Advocating neuroimaging studies of transmitter release in human physical exercise challenges studies

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Abstract: This perspective attempts to outline the emerging role of positron emission tomography (PET) ligand activation studies in human exercise research. By focusing on the endorphinergic system and its acclaimed role for exercise-induced antinociception and mood enhancement, we like to emphasize the unique potential of ligand PET applied to human athletes for uncovering the neurochemistry of exercise-induced psychophysiological phenomena. Compared with conventional approaches, in particular quantification of plasma beta-endorphin levels under exercise challenges, which are reviewed in this article, studying opioidergic effects directly in the central nervous system (CNS) with PET and relating opioidergic binding changes to neuropsychological assessments, provides a more refined and promising experimental strategy. Although a vast literature dating back to the 1980s of the last century has been able to reproducibly demonstrate peripheral increases of beta-endorphin levels after various exercise challenges, so far, these studies have failed to establish robust links between peripheral beta-endorphin levels and centrally mediated behavioral effects, ie, modulation of mood and/or pain perception. As the quantitative relation between endorphins in the peripheral blood and the CNS remains unknown, the question arises, to what extent conventional blood-based methods can inform researchers about central neurotransmitter effects. As previous studies using receptor blocking approaches have also revealed equivocal results regarding exercise effects on pain and mood processing, it is expected that PET and other functional neuroimaging applications in athletes may in future help uncover some of the hitherto unknown links between neurotransmission and psychophysiological effects related to physical exercise.

Keywords: positron emission tomography, beta-endorphins, opioids

Introduction

Regular physical exercise is associated with a wide spectrum of psychophysical effects, including anxiolysis,1 stress reduction,2 mood elevation,1,3-5 and altered pain perception.3 The underlying neurotransmitter effects (eg, dopaminergic, opioidergic, endocannabinoid, and serotonergic) in the central nervous system (CNS) and their specific roles for induction and maintenance of distinct psychophysiological phenomena are subject to both nonhuman and human exercise research. Although animal studies allow direct quantitative and regional assessments of neurotransmitter trafficking in the CNS via invasive microdialysis measurements in exercising animals,6 or postmortem autoradiography of receptor binding changes after exercise,7 until recently, human studies examining neuro-humeral effects of exercise have been derived exclusively from indirect peripheral neurotransmitter levels in plasma and receptor blockade studies (discussed later).
The central endorphinergic system, which is the focus of this article, has been linked to exercise-induced mood changes\textsuperscript{1,3,4,8–11} and antinociceptive effects referred to as stress-induced analgesia.\textsuperscript{3,9,10} The endorphinergic system can be studied in human athletes via measurements of peripheral beta-endorphin material, receptor blocking studies, or, more directly using positron emission tomography (PET) ligand displacement approaches (discussed later). This perspective, by contrasting the data derived from peripheral beta-endorphin measurements with initial PET studies in athletes, aims at highlighting the unique and unprecedented potential of PET ligand activation studies for exploring central neurotransmission related to physical exercise.

**Measurements of peripheral beta-endorphin levels in exercise studies**

Endogenous opioid peptides (endorphins, enkephalins, and dynorphins) interact with $\mu$, $\kappa$, and $\delta$ opioid receptors located in the CNS and the peripheral nervous system. During vigorous exercise, beta-endorphins are released from the pituitary gland into the blood, although with considerable intra-individual variability\textsuperscript{12} and inter-individual variability.\textsuperscript{13,14} Table 1 summarizes published data on this topic, as compiled from a PubMed search: “Exercise and Human and Plasma and Endorphin”, which revealed 185 hits spanning from 1982 to 2008. We excluded work examining the effects of resistance training on beta-endorphin plasma levels,\textsuperscript{15} and we also excluded studies conducted in patient populations. Our inquiry resulted in 65 studies covering a wide range of physical exercise challenges from low to maximal intensity. Although we can make no claim of completeness regarding included studies, the summarized papers indicate that a high percentage of exercise-induced beta-endorphin plasma elevations. As can be seen from Table 1, 59 of 65 papers identified significant increases of peripheral endorphin values, despite highly heterogeneous exercise challenges. Studies applying different exercise intensity levels have shown a positive relationship between the intensity of exercise challenges and the magnitude of peripheral endorphin increases in plasma.\textsuperscript{16–27}

