

# Physical Activity, Depression and the Neurobiological Mechanisms

Fysisk Aktivitet, Depresjon og de Nevrobiologiske Mekanismer



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# Abstract

**Title:**

Physical activity, depression and the neurobiological mechanisms

**Research Question:**

What does the recent research literature say about how the neurobiological mechanism influences the association between physical activity and depression?

**Method:**

Literature study – narrative literature review

**Purpose:**

The purpose of this thesis is to explore and research the literature regarding the connection between physical activity and depression, and acquire knowledge on the subject of the involvement and function of a few neurobiological mechanisms.

**Summary:**

Recent literature examines how brain-derived neurotrophic factor and noradrenergic neurons influence the association between physical activity and depression by promoting neuronal survival, neuroplasticity, synaptic plasticity, improvements in cognition, sleep, mood, and memory, as well as reductions of symptoms and relapses.

**Key words:**

Physical activity, exercise, aerobic exercise, mental health, depression, major depressive disorder, neurobiological mechanism, brain-derived neurotrophic factor, brain plasticity, hippocampus, noradrenergic, glutamatergic

# Table of Contents

<b>1.0 Introduction</b> .....	5
<b>2.0 Research Question &amp; Operational Definitions</b> .....	6
<b>2.1 Research Question</b> .....	6
<b>2.2 Operational Definitions</b> .....	6
2.2.1 Physical Activity: .....	6
2.2.2 Mental Health: .....	6
2.2.3 Mental Disorder: .....	6
2.2.4 Depression: .....	6
<b>3.0 Theory</b> .....	7
<b>3.1 Physical Activity &amp; Exercise</b> .....	7
<b>3.2 Mental Health</b> .....	8
3.2.1 Mental Illness & Mental Disorder: .....	8
3.2.2 Depression & Major Depressive Disorder: .....	9
<b>3.3 Neurobiological Mechanisms, Physical Activity &amp; Depression</b> .....	11
3.3.1 Introduction & Background Information: .....	11
3.3.2 Neuroplasticity: .....	11
3.3.3 Brain-Derived Neurotrophic Factor: .....	12
3.3.4 Noradrenergic Neurons & Glutamate: .....	12
3.3.5 Neurobiological Mechanisms & Depression: .....	13
3.3.6 Effect of Physical Activity on Neurobiological Mechanisms: .....	14
<b>4.0 Method</b> .....	15
<b>4.1 Design</b> .....	16
<b>4.2 Search Process</b> .....	17
4.2.1 Inclusion & Exclusion Criteria: .....	17
<b>4.3 Methodological Considerations</b> .....	20
4.3.1 Source Evaluation: .....	20
4.3.2 Validity & Reliability: .....	21
4.3.3 Ethics: .....	22
<b>5.0 Results</b> .....	24
<b>5.1 Review Article 1</b> .....	24
<b>5.2 Review Article 2</b> .....	25
<b>5.3 Review Article 3</b> .....	25
<b>5.4 Review Article 4</b> .....	26
<b>5.5 Review Article 5</b> .....	27

<b>6.0 Discussion</b> .....	31
<b>7.0 Conclusion &amp; Summary</b> .....	33
<b>8.0 Literature List</b> .....	34

## List of Tables

Table 1 - Inclusion & Exclusion Criteria .....	18
Table 2 – Search Process in Oria.....	19
Table 3 - Choosing the Review Articles.....	20
Table 4 - Summary Sheet of Results .....	28

# 1.0 Introduction

The World Health Organization projected that depression will be second only to cardiovascular disease as the world's leading cause of death and disability by the year 2020 (Weinberg & Gould, 2015, p. 405). The projection came five years prior to the Covid-19 pandemic. As our daily life has changed in such a drastic way with quarantines, restrictions, and no physical contact, the psychosocial effect and the increase in depression, anxiety and stress might have exceeded WHO's projections (Soares et al., 2021). Fofana et al. (2020) mention how messages regarding anxiety and depression presented to a Crisis Text line, which is a crisis counselor operator in the USA, UK, and Canada, have increased with 80% since February 2020.

Physical activity, exercise and mental health has become a very interesting and popular topic among researchers and scientists, and is now being explored as a therapeutic option to e.g., antidepressants, due to its numerous physiological and psychological benefits. There is also evidence supporting the use of physical activity for treating and improving depressive symptoms (Soares et al., 2021). Exploring exactly what influences the association between physical activity and mental health is both important in order to improve and expand the treatment possibilities, as well as being able to best individualize and optimize the treatments (Phillips & Fahimi, 2018). Soares et al. (2021) highlights how physical activity further has positive effects on neurodegenerative disorders and mental health. Several researchers describe how there may be possible underlying neurobiological mechanisms which have been associated with depression, but that there still is a need for a deeper understanding, and more detailed research - especially on humans (Kandola et al., 2016; Soares et al., 2021; Zhao et al., 2020).

Hence, the purpose of this thesis is to explore and research the literature regarding the connection between physical activity and depression, and acquire knowledge on the subject of the involvement and function of a few neurobiological mechanisms.

## **2.0 Research Question & Operational Definitions**

### **2.1 Research Question**

*What does the recent research literature say about how the neurobiological mechanism influences the association between physical activity and depression?*

### **2.2 Operational Definitions**

#### 2.2.1 Physical Activity:

“Physical activity refers to all movement produced by skeletal muscles that increases energy expenditure resulting in energy expenditure above the resting level” (Kanosue et al., 2015, p. 4).

#### 2.2.2 Mental Health:

“Mental health is a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community” (WHO, 2018).

#### 2.2.3 Mental Disorder:

“A mental disorder is a syndrome characterized by clinically significant disturbance in an individual’s cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning” (Bingham & Banner, 2014, p. 540).

#### 2.2.4 Depression:

“In everyday discussions, the terms “depressed” or “depression” can refer colloquially to the kinds of mundane, momentary, negative reactions that are tightly bound to our experience of particular stressors or disappointments, or to more diffuse, short-lived periods (e.g., days) of malaise and unhappiness after which we rebound to a more positive (or at least, less depressed) mood state” (Durbin & Credo, 2016, pp. 1-2).

