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Functional magnetic resonance imaging of the acute effect of intravenous heroin administration on visual activation in long-term heroin addicts: results from a feasibility study

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Abstract

This preliminary report is the first demonstration of the acute effects of diacetylmorphine (heroin) administration on functional activation in the human brain using functional magnetic resonance imaging (fMRI). Four opiate addicts who received regular prescriptions for heroin, underwent fMRI using a visual activation paradigm before and after a dose of 30 mg heroin. All four showed a decrease after the heroin dose in the extent of significant activation. This method shows promise for sequential scanning to determine brain activity in response to different drugs and routes of drug administration. © 1997 Elsevier Science Ireland Ltd.

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1. Introduction

Understanding of the mode of action of opiates in humans has progressed markedly over the past few decades. Opioid receptors were characterised and endogenous opioid peptides identified (Bloom, 1983). The psychomotor stimulant theory of addiction provided a neural basis underlying opiate addiction (Wise and Bozarth, 1987). The rapid advances which have occurred in neuroimaging now provide opportunities to develop our understanding of the effects of opiates in human drug addiction. Several animal studies examining the effects of morphine and other mu-agonists on local cerebral glucose utilisation have produced conflicting data with regard to the regional changes which occur in response to these agents (Hiesinger et al., 1983; Ito et al., 1983; Fanelli et al., 1987). In humans, there have been studies in drug abuse disorders using single photon emission computed tomography (SPET) and positron emission tomography (PET) to investigate brain function (Woods, 1992; London, 1994). In a study of polydrug abusers with histories of opiate abuse or dependence, London et al. (1990) found, using PET, that 30 mg morphine sulphate given intramuscularly (i.m.) to opiate users resulted in a reduction in glucose utilisation by 10% in whole brain and by 5–15% in telencephalic areas and the cerebellar cortex.

Functional magnetic resonance imaging (fMRI) using blood oxygenation level dependent (BOLD) contrast has been used to demonstrate neuronal activation in response to a number of exogenous stimuli including photic stimulation (Ogawa et al., 1990). Photic stimulation has been used to evaluate the effects of administra-

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Table 1
Patient characteristics and current drug treatment

Patient	Sex	Age (years)	Duration of i.v. heroin use (years)	Duration of treatment	Treatment
A	M	48	30	13	Methadone 100 mg (oral), heroin 80 mg (i.v.)
B	M	49	23	11	Methadone 80 mg (oral), heroin 40 mg (i.v.), nitrazepam 20 mg (oral)
C	M	56	33	22	Methadone 50 mg (oral), heroin 80 mg (i.v.)
D	F	35	14	10	Methadone 100 mg (oral), heroin 80 mg (i.m.)

tion of several drugs (Bruhn et al., 1994; Levin et al., 1995; Howard et al., 1996). We report here the results of photic stimulation before and after the acute administration of heroin in four long-term heroin users by two routes of administration using the BOLD functional MRI technique.

2. Materials and methods

This study was approved by the Bethlem and Maudsley Hospitals Ethical Committee.

Four heroin addicts in treatment at the National Addiction Centre (Maudsley Hospital) and four controls with no history of substance abuse were recruited to the study. All the patients had a history of poly drug use dominated by their long-standing opiate addiction. In the context of the treatment of their condition they received prescribed supplies of injectable diacetylmorphine (heroin). Table 1 shows the characteristics of the patients and their current drug treatment. Urine samples, collected before the fMRI, were positive for morphine and methadone for all patients (consistent with compliance with intake of their prescribed supply), and this accorded with the results of regular urine monitoring as part of their clinical care. The patient on nitrazepam also had a urine sample positive for benzodiazepines. The urine samples of all subjects were negative for amphetamines, barbiturates, cannabis and cocaine. Four control subjects (43-year-old male, 29-year-old male, 33-year-old female, 23-year-old female) were included to provide a comparison set of results for the specific stimulation procedure and timing.

