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The role of the cerebellum in emotional modulation: implications for the treatment of depression.

Writing Assignment

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Layman summary

The cerebellum or the *'little brain'* is one of the three parts of the midbrain. The midbrain has been long considered the part of the brain responsible for lower-order functions, that do not require cognitive capabilities. The cerebellum is most known for its role in movement control, coordination, balance, and posture. For this reason, it has not been considered as a major player in higher functions such as emotional processing and thinking which are most associated with the limbic system and neocortex. However, new studies from the last 30 years show that the *'little brain'* may be more involved in higher-order functions than previously thought. One such higher-order function would be emotional processing, with an emphasis on the structure's involvement in mood disorders like depression. Depression is a debilitating mood disorder affecting approximately 5% of the population. There are a variety of depression treatments to date, however, they are not all effective as different subsets of patients show variety in their displayed symptoms. Nonetheless, recent studies pinpointed the cerebellum as a potential structure of interest in assessing depression and negative moods. Firstly, patients that have a cerebellar condition such as lesions or tumors show increased symptoms of depression and cognitive impairment. Secondly, there is a significant change in neural activity in the cerebellum in depression compared to controls. This is observed via functional magnetic resonance imagining (fMRI) data that assesses the most active areas in the brain by measuring the blood flow in a specific brain area. Using fMRI at rest, when no task is being performed, shows that the cerebellum is more active in depression patients compared to healthy individuals. Thirdly, there are some anatomical changes seen in patients compared to healthy controls. Depression patients tend to have a smaller size of the cerebellum and weaker or abnormal axonal connections. And finally, a multitude of non-invasive stimulation studies showed the cerebellum's potential role in higher-order functions such as emotional processing and cognition. Non-invasive stimulation functions by sending an electrical signal to the brain via the skull. These signals can either activate or inhibit neuronal communication, leading to increased or decreased activity in a certain brain area. In the cerebellum, once inhibited, we see a prevalence of negative emotion. Therefore, the cerebellum is an important structure in emotional processing and mood disorders, with an emphasis on depression. Further studies could lead to new improved depression treatments via the use of cerebellar stimulation or through the discovery of depression biomarkers, making diagnosis easier. Overall, this is a new area of study, and the cerebellum has a lot of potential to bridge the gap in our misunderstanding of neuropsychiatric disorders.

Abstract

The cerebellum is the brain structure which is generally associated with movement, coordination, and equilibrium. However, studies performed in the last three decades revealed its involvement in emotional processing and the development of neuropsychiatric disorders, with an emphasis on unipolar and bipolar depression and schizophrenia. Major depression disorder (MDD) is one of the most common mood disorders that has become one of the leading causes of disease in the world. It is a life-threatening disorder due to its prevalence with suicidal ideation and further comorbidities. Therefore, it is imperative to find clinical treatments that can minimize the impact of the disorder. The cerebellum has been associated with depression in multiple research setups at a structural, functional, and molecular level. Morphological cerebellar changes in the form of decreased cerebellar volumes and white matter aberrations are observed in patients suffering from MDD. Additionally, cerebellar activation is observed through imagining setups in patients compared to controls, denoting altered activity focused at the cerebellar levels. Lesion studies and cases of cerebellar damage have shown that patients display depression symptoms. This has been collaborated via neuronal stimulation, which shows that the excitatory stimulation of the cerebellum leads to an increase in positive mood, whereas inhibitory stimulation leads to a decrease in mood and inability to identify with emotions, typical of the MDD symptomology. The exact role of the cerebellum in the propagation of the disorder remains unknown, however, the recent data makes the cerebellum a structure of interest in MDD. Promising new studies have shown that the cerebellum could be used as an additional target for depression therapies, via the use of stimulation therapy or as a potential depression biomarker for a subset of MDD patients. Therefore, the cerebellum is a new yet exciting potential target for improved clinical treatments for depression.

Keywords: cerebellum, depression, emotional processing, TMS, fMRI, negative affect, correlational study.

Introduction

The cerebellum is the part of the brain which was traditionally associated with basic motor and vestibular function but neglected as a possible player in cognitive and emotional processing (Phillips et al., 2015; Roostaei et al., 2014; Van Overwalle et al., 2020). However, data over the last three decades started showing that it may play a larger role in emotion and cognition than anticipated (Adamaszek et al., 2016; Roostaei et al., 2014; Schmahmann & Sherman, 1998; Schutter & Van Honk, 2005b; Van Overwalle et al., 2020). The cerebellum only accounts for 10% of the brain's volume but contains more than 50% of its neurons,

denoting a large processing power (Barton & Venditti, 2014; Schutter & Van Honk, 2005b; Van Essen et al., 2018). It would be a shame to be dismissed based on the older understanding of its function. Evolutionarily, there is evidence that the cerebellum evolved and developed in tandem with the neocortex, denoting the possibility of the two structures being in closer communication than initially thought (Whiting & Barton, 2003). Finally, various studies beginning from the 80s onwards show the cerebellum's potential involvement with emotional and cognitive function (Adamaszek et al., 2016; Ferrari et al., 2021; Newstead et al., 2018; Phillips et al., 2015; Schmahmann & Sherman, 1998; Schutter & Van Honk, 2005b). Schmahmann and Sherman 1998 showed that cerebellar lesions lead to affective, cognitive, and emotional disturbances that can be allocated to specific areas in the cerebellum (Schmahmann & Sherman, 1998). Further research, using more advanced techniques such as transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) have also shown that the cerebellum is activated when presented with emotional stimuli (Adamaszek et al., 2016; Ferrari et al., 2021; Newstead et al., 2018). Overall, a correlation has been made between the cerebellum with negative emotions and neuropsychiatric disorders. These findings are important as they can present alternative avenues of research for developing therapies for neuropsychiatric disorders (Phillips et al., 2015). This review will concentrate on the research found on the involvement of the cerebellum in depressive disorders. Depression is theorized to occur via disturbances in the hypothalamus-pituitary-adrenal (HPA) axis, denoting a dysregulation of the stress cycle, leading to increased cortisol and an inability to bring the system back to its normal functional state (Schutter, 2012). However, studies on the HPA axis alone do not lead to an elucidation of the mechanisms of depression (Jeon & Kim, 2016). Depressive symptoms are also correlated with activation in the left cerebellar hemisphere in imagining studies and there is a strong, yet misunderstood correlation between cerebral damage and an exacerbation of depressive symptoms (Clausi et al., 2019; Dai et al., 2022; Jung et al., 2022). Promising studies show that cerebellar activation via electrical stimulation can decrease such depressive symptoms, denoting that the cerebellum may be at least in part involved in the processing of the negative affective experiences (Ferrari et al., 2021; Newstead et al., 2018). Thus, it is imperative to elucidate the link between the cerebellum and the symptoms seen in mood disorders and other neuropsychiatric disorders. Overall, this review aims to discuss the work that has been done in the last three decades on elucidating the role of the cerebellum in emotional processing and further focus on how these findings can potentially help us find alternative therapies for depression.

