Review

Evidence and Opportunities for Studying Sensorimotor Dysfunction Beyond Supratentorial Structures in Alzheimer's Disease

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Evidence and Opportunities for Studying Sensorimotor Dysfunction Beyond Supratentorial Structures in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a debilitating neuropsychiatric disease marked by cognitive decline, but also somatosensory/motor dysfunction. No cure has been found thus far, which prompts the emphasis on both early detection and treatment of its neurodegenerative symptoms. Although the dominant narrative in AD research has focused on supratentorial structures and cognitive symptoms, there is sufficient evidence to support the role of infratentorial structures (cerebellum, brainstem, and spinal cord) that contribute to sensorimotor pathology. In this review, we discuss evidence of motor impairments in AD and how abnormalities in infratentorial structures might contribute to it. Existing literature implicates fine motor dysfunction, gait issues, agraphia, dysphagia, and other motor issues in most AD patients, some even at preclinical stages. We also found considerable evidence of cellular pathology and atrophy in the spinal cord, cerebellum, and brainstem in many AD patients. We posit that pathology in these infratentorial structures contributes, at least in part, to sensorimotor dysfunction in AD. Several important questions remain unanswered on these topics. Further research will improve our understanding of AD and contribute to the discovery of biomarkers for early and better diagnosis, prognosis, and tracking progression of this dangerous disease.

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by cognitive decline that often leads to major neurocognitive disorder (MNCD). AD is also characterized by short-term memory impairment with personality and behavioral changes that can progress to agitation, disorientation, psychosis, anxiety, and mood swings [1]. Neuroanatomically, AD studies have identified impairments in deep brain structures, predominantly the locus coeruleus (LC), as well as supratentorial regions [2,3]. AD sub-variants are determined by age of onset, either below (early-onset) or above (late-onset) the age of 65 years [4]. Each subvariant has distinct symptomatology and patterns of disease progression [4]. Although our understanding of AD is constantly updating due to new research, our current knowledge is that early onset is uniquely defined by familial inheritance

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understood to have mutations in specific genes: presenilin [1,2] and amyloid precursor protein [5,6]. Late-onset AD, on the other hand, is typically identified by a mutation of the ε4 allele of the Apolipoprotein ε (APOE) gene [6]. This gene produces a glycoprotein that plays a major role in lipid metabolism and transport, promoting the maintenance of normal cholesterol levels [7]. However, abnormal ε4 allele production leads to an increase in amyloid beta (Aβ) plaque deposits in brain tissue, which is associated with a more rapid course of AD symptoms [8].

Although extensive research has been conducted on Aβ plaques and the causal mechanisms of AD, there is a lack of therapeutic interventions. Recently, a new drug, Aducanumab, an Aβ-directed antibody, was approved by the Food and Drug Administration, USA, but even this drug's robust efficacy has been questioned [9]. Thus, there is a clinical emphasis on symptom management in the therapeutic domain of AD [10]. Early detection is imperative to delay disease progression by, for instance, incorporating various lifestyle changes, such as exercise and other cognitive activities [10].

It has been found that AD may have underlying neuromuscular pathology [11]. Accordingly, there is a marked presence of vascular disease in patients with AD, which relates to the characteristic sensorimotor dysfunction expressed as well [8]. Sensorimotor deficits in AD are found to be independent of cognitive decline and MNCD, suggesting a dependence on background genetics [12]. However, it remains unknown whether muscular decline or cognitive decline presents first or if they present concurrently. Imaging the central nervous system (CNS) to study impairments in the sensorimotor system has promise for the discovery of early biomarkers to non-invasively monitor disease onset and progression. The early biomarkers will possess significant clinical value if they precede accepted current diagnostic biomarkers. Furthermore, the degenerative nature of the disease can be monitored to understand specific effects within unique demographics.

Abnormality in supratentorial structures of the CNS that result in cognitive decline has been the dominant narrative in AD research, especially among imaging studies. However, pathological markers of AD have been reported even in infratentorial structures (brainstem, cerebellum, and spinal cord), which are mostly related to sensorimotor dysfunction in AD rather than cognitive issues. In this review, we focus on this aspect and discuss existing research on sensorimotor pathology in AD, and how infratentorial structures may play a role in its presentation. To the best of our knowledge, this is the first AD review to include the spinal cord in addition to the cerebellum or brainstem in the context of sensorimotor dysfunction. Section-2 presents relevant background on AD pathology, section-3 discusses motor impairments observed in AD patients, section-4 presents evidence on noradrenergic and dopaminergic dysfunction that might contribute to the motor pathology, and section-5 talks about gait issues that are often observed in AD patients. Section-6 presents imaging evidence on the role of infratentorial structures in motor pathology in AD. We finally draw conclusions in section-7.

2. Pathology of Alzheimer's Disease

The pathological onset of AD begins with the formation of two protein aggregates, senile Aβ plaques and neurofibrillary tangles, which lead to progressive neuronal degeneration and cell death [13]. The protein aggregates are thought to cause oxidative stress, which alters normal signaling pathways in neuronal cells and prevents proper intercellular and intracellular communication [14]. As neurons die, the cerebrum experiences distinct changes: the gyri become narrower and the sulci grow deeper [14]. Through cerebrospinal fluid (CSF) markers and imaging techniques, it is possible to monitor disease pathology. The most common CSF biomarker of AD is elevated levels of phosphorylated tau [15]. