

The Runner's High: Opioidergic Mechanisms in the Human Brain

Henning Boecker^{1,2}, Till Sprenger³, Mary E. Spilker¹, Gjermund Henriksen¹, Marcus Koppenhoefer¹, Klaus J. Wagner⁴, Michael Valet³, Achim Berthele³, and Thomas R. Tolle³

¹Nuklearmedizinische Klinik, Klinikum rechts der Isar, Technische Universität München, 81675 München, Germany, ²Radiologische Universitätsklinik, FE Klinische Funktionelle Neurobildgebung, Rheinische Friedrich-Wilhelms-Universität Bonn, Sigmund-Freud-Strasse 25, 53127 Bonn, Germany, ³Neurologische Klinik und ⁴Klinik für Anaesthesiologie, Klinikum rechts der Isar, Technische Universität München, 81675 München, Germany

The runner's high describes a euphoric state resulting from long-distance running. The cerebral neurochemical correlates of exercise-induced mood changes have been barely investigated so far. We aimed to unravel the opioidergic mechanisms of the runner's high in the human brain and to identify the relationship to perceived euphoria. We performed a positron emission tomography "ligand activation" study with the nonselective opioidergic ligand 6-O-(2-[¹⁸F]fluoroethyl)-6-O-desmethyldiprenorphine ([¹⁸F]FDPN). Ten athletes were scanned at 2 separate occasions in random order, at rest and after 2 h of endurance running (21.5 ± 4.7 km). Binding kinetics of [¹⁸F]FDPN were quantified by basis pursuit denoising (DEPCT software). Statistical parametric mapping (SPM2) was used for voxelwise analyses to determine relative changes in ligand binding after running and correlations of opioid binding with euphoria ratings. Reductions in opioid receptor availability were identified preferentially in prefrontal and limbic/paralimbic brain structures. The level of euphoria was significantly increased after running and was inversely correlated with opioid binding in prefrontal/orbitofrontal cortices, the anterior cingulate cortex, bilateral insula, parainsular cortex, and temporoparietal regions. These findings support the "opioid theory" of the runner's high and suggest region-specific effects in frontolimbic brain areas that are involved in the processing of affective states and mood.

Keywords: emotion, exercise, ligand activation, limbic system, opioid, PET (positron emission tomography), prefrontal, runner's high

Introduction

Endurance training has been reported to induce a variety of psychophysical effects, including stress reduction (Rosch 1985), anxiolysis (Morgan 1985), mood elevation (Janal et al. 1984; Wildmann et al. 1986), and reduced pain perception (Janal et al. 1984). Moreover, there are numerous reports in the popular and scientific press regarding a state of euphoria while running, commonly referred to as runner's high (Wagemaker and Goldstein 1980; Partin 1983; Morgan 1985). To date, there is no generally accepted definition as to what runner's high is, but common descriptions include feelings like "pleasantness," "inner harmony," "boundless energy," or even druglike "orgiastic" sensations. The degree of exercise-induced mood change differs considerably between individuals (Dietrich and McDaniel 2004), and currently, little is known about the mechanisms mediating euphoria upon physical exercise. The most favored theory, the "endorphin hypothesis" (Morgan 1985), ascribes these psychophysical effects to changes in central opioidergic transmission. The endorphin hypothesis was put forward because indirect measures such as raised endorphin levels in

peripheral blood (Carr et al. 1981; Gamber et al. 1981; Farrell et al. 1982; Janal et al. 1984; Wildmann et al. 1986) and cerebrospinal fluid (Radosevich et al. 1989; Hoffmann et al. 1990) as well as the reversibility of exercise-induced mood changes (Janal et al. 1984), pain perception (Janal et al. 1984), and pupillary miosis (Allen et al. 1983) by naloxone (unspecific opioid receptor antagonist) presented strong arguments for an opioidergic involvement. However, the existence of an "endorphin driven runner's high" was questioned (Markoff et al. 1982; Dietrich and McDaniel 2004) because, up to now, the entire basis for the involvement of brain-derived endorphinergic mechanisms is depicted from measurements of endorphins in the circulating blood.

The aim of this pilot study was to unravel the central opioidergic mechanisms of the runner's high and to relate these changes to perceived euphoria in runners. There are 3 major types of endorphins. β -Endorphins found primarily in the pituitary gland and released into the blood stream. It is believed that the resulting plasma changes of endorphins can hardly be related to central nervous system (CNS) effects because released endorphins can reenter the brain through the blood-brain barrier only marginally (Dearman and Francis 1983). The other major representatives of endorphins are the enkephalins and dynorphin, both distributed throughout many different structures of the CNS. All the endorphins carry variable affinities for μ , δ , and κ opioid receptors. It is well established that β -endorphins display μ and δ recognition (Raynor et al. 1994). Whereas μ -receptor activation has been linked to the generation of euphoria, κ -receptor activation is more likely to result in dysphoric mood states (Bodnar 2007). Due to current lack of clear evidence which receptor subtype is playing the predominant role for eliciting the runner's high sensation in humans and to allow for detecting central opioidergic activation effects in an exploratory setting, we employed the tracer 6-O-(2-[¹⁸F]fluoroethyl)-6-O-desmethyldiprenorphine ([¹⁸F]FDPN), a diprenorphine derivative with similar selectivity to μ , δ , and κ opioid receptors (Wester et al. 2000).