## 3.0 Theory

### 3.1 Physical Activity & Exercise

The words “physical activity” and “exercise” are often used interchangeably when describing random or spontaneous activities and when describing specific or planned exercise programs. “Physical activity (PA) refers to all movement produced by skeletal muscles that increases energy expenditure resulting in energy expenditure above the resting level” (Kanosue et al., 2015, p. 4). Formally defined, physical activity refers to any bodily movement that results in energy expenditure, which ranges from very low (e.g., typing on a computer) to very high (e.g., sprinting 100m) (Caspersen et al., 1985). “Exercise can be defined as systematic impact of the organism over time with the aim of changing the physical, coordinating, psychological and social assumptions that underpin performance” (Gjerset et al., 2016, p. 9).

Despite the two concepts referring to some type of bodily movement, there is an obvious significant difference between them. Physical activity occurs in multiple domains, including leisure time, occupations, household tasks, and even sleep. Exercise on the other hand, is the part of physical activity that is structured, repetitive, purposeful, and is performed specifically to increase fitness (Gjerset et al., 2016).

There are many types and forms of exercise, one of which is aerobic exercise (AE), which refers to exercise that improves the efficiency of aerobic energy producing systems by increasing maximal oxygen uptake and cardiorespiratory endurance. Several studies have correlated high levels of AE with greater preservation of cognitive function, especially in old age (Kandola et al., 2016).

Briefly summarized, the Norwegian recommendations for physical activity are (Hansen et al., 2014, pp. 6-7);

- Being physically active for a minimum of 150 minutes with moderate intensity, or 75 minutes with high intensity per week. Alternatively a combination of high and moderate intensity.
- Minimizing time spent being sedentary, long periods of resting/sitting should be combined with physical activity breaks.

Hansen et al. (2014), within the Norwegian Directorate of Health, explain in the analysis of the new national recommendations for physical activity, that around 2,7 million adults (<20 years old) do not fulfill the minimum recommendations of 150 minutes of physical activity,

which is problematic as sedentary time is associated with a large amount of health issues such as cardiovascular diseases, obesity, diabetes, and high blood pressure. These health issues can be prevented by living a healthy lifestyle which include the recommended amount of physical activity. Different types and forms of physical activity and exercise, offer various benefits. In general, physical activity and exercise target our general health, which means that some benefits are aimed at our physical health, as mentioned, while others are aimed at our mental and psychological health (Gjerset et al., 2016).

## **3.2 Mental Health**

According to Parekh (2018) at the American Psychiatric Association, mental health is the foundation for emotions, thinking, communication, learning, resilience and self-esteem.

“Mental health critically depends on a variety of intra- and interpersonal factors such as mood, rewarding relationships, access to resources (economical and emotional) and health care, manageable levels of stress, and involvement in social networks, all of which contribute to well-being” (Friedman, 2016, p. 173).

Mental health is important at every stage in life, and at any age. Our mental health determines how we handle stress, our ability to cope with or handle life, work, and/or school situations, how we relate to others, and our ability to make good choices. Throughout life, we may experience mental health problems, which could affect our behavior, how we think, and our mood. A few factors which can contribute to mental health problems are; biological factors such as genes or brain chemistry, life experiences such as trauma or abuse, and family history (Mental Health, 2020).

### **3.2.1 Mental Illness & Mental Disorder:**

According to Parekh (2018) at the American Psychiatric Association, mental illness is a term which collectively refers to all diagnosable mental disorders and health conditions that involve significant changes in thinking, emotion and/or behavior, and distress or problems with functioning in social, work, or family activities. There are many forms or levels of mental illnesses. Some are mild and with limited interference in daily life, while others are more extreme or severe, such as serious mental illnesses, which could lead to hospitalization. Serious mental illness can be described and/or defined as a mental, behavioral, or emotional



disorder resulting in serious functional impairment (Parekh, 2018). An example of a serious mental illness is major depressive disorder, which will be defined and described further on.

“A mental disorder (MD) is a syndrome characterized by clinically significant disturbance in an individual’s cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological, or developmental processes underlying mental functioning” (Bingham & Banner, 2014, p. 540). There are many different mental disorders, each consisting of different symptoms and levels of impact, such as depression, bipolar disorder, schizophrenia and other psychoses, dementia, and developmental disorders including autism. Even though mental disorders differ and/or vary, they are generally characterized by a combination of abnormal thoughts, perceptions, emotions, behavior and relationships with others (WHO, 2019).

### 3.2.2 Depression & Major Depressive Disorder:

According to Friedman (2016), the term depression can be used in many different scenarios and with different references, e.g. as a symptom, syndrome, or classification of disorder.

When referring to depression as a symptom, it can simply mean “being and/or feeling sad”, whilst when used as a syndrome however, depression refers to a collection of symptoms such as sadness, negative self-concept, and disturbances in sleep and appetite. Lastly, for depression to be classified as a disorder, several steps and careful diagnostic procedures are required.

Depression is a very common mental disorder, and can affect people in many different ways and at several levels such as mild, moderate, and severe depression (also defined as major depressive disorder). To become diagnosed with depression, symptoms have to last for at least two weeks and result in a change in level of functioning. As mentioned, the symptoms experienced can vary, but for a diagnosis to be placed, especially for severe depression, Torres (2020) at the American Psychiatric Association list nine criteria;

- Feeling sad or having a depressed mood
- Loss of interest or pleasure in activities once enjoyed
- Changes in appetite — weight loss or gain unrelated to dieting
- Trouble sleeping or sleeping too much
- Loss of energy or increased fatigue

- Increase in purposeless physical activity (e.g., inability to sit still, pacing, handwringing) or slowed movements or speech (these actions must be severe enough to be observable by others)
- Feeling worthless or guilty
- Difficulty thinking, concentrating or making decisions
- Thoughts of death or suicide

According to WHO (2001), a mild depressive episode may include two or three of the symptoms, and the person experiencing it is usually distressed by them, but will most likely be able to continue with most activities. A moderate depressive episode usually involves four or more of the symptoms, and will have a greater effect on the person, resulting in having great difficulty executing ordinary activities. Severe depressive episodes generally consist of most of the symptoms with a very distressing affect, especially low self-esteem and feelings of worthlessness, as well as suicidal thoughts and acts.