1. The cerebellum and emotional processing

1.1. Cerebellum anatomy and function

The cerebellum is the largest part of the hindbrain, and it is also named the *'little brain'* due to its structure that partly resembles the cerebrum having a cerebellar cortex and deep cerebellar nuclei (Van Essen et al., 2018). Its outer area is comprised of gray matter and the inside is formed of white matter, reason for which the structure is also referred to as the *'arbor vitae'* or *'tree of life'* (Jimsheleishvili & Dididze, 2022; Roostaei et al., 2014). Its overall anatomical structure is not as complex as that of the cerebrum, having its lobes and lobules organized clearly (Van Essen et al., 2018)(Figure 1). However, it does contain ten lobules and three main nuclei, namely dentate nucleus, interposed nucleus, and fastigial nucleus that aid its functions (Purves et al., 2001; Roostaei et al., 2014). Overall, the cerebellum has input and output connections with the cerebrum and relay stations (Whiting & Barton, 2003). Cerebellar inputs come from the neocortex, the spinal cord, and the vestibular system, whereas output connections go to the neocortex, with an emphasis on motor areas, and the spinal cord (Whiting & Barton, 2003).

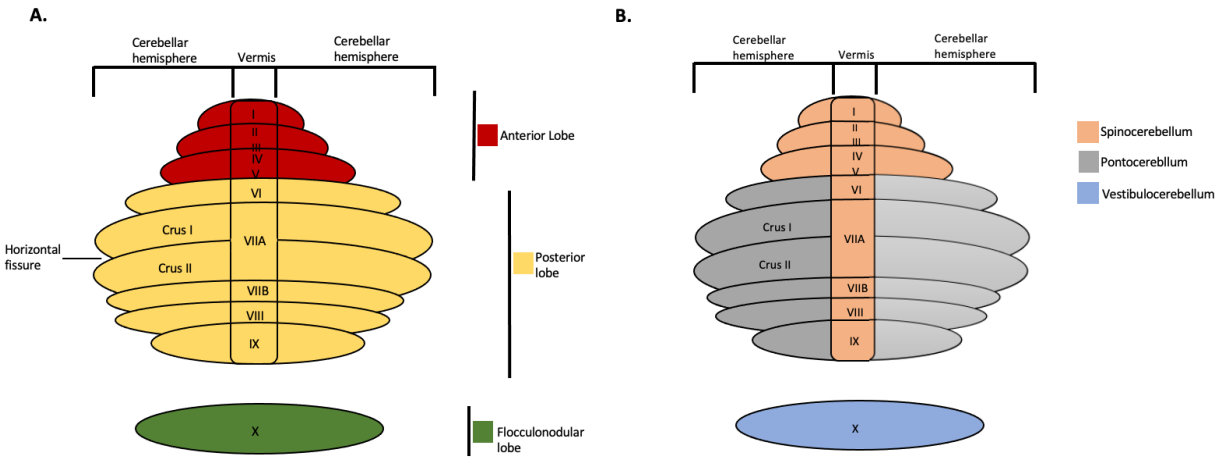

Figure 1. Unfolded view of the cerebellum and its functional systems. The figure contains a schematic view of the cerebellum distribution, containing its anatomical and functional systems. **A.** The division of the cerebellum into its three lobes, ten lobules, and the vermis. Color-coded to represent the positioning of each lobe and its related lobules **B.** The schematic division of the cerebellum into its three working systems based on function. The functional systems correlated to the anatomy of the lobes and lobules are color-coded for easier identification. Figure adapted from Depping et al., 2018 & Purves et al., 2001.

The cerebellum can also be divided into three systems based on their main function (Figure 1). The vestibular cerebellum consists of the flocculonodular lobe and nodules. This system is most associated with balance and posture, and it has connections to the vestibular nuclei for its vestibular function (Whiting & Barton, 2003). The system receives input via proprioception and further sends projections to the motor cortex to coordinate movements (Purves et al., 2001; Whiting & Barton, 2003). The spinal cerebellum is formed out of the vermis and the anterior lobe, and it is associated with maintaining muscle tone, locomotion, and adapting to environmental changes (Purves et al., 2001). Moreover, it contains somatotropic maps of the body, similar to the somatotropic maps in the cerebral sensory cortex (Purves et al., 2001). And finally, the pontocerebellum or neocerebellum is the system that connects to the cerebral cortex (Purves et al., 2001). The pontocerebellum is located in the posterior lateral side of the cerebellum and it is responsible for the planning of sequential movements of the body (Jimsheleishvili & Dididze, 2022). There are no monosynaptic connections between the cerebellum and the neocortex, as they communicate via relay stations, but it receives the input from the pontine nuclei and sends outputs to the forebrain via the thalamic nuclei (Figure 2) (Purves et al., 2001; Whiting & Barton, 2003).

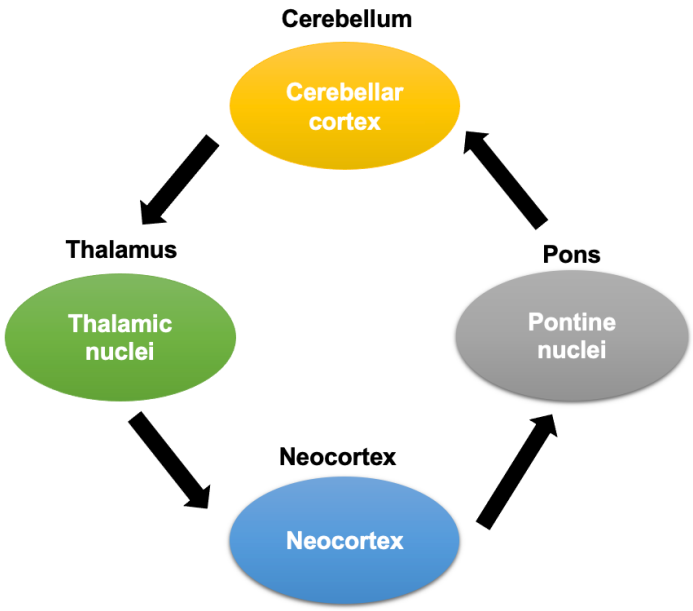

Figure 2. Schematic of the cerebellum-neocortex circuitry. The figure shows the communication between the neocortex and the cerebellum. There are no monosynaptic connections between the cerebellum and the neocortex, but the communication is maintained via relay stations. The cerebellum sends projections to the thalamic nuclei, which are further

relayed to the neocortex. The neocortex then sends motor information to the cerebellar cortex via the pontine nuclei. Figure adapted from the text of Schutter & Van Honk, 2005a.