2.1. Imaging

A 1.5 Tesla GE Signa MR system (General Electric, Milwaukee, USA) fitted with Advanced NMR hardware and software (Advanced NMR, Massachusetts, USA) was used for imaging. Daily quality assurance was carried out to ensure high signal to ghost ratio, high signal to noise ratio and excellent temporal stability using an automated quality control procedure (Simmons et al., 1997). Foam padding and a forehead strap were used to limit head motion during the study and subjects were requested to remain as still as possible. Ten near axial slices of 5 mm thickness separated by a gap of 0.5 mm were prescribed parallel to the anterior-posterior commissure line from a sagittal localiser image so as to encompass the visual cortex. A 40×20 cm field of view was used with a 128×64 acquisition matrix giving a 3.1 mm in-plane resolution. T_2^*-weighted gradient echo echoplanar images (TR = 3000 ms, TE = 40 ms, flip angle = 90°) demonstrating BOLD contrast were acquired for a total of 5 min per fMRI study. Each fMRI study consisted of an alternating series of five off/on periods of visual stimulation (30 s off, 30 s on). Thus, a total of 100 images were acquired at each slice position.

2.2. Stimulation

Visual stimulation was delivered by light-proof goggles (Grass Instruments model SV100S, Astro-Med Inc, Rhode Island, USA) containing a pattern array of red light emitting diodes that flashed on and off at a frequency of 8 Hz. From the commencement of scanning a repeating cycle of 30 s periods of darkness alternating with 30 s of visual stimulation were presented to subjects.

2.3. Procedure

Patients took their usual medication including oral methadone dose, but not their prescribed heroin, at home before coming to the imaging centre at approximately 8.30 a.m. The procedure was explained again (all had an initial explanation at the time of recruitment into the study), time allowed for further questions and informed consent for the procedure gained. The study was an open pilot and therefore patients were informed that they would be receiving 30 mg heroin. No formal measurements of mood, withdrawal or pupil size were taken. A baseline scan was carried out. Thirty milligrams of heroin were prepared for administration at room temperature. It was administered according to the patient's usual site and method of administration. The precise method of administration was determined for each individual to maintain a balance between the usual method of administration and the need for the subject

to remain still on the scanner table. Three patients used heroin intravenously (i.v.) and one intramuscularly (i.m.). In practice, the heroin was administered in a bolus, either by the patient alone or with some help from the doctor in attendance. Patients were scanned up to three times after this heroin administration (a maximum of four fMRI studies). They were instructed to remain as alert as possible during the procedure. They were asked to keep their eyes open during the procedure and were reminded of this before each scan. Eye fixation was aided by the presence of a light in the eye goggles on which they were asked to fix their line of vision. Table 2 shows route of heroin administration and timing of scans for all 4 subjects, and timing of scans for the control subjects. The precise timing of post-injection studies was dependent upon ease of heroin administration and patient compliance. The control subjects underwent three scans at time intervals similar to the patients' but no drug was administered since the aim was only to determine the temporal reproducibility of the protocol in controls.

2.4. Image analysis

An automatic 3-D technique for rigid body image registration was applied to each consecutive set of 100 ten-slice blocks of images to reduce movement artefact within each single 5-min functional study. This was accomplished by calculating a mean image from the 100 time points and minimising the absolute grey scale difference between the average image and the images at each time point using the Powell-Davison-Fletcher multi-dimensional search algorithm (Press et al., 1988). Tricubic spine interpolation was then used for image realignment. The T_2^*-weighted signal intensity time series at each voxel of the realigned images were regressed on the concomitant and lagged time series of estimated positional displacements at each voxel (Friston et al., 1996). Activated voxels were then identified using the method of Bullmore et al., 1996. The power of periodic signal change at the fundamental off-on frequency of stimulation was estimated by iterated least-squares fitting a time series regression model including sine and cosine terms to the motion-corrected time series at each voxel of all images. The fundamental power quotient (FPQ = fundamental power divided by its standard error) was estimated at each voxel and randomisation testing (involving randomly reorganising the order of images from a given study to ascertain the null distribution) then used to create inferential brain activation maps of pixels significantly activated by the experimental stimulus.

