

One-Year Follow-up of Technetium-99m-HMPAO SPECT in Mild Head Injury

Axel Jacobs, Eric Put, Michel Ingels, Theo Put and Axel Bossuyt

Department of Nuclear Medicine, Virga Jesse Hospital, Hasselt, Belgium; Department of Neurosurgery, St.-Franciskus Hospital, Heusden-Zolder, Belgium; Department of Nuclear Medicine, University Hospital, Free University of Brussels (VUB), Jette, Belgium

We evaluated the predictive capacity of ^{99m}Tc -HMPAO SPECT for clinical outcome during a follow-up period of 12 mo after mild head injury. **Methods:** We prospectively evaluated 136 patients with mild head injury who underwent initial SPECT imaging (SPECT0) within 4 wk after the trauma. Re-evaluations were made 2.9–3.3 mo (T3mo), 5.7–6.3 mo (T6mo) and 11.9–12.6 mo (T12mo) postinjury. All patients with an abnormal SPECT underwent a repeat study at the subsequent time of evaluation. Patients with a previously normal SPECT scan did not undergo a repeat study. Clinical reassessments (CLIN) were performed as long as the earlier study had been positive or until patients were completely asymptomatic. **Results:** During all follow-up evaluations, SPECT had a high sensitivity and negative predictive value, increasing from 91% and 89%, respectively, at T3mo to 100% at T6mo and at T12mo. Clinical normalization occurred earlier than scintigraphic normalization. However, at 12 mo postinjury, we observed considerable improvement in the specificity and positive predictive value of SPECT (85% and 83%, respectively). The persistent lesions on the SPECT scan were related to their severity and to localization in the frontal cortex. **Conclusion:** A normal ^{99m}Tc -HMPAO SPECT scan is a reliable tool in the exclusion of clinical sequelae of mild head injury. At 12 mo postinjury, a positive SPECT study is also a reliable predictor for clinical outcome.

Key Words: regional cerebral blood flow; SPECT; mild head injury; technetium-99m-HMPAO

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Several studies have already highlighted SPECT's ability to detect regional cerebral blood flow (rCBF) disturbances in patients having sustained craniocerebral trauma. Most of these studies addressed rather severe trauma cases and their main objective consisted of comparing SPECT with other imaging techniques, chiefly CT and MRI (1–7). Although these studies have consistently indicated that SPECT reveals lesions that are larger and more numerous than on CT, the clinical significance of lesions visualized on SPECT scans still needs to be assessed (8). This particularly applies to mild and moderate trauma in which the role of CT is probably limited (9–13).

In a previous study (14), we prospectively evaluated rCBF SPECT results in relation to clinical data, during the early post-traumatic stage and after a 3-mo follow-up in mild and moderate head injuries. SPECT alterations correlated well with the severity of the trauma, and a normal early postinjury SPECT scan proved to be a reliable predictor for favorable clinical outcome. On the other hand, an abnormal initial SPECT scan appeared to be insufficient as a prognosticator of outcome. Moreover, many patients (24%) with a positive control SPECT scan at 3 mo postinjury were completely free of symptoms, indicating the need for longer follow-up data (beyond 3 mo) to

monitor further evolution of SPECT scan changes in relation to clinical status.

In the present study, we therefore extended our data to a larger group of 136 patients who had sustained a mild head injury, according to currently used criteria (15); the follow-up period was extended up to 12 mo post-trauma. The rCBF SPECT results were analyzed in terms of sensitivity, specificity and predictive value at 3, 6 and 12 mo postinjury. The aim of our study was to determine the predictive capacity of SPECT for the clinical outcome, in terms of resolution or persistence of symptoms, and to establish its role in objective assessment of postconcussive symptoms.

MATERIALS AND METHODS

Patients

This study included 136 patients (85 men, 51 women, age 11–71 yr, mean age 36 yr) with well-documented closed-cranial trauma. Initially, 153 consecutive patients who fulfilled the inclusion criteria were enrolled. Of these, 17 did not have appropriate follow-up data and later were excluded. Informed consent was obtained from all patients and the study was approved by the local medical ethics committee. Moreover, 54 of these patients were reported in an earlier study (14), met the criteria for classification of mild head injury and were included in the present study. All other patients in the actual study population were newly included.