**Link between peripheral beta-endorphin levels and mood and pain assessments**

Despite these highly reproducible increases of beta-endorphins in peripheral blood after exercise, as shown in Table 1, the correlation of peripheral beta-endorphin values with behavioral measures of altered mood or pain processing has yielded equivocal results.\textsuperscript{28} This may be linked to the fact that most of these large molecules can only bypass the blood-brain barrier to a very minor extent.\textsuperscript{29} Table 2 summarizes those studies that have correlated peripheral endorphin values after exercise challenges with changes in mood states, whereas Table 3 summarizes those studies that have correlated peripheral endorphin values after exercise challenges with pain scores. It can be seen from Table 2 that the association between peripheral beta-endorphin values and mood is indeed highly inconsistent, with only two out of 7 studies showing a positive relationship between both factors.\textsuperscript{3,30} Only 3 studies, we are aware of, have tested the relationship between exercise-induced peripheral beta-endorphin values and changes in pain ratings (Table 3). All of them have demonstrated exercise-induced hypoalgesia; however, only two of these identified a positive relationship between endorphins and hypoalgesia.\textsuperscript{3,31}

Based on the available limited evidence, at present no clear relationship between peripheral endorphin levels and modulation of mood/pain processing can be established, thus arguing against a linear relationship between the peripheral and the central opioidergic compartments. Moreover, these negative findings are also at odds with the acclaimed role of exercise in promoting antinociception and mood enhancement. Therefore, we conclude that peripheral measurements of endorphins provide only limited information about central opioidergic mechanisms underlying psychophysiological effects. This also seems to apply to receptor blocking studies, which are not summarized here in detail, but which have also revealed equivocal results, ie, either negative\textsuperscript{32–35} or positive blocking effects in the pain domain.\textsuperscript{3,36} On the other hand, several studies have reported positive blocking effects in the mood domain,\textsuperscript{3,37,38} thus supporting the hypothesis of central opioidergic effects mediating mood enhancement. Alternatively, quantification of neurotransmitter levels in the cerebrospinal fluid compartment of the CNS\textsuperscript{39} seems to provide a more direct approach, and may yield more distinct information than plasma values. Yet, given the invasiveness of repetitive spinal fluid taps, this experimental approach has to be refuted for ethical reasons in humans. Moreover, any quantitative analysis of neurotransmitters in spinal fluid or plasma will not inform researchers about the site of neurotransmitter actions in the CNS and, therefore, will not be able to establish precise correlations with neurobehavioral measures.

**PET ligand activation of the opioidergic system**

PET studies allow noninvasively quantifying receptor binding of PET ligands within the entire CNS and, more recently,
Table 1  Papers reporting peripheral beta-endorphin values in exercise challenges

