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# The positive effect of exercise on mood, as a non-motor symptom, in Parkinson's disease

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## Abstract

Parkinson’s Disease is a degenerative neurological disease where dopaminergic neurons in the basal ganglia degenerate and die. This leads to dopamine deficiency in the basal ganglia, affecting both motor and non-motor systems, giving both motor and non-motor symptoms. Common non-motor symptoms in Parkinson’s disease are depression, anxiety and apathy. Exercise have shown to be effective in decreasing depression in otherwise healthy people. The aim of this degree project was to examine if exercise can act as a treatment against impaired mood for people with Parkinson's disease. Nine trials investigating the effect of different types of training with different duration and different exercise intervals were selected and studied. By comparing the results obtained in these trials, it was found that in seven of the nine studies, exercise have had a positive effect on depression. Fewer studies had examined anxiety and apathy, and the effect of exercise was not as clear. Anxiety decreased in two of three studies and apathy decreased in one of three. The studied material is limited but the conclusion that can be drawn from this study, is that exercise is a safe way to, without negative side effects, treat and/or counteract mood disorders including depressive symptoms in Parkinson’s disease, mild to moderate stage.

**Statement**: Due to ongoing pandemic, this degree project was conducted by comparative analysis of current literature paralleled by statistical analysis on data obtained by Serra/Mackenzie in a previous experimental study.

# Table of contents

## Abbreviations

| | |
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| **BDNF** | Brain-Derived Neurotrophic Factor |
| **BG** | Basal Ganglia |
| **DA** | Dopamine |
| **DBS** | Deep Brain Stimulation |
| **GPe** | Globus Pallidus externa |
| **GPi** | Globus Pallidus interna |
| **$HR_{max}$** | Maximum Heart Rate |
| **HRR** | Heart Rate Reserve |
| **MAO-B** | Monoamine Oxidase-B |
| **MPFC** | Medial Prefrontal Cortex |
| **NAc** | Nucleus Accumbens |
| **OFC** | Orbitofrontal Cortex |
| **PD** | Parkinson's Disease |
| **PFC** | Prefrontal Cortex |
| **SN** | Substantia Nigra |
| **SNc** | Substantia Nigra *pars compacta* |
| **SNr** | Substantia Nigra *pars reticulata* |
| **SNRI** | Serotonin and Norepinephrine Reuptake Inhibitors |
| **SSRI** | Serotonin Selective Reuptake Inhibitors |
| **STN** | Subthalamic Nucleus |
| **VTA** | Ventral Tegmental Area |
| **QoL** | Quality of Life |

# 1. Introduction

## 1.1 Aim

Research has shown that the risk of depression decreases when performing physical activity regularly (Cruise *et al.* 2011, Mammen & Faulkner 2013). Positive changes have also been seen in the brains of people with Alzheimer's and Huntington's disease when exerting aerobic exercise (Altmann *et al.* 2016). Due to impaired mood being a common problem for individuals with Parkinson's Disease (PD) (Pfeiffer 2015), the aim of this study is to investigate if exercise can have a positive effect on depression, anxiety, and apathy in PD.

## 1.2 Parkinson's disease

PD is a degenerative neurological disorder which occurs due to dopaminergic neurons deteriorating and dying in the substantia nigra *pars compacta* (SNc) in the midbrain. This leads to dopamine (DA) deficiency in the striatum (caudate and putamen) in the basal ganglia (BG), which in turn causes symptoms on the motor system (Kalia & Lang 2015). The prevalence of PD increases with age and 1% among people over the age of 65 are affected. There is also so called early-onset PD, which amounts to 3-5% of all PD cases. In early-onset PD, symptoms appear in people under 40 years of age. PD is primarily known as a motor disorder displayed as a severe difficulty in initiating movement, so called bradykinesia. Additional symptoms include tremor, rigidity, and later on postural instability. These symptoms start to occur when 60-70 % of the SNc neurons are lost (Radhakrishnan & Goyal 2018). In addition to motor symptoms, PD contains a non-motor symptom domain which affect individuals differently. Non-motor symptoms occur more frequently as disease advances, but much is still unknown about the clinical feature and affecting risk factors. Lately, non-motor symptoms are identified as a key factor affecting quality of life (QoL) and it is shown that they are an integral part of PD, but the cause is still discussed. One part of the non-motor symptom domain is correlated with affective/cognitive dysfunction, including depression, apathy, and anxiety (Zhang *et al.* 2015).

## 1.3 The BG

The BG are primarily involved in motor control, but also take part in the capacity to choose actions based on desired goals, as well as conflict monitoring and the processing of emotions. The BG consists of striatum (caudate and putamen), globus pallidus (internal and external, GPi and GPe) and the associated subthalamic nuclei (STN) and substantia nigra (SN). The motor loop of the BG also involves thalamus and the cerebral cortex (Figure 1). Two major pathways in the BG are the direct pathway and the indirect pathway. The direct pathway includes dopamine receptor subtype 1 (D1 receptors)-positive medium spiny neurons in the striatum, which project to and inhibit GPi. GPi in turn ceases to inhibit thalamus and thereby facilitates movement when DA is released from the SNc. The indirect pathway inhibits movement via striatal medium spiny neurons that express dopamine receptor subtype 2 (D2 receptors) and innervates GPe. Striatum inhibits GPe, which releases its inhibition of the STN. SNT then sends

an excitatory glutamate signal to GPi making its inhibition of thalamus stronger, leading to suppression of movement. As seen in Figure 1, DA deficiency in PD leads to a decreased disinhibition of GPi in the direct pathway and an increased excitation of GPi by the STN leading to enhanced inhibition of thalamus, thereby obstructing movement initiation (Fazl & Fleisher 2017).

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Figure 1. Simplified basal ganglia circuits in normal and parkinsonian state. Green arrows: dopamine, blue arrows: GABA, red arrows: glutamate. Thin arrows and thick arrows represent hypoactive and hyperactive circuits respectively (Lanciego *et al.* 2012).

## 1.4 The BG and emotions

The BG is also engaged in a limbic loop that involves the limbic system (Fazl & Fleisher 2017). The limbic system connects and coordinates activities in cortical and subcortical structures of the brain involved in the process of emotions, behavior, and memory (affective and cognitive functions) via association and projection tracts (Figure 2). Involved structures include the amygdala, mammillary bodies, hypothalamus, thalamus, hippocampus, and the ventral striatum, i.e., nucleus accumbens (NAc) (Catani *et al.* 2013). The limbic loop of the BG involves the NAc, which connects to cingulate and orbitofrontal cortices (OFC), both also involved in emotions and memory. The innervation of dopaminergic neurons emerges from the ventral tegmental area (VTA) of the midbrain and conveys dopamine to the prefrontal cortex (PFC) and NAc. Therefore, lesions in the BG influence limbic functions as well (Fazl & Fleisher 2017).