The diagnostic criteria consisted of history of head trauma in patients who: (a) may or may not have experienced a period of unconsciousness, with an admission score of ≥ 13 on the Glasgow Coma Scale; (b) may or may not have experienced retrograde amnesia of less than 24 hr; and (c) did not have abnormalities on their CT scans. None of the patients required intracranial surgical intervention and none had secondary neurological complications.

In 93% of these patients, the trauma was caused by a car, motorcycle or bicycle accident; the remaining patients were injured by a fall, an assault or a blow to the head during a professional activity or sports practice. Exclusion criteria consisted of previous cranial trauma, epilepsy or other previously known neurological disorder before the trauma, psychiatric disease, drug or alcohol abuse, CT scans showing important cortical atrophy or focal lesions (such as arachnoid cysts) unrelated to the trauma and unreliable anamnesis concerning the trauma.

Study Design

The study protocol is shown in Figure 1. All 136 patients underwent an initial ^{99m}Tc -HMPAO brain SPECT study (SPECT0) and CT within 4 wk after the trauma (68 of 136 within 3 days, 45 of 136 between 4 and 7 days, 13 of 136 during the second week and 10 of 136 between 2 and 4 wk after the trauma). All SPECT studies were performed within 4 days after the CT scan. The first re-evaluation took place 2.9–3.3 mo postinjury (T3mo), the second 5.7–6.3 mo (T6mo) and the third 11.9–12.6 mo (T12mo).

All patients with an abnormal SPECT study underwent repeat imaging at the subsequent time of evaluation. To avoid unjustified

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For correspondence or reprints contact: Axel Jacobs, MD Nuclear Medicine Department, Virga Jesse Hospital, Stadsomvaart 11, B-3500 Hasselt, Belgium.

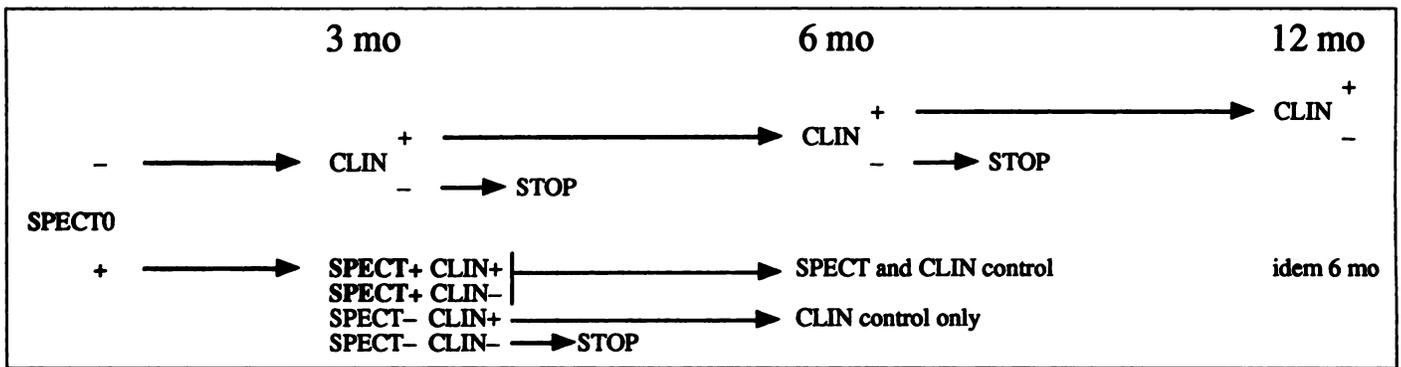


FIGURE 1. Study setup, in which SPECT0 is the early post-traumatic SPECT scan, within 1 mo after the trauma, and CLIN is the clinical evaluation.

radiation exposure, the study was designed so that patients with previously normal SPECT studies did not undergo repeat imaging unless a deteriorating clinical status was observed. Clinical reassessments were performed as long as the earlier SPECT scan had been positive or until patients were completely asymptomatic and their neurological examination had normalized. At the end of the study, all asymptomatic patients were recontacted to determine whether they had remained symptom-free. During follow-up, patients were not included in head trauma rehabilitation programs.