To quantify exercise-induced endogenous opioidergic release and to determine whether this release is related to mood changes, we performed 2 positron emission tomography (PET) scans to compare the [¹⁸F]FDPN binding under rest and after strenuous physical exercise. Previous so-called "ligand activation" studies in the opioidergic system, with and without experimental challenge, have been successful in identifying receptor availability changes reflecting endogenous release of central acting opioidergic peptides (Zubieta et al. 2001).

Because it was previously shown by Zubieta et al. (2003) that induction of negative mood states is associated with a significant

deactivation in μ -opioid neurotransmission, we hypothesized that euphoric mood states would be associated with opioidergic activation. We also expected a direct relationship between the level of euphoria and the opioid displacement.

Materials and Methods

Volunteers

We recruited 10 trained male athletes (mean age 36.9 years $\pm$ 2.6, range 33–40; mean BMI: 23.1 $\pm$ 2.1, range 19.9–27.7) from local running and sports clubs in Munich. Prior to inclusion in the study, each volunteer answered detailed questionnaires regarding running habits, occurrence of prior runner's high-like sensations, baseline demographic information, and medical history. As we aimed to investigate the cerebral correlate of the runner's high phenomenon, only subjects who affirmed the presence of previous runner's high phenomena during and/or after running were selected. This was the case in all screened subjects. We had to make sure that the participants were able to complete the requested 2-h running period safely without adverse effects. For inclusion in the study, a minimum of 4 h weekly training for the past 2 years was obligatory. The athletes had a mean weekly training of 8.6 $\pm$ 3.9 h, range 4–10 h. Eight of the 10 athletes had previously completed marathon races, all of them half-marathons. Participants were informed about the PET scanning procedure with an opioidergic ligand; however, they were not informed about the primary outcome parameters of the study.

Prior to arterial cannulation for invasive blood sampling, perfusion abnormalities of the 2 major hand vessels were excluded using the clinical Allen's test and Doppler ultrasound measurements in each subject. The study protocol was approved by the local ethics and the national radiation protection authorities. Written informed consent according to the Declaration of Helsinki was obtained from each participant after full explanation of the procedures involved.

Study Design

Each participant underwent 2 [18 F]FDPN PET scans: a resting state PET scan (>24 h without sportive activity) and a post exercise PET scan 30 min after running. The participating volunteers were randomly assigned to the order of the 2 PET conditions (6 subjects with initial rest scan, 4 subjects with initial postrun scan), and all PET scans were performed at the same time of the day (~1:00–3:30 PM). The mean time interval between the 2 [18 F]FDPN PET scans was 4.0 $\pm$ 1.9 weeks. Prior to each PET scan, a toxicological urine screening for cannabinoids and opioids ruled out substance abuse.

The current affective states before and after running as well as before the resting PET scan were evaluated with Visual Analog Mood Scales (VAMS; Aitken 1969). For the different items (sadness, tension, fear, anger, confusion, fatigue, happiness, and energy; Stern et al. 1997), subjects had to rate their current affective state: for example, "How is your sadness right now?" The verbal descriptors at the end of the visual analog scale (VAS) were as follows: "no sadness at all" on the left side versus "strongest sadness imaginable" on the right side. Accordingly, the descriptors for euphoria were, no euphoria at all versus strongest euphoria imaginable. The VAMS score was determined by measuring the distance in millimeters from the left end of the scale to the participants mark.

After the volunteers had completed the PET part of the study, they performed 2 additional 2-h runs at home under their typical training circumstances to gain rating data (VAS euphoria scale) under natural conditions.

[18 F]FDPN Synthesis and PET Methodology

The procedures used for synthesis of [18 F]FDPN have been previously described in detail (Wester et al. 2000). Compared with the radioligand [11 C]DPN ($t_{1/2}$, C-11 = 20 min), [18 F]FDPN has the advantage of a longer half-life ($t_{1/2}$, F-18 = 109.7 min) and improved signal intensity (Wester et al. 2000). The specific activity obtained was >37 TBq/mmol. The PET scans were acquired on a Siemens/CTI ECAT EXACT HR+ scanner (Knoxville, TN) in 3D mode with septa retracted. The PET scanner has a field of view covering 15.5 cm. A neck shield (NeuroShield, Scanwell

Systems, Lavigne, St Montreal, Canada) was used to reduce random count rates. The attenuation was corrected using transmission scanning prior to the [18 F]FDPN studies. The acquired data were reconstructed using filtered backprojection with a ramp filter (cut off 0.3 cycles per projection element) into 63 image planes with a 128 $\times$ 128 pixel image matrix.

[18 F]FDPN was administered as a single bolus intravenous injection (2.5 mCi), and PET images were acquired over 120 min with the following frame durations: 12 $\times$ 10 s; 3 $\times$ 20 s; 7 $\times$ 1 min; 4 $\times$ 2 min; and 20 $\times$ 5 min for a total of 46 frames. Arterial blood and metabolite samples were taken regularly throughout the scanning period for metabolite correction and quantitative modeling. The amount of intact tracer as a function of time was determined according to the published procedure (Wester et al. 2000) and subsequently used to calculate the metabolite-corrected arterial input function as described previously (Spilker et al. 2004).

