Brain Blood Flow SPET Imaging in Heroin Abusers

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ABSTRACT: To assess whether chronic heroin abuse may generate vascular central nervous deficits, we studied the profile of vascular alterations in 17 heroin addicts (14 males mean age 31 years, range 23–39 years and 3 females mean age 33 years, range 30–35 years) before and, in one of them, 10 weeks after an ultra-rapid heroin detoxification. Using the functional technique of single-photon emission tomography (SPET) with 740 MBq of ^{99m}Tc-hexametazine (HMPAO) and computational brain-mapping techniques by means of a Talairach analysis, we determined the pattern of vascular brain alterations associated with chronic heroin abuse. Compared with controls, subjects who had used heroin chronically showed a decrease of global brain perfusion that was more significant in the frontal cortex—mainly in orbito-frontal regions, as well as in the occipital and temporal lobes. All patients showed marked asymmetric perfusion of the basal ganglia and the majority of them showed also an asymmetric perfusion of cerebellum. In addition, there were small activated areas dispersed in the occipital lobe (3 of 17) and apex region (4 of 17). In conclusion, decreased perfusion in heroin addicts was found in regions involved in the control of attention, motor speed, memory and visual–spatial processing. The prefrontal cortex is involved in decision making and inhibitory control, processes disturbed in heroin addicts who have stopped heroin consumption. A reduction in regional perfusion may reflect ongoing subtle neurocognitive deficits, which are consistent with the maintenance of asymmetry of the basal nuclei.

KEYWORDS: heroin abuse; cerebral blood flow; SPET

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INTRODUCTION

Heroin abuse is epidemic in Portugal as in many other countries and the use of the intranasal route of administration is growing in popularity among heroin abusers. Just as the pharmacokinetic profile of intranasal-administered heroin mimics that of injected heroin, the adverse neurological and systemic effects may be very similar and as potentially dangerous. Vascular cerebral complications are not usually thought to be associated with heroin abuse. However, toxic disorders related to heroin may cause neuropathological changes including hypoxic and ischemic changes with cerebral edema, ischemic neuronal damage, and neuronal loss which are assumed to occur under conditions of prolonged heroin respiratory depression, stroke due to, for example, thromboembolism, vasculitis, septic emboli, hypotension, and positional vascular compression.[1–5]

The exact etiology of different neuropathological alterations associated with heroin abuse is still unclear, but may also be related to additional substances used as adulterants as well as with the occasional consumption of others drugs. All these neuropathological entities could have consequent brain vascular lesions.

This article aims to characterize possible persistent abnormalities in 17 heroin addicts, immunodeficiency virus negative, with a history of episodic use of cocaine and cannabis and regular use of tobacco and alcohol.

METHODS

A total of 17 subjects participated in this study, which was approved by the Institutional Ethics Committee of Coimbra University Hospital (Coimbra, Portugal). Informed consent was obtained.

The heroin-dependent subjects (14 males and 3 females; mean; age 31.11 years) were recruited from a program of ultra-rapid heroin detoxification from the Psychiatric Department of Coimbra University Hospital. All the subjects underwent an extensive medical and neurological examination, a routine blood work-up, and HIV antibody testing to rule out existing medical or neurological illness. All the patients were free of psychotropic medication, except three who were receiving buprenorphine (mean dosage of 7.4 mg/day) for several weeks. Exclusion criteria consisted of any significant past or current medical or neurological condition including epilepsy, migraine, unexplained loss of consciousness, or severe head trauma. All results of medical, psychiatric, and clinical laboratory evaluations were unremarkable.

Detailed clinical histories of drug and alcohol consumption were obtained for each patient. Diagnosis of opioid dependence was performed in all cases according to the criteria of the Diagnostic and Statistical Manual, Version 4 (DSM-IV) (304.00). None met DSM-IV criteria for any other Axis I diagnosis, with the exception of nicotine dependence (305.10).

TABLE 1. Clinical and demographic characteristics of the group of subjects

Patients studied	17 patients (14 males; 3 females)
Mean age	31.11 years; range (22–39 years)
Mean age of initiation	21.18 years; range (16–31 years)
Mean years of consumption	9.81 years; range (3–18 years)
Mean daily heroin	0.66 g; (smoked: 9 patients; i.v.: 5 patients)
Mean daily buprenorphine (3 patients)	7.4 mg
Sporadic use	Cocaine 7 patients; cannabis 4 patients
Mean period of time between last consumption of substances with opioid action and performance of SPET	11.93 h

All patients reported sporadic use of other illicit drugs (mainly cocaine and cannabis) but none met the criteria for abuse or dependence.

