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Spatial And Non-Spatial Attention Deficits in Neurodegenerative Diseases

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Abstract: The prevalence of neurodegenerative diseases is on the rise due to the aging global population, leading to a significant increase in cognitive impairments characterized by progressive neuronal degeneration. Within these impairments, both spatial and non-spatial attention deficits have emerged as critical features that profoundly impact the quality of life. Spatial attention, crucial for the selective processing of sensory information, involves intricate neural networks, including the parietal and frontal lobes. This review, based on a narrative literature review, synthesizes current research on the neuropathological foundations of spatial and non-spatial attention deficits in various neurodegenerative diseases.

Keywords: Neurodegenerative diseases; Spatial attention deficits; Non-spatial attention deficits.

1. Introduction

Neurodegenerative diseases are pathologies characterized by the progressive loss of vulnerable neurons through extensive and abnormal cell death, a situation that alters body movements and causes loss of neurological functions, thus affecting the central nervous system (CNS) and the peripheral nervous system (PNS) [1]. The ageing of the world's population is expected to increase the prevalence of neurodegenerative diseases. Age is the most important non-modifiable risk factor for dementias such as Alzheimer's disease (AD), which accounts for 50% of senile dementias [2], followed by individual genetic predisposition and potentially modifiable risk factors. Added to this scenario is the development of pathologies such as Parkinson's Disease, Amyotrophic Lateral Sclerosis and Huntington's Disease, of a multifactorial nature influenced by genetic, environmental, and behavioral factors [3].

Neurodegenerative diseases affect cognitive reserve, lead to cognitive decline, loss of functional capacity, dependence on the care of others to carry out daily tasks and impairment of quality of life, a situation that has an observable impact on the personal, community and global economy. Concomitant with neuronal death is the intra- or extracellular deposition of proteins with altered conformation in many neurodegenerative diseases, such as AD. In addition, another mechanism developed in the spectrum of these diseases is neuroinflammation mediated by glia cells, as in Parkinson's Disease, which, under physiological conditions, provide support to neurons. In chronic inflammation, the event occurs because of heterogeneity in the activation of the different phenotypes of micro-glia, M1 and M2, and the prevalence of M1 is harmful to the neuronal environment, as it increases the release of pro-inflammatory factors and neurotoxic mediators [4].

Neurodegenerative diseases have diverse clinical manifestations and progressive implications that affect neurons throughout the human body and some common signs are complex problems with recurring symptoms, such as mental confusion, attention disorders and muscular alterations such as hyperkinesis or fatigue [5]. Attention is the cognitive process that makes it possible to direct mental resources towards information processing, task development, wakefulness, selective and directed perception. Losses, declines or disturbances in attention can be explained by age or pathologies, including neurodegenerative diseases which can lead to disturbances in this cognitive function and, as a result, loss of functionality and quality of life. In this context, spatial attention is characterized by the set of neural processes that enable the selective processing of sensory information. This is highly important so that we can prioritize an area within the visual field and process it in such a way that we discard what is not relevant [6]. Thus, it is known that several regions of the brain are related to spatial attention, but we have the parietal region on the non-dominant side among the most relevant, which integrates the opposite side of the body and the environment, as well as the frontal lobe which acts strongly on eye movements and visual fields [7].

On the other hand, with regard to non-spatial attention, its signals modulate the response according to the stimulus provided by the action, category or reward [8]. Other non-spatial actions may not be stimulus-dependent, being responsible for coding contexts and rules before the presentation of specific targets. Despite the ubiquity of this information in individual neurons, the reversible inactivation of the parietal lobe that occurs in the modulation of the non-spatial response only affects the orientation of attention and gaze, but not aspects of performance, contributing to the determination of which targets are worthy of greater focus in a more complex situation [9, 10].

Huntington's Disease is a hereditary neurodegenerative disease characterized by the loss of the basal ganglia, damage to the brain which strongly affects attentional capacity, among other functions. Studies show that patients with HD have highly reduced visual perception processing, as well as being noticeably slower. These deficits are related to a decrease in dopamine in cortical cholinergic activation [11]. These visuospatial alterations are of great clinical relevance in view of the general cognitive impact they cause. Another neurodegenerative pathology is Alzheimer's disease, which is characterized by high clin-ical relevance, given that around 47 million people live with this progressive neurocogni-tive dysfunction worldwide [12]. It is known that in addition to memory, this disease also notably alters visuospatial processing, as it affects the temporo-parietal lobe early on, which is largely responsible for mediating spatial attention [13].