Clinical Evaluation and Data Analysis

All patients underwent a classical, complete neurological examination and an explicit questioning concerning postconcussive symptoms based on the list of symptomatology given by Rutherford et al. (16). Each patient also underwent memory and concentration tests (17). A patient was considered clinically negative (CLIN-) only if no signs and no symptoms were recorded. The presence of one symptom or sign was considered sufficient for classification as clinically positive (CLIN+).

For SPECT imaging and interpretation, we used the same methodology as previously described (14). The same grading scale was used to classify the degree of SPECT abnormalities according to the volume and severity of the hypoperfusion (score 1-4). The criterion for visual inspection used to determine a score of 0, which corresponds to a normal scan, was derived from a normal reference database generated by semiquantitative circumferential profile analysis (18).

In patients who continued to have positive SPECT results at subsequent examinations, the evolution of their SPECT abnormality score was evaluated with the Wilcoxon signed rank test for the time intervals T0-T3mo, T3mo-T6mo and T6mo-T12mo.

To describe the global trend in the evolution of the SPECT and clinical findings, the fraction of patients with persistently positive SPECT scans and clinical evaluation at subsequent times of control was expressed in relation to the total number of patients initially enrolled.

To calculate the sensitivity, specificity and predictive value of SPECT, we considered only patients who effectively underwent SPECT imaging, according to the study setup. Thus, no extrapolation was performed for CLIN+ or CLIN- patients with a negative SPECT scan at a previous time of control.

RESULTS

Global Evolution of SPECT and CLIN Results

Figure 2 gives a schematic overview of the SPECT and clinical results different at examination times. The initial SPECT scan (SPECT0) was positive in 73 of 136 patients (54%) and normal in 63 of 136 (46%). A gradual decrease in the fraction of SPECT+ patients was observed at subsequent times, but clinical normalization occurred earlier than normalization of the SPECT studies (Table 1). Only one patient, who was SPECT+CLIN- at T3mo, had to be categorized as SPECT+CLIN+ at T6mo. At 3 mo postinjury, 25 of 73 (34%)

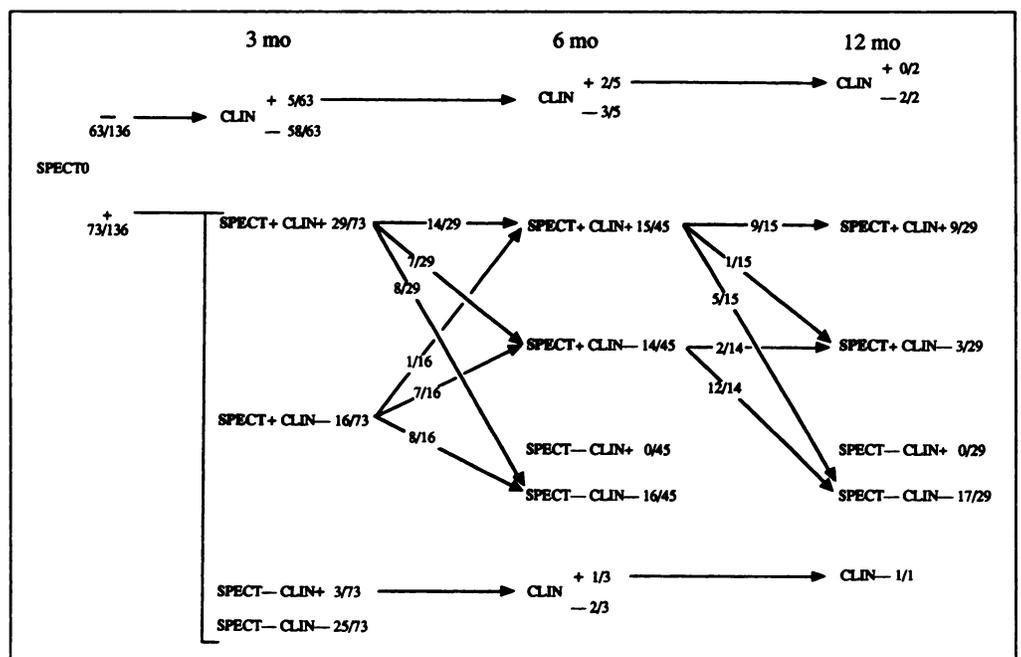


FIGURE 2. Overview of SPECT and CLIN results at different evaluation times: early post-traumatic stage (SPECT0) and during follow-up at 3, 6 and 12 mo postinjury.

