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Quantitative PET Findings in Patients with Posttraumatic Anosmia

Objective: To investigate quantitative positron emission tomography (PET) findings, particularly from orbitofrontal cortex, in patients with posttraumatic anosmia. **Setting:** Neuropsychology outpatient clinic and university brain imaging center. **Subjects:** Eleven patients with head injury resulting in severe anosmia and 11 controls matched for age. All 11 head-injured patients had their head injuries at least 2 years before involvement in the study. **Measures:** Regional cerebral glucose metabolism was measured with PET. **Results:** Quantitative evaluation of PET findings for anosmic patients as a group showed orbitofrontal hypometabolism compared with controls. Decreased activity was also noted in mesial temporal lobe. Activity in subcortical white matter was essentially identical between groups. **Conclusions:** Findings strongly suggest that posttraumatic anosmia is closely associated with hypometabolism in the orbitofrontal cortex and the medial prefrontal cortex. The results also underscore the importance of posttraumatic anosmia as a clinical sign of orbitofrontal damage, as has been shown previously with neuroSPECT (single photon emission computed tomography). Key words: *positron emission tomography, posttraumatic anosmia, single photon emission computed tomography*

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THE PRINCIPAL objective of this study was to study quantitative positron emission tomography (PET) in patients with posttraumatic anosmia. Autopsy studies dating back to the 19th century have indicated that posttraumatic anosmia is typically associated with damage to the orbitofrontal cortex, even in cases with apparently mild head trauma.[1] It is generally believed that a clear association exists between head injury severity and the degree of olfactory dysfunction.[2] Anosmia is more likely to occur when loss of consciousness exceeds 1 hour, in more severe injuries (grade II–V), and when skull fractures occur.[3] Furthermore, the presence of a hematoma or contusion in the frontotemporal region has been related to impaired olfactory recognition.[4] It is suggested that nonmissile head injury could produce at least a partial

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impairment of olfactory recognition despite relatively preserved olfactory detection.[4] It has also been demonstrated in a variety of studies that head-injured patients with posttraumatic anosmia are highly likely to show a characteristic syndrome of cognitive deficits, which are, in many cases, of disabling severity (eg, indecisiveness, mental passivity, poor judgment, an inability to plan).[5-7]

Current research reports that anosmic individuals with posttraumatic brain injury (TBI) perform significantly more poorly than do post-TBI normosmic individuals on measures of executive skills and functional outcome.[8] In this study, olfactory dysfunction was a common finding after TBI, with only 30% of these subjects being aware of their deficits. The anosmic group demonstrated longer coma and greater impairment in a variety of frontal lobe–mediated executive functions (ie, complex attention, problem solving, inhibition of perseverative behaviors, and self-awareness of deficits), leading to greater functional disability.[8] It has recently been established that single photon emission computed tomography scanning (neuroSPECT) with technetium-99m hexamethylpropyleneamine oxime (Tc-99m-HMPAO) radioisotope brain perfusion agent with a half-life of approximately 6 hours can reveal central nervous system (CNS) injuries/functional abnormalities, which are not readily apparent on computed tomography (CT) or magnetic resonance imaging (MRI).[9-12]

Recent findings suggest that anosmia may serve as a unique marker for impairment of the orbitofrontal lobe "executive" systems with personality changes, such as inappropriate humor, inappropriate sexual behavior, labile emotionality, egocentricity, insistence of immediate gratification of perceived needs, and poor inhibition of action (eg, leading to compulsive and/or perseverative behavior). It has been also shown that patients who have had apparently minor head injuries with disabling neuropsychological deficits may also show neuroSPECT abnormalities in anterior mesial temporal and anterior frontal regions.[13,14] Among patients with posttraumatic anosmia, damage demonstrated in such patients typically involved hypometabolism of orbitofrontal cortex, as would be predicted from autopsy studies. The degree of orbitofrontal injury, as indicated by degree of hypometabolism, was closely correlated with outcome variables reflecting mental inertia, indecisiveness, dysexecutive functioning, and other "orbital-frontal deficits."[14] There were no other significant correlations, either involving other regions of interest or other neuropsychological measures. Thus, posttraumatic anosmia seemed to have a close and specific relationship with a particular locus of injury and a specific set of neurobehavioral symptoms (ie, an "orbitofrontal syndrome").[14]

Given these previous findings, it seemed appropriate to use a far more detailed functional neuroimaging technology, quantitative PET, to shed further light on CNS injuries associated with anosmia.

