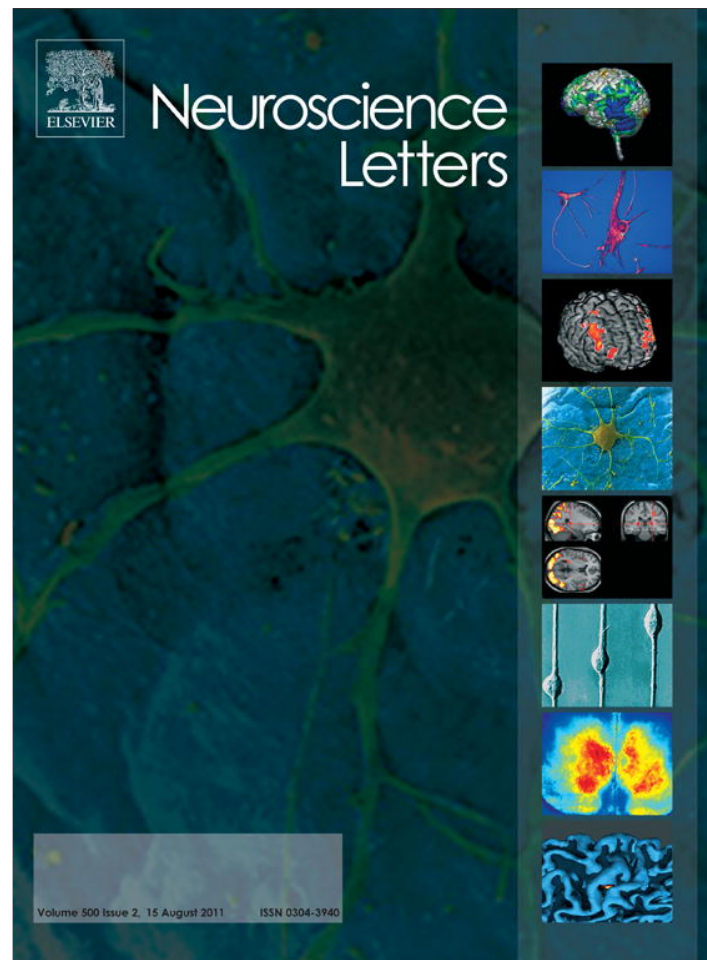




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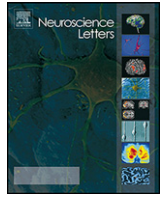
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No exercise-induced increase in serum BDNF after cycling near a major traffic road

I. Bos^{a,b}, L. Jacobs^c, T.S. Nawrot^{c,d}, B. de Geus^a, R. Torfs^b, L. Int Panis^{a,e}, B. Degraeuwe^b, R. Meeusen^{a,*}^a Department of Human Physiology & Sports Medicine, Vrije Universiteit Brussel, Brussels, Belgium^b Flemish Institute for Technological Research (VITO), Mol, Belgium^c School of Public Health, Occupational and Environmental Medicine, Unit of Lung Toxicology, K.U. Leuven, Leuven, Belgium^d Centre for Environmental studies, Hasselt University, Diepenbeek, Belgium^e Transportation Research Institute (IMOB), Hasselt University, Diepenbeek, Belgium

ARTICLE INFO

Article history:

Received 2 May 2011

Accepted 9 June 2011

Keywords:

