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ORIGINAL INVESTIGATION

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Prefrontal cortical hypometabolism during low-dose interferon alpha treatment

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Abstract *Objective:* To evaluate prospectively interferon alpha (IFN-α) associated effects on cerebral glucose metabolism and its correlation to neuropsychiatric symptoms during low-dose IFN-α-treatment. *Methods:* Eleven patients treated with low-dose IFN-α for chronic hepatitis C were prospectively evaluated by neuropsychiatric tests and cerebral [^{18}F]deoxyglucose positron emission tomography (FDG-PET) before and in the 12th week of treatment. PET images were spatially normalized, corrected for variance in global activity and pixel-based *t*-statistics were calculated for each set of PET scans using SPM96 software. Pixel-cluster with $P<0.001$ for hypo- or hypermetabolism were displayed in parametric images. Covariance analysis with neuropsychiatric tests was calculated for each cluster. *Results:* In week 12 of IFN-α treatment, significant hypometabolism with a decrease of local activity ranging from 8 to 12% was found in all patients bilaterally in the prefrontal cortex (BA 9), which correlated in a covariate analysis with changes in depression score as measured by Beck's Depression Inventory. Additionally, hypermetabolism with a maximum increase in local activity of 6–8% was seen in all patients in putamina as well as the left occipital region (BA 18). Before IFN-α treatment, only 1/11 patient showed depressive symptomatology. After 3 months of treatment, 6/11 patients were classified as having mild to moderate depressive symptoms ($P<0.1$; Wilcoxon test). *Conclusions:* Low-dose IFN-α therapy is associated with significant prefrontal hypometabolism. This hypometabolism covaried with depression score, but was even found in clinically non-depressed patients. These findings may reflect a possible predisposing factor for IFN-α associated neuropsychiatric syndromes and might contribute to a pathophysiological model of affective disorders, as endogenous IFN-α levels are elevated in a subset of psychotic patients during acute disease.

Keywords Interferon · PET · Depression · Brain metabolism · Statistical parametric mapping · Neuropsychological tests

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Introduction

Interferon alpha (IFN-α) is a cytokine which is endogenously produced by leukocytes upon viral infection. Recently, IFN-α has been introduced as a drug to treat chronic viral diseases such as chronic active viral hepatitis B and C as well as different malignancies (Baron et al. 1991; Williams and Linch 1997). Although IFN-α's role in the treatment of malignancies is controversial, IFN-α is a proven effective therapy for chronic hepatitis B and C and is therefore, in combination with other drugs such as ribavirin, the treatment of choice in these conditions (Sharara et al. 1996; Hoofnagle and di Bisceglie 1997).

Apart from its antiviral activity, IFN-α has been shown to have a wide range of neuromodulatory properties in the central nervous system (CNS). These include the regulation of endocrine systems such as the upregulation of the hypothalamic-pituitary-adrenal (HPA)-axis and the modulation of behavior, brain activity, temperature, feeding pattern and opiate activity. More recently, IFN-α has been shown to upregulate the transcription of the serotonin transporter gene (Morikawa et al. 1998) and to enhance immobility in the mouse forced swim-

ming test, an animal model of depression (Makino et al. 1998). Some or a combination of these neuromodulatory properties of IFN-α may explain why a significant proportion of patients treated with IFN-α develop neuropsychiatric side-effects (Valentine et al. 1998). These neuropsychiatric side-effects of IFN-α therapy are dose-dependent. Short-term application of very high doses of IFN-α (up to 900 MU/6 days) for the treatment of cancers and amyotrophic lateral sclerosis causes an organic mental disorder in a high percentage of patients. This syndrome develops after a relatively short latency of several days and is characterized by somnolence, confusion, mental and motor slowing, difficulty in concentrating, memory impairment, parkinsonian symptoms, hearing loss or seizures. With chronic low dose IFN-α treatment (e.g., 5 MU/3 times a week), as for the therapy of chronic viral hepatitis, a spectrum of less severe neuropsychiatric symptoms may be evoked. These range from mild forms of depression, irritability, lack of motivation, and impaired concentration to more severe forms of depression with suicidality or manic and paranoid psychoses (Valentine et al. 1998). These symptoms are observed in up to 13% of patients and mostly occur after treatment of patients for 2–3 months.