METHOD

Participants

Participants were identified from a population of patients (n = about 200) who had injuries that resulted in posttraumatic anosmia. The diagnosis of anosmia was made on the basis of olfactory testing, which indicated that participants were completely unable to identify common odors (eg, peanut butter, vanilla, peppermint) in both nostrils. All participants also reported onset of moderate to severe ageusia in association with the head injury, which rendered them anosmic, as is expected in posttraumatic anosmia resulting from first nerve damage.[14] All potential participants were originally clinically referred patients whose anosmia had been first

identified as part of their neuropsychological workup. Eight had mild head injuries, three had moderate head injuries, and none had severe injuries according to criteria established by the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine.[15]

Participants with head injury were 11 individuals (mean age = 47 years; SD = 9.6 years) with a history of head injury at least 2 years before being involved in the study. None had premorbid problems with substance abuse, mental disorders, or arrest for any reason. All participants had been gainfully employed for at least 5 years before their head trauma. This latter criterion was adopted to establish that each subject most probably had a productive and well-adjusted premorbid history. Scans were performed between 3 and 7 years after injury, guaranteeing that the injury had stabilized and was essentially permanent. At the time, all participants were taking no medications.

The 11 specific head injury cases were chosen as the first 11 to obtain PET scans from the Irvine Brain Imaging Center. These were ordered for clinical and/or forensic reasons. Age-regression matched controls were derived from a 56-participant control archive of data available at the Irvine Brain Imaging Center. Because the focus of the study was on posttraumatic anosmia and its implications for quantitative PET, it was decided to use normal controls rather than nonanosmic head-injured controls; the rationale being that this latter group might also contain patients with orbitofrontal hypometabolism or other areas of brain injury. A summary of neuropsychological testing from the 11 head-injured participants is shown in Table 1.

Previous neuroimaging

All of the 11 head injury participants had undergone CT and MRI at least once at some time before PET imaging. All had normal CT and MRI scans that had been obtained within 2 years of injury.

PET scanning

Five mCi of florine-18 deoxyglucose (FDG) was administered intravenously. A visual vigilance task was administered during the 30-minute uptake period. Thirty slices of the brain were obtained at 6.5-mm intervals parallel to the canthomeatal line on the GE 2048 head scanner (FWHM = 4.5). Raw images were reconstructed and visually interpreted by a clinician who was "blind" to diagnosis or condition. Slice heights were designated in centimeters above the canthomeatal line. The five images that best demonstrate the standard anatomy corresponding to Matsui and Hirano planes 8 to 12 were analyzed, because these slices encompass the hypothesized areas of interest that were primarily ventral frontal regions. An average of the 11 patients' PET scans for each corresponding slice was created using a previously described method.[16] An average of the 11 age-regressed control PET scans was also created using the same previously described method. A comparison of the two groups was performed using a *t* test ($P < .05$) on a pixel-by-pixel basis. A second thresholding was performed with a Monte Carlo–derived clustering threshold.[16] A statistical probability map was generated, with blue regions indicating areas that are at least two standard deviations below the mean and red regions indicating areas that are at least two standard deviations above the mean (see Fig 1).

RESULTS

Participants with head injury showed significant decreases in metabolic activity in bilateral orbitofrontal cortex (Brodmann's area [BA] 11) and rectal gyrus. There was also a decrease in frontal pole (BA10) metabolism.

Table 1. Neuropsychological testing of anosmic head-injured patients

Test	Score	Range
Full-scale IQ	114.1 (SD = 12.3)	90-133
Verbal IQ	112.8 (SD = 13.8)	83-136
Performance IQ	114.0 (SD = 12.6)	92-135
Information	10.8 (SD = 2.7)	7-19
Arithmetic	13.2 (SD = 3.2)	6-17
Similarities	12.3 (SD = 2.3)	10-18
Digit span	10.6 (SD = 2.7)	6-18
Digit symbol	11.7 (SD = 3.1)	6-17
Block design	12.3 (SD = 1.8)	11-17
Picture ar.	10.8 (SD = 3.4)	8-18
Log. mem.	9.7 (SD = 2.5)	6-15
Pair assoc.	9.9 (SD = 2.6)	6-14
BVRT correct	7.3 (SD = 2.0)	2-10
BVRT errors	3.8 (SD = 3.1)	0-11
COWA	31.6 (SD = 10.0)	15-52
Design fluency	5.3* (SD = 4.8)	1-21
WRAT reading	97.8 (SD = 17.6)	60-133
WRAT spelling	93.4 (SD = 16.3)	58-128
Dichotic left ear	31.1* (SD = 11.3)	12-47
Dichotic right ear	40.0 (SD = 8.8)	19-48
Dichotic both ears	24.3* (SD = 10.3)	8-42

*Mean test score below the 5th percentile of established norms.