Data Analysis

Each subject's dynamic PET data set was realigned to a scan with a high signal to noise ratio using a fourth degree B-spline interpolation and resliced to reduce motion artifacts during the scan. The dynamic volumes were then normalized to a ligand-specific template (Meyer and Ichise 2001). These preprocessing steps were performed using Statistical parametric mapping (SPM2) (Wellcome Department of Imaging Neuroscience, London, United Kingdom). Our previous work has indicated that the distribution volume (DV) of [18 F]FDPN can be accurately determined after metabolite-corrected arterial sampling and dynamic PET acquisitions over at least 90 min (Spilker et al. 2004; Boecker et al. 2005). Binding kinetics were quantified by basis pursuit denoising as implemented in the DEPICT software (Gunn et al. 2002). This basis function method is a data-driven modeling approach where no a priori structure is assumed to characterize the data. Instead, an impulse response function is generated from a sum of exponentials that describes the data, given the input function. The DV is then determined from the integral of the impulse response function. The resulting DV images were smoothed using an isotropic Gaussian kernel of 10 mm full width at half maximum.

Changes in ligand binding after the running period were assessed using a paired *t*-test in SPM2. As the process of absolute quantification of opioid receptor binding relies on a complex methodology (e.g., arterial blood sampling) with several theoretical sources of error, we used proportional scaling to compensate between-scan differences in global DV values. The resulting maps of *t*-statistics were transformed to the unit normal distribution SPM and thresholded at an uncorrected height threshold of $P < 0.001$ and $P < 0.05$, corrected for false-positives (false discovery rate [FDR]) correction (Genovese et al. 2002). Both threshold criteria had to be reached for a voxel to be considered significant.

In a second step, a covariation analysis accounting for differences in scan order (i.e., covariate of no interest) between opioidergic ligand binding (DV) and the postrunning euphoria ratings (VAS immediately before the PET scanning) was performed. The threshold for this regression analysis was $P < 0.001$, uncorrected; significance of regions surpassing this uncorrected height threshold was determined by small volume correction (10 voxel sphere). The anatomical localization of the activation peaks was determined by transforming the 3D coordinates from Montreal Neurological Institute space in Talairach space (Talairach and Tournoux 1988) using the mni2tal tool (MRC Cognition and Brain Sciences Unit, Cambridge, England; <http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>).

Results

Running Performance

The running exercise was completed after 115 $\pm$ 6.8 min at an average pace of 11.0 $\pm$ 2.3 km/h and an average running distance of 21.5 $\pm$ 4.7 km. The average heart rate during exercise was 144 $\pm$ 7 min⁻¹ (morning resting values in supine position: 52 $\pm$ 11 min⁻¹). At the time immediately prior to

injection of the PET tracer (i.e., 30 min after running), there were no significant differences regarding heart rate (1-sided paired *t*-test, $P = 0.097$), systolic ($P = 0.099$), and diastolic ($P = 0.302$) arterial blood pressure.

Behavioral Ratings

On the VAS ratings of the 9 mood-related items (Stern et al. 1997), the euphoria ratings and the happiness ratings were the only items that showed a significant change (Fig. 1) with exercise: The euphoria ratings increased from $37.6 \pm 19.6/100$ (prior to exercise) to $73.3 \pm 13.2/100$ (after exercise: 2-tailed paired *t*-test, $P < 0.05$ with correction for multiple comparisons). This increase was also significant when compared with the ratings during rest on the day of the baseline scan ($28.5 \pm 17.4/100$, 2-tailed paired *t*-test, $P < 0.05$ with correction for multiple comparisons). The prerun VAS euphoria ratings were not significantly different compared with the VAS euphoria rating on the resting day ($37.6 \pm 19.6/100$ vs. $28.5 \pm 17.4/100$; not significant after correction for multiple comparisons). Similar significant modulations were observed on the happiness scores, with significant increases after running compared with the ratings prior to exercise as well as during rest on the day of the baseline scan (2-tailed paired *t*-test, $P < 0.05$ with correction for multiple comparisons). No pain sensations were reported during or after the physical exercise by any of the participating runners.

To assure that the VAS ratings were not biased by the scanning procedure, we acquired additional euphoria ratings after identical running exercises on 3 different days under natural (normal training) conditions ($N = 10$). Subjects were informed about these additional ratings after completion of the PET scans. The ratings of euphoria showed nearly parallel changes under normal training conditions and were comparable to the values obtained on the days of the PET scanning (2-tailed paired *t*-tests at prerun ($P = 0.8$) and at postrun ($P = 0.9$) time points, both not significant).

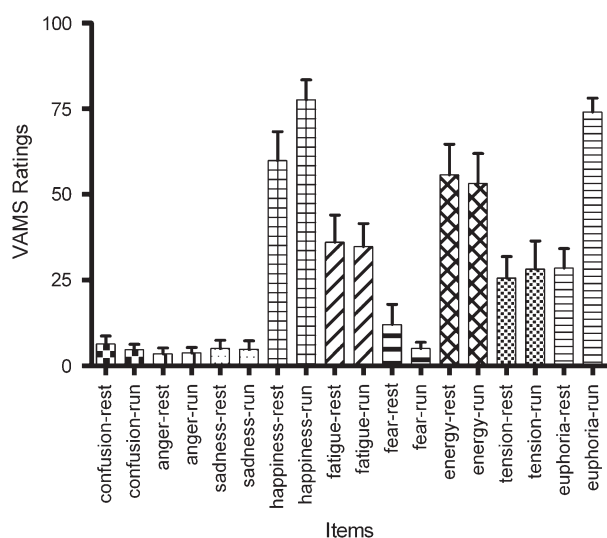


Figure 1. Box plot of euphoria VAS scores. Mean and standard error of VAMS ratings (0–100) during 2 conditions (left column of each item represents rest, right column postexercise). Differences between the conditions were significant for the items euphoria and happiness (Student's paired *t*-test, $P < 0.05$, corrected for multiple comparisons).