Therefore, neurodegenerative diseases, characterized by progressive neuronal loss, have a broad pathological spectrum and a wide variety of clinical manifestations, with the common development of attention deficits [5] through spatial and non-spatial attention disorders. Thus, based on data from recent literature, this study aims to emphasize the direct and close relationship that exists between neurodegenerative diseases and the development of spatial or non-spatial attention deficits.

2. Methodology

A narrative literature review was carried out based on PubMed data from 2021 to 2022 on spatial and non-spatial attention deficits, neurodegenerative diseases and the combined manifestation of both pathologies. The initial search in PubMed retrieved 127 articles using the descriptors Mesh (Neurodegenerative disease) AND (Attention deficit) and 15 articles using the descriptors Mesh (Neurodegenerative disease) AND (spatial and non-spatial attention deficit). Of this total, 23 articles were selected, after excluding titles that did not address the topic of 'attention deficits associated with neurodegenerative dis-eases', as well as articles that did not fit into the pre-established search period and articles not written in English. The second set of criteria was then applied: exclusion of abstracts not addressing attention deficit in neurodegenerative diseases, in which 3 articles were excluded.

In addition, the Google Scholar database found 316 articles using the descriptor (Neurodegenerative disease) AND (Attention deficit) AND (Spatial) AND (Non-Spatial), of which 9 were selected after the first set of criteria - exclusion of titles that did not address the topic 'attention deficits associated with neurodegenerative diseases', articles not in-cluded in the 2021-2022 search period, as well as articles that were not in English. The second set of criteria was applied - exclusion of abstracts not addressing attention deficit in neurodegenerative diseases, whereby 3 articles were excluded. Next, 20 articles were added manually from the list of references of eligible articles. At the end of the selection, 49 articles originally in English remained.

The methodological path followed in the review to select the studies is shown in the flow diagram detailed in Figure 1. The studies included in the review for analysis are pre-sented in Tables 1 (author, objective, method and results).

3. Results

3.1 The relationship between aging and neurodegenerative diseases

The aging of the world's population has resulted in a significant increase in the prevalence of geriatric neurodegenerative diseases, such as Parkinson's Disease and Alzheimer's Disease. Data from the Ministry of Health places Brazil as one of the world's longest-lived populations and it will be the sixth largest population of elderly people by 2025 [14]. About AD, the most recent literature points to it as the most common subtype of dementia, with figures varying, according to the literature, between 60-80% of all cases, followed by other types of dementia, such as vascular dementia and neurodegenerative subtypes, such as dementia due to Lewy bodies, the dementia-Parkinson complex and frontotemporal dementia [14, 15].

Speaking specifically of Brazil in relation to the prevalence of AD, it ranks second when the prevalence of this condition is standardized by age group in relation to the rest of the world [14, 15]. With this information, there is not enough data to predict the numbers of AD for the coming decades in Brazil, but recent studies suggest that there will be a drastic increase in this condition in the future. Based on the United States, it is estimated that there will be a jump from 4.7 million people (2010) to 16 million by 2050 [16, 18].

Also in this sense, given that neurodegenerative diseases are mostly related to cellular aging, it is possible that premature aging accelerates the onset of these pathologies through exposure to external environmental factors, such as excessive screen time and/or physical inactivity, which has increased exponentially during the pandemic and which is known to alter the circadian rhythm, sleep and promote cellular changes or the sedentary behavior in which the world population is inserted, also exacerbated by the pandemic. Therefore, we may see even higher numbers in the future than those mentioned above [14, 17].

Figure 01. Flowchart of the article selection.