| Publication | N/sex | Age       | Fitness state | Exercise type | Duration/distance | Intensity level | Significance (endorphine increase) |
|-------------|-------|-----------|---------------|---------------|-------------------|----------------|-----------------------------------|
| 48          | 9/M   | 27.6 ± 1.6| Highly fit    | Treadmill     | 30 min            | 80% VO₂ max     | P < 0.05                          |
| 49          | 15/M  | 28.5 ± 9.5| Unfit         | Cycle ergometer | 60 min             | 60% VO₂ max, 80% VO₂ max | Significant                      |
| 50          | 10/M  | 32.3 ± 10.6| Fit           | Treadmill     | 30 s               | 42.4 ± 41.9 W   | P < 0.001                         |
| 16          | 7/F   | 24.6 ± 4.2| Fit           | Cycle ergometer | 60 min             | 20 min 50%, 20 min 70%, 10 min 80–85% VO₂ max | NS, NS, P < 0.05               |
| 51          | 24/M  | 12.85 ± 0.054| Fit     | Cycle ergometer | 15 min           | 90% VO₂ max     | P < 0.01                          |
| 52          | 13/M  | 18.6 ± 0.7 | Highly fit    | Swimming (100 m freestyle) | 61.47 ± 1.9 s | Competition condition | P < 0.01 |
| 53          | 20/M  | 34.4 (27–42)| Highly fit  | Outdoor running | 30 min           | “Easy run”      | P < 0.067 (NS)                     |
| 54          | 11/M  | 20–24     | Fit to highly fit | Treadmill   | –                | Graded intensity to exhaustion | P < 0.05 |
| 55          | 11/M  | –         | Unfit        | Cycle ergometer | –                | Graded intensity to exhaustion | P < 0.05 |
| 56          | 14/M  | 26.7 ± 3.2| Fit           | Cycle ergometer | 60 min           | 112 ± 16 W (<70% max HR) | NS |
| 57          | 18/M  | 20.8 ± 0.2| Highly fit    | Treadmill     | 30 min            | Anaerobic threshold | NS |
| 58          | 19/M  | 21.9 ± 1.9| Unfit         | Cycle ergometer | 32 min           | Graded intensity to exhaustion | P < 0.05 |
| 59          | 10/M  | 33 (20–46)| Fit           | Cycle ergometer | –                | Graded intensity to exhaustion | P < 0.0001 |
| 60          | 8/M   | 26.8 ± 8.6| Unfit         | Treadmill     | 20 min            | 80% max HR      | NS |
| 61          | 5/M   | –         | Unfit         | Treadmill     | –                | Graded intensity to exhaustion | P < 0.05 |
| 13          | 5/M   | 30.0 ± 8.3| Highly fit    | Treadmill     | 30 min            | 60% VO₂ max     | P < 0.05 |
| 18          | 7/M   | 23.1 ± 2.5| Fit           | Treadmill     | 12 min            | 7 min 60% VO₂ max | NS |
| 18          | 7/M   | 23.0 ± 3.5| Unfit         | Treadmill     | –                | 3 min 100% VO₂ max | P < 0.05 |
| 62          | 10/M  | 26.3 ± 5.4| Fit           | Cycle ergometer | 120 min          | 2 min 110% VO₂ max | P < 0.05 |
| 63          | 21/F  | 14        | Fit           | Step test     | 3–6 min           | 65% VO₂ max     | P < 0.05 |
| 64          | 8/M   | 45.9 ± 8.7| Highly fit    | Outdoor running | 21–42 km        | To 66% VO₂ max | P < 0.05 |
| 65          | 9/M   | 20–28     | Unfit         | Cycle ergometer | –                | Race conditions | P < 0.001 |
| 19          | 12/M  | 26.5 ± 1.3| –             | Cycle ergometer | 30 min           | 60% VO₂ max     | NS |
| 20          | 6/M   | 28.0 ± 2.2| Fit           | Cycle ergometer | 30 min           | 70% VO₂ max     | P < 0.05 |
| 21          | 6/M   | 25.0 ± 1.4| Unfit         | Cycle ergometer | 2 × 25 min      | 80% VO₂ max     | NS |
| 21          | 12/M + F | 26.4/26.8| –             | Cycle ergometer | 2 × 25 min      | 60% VO₂ max     | P < 0.05 |