1.2.Cerebellum in emotional processing

There are a few principles as to why the cerebellum may have more functions than previously thought. In 1998, Schmahmann and Sherman reported that patients suffering of cerebellar tumors show affective and cognitive problems. Lesions to the lateral/posterior cerebellum and the cerebellar vermis were associated with cognitive abnormalities and comorbidity with mood disorders, respectively (Schmahmann & Sherman, 1998). This discovery led to the *"Cerebellar Cognitive Affective Theory",* which involves the cerebellum as a structure important in emotional and behavioural control. Over the years, additional studies have confirmed Schmahmann and Sherman's findings and it was pinpointed that the cerebellum is also involved in mood disorders (Adamaszek et al., 2016; Clausi et al., 2019; Depping et al., 2018; Frodl et al., 2008; Pillay et al., 1997; Schmahmann & Sherman, 1998; Schutter & Van Honk, 2009; Van Overwalle et al., 2020; Wagner & Luo, 2020).

However, there are also other multiple factors to consider that pinpoint the involvement of the cerebellum in emotional processing or higher-order functioning. Firstly, the cerebellum evolved in tandem with the cerebrum, and therefore it can be expected that during this evolution a connection has developed between the two (Whiting & Barton, 2003). The cerebellum is generally considered *'archaic'* compared to the cerebrum. However, as their functions and structure evolved together, it can be expected that the human cerebellum could have a greater cognitive function. It is also important to mention that the cerebellum contains 80% of the total neurons in the brain, denoting a high processing power (Barton & Venditti, 2014; Van Essen et al., 2018). Secondly, the size of the cerebellum can be correlated with cognitive afflictions, as a lower size of the cerebellum has been correlated with depression episodes (Abe et al., 2010; Pillay et al., 1997). Thirdly, the cerebellum has monosynaptic connections to the thalamus and therefore could play a role in mediating homeostatic control (Schutter, 2012; Whiting & Barton, 2003). And finally, the cerebellum was linked with neuropsychiatric disorders such as depression, bipolar disorder, schizophrenia, autism, ADHD, and PTSD (Adamaszek et al., 2016; Fatemi et al., 2005, 2004; Peng et al., 2013; Pillay et al., 1997; Shun-Chin et al., 2022; Vasic et al., 2009; Wang et al., 2016). Therefore, the cerebellum has become a structure of interest and the neurobiological field is assessing its involvement in higher-order functions than before.

2. Major Depression Disorder

2.1. Symptomology

Major depression disorder (MDD) is one of the most common mood disorders, that affects almost 5% of the population (WHO, 2023). MDD can occur acutely (single-time occurrence) or chronically (recurring more than twice) and its symptoms include a decrease in cognitive abilities such as concentration, low energy or fatigue, sleep disturbances, hopelessness, feelings of guilt, as well as suicidal ideation (Akiskal & Van Valkenburg, 1994; Liu et al., 2021, WHO, 2023). It is particularly dangerous due to its link to suicidal ideation, as more than half a million individuals lose their life to suicide every year (WHO, 2023). The patients suffering from MDD also report low motivation and a *'numbness'* or psychomotor retardation leading to the inability to carry out normal day-by-day function (Buyukdura et al., 2011). Additionally, MDD can lead to comorbidities such as cardiac disease and diabetes (Krishnan & Nestler, 2008). MDD symptoms can be debilitating for the patients, ultimately having a big impact on their and their family's well-being as well as on society and the healthcare economic system as a whole (Clausi et al., 2019; Dean & Keshavan, 2017). As a result, a large effort is being put into finding out the biological mechanisms of depression and developing successful treatments for the patients.

2.2.Depression mechanism

Depression occurs because of an amalgamation of biological, psychosocial, and environmental factors. (Dean & Keshavan, 2017; Jeon & Kim, 2016). Due to the heterogeneity of symptoms and the lack of neurological diagnostic tools available, the exact cause and risk factors through which it develops are still not entirely understood (Dean & Keshavan, 2017; Krishnan & Nestler, 2008). However, a great effort is being placed into identifying the neurological mechanisms behind MDD. To date there are several theories for its functioning, including the hyperactivity of the HPA stress pathway, monoamine neurotransmitter imbalances, genetic predisposition, inflammation, and dysregulation of neural networks (Dean & Keshavan, 2017; Jeon & Kim, 2016; Krishnan & Nestler, 2008; Nestler et al., 2002; Schutter, 2012).

One of the main mechanisms proposed for the development of MDD is the monoamine hypothesis of depression (Kaltenboeck & Harmer, 2018; Krishnan & Nestler, 2008). This mechanism got proposed due to the *'monoamine theory of depression'* that suggests that depression occurs due to decreased levels of monoamine neurotransmitters in the brain (i.e. dopamine, serotonin and norepinephrine), with an emphasis on serotonin (Krishnan & Nestler, 2008; Moncrieff et al., 2022). Back in the 1960s, it was proposed that decreased levels of

serotonin are linked to depressive disorders, and this has been the basis for serotonin reuptake inhibitors being used as a main antidepressant therapy (Moncrieff et al., 2022). However, despite the lower levels occurring in some patients, it is not the case for every patient (Moncrieff et al., 2022). Recently, several MDD patients were found with increased serotonin levels, and animal setups show that the use of antidepressants can also decrease serotonin levels, which questions the serotonin theory of depression (Moncrieff et al., 2022). Nonetheless, monoamine reuptake inhibitors are routinely prescribed, as they work in a subset of patients (Berton & Nestler, 2006).

The second proposed mechanism of depression is based on neuroendocrine imbalances. Studies have found a particularly important relationship to the HPA axis involved in stress control (Figure 3)(Krishnan & Nestler, 2008; Nestler et al., 2002; Schutter, 2012). It was found that about 50% of patients suffering from depression have increased serum cortisol levels denoting an aberrant hyperactivation of the HPA axis (Nestler et al., 2002). Moreover, stress has also been related to an increase in depression-like symptoms in rodents (Krishnan & Nestler, 2008). The hyperactivation of the HPA axis can cause additional health issues, as it is linked with many bodily dysfunctions from diabetes to cardiac disease (Krishnan & Nestler, 2008). The hypothalamus is the main structure involved in homeostatic control, and the overactivation of the axis could affect proper hypothalamic function, leading to possible dysfunctions in other biorhythm functions (Schutter, 2012). Internal homeostasis changes such as alterations in eating and sleep patterns that are overseen by hypothalamic function are also decreased in depression patients (Liu et al., 2021). Depression can be considered as a maladaptive mechanism due to increased stress on the system (Schutter, 2012). Furthermore, it has also been proposed that some of the cognitive abnormalities, such as memory issues, could occur due to the prolonged activation of the axis (Nestler et al., 2002). One of the proposed reasons for the cognitive impairment is that HPA hyperactivation leads to an increase in cortisol, which could be toxic to the hippocampus (Nestler et al., 2002). The hippocampus is also an important structure in the regulation of the HPA axis as it sends inhibitory signals to the hypothalamus via the fornix (Schutter, 2012). Moreover, it was shown that dysfunction in the hippocampus leads to a dysfunction in the HPA axis by promoting increased cortisol production and further propagating the axis (Schutter, 2012). This theory could explain the hippocampal structural alterations observed in some patients as well as some of the cognitive inabilities. However, it remains unknown whether the hyperactivation of the HPA is one of the main causes of depression or just a secondary mechanism resulting from the initial cause (Nestler et al., 2002). Nonetheless, the presence of increased serum cortisol levels became a

biological biomarker of depression at least in a subset of patients (Schutter & Van Honk, 2005a).