TABLE 1

Fraction of CLIN+ and SPECT+ Patients at 3, 6 and 12 Months Postinjury

Time (mo)	CLIN+	SPECT+
3	37/136 (27%)	45/136 (33%)
6	18/136 (13%)	29/136 (21%)
12	9/136 (7%)	12/136 (9%)

CLIN+ = positive clinical evaluation; SPECT+ = positive SPECT result.

patients with an initial positive SPECT scan had completely negative clinical as well as SPECT findings and did not require further evaluation.

The fraction of patients with the combination of SPECT- and CLIN+ (false-negative SPECT fraction) at 3 mo postinjury was only 3 of 73 (4%). At 6 and 12 mo this combination did not occur anymore. A clear evolution in the fraction of patients with the combination SPECT+ and CLIN- (false-positive SPECT fraction) was observed. At T3mo, this combination occurred in 16 of 73 (22%) patients; at T6mo it occurred in 14 of 45 (31%) patients. However, at T12mo, this fraction had markedly decreased to 3 of 29 (10%). A gradual decrease in the number of patients presenting with the combination of SPECT+ and CLIN+ at T3mo (29 of 73 or 40%) was observed during further follow-up at 6 and 12 mo postinjury (15 of 45 or 33% and 9 of 29 or 31%, respectively).

Sensitivity, Specificity and Predictive Value of Initial and Follow-up SPECT Studies

The negative predictive value of SPECT₀, given as P(CLIN_{3mo-}/SPECT₀₋) was 58 of 63 (92%). Of the remaining five patients with the combination (CLIN_{3mo+}/SPECT₀₋), 2 of 5 still presented clinical signs at T6mo, but they all eventually became CLIN- at T12mo. None of the patients who had become SPECT-CLIN- had to re-enter the study. This results in a negative predictive value P (CLIN_{12mo-}/SPECT₀₋) of 100%. In contrast, the positive predictive value of the initial SPECT, given as P (CLIN_{3mo+}/SPECT₀₊), was only 32 of 73 (44%).

For all follow-up evaluations (Table 2), high-sensitivity and negative predictive values were found, increasing from respectively 91% and 89% at T3mo to 100% at T6mo and T12mo. The specificity and positive predictive value, however, remained low at T3mo and T6mo. These values had increased to 85% and 83%, respectively, only at T12mo.

Severity and Localization of SPECT Lesions

In those patients with persistent SPECT abnormalities, the extent and the severity of the lesions tended to decrease. For all considered time intervals, a significant decrease in SPECT+ scores was observed (Table 3). Persistency of the SPECT lesions was related to a higher score.

Also, a significantly higher SPECT₀₊ score was observed in the CLIN_{3mo+} group (mean score 1.8) as compared to the

TABLE 2

Sensitivity, Specificity, Negative Predictive Value (NPV) and Positive Predictive Value (PPV) of SPECT at 3, 6 and 12 Months Postinjury

Time (mo)	Sensitivity	Specificity	NPV	PPV
3	29/32 (91%)	25/41 (61%)	25/28 (89%)	29/45 (64%)
6	15/15 (100%)	16/30 (53%)	16/16 (100%)	15/29 (52%)
12	9/9 (100%)	17/20 (85%)	17/17 (100%)	10/12 (83%)

TABLE 3

Evolution of Mean SPECT+ Scores During Follow-up

Time interval (mo)	Number of patients	Evolution of SPECT scores
0-3	45	1.8-1.4 (p < 0.001)
3-6	29	1.6-1.3 (p = 0.003)
6-12	12	1.9-1.6 (p = 0.01)

*Only those patients with a persistently positive SPECT at subsequent times of evaluation were considered.

CLIN_{3mo-} group (mean score 1.4) (p = 0.008). At later stages, however, no significant differences in SPECT_{t+} score were found between CLIN_{t+} and CLIN_{t-} subgroups (t = 3 mo, 6 mo, 12 mo).