Commuting

Acute exercise

Traffic

Air pollution

Brain-derived neurotrophic factor

Particulate matter

ABSTRACT

Commuting by bike has a clear health enhancing effect. Moreover, regular exercise is known to improve brain plasticity, which results in enhanced cognition and memory performance. Animal research has clearly shown that exercise upregulates brain-derived neurotrophic factor (BDNF – a neurotrophine) enhancing brain plasticity. Studies in humans found an increase in serum BDNF concentration in response to an acute exercise bout. Recently, more evidence is emerging suggesting that exposure to air pollution (such as particulate matter (PM)) is higher in commuter cyclists compared to car drivers. Furthermore, exposure to PM is linked to negative neurological effects, such as neuroinflammation and cognitive decline. We carried-out a cross-over experiment to examine the acute effect of exercise on serum BDNF, and the potential effect-modification by exposure to traffic-related air pollution. Thirty eight physically fit, non-asthmatic volunteers (mean age: 43, 26% women) performed two cycling trials, one near a major traffic road (Antwerp Ring, R1, up to 260,000 vehicles per day) and one in an air-filtered room. The air-filtered room was created by reducing fine particles as well as ultrafine particles (UFP). PM₁₀, PM_{2.5} and UFP were measured. The duration (~20 min) and intensity of cycling were kept the same for each volunteer for both cycling trials. Serum BDNF concentrations were measured before and 30 min after each cycling trial. Average concentrations of PM₁₀ and PM_{2.5} were 64.9 $\mu\text{g}/\text{m}^3$ and 24.6 $\mu\text{g}/\text{m}^3$ in cycling near a major ring way, in contrast to 7.7 $\mu\text{g}/\text{m}^3$ and 2.0 $\mu\text{g}/\text{m}^3$ in the air-filtered room. Average concentrations of UFP were 28,180 particles/cm³ along the road in contrast to 496 particles/cm³ in the air-filtered room. As expected, exercise significantly increased serum BDNF concentration after cycling in the air-filtered room (+14.4%; $p=0.02$). In contrast, serum BDNF concentrations did not increase after cycling near the major traffic route (+0.5%; $p=0.42$). Although active commuting is considered to be beneficial for health, this health enhancing effect could be negatively influenced by exercising in an environment with high concentrations of PM. Whether this effect is also present with chronic exercise and chronic exposure must be further elucidated.

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Physical activity has significant health benefits, for example in the prevention of cardiovascular diseases [24]. Extensive research is now showing that it also has substantial benefits for psychological health and cognition [16]. Exercise not only improves cognitive function in normal individuals, but is also associated with a lower risk for depression, Alzheimer's disease and other types of neurodegenerative diseases [21]. Both clinical and animal studies have repeatedly demonstrated that exercise benefits neuronal function [30], promotes brain vascularisation [18], stimulates neu-

rogenesis and enhances learning [29]. Exercise elevates levels of neurotrophic factors, factors that regulate the proliferation and differentiation of cells in the central nervous system. Among these factors brain-derived neurotrophic factor (BDNF) is a molecule that is consistently demonstrated to be upregulated with exercise. BDNF has been shown to be necessary for long-term potentiation, a neural analogue of long-term memory formation, and for the growth and survival of new neurons. Both animal [7,29], and human studies [14,20] have demonstrated that BDNF increases with exercise.

The health-enhancing potential of physical activity can be accomplished by incorporating physical activity into the daily life routine, this can be performed by active commuting to work (commuter cycling). Our previous studies clearly showed that cycling to work improves physical performance in untrained middle-aged men and women and decreases the risk of coro-

* Corresponding author at: Faculty of Physical Education and Physiotherapy, Department of Human Physiology and Sports Medicine, Vrije Universiteit Brussel, Pleinlaan 2, B-1050 Brussels, Belgium. Tel.: +32 2 6292222; fax: +32 2 6292876.

E-mail address: rmeeusen@vub.ac.be (R. Meeusen).

nary heart diseases [9,10]. However, most of the commuting is performed in urbanised environment where traffic-related air pollution is becoming increasingly important [33]. Moreover, exercise increases ventilation. Recently, Int Panis et al. [17] calculated that minute ventilation while cycling is on average 4.3 times higher compared to driving a car, with significant increases in inhaled μg PM_{2.5}/km and μg PM₁₀/km as a result. Evidence showed that an athlete running at 70% of maximal oxygen uptake for the length of a marathon (ca 3 h) inhales the same volume of air as a sedentary person would in 2 days [22]. In addition to the elevated ventilation rate, the switch from nasal to mouth breathing during intensive exercise and an increased airflow velocity carries pollutants deeper into the lungs, and further amplifies the subject's inhaled dose of pollutants [22].

It is now reasonably well established that both short-term and chronic air pollution exposures are related to cardiovascular diseases, but there is also mounting evidence that exposure to air pollution can cause brain damage and neurodegeneration. Calderon-Garcidueñas et al. [5] have previously shown that long-term exposure to air pollution causes neuroinflammation and a disruption of the Blood-Brain Barrier. These authors documented with MRI prefrontal lesions and cognitive deficits in children exposed to ambient air pollution in Mexico City [5]. Also other studies emerged showing associations between long-term exposure and cognitive impairments in healthy adults and children [25,31]. The molecular toxicity of air pollution and especially diesel exhaust is suggested to include oxidative stress-mediated inflammation [8]. The smaller fraction of inhaled PM is able to move to the brain via olfactory nerves, or through inhalation and circulation, but it also indirectly affects the brain through induction of systemic inflammation [2]. We recently found that cyclists that were briefly exposed to traffic-related air pollution showed an increase in inflammatory blood cells [19].