Main Effect of Running on Opioidergic Activation

$[^{18}\text{F}]\text{FDPN}$ binding (DV) decreased significantly (uncorrected height threshold <0.001 , FDR correction of suprathreshold voxels <0.05) after physical exercise (PET scan starting 30 min after running) in widespread cortical brain areas including prefrontal/orbitofrontal cortices, dorsolateral prefrontal cortex, anterior and posterior cingulate cortex, insula and parahippocampal gyrus, and sensorimotor/parietal regions (Fig. 2). Subcortical $[^{18}\text{F}]\text{FDPN}$ binding (DV) decreases were observed in cerebellum and basal ganglia. No significant increases of $[^{18}\text{F}]\text{FDPN}$ binding were observed after endurance training (identical threshold as for decreases). Table 1 summarizes all regions with decreased $[^{18}\text{F}]\text{FDPN}$ binding after exercise.

Relationship of Opioidergic Activation and Affective Modulation

Having established the presence of $[^{18}\text{F}]\text{FDPN}$ binding reductions in the brain after endurance training, we sought to investigate whether the degree of ligand binding correlated with the individual VAS euphoria ratings, which changed significantly with running. The regression analysis indicated that the VAS ratings of euphoria were inversely correlated with $[^{18}\text{F}]\text{FDPN}$ binding in prefrontal/orbitofrontal cortices, the anterior cingulate cortex, bilateral insula and parainsular cortex, along with temporoparietal regions (uncorrected height threshold <0.001 , significant after small volume correction using 10 voxel sphere; Table 2 and Fig. 3). Figure 4 is a composite of the SPM correlation analysis with scatter plots from 3 selected regions showing how the VAS euphoria ratings are correlated with the tracer binding. No significant positive correlations of $[^{18}\text{F}]\text{FDPN}$ binding and VAS euphoria ratings were observed.

Discussion

Exercise-induced changes in mood were described as being a consequence of alterations in endogenous opioid release. Because objective demonstration of central opioidergic release was precluded for technical and ethical reasons, up to now, the “opioid hypothesis” was based entirely on findings of enhanced endorphins levels in the peripheral blood. To disclose the central opioidergic mechanisms and to identify a relationship to perceived euphoria during strenuous exercise, we performed a PET ligand activation study with the nonspecific opioidergic ligand $[^{18}\text{F}]\text{FDPN}$. This study succeeded in demonstrating regional specific changes in opioid binding after strenuous exercise, thereby providing a basis for understanding the link between exercise-induced psychophysical effects and changes in central opioidergic neurotransmission. Changes in central opioid receptor binding after 2 h of long-distance running were identified preferentially in prefrontal and limbic/paralimbic brain regions. Specifically, the perceived levels of euphoria were inversely correlated with opioid binding in prefrontal/orbitofrontal cortices, the anterior cingulate cortex, bilateral insula, and parainsular cortex, along with temporoparietal regions.

For decades, the mechanisms underlying euphoria during and after sustained endurance training have captured the interest of scientists. Participation of central opioidergic pathways has been suggested based on work in rats showing that running can alter opiate cerebrospinal fluid levels (Hoffmann et al. 1990) and receptor occupancy (Tendzegolskis