TABLE 1 summarizes the clinical and demographic characteristics of the group of subjects.

Imaging Protocol

Patients were studied using the functional technique of single-photon emission tomography (SPET) and computational brain-mapping techniques through a Talairach analysis to determine the patterns of vascular brain alterations associated with chronic heroin abuse.

In a quiet, dark room, each patient received 740 MBq of ^{99m}Tc-hexametazine (HMPAO) (Ceretec®, Amersham, United Kingdom) via an intravenous line, to avoid noxious stimuli and cerebral activation. To prevent frontal lobe activation as a result of total sensory deprivation, the patients were allowed to leave the ears unplugged. Oppositely, the patients close their eyes to avoid the activation of visual areas.

These environmental conditions were maintained during the ^{99m}Tc-HMPAO uptake period ($\sim$30 min). After the uptake period, patients were transported in bed to the gantry room to reduce voluntary movements. One of the male patients repeated the protocol 10 weeks after suppression due to an ultra-rapid heroin detoxification with naloxone.

Imaging of the brain, via a gamma camera with three detectors (Neurocam, GE, Milwaukee, WI) connected to a computer, began 30 min after tracer injection in all 17 patients.

Tomography was performed in a 128 $\times$ 128 matrix using 128 stops at 30 s per view in a 360° circular rotation. The energy setting was 140 keV with a 20% window. The time required for SPET data acquisition was 25 min. Images were reconstructed by filtered back-projection with a Butherworths filter of 0.5 Nyquist cutoff frequency associated with a ramp filter without attenuation correction. Image pixel size was 4 mm in a 128 $\times$ 128 array.

Neurogam software was used to evaluate the cerebral blood flow (CBF) using statistical parametric mapping. This program contains a database of CBF normal results with which we can compare our findings.

RESULTS

In general terms, the most evident change was a marked decrease of perfusion in some preferential lobes, with minus 3 or 4 standard deviation when compared with the normal controls included in the software database. Compared with those controls, subjects who had used heroin chronically showed a decrease of global brain perfusion that was more significant in the frontal cortex (12 of 17), mainly in orbito-frontal (FIG. 1) and temporal regions (12 of 17). The occipital (7 of 17) and parietal lobes (5 of 17) have also hypoperfused areas (FIG. 2). All the studied patients showed marked asymmetric perfusion of the basal ganglia (FIG. 3). Cerebellum showed also decreased perfusion in 16 patients, 7 with symmetric (FIG. 4) and 9 with asymmetric (FIG. 1) alterations. Simultaneously, there were small activated areas dispersed in the frontal lobes (10 of 17), temporal lobes (4 of 17), occipital lobes (3 of 17), and apex region (4 of 17) (FIG. 4). The patient who had repeated brain perfusion study 10 weeks later did not show any improvement on the second scan.

DISCUSSION AND CONCLUSIONS

Functional neuroimaging techniques, such as positron emission tomography (PET), single photon emission computerized tomography (SPECT), and magnetic resonance imaging (MRI) have revealed altered regional cerebral activity by all drugs of abuse.[6]

Several groups have found that opioids, such as morphine or heroin, decrease global or regional CBF after acute administration in normal laboratory animals.[1,7–13]

The effect of chronic administration of heroin in animals and in patients is less clear. Morphine has usually a vasodilator effect on cerebral arterial circulation but this effect could be related with hypercapnia as a consequence of alveolar hypoventilation induced by the drug.[14–16] The cerebral circulation is not modified by therapeutic doses of morphine. However, the respiratory depression and CO_2 retention induced by opioids could originate cerebral vasodilation and rise LCR pression.[17]

The symmetrical involvement of functional brain systems strongly indicates a toxic or metabolic etiology.[18,19] Chemical agents may damage functional brain systems selectively. Certain brain regions and systems have a greater sensitivity to specific types of toxins. These regions of identical vulnerability frequently involve a whole functional chain of neurons and tracks and