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Figure 2. Left: A schematic illustration of the limbic system. Right: Tractography of the main limbic pathways. The figure colors correspond to the legend tracts (Catani *et al.* 2013).

## 1.5 Non-motor symptoms in PD

Non-motor symptoms in PD are represented by physiological, cognitive and/or affective effects. Common physiological problems are sleep disorders, pain, olfactory and visual disturbances, urogenital symptoms, and constipation. Cognitive impairment includes hallucinations, concentration difficulties and memory problems. Depression and anxiety and are affective disorders that influence the mood of the patient (Pfeiffer 2016). Apathy also affects the mood but is not purely affective, because it contains simultaneous cognitive, behavioral and affective features including lack of motivation, reduced interests and emotions (Pagonabarraga & Kulisevsky 2017).

One study made by Zhang *et al.* (2015) showed that 98,88 % of the participants with PD experience at least one non-motor symptoms. However, many patients do not talk about them, and they are less known than the motor symptoms of PD. This can perhaps to some extent be explained by the patients being embarrassed or by unawareness. Many patients do not know that non-motor symptoms exist or that the symptoms can be associated with PD. Also, many neurologists do not mention non-motor symptoms to their patients (Zhang *et al.* 2015, Armstrong & Okun 2020). Possible risk factors and clinical features affecting non-motor symptoms remains unclear but the awareness of non-motor symptoms and their correlation with PD has increased during the last decades. It has also been realized how important the role of non-motor symptoms is in the management and diagnosis of PD. 68-88% of normal, healthy individuals, comparably aged, also experience non-motor symptoms. Therefore, not all the symptoms can automatically be attributed to the PD, but the number, frequency and severity of symptoms that form the non-motor symptoms domain in PD, seem to be higher for the PD patients (Pfeiffer 2016).

Non-motor symptoms in PD may lead to a lower QoL, sometimes even more than motor symptoms. The low QoL due to non-motor symptoms provides a good reason for investigating

predictors, markers that precede the disease, in order to facilitate anticipation and management of non-motor symptoms in progressing PD. A study with 227 idiopathic PD patients showed a positive correlation between QoL (where a higher score indicates a lower QoL) and both motor symptoms and severity of non-motor symptoms but indicate that non-motor symptoms influence QoL more than motor symptoms over time. Mood disorders were not as prevalent as for example urogenital problems, but still showed significance in predicting change in QoL, indicating a greater impact (Prakash *et al.* 2016).

## 1.6 Mood disorders in PD

Depression can emerge at any stage of PD, often even before the motor symptoms occur, and can thereby be a prodromal symptom, an indicator preceding the onset of PD. If depression develops early in the disease course, the risk of impairment in the motor system over time is increased (Pfeiffer 2015). Depressive symptoms may include various degrees of insomnia, hypersomnia, sadness, irritability, change in appetite/weight, self-blame, panic, loss of interest/energy/pleasure and/or suicidal thoughts (Fried *et al.* 2016).

A study review aiming to determine the prevalence of depression in PD analyzed 36 studies and concluded that depressive symptoms of some sort occurred in 52 % of the patients. The distribution was 17 % with major depressive dysfunction, 22 % with minor depression and 13 % with dysthymia, a mild but persistent depression that lasts for more than two years. It is mentioned in the article that despite a lower number determined than in previous reports, the percentage obtained can differ due to diagnostic criteria used; the review still confirms depression to be a commonly occurring problem in (Reijnders 2008).

The severity of depression has also been found to correlate with the severity of motor symptoms, the more severe the motor symptoms, the more severe the depressive symptoms (Prado & Barbosa 2005).

Depression often coexists with other behavioral changes, such as anxiety and apathy (Wen *et al.* 2016). Anxiety can involve shortness of breath, sweating episodes, palpitations, dizziness, panic attacks or feeling fear or agitation, but without any specific reason (Rana *et al.* 2018). Apathetic symptoms may include loss of interest or lack of motivation. Apathy also shares many features with depression, such as anhedonia (inability to feel pleasure) and decreased enthusiasm about usual interests. There is a large overlap. Depression can include apathy and apathy can also be driven by depression (Pagonabarraga & Kulisevsky 2017). The many similarities in the complex pathways regulating the separate mood symptoms (Figure 3) makes it difficult to differentiate them. The neural areas associated with mood symptoms implicated as DA deficiency progresses in PD, involve the PFC (including OFC and medial prefrontal cortex, MPFC) and extend to some subcortical regions and areas in the anterior parietal and temporal lobes. Brain regions in the frontostriatal circuits, connecting the BG with the frontal lobe areas, are commonly affected in mood disorder (Wen *et al.* 2016)

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Figure 3. Similarities and differences in the depression, anxiety and apathy pathways shown by simplified schemes of the networks in Parkinson's disease. Grey squares: frontostriatal pathway, ACC, anterior cingulate cortex, AMG: amygdala, DA: dopamine, HIPP: hippocampus, PCC: posterior cingulate cortex, SMC: supplementary motor cortex, SNr: substantia nigra *pars reticulata* (Wen *et al.* 2016).

## 1.7 Treatments of PD symptoms

No treatments available can cure PD. Further, no treatments that stop, or slow down, the degeneration of dopaminergic neurons exist. However, some treatments can alleviate motor and non-motor symptoms and improve QoL (Radhakrishnan & Goyal 2018, Armstrong & Okun 2020).

### 1.7.1 Treatment of motor symptoms

The most common medical treatment for people with PD is levodopa, a precursor to DA, or a DA agonist, used in order to counteract the DA deficiency. This treatment can help with easing the motor symptoms, while most non-motor symptoms do not respond to levodopa. A correlation has even been reported between higher doses of dopaminergic medications and increased autonomic symptoms, like constipation and urinary troubles. Treatment with monoamine oxidase-B (MAO-B) inhibitor is another medical therapy that can be used to reduce the effect of the DA deficiency. This treatment is also used against cognitive impairment in PD. MAO-B blocks the DA degrading enzymes and prolong the beneficial effect of levodopa (Radhakrishnan & Goyal 2018).