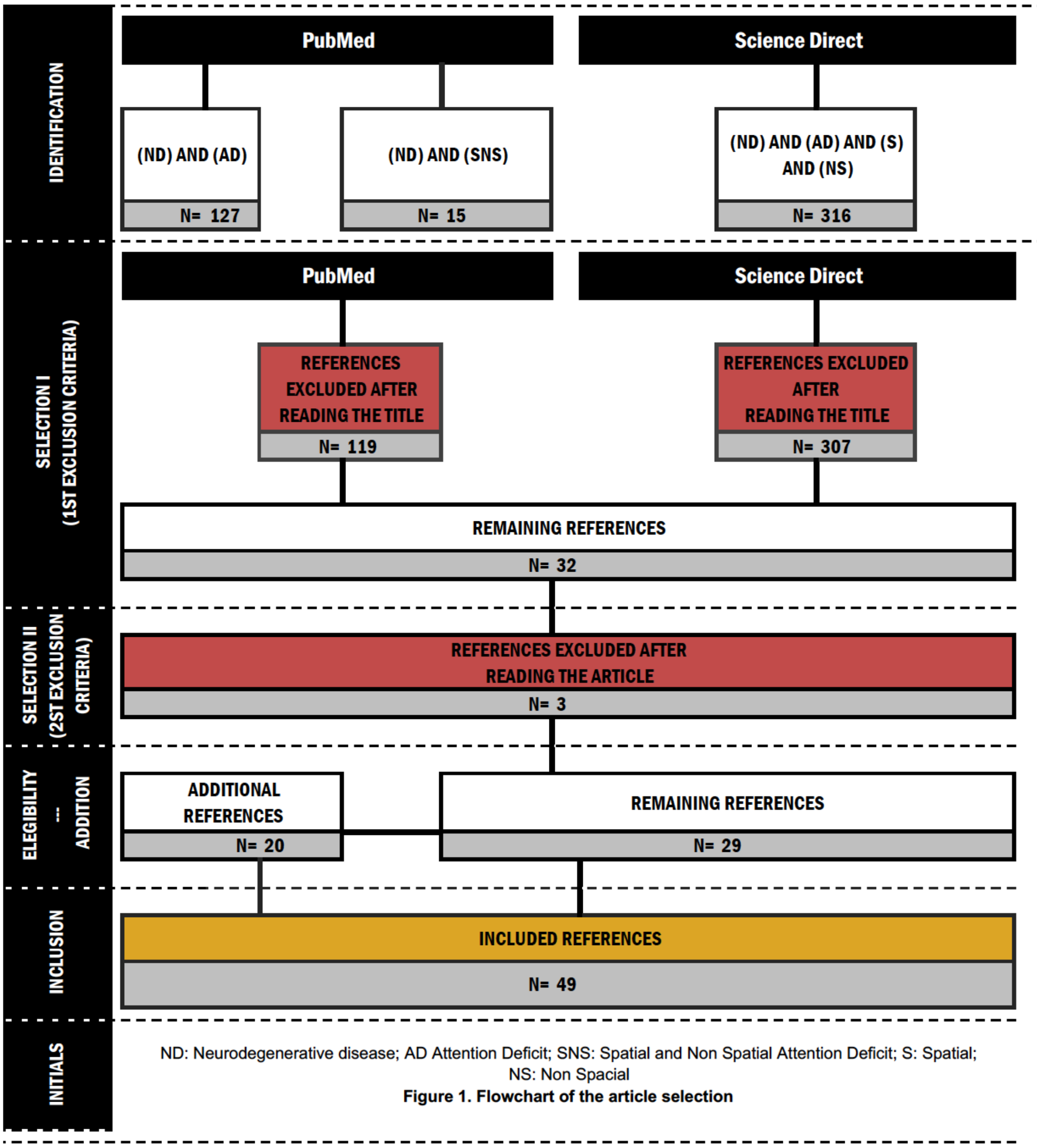

Figure 1. Flowchart of the article selection

The COVID-19 pandemic has caused people to isolate themselves socially and remain immersed in the virtual environment for long periods. For example, during the first wave of the pandemic, there was a reduction in physical activity time, below 150 minutes per week, and an increase in exposure to screens, more than 4 hours per day [18, 20], generating more immobility and compromising regular physical exercise, which goes against the guidelines of the World Health Organization, which recommends between 150 and 300 minutes of moderate activity per week [19]. The same guideline also recommends that people reduce sedentary behavior, such as excessive time spent working in prolonged postures such as sitting, reclining, and even lying down, activities with low energy expenditure and which have been associated with deleterious outcomes in general health [20].