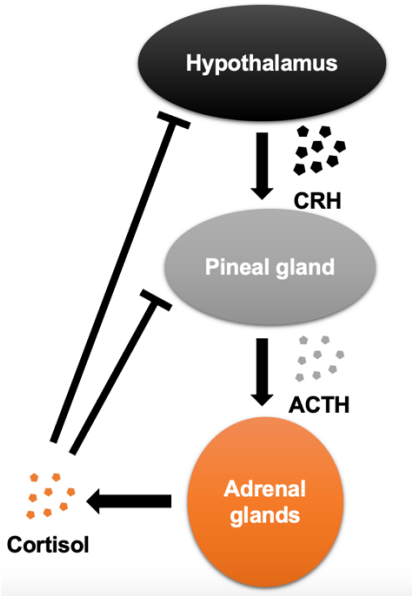

Figure 3. Schematic of the HPA stress axis. The main three components of the represented axis are the hypothalamus, pineal gland, and adrenal glands. The hypothalamus secretes cortisol-releasing hormone (CRH), which in turn binds to receptors on the pineal gland leading to the secretion of adrenocorticotropic hormone (ACTH**)**. ACTH then binds to receptors on the adrenal glands in the kidneys and produces the release of cortisol. Cortisol is a glucocorticoid product that is produced in conditions of stress. The pathway comprises of a feedback loop, as cortisol can inhibit the hypothalamus and pineal gland from further producing CRH and ACTH, thus inhibiting the HPA pathway. Figure adapted from Schutter, 2012.

There is also a structural level of abnormalities seen in MDD patients, such as a decrease in gray matter, as well as decreased glial cell density in cortical areas and the hippocampus (Krishnan & Nestler, 2008). Other causes such as genetics, epigenetics, and the brain-gut connection are also researched, but these will not be further discussed in this paper, as despite many potential candidates, no particular targets or genes have been identified to be relevant to the vast majority of MDD patients (Berton & Nestler, 2006; Kraus et al., 2019; Krishnan & Nestler, 2008). And lastly, correlations with other hormones have been made, such as melatonin, which could denote the disturbed sleep patterns reported by MDD patients (Kaltenboeck & Harmer, 2018). Inflammation and cytokine aberrations have also been explored (Kaltenboeck & Harmer, 2018).

The above-mentioned dysfunctions have all been identified in multiple studies and they may all be in part responsible for the development of depression; however, the research of new targets and possible mechanisms is imperative in other to ensure a good understanding of the biological basis of the disorder and to develop proper clinical treatments.

2.3.Depression treatments

MDD is a complex mood disorder and the diagnostic methodology to date largely consists of identifying the symptoms experienced by the patients via psychological evaluation (Krishnan & Nestler, 2008). The diagnostic tools used are very subjective and do not provide biological information about the patient (Krishnan & Nestler, 2008). Therefore, because of the diagnostic methodology combined with the heterogeneity of symptoms and risk factors for developing the disorder, the therapeutical interventions are given on a case-by-case basis and in many cases must be revised after a few months (Krishnan & Nestler, 2008). Nonetheless, there are a variety of treatments available to date, all of which help a subset of patients suffering from MDD.

There are multiple areas involved and multiple possible therapeutic targets. They include electroconvulsive therapy (ECT), psychotherapy, cognitive behavioural therapy, and pharmacotherapy (Berton & Nestler, 2006; Krishnan & Nestler, 2008). As there are various levels of action, there are multiple pharmacological interventions that can be done. The most common medicines prescribed either inhibit the monoamine neuronal reuptake (e.g. SSRIs) or inhibit monoamine degradation (e.g. monoamine oxidase inhibitors) (Krishnan & Nestler, 2008). This can be related to the *'monoamine theory of depression'* which states that the monoamine concentrations in the brain are decreased for MDD patients (Moncrieff et al., 2022). Monoamine reuptake inhibitors such as SSRIs work by increasing the level of serotonin in the brain. This is because it was initially thought that depression is a low serotonin disorder (Moncrieff et al., 2022). That has since been questioned, as a small subset of patients have been found to have larger levels of serotonin compared to controls (Moncrieff et al., 2022). Moreover, the use of SSRIs treatment especially has its downsides, as it shows unpleasant and even dangerous side effects, such as insomnia, sexual dysfunction, and an initial increase in suicidal ideation, which could be life-threatening (Campos et al., 2021)**.** Moreover, less than 50% of the patients show remission (Berton & Nestler, 2006). All in all, the treatments to date can be effective for subsets of patients, but they do have serious side effects and the remission rate is relatively low. As an additional potential treatment, there are now clinical trials for the use of ketamine which seems to work well on low-grade depression and suicidal ideation, with fewer reported side effects (Karrouri et al., 2021). Nonetheless, despite the large array of

possible treatments, there are no universal pharmacological interventions that work for all depression patients, and the side effects and low remission rates denote the need for better therapies. Therefore, it is imperative to assess our current models of depression and find improved therapeutical interventions.

2.4. MDD connection to the Cerebellum

The role of the cerebellum in depression can be linked back to the discovery that the cerebellum may be involved in emotion and cognition. Structurally, MDD patients have a lower cerebellar volume and white matter abnormalities (Abe et al., 2010; Peng et al., 2013; Pillay et al., 1997). Functionally, the areas most involved in depression according to resting-state imaging data that show dysfunction and structural abnormalities are the pallidum, putamen, caudate, hippocampus, amygdala, thalamus, cingulate gyrus, insula, prefrontal cortex, and limbic system (Dai et al., 2022). Additionally, a correlation has been made between the abnormal activity in the cerebellum and decreased mood and depression symptoms, due to cerebellar damage patients displaying depression symptoms (Clausi et al., 2019). These symptoms have shown improvement upon cerebellar stimulation (Ferrari et al., 2021; Newstead et al., 2018; Schutter & Van Honk, 2009). Further cerebellar neurostimulation research correlated cerebellar activation with emotional and cognitive affects, such as emotional recognition and the ability to identify with negative moods (Adamaszek et al., 2016; Ferrari et al., 2021). And finally, the motor retardation symptoms displayed by MDD patients could be in part explained by a dysregulation in the motor areas of the cerebellum (Liu et al., 2021). Therefore, the cerebellum may play an important role in the development of depression. Another proposed theory would be its potential regulation of the HPA axis, known to play a role in depression (Schutter, 2012).

Overall, depression is a very complex disorder, and to date, a full overview of the way it develops has not been reached. However, there are multiple factors involved in the development and progression of the disorder. A continued effort should be made to identify all the major players in the disorder and based on the informative research in the last three decades, the cerebellum may be one such major player to be considered.