Table 4 gives an overview of the number of SPECT lesions according to their anatomic localization as well as the fraction of lesions persisting at T3mo, T6mo and T12mo, relative to the number at T0. Of the total number of lesions detected at T0, 13% were still found at T12mo; the same percentage was observed for left temporal and adjacent regions. In contrast, a markedly larger fraction (24%) of left and right frontal lesions persisted at T12mo. Figure 3 shows an example of a patient who remained CLIN+ during the 12-mo follow-up period and in whom persistent frontal hypoperfusion was observed on the rCBF SPECT scan.

DISCUSSION

Several studies on patients with head injury have already demonstrated that brain perfusion SPECT can depict more lesions than CT and, in many cases, SPECT lesions were found earlier and appeared to be larger than the corresponding morphological abnormalities. High sensitivity alone, however, does not make SPECT the imaging modality of choice in traumatic brain injury. In the present study, only mild head injury patients with a normal CT were included. SPECT data were correlated with clinical assessments in the early post-traumatic period and during a 12-mo follow-up. Two major issues were considered: assessing the predictive value of SPECT for clinical outcome and estimating its role in the evaluation of persistent postconcussive complaints.

The data from the early postinjury evaluation confirm our previously reported results (14), that showed a negative initial rCBF SPECT scan is a reliable predictor for favorable clinical outcome. This is an important finding in estimating the patient's ability to return to work. In contrast to its high negative predictive value, the positive predictive value of the early postinjury SPECT scan for outcome at 3 mo was low (44%). However, a higher score for SPECT abnormality involved

TABLE 4

Number and Localization of SPECT Lesions and Fraction of SPECT Lesions Persisting at 3, 6 and 12 Months Postinjury

	0	3 mo	6 mo	12 mo
Left temporal/frontotemporal and temporoparietal	54	34 (63%)	19 (35%)	7 (13%)
Left and right frontal	29	15 (52%)	12 (41%)	7 (24%)
Left and right parieto-occipital	32	15 (47%)	8 (25%)	2 (6%)
Other localizations	24	10 (42%)	4 (17%)	2 (8%)
Total	139	74 (53%)	43 (31%)	18 (13%)

Percentages in parentheses represent the fraction of persisting lesions relative to their initial number at T0.

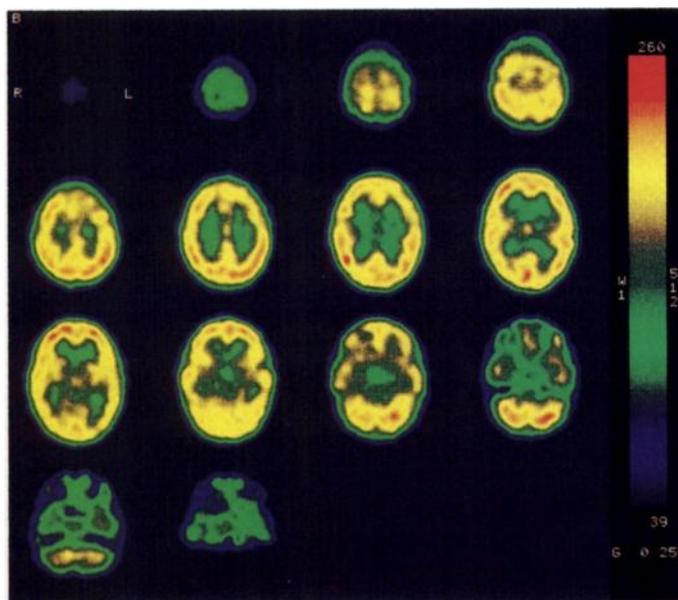
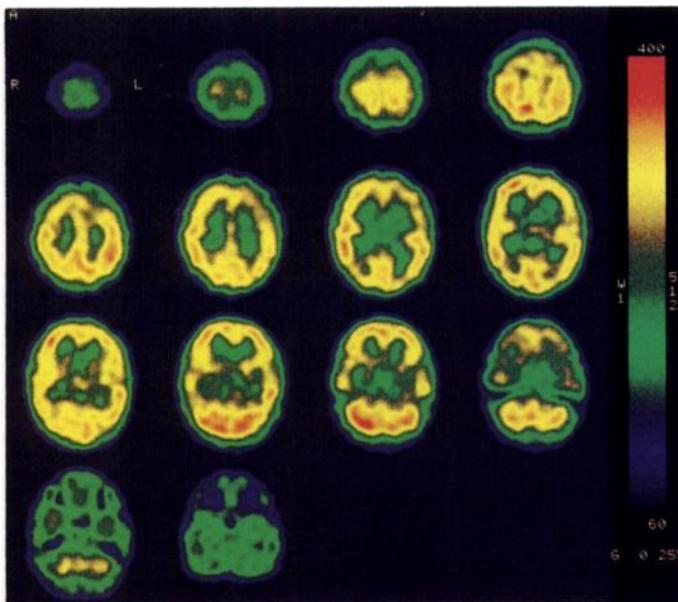