IFN-α treatment of patients with chronic viral hepatitis C may be looked at as a "model" to investigate the effects of IFN-α on CNS functioning. This model may not only help to explain the nature and underlying brain pathology of neuropsychiatric side-effects of IFN-α therapy, but may also contribute to an understanding of the etiopathology of endogenous psychoses, in which IFN-α has been suggested to be involved (e.g., Preble and Torrey 1985). In recent prospective studies investigating patients treated with IFN-α, an increase of depressive symptomatology during IFN-α therapy has been reported (Hunt et al. 1997; Malaguarnera et al. 1998). However, for patients treated with low dose IFN-α, no data are available so far either on changes in neuropsychological functioning or on changes in functional brain imaging.

The present study prospectively investigated patients with chronic viral hepatitis C before and after 3 months of low dose IFN-α therapy by neuropsychological tests and [^{18}F]deoxyglucose positron emission tomography (FDG-PET), thus allowing for detection of changes in cerebral glucose metabolism during therapy and for a covariance analysis of neuropsychiatric side-effects and cortical dysfunction.

Materials and methods

The study was approved by the local ethic committee of the University of Freiburg. Informed consent was obtained by all patients. Eleven patients (ten males, one female, 31–63 years, mean 46) with chronic active viral hepatitis C were investigated. The patients received 3–6 MU IFN-α 3 times a week with a mean IFN-α dose of 5±1 MU per injection. None of the patients had a history of neurovascular or neurodegenerative brain disorder, hepatic encephalopathy or other neuropsychiatric disorder. The PET investigation was performed at the same day before the first injection of IFN-α and after 3 months of IFN-α therapy. Directly before the PET procedure, all patients underwent a neuropsychological test battery including an auditory verbal learning test (AVLT; Mueller 1998), a verbal fluency test (controlled oral word association, COWA) and the trail making test part A. Furthermore, the patients were asked to fill out three self rating scales assessing their psychopathological state, namely the Beck Depression Inventory (BDI; Beck et al. 1961), the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith 1983) and the Symptom Check List SCL-90-R.

The PET procedure was performed according to previously defined standards (Juengling et al. 1999, 2000). In brief, the patients were allowed to rest for at least 10 min before injection of 200±20 MBq 18-FDG and during the uptake period for another 20 min in an acoustically isolated and dimmed room. The patients were then transferred to the scanner (Siemens CTI ECAT EXACT tomograph, 10.8 cm FOV, 6.8 mm FWHM), where the patients' heads were positioned according to the orbitomeatal line. Image acquisition was started 30 min after injection. Six dynamic frames of 5 min duration each were acquired. Images were then reconstructed using filtered back-projection by Shepp-Logan filter (cut-off 0.35 cycles/pixel). Attenuation correction was performed using the standard mathematical algorithm implemented in ECAT software. The dynamic frames were then checked for motion artifacts and summed up to generate a single dataset of 31 transaxial planes.

Data analysis

For statistical parametric mapping, image data were converted to ANALYZE format, and automated spatial normalization was performed using rigid body affine transformations as well as zooming in the *x* and *y* direction (SPM96, SPM95 PET template, 4×5×4 transformations) in order to realign the dataset according to the 3-D stereotaxic grid by Talairach and Tournoux (1988). For pairwise comparison of the pre- and during therapy investigations, the scans of the individual patients were first registered onto each other using the Automated Image Registration (AIR 3.08) algorithm by Woods (1998) and then normalized to stereotaxic Talairach space using SPM96. Prior to voxel-based statistical analysis, images were smoothed using a 10×10×10 mm Gaussian kernel. The global cerebral metabolic rate for glucose (gCMRGlc) was normalized to an arbitrary mean of 50 µmol/100 ml per minute by a group-wise analysis of covariance (ANCOVA) (Friston et al. 1990). The normalized FDG-PET data of the pretherapeutic investigation was compared to a normal data base constituted from 11 subjects without morphological or neurological pathology by computing a pixel by pixel *t*-statistics for detection of a priori hypo- or hypermetabolic areas (Juengling et al. 1999; Signorini et al. 1999).

