Does Psycho-Motor Therapy Ameliorate Depression and Alter Striatal Dopaminergic Signaling and Brain Neuronal Connectivity During Depression?

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Primary objectives* To determine if 3-month PMTERGO decreases depressive symptoms in subjects with MDD* To determine if 3-month PMTERGO alters in vivo striatal DRD2/3 BP compared to pre-intervention levels in subjects with MDDSecondary objectives:*...

Ethical review	Not approved
Status	Will not start
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON48201

Source
ToetsingOnline

Brief title
FIT-BRAIN

Condition

- Mood disorders and disturbances NEC

Synonym
Depression

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Dopamine, fMRI, Psycho-motor Therapy (PMT), SPECT

Outcome measures

Primary outcome

Primary objectives

* To determine if 3-month PMTERGO decreases depressive symptoms in subjects with MDD

* To determine if 3-month PMTERGO alters in vivo striatal DRD2/3 BP compared to pre-intervention levels in subjects with MDD

Secondary outcome

Secondary objectives:

* To determine if medium-intensity ergocycle exercise acutely lowers in vivo striatal DRD2/3 BP in subjects with MDD compared to pre-ergocycle exercise levels.

* To determine whether 3-month PMTERGO modulates reward processing between key reward-related brain regions.

* To determine correlations between acute medium-intensity ergocycle exercise-induced changes in neuroendocrine hormones and metabolites and acute changes in in vivo striatal DRD2/3 BP.

* To assess 3-month PMTERGO-induced changes in neuropsychological function, lifestyle and dietary patterns.

* To determine correlations between 3-month PMTERGO-induced changes in fasting

neuroendocrine hormones and in vivo striatal DRD2/3 BP.

Study description

Background summary

Increasing physical activity, for example using exercise training (ET), is an important non-pharmacological low-cost strategy that improves myriad aspects of general health and mental well-being. Moreover, ET can alleviate health impairments during several common disease states, including major depressive disorder (MDD), obesity, type 2 diabetes mellitus, and drug addiction. All these disorders are characterized by abnormalities in dopamine signaling in the reward-related brain circuitry. For example, both the obese and drug-addicted state are associated with lower in vivo striatal dopamine D2/3 receptor binding potential (DRD2/3 BP). However, for MDD, which is a very heterogeneous psychiatric condition, results have been inconsistent, reporting either higher or unchanged in vivo striatal DRD2/3 BP in depressed subjects compared to healthy controls. Preclinical studies with rodents have demonstrated that ET modulates dopaminergic signaling in the reward-related brain circuitry. In line with these preclinical observations, ET in two subjects with early Parkinson*s disease, as well as in a cohort of methamphetamine-addicted subjects, increased striatal DRD2/3 BP compared to non-exercised controls. Also, preclinical data suggest that an increase in striatal DRD2/3 function may prevent drug addiction. Together, these observations suggest that functional improvements in striatal dopaminergic signaling may underlie some of the health benefits associated with ET. Thus, it is crucial that we understand how ET modulates striatal dopaminergic signaling, as this will allow us to optimize behavioral or pharmacological treatments.
A consistent observation in MDD-related research is that ET intervention programs can decrease depressive symptoms in human subjects. The effects of ET can be quite acute, as a single exercise challenge can result in immediate improvements in depressive symptoms. Despite the consistency and clinical importance of these beneficial effects of ET on mental health, the underlying biological mechanism(s) have remained incompletely characterized. Pre-clinical data have revealed that functional adaptations in the dopaminergic reward-related brain circuitry are likely involved. More specifically, increases in ex vivo striatal DRD2/3 BP have been observed in endurance-trained rats compared to sedentary controls 37,38. Interestingly, treatment with antidepressants results in a similar effect in rodents, suggesting potential mechanistic overlap. In humans, the effects of antidepressant treatment on striatal DRD2/3 BP have been mixed, with studies reporting either higher, similar or lower in vivo striatal DRD2/3 BP compared to pre-treatment levels