3. Cerebellar Structural Studies in MDD

The cerebellum involvement in emotional processing and mood disorders can be investigated in part via structural studies, assessing anatomical and volumetric differences observed in the brains of patients compared to controls. Several studies identified the cerebellum as being one of the areas affected in MDD patients, through significant decreases

in cerebellar volume and white matter abnormalities (Depping et al., 2020; Frodl et al., 2008; Kraus et al., 2019; Nestler et al., 2002; Peng et al., 2011).

3.1.Smaller cerebellar volume in MDD

Gray matter density can be used to assess structural differences in healthy controls compared to patients. Several studies have correlated a decrease in gray matter to the presence of MDD especially in the hippocampus, amygdala, and prefrontal regions (Frodl et al., 2008; Krishnan & Nestler, 2008; Nestler et al., 2002). The hippocampal decrease is even proposed as a biomarker for depression (Kraus et al., 2019). Therefore, structural abnormalities are routinely assessed to find a correlation with disease.

Analysis of the whole brain shows that another particularly affected area is the cerebellum, especially on the posterior left side (Frodl et al., 2008). The gray matter density is decreased for the cerebellum in MDD patients but not in healthy controls (Depping et al., 2020; Frodl et al., 2008; Peng et al., 2011). The finding was corroborated by a voxel-based morphometry (VBM) study performed by Peng et al, who identified a significant decrease in gray matter density in the left cerebellum of first-time MDD patients (Peng et al., 2011). They have found a significant decrease in the left cerebellum of patients compared to controls.

In more recent years, Depping et al. 2020 have also found a decrease in the cerebellar volume of MDD patients showing cognitive deficits (Depping et al., 2020). The significant decrease in volume was especially observed in lobule VII (Depping et al., 2020). Lobule VII has non-motor connections to the cerebral cortex and is believed to be important in cognition (Bogoian et al., 2020). As a result of the finding, Depping proposes that lobule VII may be a viable candidate for TMS therapy in MDD patients (Depping et al., 2020). Additionally, an increase in the size of the vermis VI and VIII was found in depression patients with higher severity of symptoms. Cerebellar vermis areas VI and VIII have been associated with emotional processing, vermis VI being associated with the salience network, and vermis VIII having strong connections to the amygdala (Bogoian et al., 2020; Habas, 2018). Additionally, a decrease in lobule VIII was found bilaterally in a successive study in patients suffering from non-cognitive symptoms, possibly suggesting that an increase occurs for cognitive symptoms to act as a cognitive compensation mechanism (Depping et al., 2020).

Therefore, there are structural changes observed in the volumes of cerebellar gray matter in patients suffering from depression compared to controls. The studies presented however have small sample numbers and cannot yet be extrapolated to the whole population. However, as multiple research papers have pinpointed a significant difference in cerebellar

volume, this is likely the case for at least part of the patients, and it could explain some of the symptoms displayed.

3.2.White matter abnormalities

White matter abnormalities have been correlated with recurrent depression, especially in the prefrontal cortex and amygdala. Low fractional anisotropy (FA) in frontal lobes and higher FA values between the raphe and amygdala have been previously correlated with depression, denoting that there may be axonal aberrations either casing or as a result of MDD (He et al., 2022; Peng et al., 2013). Low FA values are generally related to poor white matter structure and poor connectivity (Zhai et al., 2020). Voxel-based analysis of DTI was also performed in the cerebellum and the results showed a significant decrease in FA in the right cerebellar lobe (Peng et al., 2013). In an additional study using voxel-based analysis an increase in mean-diffusivity was observed in the cerebellum of depression patients compared to healthy controls (Abe et al., 2010). Increased mean diffusivity is also correlated with poor connectivity (Zhai et al., 2020). However, not all studies find a significant alteration in white matter in depression (He et al., 2022). He et al. state that white matter abnormalities are significant in schizophrenia and bipolar but not depression in cerebellar areas and that this difference could diagnostically distinguish the disorders (He et al., 2022).

Nonetheless, the white matter abnormalities could pinpoint to a dysfunction in the connectivity of the cerebellum with the rest of the brain. Disrupted connectivity is not necessarily a cause of depression, however, reported alteration in patients pinpoint to disruption in the normal functioning of the cerebellum.

4. Cerebellar Functional Studies in Emotion and Depression

4.1.Functional imaging

Functional cerebellar differences have been reported in a few cases for patients suffering from depression (Dai et al., 2022; Depping et al., 2018, 2020; Diedrichsen et al., 2019; Helm et al., 2018; Zhu et al., 2020). Meta-analysis data assessing the resting state connectivity at the level of the entire brain have pinpointed the areas most affected in MDD patients. The most affected structures are the orbitomedial prefrontal cortex, anterior cingulate cortex, amygdala, hippocampus, basal ganglia, and the cerebellum (Helm et al., 2018; Kraus et al., 2019; Krishnan & Nestler, 2008). The initial studies performing functional imaging did not look at the cerebellum, however, in the available data analyzed in the systemic reviews, the cerebellum appears as an area with increased connectivity (Diedrichsen et al., 2019; Helm et al., 2018). However, resting state connectivity has shown that the neocortex and cerebellum are

functionally connected, pinpointing to stronger communication or the presence of feedback loops (Diedrichsen et al., 2019). Abnormal functional connectivity was observed especially with the neocortex, affective limbic system, and the default mode (DNM) and frontoparietal function networks (FNM) (Dai et al., 2022; Depping et al., 2018; Wang et al., 2023; Zhu et al., 2020). There was a noted altered effective connectivity (EC) in resting state fMRI (rs-fMRI) in the neocortex-cerebellum and cerebellum-basal ganglia circuits in patients versus controls (Dai et al., 2022). One study observed increased EC for patients from the lobule X in the right cerebellum and the left lobule VIIB to the neo-cortex. An increase in EC was also noted from the lobule VIII vermis to the thalamus, neocortex, and basal ganglia (Dai et al., 2022). There was also a general decreased connectivity recorded between lobule VII to the cortical cognitive components in MDD (Depping et al., 2018). The particular areas of altered connectivity are structures of the DMN and FPN, denoting connectivity changes at resting state (Dai et al., 2022; Depping et al., 2018). Additional areas of interest where functional connectivity was altered was a decreased connectivity between the cerebellum, neocortex, and limbic structures (Zhu et al., 2020). Limbic structures are important in emotional processing and fear, which could explain some of the decreased motivation and negative emotions experienced by MDD patients (Wang et al., 2023; Zhu et al., 2020)**.** However, these differences in connectivity are observed in the FPN during the participation of active tasks but not at rest. Dichter et al, 2012 found that following an MDD episode, patients show an increase in cerebellar activation as a result of reward prediction, but a decrease as a result of the reward outcome (Dichter et al., 2012). Additionally, a decrease in RSFC between the habenula and cerebellum in MDD was reported (Jung et al., 2022). The habenula is an area of the brain associated with reward processing, which could explain in part the abnormal reward prediction in MDD patients (Dai et al., 2022; Jung et al., 2022). Therefore, the functional dysconnectivity between the cerebellum and reward pathways pinpoints to the possibility of a regulatory role of the cerebellum in the reward prediction mechanism.