An image of unpaired *t*-values was then calculated with each voxel consisting of the difference in mean metabolic activity divided by local variance between pre- and during therapy scans. The applied activity of injected FDG and the time delay between injection and start of acquisition were defined as confounding covariates. Only those voxel clusters were kept which exceeded *t*-values corresponding to $P<0.001$ in a single test and a minimal cluster size of 12 voxels. The *t*-statistics was transformed to a normal statistic yielding a *Z*-score for each pixel. For visualization of the *Z*-score statistics, the *Z*-score voxel clusters were projected onto the standard MRI data set provided by SPM96, using the SPM projection routine which additionally displays the Talairach coordinates, thus allowing anatomic identification. Neuropsychological test results were defined as covariates of interest. Conjunction analyses were performed to determine which brain areas showed changes that covaried with them. For visualization of the results, adjusted normalized regional activity across pre- and during therapy groups was plotted for each voxel cluster at the voxel with maximal *Z*-score.

Results

Data for the psychopathological status before and during IFN-α therapy are given in Table 1. Depressive symptoms increased during the 3 months therapy with IFN-α on the BDI, the HADS depression subscale, and the SCL-90-R depression subscale. However, these increases were not statistically significant. Only the BDI scale showed a trend towards deterioration ($P<0.1$; see Table 1). Patients were further classified into three groups with a BDI score ≤10 (group 1; no depression), a BDI score between 11 and 17 (group 2; mild depression), and a BDI ≥18 (group 3; moderate depression). Before IFN-α therapy, all but one patient were classified into group 1, i.e., as having no depressive symptomatology. After 3 months of IFN-α therapy, two patients were allocated into group 2 and three patients into group 3; the remainder were classified as group 1 (Wilcoxon test; $P<0.1$). Anxiety decreased during IFN-α therapy (but again not statistically significant) as measured by the HADS anxiety subscale and the anxiety subscale of the SCL-90-R. Significant changes on the SCL-90-R scale were an increase in somatization and a decrease in uncertainty. All other measures revealed no significant changes.

Data for neuropsychological functioning before and during IFN-α therapy are given in Table 2. A statistically significant worsening of neuropsychological functioning was seen for the auditory verbal learning test (AVLT), which measures the learning capabilities related to fronto-subcortical structures. Both the immediate recall and the total score decreased significantly after 3 months of IFN-α therapy. No changes were seen for verbal fluency and the trail making test part A.

Table 1 Psychopathological status of 11 patients with chronic active viral hepatitis C before and after 3 months of interferon-α (*IFN-α*) therapy. Psychopathological status was assessed by the Beck Depression Inventory (*BDI*), the Hospital Anxiety and Depression Scale (*HADS*), and the Symptom Check List SCL-90-R. Values are means±SD. Significant differences were determined by *t*-test for paired samples. *NS* not significant

Test	Before IFN-α	After 3 months IFN-α	*P*-value
BDI	4.73±4.67	6.36±4.52	<0.1
HADS anxiety	4.36±3.07	3.82±3.09	NS
HADS depression	3.36±3.72	4.27±3.20	NS
SCL-90-R somatization	49.00±11.62	55.27±6.97	<0.05
Obsessive behavior	48.27±13.12	50.45±13.52	NS
Uncertainty	46.55±8.23	41.55±8.17	<0.1
Depressive	49.45±9.91	52.55±8.85	NS
Anxiety	48.45±9.93	47.09±10.92	NS
Aggression	46.18±9.25	47.64±10.43	NS
Phobia	46.36±5.52	45.73±5.88	NS
Paranoid	46.36±7.63	43.55±6.73	NS
Isolation	48.45±6.38	46.64±8.56	NS
GSI	46.91±10.02	47.91±11.09	NS
PST	47.55±10.34	48.36±11.82	NS
PSDI	45.82±8.94	50.00±8.79	NS

PET findings before and during IFN-α therapy

All PET investigations before IFN-α therapy showed physiological cortical and subcortical metabolism without detection of hypo- or hypermetabolic areas when compared to the normal database. In the pairwise comparison of the pre- and during therapy investigations, however, several regions were identified to differ statistically highly significant in glucose metabolism in distinct cortical and subcortical areas, which in terms of anatomical localization were identical throughout the whole patient group.