FIGURE 3. A 20-yr-old man who had suffered a mild head injury during a car accident. (A) The ^{99m}Tc -HMPAO SPECT at 3 mo postinjury showed a large region of markedly decreased perfusion in the left frontal cortex and a smaller area of reduced tracer uptake in the left temporal area. (B) At 12 mo postinjury, the SPECT showed a persistent though less severe left frontal hypoperfusion, whereas the left temporal hypoperfusion had disappeared. During the 12-mo follow-up period this patient continued to have postconcussive symptoms.

increased probability for persistence of symptoms at 3 mo and suggests that the degree of abnormality has some predictive significance.

During the 12-mo follow-up period, a gradual decrease was observed in both the fraction of patients with persistent clinical signs or symptoms as well as the fraction of patients with persistently positive SPECT scans. The disappearance of lesions on the SPECT image, as compared to clinical improvement, was slower so that the fractions of CLIN+ and SPECT+ patients were comparable only at 12 mo postinjury. A significant decrease in SPECT abnormality scores was observed over the different time intervals during follow-up.

During all follow-up evaluations, SPECT had high sensitivity and high negative predictive values, suggesting that a negative

SPECT study is a reliable criterion in the exclusion of clinical sequelae. The specificity and positive predictive value of the follow-up SPECT study was low at 3 and 6 mo but had markedly increased at 12 mo postinjury. This finding is important because, in many cases, a 12-mo interval has elapsed before a final decision is made on the patient's ability to go back to work or to issue disability benefits. Therefore, this may have significant consequences in the medicolegal issue frequently encountered after mild head injury.

In this study, a scan was considered normal if defects were completely absent. This is a stringent criterion since no absolute certainty can be obtained about the absence of brain perfusion alterations before the head trauma. This may be of particular importance in patients younger than 20 yr or older than 50 yr. The use of such a strict criterion may explain, at least in part, the earlier disappearance of clinical symptoms as compared to the scintigraphic evolution.

Due to a considerable false-positive fraction at 3 mo and 6 mo postinjury, caution is warranted in ascribing a positive SPECT result to post-traumatic sequelae in mild head injury patients with postconcussive symptoms. However, several arguments do support that statement for the lesions persisting at 12 mo postinjury. First, the probability of finding clinical abnormalities in the absence of SPECT lesions was very low. Moreover, no recurrence of symptoms was observed in patients with a negative SPECT scan. Second, in the fraction of patients with persistent clinical signs throughout the 12-mo follow-up period, the SPECT abnormalities still present at 12 mo postinjury had already been observed during the early post-traumatic stage. Finally, the localization of SPECT lesions appears to play a role. On the one hand, the previously reported predominance of lesions located in the left temporal and adjacent areas, depicted by the early postinjury SPECT image, was confirmed (14). On the other hand, at 12 mo postinjury, we observed relatively more pronounced persistence of frontal SPECT abnormalities compared to other locations. No straightforward explanation can be given for that finding.

Since a well-defined gold standard, based on pathophysiological criteria, for independent testing of SPECT results is lacking, an approach based on establishing the correlation of SPECT data with the clinical evolution was used to estimate whether the SPECT result accounts for the patient's clinical findings. We intentionally used the lowest possible threshold for deciding a positive clinical status. Indeed, postconcussive symptoms frequently are vague and nonspecific. Furthermore, it is known that patients with minor head injury may over-report symptoms. Also, detailed neuropsychological testing may reveal residual deficits in patients with apparently good recovery (19). Therefore, the sole basis on which a reasonable consensus can be reached on a clinically negative classification is complete absence of clinical signs and symptoms. This approach decreased the probability of obtaining false-positive test results and consequently enhanced the significance of the high sensitivity and negative predictive value obtained in this study.