(Continued)
| Publication | N/sex | Age | Fitness state | Exercise type | Duration/distance | Intensity level | Significance (endorphine increase) |
|-------------|-------|-----|---------------|---------------|------------------|----------------|----------------------------------|
| 66          | 14/M  | 25.6 ± 2.1 | Fit | Outdoor running + upstairs running (8 floors) | 3 km | Individual maximal pace | P < 0.05 |
| 30          | 11/M  | 31.3 | Highly fit | Outdoor running | 60 min/15 km | Fast training pace | P < 0.0001 |
| 31          | 50/F  | – | – | Cycle ergometer | 20 min | Moderate intensity | P < 0.001 |
| 67          | 9/M, 7/M | 21.1 ± 2.52, 66.0 ± 5.85 | Unfit | Cycle ergometer | – | Graded intensity to exhaustion | P < 0.001 |
| 68          | 16/M  | 38 | Highly fit | Outdoor running | 42 km | Graded intensity to exhaustion | Race condition (83% Vo2 max) | P < 0.001 |
| 69          | 14/F  | – | Highly fit | Outdoor running | 3.22 h/42 km | Race condition | Significance |
| 70          | 23/F  | 21.7 ± 1.9 | Unfit | Treadmill running | 30 min | Graded intensity to exhaustion | P < 0.05 |
| 71          | 5/M, 18/F | 22.6 ± 1.3, 20–23 | Highly fit | Cycle ergometer | 60 min | Vo2 max | P < 0.05 |
| 72          | 12/M  | 38.3 | Highly fit | Outdoor running | 43.9 min/6.3 miles | 85% Vo2 max | P < 0.01 |
| 73          | 6/M, 10/M | 26.5 ± 4.5, 23.9 ± 3.8 | Fit, – | Cycle ergometer | 120 min, <1–4 min | 50% Vo2 max, 115% Vo2 max, 175% Vo2 max, 230% Vo2 max, 318% Vo2 max | P < 0.05 |
| 74          | 8/M + F, 10/M + F, 7/M + F | 26.5 ± 5.0, 23.1 ± 4.1, 21.9 ± 3.1 | Unfit, – | Cycle ergometer | Treadmill, 7–8 min | Maximal intensity | P < 0.05 |
| 75          | 6/M, 22 | 22 ± 2 | Fit | Cycle ergometer | 7–8 min | 3 min 90% Vo2 max, 3–4 min 100% Vo2 max | P < 0.05 |
| 77          | 8/M, 5/F, 5/M, 5/F | 31.5 ± 30.4, 29.6 ± 28.8 | Fit, Unfit | Treadmill | 30 min, 80% max HR, 0% Vo2 max | NS |
| 78          | 5/M, 5/M | 22 ± 2, 22 ± 2 | Fit, Fit | Cycle ergometer, Treadmill | 60 min, 60 min | 0% Vo2 max, 60% Vo2 max | NS |
| 79          | 6/M | 33.5 ± 8.6 | Fit | Cycle ergometer | – | Graded intensity to exhaustion | P < 0.05 |
| 80          | 7/F | 23.4 ± 1.4 | Fit | Treadmill | 2 × 60 min | 80% Vo2 max | P < 0.05 |
to capture endogenous neurotransmitter release in the CNS under experimental challenges (e.g., pharmacological, cognitive, or sensorimotor). Currently, studies investigating neurotransmitter release cannot be performed with magnetic resonance imaging or other neuroimaging techniques. The so-called “displacement” or “ligand activation studies” allow quantifying and localizing ligand binding changes by comparing rest and postexercise conditions. Compared with animal work, the major advantage of studying central neurotransmission directly in human athletes is that

| Publication | N/sex | Age | Fitness | Exercise type | Duration/distance | Intensity level | Significance (endorphine increase) |
|-------------|-------|-----|---------|---------------|------------------|----------------|-----------------------------------|
| 24          | 5/M + 5/F | 26.9 ± 6.7 | Fit | Cycle ergometer | 3 × 20 min | 40% VO₂ max | NS |
|             | 5/M + 5/F | 21.0 ± 2.9 | Fit | Cycle ergometer | 3 × 20 min | 60% VO₂ max | NS |
| 81          | 14/M | 18–25 | Mixed | Cycle ergometer | 4 × 30 min | 85% VO₂ max | P < 0.05 |
| 82          | 10/F | 18–21 | Highly fit | Cycle ergometer | – | Graded intensity | P < 0.001 |
| 83          | 8/M | 22.1 ± 2.7 | Fit | Cycle ergometer | 90 min | 65% watt max | P < 0.05 |
| 84          | 11/M | 34 ± 2.3 | Highly fit | Ski race | 75.7 km | Race conditions | P < 0.001 |
| 85          | 6/M | 38.1 ± 4.3 | Fit | Treadmill | 15 min | Graded intensity | P < 0.01 |
| 86          | 9/M | – | Highly fit | Outdoor running | 70–80 min/22 km | Race condition | P < 0.05 |
| 95          | 8/F | 34 | Highly fit | Outdoor running | 7 d 23 h/1,000 km | Race condition | NS |
| 88          | 8/M | 30.1 ± 7.2 | Highly fit | Outdoor running | 10,000 m | Race condition | P < 0.01 |
| 91          | 7/M | 25 ± 2 | Highly fit | Outdoor running | 1,500 m | Race condition | P < 0.01 |
| 89          | 5/M | 24–41 | Highly fit | Outdoor running | 100 m | Race condition | P < 0.01 |
| 90          | 8/M | 24.6 ± 2 | Fit | Cycle ergometer | 89 ± 1 min | 65% watt max | P < 0.05 |
| 91          | 8/F | 29.7 ± 4.0 | Fit | Aerobic dance | 45 min | High intensity | Significant |
| 92          | 5/M | 25 ± 2 | Highly fit | Treadmill 30/1 min | 29 ± 1 min | Graded intensity | P < 0.001 (M + F) |
| 25          | 10/M | 23–36 | Highly fit | Marathon race | 90 min | 50% VO₂ max | P < 0.01 |
| 93          | 23/M | 26.0 ± 0.9 | Fit to highly fit | Rowing ergometer | 9 min | Aerobic exercise | P < 0.001 |
| 94          | 8/M | 18–23 | – | Cycle ergometer | 25 min | 50% VO₂ max | P < 0.05 |
| 95          | 32/M | 24–63 | Highly fit | Mountain running | 46 km | Race condition | P < 0.001 |
| 96          | 9/F | 25–55 | Highly fit | Mountain running | 46 km | rRace condition | NS |
| 26          | 12/M | 23.0 ± 0.8 | Fit | Cycle ergometer | 2 × 120 min | 45% VO₂ max | P < 0.05 |
| 27          | 6/M | 21.8 ± 0.7 | – | Cycle ergometer | <50 min | 60% VO₂ max | P < 0.05 (only fit) |
|             | 6/F | 23.7 ± 1.4 | – | Cycle ergometer | <50 min | VO₂ max | NS |

