

LATE-LIFE DEPRESSION & ALZHEIMER'S DISEASE

A PROPOSAL FOR THE BI-DIRECTIONAL THRESHOLD MODEL

Does curing one work as a treatment for the other?

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Abstract Until now, the relationships between late-life depression and Alzheimer's Disease (AD) and vice versa have only been investigated in terms of one-directional relationships. However, due to the central neuropathological mechanisms underlying both diseases, it is proposed that the interaction is bi-directional. These mechanisms include the stress-response hypothesis, amyloid hypothesis, inflammatory hypothesis, and genetic hypothesis. By reviewing these shared underlying mechanisms, as well as investigating the evidence for both one-directional relationships, a new model is proposed, namely the bi-directional threshold model. Whereas previous research only focused on one-directional interaction, this model is novel in accounting for the bi-directional interaction between AD and late-life depression. Thereby the model contributes to the literature on late-life depression and AD by serving as a starting point for further research. A better understanding of this new model could have major implications in ameliorating the course of both clinical conditions.

I Introduction

Over 25% of the total population in the United States has reached the age of 65 years or older and with an increasingly ageing population, the prevalence of old-age related diseases increases as well (McCall & Kintziger, 2013). The most well-known types of old-age related diseases are late life depression and dementia, with Alzheimer's Disease (AD) as one of the most common types (Barnes et al., 2012). Due to the enormous societal impact of both diseases, the topic is largely discussed in all disciplines. At this point, research has been directed to the one-directional relationships between late-life depression and AD and vice versa, because of the increased risk of developing the second disease (Maghoub & Alexopoulos, 2016; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006). Although similarities can be found in the pathology of both diseases, no research is directed to a possible bi-directional relationship (Ownby et al., 2006). To close this research gap, this paper investigates the following research question: How do late-life depression and AD affect each other? To do so, the two previously established one-directional relationships are first investigated to answer the following sub-questions: (1) Is late-life depression an early symptom of the prodromal phase of AD or an independent risk factor? and (2) do AD patients develop late-life depression due to the reactive knowledge and having to deal with a life-threatening disease or due to loss of neuronal tissues in mood-related areas? It is hypothesized that late-life depression is both a prodromal symptom as well as an independent risk factor for the development of AD, as a correlation has been found between time of late-life depression onset and developing AD (Ownby et al., 2006). Furthermore, AD is hypothesized to cause late-life depression due to both the reactive knowledge of the disease and due to neuronal loss in mood-related brain regions (Lyketsos & Olin, 2002). First, a theoretical framework for both diseases is provided, followed by a literature review on both one-directional relationships. By means of an analysis of the shared underlying mechanisms involved in the pathology of both diseases, this paper proposes a novel bi-directional threshold model. This new model, proposed for the first time, makes important theoretical contributions by closing the research gap and serving as a basis for further research into the bi-directional relationship and possibly ameliorate the course of both clinical diseases. Furthermore, a better understanding of risk factors for AD and late-life depression could have major implications for the (preventative) care of elderly and its policies.

2 Theoretical framework

2.1 Late-life depression

Late-life depression is defined as having a Major Depressive Episode (MDE), as defined in the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V), for patients over 65 years old (American Psychiatric Association, 2013; Burroughs et al., 2006). Furthermore, late-life depression, as opposed to regular-onset depression, also includes symptoms of mild cognitive impairments (MCI), such as working memory deficits and slowed information processing skills (Butters et al., 2008). The for this article relevant neuropathology caused by late-life depression include the following affected brain regions: the dorsal and medial prefrontal cortex (PFC), the orbital frontal cortex and the anterior cingulate cortex. These areas are involved in emotion regulations and problem-solving tasks. Furthermore, abnormalities of the limbic system are also observed, which is involved in regulation of emotions and reward processing – including the amygdala, hippocampus, and thalamus (Pandya, Altinay, Malone, & Anand, 2012).

Apart from brain abnormalities, other mechanisms found to affect late-life depression include abnormal responses to stress and genetic influences. To date, not one specific genetic abnormality can be identified with certainty as a risk factor for late-life depression. However, it seems depression is caused by a complex phenomenon of many different genetic influences (Nestler et al., 2002). Furthermore, depression is often described as a stress-related disorder. Leszek et al. (2016) found abnormalities in the negative feedback loop of the stress-response for depressed patients, increasing symptom severity. These mechanisms are further explained in the shared underlying mechanisms section of this paper.