During the course of IFN-α therapy, pairwise comparison revealed a statistically significant ($P<0.001$) hypometabolism bilaterally in the prefrontal area (BA 9) as well as in the right parietal cortex (Fig. 1a). In the voxel cluster showing peak hypometabolism (Talairach coordinates –8/55/19), local activity was reduced to 88% of the initial measures (Fig. 1b). Additionally, a significant hypermetabolism ($P<0.001$) was found in both putamina prevailing left (Fig. 2a), with a local increase of 8% of initial metabolic activity (Fig. 2b). In the posterior part of the right thalamus and in the left occipital area (BA 18), additional hypermetabolism was detected.

The Talairach space localizations of the centers of significant voxel clusters and the maximum *Z*-scores each are summarized in Table 3. In individual patients, cerebellar hypometabolism was observed as well, while those findings were not consistent throughout the whole patient group.

The conjunction analysis of regional metabolism and depression score as measured by BDI revealed that the hypometabolism in the prefrontal areas covaried strongly with the BDI score ($P<0.001$), while there was no interrelationship between metabolism in the occipital areas and BDI-score. More specifically and in addition to the regions revealed in the initial pairwise comparison, conjunction analysis indicated a strong covariance ($P<0.001$) of BDI-score and reduced metabolism in the left frontal cortex (middle frontal gyrus, MFG) (Fig. 3). To a lesser extent, and by a lower statistical inference, there was also a covariance between BDI-score and reduced metabolism in the right primary somatosensory cortex. The Talairach space localizations of the

Table 2 Neuropsychological assessment of 11 patients with chronic active viral hepatitis C before and after 3 months of interferon-α (*IFN-α*) therapy. Neuropsychological tests included the audioverbal learning test (*AVLT*), a verbal fluency test (controlled oral word association: *COWA*), and the trail making test part A (trail A). Values are means±SD. Significant differences were determined by *t*-test for paired samples. *NS* not significant

Test	Before IFN-α	After 3 months IFN-α	*P*-value
Verbal fluency	24.36±6.09	24.36±9.54	NS
AVLT immediate recall	7.73±1.56	6.00±1.34	0.01
Total score	57.27±6.00	51.36±6.30	<0.05
Trail A	175±31	187±56	NS