Major depressive disorder (MDD) is an extensive and pervasive illness characterized by symptoms of persistent low mood, hopelessness, an inability to feel pleasure, loss of energy, and cognitive dysfunction (McIntyre & McIntyre, 2020, p. 51). Even though symptoms have to last for a period of two weeks, this complex mental illness can be defined as chronic, meaning it can be persistent for a long time or constantly recurring - experiencing several episodes/relapses. Cognitive dysfunction or impairment such as difficulties with decision making, poor concentration, and downgrade in psychomotor function, is one of the core features of MDD. These cognitive dysfunctions typically increase alongside the symptoms of MDD, the more severe symptoms, the greater cognitive dysfunction (McIntyre & McIntyre, 2020).

According to Vågen and Johannessen (2021), 264 million people worldwide suffered from depression in 2020, and approximately every 5<sup>th</sup> European is estimated having to deal with some form of depression throughout their life. They also mention how in Norway, the cost of treating depression is estimated being around 1,5 billion NOK annually, whilst in the United States, they estimate a cost of approximately 210 billion dollars annually (Phillips, 2017a). Støren et al. (2020) present results from a survey in Norway, where 59% of people who have experienced symptoms of anxiety and/or depression in the last 14 days, exhibit/express low satisfaction with life.

### **3.3 Neurobiological Mechanisms, Physical Activity & Depression**

#### 3.3.1 Introduction & Background Information:

Throughout life, all types of experience have power to produce immediate communication between and among neurons. It can also initiate molecular processes that have the ability to remodel synaptic connections. This process literally changes the physical structure of the brain, and is called synaptic plasticity. New synapses can be created, old ones can be removed, and existing ones can be either strengthened or weakened. Hence information processing within the circuit can change to accommodate the new experiences (WHO, 2001).

Neurotransmitters are chemical messengers made specifically to transmit a signal made by the neuron, across the synapse, and to a target cell. This allows impulses to be passed from one cell to the next throughout the nervous system. Neurotransmitters are synthesized by neurons, and are essential to the function of complex neural systems. There are several types of neurotransmitters, some of which are amino acids such as glutamate, or monoamines such as norepinephrine. Abnormalities or disfunctions in neurotransmitter activity are associated with different diseases and disorders, especially neuro-degenerative disorders (Encyclopædia Britannica Inc, 2020).

Neurotrophins are closely related to the proteins in the brain that contribute to the survival, growth, and maintenance of neurons, which also participate in a variety of learning and memory functions (Phillips, 2017a). Neuroprotection on the other hand, refers to the prevention of neuronal cell death by intervening and inhibiting the pathogenetic process that causes cellular dysfunction and death (Mahalakshmi et al., 2020).

According to Lubans et al. (2016), the neurobiological mechanism hypothesis proposes that physical activity enhances cognition and mental health via changes in the structural and functional composition of the brain. The following paragraphs present a few neurobiological mechanisms which can possibly be associated with, and influence, mental health through physical activity.

#### 3.3.2 Neuroplasticity:

Neuroplasticity, which is the dynamic nature of the brain, refers to the brain's capacity to change and reorganize itself in response to internal and external influences. According to Kandola et al. (2016), the positive impact of brain plasticity is that these influences can be

adaptive, while the consequences of brain plasticity is that the influences can be maladaptive. The influences are e.g. adaptive when learning a skill, or when helping a person survive, but they are maladaptive when plasticity is insufficient to meet a specific demand which then could contribute toward disease conditions (Kandola et al., 2016).

### 3.3.3 Brain-Derived Neurotrophic Factor:

Brain-derived neurotrophic factor (BDNF) is a neurotrophin which belongs to the family of neurotrophic factors, and is important in regulating neuroplasticity. BDNF is expressed in the hippocampus, which is the part of the brain related to our memory, hence BDNF's important involvement in the processes related to memory and learning (Mahalakshmi et al., 2020; Sheng et al., 2017).

Cognitive function, which Lubans et al. (2016) define as a mental process contributing to perception, memory, intellect, and action, provides a core foundation which mental health is established upon. BDNF plays an important part in, and is vital to the growth, maintenance, and survival of the neurons involved in emotional and cognitive function. The levels of BDNF have the ability to, and play an important part regarding the size/volume and "safety" of the hippocampus. When levels of BDNF decrease, the hippocampus gets vulnerable, which can lead to hippocampal dysfunction and loss of emotion regulation. When levels of BDNF increase on the other hand, and become optimized and upregulated, hippocampal size/volume also increases, which then leads to synaptic plasticity and remodeling (Phillips, 2017a).

### 3.3.4 Noradrenergic Neurons & Glutamate:

Norepinephrine (NE) is an organic chemical that functions in the brain and body as both a neurotransmitter and as a hormone. The parts of the body that produce and/or are affected by norepinephrine, are referred to as noradrenergic (Kara, 2020). Noradrenergic neurons are vital to the fight-or-flight response, whilst reductions in level and function of norepinephrine is thought to cause a depressed mood (Encyclopædia Britannica Inc, 2020; Kara, 2020).

Noradrenergic synthesizing neurons are primarily located in the locus coeruleus (LC), which is a brainstem structure involved with physiological responses to stress and panic (Chandley et al., 2014; Phillips & Fahimi, 2018). Glutamate is the most prominent neurotransmitter in the body, as well as the most excitatory input to the noradrenergic LC. It is also the glutamatergic input that activates the LC through stress, which has been suggested to be the

key mediator of abnormal LC activity in depression. Glutamatergic activation of LS may be abnormal in people suffering from depression on grounds of two specific findings in suicide victims; increased extraneuronal glutamate levels and altered expression of glutamate related genes (Chandley et al., 2014).

### 3.3.5 Neurobiological Mechanisms & Depression:

#### 3.3.5.1 *BDNF*:

Within the research regarding mechanisms of disease (pathobiology), specifically in MD's and MDD, the involvement and changes in brain structure, brain plasticity, brain function, synaptic plasticity, and neurotrophins (specifically BDNF), is well-established and supported by clinical evidence (Kandola et al., 2016; Phillips, 2017a; Zhao et al., 2020). Phillips (2017a) suggests that the neurotrophic hypothesis of depression proposes that stress-related alterations in BDNF levels contribute to the development of MDD, which is based on evidence that people with MDD exhibit region-specific alterations (downregulations) in the level and function of BDNF. Rawdin et al. (2014) mention a somewhat similar suggestion, where the neurotrophin hypothesis of depression emphasizes the importance of neurogenesis and neuronal plasticity in the disordered physiological process that cause, and treat depression.