2.2 Alzheimer's Disease

AD is one of the most common types of dementia. The disease is progressive and is hallmarked by gradual cognitive decline. The first clinically observable symptoms include memory loss and MCI, before the neurological decline worsens and starts to affect daily life (Lyketsos & Olin, 2002). This paper follows the diagnostic criteria as stated in the DSM-V and only focusses on AD starting after the age of 65 years to be able to investigate the relationship with late-life depression (American Psychiatric Association, 2013). The main affected brain region is the hippocampus, which is involved in short-term memory formation and emotional regulation. Other affected areas include the PFC and frontal lobes, which play a role in memory preservation and decision-making (Mattson, 2004). The neuropathology of AD has several characteristics. First, the amyloid hypothesis states that “accumulation of the amyloid β -peptide ($A\beta$) in the brain is the primary

influence driving AD pathogenesis” (Hardy & Selkoe, 2002, p. 353). These AB peptides cause accumulation of senile plaques, which induces synaptic dysfunction, disruption of neural connectivity and neuronal cell death (Carter & Lippa, 2001). Another important characteristic of AD includes the neurofibrillary tangles (NFTs) found inside the brains cells of AD patients. The NFTs consist of abnormal tau-proteins and affect the transportation of nutrients in the cell, thereby disrupting neuronal communication (Guillozet, Weintraub, Mash, & Mesulam, 2003). Furthermore, similar to depression, abnormalities in the negative feedback loop of the stress-response is part of AD pathophysiology, affecting the PFC and the hippocampal volume in the brain (Leszek et al., 2016). Lastly, AD is largely inherited due to genetic markers (Carter & Lippa, 2001). These mechanisms are further explained in the shared underlying mechanisms section of this paper.

2.3 One-directional relationships

2.3.1 *Late-life depression on Alzheimer’s Disease*

Patients with a history of late-life depression show an increased risk of developing AD. Estimations show a number of 781.000 cases of patients with AD attributed to depression in the US, thereby indicating a one-directional relationship between late-life depression and AD (Diniz, Butters, Albert, Dew, & Reynolds, 2013). To date, it remains unclear whether late-life depression acts as an independent risk factor for AD development or is an early symptom of the prodromal phase (Panza et al., 2010). The time interval between the onset of both diseases could support either one of the two hypotheses. A short time interval between an MDE and AD diagnosis would indicate that late-life depression is a prodromal symptom, whereas a longer time interval would indicate the disease acts as an independent risk factor for AD development (Ownby et al., 2006).

The large-scale family-based case-control study of Green et al. (2003) studied both the prodromal and causative relationship of depression and risk of AD development. The results showed the strongest and most robust causative relationship between depressive symptoms and AD when MDE onset occurred within one year of AD onset. Due to the short time interval between the onset of both diseases, late-life depression is most likely a prodromal symptom of AD. However, the authors also discovered a significant positive relationship for longer time intervals between onset of AD and late-life depression, although less robust. Even for a time interval of 25 years modest, yet significant results were found, indicating that depression is also an independent risk factor for AD development.

The relationship of depression being an independent risk factor for AD has also been studied in terms of neuropathology. First of all, the results of Butters et al.’s (2008) structural magnetic resonance imaging (MRI) study shows how late-life

depression worsened the hippocampal atrophy as compared to early-onset depression, due to damage to the negative feedback loop of the stress-response. Damage to the hippocampus and stress-response results in more depressive symptoms, as well as dysfunctioning of memory formation and MCI. Even after effective treatment of the MDE, many patients still suffer from MCI. Therefore, late-life depression can cause early AD symptoms and thus indicates the pre-dispositional risk for AD development. Secondly, additional support for late-life depression being an independent risk factor for developing AD has been provided by post-mortem studies. AD patients with a history of late-life depression show significantly more amyloid plaques and NFTs in the brain compared to patients without such history. Thus, a direct pathophysiological link is found between late-life depression and AD (Maghoub & Alexopoulos, 2016). Lastly, Wilson et al. (2002) did a follow-up study for late-life depressed patients without a AD diagnosis. Patients were tested with various memory tests and depression scale tests for up to seven years. Their findings include an increased risk of 19% for annual cognitive decline for each additional depressive symptom at base-line. Thus, the more depressive symptoms at base-line, the higher the risk of AD development. Therefore, late-life depression seems to be an independent risk factor for AD.