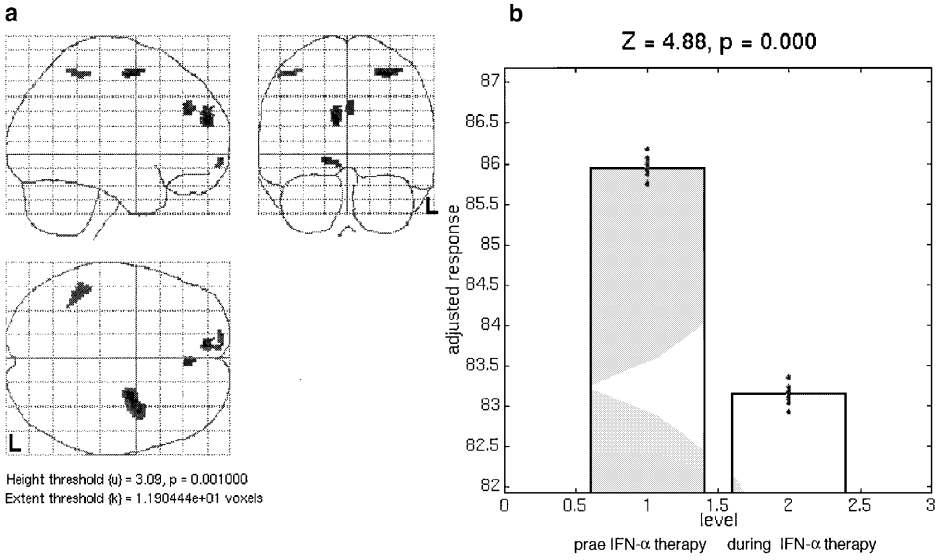

Fig. 1a, b Distribution of hypometabolic areas in pairwise comparison during interferon-α (*IFN-α*) therapy versus before IFN-α therapy. **a** Maximum intensity projection of *Z*-scores onto the standard SPM glass brain. The maximum *Z*-value within the right prefrontal area is demonstrated at Talairach coordinates *x*=8; *y*=55; *z*=19. **b** Plot of adjusted normalized regional activity across pre- and during therapy groups at the voxel cluster with Talairach coordinates *x*=8; *y*=55; *z*=19

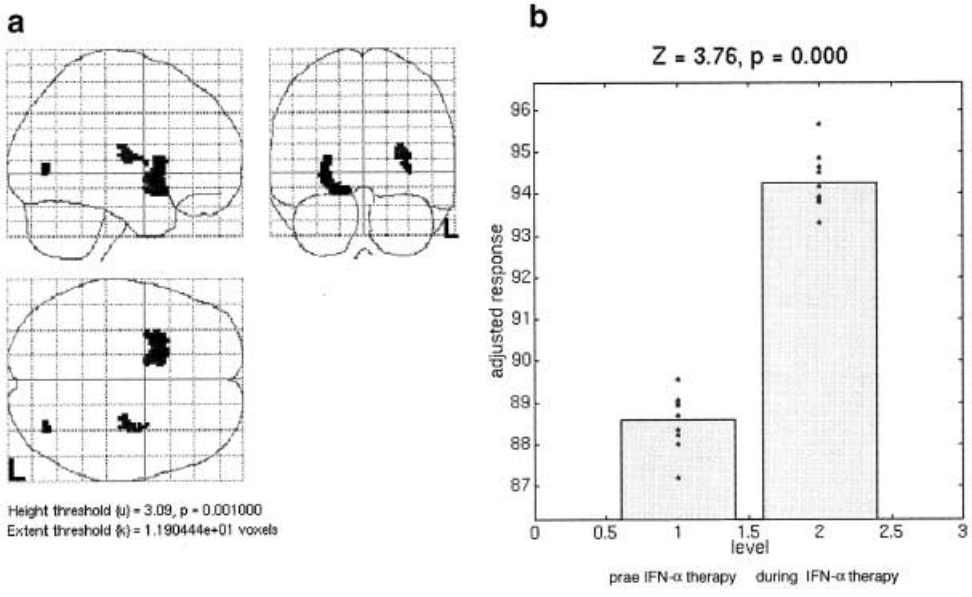

Fig. 2a, b Distribution of hypermetabolic areas in pairwise comparison during interferon-α (*IFN-α*) therapy versus before IFN-α therapy. **a** Maximum intensity projection of *Z*-scores onto the standard SPM glass brain. The maximum *Z*-value within the left putamen is seen at Talairach coordinates *x*=–27; *y*=10; *z*=5. **b** Plot of adjusted normalized regional activity across pre- and during therapy groups at the voxel cluster with Talairach coordinates *x*=–27; *y*=10; *z*=5

Table 3 Change in metabolism in pairwise comparison during interferon-α (*IFN-α*) therapy versus before IFN-α therapy. Given are the regions of interest, the Talairach coordinates of each ROI center (in *x*-, *y*-, *z*-direction), the corresponding anatomical structure and the *Z*-scores for the pre- versus during therapy comparison

Effect	Hemisphere	*x y z* – Talairach coordinates[a] (center)	Anatomical structure	Maximum *Z*-score
Hypometabolism	Right	–8 55 19	Prefrontal cortex (BA 9)	4.82
Hypometabolism	Left	4 40 27	Prefrontal cortex (BA 9)	3.86
Hypometabolism	Right	–44 –42 53	Parietal cortex	3.61
Hypermetabolism	Left	27 10 5	Putamen	3.76
Hypermetabolism	Right	–32 –13 10	Putamen	3.49
Hypermetabolism	Left	20 –97 –3	Occipital cortex (BA 18)	3.28
Hypermetabolism	Right	–22 –13 12	Thalamus	3.37

[a] Image orientation is according to radiological convention, i.e., negative *x*-coordinates correspond to the right hemisphere

centers of significant voxel clusters of the covariance analysis and the maximum *Z*-scores each are summarized in Table 4. Other neuropsychological test results did not covary with any of the observed changes in glucose metabolism.