### 1.7.2 Treatment of non-motor symptoms

Mood disorders that do not respond to dopaminergic treatments are correlated with dysfunctions in other neurotransmitter systems, such as norepinephrine, serotonin, and acetylcholine. These symptoms are treated with non-dopaminergic medications, like serotonin selective reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI)

and/or tricyclic antidepressants. For apathy in PD, no pharmacological treatments are available (Armstrong & Okun 2020).

### 1.7.3 Non-medical treatment in PD – including exercise

In addition to medication, complementary intervention focused on exercise, such as resistance training, gait training with cues or treadmill, balance training and tai chi, is used to improve or preserve motor symptoms (Armstrong & Okun 2020). These types of exercise have been proven to counteract reduced muscle strength, reduced aerobic capacity and gait dysfunction, to improve balance and to reduce fall frequency (Mak & Wong-Yu 2019). Cognitive-behavioral therapy is used for treating depression and other psychological disorders. Also, speech therapy (speech and swallowing), physiotherapy and occupational therapy is used. (Armstrong & Okun 2020).

### 1.7.4 Deep Brain Stimulation

A common side-effect after long duration of treatment with levodopa, is levodopa-induced dyskinesia. This side-effect can occur already after days or months. Another frequent problem is that the effect of levodopa decreases with progressing PD leading to continued motor fluctuations, tremor, and dyskinesia even with levodopa treatment. If this happens, the patient can be a candidate for deep brain stimulation (DBS), which is a surgical treatment where unilateral or bilateral high frequency stimulating electrodes are transcranially placed in either the STN or GPi. Studies have shown that bilateral stimulation of STN and GPi improves bradykinesia, tremor and gait and allows a reduction of dopaminergic medications (Perlmutter & Mink 2006).

### 1.7.5 Adverse side-effects of treatments

Adverse or negative side effects can occur during the treatments. For example, levodopa treatment can give nausea, somnolence, mood disorders and dyskinesia (Salat & Tolosa 2013). Side effects from SSRI can include agitation and akathisia (restlessness), gastrointestinal dysfunction with nausea and/or diarrhea, sexual dysfunction, sleep disruption or insomnia, anxiety or headache (Stahl 1998). Reported adverse side-effects from DBS include cognitive impairment, such as memory deficits and disorientation, hallucinations, deteriorated mood and generation of inaccurate emotional responses, including manic responses (Perlmutter & Mink 2006).

## 1.8 Mood disorders and the brain

Amygdala and the prefrontal cortex (PFC) are two brain structures involved in regulation of emotion and cognition. The amygdala (Figure 4) is important in the perception of emotional signals and in the generation of emotional responses, including stress and aggression. Amygdala is also associated with motivation and plays an important role in associative aversive

learning and the production and perception of particularly fear-related negative affect (Davidson & Irwin 1999).

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Figure 4. A coronal section of the human brain, showing the location of amygdala (Davidson & Irwin 1999).

PFC consists of the OFC and the dorsolateral, dorsomedial, ventromedial and ventrolateral PFC, and connects with the ACC (Figure 5). These areas are associated with various processes, including perceptual, social, motivational and emotional. PFC also has a central role in mental activity, goal-directed behavior and cognition, such as decision-making and attention. Some of these functions, for example goal-directed behavior and decision-making, require forward-looking and analysis of possible outcome based on pervious experiences, which indicates that the PFC collaborates and uses memories and knowledge from the whole cortex. (Carlén 2017).

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Figure 5. Functional structures of the prefrontal cortex in the human. dmPFC: dorsomedial prefrontal cortex, dlPFC: dorsolateral prefrontal cortex, vmPFC: ventromedial prefrontal cortex, vlPFC: ventrolateral prefrontal cortex, OFC: orbitofrontal cortex, ACC: anterior cingulate cortex (Carlén 2017)

The amygdala and the medial PFC are interconnected in the brain and work together to adjust the expression of emotions. The medial PFC can limit the output of amygdala and thereby exert inhibitory control to prevent unfit emotional expression. If the medial PFC control over amygdala gets dysfunctional, this can lead to development of psychiatric diseases such as anxiety or depression. (Liu *et al.*2020).

The reward circuit, including the mesolimbic pathway with dopaminergic neurons in the VTA projecting to NAc, is another important key system in mood and mood disorders. Dopaminergic neurons in the VTA also innervate several additional regions, including amygdala, hippocampus, and the PFC. In addition to dopaminergic neurons, the reward circuit involves

glutamatergic, cholinergic, serotonergic, and noradrenergic innervation connecting the various regions in different ways (Russo & Nestler 2013).

The hippocampus is important in cognitive function, such as memory and learning. Studies in humans reveal smaller hippocampal volume in patients with cognitive impairments and depressive illness, together with alterations in the PFC and amygdala. Atrophy of neurons in the hippocampus and PFC leads to a decrease of volume, and hypertrophy of neurons in the amygdala, enlarges that brain structure. Thus, the capacity to remember and make decisions can be comprised at the same time as levels of fear and aggression from amygdala may increase (McEwen 2006).

## 1.9 Types of exercise and intensity measurements

Physical activity can be defined as bodily movement that results in energy consumption and that is positively correlated to physical fitness (attributes relating to the ability to perform physical activity). Exercise, is physical activity when it is planned, organized, and performed regularly in order to maintain or achieve improvements in components of physical fitness.

- Cardiorespiratory/aerobic endurance exercises (e.g., walking, running, cycling, or dancing) increases the heart rate and respiratory rate and improves the ability of the circulatory and respiratory systems to deliver fuel (e.g., oxygen) during sustained physical activity, while also enhancing muscular endurance.
- Strength/resistance training (e.g., weightlifting or using resistance bands) increases muscle strength, i.e., the amount of force a muscle can exert.
- Stretching exercises is used to lengthen the muscles and improve the flexibility of the joints.
- Balance training improves the ability to maintain equilibrium while standing still or moving, which can reduce the risk of falling (Caspersen *et al.* 1985).

To assess the intensity of exercise, maximum heart rate ($HR_{max}$) or heart rate reserve (HRR) are often used. With these measurements it is possible to prescribe an approximately equivalent exercise intensity in individuals with different capacities. $HR_{max}$ is the maximum capacity of the heart and HRR is $HR_{max}$ minus resting heart rate. (Mann *et al.* 2013) Effective endurance training can be achieved with an intensity of 65-75% of HRR, which correspond to 75-85% of $HR_{max}$ (Fikenzer *et al.* 2018).

## 1.10 Exercise and depression

Anxiety and depression are common neuropsychiatric disorders of the affective domain (Carek *et al.* 2011).