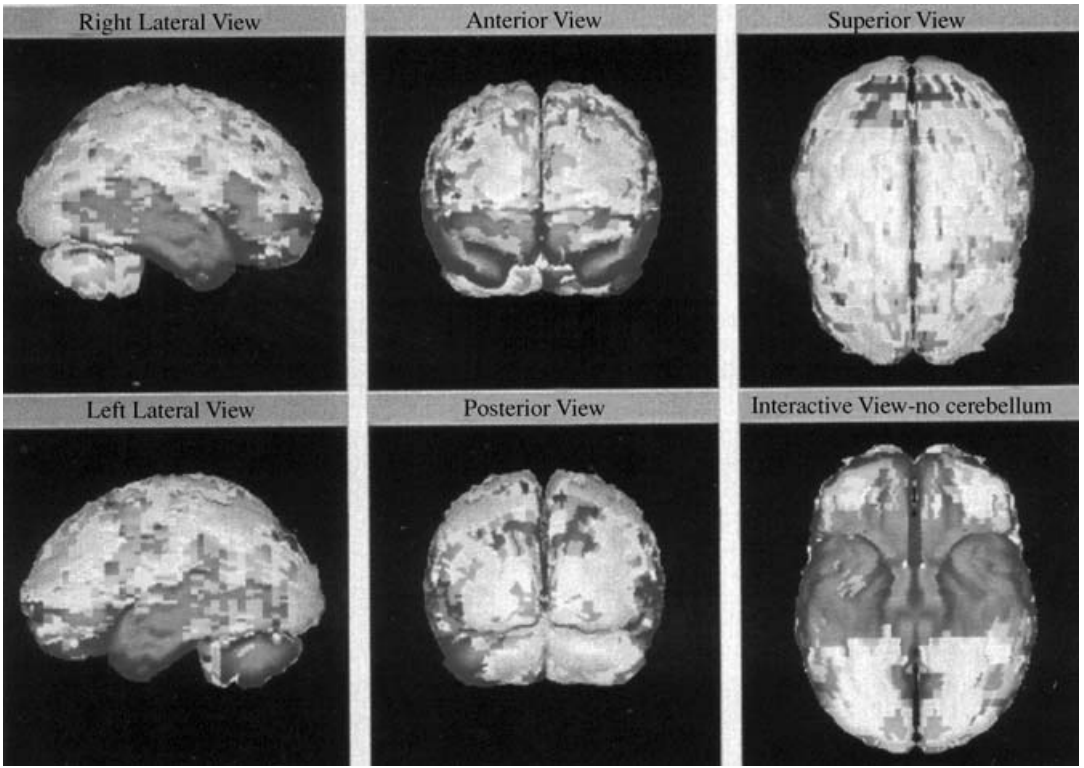

FIGURE 1. Example of a patient studied before ultra-rapid heroin detoxification with naloxone. The images show decreased brain perfusion in the frontal cortex mainly in orbito-frontal regions and temporal lobes. Notice that the cerebellum also shows decreased perfusion in an asymmetric way.