It is clear that exercise has positive effects on brain health, and that air pollution can negatively influence cognition. Since exposure during commuting may represent an important fraction of the daily exposure to air pollution [11], we designed a controlled cross-over experiment in which we measured the exercise-induced release of BDNF in healthy subjects while cycling near a major motorway with busy traffic and in a room with filtered air. We hypothesize that the exercise-induced increase of serum BDNF will be reduced while cycling in polluted air.

All subjects were taking part in the 'SHAPES injury surveillance system' [17]. A part of this study was already published, see Jacobs et al. [19], for detailed materials and methods.

The study was approved by the Ethics Review Board of the Medical Faculty of the Free University of Brussels. All subjects signed a written informed consent. Participants performed two cycling trials, one near a major traffic road and one in a "clean room", 12–29 days apart. The major traffic road, called the Antwerp Ring, is a 10-lane motorway with approximately 260,000 vehicles (including ~50,000 trucks) per day, making it the busiest road section in Belgium. The preselected route along the Antwerp Ring is a dedicated cycling path situated between 10 and 100 m from the edge of the motor way. Participants cycled at the same intensity and speed as their everyday cycling to and from work, carrying a heart rate monitor (Polar X-Trainer Plus, Polar Electro OY, Kempele, Finland). The bicycle was equipped with a GRIMM (1.108 Dust Monitor) measuring PM₁₀ and PM_{2.5} and a P-TRAK Ultrafine Particle Counter (TSI Model 8525) measuring UFP. PM₁₀, PM_{2.5} and UFP were removed from the air in the clean room by use of a Bionaire® Mini Tower air purifier (The Holmes Group, Inc., Milford, USA), MadicCleanAir® (Häri-Prolectron AG, Bronschhofen, Switzerland) and the Genano® 310 (Genano OY, Espoo, Finland). In the clean room, load of the cycle ergometer was adapted for each participant to achieve a steady state heart rate equal to the individual

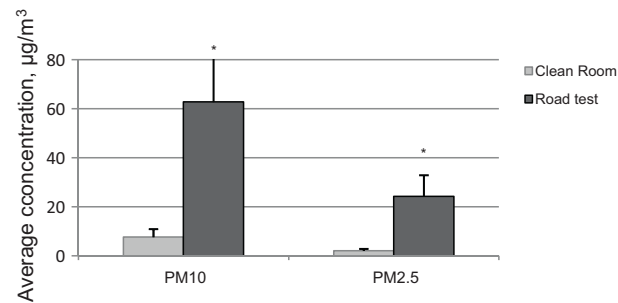


Fig. 1. Concentrations of PM₁₀ and PM_{2.5} in $\mu\text{g}/\text{m}^3$ in the clean room and road test (mean $\pm$ SD). Particle concentrations of PM₁₀ and PM_{2.5} were significantly higher during the road test compared to the clean room (* $p < 0.001$).

average heart rate reached during the road test. Duration of the trial was for each individual equal to that of the road test. GRIMM and PTRAK measured particles in the direct surrounding of the participant. Temperature and relative humidity were constantly measured using a portable thermo-Hygro-Barometer (ATC-09, Atal Commeter, Purmerend, The Netherlands) and adjusted if necessary.

A venous blood sample was drawn, before and 30 min after the exercise bout. Serum was analyzed for concentration of BDNF (ELISA; Chemicon, Temecula, CA).

Differences in concentrations of PM₁₀, PM_{2.5} and UFP between road test and clean room test were compared by paired *T*-test statistics. Duration and intensity of cycling as well as average ventilation per minute was compared by paired *T*-test statistics. Baseline BDNF concentrations of both exposure scenarios (clean room and Antwerp Ring) as well as the post-cycling concentrations were compared by analysis of variance (Friedman post test).