Regular exercise improves both psychological wellbeing and cognition in elderly and reduces depression in all ages (Cruise *et al.* 2011, Mammen & Faulkner 2013). The effect of aerobic exercises, including walking, jogging or aerobics, on depression is most frequently investigated, but also strength training has been shown to have a positive effect on

depression. Only studies with over 12 sessions in their interventions could register a significant improvement. A decrease of depressive symptoms has been assessed after 3 strength training sessions per week, each 1 hour, for 8 weeks. Further, a positive effect has been seen on depression after aerobic exercise (walking, running, rowing, gymnastics, stationary cycling, and dance) at least 3 times per week 30-40 minutes per session, for 8-12 weeks (Cooney *et al.* 2013).

Improvements seen with regular exercise are related to a positive influence on the brain plasticity. This effect is correlated with an increase in the expression of several genes encoding neurotrophins, such as brain-derived neurotrophic factor (BDNF), a growth factor supporting the survival, differentiation, growth of neurons and the dendritic branching (Dishman *et al.* 2006). The increase of BDNF related to aerobic exercise can lead a to larger hippocampal volume and a larger volume of grey and white matter (Colcombe *et al.* 2006). Exercise has also shown to increase functional connectivity between areas of the temporal, frontal and posterior cortices. These regions form brain networks central to brain dysfunction that can occur when aging, named the Default Mode Network and a Frontal Executive Network (Voss *et al.* 2010).

Positive changes of this sort have also been seen in individuals with Alzheimer's and Huntington's disease and in people with mild cognitive impairment, indicating that, even with brain pathology, the improvements can occur (Altmann *et al.* 2016).

# 2. Method

## 2.1 Selection of studies

Pubmed (https://pubmed-ncbi-nlm-nih-gov.ezproxy.its.uu.se/) was used to search for studies. The keywords "exercise depression parkinson", "exercise mood parkinson" and "exercise parkinsons disease mood" in the search for "clinical trial" and "randomized controlled trial" generated 47, 39 and 38 articles, respectively. The abstracts were read and studies in which the effect of exercise of some sort, on mood disorders as a non-motor symptom in PD, were selected. Also, some articles were found in the category "similar articles" listed below the abstract in the database and several articles were identified via references. Articles not included in this degree project were those in which trials did not present a control group or trials focusing on motor symptoms, together with trials that compared instructor-led exercise with home exercises and trials were the full text article did not have an open access. A total number of 9 trials were then included in this degree project.

## 2.2 Analyzed forms of exercise

The different types of exercises, and their effect on mood disorders in PD, investigated in the trials were aerobic exercise on treadmill, balance/stretch, Nordic walking with poles, cycling, dance, specific PD exercise, mindfulness yoga, resistance training and exergaming.

## 2.3 Assessment scales

In order to evaluate treatment, symptoms are assessed with different scales. The rating scales used in the included trials and relevant for this study were:

**The Hoehn and Yahr scale** (HY) grade the level of clinical disability (Hoehn & Yahr 1967).

- **Stage I** - unilateral involvement with minimal or no functional impairment.
- **Stage II** - bilateral or involves midline, but with maintained balance.
- **Stage III** - balance impairment and mild to moderate disability, yet the patient is physically independent.
- **Stage IV** – disease is severely disabling, but the patient can walk and stand unassisted.
- **Stage V** - the patient needs a wheelchair or is confined to bed when not assisted.

**Unified Parkinson's Disease Rating Scale** and **Movements Disorder Society - Modified Unified Parkinson's Disease Rating Scale** (UPDRS and MDS-UPDRS) are divided into four parts, where part I (UPDRS-I) involves assessing non-motor symptoms including mood-related apathy, anxiety and depression. Part II-IV evaluates motor symptoms. The original UPDRS had yes- and no-questions in part IV, which is changed in the modified MDS-UPDRS. Also, the original version had a total of 42 questions, and the revised version has 50 questions. The parts can be analyzed individually or summed. This scale estimates the severity and progression of Parkinson´s disease. Higher score means more severe symptoms (Goetz *et al.* 2007).

**Parkinson's Disease Questionnaire** (PDQ-39) is a QoL questionnaire that covers eight dimensions of PD with 39 questions. One of the dimensions is emotional wellbeing. The score from each dimension is calculated into a scale, 0-100, where 0 means no problem and 100 means maximum problem. The dimensions can be reviewed and compared individually. They can also be summed and recalculated into an overall single index number, to assess the overall impact of PD (Peto *et al.* 1998).

**EuroQoL questionnaire** (EQ-5D) is a health related QoL questionnaire consisting of 5 dimensions. Anxiety/depression is one of the dimensions. The result can be recalculated into an index number between 0-1, where 1 is best possible health and 0 is equivalent to death (Oliverira & Hayes 2020).

**Beck Depression Inventory-II** (BDI) grades the severity of depression. 21 items related to depression are evaluated and the points summed to a total score between 0-63. Higher total score indicates more severe depressive symptoms (Lee *et al.* 2018).

**Self-Evaluation Depression Scale** (SDS) incudes 20 items to gauge depression and can give a total score between 20-80. Higher score, more depressive symptoms (Zung *et al.* 1965).

**Hamilton Depression Rating Scale** (HAM-D17) assesses depressive symptoms. Comprises 17 items and total score ranges from 0 to 52, where higher score means severer depressive symptoms (de Lima *et al.* 2019).

**Hospital Anxiety and Depression Scale** (HADS) has 7 items that evaluate depression and 7 items addressing anxiety, which gives a total of 14 items. These can either be summed to a total of a total score of 0-42 or calculated per subscale, giving separate scores to anxiety and depression, both 0-21. Higher score equals more severe problems (Marinus *et al.* 2002).

**Beck Anxiety Inventory** (BAI) is used to assess the severity of anxiety with 21 items, including assessment of symptoms like dizziness, nervousness, and incapability to relax. Score range 0-63 and a higher score indicates more anxiety (Julian 2011).

**Apathy Evaluation Scale** (AES) evaluates apathy, including amotivation (lack of motivation), lack of concern and disinterest. Consists of 18 items to evaluate, a higher total score, range 0-shows a greater apathy (Lee *et al.* 2020).

**Starkstein Apathy Scale** (SAS) assesses apathy and consists of 14 items. The total score range is between 0-42 and a higher score indicates a more severe apathy (Pedersen *et al.* 2012)

# 3. Result

I have studied the non-motor symptoms in PD and compared the result on depression, anxiety and apathy in nine studies.