The relationship and connection between MDD and BDNF have been well documented as several studies report decrements in BDNF protein in the hippocampus, as well as smaller hippocampus volumes. Genetic studies have also reported that depressive behavior is associated with altered BDNF functioning (Phillips, 2017a).

#### 3.3.5.2 *Noradrenergic*:

The brain regulates central and peripheral immune processes via modulation of neurotransmitters, among other things, a process which can get disrupted in cases of depression. Agents that induce inflammation in humans recap symptoms of depression, which can be avoided and treated by using antidepressants. The immune system acts as a regulatory system which communicates with the nervous system through neurotransmitters. An imbalance in this system can induce chronic disease conditions such as depression (Phillips & Fahimi, 2018).

When there is a decrease in NE, especially in people with a history of depression, this decrease can re-induce depression, and/or a depressive episode. Major depressive disorder is

associated with a disturbance in the communication between glutamatergic and noradrenergic LC neurons. A reduction of the glutamatergic activation of the LC may lead to a reduction in depressive behaviors (Chandley et al., 2014), which is why inflammation and therapeutics that mitigating depression may be able to alter depression's pathobiology through influencing and affecting the function and levels of the key neurotransmitters that regulate the depression circuits (Phillips & Fahimi, 2018). Chandley et al. (2014) also present growing evidence that there actually is altered glutamatergic input to the noradrenergic LC in MDD, hence a suggestion that parts of the antidepressant's benefits and success may be mediated by reducing the elevation of the glutamatergic input to the noradrenergic LC which is associated to MDD.

### 3.3.6 Effect of Physical Activity on Neurobiological Mechanisms:

Physical activity, exercise, and aerobic exercise have been shown to have a positive effect on not only mental status, general health, and well-being, but to also be beneficial for people suffering from neuro-degenerative diseases. This is because PA promotes neuronal survival, neuroplasticity, synaptic plasticity, and also carries out protective and preventive activities such as improvements in cognition, sleep, mood, memory, and much more (Kandola et al., 2016; Mahalakshmi et al., 2020; Phillips, 2017b; Phillips & Fahimi, 2018; Zhao et al., 2020). As a result, PA may reduce the risk for MD's, the degree and level of symptoms, frequency of relapses, and also caregiver burden. Long-term PA is evidenced to positively correlate with positive neurobiological and cognitive outcomes (Phillips, 2017b). PA and exercise has been demonstrated to have a positive effect on brain structure and cognitive function, where BDNF has been identified as the crucial mediator of the benefits on brain health (Huang et al., 2014). BDNF levels in the hippocampus increase by voluntary PA and exercise, but when blocking the BDNF action in the hippocampus, it suppresses the positive effects of PA and exercise (Huang et al., 2014). PA also regulates the noradrenergic system both directly and indirectly to reduce the depressive symptoms, especially in people with inflammation. Long-term PA has been shown to increase NE levels in the hippocampus to improve cognitive outcome, which is useful considering that maintenance of NE is important because it stimulates a release of trophic factors such as BDNF for neuroprotection (Phillips & Fahimi, 2018).

## 4.0 Method

"The object of research is to determine how things are as compared to how they might be" (Thomas et al., 2015, p. 3). Research implies a careful and systematic means of solving problems and involves these five important characteristics: systematic, logical, empirical, reductive, and replicable (Thomas et al., 2015).

There are many types of research, as well as many ways of conducting and defining research, but in general we could say that it is all some sort of way, and/or type of problem solving. The method for problem solving can be structured, scientific, or even unscientific. But in general, if the research is to be considered acceptable, the research has to follow certain techniques, and has to be concerned with problem solving which could lead to new knowledge (Thomas et al., 2015)

A scientific method of problem solving is defined as "a method of solving problems that uses the following steps: defining and delimiting the problem, forming a hypothesis, gathering data, analyzing data, and interpreting the results" (Thomas et al., 2015, p. 10). Even though there are many different methods of problem solving, such as qualitative, quantitative, and mixed methods, each method should follow certain techniques and steps to ensure the quality of their research. Thomas et al. (2015) explain how a scientist must not only "do" science, they must also "write" science. High-quality research can easily be hidden by weak and boring writing which makes reading tedious. A good scientific format or style for a thesis or dissertation is structured and easy to follow, such as the IMRD format. The different methods might include or exclude certain parts of the format because the information needed, and the data gathered, varies. The IMDR format is typical for scientific studies reported in journal style, such as a research article. The IMRD format is commonly used and is appropriate for graduate students when writing their theses or dissertations. The IMRD format, which is the body of the thesis or dissertation, involves and answers the fundamental questions a research article is built on (Støren, 2013, p. 15; Thomas et al., 2015, p. 431);

- Introduction: What is the study about, and why is it important?
- Method: What did you do, and how did you do it?
- Results: What is your contribution to knowledge, and what did you find?
- Discussion: What does it mean, and why is it important?

## 4.1 Design

This bachelor thesis uses a literature study design. A literature study is based on studying available literature and research articles that can be found through searching different databases. This also means that literature studies do not create new, groundbreaking knowledge or information, but they are used as a tool to systematize the knowledge and information found. To systemize the knowledge and information means to search for it, gather it, evaluate it, and summarize it (Støren, 2013).

There are different types of literature studies, and this thesis presents a narrative literature review. A narrative literature review critiques and summarizes a body of literature about a certain topic, and is generally very selective in the material used. The main purposes of a narrative review is to give the author and reader a comprehensive overview of the topic and to highlight significant areas of research. They can also help to identify gaps in the research and help to refine and define research questions (Griffith, 2020).

Conducting a narrative review requires an extensive search of existing literature. When searching for already existing knowledge and information, we have to conduct the search through databases. There are several different databases to choose from. Some databases are set up specifically for researching within specific topics such as humanities, science and technology, or health care and social work to mention a few. The search engine used in this thesis was Oria. Oria is a commonly used portal to the collected material found at most Norwegian topics and research libraries. Oria provides unified access to various materials, and is supplemented with a large amount of electronic materials from many different open sources (Unit, 2020).