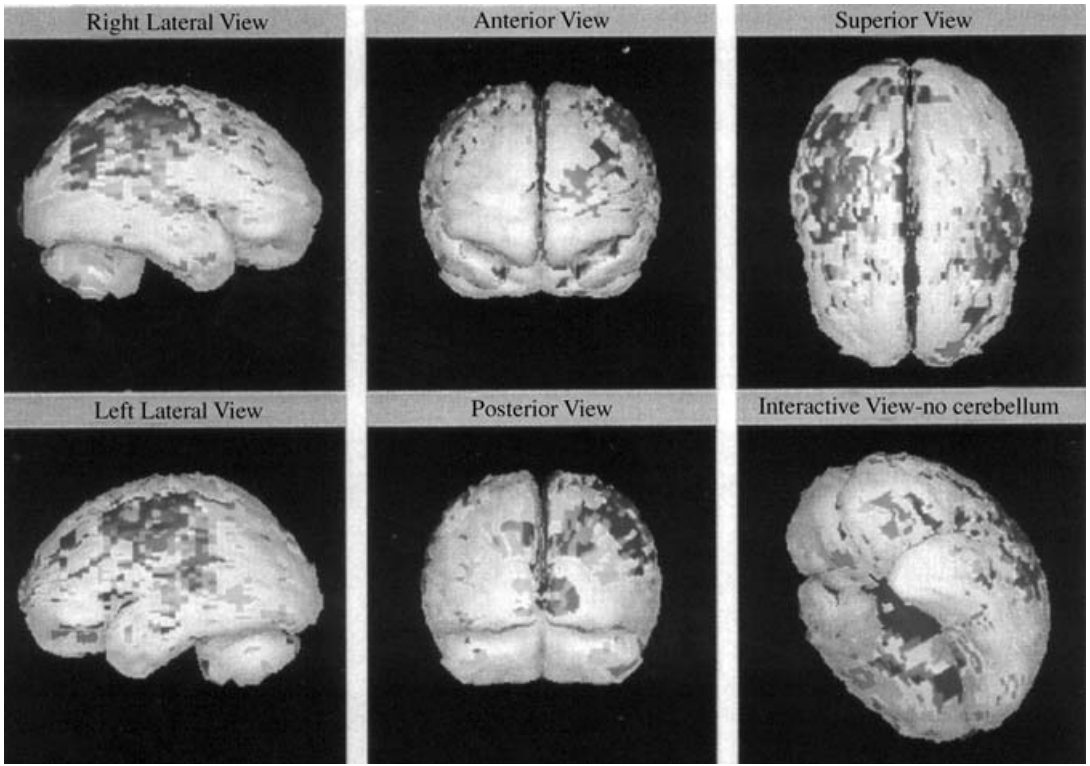

FIGURE 2. Example of a patient studied before ultra-rapid heroin detoxification with naloxone. The images show decreased brain perfusion in the parietal and occipital lobes.

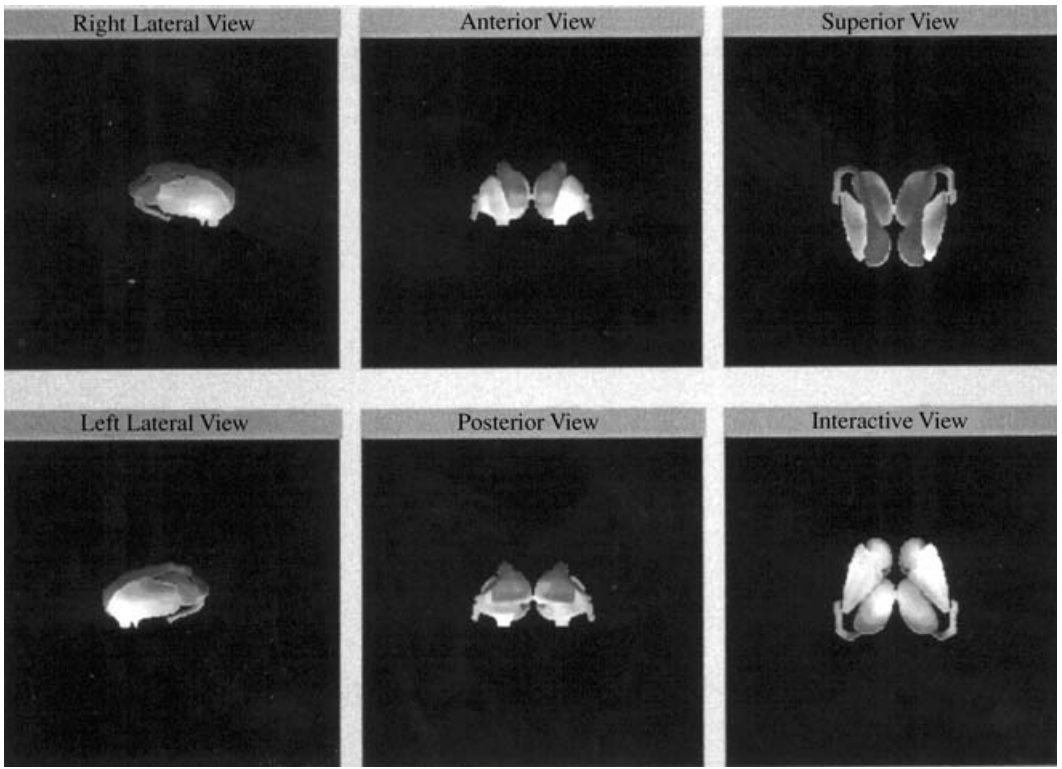

FIGURE 3. In this patient, a marked asymmetric perfusion of the basal ganglia is apparent. This event was seen in all the studied patients.