treatment. Notably, antidepressant treatment is not effective in a substantial number of subjects with MDD, and this might underlie the inconsistent findings in mechanistic studies.
Psycho-Motor Therapy (PMT) is a validated psychosocial behavioral activation strategy that helps individuals to become more active in ways that are meaningful to them, often by including various aspects of ET, with the overarching goal to improve mood and quality of life. PMT programs are effective in reducing depressive symptoms in subjects with MDD. Despite the clinical importance that PMT programs or antidepressants can result in similar improvements in mental health in subjects with MDD, a very limited number of clinical studies have investigated the effects of PMT on functional adaptations in the dopaminergic reward-related brain circuitry. Currently it has not been investigated if an PMT intervention modulates striatal DRD2/3 BP in subjects with MDD.
Aside from long-term molecular adaptations induced by ET, it is also not clear if an acute exercise challenge can acutely increase striatal dopamine signaling, which will result in a lower in vivo DRD2/3 BP (as DRD2/3 is competitively bound by endogenous dopamine and thus becomes less available). A previous study reported no effects on striatal dopamine release in response to an exhaustive 30-minute treadmill run in a cohort of highly-trained subjects. However, no information is currently available on (*non-stimulated* or acute exercise-induced) dopamine release in other subject populations, including subjects with MDD, in response to medium-intensity exercise. Full understanding of how exercise or ET modulates striatal dopamine function will provide mechanistic insight that can be used to optimize the therapeutic potential of ET and PMT programs to prevent or treat disease states characterized by deficits in dopaminergic signaling in the reward-related brain circuitry, such as MDD. Furthermore, such mechanistic insight might also be used to prevent or treat other diseases characterized by deficits in dopaminergic signaling in the reward-related brain circuitry, such as obesity, type 2 diabetes mellitus, and drug addiction.
To this end, we will measure *non-stimulated* and acute exercise-induced striatal DRD2/3 BP in subjects with MDD before and after a 3-month in-house supervised PMT program, which is a primary and validated intervention method for MDD at the Psychiatry clinic of the Amsterdam UMC (AMC location). To increase the therapeutic potential and ensure high levels of ET during the PMT program, all study subjects will participate in a specialized PMT program. This program combines the standard PMT program at the AMC Psychiatry clinic with an extra 3x 1h ergocycle exercise per week (hereafter called PMTERGO). The PMTERGO program will be supervised by qualified and experienced personnel of the Psychiatry clinic of the Amsterdam UMC (AMC location), including a psycho motor-therapist, ergo-therapist, psychiatrists (in training), and psychologists. We hypothesize that a successful 3-month PMTERGO program decreases depressive symptoms, increases striatal DRD2/3 BP compared to pre-intervention levels, and that changes in depressive symptoms correlate to changes in striatal DRD2/3 BP. We consider the PMTERGO intervention to be successful if the depressive symptoms of the patients are

decreased by 50% after the 3-month PMTERGO program. We also hypothesize that an acute medium-intensity ergocycle exercise challenge lowers in vivo DRD2/3 BP compared to pre-ergocycle exercise levels, indicative of acute striatal dopamine release. Finally, functional Magnetic Resonance Imaging (fMRI) will be used to assess differences in reward processing before and following the 3-month PMTERGO program.

Study objective

Primary objectives
* To determine if 3-month PMTERGO decreases depressive symptoms in subjects with MDD
* To determine if 3-month PMTERGO alters in vivo striatal DRD2/3 BP compared to pre-intervention levels in subjects with MDD

Secondary objectives:
* To determine if medium-intensity ergocycle exercise acutely lowers in vivo striatal DRD2/3 BP in subjects with MDD compared to pre-ergocycle exercise levels.
* To determine whether 3-month PMTERGO modulates reward processing between key reward-related brain regions.
* To determine correlations between acute medium-intensity ergocycle exercise-induced changes in neuroendocrine hormones and metabolites and acute changes in in vivo striatal DRD2/3 BP.
* To assess 3-month PMTERGO-induced changes in neuropsychological function, lifestyle and dietary patterns.
* To determine correlations between 3-month PMTERGO-induced changes in fasting neuroendocrine hormones and in vivo striatal DRD2/3 BP.