Thirty-eight non-asthmatic, physically fit subjects (26% women, mean age 43 years, mean BMI 24 kg/m²) participated in this study. Three subjects were excluded from the data analysis due to technical failure. Participants cycled at $74.0 \pm 8.6\%$ and at $74.1 \pm 8.8\%$ of the maximal heart rate in the road test and in the clean room, respectively. The duration of cycling, the heart rate and the average ventilation per minute did not differ significantly between the two experimental settings (Antwerp ring and clean room). Average temperature was higher in the clean room and relative humidity was lower.

The ambient air pollution (PM₁₀), measured in the automatic monitoring network, was the same in the week of the road test compared with the week of the 'clean room' ($24.4 \mu\text{g}/\text{m}^3$ versus $23.3 \mu\text{g}/\text{m}^3$, $p = 0.77$). The average concentrations of particles the participants were exposed to during the road test were significantly higher compared to the test in the clean room. Average concentrations of PM₁₀ and PM_{2.5} were $64.9 \mu\text{g}/\text{m}^3$ and $24.6 \mu\text{g}/\text{m}^3$ respectively, in contrast to $7.7 \mu\text{g}/\text{m}^3$ and $2.0 \mu\text{g}/\text{m}^3$ in the clean room (Fig. 1). The average concentrations of UFP were 28,180 particles/cm³ along the road in contrast to 496 particles/cm³ in the clean room (Fig. 2).

Comparison of serum BDNF concentrations in the four conditions, which were before and after cycling in Antwerp and in the clean room, showed a significant difference in the serum BDNF concentrations ($p = 0.04$). Serum BDNF concentrations increased significantly after cycling in the clean room ($p = 0.02$; Fig. 3). In contrast, BDNF serum concentrations pre/post cycling along the Antwerp Ring did not differ significantly ($p = 0.42$; Fig. 3). Baseline values of BDNF (before cycling) did not differ significantly between the clean room test and the road trial ($p = 0.07$; Fig. 3). Comparison of the values post-cycling did not show any significant differences ($p = 0.74$; Fig. 3).

BDNF values pre/post cycling showed a significant increase after cycling in the clean room, which was not found in response to cycling along the Antwerp Ring.

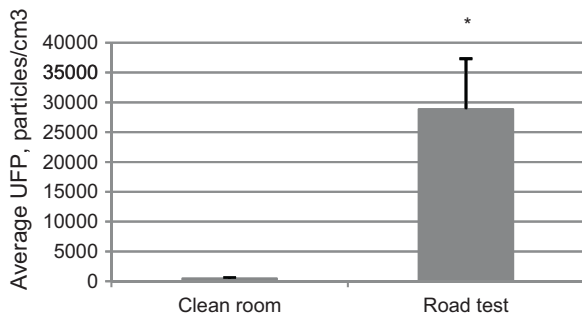


Fig. 2. UFP concentration in particles/cm³ in the clean room and road test (mean ± SD). UFP concentration was significantly higher during the road test compared to the clean room (**p* < 0.001).

The average UFP concentration measured along the road was 28,867 particles/cm³, which is lower compared to Strak et al. [27] and McCreanor et al. [23], in which participants were exposed to a mean particle number concentration of 44,090 particles/cm³, and 64,000 particles/cm³ respectively. However, these studies compared the high exposure scenarios with low-exposure scenarios, which still had an average concentration of 27,813 particles/cm³ and 18,300 particles/cm³. Unlike these studies, the low exposure scenario in our study was done in an air-filtered room, with an UFP concentration as low as 496 particles/cm³. Exposure duration of 20 min was short compared to 1 h in Strak et al. [27] and 2 h in McCreanor et al. [23]. However, in this study participants cycled at 75% VO₂ max, which results in enhanced ventilation rate and increases exposure compared to walking which was performed by the participants in McCreanor et al. [23].

The increase in serum BDNF (+14%) after exercise in the clean room is consistent with literature, where a transient increase of BDNF in serum is found in response to a single exercise bout [15,20]. Most studies on human subjects found an increase in BDNF ranging from 11.7% to 410.0% following acute exercise, with acute high intensity exercise protocols having larger increases in BDNF concentrations than acute low intensity exercise protocols [20]. The exercise intensities in both experimental settings described in this paper were mild, being 75% of maximal heart rate. The duration of both cycling trials was the same and set to be approximately 20 min, as this is the duration of an average commuting trip. The short duration and moderate intensity of the exercise trials can explain the rather small increase of 14% in peripheral BDNF after cycling in the clean room.