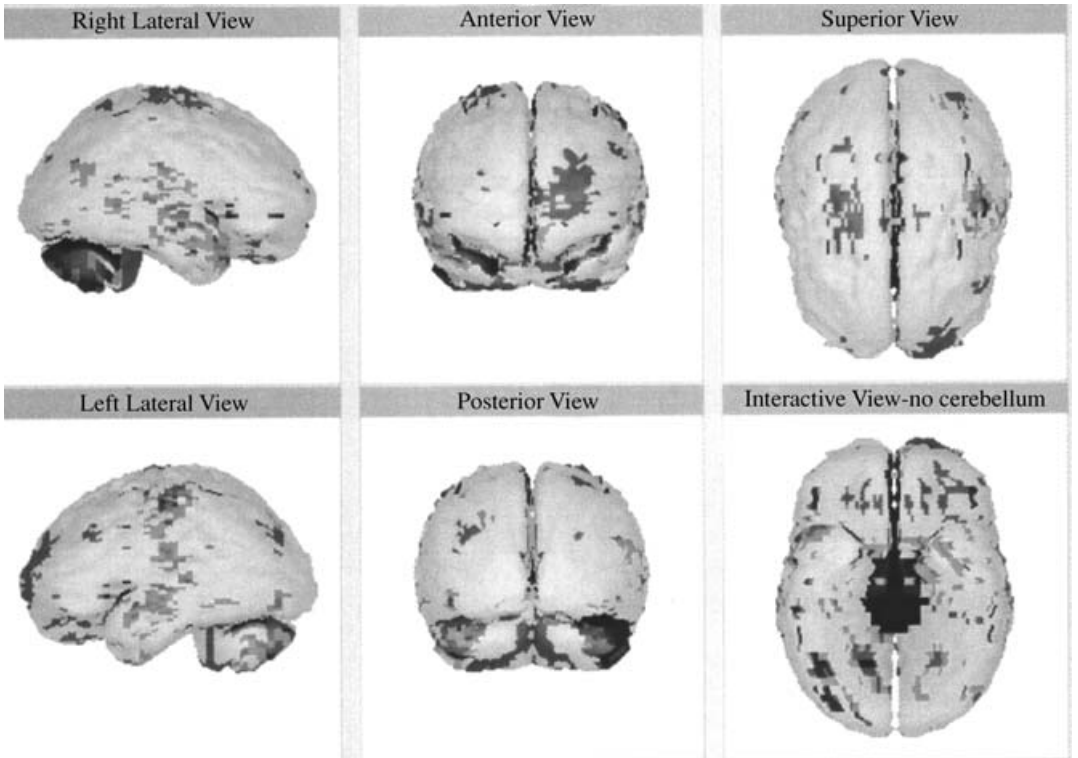

FIGURE 4. Images obtained in a male patient studied before ultra-rapid heroin detoxification with naloxone, showing dispersed small activated areas in frontal and occipital cortex and apex region. In this example, we can appreciate a symmetric cerebellar decreased perfusion.

not a single structure. Brain areas that form functional systems show a synchronous development, including myelination, during phylo- and ontogenesis. Demyelination due to degeneration or toxic damage may also be synchronous. Selective vulnerability may also be related to similarity and particular characteristics (e.g., oxygen requirements, chemical composition, and neurotransmitters). The selective vulnerability of myelin to lipophilic agents results from a specific chemical composition. Myelin[20] is characterized by a higher specific lipid content and a slow turnover.[20] Once in the blood, heroin is rapidly hydrolyzed to monoacetylmorphine (MAM) which is then hydrolyzed to morphine. Heroin and MAM are more lipid soluble than morphine and enter the brain more readily. Morphine and MAM are believed to be responsible for the pharmacologic action of heroin. Cone *et al*.[21] found that the intranasal administration of heroin resulted in a rapid appearance of heroin, MAM, and morphine in blood. Morphine was present for a longer time (2–4 h) than heroin or MAM because of its lower clearance rate. Morphine time course coincided with the observed–induced effects of intranasal heroin.

The imaging findings after heroin consumption are highly specific. The neurological deficit is, as a rule, irreversible. There is no effective therapy. The image findings are almost always unchangeable at follow-up examinations.