I chose Oria for this bachelor thesis because this is the database we were introduced to, and use at the University of Stavanger. It therefore made sense to use it since I already had knowledge and experience with it, and I wouldn't have to spend time learning how to use a new and different database. Oria also gives access to, and is indexed with different journals and several databases which are relevant for this bachelor thesis. Consequently it was unlikely that I would miss out on important information and research.



## 4.2 Search Process

The search process depends considerably on the initial familiarity with the topic. Hence the search process for this thesis consisted of two parts, an unsystematic search and a systematic search. The first part, the unsystematic search, consisted of a computer search, which is a fundamental part of every literature search. A computer search is a good approach to gaining access to certain preliminary sources that locate secondary sources, which are helpful when trying to gain some familiarity with the topic. The unsystematic search gave an impression of what information is already to be found, and in which area. This also led to different primary sources, meaning original studies which usually exist in the form of journal articles.

The second part of the search process, the systematic search, consisted of delimitating the search criterias to find articles suited to help answer the research question. The systematic search process started with search words within the topics of mental health and physical activity. Since mental health is such a wide term, the research found involved many different aspects of mental health such as depression, anxiety, personality disorder, psychological well-being, schizophrenia, dementia and so on. Physical activity, which is also a quite wide term, resulted in a large number of hits, especially when paired with mental health.

To specify the search for recent literature regarding how the neurobiological mechanism influences the association between physical activity and depression, the search words had to be as precise as possible. In the first systematic search, no limitations or inclusion/exclusion criteria were used, simply the search words “physical activity” AND “exercise”, which resulted in 353,385 hits. To limit the search even more, the search words “depression” AND “neurobiological mechanism” were added to the first search combination, resulting in 2,885 hits. Since the search words were specific and precise, but the number of hits were still too large, delimitations, limitations and inclusion and exclusion criterias were added to the search.

### 4.2.1 Inclusion & Exclusion Criteria:

Limitations are shortcomings or influences that either cannot be controlled or are the results of the delimitations imposed by the investigator, while delimitations are choices the experimenter makes to define a workable research problem (Thomas et al., 2015, p. 64).

Inclusion criteria are characteristics which the prospective subjects must have if they are to be included in the study, while exclusion criteria are those characteristics that disqualify prospective subjects from inclusion in the study (Yale University, n.d.).

*Table 1 - Inclusion & Exclusion Criteria*

<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
Published between 2015-2021	Published earlier than 2015
Peer reviewed journal	Not peer reviewed journal
Review articles	Articles / not review articles
English language	Non English language

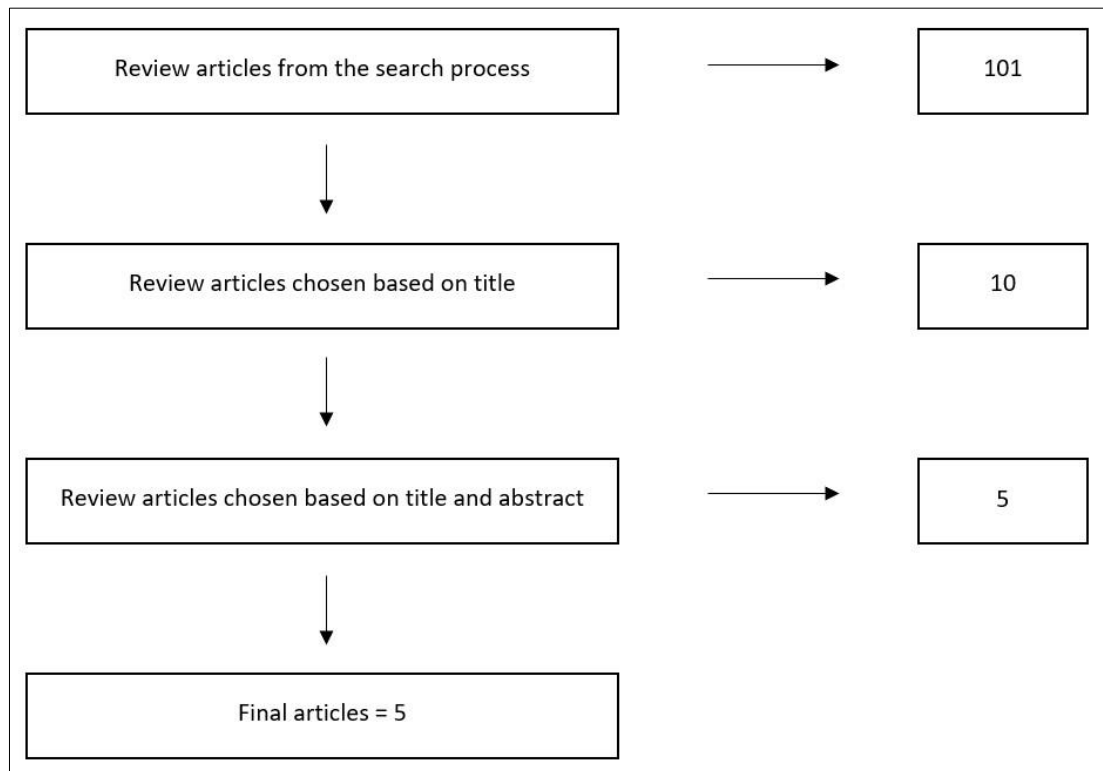
The first, and most important inclusion criteria were that the articles had to be peer reviewed journals, in English language, and published between the year 2015 and 2021. Peer reviewed journals means that the articles have been reviewed and approved by experts within the same subject area (Dalland, 2012). To limit the amount of articles even more, a few disciplines and filters were used. Disciplines such as “biology”, “public health”, and “pharmacy, therapeutics & pharmacology” were used. Filters were also used to limit the amount of articles even more. The filters used were, as mentioned earlier, “article”, “English language”, and the years “2015-2021”. The first search with these limitations resulted in 361 hits. This is still a very large number of articles to read through, so there were put even more filters in place. After adding the filters “mental disorders”, “mental depression”, “humans”, “depression”, “exercise”, and “neurosciences” the search resulted in 101 hits.

To limit the amount of articles further, I read the titles of all 101 articles, and excluded the ones I interpreted to be irrelevant for the present research question. This resulted in 10 articles. The abstracts of the 10 articles were read. Based on the contents of the abstracts, articles that did not contribute to answering the present research question, were excluded, resulting in five final research articles.