Table 2
Times of scans in each patient after the heroin injection, and times of scans of the control subjects

Subject	Route	Post 1 (min)	Post 2 (min)	Post 3 (min)
A	i.v.	+7	+15	n/a
B	i.v.	+1	+12	+27
C	i.v.	+9	+18	n/a
D	i.m.	+9	+25	+44
Controls	n/a	0	+10	+20

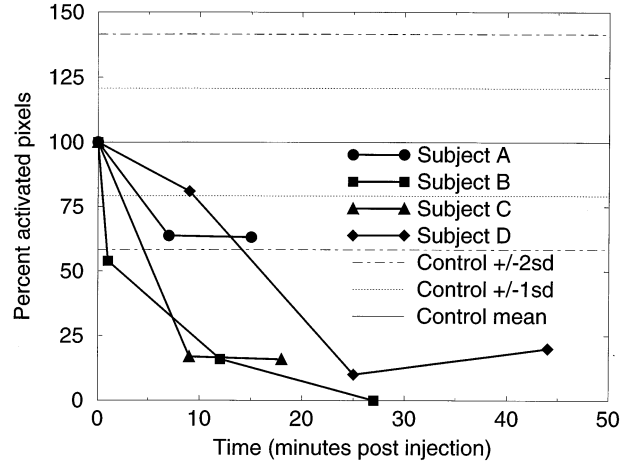

Fig. 1. Number of activated pixels ($P < 0.01$) for patients expressed as a percentage of the number activated at the baseline scan as a function of time post-injection. The variation of control response is illustrated by the mean control response ± 1 and 2 S.D.s.

The time course of activation was assessed by summing the number of activated voxels within the visual cortex for each fMRI study. Movement between different functional scans was excluded by direct visual comparison of slices from the first time point of each registered functional dataset.

3. Results

Fig. 1 illustrates the variation with time of the number of activated pixels for each patient relative to the time of injection. The data for control subjects showed no consistent pattern of increase or decrease and was therefore displayed as a mean ± 1 and 2 S.D.s to allow clear comparison with the patient data. The extent of activated pixels decreased substantially for each patient following injection. Fig. 2 illustrates the activated pixels for patient A for the three fMRI studies starting prior to injection, 7 min post-injection and 14 min post-injection respectively.

4. Discussion

These four cases are the first in vivo demonstration, using functional magnetic resonance imaging, of an effect of heroin on cortical brain function. They demonstrate a marked reduction in BOLD activation in

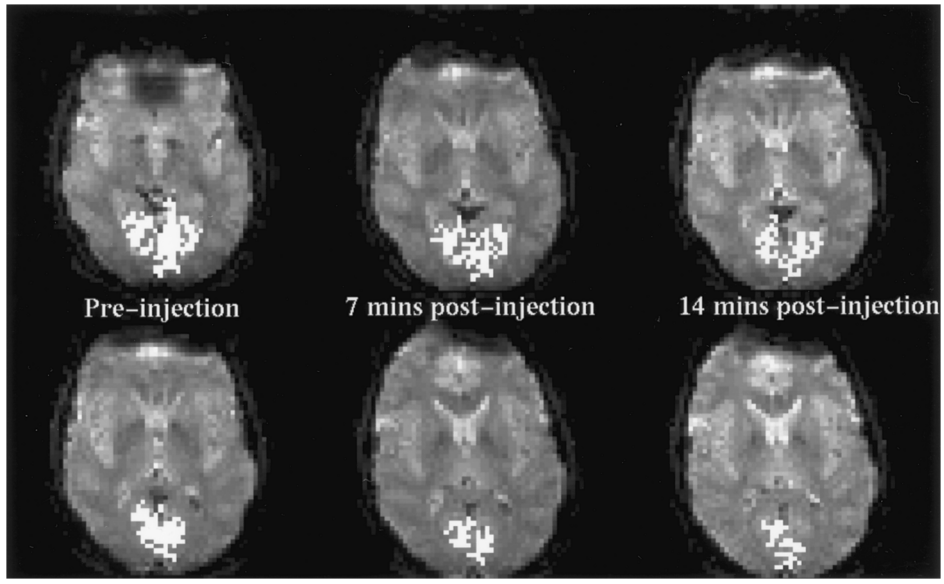

Fig. 2. Activated pixels ($P < 0.01$) due to visual stimulation overlaid on the original images for patient A. Two of the ten slice positions are illustrated for fMRI studies starting prior to injection, 7 min post-injection and 14 min post-injection.

the visual cortex in response to visual stimulation of from 37–100% after i.v. administration of 30 mg diacetylmorphine (heroin). The underlying mechanism which would explain these findings remains unclear. Clearly the reduction in BOLD activation can represent a real decrease in blood oxygenation in the visual cortex or an apparent decrease consequent on an increase in total blood oxygenation. Changes in blood oxygenation relate to changes in blood volume or, more likely, changes in blood flow.