## 3.1 Summaries of the selected studies

1. Altmann *et al.* (2016) Exercise: **Aerobic treadmill exercise**
    - *Purpose:* Test the effect of aerobic exercise, performed on a treadmill, on mood disorders and other non-motor symptoms in people with PD.
    - *Assessment scales:* HY, UPDRS, BDI, AES and BAI.
    - *Exclusion criteria:* secondary parkinsonism (symptoms like Parkinson's but caused by other factors), severe or unpredictable episodes of motor fluctuations, high frequency of falls, mild cognitive impairment or dementia, history of psychiatric disturbance or cardiovascular disease.
    - *Participants:* A total of 30 participants, HY scale scores I-III with medication, were randomized into three groups.
    - *Trial groups:* 1) aerobic exercise (n=11); 2) stretch and balance (n=9); 3) control group (n=10, no special activity). The aerobic exercise group started with 20 minutes per treadmill session and successively increased the training time to 45 minutes per session in the end, beginning at low intensity with 50 % of $HR_{max}$, and increased 5 % each week up 75 % of $HR_{max}$. They performed 3 week for 16 weeks. The stretch-balance group performed stretch exercises mostly sitting

down, and balance exercises on force platforms, with same frequency as the aerobic group. The control group were advised not to start with any physical activity during the study.

- ***Summary result****:* After the 16 weeks, no significant improvements were seen in the BDI, AES or BAI scores for the participants in the aerobic group or the balance group, but in the control group the depressive symptoms increased.

2. Cugusi *et al.* (2015) Exercise: **Nordic Walking**
    - *Purpose:* Examine the effect of Nordic Walking on motor symptoms and non-motor symptoms in PD. Nordic walking is an aerobic walking training that combines the activation of upper limbs and trunk with classic walking, using specific poles, which gives a full body workout.
    - *Assessment scales:* HY, BDI and SAS.
    - *Exclusion criteria:* symptoms of cognitive impairment or dementia, vision impairment or debilitating conditions that would prevent a full study participation, disorders that could interfere with assessing the disease or unavailability during the study.
    - *Participants:* 20 participants with idiopathic PD, HY stage I-III with stable medication use were randomly assigned groups.
    - *Trial groups:* 1) Nordic Walking (n=10); 2) control group (n=10). The Nordic Walking group was assigned a program with 2 Nordic Walking sessions per week, each session1 hour, for 12 weeks. Sessions included a warmup and a cool down period and intensity target was 60-80 % of HRR, increased gradually during the trial period. The control group went on with regular care.
    - ***Summary result:*** No adverse effects or accidents were reported. After 12 weeks, the level of clinical disability, the depressive symptoms and the severity of apathy had decreased in the Nordic walking group, according to reduced scale scores in HY, BDI-II and SAS. No change was seen in the control group.
3. Harper *et al.* (2015) Exercise: **High cadence cycling**
    - *Purpose:* Investigate if high cadence cycling, a type of aerobic exercise, three times in one week can influence depressive symptoms in people with idiopathic PD.
    - *Assessment scales:* EQ-5D-3L and BDI.
    - *Exclusion criteria:* cardiovascular disease, stroke, surgery to treat PD (e.g., DBS) of persons identified as high risk.
    - *Participants:* The study included 35 completing participants using PD specific medication, divided into groups.
    - *Trial groups:* 1) cycling (n=20); 2) control croup (n=15). The cycling group exercised 40 min (including 5 minutes warm up and 5 minutes cool down) three times. The control group were instructed to maintain normal levels of activity.
    - *Summary result:* No significant change in the cycling group or the control group was detected after the trial week.
4. Hashimoto *et al.* (2015) Exercise: **Dance**
    - *Purpose:* Examine the effect of dance on mental symptoms in PD.
    - *Assessment scales:* HY and AES.

- *Exclusion criteria:* Not being able to walk independently. Medication changes resulted in exclusion from the data analysis.
- *Participant:* 46 participants, HY stage II-V (two participants in control group stage V) were randomly separated into groups.
- *Trial groups:* 1) dance exercise (n=15); 2) PD exercise (n=17); 3) no-contact control group (n=14). Both the dance group and the PD exercise group engaged in 1 session per week for 12 weeks. The dance group performed dance exercise with music for 1 hour, including 20 minutes of warmup with stretch while sitting down, 35 minutes of dance, either standing or sitting and then 5 minutes of stretch and relaxation. The PD exercise group performed PD exercise for 1 hour, including 20 minutes of warm up and stretching while sitting down, 35 minutes of leg strength (rising from chair and sitting down), balance training (shifting leg from one side to the other and walking along a line) and walking on the spot, ending the session with 5 minutes of relax and stretch. The control group continued with their regular life.
- ***Summary result:*** Significant decrease in both apathy and depressive symptoms in dance group, major decrease of apathy. No significant change in the PD exercise group or in the control group.

5. Kalyani *et al.* (2019) Exercise: **Dance**
    - *Purpose:* Explore if dance can have a positive impact on non-motor symptoms and QoL in PD.
    - *Assessment scales*: MDS-UPDRS-I, PDQ-39 and HADS.
    - *Exclusion criteria:* dementia or medical, neurological (only PD), musculoskeletal, cardiovascular or respiratory abnormalities.
    - *Participants:* 33 participants with idiopathic PD, on stable medication, HY stage I-III finished. Group allocation were based on individual convenience.
    - *Trial groups:* 1) dance (n=17); 2) control group (n=16). The dance group engaged in 2 dance sessions per week, 1 hour per occasion, including 30 minutes of seated warmup, followed by 15 minutes of dance with support and ending with 15 minutes of mixed dance across the floor, for 12 weeks. A social coffee/tea break followed each session. The control group continued with their usual treatment without specific exercise.
    - ***Summary result:*** No adverse events were reported. In the dance group there was a significant decrease in depression and anxiety according to HADS and in depression, anxiety, and apathy according to MDS-UPDRS-I scale, together with an improvement in QoL, based on PDQ-39.
6. Kwok *et al.* (2019) Exercise: **Mindfulness Yoga**
    - *Purpose:* Test if mindfulness yoga, combining strength, stretch, balance and relaxation, could have a positive effect on mood impairment in PD.
    - *Assessment scales:* HY and HADS.
    - *Exclusion criteria:*
    - *Participants:* 112 participants with PD in HY stage I and III, completed the study, randomized into groups.