Table 2 – Search Process in Oria

Search words	Limitations	Hits
Physical activity & Exercise		353,385
Physical activity & Exercise & Depression		77,928
Physical activity & Exercise & Depression & Neurobiological mechanism		2,885
Physical activity & Exercise & Depression & Neurobiological mechanism	<u>Disciplines:</u> Biology + Public health + Pharmacy, therapeutics & pharmacology  <u>Filters:</u> Article + 2015-2021 + English language + Review	361
Physical activity & Exercise & Depression & Neurobiological mechanism	<u>Disciplines:</u> Biology + Public health + Pharmacy, therapeutics & pharmacology  <u>Filters:</u> Article + 2015-2021 + English language + Review  <u>Extra filters:</u> Mental disorders + Mental depression + Humans + Depression + Exercise + Neurosciences	101

Table 3 - Choosing the Review Articles



## 4.3 Methodological Considerations

### 4.3.1 Source Evaluation:

“Referring to sources is a vital part of scientific communication” (Kildekompasset, n.d.), consequently it is important to be critical of the chosen sources, and in which way they are relevant for this bachelor thesis.

When evaluating a source, a few important questions to ask are (Kildekompasset, n.d.);

- Who is the responsible publisher?
- Is the source still relevant?
- Are there any references in the source?
- Is the author credible?
- How is the language and layout?
- Does the source show a high academic level?
- Is the source suitable?
- With which purpose has the source been written?

- What is a scholarly article?

These questions take on important points and views of how to evaluate the sources. Source evaluation, or source criticism, is an important method to use in order to determine if a source is true. We evaluate and are critical of the sources to prevent that the data chosen influences the results of the research. The results might not always please the researcher or turn out as expected, but they are still important findings even though they should not match the hypothesis set. The tricky thing here is to make sure not to make biased decisions and/or influence the results when conducting research.

#### 4.3.2 Validity & Reliability:

There are two forms of validity, internal and external validity. Internal validity refers to the extent to which the results can be attributed to the treatments used in the study, while external validity pertains to the generalizability of the results (Thomas et al., 2015, p. 13). Reliability, on the other hand, refers to the consistency, or repeatability, of a measure. For something to be considered valid, it has to be reliable as well (Thomas et al., 2015).

When an article is chosen, it is important to check the validity and reliability of the source. What type of research is it, who is the author, for whom is the research, why is this particular topic chosen, what is the purpose or aim of the research, and how old is it? The reliability of a source is strengthened when the search process and the researchers procedure is described in detail. It is important to check whether the articles research what they claim to research, or in other words, if the purpose of the research is researched, which then shows to internal validity. It is also possible to check the articles' external validity, if the results are transferable, meaning if they are useful in other relevant/similar areas (Johannessen et al., 2010).

The sources in this bachelor thesis each have their own point of view, a unique research question, different purposes and aims, and therefore illuminate the research question from different angles. The search process and design is described in detail, and the inclusion and exclusion criteria are clear, relevant and explained. Since the topic of the sources was, and still is, relatively new, there was probably a lack of literature, which made it unnecessary for the authors to conduct a systematic search with limitations.

### 4.3.3 Ethics:

Research ethics are a set of guidelines for the responsible conduct of research which educate and monitor scientists conducting research to ensure a high ethical standard. These guidelines consist of several principles, scientific misconducts and scientific dishonesty.

The ethical principles involve honesty, objectivity, integrity, carefulness, openness, respect for intellectual property, confidentiality, responsible publication, responsible mentoring, respect for colleagues, social responsibility, non-discrimination, competence, legality, animal care, and human subject protection (City University of Hong Kong, 2021).

Scientific misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results (Thomas et al., 2015, p. 83).

In addition to the already mentioned ethical guidelines, the seven areas of scientific dishonesty are a few of the major topics and areas in which students might face the most difficulties. The seven areas of scientific dishonesty regard plagiarism, fabrication and falsification, nonpublication of data, faulty data-gathering procedures, poor data storage and retention, misleading authorship, and unacceptable publication practices (Thomas et al., 2015, pp. 83-88). When choosing a literature study as method for the bachelor thesis, the most relevant area of scientific dishonesty is plagiarism. Another ethical issue among students regards copyright and the concept of fair use which include purpose, nature, amount, and effect as the four basic rules (Thomas et al., 2015, p. 88);

- Purpose: Is the use to be commercial or educational?
- Nature: Is copying expected and reasonable?
- Amount: How much is to be copied?
- Effect: How does copying affect the market for the document?

As this is a literature study, a major part of the ethical issues with conducting research are irrelevant. An issue which is very relevant considering the design of this thesis however, is whether the articles selected best suit the research question, or/and if there were articles excluded due to unfavorable results. A key problem with narrative literature reviews is that the authors frequently have expert opinions and biases and will therefore find studies to support their positions (selection bias). However, this thesis is a part of a bachelor degree, which means there is no expert opinion or position to support/justify. Articles were selected

on the background of a systematic search, and is thoroughly described and explained in the research process.

Ethics involve different rules, guidelines and principles which are used to evaluate whether an act is right or wrong (Johannessen et al., 2016). Since the research question for this thesis involves a sensitive topic such as mental health, I consider it important to be aware of, and keep in mind that depression is an extensive issue affecting many people worldwide. Information should consequently be dealt with and presented in a respectful manner.

## 5.0 Results

The results are presented in a separate and organized manner, consisting of title with source, purpose and/or aim, key words, method, and a brief summary of conclusions. I chose to present the entire purpose of the review articles, and not just those directly relevant to this thesis research question, as it properly presents the complete scope of the study. The summary presents conclusions drawn by the authors which were more relevant and suited for the aim of this thesis. Lastly, a brief summary of the most important findings from each study targeted at how the neurobiological mechanism influences the association between physical activity and depression, were put together in a summary sheet for a neatly and specific overview.

### 5.1 Review Article 1

**Title:** Brain-Derived Neurotrophic Factor, Depression, and Physical Activity: Making the Neuroplastic Connection (Phillips, 2017a)

**Purpose:** The purpose of this review was to;

“1. Explicate the putative neurobiological mechanisms involved in MDD and how trophic factor relate to those mechanisms  
2. Review clinical and preclinical evidence of altered BDNF in persons with MDD  
3. Discuss the relationship of BDNF to neuroplasticity  
4. Discuss the effect of PA on BDNF  
5. Highlight current and future implications for clinicians and scientists”  
(Phillips, 2017a, p. 1).