2.3.2 Alzheimer's Disease on late-life depression

Almost half of all AD patients develop depressive symptoms or MDEs later in life and the prevalence of depression reported for AD patients is between 30% and 50%, compared to only 13% of older patients without cognitive impairment (Farrand, Matthews, Dickens, Anderson, & Woodford, 2016). The increased risk of developing of depression indicates a one-directional relationship which could be due to the reactive knowledge of AD and having to deal with a life-threatening disease, or due to neuropathological effects of AD on mood-related brain regions (Lyketsos & Olin, 2002).

Some arguments in favor of the first hypothesis, that depression is caused by the reactive knowledge of an AD diagnosis, include the psychological and behavioral changes for patients at the start of their diagnosis. Often, they develop a tendency towards isolation, a lack of interest in activities, or even obsessive behavior which is often due to fear of the disease progression and the discomfort one experiences from MCIs (Lyketsos & Olin, 2002). Although this hypothesis could account for a certain percentage of cases, the percentage of AD patients developing depression is significantly higher compared to patient groups of other life-threatening diseases such as cancer (Kállly, Pinteá, & Dégi, 2016; Lyketsos & Olin, 2002). Therefore, the extremely high number of AD patients developing depression can only partly be explained by the reactive knowledge of the disease.

As the reactive knowledge of having AD is most likely not the only contributor to the development of AD-related depression, it is suggested that more factors would have an effect on the development and severity of the depression (Maghoub & Alexopoulos, 2016). Another study investigated and compared the occurrence and severity of depression in different phases of cognitive decline in AD patients. Their results showed that the prevalence of depressive symptoms increase as the level of cognitive decline increase (Bierman, Comijs, Jonker, & Beekman, 2007). Moreover, Maghoub and Alexopoulos (2016) found $A\beta$ accumulation due to AD neuropathology causing impairments of neuronal networks, especially in the hippocampus. Neuronal degeneration in this brain area also causes loss of mood-related neurons, which increases the risk of developing depressive symptoms. Thus, the affected brain areas involved in mood-regulation due to AD neuropathology could explain the extremely high number of patients developing AD-related depression.

2.4 Shared underlying neuropathological mechanisms

From the above-mentioned one-directional relationships it can be concluded that late-life depression is both a prodromal symptom as well as an independent risk factor. Therefore, late-life depression increases the risk of developing AD. Similarly, AD pathology is found to affect mood-related areas and increases the risk of developing late-life depression, which explains the extremely high number of cases for AD-related depression. Even more interesting are the shared underlying mechanisms of both diseases. Affected mechanisms and brain areas caused by late-life depression seem to evoke AD symptom severity and vice versa. Thus, based on four shared underlying mechanisms, it is proposed that the effects of late-life depression and AD on each other are bi-directional. To understand this bi-directional relationship and its interaction, the following section explains the mechanisms of the stress-response hypothesis, the amyloid hypothesis, the inflammatory hypothesis, and the genetic hypothesis.

2.4.1 Stress-response hypothesis

The stress-response hypothesis is an important indicator for the bi-directional relationship as for both patients with late-life depression or AD, abnormalities can be observed in the mechanisms of the stress-response. For healthy individuals, stress triggers the activation of the hypothalamic pituitary adrenal axis (HPA-axis). In reaction to stressful stimuli, the hypothalamus releases a specific hormone, namely the CRF agent. This hormone, in turn, triggers the pituitary gland to release the hormone adrenocorticotrophic (ACTH). ACTH then stimulates adrenal glands to release glucocorticoids (GCs). GCs, together with epinephrine and

norepinephrine, stimulate the bodily changes needed during stressful situations, such as the sharpening of cognitive functions. A negative feedback loop ensures that when high levels of GCs occur, the HPA-axis gets inhibited and normal levels are restored. However, in both depression and AD, this negative feedback loop is reduced and as a result, GCs levels stay elevated in the brain. These elevated GCs levels have been shown to play a pathophysiological role in both diseases, as this can result in the reduction of the neurogenesis and collapsing dendrites in the hippocampus, apoptosis of hippocampal neurons, and an increased vulnerability of neurons releasing amyloid β . As a result, the PFC and hippocampus suffer from a diminished volume. The PFC and hippocampus are both connected and important for regulating mood and memory performance. Thus, both disorders share one similar mechanism as pathology (Leszek et al., 2016).