One of the consequences of physical inactivity and prolonged exposure to screens is changes in chronotype, which are known to have a negative impact on the central nervous system and are associated with neuropathological events related to neurodegenerative diseases [21], since sleep plays a fundamental role in promoting and restoring important neuronal circuits and in cell signaling, helping our bodies to maintain homeostasis [22]. Based on the above, we can infer that sleep deprivation, which is common in these patients, is associated with a greater deposition of substances that degrade the nervous system and promote a significant long-term decline in cognitive functions. Amyloid beta, for example, is cleared by interstitial fluid in REM sleep stages via a pathway called "glymphatic" [23].

Among the alterations resulting from the cognitive decline caused by neurodegenerative diseases, we pay special attention to the spatial and non-spatial attention deficits present in these conditions.

3.2 Spatial attention deficit

The brain receives more sensory information than it can fully process [24] (Table 01). In this context, spatial attention is defined as the process by which the brain selects and prioritizes information collected from a specific location in space [25]. The control of spatial attention can be divided into reflexive 'bottom-up' or voluntary 'top-down' [26]. It has been proposed that two different neural networks control these types of attention. The first involves the dorsal-frontal parietal attention circuit, which encompasses dorsal posterior parietal areas, especially the intraparietal sulcus, and an area around the frontal visual field in the frontal cortex. The second area, called the right frontal parietal circuit, involves the temporoparietal junction and the ventral frontal cortex [27].

Table 01. Spatial and non-spatial attention deficits in neurodegenerative diseases.

Author/year	Title	Objective	Correlated Disorders	Results/ conclusion
[1]	Neuronal Cell Death Mechanisms in Major Neurodegenerative Diseases	To study the general pathway of death cells and describe evidence for cell death in the context of common neurodegenerative diseases	Amyotrophic Lateral Sclerosis, Huntington's Disease, Alzheimer's Disease, Parkinson Disease	It is important to understand, in the context of different diseases, how a neuron incites a death pathway to commit self-termination wich molecular mechanism drives such a decision and whether different cell death programs dictate specific disease contexts or physiological circumstances

[4]	Differential Roles of M1 and M2 Microglia in Neurodegenerative Diseases	To study the potential role of M1 and M2 microglia and the dynamic changes of M1/M2 phenotypes that are critically associated with the neurodegenerative diseases	Parkinson’s Disease, Alzheimer’s Disease, and Amyotrophic Lateral Sclerosis	The demonstrated role of microglial phenotypes may boost the research of M1/M2 paradigm in the human body. The balance of M1 and M2 microglial activation is broken down during the chronic inflammation progress in neurodegenerative diseases, with the highest complexity in AD.
[6]	Spatial and non-spatial attention deficits in neurodegenerative diseases: assessment based on Bundesen's theory of visual attention (TVA)	To present evidence that, similarly as in neglect, a combined pattern of spatial and non-spatial deficits of visual attention can also be typically observed in patients suffering from neurodegenerative disorders.	Huntington's disease (HD), mild cognitive impairment (MCI), Alzheimer's disease (AD)	Processing speed was severely slowed in HD, and also reduced, although to a lesser degree, in MCI and AD patients. In HD and AD patients, but not in MCI patients, a strong leftward bias of spatial attention was observed.
[8]	Spatial and non-spatial functions of the parietal cortex	Review relevant results from neuron recording studies showing that inferior parietal neurons integrate information regarding target location with a variety of	Non-spatial deficits	The study proposes that the non-spatial feedback found in the parietal lobe may reflect, in part, this type of computation, through which the brain identifies stimuli that are associated with - and thus can predict - other variables of interest such as an action, rule or expected reward

