NeuroImage xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

A perspective on the future role of brain pet imaging in exercise science

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ARTICLE INFO

Article history:
Accepted 8 October 2015
Available online xxxx

Keywords:
Exercise
Physical exercise
Neuroprotection
Brain plasticity
Positron emission tomography
PET
Cerebral metabolism
FDG
Neuroreceptor
Neurotransmission
Ligand
Ligand activation
PET/MR

ABSTRACT

Positron Emission Tomography (PET) bears a unique potential for examining the effects of physical exercise (acute or chronic) within the central nervous system in vivo, including cerebral metabolism, neuroreceptor occupancy, and neurotransmission. However, application of Neuro-PET in human exercise science is as yet surprisingly sparse. To date the field has been dominated by non-invasive neuroelectrical techniques (EEG, MEG) and structural/functional magnetic resonance imaging (sMRI/fMRI). Despite PET having certain inherent disadvantages, in particular radiation exposure and high costs limiting applicability at large scale, certain research questions in human exercise science can exclusively be addressed with PET: The "metabolic trapping" properties of ^{18}F-FDG PET as the most commonly used PET-tracer allow examining the neuronal mechanisms underlying various forms of acute exercise in a rather unconstrained manner, i.e. under realistic training scenarios outside the scanner environment. Beyond acute effects, ^{18}F-FDG PET measurements under resting conditions have a strong prospective for unraveling the influence of regular physical activity on neuronal integrity and potentially neuroprotective mechanisms in vivo, which is of special interest for aging and dementia research. Quantification of cerebral glucose metabolism may allow determining the metabolic effects of exercise interventions in the entire human brain and relating the regional cerebral rate of glucose metabolism (rCMRglc) with behavioral, neuropsychological, and physiological measures. Apart from FDG-PET, particularly interesting applications comprise PET ligand studies that focus on dopaminergic and opioidergic neurotransmission, both key transmitter systems for exercise-related psychophysiological effects, including mood changes, reward processing, antinociception, and in its most extreme form 'exercise dependence'. PET ligand displacement approaches even allow quantifying specific endogenous neurotransmitter release under acute exercise interventions, to which modern PET/MR hybrid technology will be additionally fruitful. Experimental studies exploiting the unprecedented multimodal imaging capacities of PET/MR in human exercise sciences are as yet pending.

Introduction

Regular physical exercise is associated with clear health benefits, not only the cardiovascular improvements promoting 'physical health', but also central nervous system (CNS) effects believed to promote 'brain health' (Boecker et al., 2012). Physical activity can induce acute and sustained psychophysiological effects, including mood changes (Boecker et al., 2008; Brene et al., 2007), hypoalgesia (Scheef et al., 2012), stress reduction and anxiolysis (DeBoer et al., 2012). At the cognitive level, being by far the most intensively studied domain using exercise, improvements have been observed in hippocampus-dependent spatial and associative learning (Barak et al., 2014; Herting and Nagel, 2013); memory encoding/consolidation (Roig et al., 2013); as well as frontal lobe dependent functions such as selective attention, planning and scheduling, inhibition of prepotent responses, task switching, and working memory capacity (Guiney and Machado, 2013; Ratey and Loehr, 2011).

While the impact of physical activity and aerobic fitness on childhood cognitive functions has only recently gained attention (Khan and Hillman, 2014), there is a large body of literature in older adults suggesting that exercise promotes neuroprotective mechanisms and associated plasticity of brain structure and function, counteracting age-related changes (Yau et al., 2014). On the other hand, physical inactivity (i.e. sedentary behavior) increases the risk for developing chronic disease conditions across the lifespan, in particular within the cardio/neurovascular spectrum. Despite considerable progress in unveiling the underlying neurobiological mechanisms by which exercise mediates neuroprotective mechanisms and improves cognitive functioning, including neurotrophic factor release (Gomez-Pinilla, 2008; Vaynman and Gomez-Pinilla, 2006; Vaynman et al., 2004), neurogenesis/angiogenesis (van Praag, 2008), and neuroplasticity (Cotman and Berchtold, 2002), the central mechanisms mediating reward and pleasure in athletes remain far less well understood. Moreover, the mechanisms necessary for initiating and maintaining a

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http://dx.doi.org/10.1016/j.neuroimage.2015.10.021
1053-8119/

physically active lifestyle are still not understood, despite evidence for heritability (Bray et al., 2009; Kelly and Pomp, 2013; Stubbe et al., 2006).