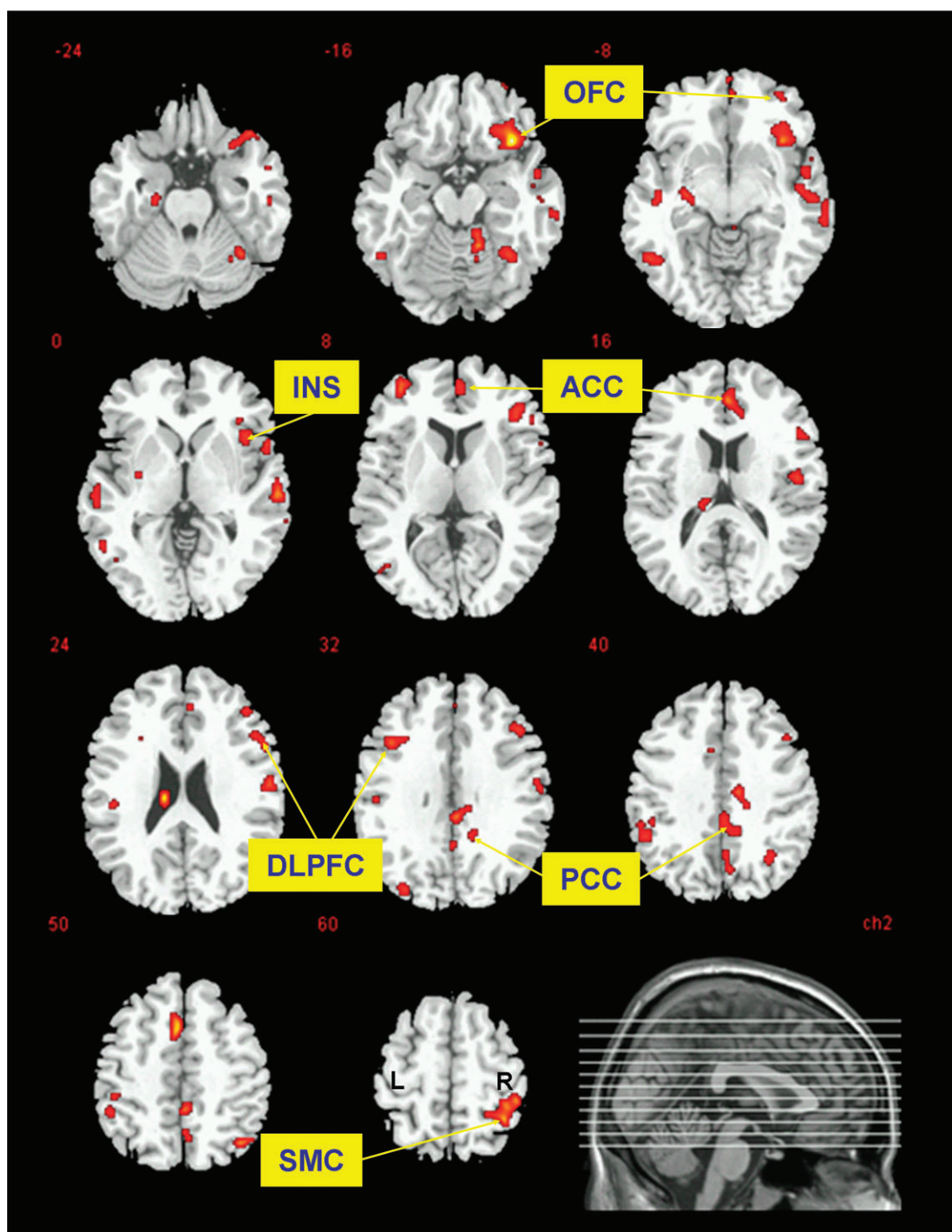


Figure 2. Reductions in opioidergic receptor availability after endurance running in comparison with the rest condition. Statistical parametric maps of the categorical comparison (regions where [^{18}F]FDPN binding is reduced after physical exercise) in standard stereotactic space (Montreal Neurological Institute [MNI] space) are overlaid in color on axial slices of a skull-stripped normalized brain (MNI single subject brain as provided by MRIcro program). Z values indicate the location of the slice planes relative to the AC-PC line. For display purposes, the statistical analysis is thresholded at an uncorrected height threshold of $P < 0.001$. L, left side of figure; R, right side of figure. The signal in the left ventricle is supposed to represent an artifact because this region is devoid of opioid receptors.

et al. 1991; Aravich et al. 1993). On the behavioral level, it has been demonstrated in mice subjected to a regular swimming schedule that naloxone induces withdrawal symptoms similar to those following chronic morphine treatment (Christie and Chesher 1982) and forced swimming in cold water has been shown to cause brain decreases in

[^3H]diprenorphine binding (Seeger et al. 1984). In humans, however, the closest information gathered thus far on exercise-induced opioidergic mechanisms was derived from peripheral blood. Different research groups have reported up to 5-fold increases of plasma β -endorphin levels after physical exercise (Carr et al. 1981; Farrell et al. 1982; Wildmann et al. 1986).

Table 1

Reductions in opioidergic receptor availability after endurance running in comparison with the rest condition

Brain region	K (cluster size)	t values	Z scores	x, y, z (mm) Talairach coordinates
Frontal areas				
Right inferior frontal gyrus, BA 47	715	12.40	5.00	38, 21, -15
Left middle frontal gyrus, BA 10	60	8.75	4.40	-34, 49, 4
Medial frontal gyrus, BA 6	154	8.55	4.36	0, 16, 46
Right inferior frontal gyrus, BA 9	206	6.92	3.98	58, 17, 22
Right middle frontal gyrus, BA 9		5.86	3.67	46, 27, 29
Right middle frontal gyrus, BA 46		5.14	3.43	52, 23, 21
Left middle frontal gyrus, BA 9	92	6.61	3.90	-38, 17, 27
Right middle frontal gyrus, BA 46	31	5.52	3.56	46, 39, 23
Right middle frontal gyrus, BA 11	65	5.42	3.53	38, 50, -11
Right middle frontal gyrus, BA 10		4.92	3.34	36, 58, -13
Right middle frontal gyrus, BA 10	35	4.98	3.37	4, 53, -8
Limbic/paralimbic areas				
Right posterior cingulate, BA 31	384	7.75	4.19	4, -32, 33
Right middle cingulate gyrus		6.52	0.87	14, -14, 38
Left parahippocampal gyrus, BA 35	45	7.38	4.10	-20, -13, -25
Left parahippocampal gyrus, BA 28		5.63	3.60	-22, -19, -18
Right anterior cingulate, BA 32	224	7.04	4.01	4, 44, 13
Left superior temporal gyrus/insula	34	6.91	3.98	-46, -18, -8
Left insula	33	5.66	3.61	-44, -23, 24
Temporoparietal areas				
Right fusiform gyrus, BA 37	371	9.16	4.48	34, -52, -15
Right postcentral gyrus, BA 5	291	8.44	4.34	38, -44, 56
Right inferior parietal lobule, BA 40		7.39	4.10	46, -33, 57
Right superior parietal lobule, BA 7	119	8.01	4.24	42, -58, 53
Left inferior parietal lobule, BA 40	184	7.72	4.18	-46, -41, 45
Right precuneus, BA 7	133	7.62	4.15	8, -64, 42
Right precuneus, BA 31		4.92	3.35	4, -47, 34
Left precuneus, BA 19	57	7.41	4.10	-32, -76, 37
Right superior temporal gyrus, BA 21	512	7.40	4.10	64, -20, 1
Left fusiform gyrus, BA 37	194	6.60	3.89	-50, -55, -10
Right precentral gyrus, BA 4	103	6.16	3.76	60, -9, 23
Subcortical areas				
Right cerebellum, anterior lobe	147	7.40	4.10	16, -48, -12
Left caudate nucleus	97	9.64	4.57	-10, -19, 24
Right cerebellum, posterior lobe	37	6.43	3.84	20, -80, -29
Left lentiform nucleus	59	6.11	3.75	-26, -14, -7

The statistical analysis is thresholded at an uncorrected height threshold of $P < 0.001$ and $P < 0.05$ corrected for false positives (FDR correction). The regions are grouped according to location. BA, Brodmann area; K, cluster size (number of voxels).