**Method:** Do not state a clear method.

**Summary:** Phillips (2017a) conclude her review article by explaining how evidence show that stress-induced depressive pathology contributes to alterations in BDNF levels and functions in people that suffer from MDD, and how this alteration of BDNF causes disruptions in the neuroplasticity at regional and circuit levels. Additionally, she points to evidence of how PA optimizes these BDNF levels and therefore promote neuronal health and recovery of function in MDD-related circuits. Interestingly, she suggests how a combination of aerobic and strength-training activities, instead of aerobic activities alone, are more effective at enhancing emotional and cognitive health. Lastly, Phillips (2017a) concludes her



research with suggestions that moderate PA optimizes BDNF and plasticity, particularly in people with depression.

## 5.2 Review Article 2

**Title:** Exercise, brain plasticity, and depression (Zhao et al., 2020)

**Purpose:** The purpose of this review was to;

- “1. Summarize the effects of exercise on depression
2. Analyze different exercise modes in depressed people
3. Explain the changes in brain plasticity in exercise-induced antidepressant”

(Zhao et al., 2020, p. 886).

**Key words:** Brain function, brain plasticity, brain structure, depression, exercise

**Method:** Retrieved related literature from Web of Science, PubMed, EBSCO host, and CNKI using depression, depressive disorder, exercise, brain plasticity, brain structure and brain function as key words.

**Summary:** Zhao et al. (2020) conclude their review article by summarizing important findings regarding the effects of exercise on depression, and the resultant brain plasticity changes. They explain how different exercise patterns and amounts are associated with reductions in risks, symptoms, and levels of depression. They also explain how depressed people have different degrees of impairments in the brain structure and function, and how exercise has had a positive effect on brain plasticity and the rebuilding of brain structures. Further, they point to how exercise can activate related brain regions and promote adaptive changes in behavior, which can improve the brain nerve processing efficiency and delay degradation of cognitive function.

## 5.3 Review Article 3

**Title:** Aerobic Exercise as a Tool to Improve Hippocampal Plasticity and Function in Humans: Practical Implications for Mental Health Treatment (Kandola et al., 2016)

**Purpose:** The purpose of this review was to;

- “1. Review the cognitive benefits associated with aerobic exercise (AE)
2. Discuss the capacity of AE to stimulate macro- and micro-scale neuroplastic mechanisms

related to hippocampal functioning

3. Address the suitability of AE to be used as a novel therapeutic intervention for psychiatric disorders”

(Kandola et al., 2016, p. 2).

**Key words:** Aerobic fitness, hippocampus, plasticity, schizophrenia, depression, dementia, memory, neurogenesis

**Method:** Do not state a clear method.

**Summary:** Kandola et al. (2016) conclude their review article by first explaining that the beneficial impact that AE has on the brain, could have a useful clinical application when treating disorders where damage to the hippocampal is a significant part of the symptomatology. They continue by mentioning how AE interventions represent an effective method for promoting hippocampal neuroplasticity and function, and as AE consists of fewer risks and side effects than pharmaceuticals, it would be more beneficial for the patients.

## 5.4 Review Article 4

**Title:** Immune and Neuroprotective Effects of Physical Activity on the Brain in Depression (Phillips & Fahimi, 2018)

**Purpose:** The purpose of this review was to;

“1. Underscore the link between inflammatory correlates and depression

2. Explicate immune-neuroendocrine foundations

3. Elucidate evidence of monoaminergic and cytokine crosstalk in depressive pathobiology

4. Articulate the immunomodulatory mechanisms and pathways that confer the benefits of PA in depression

5. Examine protocols used to effectuate the benefits of PA in depression

6. Highlight implications for clinicians and scientists”

(Phillips & Fahimi, 2018, p. 3).

**Key words:** Immune, stress, depression, physical activity, neuroprotection, peroxisome proliferator-activated receptor gamma coactivator 1-alpha, growth factors, glutamate

**Method:** Do not state a clear method.

**Summary:** Phillips and Fahimi (2018) start their conclusion by pointing out how psychiatric illness is defined by a constellation of different symptoms which can be influenced by multiple neural processes and circuits. Even though they comment on how further research is needed to properly define the relationship between inflammation and depression, they suggest that a specific subtype, or subgroup, of depression with comorbid chronic inflammation exists, which has been shown to be resistant to conventional antidepressant pharmacotherapy. Furthermore, Phillips and Fahimi (2018) discuss the importance of being able to personalize and maximize the adherence of treatments and prescriptions of PA for people with depression. This is because the activation of the inflammatory response may trigger different reactions to various activity programs, and also because depression is linked to increased morbidity and mortality.

## 5.5 Review Article 5

**Title:** Physical Activity Modulates Common Neuroplasticity Substrates in Major Depressive and Bipolar Disorder (Phillips, 2017b)

**Purpose:** The purpose of this review was to;

- “1. Elucidate key substrates implicated in MD pathobiology
2. Explore the mechanisms by which PA can mitigate them
3. Examine protocols used to effectuate the positive effects of PA in MD’s
4. Highlight implications for clinicians and scientists”

(Phillips, 2017b, p. 1).

**Method:** Do not state a clear method, but systematically reviewed available intervention studies.

**Summary:** Phillips (2017b) concludes her review article by emphasizing how biomedical evidence implies that PA has the ability to optimize neuroplasticity substrates/foundations and processes across brain regions. As a result, the neuronal networks responsible for the emotional and cognitive regulation, can reestablish their connection in a form that improves their ability to meet the environmental and biological demands in a use-dependent manner. Furthermore, she points to evidence that PA interventions are more likely to reduce MDD symptoms when applied in the early stages of diagnosis; PA interventions still have a significant, but more limited effect when applied in later stages. She also displays how

exercise produced effects were equivalent to treatment with antidepressants, and that AE of moderate intensity was successful in treating depression. Lastly, Phillips (2017b) explains how PA should be advocated to reduce symptoms, prevent relapse, and alleviate remaining symptoms to promote good health habits.