The visual response to administration of heroin can be compared to that for other drugs. Levin et al. (1995) showed that oral administration of 0.7 g/kg of ethanol led to a BOLD response to visual simulation at peak blood alcohol level of almost half that of controls. Howard et al. (1996) studied the effect of 10 mg of oral dexamphetamine on visual and auditory activation in narcoleptics and controls pre- and 90-min post-administration. They showed a decrease in activation as determined by pixel count in the controls and on average, a more than doubling of response in narcoleptics post-drug. Bruhn et al. (1994) investigated the effect of 1.0 g of acetazolamide on visual activation by one pre- and two-post administration scans. They showed a markedly attenuated mean signal change post-injection, but there was a large inter-individual variability.

Morphine exerts a combination of depressant and stimulatory effects in the central nervous system. The general cerebral depression of morphine results in reduced ability to concentrate and to deal with complex thought processes, impairing mental and physical performance (Duthie and Nimmo, 1987). On the other hand it produces stimulation of the chemoreceptor trigger zone, spinal reflexes and the para-sympathetic portion of the occulomotor nucleus (Martin, 1983). Mechanisms underlying opiate dependence invoke activation within the meso-limbic and meso-cortical dopamine system (Wise and Bozarth, 1987; Altman et al., 1996). An explanation on the basis of an increase in whole brain blood flow is consistent with results of morphine administration to animals (Koskinen and Bill, 1983; Trusk and Stein, 1987). Trusk and Stein (1987) demonstrated a 36% increase in cerebral blood flow in 37 of 40 brain areas in rats studied 1 min after heroin administration (200 μg/kg). Blood flow specifically to the visual cortex significantly increased by 60% in this study. This was interpreted as showing an opiate mediated effect in the visual cortex, either through receptors in the visual cortex or through receptors at some distal site. However, the human study (London et al., 1990) referred to earlier reports a reduction in whole brain glucose utilisation following the administration of morphine; no statistically significant effect of 30 mg morphine i.m. being obtained in the areas of the visual cortex. The injection of the mixed agonist-antagonist buprenorphine 1 mg (i.m.) has been found to result in a significant reduction in cerebral metabolic rate for glucose (CMRglc) and the regional CMRglc by up to 32% in 19 bilateral and in four midline regions in poly drug users (Walsh et al., 1994). Thus, other evidence is contradictory. Hypotheses about the site of action of opiates most commonly include areas other than the visual cortex, such as the ventral striatum, ventral tegmental area and pre-frontal cortex (Wise and Bozarth, 1987; Altman et al., 1996). Development of stimulus paradigms to measure variations in blood flow in these brain areas is desirable. The stimulus used in this study has been chosen because it has previously

used by our group but also because of pre-existing work in which it had been associated with other drug effects (Bruhn et al., 1994; Levin et al., 1995; Howard et al., 1996).

In considering whole brain blood flow, it is possible that the patients studied here have cerebral perfusion deficits as a result of their long history of poly drug misuse and that their response to stimuli is abnormal as a result. Cerebral perfusion abnormalities in the frontal and temporal cortex in four women who were cocaine and heroin dependent have been reported (Levin et al., 1994). This does not, however, provide an explanation for the pattern of results demonstrated here; rather it would argue for an overall abnormality.

Explanations which invoke an actual decrease in visual cortex blood flow could possibly include a kappa mediated opiate response since the area is rich in kappa receptors whose actions in humans are less well characterised than those of mu-opiate receptors (Pfeiffer et al., 1982). Alternatively an actual decrease in blood flow could result from a peripheral effect or artefact. Possibilities include an effect on pupil size, eye movement, fixation and accommodation (Murray et al., 1983). Our study procedure included measures designed to reduce eye movement and improve fixation. Normal subjects have undergone visual stimulation fMRI in our scanner with eyes closed. Some diminution of visual cortex response is found, but of a much lesser degree than that displayed by the subjects reported on here (unpublished data).