However, peripheral opioid levels most likely do not reflect those in the CNS (Rossier et al. 1977; Dietrich and McDaniel 2004).

The measured DV changes cannot be erroneously attributed to running-associated changes in systemic cardiovascular measures because blood pressure and heart rate were reverted to resting levels at the time of tracer injection (approximately 30 min postexercise). Mechanisms such as receptor internalization or downregulation might potentially add to the reduced DV values (Laruelle 2000; Sprenger et al. 2005). However, this would also be indicative of receptor activation by endogenous opioidergic ligands and add to the observation of opioidergic neurotransmission in the brain areas with reduced DV values. Moreover, the absence of pain or discomfort during and after exercise (see Results), argues against any potentially confounding pain-related releases of endogenous opioids (Zubieta et al. 2001; Sprenger et al. 2006). Although recent work by Hume et al. (2007) has questioned the suitability of radiolabeled diprenorphine to depict changes in opioid binding after application of exogenous/synthetic opioid, we are convinced that [^{18}F]FDPN is a suitable ligand to detect changes in opioid receptor binding induced by release of endogenous opioids, such as in endurance running because a previous autoradio-

Table 2

Correlation of opioidergic binding in runners with VAS ratings of euphoria

Brain region	K (cluster size)	t values	Z scores	x, y, z (mm) Talairach coordinates
Frontal areas				
Left middle frontal gyrus, BA 9	45	4.12	3.35	-38, 19, 30
Right superior frontal gyrus, BA 9	95	4.10	3.34	18, 46, 18
Right superior frontal gyrus, BA 11	66	4.07	3.32	32, 56, -15
Right medial frontal gyrus, BA 10	87	3.96	3.26	14, 61, 8
Right inferior frontal gyrus, BA 47	50	3.82	3.17	57, 18, -11
Limbic/paralimbic areas				
Right anterior cingulate	95	3.83	3.18	10, 38, 15
Right insula/superior temporal gyrus	148	4.92	3.79	54, 2, -4
Left insula/superior temporal gyrus	115	4.25	3.42	-46, -14, -8
Left insula	90	3.77	3.15	-48, -26, 18
Left insula	69	3.77	3.14	-38, 19, -6
Temporoparietal areas				
Left inferior parietal lobule, BA 40	154	5.28	3.96	-52, -40, 46
Left precuneus, BA 19	45	4.56	3.60	-30, -78, 35
Left fusiform gyrus	113	4.46	3.54	-22, -66, -5
Right superior temporal gyrus, BA 13	91	4.44	3.53	52, -42, 15
Right fusiform gyrus, BA 37	72	4.03	3.30	38, -59, -11

The statistical analysis is thresholded at $P < 0.001$, uncorrected. All regions are also significant after small volume correction (10 voxel sphere). The regions are grouped according to location. BA, Brodmann area; K, cluster size (number of voxels).

graphic study using [^3H]diprenorphine evidenced stress-induced decreases in opioid receptor binding in the rat brain (Seeger et al. 1984). Furthermore, we have previously shown in humans using [^{18}F]FDPN pain-related opioidergic activation using this ligand (Sprenger et al. 2006).

It is shown here (Fig. 2) that the endogenous release of central opioids occurs preferentially in brain regions belonging to frontolimbic circuits that are known to play a key role in emotional processing (Dalglish 2004). Importantly, no significant increases in [^{18}F]FDPN ligand binding were detected. Hence, the main effect of physical exercise on opioidergic release is fundamentally different compared with induction of temporary sadness states, as elicited by recall of emotionally negative autobiographical events (Zubieta et al. 2003). Whereas sadness states are associated with deactivations in μ -opioid neurotransmission in limbic structures (including rostral anterior cingulate, ventral pallidum, and amygdala), physical exercise is associated with opioidergic activation in frontolimbic brain regions.

It can be assumed that euphoria is associated with reward, especially in runners with repetitive experiences of euphoric sensations related to endurance training. Hence, one might have expected changes in opioidergic neurotransmission in the nucleus accumbens, a key structure for reward processing with known opioid-dopamine interactions. Although we did not observe relevant running-related opioidergic changes in this brain structure, it might be feasible to detect such changes in the dopaminergic system. This has been attempted by Wang et al. (2000) using [^{11}C]raclopride PET to study striatal dopamine release in healthy volunteers running on a treadmill for 30 min. These authors could not show such changes in the dopaminergic system. However, no psychophysical data were acquired and it is therefore not clear whether the treadmill running induced euphoria and/or reward in these volunteers. Therefore, it remains to be shown how the dopaminergic system behaves in prolonged physical exercise with induction of euphoria, as studied here.