There were significant decreases in medial prefrontal cortex metabolism (BA32). There were significant decreases in temporal cortex regions, such as the temporal tip (BA38) and middle temporal gyri (BA21). There were no significant differences between groups in metabolic activity in the putamen. There were no significant differences between groups in occipital radiation (white matter near the occipital cortex) metabolic activity. There were significant increases in activity in visual association cortex, resulting in a pattern of metabolic hypofrontality (see Table 2).

DISCUSSION

The results of this study clearly demonstrate that posttraumatic anosmia is typically associated with diminished metabolic activity in the orbitofrontal cortex. Medial prefrontal cortical decreases were also noted, and injury to temporal lobe was observed. The orbitofrontal and frontal pole injuries are entirely consistent with previously reported findings involving neuroSPECT.

The question as to whether orbitofrontal abnormalities would be found in anosmic patients was viewed as significant for a variety of interrelated reasons. First, posttraumatic anosmia is well established as a possible sequelae of TBI, even mild TBI.[14,17] As such, it is included as a feature of interest in the current *DSM-IV*[18] and the *American Medical Association Guidelines for Evaluation of Disability*[19] with regard to head injury and postconcussive syndrome. Autopsy studies have found that posttraumatic anosmia is closely associated with lacerations,

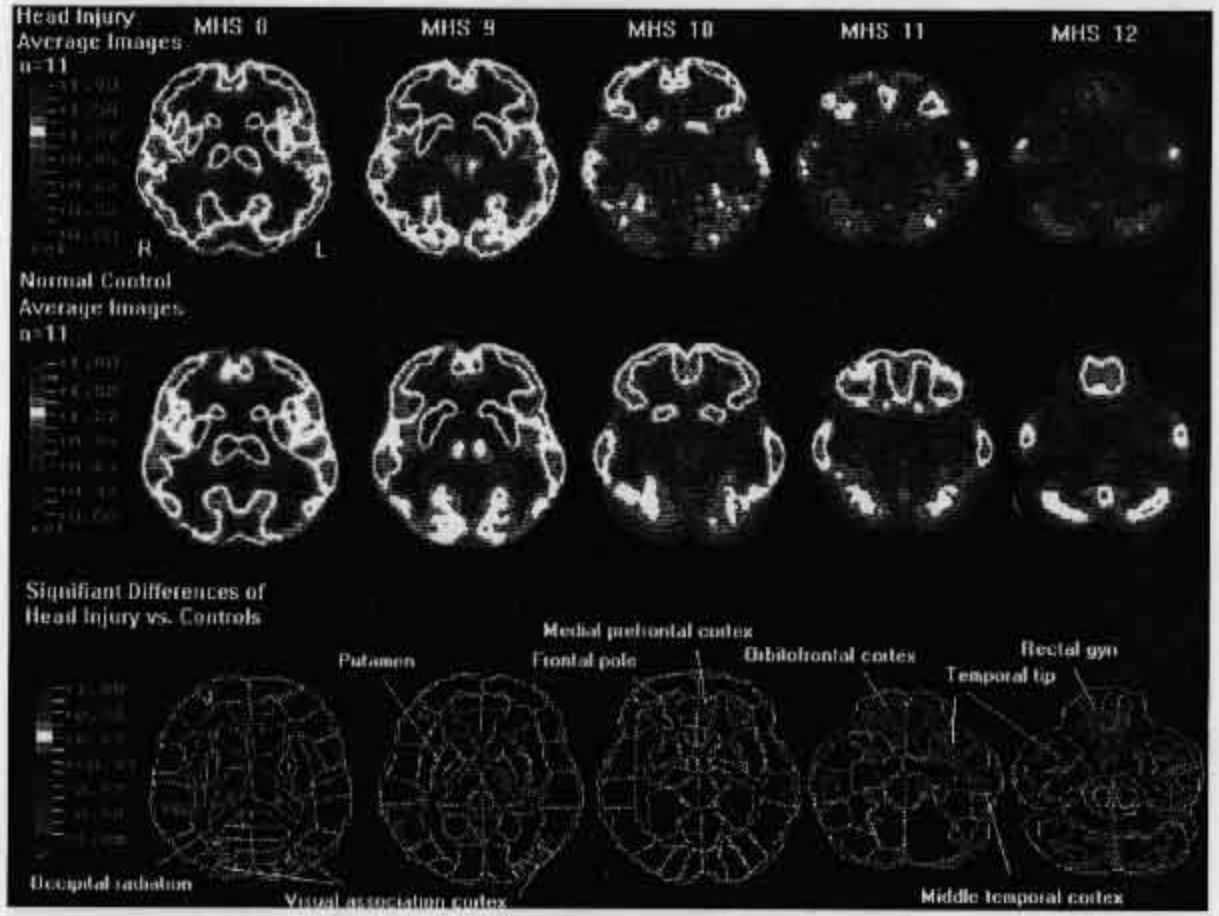

Fig 1. Composite PET scan images of anosmics and controls. The first and second lines of images are, respectively, the averages of the PET scans from the 11 head-injured participants and the 11 normal control participants. The third line of images represents a *t* test comparison of the two groups on a pixel-by-pixel basis. Blue regions indicate areas that are at least two standard deviations below the mean, and red regions indicate areas that are at least two standard deviations above the mean.

Table 2. Results of significance testing between groups on metabolic activity for regions of interest

Region of interest	*P* value	NC participants		TBI participants	
		M	SD	M	SD
Orbitofrontal, left	<.05	1.11	0.03	0.94	0.21
Orbitofrontal, right	<.05	1.34	0.01	1.18	0.11
Frontal pole	<.05	1.25	0.01	0.99	0.19
Medial prefrontal	<.05	1.38	0.02	1.22	0.16
Temporal tip	<.05	1.00	0.02	0.87	0.11
Middle temporal gyri	<.05	1.08	0.00	0.96	0.10