2.4.2 Amyloid hypothesis

The bi-directional relationship of amyloid accumulation is two-fold. First, Hardy and Selkoe (2002) found AD patients with higher levels of $A\beta$ plaques in the brain show more severe cognitive dysfunction. In addition, Maghoub and Alexopoulos (2016) found for preclinical AD patients without a history of depression that $A\beta$ accumulation may resolve into a prodromal depressive syndrome. The deposition of AD-related $A\beta$ accumulation may be able to impair some neurological processes and networks that are involved in depression, by means of degeneration of mood-related neurons, vascular damage, or abnormal functional connectivity, thus contributing to the development of late-life depression.

Secondly, a new pilot study of Li et al. (2017) discovered increased $A\beta$ accumulation in late-life depressive patients without cognitive deficits. Elderly depressed patients with a lifetime history of depression show significantly higher levels of $A\beta$ accumulation in mood-related areas of the brain, indicating that a depressive history could increase the risk of developing AD. The results of the pilot study provided evidence that late-life depression might be a preclinical or even prodromal stage of AD according to three main findings. First, late-life depressive patients with amnesic MCI symptoms showed higher levels of $A\beta$ accumulation in similar brain regions as those affected in AD patients, such as the hippocampus and PFC. Furthermore, patients with moderate-to-severe resistance to antidepressant treatments also showed $A\beta$ plaque distributions similar to patients with early AD. Lastly, findings showed that the more severe depressive symptoms occur late in life, the more $A\beta$ plaques occurred. Compared to healthy controls, depressed patients without AD symptoms showed elevated amyloid plaques in the PFC, left superior temporal and left parietal regions. These regions correspond to the $A\beta$ affected regions in AD patients. The similarities in

region-specific A β depositions in the brain between late-life depression and AD indicate the existence of a relationship between the two. Furthermore, Rapp et al. (2006) showed that for AD patients, the presence of a lifetime history of depression corresponded with higher levels of A β plaques in the hippocampus and more rapid cognitive decline, as compared to those without a lifetime history of depression. Thus, these studies show an interaction between late-life depression and AD in A β -neuropathology, thereby supporting the bi-directional hypothesis.

2.4.3 Inflammatory hypothesis

Another similarity in the pathology of late-life depression and AD can be found in the effects of certain inflammatory processes of the immune response, again indicating a bi-directional relationship. For AD patients, a stronger activation of inflammatory systems occurs compared to healthy controls, indicating that additional immune-stimulants are present due to the disease. One of these immune-stimulants is the presence of A β , which is able to activate and trigger the release of interleukin-6 (IL-6), IL-1, and tumour necrosis factor alpha (TNF α). IL-6 is found to be involved in memory formation, whereas IL-1 is associated with the regulation of A β production. Lastly, TNF α is able to suppress the formation of long-term potentials in the hippocampus, which are essential for learning and long-term memory formation. Thus, long-term effects of abnormal pro-inflammatory levels can increase cognitive decline by dysregulating the process of memory formation and increasing A β production and a negative cascade occurs (Heneka & O'Banion, 2007).

The exact same cytokines as described above are also excessively released in depressed patients, yet their effects differ. From both human and animal studies, we know that patients with higher levels of TNF α and IL's display fatigue, apathy, depressive symptoms, and mental slowing, independent of the presence of a history of depression for the patient. Some of the behavioral changes that occur due to inflammation are also associated with hyperactivity of the HPA-axis and the stress-response (Dantzer, O'Connor, Freund, Johnson, & Kelley, 1999). AD and late-life depression thus seem to share the same underlying pathophysiological relationship due to inflammation. In both disorders, excessive levels of ILs and TNF α cause depressive symptoms and cognitive decline, as well as A β accumulation and the activation of HPA-axis, thus, in turn, contributing to both the amyloid hypothesis and stress-response hypothesis.