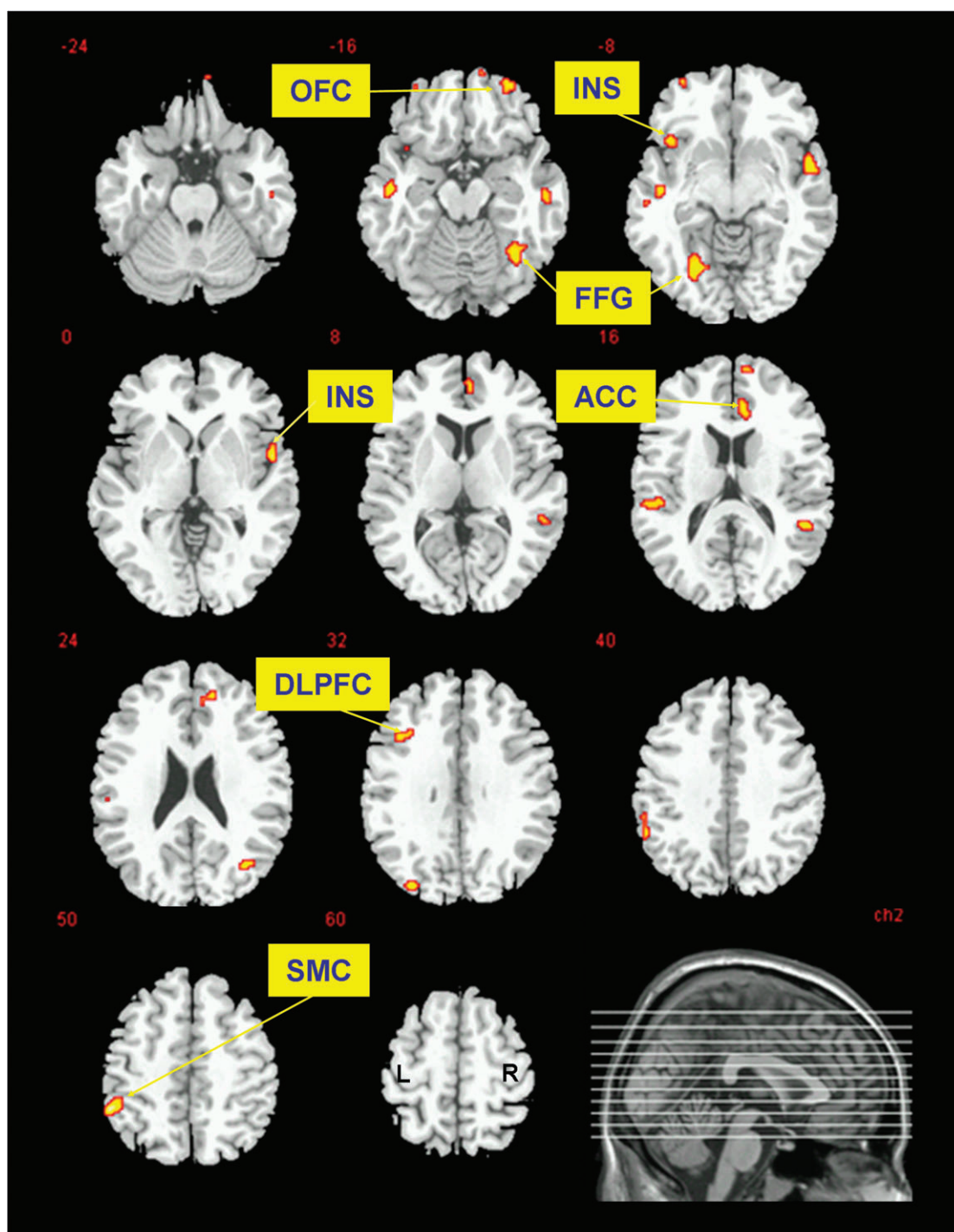


Figure 3. Correlation of opioidergic binding in runners with VAS ratings of euphoria. Statistical parametric maps of the regression analysis (regions where VAS ratings of euphoria are inversely correlated with $[^{18}\text{F}]\text{FDPN}$ binding) in standard stereotactic space (Montreal Neurological Institute [MNI] space) are overlaid in color on axial slices of a skull-stripped normalized brain (MNI single subject brain as provided by MRICro program). Z values indicate the location of the slice planes relative to the AC-PC line. For display purposes, the statistical analysis is thresholded at an uncorrected height threshold of $P < 0.001$. All regions are also significant after small volume correction (10 voxel sphere). L, left side of figure; R, right side of figure.

Beyond these main effects of opioidergic activation, we were able to demonstrate that the amount of opioidergic release in frontolimbic brain structures is tightly linked to the degree of affective modulation (Figs 3 and 4). This is reflected by the inverse correlation between $[^{18}\text{F}]\text{FDPN}$ binding and the VAS euphoria ratings in the prefrontal/orbitofrontal cortices, the

anterior cingulate cortex, and the insula/parainsular cortex (Table 2 and Fig. 4). Knowing that frontolimbic circuits are pivotal for the generation of affect and mood states, we conclude that this differential release of endogenous opioids in relation to perceived euphoria is very likely responsible for the generation of the runner's high sensation. Euphoria-related