**Abbreviations:** NS, nonsignificant; HR, heart rate.
detectable binding changes can be tested for correlation with psychophysical effects, as detectable via standardized neuropsychological assessments. Moreover, compared with microdialysis studies in animals, which are restricted to selected brain areas, PET ligand studies provide quantitative measures of tracer binding in the entire human brain.

**Basic mechanisms and methodological limitations of PET ligand activation studies**

Ligand activation studies derive quantitative measures of endogenous transmitter trafficking from ligand binding changes that result from competition at specific receptor binding sites in the brain. Although the temporal resolution of PET is low in comparison to other functional brain imaging techniques and does not suffice to capture real-time dynamics of transmitter release in the human brain, PET ligand activation studies allow calculating sustained tracer binding changes induced by previous exercise, ie, manifesting as prolonged changes in ligand binding status. It has to be pointed out that depending on the experimental challenge, either increased or decreased ligand binding changes have been identified in identical brain regions related to fundamentally different experimental challenges, ie, decreased binding reflecting enhanced release of the endogenous transmitter relative to rest, or increased binding reflecting decreased release of the endogenous transmitter relative to rest.

**Table 2** Papers reporting peripheral beta-endorphin values in relation to mood changes induced by exercise challenges

| Publication | Endorphin increase | Mood elevation | Relationship |
|-------------|-------------------|----------------|--------------|
| 13          | P < 0.05 (60% VO2 max) NS | NS | No relationship |
| 65          | P < 0.05          | NS | No relationship |
| 30          | P < 0.0001 Significant | Significant | Positive relationship |
| 67          | P < 0.001 Significant | NS | No relationship |
| 3           | P < 0.01          | Significant | Positive relationship |
| 77          | NS                | Significant | No relationship |
| 81          | P < 0.003         | NS | No relationship |

*Abbreviation: NS, nonsignificant.*

The methodological details of PET ligand activation studies (eg, study designs, suitable PET tracers, ligand modeling approaches, etc) have been summarized extensively in a recent review article by Boecker et al. Nonetheless, it is important to point out here again that PET is associated with radiation exposure, and, depending on the used tracer, with arterial cannulation for calculating the arterial input function. These methodological issues limit repeated PET acquisitions in the same patient, for instance PET scans under different experimental conditions, or longitudinal study designs. Usually, either separate acquisitions (eg, “baseline” scan and “experimental” scan in counterbalanced order) or one acquisition with an intermediate challenge are performed. In the context of exercise challenge studies, however, intermediate challenges (for instance, using a cycling device installed in the PET unit) are difficult to perform, as exercise challenges risk of being associated with severe head movement artifacts. This will be particularly limiting when intending to study the effects of high intensity or long intensity exercise challenges. Therefore, previous ligand activation work investigating exercise challenges has employed two separated scans, ie, one scan under baseline conditions and one scan immediately after exercise. In such a scenario, PET scanning typically starts with the injection of the radiotracer (to capture the tracer input function) and is continued for a prolonged time period (to capture specific neuroreceptor binding of the PET tracer using parametric and nonparametric kinetic modeling). It has to be considered, however, that enduring experimental challenges, such as continuous exercise, may induce receptor internalization or downregulation, and can hardly be distinguished by means of PET from decreased binding due to enhanced endogenous transmitter release.