Representative slices of the FDG-PET investigation in an individual case before and during IFN-α therapy are shown in Fig. 4, demonstrating marked hypometabolism in prefrontal areas bilaterally, and moderate hypermetabolism in both putamina prevailing left.

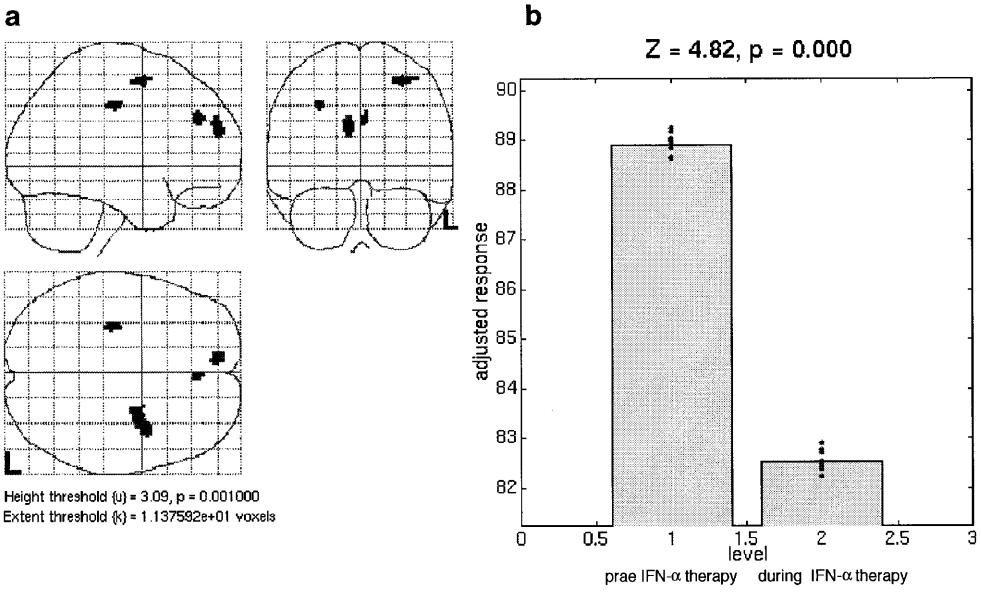

Fig. 3a, b Covariance analysis of score in Beck Depression Inventory (*BDI*) and metabolic changes in pairwise comparison during interferon-α (IFN-α) therapy versus before IFN-α therapy. **a** Maximum intensity projection of *Z*-scores onto the standard SPM glass brain. The maximum *Z*-value within left frontal cortex is seen at Talairach coordinates *x*=26; *y*=–1; *z*=52. **b** Plot of adjusted normalized regional activity covarying with BDI score across pre- and during therapy groups at the voxel cluster with Talairach coordinates *x*=26; *y*=–1; *z*=52