- *Trial groups:* 1) mindfulness yoga (n=57); 2) control group (n=55). The control group in this study was active, performing stretch and resistance training as an attempt to counteract the difference in effect of social actions. Both groups exercised 1 time per week for 8 weeks. The yoga mindfulness groups performed 90 minutes sessions, with yoga poses, including 60 minutes of sun salutations, 15 minutes of controlled breathing and 15 minutes of mindfulness meditation. The stretch and resistance control group engaged in 60 minutes per session, including warmup, stretch and resistance training and cool-down.
- ***Summary result:*** A total of five participants, three in the mindfulness yoga group and two in the stretch and resistance training group, reported mild, temporary knee pain, but no serious adverse effects were reported. A reduction of depression and anxiety was seen in the mindfulness yoga group.

7. De Lima *et al.* (2019) Exercise: **Resistance training**
    - *Purpose:* Analyze if resistance training can have an impact on depression in elderly with PD.
    - *Assessment scales:* HY, HAM-D17, PDQ-39 and UPDRS.
    - *Exclusion criteria:* Unstable cardiovascular disease, indication of cognitive impairment or dementia, conditions interfering with safety, no ability to independently walk and neurological, cardiopulmonary or orthopedic diseases.
    - *Participant:* 33 PD patients, >60 years old in HY stage I-III, completed the study randomly divided into groups.
    - *Trial groups:* 1) resistance training (n=17); 2) control group (n=16). The resistance training group performed resistance training 2 times per week for 20 weeks, 30-40 minutes per occasion, including 2 sets of 8-12 repetitions with bench press, standing calf raise, deadlift, unilateral rowing, and abdominal reverse crunch. The control group continued without exercise.
    - ***Summary result:*** The resistance training group gained improvements in HAM-D17, PDQ-39 and UPDRS, while there was no significant change in the control group.
8. Solla *et al.* (2019) Exercise: **Sardinian folk dance**
    - *Purpose:* Investigate the effect of Sardinian folk dance on depression and apathy in PD.
    - *Assessment scales:* HY, BDI and SAS.
    - *Exclusion criteria:* HY stage >3, dementia, atypical Parkinsonism, treatment with medications not approved for PD, high fall frequency, freezing, dyskinesias, postural instability, health condition contradicting exercise or the presence of other problems precluding the training.
    - *Participants:* 19 participants with PD in HY stage I-III finished the study, randomly divided into groups.
    - *Trial groups:* 1) dance (n=10); 2) control group (n=9). The dance group performed dance exercise 2 times per week, 90 minutes per session for 12 weeks and the control group was getting regular care as before the study period.
    - ***Summary result:*** No muscle or joint injuries or pain was reported after the

intervention. Depressive symptoms decreased significantly in the dance group, while apathy increased significantly in the control group.

9. Tollar *et al.* (2019) Exercise: **Agility exergaming and stationary cycling**
    - *Purpose:* Test the effect of agility exergaming (exercise with video games that track body movement) and stationary cycling, both aerobic exercises, with similar intensity on depressive symptoms and QoL in PD.
    - *Assessment scales:* HY, BDI, PDQ and EQ-5D.
    - *Exclusion criteria:* signs of dementia or cognitive impairment, severe cardiac disease, uncontrolled diabetes, stroke in the past, seizures, DBS, ongoing orthopedic surgeries, pacemaker, hemophilia (the blood's ability to clot is reduced) clinically significant motor fluctuations, levodopa induced dyskinesia or participation in exercise program.
    - *Participants:* 74 p, HY stage II-III, participated randomly divided into group.
    - *Trial groups:* 1) agility exergaming (n=25); 2) cycling (n=25); 3) control group (n=24). The exergaming group and the cycling group attended to exercise sessions of similar intensity (110-140 heart beats per minute), 5 times per week, 1 hour per session (including 5 minutes of warm up, 5 minutes of cool down and 5 minutes of rest spread out over the hour) for 5 weeks. The exergaming group session included 15 minutes of reflex enhancing exercises, 15 minutes of spatial orientation improvement exercises and 15 minutes of dance, to exercise the ability to generate and combine movements. The cycling group attended spinning classes, which included 5-minute intervals with 1 minute of freewheeling in between. The control group continued with their usual activities. All the participants were asked not to change medication, diet, or habits of exercise during the study.
    - ***Summary result:*** Depression and QoL improved similarly and significantly in both the exergaming group and in the cycling group, but not in the control group.

### 3.2 Compilation of gathered information

The severity of the PD disability was assessed with HY in all the trials investigated, except for "One week of high cadence cycling"-study by Harper *et al.* (2019), which did not assess the severeness of disability. All participants that were assessed, in all the studies, had mild to moderate stage disease (HY stage I-III), except for two participants, in the control group of Hashimoto's study (2015), investigating the effect of dance on symptoms in PD, compared to regular PD exercise and a nonintervention control group. Besides the use of HY, used in most studies, the assessment scales varied over the studies (Table 1).

Table 1. Shows assessment scales used in the studies to evaluate disease severity, Quality of Life, and mood. **A**: Hoehn and Yahr, **B**: Unified Parkinson's Disease Rating Scale, **C**: Movements Disorder Society - Modified Unified Parkinson's Disease Rating Scale, **D**: Parkinson's Disease Questionaire-39, **E**: EuroQoL questionnaire **F**: Beck Depression Inventory-II, **G**: Self-Evaluation Depression Scale, **H**: Hamilton Depression Rating Scale, **I**: Hospital Anxiety and Depression Scale, **J**: Beck Anxiety Inventory, **K**: Apathy Evaluation Scale, **L**: Starkstein Apathy Scale

| **Scale→**<br>**Study↓** | **A** | **B** | **C** | **D** | **E** | **F** | **G** | **H** | **I** | **J** | **K** | **L** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.<br>Aerobic<br>Balance/stretch<br>(Altmann *et al.* 2016) | **X** | **X** | | | | **X** | | | | | | |
| 2.<br>Nordic Walking<br>(Cugusi *et al.* 2015) | **X** | | | | | **X** | | | | | | **X** |
| 3.<br>High cadence cycling<br>(Harper *et al.* 2019) | | | | | **X** | **X** | | | | | | |
| 4.<br>Dance<br>PD exercise<br>(Hashimoto *et al.* 2015) | **X** | | | | | | | | | | **X** | **X** |
| 5.<br>Dance<br>(Kalyani *et al.* 2019) | **X** | | **X** | **X** | | | | | **X** | | | |
| 6.<br>Mindfulness Yoga<br>(Kwok *et al.* 2019) | **X** | | | | | | | | **X** | | | |
| 7.<br>Resistance training<br>(de Lima *et al.* 2019) | **X** | **X** | | **X** | | | | **X** | | | | |
| 8.<br>Sardinian Folk Dance<br>(Solla *et al.* 2019) | **X** | | | | | **X** | | | | | | **X** |
| 9.<br>Exergaming<br>Cycling<br>(Tollár *et al.* 2019) | **X** | | | **X** | **X** | **X** | | | | | | |

The total number of completing participants in the studies varied between 19 in the Sardinian folk dance trial made by Solla *et al.* (2019) up to a maximum of 112 participants in the study investigating mindfulness yoga (Kwok *et al.* 2019). The duration span reached from 1 week of high cadence cycling (Harper *et al.* 2019) up to 20 weeks of resistance training (Table 2) (de Lima *et al.* 2019).