Studies in humans exposed to experimentally controlled air pollution in exposure chambers as well as real-life exposure along traffic routes already showed acute increases in both lung and

systemic inflammation markers [3,13,23,27]. We suggest that the exposure to air pollution resulted in activation of an inflammatory response and that this could be a potential cause of the blunted exercise-effect on BDNF-levels. This is supported by the finding that the percentage of blood neutrophils was increased after cycling along the Antwerp Ring, previously reported by Jacobs et al. [19].

Multiple studies have linked systemic inflammation with an acute reduction of hippocampal BDNF levels. Recently Wu et al. [32] found that inducing systemic inflammation by injecting in rats LPS intraperitoneally, caused within 3 h an inflammatory status in the substantia nigra and striatum and reduced the BDNF levels in the substantia nigra (not in striatum). It is known that older individuals frequently suffer from significant cognitive decline after an inflammatory event like an injury, surgery or infection [12,28]. In aged rodents, induction of systemic inflammation by an intraperitoneal injection of *E. coli* reduces mature BDNF concentration in hippocampus and disrupts hippocampus-dependant memory, which is strongly dependant on BDNF [1]. It is thought that systemic infection disrupts the production of mature BDNF by increased expression of IL1β, because administration of IL1 receptor antagonist can block the reduction of BDNF levels. In these animals, events that triggered the activation of the peripheral innate immune system induced an inflammatory response in the hippocampus, which reduced the hippocampal BDNF levels [6].

On the other hand, it is suggested that exercise increases serum BDNF levels, by increasing production and release from brain regions like hippocampus [26]. Considering that systemic inflammation is linked to a reduction of the hippocampal BDNF levels, it is plausible that both effects counteracted in the cycling trial along the Antwerp Ring.

Strength of the study is that differences in BDNF concentrations cannot be caused by interplate differences because all BDNF values were analyzed on the same ELIZA plate.

The study has limitations. Serum BDNF is known to originate from multiple sources, for instance neurons, immune cells, etc. In addition, serum BDNF levels vary in response to multiple triggers, like time of the day, stress, diseases, etc. [4]. Although the study was tightly controlled, for example for time of day, both trials were done on different days and in different environments. The possibility exists, therefore, that confounding factors coupled to the different days or environments, other than air pollution exposure, influenced the changes in BDNF levels during cycling. In other words, we do not exclude that other factors along the Antwerp Ring could have interfered with the exercise and affect the BDNF levels. However, knowledge about determinants that influence BDNF is lacking and only recently studies addressing this puzzle are emerging [4].

This study showed that exercise-induced increase in BDNF is absent while cycling near a busy road where the concentration of PM₁₀ and UFP is much higher than in a controlled clean room. Although it is tempting to speculate that the inflammation caused by PM could be the explanation for these results, further research is necessary to confirm this finding and to detect the possible mechanism. It is suggested that increases in serum BDNF levels in response to exercise, originate from increased production and release from the brain [26]. For this reason, exercise is believed to benefit brain plasticity and cognition. More research is needed to investigate the effects of air pollution exposure on the neurological benefits of acute and regular exercise.

Acknowledgements

The work reported in this paper was partly financed by the Belgian science policy under the Science for Sustainable Development program (Project No.: SD/HE/03 and SD/HE/01A).

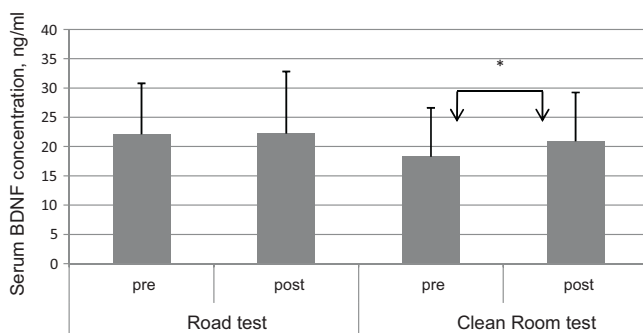


Fig. 3. Serum BDNF concentrations (ng/mL) before and after cycling in the road test and the clean room test (mean ± SD). Serum BDNF concentrations were significantly different (*p* = 0.04). BDNF concentrations increased significantly after cycling in the clean room (**p* = 0.02; *n* = 35).

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