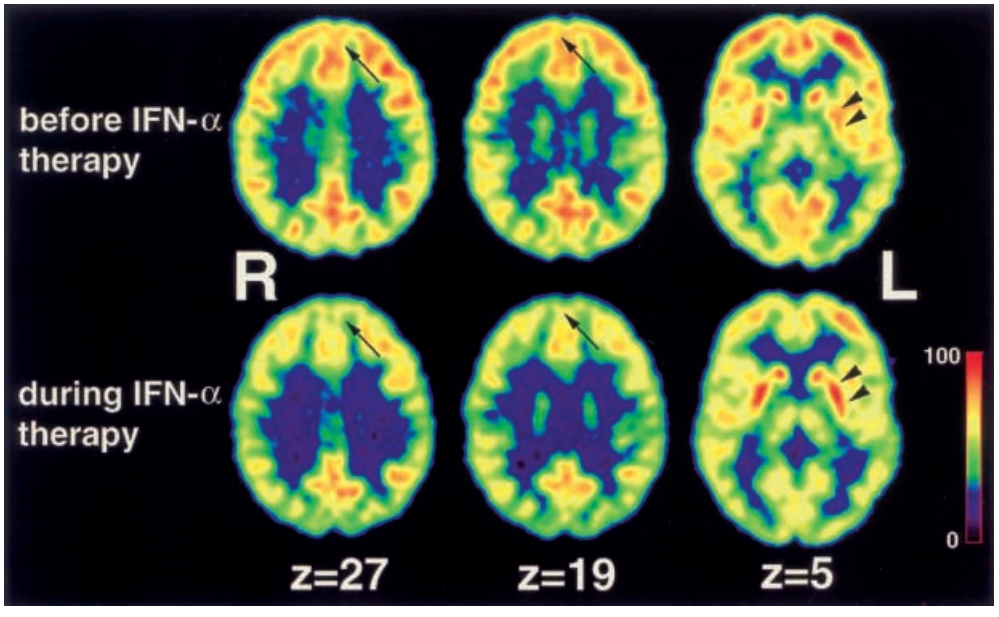

Fig. 4 Representative slices of the FDG-PET investigation in an individual case (realigned to the stereotaxic coordinate grid by Talairach) before (*upper row*) and during interferon-α (*IFN-α*) therapy (*lower row*). *Z*-coordinates are given at the bottom of each column. Color encoding in percentages of global maximum activity (ECAT counts/pixel per second) is indexed by the *red color bar*. *Black arrows* at *Z*-coordinate 27 and 19 indicate regions of marked prefrontal hypometabolism during IFN-α therapy, corresponding to coordinates given in Table 3. *Black arrowheads* at *Z*-coordinate 5 point to hypermetabolism in the left putamen in the course of IFN-α therapy

Table 4 Covariance analysis of score in Beck Depression Inventory (*BDI*) and metabolic changes in pairwise comparison during interferon-α (*IFN-α*) therapy versus before IFN-α therapy. Given are the regions of interest (*ROI*), the Talairach coordinates of each ROI center (in *x*-, *y*-, *z*-direction), the corresponding anatomical structure and the Z-scores for the pre- versus during therapy comparison

Effect	Hemisphere	*x y z* – Talairach coordinates[a] (center)	Anatomical structure	Maximum *Z*-score
Hypometabolism	Right	–8 55 19	Prefrontal cortex (BA 9)	4.88
Hypometabolism	Left	4 40 33	Prefrontal cortex (BA 9)	4.67
Hypometabolism	Left	26 –1 52	Frontal cortex	4.82
Hypometabolism	Right	–30 –20 38	Primary somatosensory cortex	4.55
Hypermetabolism	left	28 9 –9	Putamen	3.72
Hypermetabolism	Right	–32 –14 10	Putamen	3.33
Hypermetabolism	Left	20 –97 5	Occipital cortex (BA 18)	3.24

[a] Image orientation is according to radiological convention, i.e., negative *x*-coordinates correspond to the right hemisphere

Discussion

This study investigated the effects of low-dose IFN-α treatment on cerebral glucose metabolism using FDG PET. Eleven patients suffering from hepatitis C were scanned twice, the first time before IFN-α therapy, the second time 3 months after the beginning of IFN therapy.

Statistical parametric mapping analysis revealed that glucose metabolism significantly decreased in all patients in the right and left prefrontal cortex and in the right parietal cortex and increased in the right and left putamen, the left occipital cortex and the right thalamus region.

Three interpretations of the data seem possible and will be discussed: an effect of the time of investigation, an effect of depression or neuropsychological functioning, or an effect of IFN-α.