Putamen, left	ns	1.04	0.00	0.99	0.13
Putamen, right	ns	1.25	0.01	1.20	0.15
Occipital radiation	ns	0.97	0.02	0.97	0.15
Visual association cortex	ns	1.23	0.04	1.42	0.23

M = median; NC = normal control participants; ns = nonsignificant difference; SD = standard deviation; TBI = traumatic brain injured participants.

contusions, and abrasions of orbitofrontal cortex.[1] By implication, the presence of anosmia in a head-injured patient should indicate substantial risk for orbitofrontal injuries. It is noteworthy in this regard that the nature and location of injuries associated with anosmia, as demonstrated by autopsy study, would be difficult to detect with CT or MRI, both because lesions involve lacerations and contusions and because of bony artifact. Thus, for many patients, posttraumatic anosmia may be a key to suspecting that orbitofrontal injury is also present. Findings from studies that use functional neuroimaging support this clinical inference.

Findings also underscore the value of functional neuroimaging, quantitative PET in particular, as a useful adjunct to the evaluation of chronic head injury. In this regard, present findings support the conclusion that functional neuroimaging is more informative in TBI than CT or MRI.[20] The superiority of quantitative PET has also been seen in investigations of brain damage resulting from other causes as well (eg, carbon monoxide,[21] solvents[22]). This was certainly the case in this study, in which the results are also closely similar to findings indicating substantial hypometabolism but not outright tissue death. Indeed, in even the worst cases, findings indicated that the orbitofrontal cortex and related regions of interest were still working, but their activity was reduced by as much as, but no more than, half.

Just as MRI, CT, and electroencephalography mistakenly find "normality" in persons who are brain injured, so too does PET. The technology does not catch all patients with anosmia. Similarly, not all patients with orbitofrontal injury are anosmic, and not all patients with head injury have damage to orbitofrontal cortex. However, the findings obtained here, in previous studies involving SPECT, and in the autopsy literature all indicate that when a patient has anosmia, it is highly probable that they will have neuropsychological symptoms typical of orbitofrontal injury. Thus, posttraumatic anosmia reliably identifies orbital frontal injury despite the issues noted earlier.

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