Dysconnectivity between the cerebellum and frontal attention network was also observed in a recent study, assessing adolescent patients suffering from MDD and ADD as well as healthy controls (Shun-Chin et al., 2022). The frontal attention network is of importance in a variety of neuropsychiatric disorders, including ADHD and depression. The recorded dysconnectivity could be involved in the attention and mood issues observed in patients. (Shun-Chin et al., 2022).

Overall, significant connectivity abnormalities were reported between the cerebellum, frontal cortex, and limbic system in patients suffering from MDD compared to healthy

participants. These studies denote that the communication between the cerebellum and high-order structures is of importance either in the development of the disorder or as a result of its presence. This is especially the case for the connection between the cerebellum and the main working networks i.e. FNC, CCN, and DMN. However, it is unknown whether the disrupted communication with the cerebellum is a main cause of depression, a result of the disrupted communication in cortical areas, or as a compensatory mechanism to alleviate some of the depression symptoms.

4.2. Stimulation studies

Neurostimulation is a technique that allows the invasive and non-invasive modulation of brain activity, which can give important insight into the functions of different brain areas (Schutter & Van Honk, 2005a). Invasive neurostimulation performed in the past has given insight into the relation between the cerebellum and MDD (Heath et.al, 1980). A significant intracranial electric stimulation study on the involvement of the cerebellum in emotion was done in 1980. Heath et al. discovered that the stimulation of the cerebellum leads to activation in emotional centers of the brain (i.e., amygdala and hypothalamus) and that an improvement is seen in behavior and emotion following stimulation (Heath et al, 1980). Heath's studies were the first to link emotion to the cerebellum and the first to attempt behavioural change through the stimulation of the cerebellum (Ponce et al., 2022).

However, recently, non-invasive techniques such as TMS and tDCS can be used more frequently as they allow for the safe and ethical studying of functional neuroanatomy (Ponce et al., 2022). TMS works by generating electric current via a magnetic field. It works by placing a coil or a wire on the brain and applying electric current to it (Schutter & Van Honk, 2005a). When this happens, the generated magnetic field pulsates, depolarising the nerve tissue (Schutter & Van Honk, 2005a). The use of low-frequency TMS bursts, or repetitive TMS (rTMS) can lead to neuronal inhibition (Schutter & Van Honk, 2005a). Alternatively, using high-frequency rTMS can lead to neuronal excitation. In this way, rTMS can be applied to specific cortical areas via the scalp, and either excite or inhibit subsets of neurons, to observe whether there are any changes in behavioural and emotional responses displayed by the patients or participants (Schutter & Van Honk, 2005a). In a pilot study, Schutter et al. showed that applying rTMS over the medial part of the cerebellum leads to an increase in mood and alertness (Schutter et al., 2003). A further study found that cerebellar inhibition with TMS leads to the inability to downregulate emotions as well, resulting in an increased negative affect

compared to control sham stimulation (Schutter & Van Honk, 2009). Alternatively, excitatory stimulation leads to better processing of positive emotional stimuli (Ferrari et al., 2021).

An alternative non-invasive stimulation technique is tDCS. tDCS uses the same methodology of selectively exciting or inhibiting targeted areas of the brain via the scalp. The use of tDCS stimulation over the frontal cerebellar area led to similar reported increases in mood as seen with TMS (Newstead et al., 2018).

Overall, inhibitory TMS decreases cerebellar activity and leads to the inability to regulate emotion and a more negative mood; whereas excitatory TMS leads to an increase in improved mood and a decrease in depression symptoms (Schutter, 2012).

5. Cerebellar Molecular Studies in Emotion and Depression

Aberrant gene expression can be correlated with disease and negative affect (Zhang et al., 2021). In the case of the cerebellum's involvement in depression, several studies have identified abnormal gene expression in the cerebellum of patients suffering from MDD compared to healthy controls (Fatemi et al., 2005, 2004).

Postmortem brain analysis showed that both glutamic acid decarboxylase (GAD) and Relin were found to be significantly decreased in the cerebellum of MDD patients (Fatemi et al., 2005). GAD is an enzyme responsible for the conversion of glutamate to GABA to ensure the correct levels of the two neurotransmitters in the brain (Fatemi et al., 2005). Relin is an extracellular matrix protein important for the development of the embryonic brain and also plays a role in synaptic plasticity later on in adulthood (Fatemi et al., 2005). Both proteins are significantly decreased in the cerebellum of patients compared to controls ($P<0.05$) (Fatemi et al., 2005). This can denote abnormal neuronal communication in the cerebellum of affected patients. Another aberrant gene expression was observed for the Glial fibrillary protein (GFAP) in the cerebellum (Zhang et al., 2021). GFAP is released by astrocytes and is involved in proper neuronal signaling. GFAP was significantly decreased in the cerebellum of MDD patients in post-mortem studies (Fatemi et al., 2004). Abnormal GFAP can signify abnormal neuronal transmission and synaptogenesis, which can be a sign of neuropathology (Zhang et al., 2021). However, GFAP may be a structure of interest, as altered GFAP expression has also been identified in post-mortem studies in the cerebral cortex (Zhang et al., 2021).

The molecular data available on the relationship between the cerebellum and MDD is only at its initial stages. Similar gene expression deregulations are observed in the cerebellum, as in the cortical areas of interest. Therefore, it cannot be stated whether the abnormal gene expression starts at the level of the cerebellum, or it is only as a result of the spread of the

disorder, and overall dysfunction of the system. However, given that these differences are not seen in all brain areas, it still pinpoints to the cerebellum as a structure of interest in MDD.

Overall, the multitude of studies performed in the last three decades have shown the possible involvement of the cerebellum in depression disorders, via imaging techniques, stimulation, and molecular testing. They all give pieces of insight into the involvement of the cerebellum with MDD and allow for a better overview of the disorder, as well as the creation of cerebellar MDD models and theories, which will be further addressed in the discussion.

6. Discussion

6.1.Theories of the cerebellar involvement in depression

There is an increased amount of data that shows the involvement of the cerebellum in emotion and cognition(Adamaszek et al., 2016; Schmahmann & Sherman, 1998; Schutter & Van Honk, 2005b; Shun-Chin et al., 2022; Van Overwalle et al., 2020). Numerous studies have been done in the last few years that show the potential role of the cerebellum in MDD(Clausi et al., 2019; Depping et al., 2018, 2020; Fatemi et al., 2004; Rizvi & Khan, 2019; Schutter & Van Honk, 2005a). However, most of these studies have been performed on small samples, and overall, the field is still relatively young and needs more research. Nonetheless, the cerebellar contributions must be considered as a potential addition to current depression models. Based on the available structural, functional, and molecular abnormalities observed in the cerebellum in depression patients a few theories have emerged.