Since all patients receiving IFN-α were investigated by the second of the two scans, with no placebo control we cannot exclude the possibility that the described metabolism effects are caused by decreased activation of an attentional network during the second scan. Selective attention of the patients may be decreased during a second scan, and the prefrontal and the parietal cortex are part of an anatomical network sustaining attention. For ethical and legal reasons, however, we were not allowed to investigate a control group twice or performing a cross over design by stopping IFN-α therapy before a second scan. However, a recent study measuring reproducibility of regional brain metabolic responses to lorazepam using statistical parametric maps did not demonstrate any test-retest effect in the baseline (placebo) investigations (Wang et al. 1999).

The second explanation of the changed metabolic activity during IFN-α therapy may be that an altered neuropsychological or psychopathological state caused the changes. In depressive disorders, brain metabolism is often decreased in the left frontal cortex, the prefrontal cortex, and some studies also described increases in the basal ganglia or decreases in the parietal cortex (Bench 1993; Cummings 1993; George et al. 1993; Drevets et al. 1997; Elliott 1997; Drevets 1998). As depression ratings increased during therapy, the metabolism effects might be due to depression. Furthermore, covariance analysis revealed that the higher the depression ratings, the more frontal and prefrontal cortex metabolism decreased. However, evidence for this explanation is reduced by the fact that the above mentioned abnormalities were originally described in severely depressed patients (Drevets et al. 1997), and the patients investigated in this study had no clinical significant depression. This fact also implies that the metabolism in the prefrontal cortex can be lowered considerably without any severe consequences for the mood of the patient. Furthermore, PET findings in the more depressed patients were not different from the non-depressed ones.

The third explanation for the changed metabolic activity may be that the effects are effects of IFN-α itself. If this could be true, the observed metabolism effects could explain why IFN-α has neuropsychological, motor or affective side-effects. If it reduced prefrontal and parietal metabolism, it would affect those regions that are part of attentional or emotional networks, and increased metabolism in the basal ganglia may cause extrapyramidal side-effects.

The changes in frontal metabolism are in line with the interpretation of several authors explaining the neuropsychiatric effects of IFN-α as a manifestation of a "frontal lobe encephalopathy". This assumption was based on the observations that high dose IFN-α causes neuropsychological deficits with slowing of cognitive processes, diminished executive skills and memory difficulties as well as an "adynamic state" presenting with loss of cognitive, verbal, and motor spontaneity, incentive, and interest which are consistent with a frontal-subcortical dysfunction (Meyers et al. 1991b; Pavol et al. 1995). Furthermore, EEG studies during high-dose IFN-α therapy have shown global EEG abnormalities with pronounced slowing of frontal lobe waveforms (Honigsberger et al. 1983; Mattson et al. 1983; Rohatiner et al. 1983; Meyers et al. 1991a). The way in which exogenous application of IFN-α could affect cerebral metabolism, however, remains unclear. IFN-α is a molecule with a molecular weight of approximately 19 kDa and is therefore hardly able to cross the blood-brain and brain-cerebrospinal barriers (Frei and Fontana 1989). In line with that, measurable amounts of IFN-α in the human CSF occur only after application of very high doses of IFN-α (e.g., 100–200 MU/day) and repeated IV infusions (Mattson et al. 1983; Rohatiner et al. 1983; Farkkila et al. 1984). Nevertheless, IFN-α may enter the brain via the circumventricular organs associated with the hypothalamus where there is no blood-brain barrier (Frei and Fontana 1989). This makes it able to influence directly endocrine functions of hypothalamic neurons, for example. However, as shown in a study by Dafny et al. (1996), in which single cell recordings in different brain regions were performed, IP or IV given IFN-α modulated neuronal activity not only in the hypothalamus, but also in cortical regions and regions of the limbic system. This indicates that IFN-α may affect functioning of different brain regions apart from the circumventricular organs, which may be reflected by changes in cortical and subcortical metabolism as measured by FDG-PET.

In conclusion, the present study shows that peripherally given IFN-α has significant effects on cerebral glucose metabolism in human subjects. These metabolic changes predominate in the prefrontal cortex and covary with depression scores. The changes in prefrontal cortical activity might be interpreted as a "vulnerability factor" for the development of depressive symptomatology of patients treated with IFN-α.

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