Table 2. Studies, duration time, frequency, exercise time and number of participants, completing (enrolled and assessed) in the different studies.

| Study | Duration, frequency & time | Participants |
|---|---|---|
| 1.<br>Aerobic<br>Balance/stretch<br>(Altmann *et al.* 2016) | 16 weeks<br>3 times/week<br>20-45 min/session | total n=30 (37)<br>aerobic n=11<br>balance/stretch n=9<br>control group n=10 |
| 2.<br>Nordic Walking<br>(Cugusi *et al.* 2015) | 12 weeks<br>2 times/week<br>1 hour/session | total n=20 (20)<br>nordic walking n= 10<br>control group n=10 |
| 3.<br>High cadence cycling<br>(Harper *et al.* 2019) | 1 week<br>3 times/week<br>40 min/session | total n=35 (38)<br>cycling n=20<br>control group n=15 |
| 4.<br>Dance<br>PD exercise<br>(Hashimoto *et al.* 2015) | 12 weeks<br>1 time/week<br>1 hour/session | total n=46 (59)<br>dance n=15<br>PD exe n=17<br>control group n=14 |
| 5.<br>Dance<br>(Kalyani *et al.* 2019) | 12 weeks<br>2 times/week<br>1 hour/session | total n=33 (38)<br>dance n=17<br>control group n=16 |
| 6.<br>Mindfulness Yoga<br>(Kwok *et al.* 2019) | 8 weeks<br>1 time/week<br>mindfulness yoga: 90 min/session<br>control group: 60 min/session | total: n=112 (138)<br>mindfulness yoga n=57<br>control group n=55 |
| 7.<br>Resistance training<br>(de Lima *et al.* 2019) | 20 weeks<br>2 times/week<br>30-40 min/session | total n=33 (33)<br>resistance training n=17<br>control group n=16 |
| 8.<br>Sardinian Folk Dance<br>(Solla *et al.* 2019) | 12 weeks<br>2 times/week<br>90 min/session | total n=19 (20)<br>Sardinian folk dance n=10<br>control group n=9 |
| 9.<br>Exergaming<br>Cycling<br>(Tollár *et al.* 2019) | 5 weeks<br>5 times/week<br>1 hour/session | total n=74<br>exergaming n =25<br>cycling n=25<br>control group n=24 |

Depression:

All nine trials in this degree project investigated the effect of exercise on depression in PD. In seven out of these nine (7/9) a positive development could be seen in their intervention groups. Altmann *et al.* (2016) did not see a positive effect on depression, apathy or anxiety in their exercising groups, but the depressive symptoms increased significantly in their control group. The other studies showed no change in depressive symptoms in their control groups.

Anxiety:

Three studies determined the effect of exercise in anxiety in PD and two saw a positive effect in their intervention groups. No significant change in anxiety in any of the control groups.

Apathy:

Three trials evaluated the effect of exercise on apathy in PD, a positive change was observed

in the intervention group in one of the trials. The control groups in two of the studies had a significant negative development on apathy.

Three studies analyzed the effect of dance (Hashimoto *et al.* 2015, Kalyani *et al.* 2019, Solla *et al.* 2019), they could all see positive effects on depression in PD (Table 3).

Table 3. The effect of exercise in the different trials.
+: significant positive effect, −: significant negative effect, ns: no significant effect, ×: not investigated

| **Study** | **Exercise** | **Effect** | | |
|---|---|---|---|---|
| | | **Depression** | **Anxiety** | **Apathy** |
| 1. (Altmann *et al.* 2016) | Aerobic | ns | ns | ns |
| | Balance/stretch | ns | ns | ns |
| | Control group | − | ns | ns |
| 2. (Cugusi *et al.* 2015) | Nordic Walking | + | × | + |
| | Control group | ns | × | − |
| 3. (Harper *et al.* 2019) | High cadence cycling | ns | × | × |
| | Control group | ns | × | × |
| 4. (Hashimoto *et al.* 2015) | Dance | + | × | × |
| | PD exercise | ns | × | × |
| | Control group | ns | × | × |
| 5. (Kalyani *et al.* 2019) | Dance | + | + | × |
| | Control group | ns | ns | × |
| 6. (Kwok *et al.* 2019) | Mindfulness Yoga | + | + | × |
| | Control group | ns | ns | × |
| 7. (de Lima *et al.* 2019) | Resistance training | + | × | × |
| | Control group | ns | × | × |
| 8. (Solla *et al.* 2019) | Sardinian Folk Dance | + | × | ns |
| | Control group | ns | × | − |
| 9. (Tollár *et al.* 2019) | Exergaming | + | × | × |
| | Cycling | + | × | × |
| | Control group | ns | × | × |

## 4. Discussion

Non-motor symptoms are common in PD. Among these, mood disorder has received some attention with the finding that exercise can alleviate depression in otherwise healthy individuals. The question addressed in this study was if there is evidence that exercise can relieve mood disorders, especially depression, when presented as non-motor symptoms in PD. That is, can exercise be beneficial to PD patients in terms of alleviating non-motor symptoms?

Seven out of nine trials show that exercise have a positive impact on depression. This indicates that exercise can be an alternative or complementary treatment of depression in PD. This indication is supported by Wu *et al.* (2017) and their review investigating the effect of exercise on depression in PD. The review included 11 trials examining different kinds of exercise. They concluded that notably aerobic exercise could assuage the impairment on motor skills and depression and at the same time improve QoL.

Altmann *et al.* in study number one (2019) did not see a significant improvement in depressive symptoms in their intervention group but increasing symptoms in the control group. Interpretation of this is that aerobic exercise can have a protective effect against depressive symptoms.

Harper *et al.* (2019) in study number three, analyzing three sessions in one week of high cadence cycling, were one of the studies that did not assess any positive effect on depressive symptoms. The lack of effect may be explained by the trial period being too short and the sessions to few.

Anxiety decreased in two of three studies and apathy decreased in one of three. Neither anxiety nor apathy increased in in any of the intervention groups. Although the data is very limited, it still points towards exercise having a positive impact on these factors as well.