A proposed theory of cerebellar involvement in MDD is that it could be a regulatory structure of the HPA axis, forming the cerebellar-HPA axis (Figure 4) (Schutter, 2012). The hypothesis is based on the presence of the monosynaptic projections between the cerebellum and the hypothalamus, as well as the high concentration of glucocorticoid receptors (GR) receptors on the cerebellar cortex to which cortisol can bind (Schutter, 2012). It is hypothesized that the monosynaptic connections between the cerebellum and hypothalamus, together with the GR receptors in the cerebellum, allow for a feedback mechanism that feeds information about the HPA axis status to the hypothalamus (Schutter, 2012). If the hypothesis is correct, and the cerebellum has a direct link to the HPA axis, disruptions in the stress pathway could be mitigated via the stimulation of the cerebellum through techniques such as TMS (Schutter, 2012).

The link to the HPA axis can be further hypothesized through the cerebellar similarities to the hippocampus of MDD patients (Frodl et al., 2008). There is a reported hippocampal decrease in MDD patients, which has been theorized to occur due to the toxicity of cortisol

(Nestler et al., 2002). Similarly, the cerebellar volumetric decrease could potentially occur for the same reason. If this is the case, the decrease in volume could also be a potential signaling of the aberrant HPA axis, pointing to depression or other mood and neuropsychiatric disorders. Furthermore, the cerebellar vermis has the most glucocorticoid receptors in development, even more than the hippocampus, and that makes it a possible target for the stress hormones such as cortisol (Frodl et al., 2008). As vermal lesions have been related to neuropsychiatric disorders, this connection should be further examined in future setups (Peng et al., 2013; Purves et al., 2001).

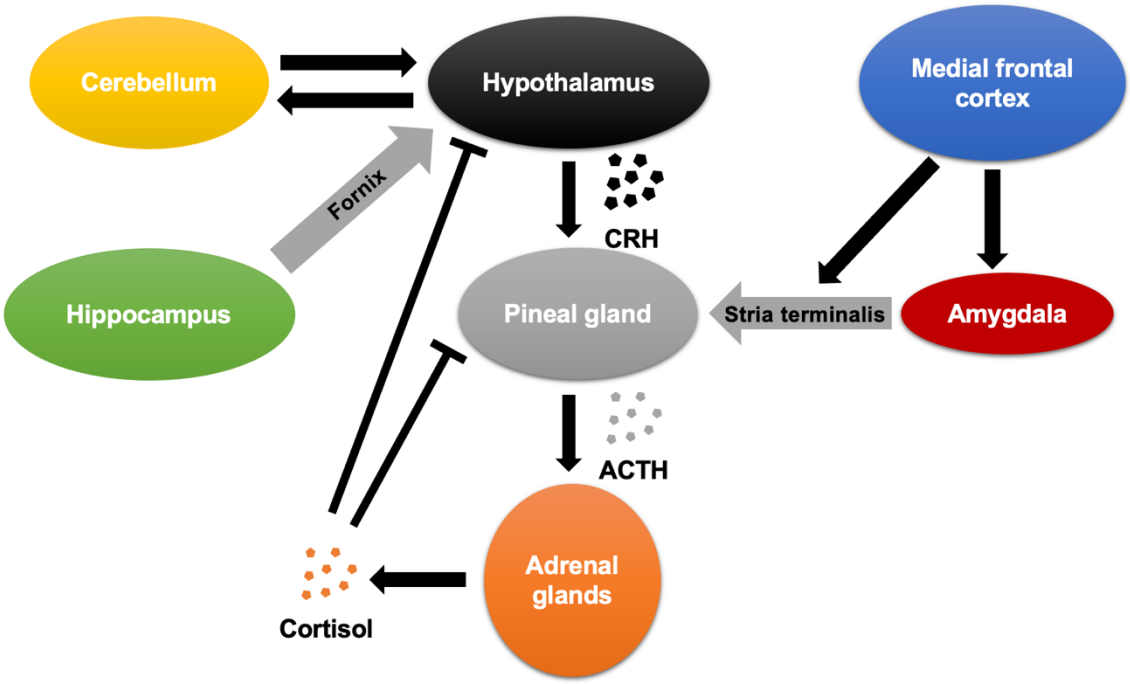

Figure 4. Cortico-Limbic-Cerebellar-HPA axis. The above axis contains the cerebellum as a potential regulatory structure. The cerebellum modulates the HPA axis via projections to the thalamus, therefore increasing or decreasing the activation of the stress pathway. The figure contains the contributing projections from the hippocampus and amygdala to the hypothalamus and pineal gland, which can also regulate the amount of hormone released by each structure. The medial prefrontal cortex receives information on the state of the HPA axis from the hypothalamus The medial prefrontal cortex then projects to the amygdala and the stria terminalis to regulate its input to the pineal gland. *White matter tracts Fornix and Stria terminalis are denoted in larger gray arrows. Figure adapted from Schutter, 2012.

Structural differences are important as they can give a possible objective diagnosis criterium for depression (He et al., 2022). The white matter abnormalities presented denote that there is a disruption in cortico-cerebellar and limbic-cerebellar communication in at least a subset of patients. Important values to assess are low FA and high MD values, which have been correlated with poor connectivity and decreased motor function (Zhai et al., 2020). It would be noteworthy to assess whether the perceived dysfunction is particularly visible in the patients suffering from more pronounced psycho-motor retardation symptoms of depression. Alternatively, Peng et al. 2013 propose that abnormalities in white matter tracts between the cerebellum and the prefrontal cortex play an important role in depression and they may be involved in the resistance to current depression treatments (Peng et al., 2013). Peng et al performed a voxel-based analysis of DTI data of patients suffering from treatment-resistance depression. They have identified low FA in the left middle frontal gyrus, left limbic lobe uncus, and the right cerebellum posterior lobe (Peng et al., 2013). The observed connection between the cerebellum and the prefrontal cortex was observed simultaneously. They propose that the aberrant connectivity leads to an even higher decline in cognitive function and the decline leads to resistance to treatment (Peng et al., 2013). This is especially as higher depressive symptoms led to lower FA scores, supporting the theory that the poorer the white matter integrity, the lower the cognitive performance and impact of the disorder (Peng et al., 2013). Overall, structural studies can give important insight into the district changes that can be observed between patients and controls, which can help elucidate important structures in the development of depression.

The connection of the cerebellum with the limbic system, and especially the amygdala, is also an important factor to assess (Habas, 2018). The amygdala is part of the limbic system associated with fear and emotional processing (Habas, 2018; Schutter, 2012). Connectivity was reported between lobules VI, VIII, and the basolateral amygdala, showing a decrease in cerebellar mass (Habas, 2018)**.** Therefore, a larger attention should be placed on the subsystems of the cerebellum. Despite the division into the cerebellar functional system, the lobules and vermis area of the cerebellum seem to be specialized. Lobule VII is particularly important in non-motor function, and it communicates with the cortical areas (Depping et al., 2018)**.** The vermis is also considered a structure of interest, as vermal lesions can cause neuropsychiatric disorders (Peng et al., 2013; Purves et al., 2001). Further approaches could potentially combine stimulation and imagining techniques such as TMS and PET to see the clear activation differences in the emotional centers of the brain. Further repeating studies of the activation of the hypothalamus and amygdala because of cerebellar stimulation could further pinpoint to the

involvement of the cerebellum in the HPA axis, therefore offering an additional target for the treatment of depression.