Animal research has contributed most to the improved understanding of exercise-induced CNS effects at behavioral (e.g. water maze-type tests), cellular (e.g. neurogenesis, neuroangiogenesis), and humoral (e.g. neurotrophic factors, inflammatory cytokines) levels (Hotting and Roder, 2013; van Praag, 2009; Vivar et al., 2013). For obvious reasons, the majority of the human studies in exercise research have been limited to behavioral measures, as well as indirect assessments of neurotrophic factors and neurotransmitters in blood. Today, different functional neuroimaging techniques allow for the direct investigation of acute and chronic effects of physical exercise in the human brain, as well as the correlation of physiological in vivo signals with behavioral outcomes recorded during and after exercise (Boecker et al., 2012). A wide range of techniques has been applied to human exercise research, ranging from electroencephalography (EEG), magnetoencephalography (MEG), near infrared spectroscopy (NIRS), magnetic resonance imaging (MRI), to positron emission tomography (PET), each method associated with inherent differences in spatial and temporal resolution, availability, cost, and risks. It appears that the field of neuroimaging has an unprecedented potential to unravel the neurobiology of human exercise, covering a wide spectrum from structural plasticity in gray and white matter, evoked neuronal responses, neuronal network dynamics, global and regional perfusion and metabolism, receptor binding studies and neurotransmitter release.

In this 'perspective paper', we focus on the distinct, but as yet emerging role of PET for studying exercise-induced functional changes in the human brain. So far, only a few PET studies have been published in exercise research. This shortage of research is difficult to retrace, as Neuro-PET is a 'gold standard' for quantifying cerebral metabolism and receptor binding in vivo. This 'perspective paper' emphasizes the current, but more importantly, the potential future role of PET in the fields of metabolic imaging, delayed metabolic imaging ('FDG activation studies'), neuroreceptor PET, PET ligand activations, and multimodal PET/MR. Beyond acute physiological effects, the potential role of PET in examining long-term neuro-preventive and restorative effects of exercise in clinical conditions is discussed, in particular in the eminent context of neurodegenerative diseases.

Brain pet measurements of glucose metabolism in exercise physiology

Background, methodology and current applications of ^{18}F-FDG brain PET

^{18}F-fluoro-deoxy-glucose (^{18}F-FDG) PET allows the measurement and quantification of the regional cerebral rate of glucose metabolism (rCMRglc). ^{18}F-FDG uptake is directly proportional to regional neuronal activity (Kennedy et al., 1975). ^{18}F-FDG PET measurements of rCMRglc can be conducted within different experimental settings for studying the mechanisms and consequences of movement and physical exercise; for a review of ^{18}F-FDG PET studies in sports sciences please also see: (Tashiro et al., 2008). Studies have, for example, investigated (Sakurai et al., 2014) ^{18}F-FDG brain uptake during the performance of different movement types or exercise training, i.e. quantifying acute exercise-dependent rCMRglc changes in the CNS. This is possible as ^{18}F-FDG is trapped in the brain during an initial uptake phase of 10–30 minutes post injection. Consequently, the tracer can be applied during defined test conditions and the resulting changes in cerebral glucose metabolism can be measured subsequently, i.e. with temporal delay. This principally allows the visualization of "brain metabolic signatures" associated with different forms of exercise. Importantly, these 'metabolic trapping' properties make it possible to inject ^{18}F-FDG even in realistic sport settings outside the PET scanner, i.e. without the obvious constraints of the imaging setup (as it is the case, e.g. in functional MRI-studies). Also to be considered are defined control conditions (including 'active control conditions' in identical environments), as these provide means for experimentally controlling unspecific (not exercise related) effects. It needs to be mentioned, however, that such an experimental approach will reflect a mean image of brain activation/deactivation during the tracer uptake phase, i.e. the results cannot be compared to classical brain activation studies which aim for the isolated localization of brain regions specifically activated by processing of a dedicated task.