*Table 4 - Summary Sheet of Results*

<b>Characteristics of sources</b>			
<b>Study</b>	<b>Mechanism studied</b>	<b>Influence of PA or exercise</b>	<b>Influence on Depression</b>
<b>1</b> Phillips (2017a)	Neuroplastic mechanisms involving BDNF.	PA effectuates central neuroplastic adaptations via optimization of BDNF levels.	Decrements in BDNF levels and function can confer vulnerability for hippocampal dysfunction and loss of emotional regulation, which may contribute to an increased risk of depression and suicidal behavior.
<b>2</b> Zhao et al. (2020)	Changes in brain plasticity (neuroplasticity).	Exercise affects brain plasticity by rebuilding brain structure, activating functions of related brain regions, promoting adaptive behavioral changes, which leads to exercise being able to effectively protect brain plasticity and promote brain health.	Reductions in brain volume and decreased hippocampal volumes are related to depressive episodes, and may possibly prolong the depression course and increase the frequencies of relapse.

<p><b>3</b> Kandola et al. (2016)</p>	<p>Neuroplastic mechanisms that support improvements in hippocampal functioning.</p>	<p>AE is associated with increases in hippocampal volume and some indirect indicators of neuroplasticity, which correlate with improved performances on hippocampus dependent tasks, indicative of an enhanced hippocampal functioning.</p>	<p>Hippocampal dysfunction in MDD may disrupt the correct formation of episodic memories and potentially exasperate other psychiatric symptoms, as well as contribute toward deficits in the regulation of emotional processing and stress responses.</p>
<p><b>4</b> Phillips and Fahimi (2018)</p>	<p>Immune mechanisms and processes via modulation of neurotransmitters, and noradrenergic interactions.</p>	<p>PA can optimize neuroplasticity substrates and processes across brain regions so that neuronal networks responsible for emotional and cognitive regulation can reestablish their connectivity to better meet environmental and biological demands in a use-dependent manner.</p>	<p>Robust evidence demonstrates that proinflammatory cytokines (signaling molecules) alter the functional status of the noradrenergic system in the LC and beyond, providing a mechanistic explanation for the noradrenergic abnormalities and associated symptoms seen in people with depression.</p>

<b>5</b> Phillips (2017b)	Pain- and depression- induced neuroplasticity changes, and neurobiological mechanism changes.	PA modulates the underlying pathobiology of MDD by altering the levels of key neurotransmitters which regulate emotional and cognitive health.	Changes in structural and functional plasticity at the synapse are relevant to MD's and can adversely affect emotional and cognitive function. Loss of synapses results in disconnection and loss of function in key brain regions.
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## 6.0 Discussion

Physical activity, aerobic exercise, and exercise all have great health benefits, specifically mental health benefits, as well as functioning as a great option next to, or combined with pharmaceuticals (Phillips & Fahimi, 2018). PA also has many positive effects on brain health, some of which are optimizing central levels of BDNF, optimizing neurotransmitter system levels and functions (Phillips, 2017a), promoting and affecting brain function, protection of brain plasticity (Zhao et al., 2020), increasing hippocampal volume and functioning, and improving hippocampus dependent tasks (Kandola et al., 2016), as well as promoting release of norepinephrine and glutamate (Phillips, 2017b).

Depression and MDD are mental disorders which, as Bingham and Banner (2014) mentioned, are characterized by a significant disturbance in cognition, emotion regulation and a dysfunction in biological processes. According to Phillips (2017a), it is the hippocampus that is the most vulnerable part of the brain in MDD. It is there the function and level of BDNF plays an important part of both protecting and rebuilding the hippocampus. Zhao et al. (2020) support this notion and add on how exercise has a positive impact on maintaining the integrity of hippocampal volume, as well as promoting the regeneration of the hippocampus. Enhancing hippocampal volume and functioning through neuroplastic changes is useful due to its ability to improve certain domains of cognitive function such as learning and memory (Kandola et al., 2016). In addition, Phillips and Fahimi (2018) explain how the changes in neuroplasticity happen at approximately the same rate through PA as antidepressant therapy. They also present results that people in an exercise group exhibited lower relapse rates than people in a medication group, which is interesting since Kandola et al. (2016) present that people who have been through a successful antidepressant treatment, still continue to experience cognitive deficits – specifically in executive function and memory.

As Phillips (2017a) explain, many of the positive effects of PA come from its ability to optimize central levels of BDNF. In addition, PA's ability to modulate changes in BDNF is also relevant for stress-induced depression given its interaction with neuroinflammatory and neuroplasticity pathways. Phillips and Fahimi (2018) contribute with the notion that depression is associated with an activation of the inflammatory response which may respond differently to both medication and various activity regimes. Phillips (2017a) continues by explaining how PA optimizes neurotransmitter system levels and functions, such as glutamate and norepinephrine. An increase in NE levels is important according to Phillips and Fahimi

(2018) as it stimulates the release of BDNF for neuroprotection. They also mention how PA modulates the noradrenergic system to mitigate depressive symptoms in people with inflammation. Changes in neurotransmission mediate changes in BDNF gene expression in the hippocampus as well as other brain regions. PA also increases neurogenesis and plasticity via BDNF-dependent mechanisms. Furthermore, the fact that PA modulates BDNF levels, as well as depressive symptoms, suggests that BDNF gene interactions with PA may influence depressive symptoms (Phillips, 2017a). Furthermore Zhao et al. (2020) explain how exercise can promote generation of positive emotions.



## 7.0 Conclusion & Summary

The purpose of this narrative literature review has been to attempt to understand a few of the neurobiological mechanisms that are associated with, and can influence the effect of physical activity on depression. Through a systematic search which resulted in five review articles, a collection of information and knowledge regarding what seems to be two of the “biggest” or more important mechanisms was gathered, namely brain derived neurotrophic factors and noradrenergic neurons. Regardless, it is strongly demonstrated that physical activity has a positive effect on our mental health and that it would be a huge benefit to incorporate physical activity as part of a treatment plan for depression and other mental disorders as well.

Evidence present a change in hippocampal volume and size in people suffering from depression which alters the function and production of BDNF. There is also evidence presenting how decrements in noradrenergic neurons can re-induce depression or lead to a depressive episode. Both BDNF and noradrenergic neurons are positively affected by physical activity. PA increases the level of both BDNF and NE in the hippocampus, which again improves the cognitive outcome.

Even though there is still a need for more research, the recent literature explains how BDNF and noradrenergic neurons influence the association between PA and depression, which leads to improvements in both cognition and several neurobiological mechanisms.

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