The patients in this study were opiate dependent subjects on methadone maintenance. Thus, the brain changes following administration of heroin do not reflect the effect on an opiate free substrate. On the basis of patient interview and observation by experienced clinicians, the subjects can be considered to be in an intermediate state. The dose of methadone they had taken was sufficient to prevent any individual from being in frank withdrawal. However, all subjects report an opiate effect after using their daily heroin dose in addition to the effect obtained by methadone alone. We were, therefore, able to study the effects of heroin administration on opiate dependent patients who were not in withdrawal. It should not be assumed that administration of heroin to abstinent, i.e. previously but not currently dependent subjects, or administration to currently dependent subjects who are in withdrawal before administration, would provide the same results; this is clearly an area for further study.

This preliminary study is an open study carried out with small numbers of subjects. We offer two arguments to support the conclusion that we have demonstrated a specific opiate effect rather than an effect of habituation to the procedure itself or of subject expectation. It has been demonstrated elsewhere (Howseman et al., 1996) that activation in response to visual stimulation can be maintained during a testing procedure with no effect of habituation. This was observed in the response of the controls included in our study. Our study included heroin administered by two different routes. The time of onset of opiate effects following an i.v. injection would be expected to occur within a very few minutes while that of i.m. heroin will be delayed, the exact time depending on circulatory state and local factors at the site of injection. This corresponds to our findings that subject D showed a delayed decrease in relative visual cortex blood flow in response to visual stimulation, but the small numbers means that no firm conclusions can be drawn from this observation.

We have found functional MRI to be capable of demonstrating that the acute administration of heroin has caused a reduction in visually induced BOLD contrast in these four heroin addicts. The underlying mechanism giving rise to this effect of heroin is not yet clear. This is a preliminary study with an open design and with few subjects and thus no hard conclusions can be drawn. However, it suggests that a specific effect of heroin can be demonstrated using this technique. Further studies using a placebo controlled design, alternative stimuli and larger numbers are recommended.

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References

Altman, J., Everitt, B.J., Glautier, S., Markou, A., Nutt, D., Oretti, R., Phillips, G.D., Robbins, T.W., 1996. The biological, social and clinical bases of drug addiction: commentary and debate. Psychopharmacology 125, 285–345.

Bloom, F.E., 1983. The endorphins: a growing family of pharmacologically pertinent petides. Annu. Rev. Phamacol. Toxicol. 23, 151–170.

Bruhn, H., Kleinschmidt, A., Boecker, H., Merboldt, K.D., Hanicke, W., Frahm, J., 1994. The effect of acetazolamide on regional blood oxygenation at rest and under stimulation as assessed by MRI. J. Cereb. Blood Flow Metab. 14, 742–748.

Bullmore, E.T., Brammer, M.J., Williams, S.C.R., Rabe-Hesketh, S., Janot, N., David, A.S., Mellers, J.D.C., Howard, R., Sham, P., 1996. Statistical methods of estimation and inference for functional MR image analysis. Magn. Reson. Med. 35, 261–277.

Duthie, D.J.R., Nimmo, W.S., 1987. Adverse effects of opioid analgesic drugs. Br. J. Anaesth. 59, 61–77.

Fanelli, R.J., Szikszay, M., Jasinsky, D.R., London, E.D., 1987. Differential effects of mu and kappa opioid analgesics on cerebral glucose utilisation in the rat. Brain Res. 422, 257–266.

Friston, K.J., Williams, S.C.R., Howard, R., Frackowiak, R.S.J., Turner, R., 1996. Movement-related effects in fMRI time series. Magn. Reson. Med. 35, 346–355.

Hiesinger, E.M., Voorhies, R.M., Lipschutz, L., Basler, G., Shapiro, W.R., Pasternak, G.W., 1983. The effects of morphine on glucose metabolism in rat brain as measured by quantitative autoradiography. Soc. Neurosci. 9, 138.