Study design

A one-arm 3-month PMTERGO study

Intervention

Subjects with MDD will enter a 3-month in-house supervised PMTERGO at the Psychiatry clinic of the Amsterdam UMC (AMC location).

Study burden and risks

Subjects with MDD that will participate in the supervised in-house PMTERGO intervention program at the Psychiatry clinic of the Amsterdam UMC (AMC location) will be contacted whether they want to participate in the FIT-BRAIN study. Eligible subjects will visit the Amsterdam UMC (AMC location) on two occasions before PMTERGO [for a cardiopulmonary exercise test (CPET) day and a study day] and on two occasions after a 3-month PMTERGO intervention (a CPET

test day and a study day) (total study time: approximately 16 hours).
Fitness before and after the PMTERGO intervention will be assessed using a CPET to assess (improvements in) VO2max, a well-accepted indication of fitness. The effect of the PMTERGO intervention on dopaminergic reward processing will be assessed by fMRI, which is a non-invasive imaging modality. At the start of the study day, a venous puncture will be used to draw blood samples (60mL) to measure fasting neuroendocrine hormones and blood-borne neurotransmitters. A blood sample (20mL) will also be collected before and after the acute medium-intensity ergocycle exercise challenge. Participants will undergo 30 minutes of MRI scans. In addition, all participants will perform approximately 60 minutes of neuropsychological tests probing reward-related function and questionnaires to assess lifestyle and dietary behavior. The effect of the PMTERGO intervention as well as an acute medium-intensity ergocycle exercise challenge on striatal DRD2/3 BP will be assessed by a SPECT session using the radioligand [123I]iodobenzamide ([123I]IBZM). [123I]IBZM has a European (CPMP) registration, and has been shown to have no serious side effects. The dose equivalent per IBZM-SPECT session is 4.9 mSv (in total 144 MBq [123I]IBZM will be administered per session). Thus, the total dose equivalent will be 9.8 mSv, which falls within the maximum recommended dose equivalent for the proposed research participants, i.e. 9.8 mSv (WHO category IIb, males > 30 years) 46.To minimize the risks associated with participation, subjects with MRI contraindications are excluded, and the study is designed so that each participant will not be exposed to more than two SPECT sessions.
Our study will determine if PMTERGO decreases depressive symptoms in male subjects with MDD. As both PMT and ET programs are effective in reducing depressive symptoms in subjects with MDD 8,42-44, we hypothesize that a combination of both approaches, in the form of PMTERGO, has strong therapeutic efficacy in MDD. This study will not only be of value to prevent or treat MDD, it will also acquire mechanistic knowledge on how PMTERGO may influence the dopaminergic brain circuitry. This is important for the prevention and treatment of MDD, the most common neuropsychiatric disorder, but also for the prevention and/or treatment of other common diseases characterized by a dysregulated DRD2/3 BP, such as obesity, type 2 diabetes mellitus and drug addiction. Therefore, we believe that the value of our findings will outweigh the burden and risks associated with participation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Male;
* Age 30-69 years;
* BMI 18.5-30 kg/m2;
* Stable body weight (i.e. <10% change) for three months prior to study inclusion;
* Consistent intake of one antidepressant class [e.g. selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs)] for two weeks prior to study inclusion.

Exclusion criteria

- General contraindications for MRI (such as claustrophobia);
- Occupational radiation exposure;
- Any significant somatic disease (e.g. cancer, diabetes, gastrointestinal disease, etc.);
- History of cerebro- and/or cardiovascular diseases;
- Excessive alcohol use (>21 units/week), or any current use of any recreational drug.
- Indications of disturbed glucose homeostasis, suggestive of glucose resistance (>7.8 mmol/L will be excluded);

- Shift workers;
- Severe insomnia;
- Psychotic or bipolar MDD;
- Currently undergoing treatment with antipsychotics;
- Currently undergoing electroconvulsive therapy treatment.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	22
Type:	Anticipated

Ethics review

Not approved

Date:	20-12-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL70497.018.19