		non-spatial signals.		
[39]	Neural correlates of spatial and nonspatial attention determined using intracranial electroencephalographic signals in humans	To investigate the neural correlates of spatial and non-spatial attention in humans using intracranial electroencephalography.	Spatial and non-spatial attention deficits	Spatial attention and expectation are closely intertwined in almost all circumstances of everyday life. Yet, despite their intimate relationship, attention and expectation rely on partly distinct neural mechanisms
[42]	Spatial Neglect Subtypes, Definitions and Assessment Tools: A Scoping Review	Capture the reported definitions for the subtypes of neglect post stroke and map the range of assessment tools employed for each neglect subtype.	Stroke and Spatial neglect	The study shows that there are hundreds of neglect tools available, however many are not able to differentiate presenting subtypes and that it's important for clinicians and researchers to critically evaluate the neglect tools being used for the screening and diagnosis of neglect.
[25]	The Intricate Interplay of Spatial Attention and Expectation: a Multisensory Perspective	Attempt to dissociate the mechähisms of attention and expectation and characterize their interactive or additive influences on perception.	Spatial attention deficits	Spatial attention and expectation are closely intertwined in almost all circumstances of everyday life. Yet, despite, their intimate relationship, attention and expectation rely on partly distinct neural mechanisms.

[35]	Attention and spatial cognition: Neural and anatomical substrates of visual neglect	Review the neuroanatomical correlates of visuospatial attention and spatial neglect.	Stroke and Spatial neglect	Attentional processes are supported by frontoparietal functional and anatomical networks. Damage to these networks can trigger the appearance of rieglect, with a dramatic deficit of awareness for events occurring on the side contralateral to the lesion.
[31]	Unraveling Causal Mechanisms of Top-Down and Bottom-Up Visuospatial Attention with Non-invasive Brain Stimulation	Explore the literature devoted to investigating the role of fronto-parietal brain regions in top-dewn and bottom-up attention with transcranial magnetic stimulation and highlight key areas of convergence and debate	Attention deficits	Studies have shown that the inferior frontal gyrus could mediate selection of relevant stimuli during object-based attention. Noninvasive neurostimulation will be key to unraveling whether brain regions and neural mechanisms for object-based or auditory attention control are shared with those for top-down and bottom-up visuospatial attention.
[48]	Dissociable spatial and non-spatial attentional deficits after circumscribed thalamic stroke	To study about the thalamic nuclei and it's role in cognitive functions such as executive functioning, memory and attention and to review how the thalamic stroke can affect those areas.	Stroke, Spatial and non-spatial attention deficits	Not only the visual thalamus is relevant for distinct parameters of visual attention. Instead also anterior, medial and lateral nuclei of thalamus are relevant and lead to distinct visual attentional deficits if damaged.

Still within this context, the 'top-down' hypothesis describes that high-level perception, such as anticipation and working memory, help the individual to focus their attention on targets. This type of attention is linked to voluntary control and takes longer to establish and can be sustained for the total time required for a given task [28]. The 'bottom-up' hypothesis, on the other hand, refers to the rhythmic and automatic process used for unforeseen targets. In this last type, there is a faster deployment, but it is usually more temporary [29, 30].

Similar to hemineglígence, there is evidence that a pattern of combined spatial and non-spatial attention deficits can be observed in patients with neurodegenerative diseases. Traditionally, heminegligence results from the impossibility of orienting spatial attention in the hemibody contralateral to the lesion [31, 32]. Heminegligence occurs more frequently on the left, due to the dominance of the right cerebral hemisphere in governing spatial attention functions in the general population, together with the right temporo-parietal junction region which plays an important role in this function [33, 34] (Table 01).

An example of a neurodegenerative disease that affects the frontoparietal circuit is Alzheimer's disease, where its neurophysiopathology consists of the deposition of beta-amyloid peptide and neurofibrillary tangles35. In the early stages of the disease, this neurophysiopathology is observed in the frontal and sensory areas, and in some cases, it affects these regions even before it appears in medial temporal structures. Thus, these patients have deficits in cognitive functions that involve the frontoparietal circuit, such as attention and motor planning36.

In addition, in Huntington's disease, there is progressive atrophy of the caudate nucleus and putamen, causing progressive dysfunction of the frontoparietal circuits37. Although there is a bilateral reduction in volume in the striatum in this pathology, evidence suggests an asymmetrical degeneration pattern, with a greater predominance of volume reduction on the left side. The striatum is intimately involved in the control of visuomotor behavior and attention [6].