Our results differ, however, from those obtained in a group on 16 heroin-dependent patients where the CBF was measured using SPET with ^{99m}Tc-HMPAO showing that the temporal lobes were the most affected area; hypoperfusions of the right and left temporal lobe were observed in five and five patients, respectively. Three of the patients had a hypoperfusion of the right frontal lobe, two patients showed perfusion defects in the left frontal lobe, right parietal lobe, and left parietal lobe.[22] In another study, the heroin addicts showed a nonsignificant reduction of whole brain perfusion values. Significant hypoperfusion in the right frontal and left temporal lobes was found in addicts with comorbid depression, and a significant decrease in CBF in the right frontal lobe was observed in those with antisocial tendencies.[23]

In our group, the symmetrical findings in cortical CBF may mainly be attributed to substance abuse per se than to mood and behavioral traits, where the asymmetrical findings are more common.[23]

The patients in this study were nicotine dependent, many for several years, and it was uncertain how cerebral perfusion would be affected by heroin plus nicotine.

Using ^{99m}Tc-HMPAO and Talairach analysis, heroin abuse associated with cigarette smoke was found to have an effect on CBF, similar to that obtained by cigarette smoke alone.[24] The results indicate that heroin and smoking induce a significant reduction in CBF related to normals of the same gender and age, included in the database.

In fact, a chronic smoking habit is known to be significantly associated with a reduction in CBF, and smoking is known to accelerate cerebral arteriosclerosis.[5] The influence of cigarette smoking on CBF seems likely to

be a net effect of not only nicotine but also the other constituents of main stream cigarette smoke (e.g., tar, phenol, acetic acid, CO, CO_2, NO, and NO_2) and some vasoconstrictors—thromboxane A2, plasma endothelin, and cerebral cortex serotonin, that have been found to be elevated after smoking.[25] So, smoking in heroin users also reduced central blood flow as assessed by SPET. Since cerebral perfusion decreased, will ultimately result in a high incidence of cerebral vascular disease in smokers, our study seems to appoint to a sum effect of the two drugs.

Young drug abusers also have very high alcohol consumption parallel to narcotic drug abuse.[26] A magnetic resonance study[27] in 23 drug abusers always combined with heavy alcohol consumption demonstrated that chronic drug abusers may develop structural brain changes early in life consisting of cerebral atrophy, both manifesting itself as cortical atrophy, a mild enlargement of the lateral ventricles, and atrophy of the cerebellum. In our group of patients, the decrease of cerebellar perfusion could be consistent with the changes referred above.

Cerebral perfusion, studied with ^{99m}Tc-HMPAO SPET, in cocaine dependent-women, 40 of whom were also heroin dependent, was abnormal. The concurrent abuse of heroin and cocaine was associated with more perfusion abnormalities in both sexes, located in anterior brain structures, such as the frontal and temporal cortex and the basal ganglia.[28–30]

Basal ganglia dysfunction has been associated with disturbances of movement and in addition to motor dysfunction cognitive abnormalities were described.[31] In our study, decrease perfusion in the occipital cortex was not associated with a strong cognitive decline and we were unable to find consistent relationships between motor scores and topographic network in the brain for heroin abuse, suggesting that various levels of regional activity may exist and pointing to the complexity of studying the underlying pathophysiology with a direct topographic analytic approach directed at functional localization.[31]

In this study, only relative CBF values were used, which are susceptible to general arousal, years of consumption of heroin, and other drug effects; in view of the differences found, this still indicates that additional differential diagnostic information can be obtained using clinically available relative perfusion measurements.

Our images show some regions of hyperperfusion in another wise normal cortex and this increase did not vary significantly by location; it is likely that these changes could reflect the different emotional status of opioid-dependent patients.[32]

In conclusion, this ^{99m}Tc-HMPAO SPET and Talairach analysis suggest that the chronic use of opiates results in a decrease of global brain perfusion abnormalities more significant in frontal cortex, mainly in orbito-frontal regions, as well as in temporal and occipital lobes. All the studied patients showed marked asymmetric perfusion of basal ganglia. Simultaneously dispersed small activated areas in the occipital lobes and apex region were observed. The decreased

perfusion is found in regions mediating attention, motor speed, memory, and visual and spatial processing. The prefrontal cortex is involved in decision making and inhibitory control, processes that are disturbed in heroin addicts. The decrease of regional perfusion may reflect continuing subtitle neurocognitive deficits that are sustained with the maintenance of basal nuclei asymmetry.

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