All three studies investigating dance has shown to be effective in reducing depressive symptoms. The element of movement and exercise can be an affecting factor, but also music and socializing in a group of people can influence the mood. Dance also involves planning the next move while giving attention to music and signals, which makes the exercise both physiological and psychological.

Considering that all intervention groups in all the studies contain weekly interactions with people outside the home, positive effect may stem from socializing, and not just a particular intervention. This can be tested in future studies by investigating if only social interventions involving events every week show a similar protective or positive effect as exercise on depressive symptoms.

Not all studies mention adverse effects in their report, but among the ones that do, no one has any serious negative side effects to declare. This shows that the exercises in these studies are safe ways to reduce or counteract depressive symptoms in PD.

A correlation has been found between higher depressive symptoms and more severe motor

symptoms. The use of exercise to ease motor symptoms is already a part of PD treatment. Also, a mood enhancing and brain volume increasing effect has been seen from chronic exercise. This indicate that exercise may be a way to tackle the problem of depression from two different angles, both by raising the level of neurotrophins in the brain and thereby giving growth to areas of the brain that affect the mood positively, but also by reducing motor symptoms, the increase of which has been seen to correlate with more severe depressive symptoms.

## 5. Limitations

There are some limitations in this project. The number of trials examining the effect of exercise on mood disorders in PD matching the criteria I was looking for was limited and the number of participants in each study was rather low. Also, the studies investigated different types of exercise, had different duration and used different scales to assess the severity of symptoms. Another difference between the studies were that some of them had no-contact control groups and some of them had control groups performing some other type of exercise. These differences between the studies makes it difficult to compare them equally and to draw specific conclusions.

To investigate this subject further, more studies can be made investigating if different types of exercise have different effect and compare the magnitude. Preferably with a larger number of participants in the studies, in the same format and with the same assessment scales. Also, a more thorough investigation of the effect on exercise on anxiety and apathy can be made.

## 6. Conclusions

Conclusion that can be drawn from this study, is that exercise is a safe way to, without negative side effects, treat and/or counteract mood disorders including depressive symptoms in PD, mild to moderate stage.

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# Appendix: **Summary of analysis - investigation of the role of the subthalamic nucleus (STN) in motor control using optogenetics in mice**

Marina Sammils Baleiro
Additional task in degree project C
Information and data from Guillaumin *et al* (2021)

## Background

Subthalamic nucleus (STN) plays an important role in the execution of voluntary movement. In the basal ganglia there is two main pathways, the direct, enabling movement and the indirect, obstructing movement. The STN is active in the indirect pathway and excites the inhibition of movement. Damage or dysfunction of the STN is highly correlated with motor system disorders. In Parkinson's disease, hyperactivity of STN leads to difficulties initiating movement. The use of optogenetics allow precise temporally and spatially control over neural activity with the use of inhibitory and excitatory opsins activated with photostimulation.

## Aim

The goal is to isolate the impact of STN on various motor functions in non-pathological conditions with inducement of glutamate release in target areas of the basal ganglia upon photostimulation.

## Method

Mice were injected in the STN with virus containing a DNA vector encoding Cre-dependent channel rhodopsin (ChR2) or a control virus with a DNA vector without opsin. Above STN optical cannulas were implanted. The mice were observed, and number of rearing counted during no photostimulation (OFF) and during photostimulation (ON).

## Result

Anova analysis show no significant difference between groups ($p=0.256$) and no significant difference in stimulation effect ($p=0.426$), but there is a significant difference in group x interaction effect ($p=0.036$). T-test was used to conclude significant difference between ChR2 x OFF and CtR2 x ON ($p=0.017$), less rearing during ON, and between Ctrl x ON and ChR2 x ON ($p=0.034$), less rearing in ChR2 (figure 1). The reduction of rearing upon activation of the STN optogenetically (ON) verifies the expectation of STN obstructing movement when excited.

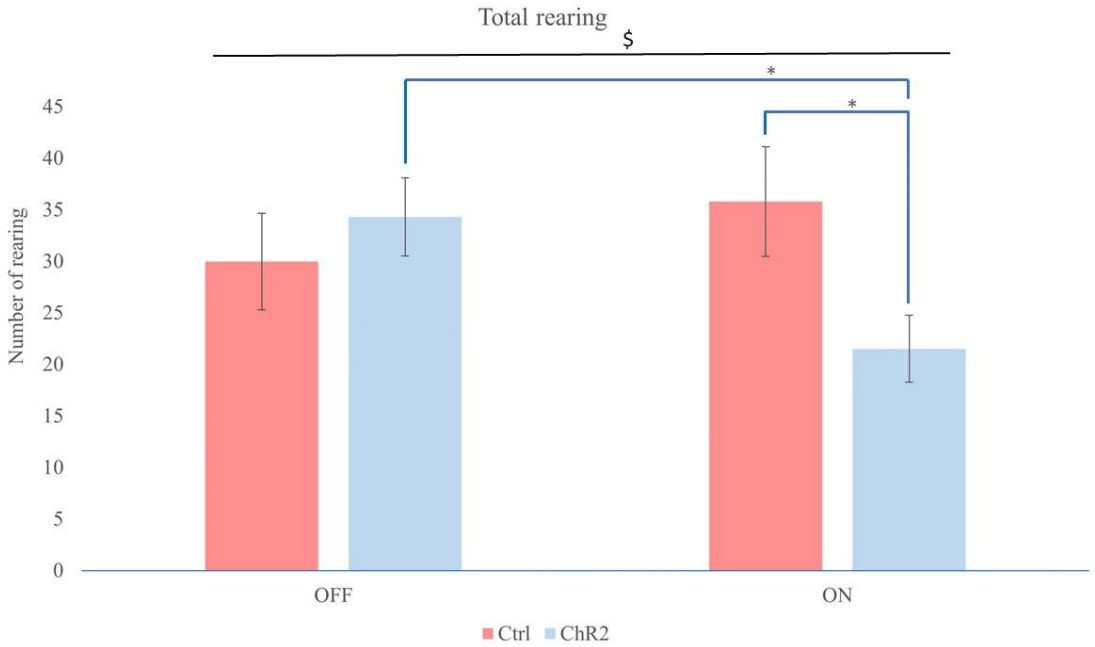


Figure 1. Number of rearing in mice treated with ChR2 compared to mice in control group (Ctrl) when light is OFF and when it is ON. $ = significant ($p<0.05$) interaction effect, * = $p<0.05$