINFF1	0.08(-)	
LIFG2			LSUPF0		
RIFG2			RSUPF0		
LP2			LMIDF0	0.04(-)	
RP2			RMIDF0		
LT2			LINFF0		
RT2		0.009(-)	RINFF0	0.01(+)	
LO2			LACING3		
RO2	0.07(-)		RACING3		
LCAUD1			LPAR3		
RCAUD1			RPAR3		
LPUT1			LACING4		
RPUT1			RACING4		
LCAUD2			LPAR4		
RCAUD2	0.04(-)		RPAR4		
LPUT2			LPAR5		
RPUT2			RPAR5		