3.3 Non-spatial attention deficit

Non-spatial attention is defined as attention to a specific resource rather than a specific location38. It involves broad brain networks, including the bilateral parietal, frontal and temporal regions, with maximum activity occurring in the right parietal lobe, with the inferior parietal lobe (IPL) being important when it comes to performing tasks that are not spatial or not necessarily spatially lateralized [39].

Alterations in non-spatial attention can lead to various impairments, including deficits in engagement and disengagement in certain activities and in maintaining attention, which can be crucial in the development of spatial neglect syndrome [40] and is related to negative functional results, such as reduced independence in activities of daily living, a greater likelihood of falls, as well as a propensity to hospitalization and low prospects of discharge home [41] (Table 01).

A combined pattern of spatial and non-spatial deficits in visual attention can also be typically observed in patients suffering from neurodegenerative disorders [42], such as in mild cognitive decline, Alzheimer's dementia (AD), Parkinson's disease (PD) and Huntington's disease (HD) [43]. Unlike healthy individuals, AD patients and PD patients exhibit significant impairment in both the ability to disengage attention from an incorrectly located location and the ability to use a visual cue to produce a warning effect.

3.4 Etiologies of spatial and non-spatial attention deficits

Attention Deficit Hyperactivity Disorder (ADHD) is a psychiatric condition associated with social and personal factors. This disorder is characterized by impaired attention levels44. From this perspective, attention deficits are related to neurodegenerative diseases, since these pathologies cause specific deficiencies in cognitive abilities45. However, few studies have explored the association between ADHD and neurodegenerative diseases such as AD and PD. In this sense, the lack of knowledge about possible long-standing learning disorders can lead to erroneous conclusions about the decline in cognitive functioning in elderly patients44,45. In addition, it is very common for individuals to experience mild cognitive decline as they get older, due to sensory deprivation. However, it is possible to recover sensory functions lost over the years with sensory stimulation and physical activity [46].

The thalamus is believed to be one of the main areas of consciousness and is involved in almost all behavioral functions. It is known that visual information is first processed in a wave from the retina to the lateral geniculate nucleus of the thalamus and then to the striatal visual cortex. From this point of view, executive dysfunctions and attention deficits have been associated with lesions of the intralaminar and mediodorsal nuclei [47] (table 01).

In this respect, various neurological conditions can lead to attention deficits due to involvement of the parietal cortex, especially the right parietal cortex. Parietal cortex activity contributes to higher-level cognitive processes, including visual attention and saccadic movements [48]. In this context, patients who have suffered unilateral strokes commonly show hemispatial neglect or milder contralesional visual attention deficits. Furthermore, a clinically important aspect of these findings is the fact that if there are non-lateralized attention deficits, they modulate the lateralized ones. In other words, hemispatial neglect is aggravated in patients with this condition [49].

Utilizing the articles selected, it was possible to produce a table presenting many disorders associated with the spatial and non-spatial deficits in neurodegenerative diseases. On top of that, the identification of pertinent information on the topic supports the relevance of the production. Furthermore, the table consists of data referring to the authorship of the article, the title of the productions, the diseases correlated to the current topic and the conclusions of each study. Therefore, the analysis of the results found was more efficient, making it possible to evidently visualize the considerations exposed in the discussion.

4. Conclusion

The neural mechanisms involved in the physiology of spatial attention and non-spatial attention depend on the coordination of various processes that recruit different areas of the brain and are especially vulnerable to neurodegenerative processes. These processes are characterized by the progressive and extensive loss of neurons and can have different etiologies. This study found an association between spatial and non-spatial attention deficits in various neurodegenerative diseases, such as Alzheimer's Disease, Parkinson's Disease, Amyotrophic Lateral Sclerosis, and others, as well as associated with population aging, increased exposure to screens, sleep disorders, sedentary lifestyle, and ADHD.

The combination of deficits does not affect just one specific area of the brain, but predominantly some with involvement of other underlying areas. The clinic associated with neurodegenerative disease corresponds to the topography of the brain, which demonstrates the diversity of symptoms that arise from the respective deficits. Whether through visible or behavioral symptoms, the relationship of the attention deficit mentioned in the body of the text has an influence on the progressive clinic of neuronal loss.

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