Howard, R.J., Ellis, C., Bullmore, E.T., Brammer, M., Mellers, J.D., Woodruff, P.W., David, A.S., Simmons, A., Williams, S.C.R., Parkes, J.D., 1996. Functional echoplanar imaging correlates of amphetamine administration to normal subjects and subjects with the narcoleptic syndrome. Magn. Reson. Imaging 14, 1013–1016.

Howseman, A.M., Josephs, O., Porter, D., Muller, E., Frackowiak, R.S.J., Turner, R., 1996. Sustained activation in visual cortex using EPI and FLASH fMRI. Neuroimage 3, 58.

Ito, M., Suda, S., Namba, H., Sokoloff, L., Kennedy, C., 1983. Effects of acute morphine administration on local cerebral glucose utilisation in rat. J. Cereb. Blood Flow Metab. 3, 574–575.

Koskinen, L.O., Bill, A., 1983. Regional cerebral, ocular and peripheral effects of naloxone and morphine in unanesthetized rabbits. Acta Physiol. Scand. 119, 235–241.

Levin, J.M., Holman, B.L., Mendelson, J.H., Teoh, S.K., Garada, B., Johnson, K.A., Springer, S., 1994. Gender differences in cerebral perfusion in cocaine abuse: Technetium-99-HMPAO SPECT study of drug abusing women. J. Nucl. Med. 3, 1902–1909.

Levin, J.M., Ross, M.H., Mendelson, J.H., Kaufman, M.J., Yurgelun-Todd, D.A., Cohen, B.M., Renshaw, P., 1995. Reduction in BOLD response to photic stimulation after ethanol administration. Proc. Soc. Magn. Reson. Vol. 1, 162.

London, E.D., Brousolle, E.P.M., Links, J.M., Wong, D.F., Cascella, N.G., Dannals, R.F., Sano, M., Herning, R., Snyder, F.R., Rippetoe, L.R., Toung, T.J.K., Jaffe, J.H., Wagner, H.N., 1990. Morphine-induced metabolic changes in human brain. Arch. Gen. Psychiatry 47, 73–81.

London, E.D., 1994. Positron emission tomography in studies of drug abuse. NIDA Res. Monogr. Ser. 138, 15–24.

Martin, W.R., 1983. Pharmacology of opioids. Pharmacol. Rev. 35, 283–323.

Murray, R.B., Adler, M.W., Korczyn, A.D., 1983. The pupillary effects of opioids. Life-Sci. 33, 495–509.

Ogawa, S., Lee, T.M., Kay, A.R., Tank, D.W., 1990. Brain magnetic resonance imaging with contrast dependent blood oxygenation. Proc. Natl. Acad. Sci. 87, 9868–9872.

Pfeiffer, A., Pasi, A., Mehraein, P., Herz, A., 1982. Opiate receptor binding sites in human brain. Brain Res. 248, 87–96.

Press, W.H., Flannery, B.P., Teukolsky, S.A., Velterling, W.T., 1988. Numerical recipes in C: The art of scientific computing, Cambridge University Press.

Simmons, A., Moore, E., Williams, S.C.R., 1997. Automated quality control for functional MRI studies. Neuroimage 5, S466.

Trusk, C.T., Stein, E.A., 1987. Effect of intravenous heroin and naloxone on regional cerebral blood flow in the conscious rat. Brain Res. 406, 238–245.

Walsh, S.L., Gibson, S.F., Janinski, D.R., Stapleton, J.M., Phillips, R.L., Dannals, R.F., Schmidt, J., Preston, K.L., Grayson, R., Bigelow, G.E., Sullivan, J.T., Contoregii, C., London, E.D., 1994. Buprenorphine reduces cerebral glucose metabolism in poly drug users. Neuropsychopharmacology 10, 157–170.

Wise, R.A., Bozarth, M.A., 1987. A psychomotor stimulant theory of addiction. Psychol. Rev. 94, 469–492.

Woods, S.W., 1992. Regional cerebral blood flow imaging with SPECT in psychiatric disease; focus on schizophrenia, anxiety disorders and substance abuse. J. Clin. Psychiatry 53, 20–25.