2.4.4 Genetic hypothesis

While genetic primers for both depression and AD have been largely investigated, clear genetic markers have still not been discovered. However, a genetic correla-

tion has been found for patients suffering from both late-life depression and AD, compared to healthy controls or those suffering from either AD or late-life depression, but not both. Some of these genetic variations include the gene encoding the brain-derived neurotrophic factor (BDNF) and the serotonin receptor genes 5-HT2A and 5-HT2C (Borroni et al., 2009; Holmes, Arranz, Collier, Powell, & Lovestone, 2003). These findings suggest a correlation between genetic markers and development of AD and depression, thereby contributing to the bi-directional relationship.

3 Proposed bi-directional threshold model

Based on the reviewed literature of AD and late-life depression, the two previously explained one-directional relationships, and the shared underlying mechanisms, a new bi-directional threshold model is proposed. The new bi-directional model is based on the threshold model of Butters et al. (2008) in which the one-directional relationship of late-life depression on AD is explained (figure 1). This theory by Butters et al. states that a number of different processes associated with late-life depression, such as the deficit in the negative feedback loop of the HPA-axis as described in the shared underlying mechanisms section, add to the risk of AD development. The threshold model of Butters et al. describes the pathways as synergistic in the way that they act in different degrees to each individual, meaning that not all individuals who share the same neuropathological deviations in similar severity develop identical outcomes. Therefore, it accounts for the individual differences in the risk of developing an increased risk for the AD development.

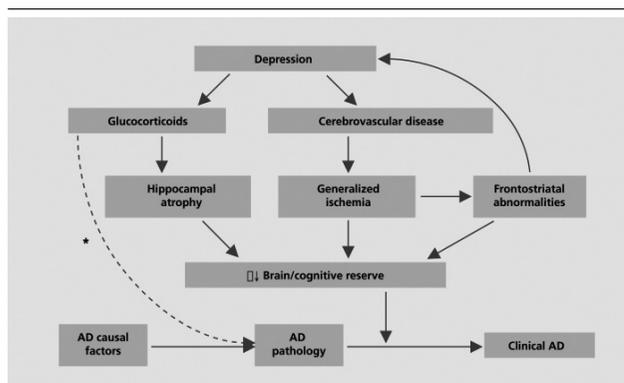


Figure 1 One-directional threshold model (Butters et al., 2008).

However, the one-directional threshold model of Butters et al. (2008) is incomplete as it does not account for the proposed bi-directional relationship. As explained above, the main arguments for this novel model are the shared underlying mechanisms that have not been accounted for in previous studies. For example, the amyloid hypothesis shows how the neurophysiology of AD can cause neuronal loss in mood-related areas in the brain, which in turn can cause the development of late-life depression. On the other hand, late-life depression is known to cause increased A β plaques and NFTs, which contribute to cognitive decline and AD development. Therefore, the relationship between AD and late-life depression is bi-directional. Similar mechanisms occur for inflammatory processes and GSS levels in the brains of depressed patients as well as AD patients. The elevated cytokine- and GSS levels in the brain can affect both cognitive decline and mood processes, thus having a bi-directional relationship on each other. Lastly, deviations in the BDNF gene, as well as the 5-HT2A and 5-HT2C genes, also account for a bi-directional relationship of both diseases.

In addition to the evidence of the shared underlying mechanisms of AD and late-life depression for the bi-directional model, the evidence of both one-directional relationships also account for this novel model. This is because longer time intervals between late-life depression onset and AD onset show how late-life depression is an independent risk factor for AD development. Therefore, it is hypothesized that the shared underlying mechanisms account for the increased risk. Furthermore, the model also explains the additional risk of developing AD-related depression after the first stages of AD, not attributed to the reactive knowledge of the disease. Again, the shared underlying mechanisms are used to explain this increased risk for development of AD-related depression.

The proposed bi-directional threshold model (figure 2) is novel in the sense that it accounts for the bi-directional interaction between AD and late-life depression, whereas previous research only focused on the one-directional interaction. The upward arrows represent the one-directional relationship of AD on late-life depression, whereas the downward arrows represent the one-directional relationship of late-life depression on AD. By combining the two one-directional relationships within one model, the bi-directional relationship is shown. The threshold aspect of the model accounts for the individual differences as to the degree of possibly developing either AD or late-life depression.