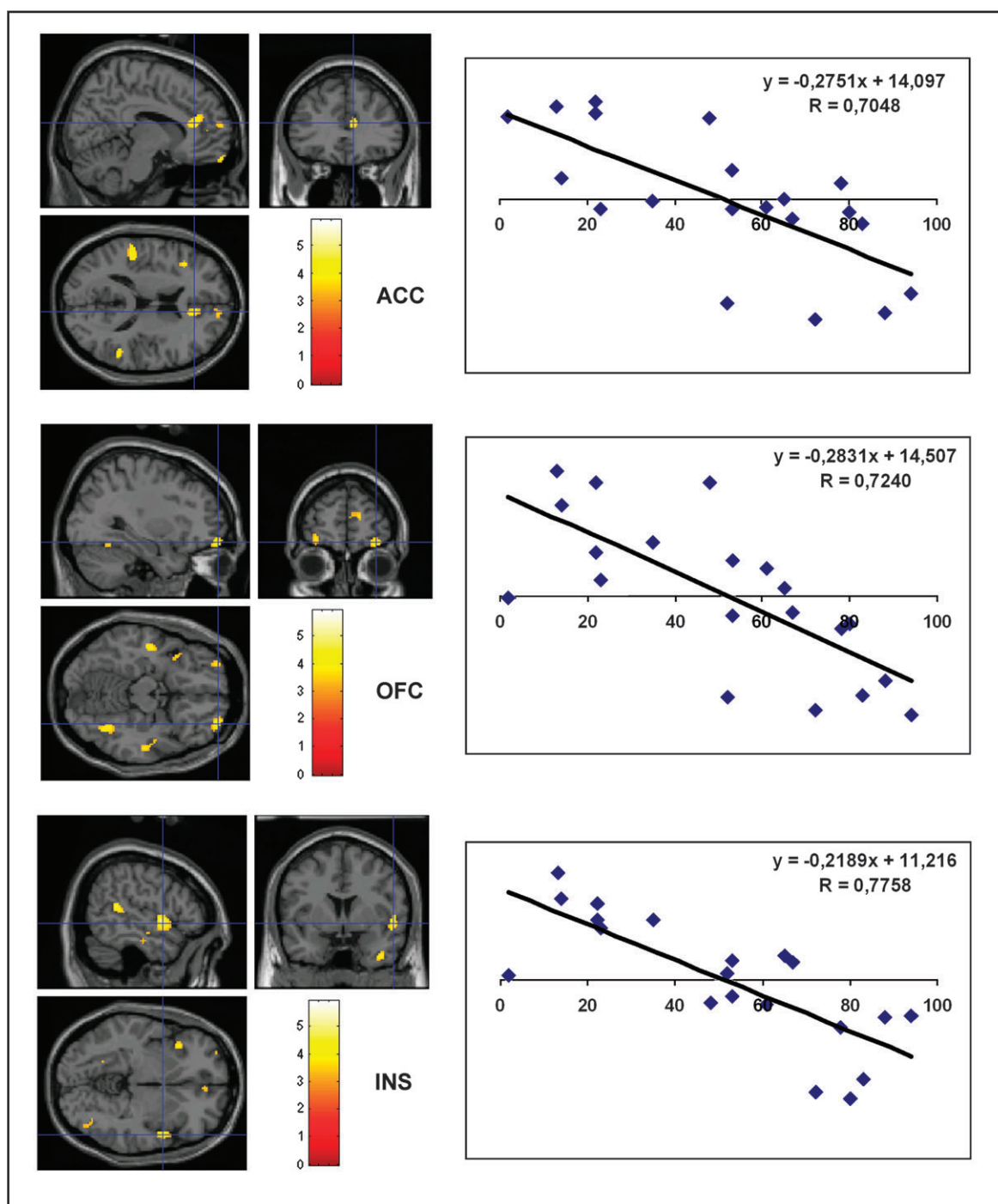


Figure 4. Correlation of opioidergic binding in runners with VAS ratings of euphoria. Scatter plots of opioid receptor binding (DV) with individual VAS euphoria ratings (VAS post run) are shown from 3 regions (top row: right anterior cingulate cortex, ACC; middle row: right orbitofrontal cortex, OFC; bottom row: right insula, INS). The [^{18}F]FDPN binding in the respective areas is plotted in relation to perceived euphoria (abscissa: VAS rating from 0–100, ordinate: SPM-scaled DV values). The SPMs are overlaid in color on axial, coronal, and transversal sections of a stereotactically normalized brain (Montreal Neurological Institute single subject brain as provided by SPM2). For display purposes, the statistical analysis is thresholded at an uncorrected height threshold of $P < 0.001$.

effects were also noted in the fusiform gyrus, a brain region responding to different emotional expressions (Geday et al. 2003; Winston et al. 2003; Baumgartner et al. 2006) and even recapitulation of emotions (Fenker et al. 2005).

The applied receptor ligand [^{18}F]FDPN labels μ , κ , and δ opioid receptors in a nonspecific way. Therefore, no conclusion can be drawn from our data, with respect to which

of these opioid receptors is dominating the opioidergic effects related to endurance training. As antinociceptive effects in runners have been described (Janal et al. 1984; Koltyn 2000) and these effects are thought to be predominantly μ -dependent, it might be deduced that the observed changes in opioid receptor availability are at least partly μ related. Further studies will have to clarify the specific contribution of the

different opioid receptor types. This is of particular interest as the different opioid receptor types have complex and partly opposing functions not only in nociception but also in the modulation of mood states.

In conclusion, this study provides first in vivo evidence that release of endogenous opioids occurs in frontolimbic brain regions after sustained physical exercise and that there is its close correlation to perceived euphoria of runners. This suggests a specific role of the opioid system in the generation of the runner's high sensation. In a more general view, it might also be assumed that opioidergic effects in frontolimbic brain structures mediate not only some of the therapeutically beneficial consequences of endurance exercise on depression and anxiety in patients (Morgan 1985) but also the addictive aspects of excessive sports, where injured athletes continue their training in spite of detrimental consequences to their health (Chapman and De Castro 1990). Such phenomena will have to be addressed in future studies focusing on not only physical exercise, mood, and reward but also interactions between endogenous opioids and other neurotransmitter systems and modulators, particularly dopamine and endocannabinoids (Dietrich and McDaniel 2004; Gardner 2005).

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Address correspondence to email: henning.boecker@ukb.uni-bonn.de.

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