^{18}F-FDG PET was hitherto employed for direct assessments of brain metabolism during unaccustomed treadmill walking, i.e. by comparing rest and 25 min of treadmill walking (Shimada et al., 2013). ^{18}F-FDG PET revealed relative metabolic increases during treadmill walking in the primary sensorimotor areas, occipital lobe, and anterior and posterior lobe of the cerebellum (Shimada et al., 2013). Further division into low and high step-length variability groups (based on step length recordings), allowed these researchers to relate walking-induced rCMRglc changes with parameters of gait. Activation of the primary sensorimotor cortex, prefrontal cortex, and temporal lobe were associated with gait adaptability during unaccustomed treadmill walking (Shimada et al., 2013). In another study, ^{18}F-FDG was injected while subjects either walked or purely imagined walking. Both, real and imagined locomotion activated a "basic locomotion network", including frontal cortex, cerebellum, ponto-mesencephalic tegmentum, parahippocampal, fusiform and occipital gyri; whereas the multisensory vestibular cortices were deactivated. Differential activity was identified in primary motor and somatosensory cortices for real steady-state locomotion, whereas imagined modulatory locomotion was associated with relatively elevated metabolism in the supplementary motor cortex and basal ganglia (la Fougere et al., 2010). Two recent studies by Kindred et al. have also used ^{18}F-FDG PET to integrate brain and muscle responses during task performance: relatively higher ^{18}F-FDG uptake was found during a position task than during a force task in occipital and temporal cortices, possibly reflecting enhanced processing of visuospatial feedback (Kindred et al., 2015a). In another study (Kindred et al., 2015b), eight healthy controls performed 15 min of treadmill walking at a self-selected pace, during which ^{18}F-FDG was injected. In several task-related brain areas, they found "strong to moderate correlations" between ^{18}F-FDG uptake and walking speed; the ^{18}F-FDG uptake was altered in eight patients with multiple sclerosis (Kindred et al., 2015b).

Exercise training was also investigated using this approach: Tashiro et al. examined rCMRglc changes in 17 healthy male volunteers induced by free running in upright posture (Tashiro et al., 2001). Participants were divided randomly into two groups, either performing a 4–5 km run, or simply resting. Running augmented energy consumption particularly in the parieto-occipital region that was interpreted as being due to relatively higher energy costs for integrating multimodal sensory information during running rather than for generating motor output. Relative increases of glucose uptake during running were also found in temporo-parietal association cortex, occipital cortex, premotor cortex and cerebellar vermis. As to be expected, activity in the primary sensorimotor cortex was highest in the 'leg motor area'. Another study (Kemppainen et al., 2005) assessed how 'high intensity exercise' affects regional and global brain glucose uptake. Scans were acquired in 14 male volunteers after 35 min of bicycle exercise (intensities corresponding to 30, 55 and 75%) with ^{18}F-FDG being injected 10 min after the start of the exercise. Kemppainen et al. observed that glucose uptake decreased as exercise intensity increased, the mean decrease from the lowest to the highest exercise intensity being 32% globally (Kemppainen et al., 2005). Interestingly, brain glucose uptake correlated inversely with the measured lactate accumulation during exercise (Kemppainen et al., 2005).

These data indicate that by using the "metabolic trapping" properties of ^{18}F-FDG PET, deeper insights can be gained into the mechanisms of different kinds of movement; moreover, the potential to correlate rCMRglc with parameters of locomotion, endurance exercise, and even neuropsychological effects bears an enormous potential; similar studies can also be conducted using delayed single photon emission computed tomography (SPECT) perfusion imaging, although at typically lower

Please cite this article as: Boecker, H., Drzezga, A., A perspective on the future role of brain pet imaging in exercise science, NeuroImage (2015), http://dx.doi.org/10.1016/j.neuroimage.2015.10.021