CONCLUSION

Our study suggests that rCBF SPECT may play an important role in decisions involving mild head injury patients' return to work and may offer a reliable tool in legal and insurance issues. During the whole evaluation period, a normal SPECT study has a high negative predictive value for the clinical outcome. During early stages (≤ 6 mo postinjury), however, a positive SPECT study does not exclude a favorable outcome. In those patients who remained symptomatic 12 mo after the trauma, lesions persistent on the SPECT scan were related to rCBF

alterations observed during the early post-traumatic study. In particular, frontal localizations and more extended lesions appear to have a worse prognosis.

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Reproducibility of Regional Brain Metabolic Responses to Lorazepam

Gene-Jack Wang, Nora D. Volkow, John Overall, Robert J. Hitzemann, Naomi Pappas, Kathy Pascani and Joanna S. Fowler
Medical and Chemistry Departments, Brookhaven National Laboratory, Upton, New York; Departments of Radiology and Psychiatry, SUNY, Stony Brook, New York; Department of Psychiatry and Behavioral Sciences, University of Texas, Houston, Texas; and Psychiatry Service, VA Medical Center, Northport, New York

Changes in regional brain glucose metabolism in response to benzodiazepine agonists have been used as indicators of benzodiazepine-GABA receptor function. The purpose of this study was to assess the reproducibility of these responses. **Methods:** Sixteen healthy right-handed men underwent scanning with PET and [^{18}F]fluorodeoxyglucose (FDG) twice: before placebo and before lorazepam (30 $\mu\text{g}/\text{kg}$). The same double FDG procedure was repeated 6-8 wk later on the men to assess test-retest reproducibility. **Results:** The regional absolute brain metabolic values obtained during the second evaluation were significantly lower than those obtained from the first evaluation regardless of condition ($p \leq 0.001$). Lorazepam significantly and consistently decreased both whole-brain metabolism and the magnitude. The regional pattern of the changes were comparable for both studies ($12.3\% \pm 6.9\%$ and $13.7\% \pm 7.4\%$). Lorazepam effects were the largest in the thalamus ($22.2\% \pm 8.6\%$ and $22.4\% \pm 6.9\%$) and occipital cortex ($19\% \pm 8.9\%$ and $21.8\% \pm 8.9\%$). Relative metabolic measures were highly reproducible both for pharmacologic and replication condition. **Conclusion:** This study measured the test-retest reproducibility in regional brain metabolic responses, and although the global and regional metabolic values were significantly lower for the repeated evaluation, the response to lorazepam was highly reproducible.

Key Words: cerebral glucose metabolism; lorazepam; pharmacological challenge

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The measurements of regional brain glucose metabolism with PET and 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) has been used to assess cerebral dysfunction in neuropsychiatric disorders (1) and disease progression (2) and to evaluate the effects of treatment (3,4). This is feasible because baseline regional brain metabolism has been reported to be reproducible (5,6).

PET-FDG has been used to assess effects of acute drug interventions on regional brain metabolism. This allows physicians to identify those areas of the brain that are most sensitive to the drug and thus provides some direction in understanding the mechanisms of drug action (7,8). It also enables researchers to assess if there are differences in drug response between subjects groups indicative of specific neurotransmitter involvement (7). The brain metabolic responses to benzodiazepine agonists have been one of the most widely investigated. Benzodiazepine agonists, which facilitate GABA induced chloride flux at the GABA-benzodiazepine receptor complex (9) decrease regional brain glucose metabolism (8,10,11). These decrements are reverted by benzodiazepine antagonists indicating that they involve interaction with benzodiazepine receptors (12). Regional metabolic decreases, induced by benzodiazepine agonists, have been found to be blunted in alcoholics (11) and in subjects at risk for alcoholism (13). Because these differences could reflect the subject's state when the drug is given it is important to evaluate the reproducibility of these responses.

This study evaluates the reproducibility of the regional brain metabolic responses to benzodiazepine agonists in 16 healthy controls. We evaluated their responses to lorazepam twice at 6-8-wk intervals.

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For correspondence or reprints contact: Gene-Jack Wang, MD, Medical Department, Brookhaven National Laboratory, Upton, NY 11973.