It is becoming clear that the cortico-limbic circuit is a major part in the development of MDD (Peng et al., 2011). However, the cortico-cerebellar circuit should also be looked at as a possible important player. Cerebellum lesions lead to executive function disturbances, similar to what would be experienced in prefrontal cortex regions such as lack of control and inadequate planning (Peng et al., 2011; Schmahmann & Sherman, 1998). The cerebellum projects contralaterally to the DLPFC. There are cortical regions that also projects back to the cerebellum, forming a prefrontro-cerebellar neuronal circuit (Peng et al., 2011). The communication between the two regions could be a major part in the cerebellum's involvement in higher-order processing (Peng et al., 2011). An increase in activity was observed between the dorsolateral prefrontal cortex and the cerebellum in MDD patients when performing working memory tasks (Vasic et al., 2009). Additionally, this increase was also reported in patients with high levels of anhedonia (Zhu et al., 2020). Vasic et al. and Zhu et al. hypothesize that the connectivity between the DL-PFC and the cerebellum may be used as a compensation mechanism to optimize cognitive performance in MDD patients (Vasic et al., 2009; Zhu et al., 2020).

Overall, the cerebellum may play an important role in depression development. However, it is likely that cerebellum models of MDD could only work in a subset of patients. Nonetheless, offering an alternate possibility for the treatment of depression would be favorable. Moreover, further research into the involvement of the cerebellum in depression would contribute additional information on the depression mechanisms as a whole and therefore aid the elucidation of the depression mechanism.

6.2.Cerebellum as a target for therapies

There is a pressing need for better depression treatments with fewer side effects and higher remission rates. The cerebellum could be potentially used in MDD diagnostic tools or as an additional target for current treatments. To date, a critical factor in the remission rates of depression is early detection (Kraus et al., 2019). However, the current diagnostic tools available cannot always detect the disorder at its initial stages. There is a need for better-developed diagnostic tools that could not only catch the disease faster but also offer an objective view (Kraus et al., 2019). The use of biomarkers of depression could resolve this issue (Kraus et al., 2019). Biomarkers have the advantage of potentially identifying different subsets of depression that can then be better targeted. The need for biomarkers and enhanced diagnostic tools is high as early detection is extremely important in depression outcomes based

on the current pharmacological interventions (Kraus et al., 2019). There are a few proposed biomarkers of depression such as cortisol, hippocampal size, brain-derived neurotrophic factor (BDNF), and inflammatory markers like interleukin-6. (Kraus et al., 2019; Schutter, 2012). Similar biomarker propositions have been made about the cerebellum, by looking at its structural and functional imagining characteristics seen in MDD patients. One proposed biomarker can be the volumetric difference seen in the cerebellum, with an emphasis on the areas of interest i.e. lobule VI, VII, VIII, and the vermis (Bogoian et al., 2020; Depping et al., 2020; Habas, 2018; Schmahmann & Sherman, 1998). For now, the studies in which the data was gathered contained small sample sizes and cannot yet be extrapolated. However, for the structural changes to become accurate biomarkers, the perceived volumetric decrease should be present in the vast majority of MDD patients. Moreover, it would have to be clearly localized to subsets within the cerebellum. If that occurs, it will allow for better and more personalized depression treatments.

The optimal proposition for treatment at this moment would be the use of excitatory cerebellar TMS as a treatment option to increase good mood and ameliorate some of the negative effects of depression. It was shown that the application of TMS over the parietal cortex, that is disrupted during depression episodes, leads to a decrease in depressive symptoms. (Schutter & Van Honk, 2005a). TMS is non-invasive and has already been shown to increase mood, acting like an antidepressant when applied over the PFC (Rizvi & Khan, 2019). The remission rates following TMS are still relatively low (less than 50%), but that is similar to what is experienced with general antidepressants (Rizvi & Khan, 2019). However, it has the added benefit of having fewer reported side effects. As similar results have been seen following TMS application on the cerebellum, this can be used as a treatment option. Ideally, a combined treatment option with PFC and cerebellar stimulation could work to potentially increase the effect of the treatment.

Additionally, sport and movement should be another recommended therapy, as many MDD patients suffer from psychomotor retardation (Buyukdura et al., 2011). The practice of sport and movement has been shown to promote recovery in MDD patients (Buyukdura et al., 2011; Krishnan & Nestler, 2008). Furthermore, the impact of movement on cerebellar aberrations could be a noteworthy observation.

Depression is a very heterogeneous disorder; therefore, it is unlikely that there will be a universal treatment option available. However, efforts should be unified to increase remission rates while decreasing side effects. More objective diagnostic criteria, as well as identification of the predominant neurological dysfunction for each patient should be considered. The best-

case development in the near future would be personalized combination treatments. Ideally, the patient could be prescribed a combination of cerebellar and PFC rTMS together with specific pharmacological treatments based on the main predominant neurobiological feature. The patients showing increased cortisol could be given glucocorticoid antagonists, such as mifepristone, whereas patients that show low serotonin levels could be prescribed monoamine oxidase inhibitors (Berton & Nestler, 2006; Schutter, 2012). Additionally, the combination of cognitive behavioural therapy and frequent exercise should remain part of the prescribed tools to better manage depression.

7. Conclusion

There is an increasing amount of data portraying the involvement of the cerebellum in emotion and depression. It becomes clear that the cerebellum does play a role in the development of the mood disorder, but the degree to which it is involved is yet unknown. It is proposed that it could be part of the dysregulated propagation of the HPA stress pathway, by acting as a regulatory center. Alternatively, the cerebellum could be part of the compensation mechanism for taking over some functions of the prefrontal cortex. Nonetheless, more research needs to be performed to identify its exact role to elucidate the biological mechanism of depression and also to allow the development of better clinical possibilities for patients suffering from depression and other mood disorders. Its promising role in the development of depression offers potential new avenues of treatment. To date, it is unlikely that the cerebellum could be a main target for depression therapies. It can however be an additional target that improves treatment results in a subset of patients. Additionally, it can be used as a combined therapy with already existing pharmacological interventions. The most promising cerebellar treatment to date is cerebellar rTMS or tDSC sessions to improve mood and symptoms, while also continuing the prescribed medicine and treatment. Finally, cerebellar volume and abnormal white matter tracts could be used as a depression test at least in a subset of patients, or as a biomarker in the future if the data becomes statically higher. Nonetheless, numerous studies have shown that the cerebellum is involved in emotional and cognitive processing and the structure has been correlated with a variety of neuropsychiatric disorders, denoting it an important structure to further asses to reach an enhanced understanding of the development of such disorders, as well as provide additional treatment targets to improve the lives of the patients.

Word count: ±8056

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