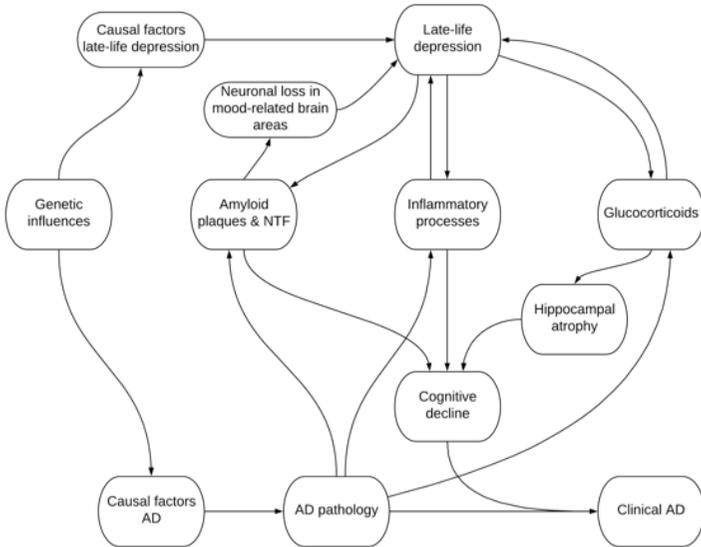


Figure 2 Proposed bi-directional threshold model of the relationship between Alzheimer's disease (AD) and late-life depression. Downward arrows represent the one-directional relationship of late-life depression on AD. Upward arrows represent the one-directional relationship of AD on late-life depression. Both late-life depression and AD are caused by some causal factors of the diseases, on which genes can have an influence. Once one has developed either late-life depression or AD pathology, several mechanisms start, namely the formation of amyloid plaques and NTF tangles, some inflammatory processes such as the increased release of ILs and $TNF\alpha$, and the higher levels of glucocorticoids due to a deficit in the negative feedback loop of the stress-response. These three mechanisms are shared by both AD pathology as well as the pathology of late-life depression. Furthermore, these three mechanisms can contribute to the development of the other disease, either late-life depression or AD, depending on which disease first develops. This model is based on one's threshold, meaning that the pathways are synergistic in the way that they act in different degrees to each individual, thus accounting for the individual differences.

4 Discussion

Two of the most common diseases of the elderly, late-life depression and AD, have been found to affect each other. Late-life depression is found to be both a prodromal symptom of AD, as well as an independent risk factor for the development of AD later on. On the other hand, AD is found to increase the risk for the development of depression, both due to the reactive knowledge of having the disease and due to degeneration of neurological structures that are involved in depression, therefore altering the brain and decreasing mood-related volumes in the brain. Until now, these effects have only been investigated in terms of the one-directional relationships. However, the shared underlying mechanisms of both diseases suggest a bi-directional relationship and a novel bi-directional threshold model is proposed. Although this model still needs sufficient empirical support, it acts as a starting point for further research. The first step would be to investigate the coefficients of each shared underlying mechanisms and to find the strength of the different pathways within the model. Furthermore, the entire model should be empirically tested. Lastly, research should be conducted into finding other possible contributors to the bi-directional relationship of both AD and late-life depression. A better understanding of the proposed bi-directional threshold model could have major implications in ameliorating the course of both clinical conditions. For example, health care institutions should adapt their policy and consistently check for symptoms that indicate whether a patient is developing late-life depression next to AD, and vice versa. These policy changes could ensure treatment is provided at the early stages of the diseases and could therefore help ameliorating them. Furthermore, the proposed model also provides pathophysiological evidence that the two diseases are directly affecting each other. This would have major implications for ethical and philosophical questions. When two diseases of the mind are found to affect each other and function as independent risk factors, do we still need to see them as two separate diseases? Are other diseases of the mind connected to each other? As shared underlying mechanisms in the body are found to affect or perhaps even cause the development of the diseases, should they not be seen as physical illnesses instead of illnesses of the mind? The proposed model could help in answering such questions.

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