**PET ligand activation studies in the sport sciences**

The first study to apply ligand PET to exercising humans was published in 2000 by Wang et al. These authors studied 12 healthy volunteers using the dopaminergic PET tracer 11C-Raclopride which binds to striatal D2-receptors. Examining subjects twice allowed testing for the effects of a 30-minute treadmill exercise (average speed of 8.7 ± 0.5 km/h; 5.4 ± 0.3 mph) and at an inclination of 3.3° ± 2°) upon dopaminergic release; however, no significant differences in binding at the D2 receptors were identified in this cohort after subjects exercised vigorously for 30 minutes. In the second previous study, which was performed at the Technical University Munich, 10 trained athletes were scanned at rest and after 2 hours of

**Table 3** Papers reporting peripheral beta-endorphin values in relation to changes in pain perception induced by exercise challenges

| Publication | Endorphin increase | Pain (hypoalgesia) | Relationship |
|-------------|-------------------|--------------------|--------------|
| 59          | P < 0.0001        | P < 0.01 Significant | No relationship |
| 31          | P < 0.001         | Significant        | Positive relationship |
| 3           | P < 0.01          | Significant        | Positive relationship |
outdoor running using the nonselective opioidergic ligand 6-O-(2-[18F]fluoroethyl)-6-O-desmethyldiprenorphine ([18F]FDPN). These studies were performed to examine whether endogenous opioids are released after exercise and if so, whether such effects are linked to mood changes. In line with the “endorphin hypothesis”, this study identified significant reductions in [18F]FDPN binding in certain regions of the brain. The strongest effects were seen in orbitofrontal cortex and in areas belonging to the limbic system, including the anterior cingulate cortex and the anterior insula. Although this work has been conducted in a rather small sample of N = 10 athletes undergoing 2 PET scans each, it is noteworthy that the displacement effects were clustered in brain regions associated with affective processing and current theories of opioid-mediated pleasure generation. Regression analyses further indicated that the amount of endogenous opioidergic release was inversely correlated to the level of euphoria determined after exercise on visual analog mood scales. We, therefore, conclude that ligand PET is able to noninvasively monitor transmitter release induced by exercise and to link these central neurotransmitter effects to behavioral measures that will inform researchers about the biology of exercise.

Based on this initial feasibility study, future PET work should try to image larger samples of athletes, possibly using subtype-selective tracers like 11C-Carfenaltin that do not require arterial cannulation. Furthermore, future work should attempt to stratify individual exercise challenges based on appropriate physical fitness tests. Moreover, careful monitoring of exercise load, use of appropriate neuropsychological tests designed for repeated testing, and incorporation of biomarkers like lactate, beta-endorphins, etc would advance PET ligand applications in the field of exercise research. Considering the duration of PET ligand studies, an improvement to our previous work would be to avoid any time delay between the end of exercise and the beginning of the study (injection of the PET tracer). This might be achieved with tracers that do not require arterial cannulation and may, thereby, be more suitable to detect the full range of neurotransmitter change in the immediate postexercise period. Of course, it is well conceivable that the extent of detectable neurotransmitter change may be further amplified with more strenuous exercise challenges, but these various effects will have to be systematically studied in the future. Having said this, the investigation of other neurotransmitter systems such as the endocannabinoid system or the serotonergic system may represent alternative targets for future studies.

Conclusion

The value of measuring plasma levels of neurotransmitters for understanding the neuro-psychophysiology of exercise is uncertain. Based on a literature survey spanning approximately 3 decades, we conclude that beta-endorphins levels in plasma after exercise challenges gives only limited information regarding putative central opioidergic effects and, thus, functional mechanisms of behavioral change. In particular, the amount of neurotransmitter detectable in the peripheral blood does not mirror the magnitude of central neurotransmission.

PET is proposed here as a powerful tool for human exercise research, with a hitherto unprecedented potential to unravel the “missing link” between neurotransmission in the CNS under exercise conditions and associated neurobehavioral effects in athletes. It is expected that PET will allow advancing our understanding of underlying neurochemical mechanisms involved in physical exercise. In particular, the correlation between neurochemistry and validated neuropsychological assessments has a strong potential to advance our knowledge about the central underpinnings of exercise-induced psychophysical effects. In conclusion, although still in its infancy, PET ligand activation studies provide a powerful tool for human exercise research.

Disclosure

The authors report no conflicts of interest in this work. Henning Boecker holds an endowed professorship (Philips).

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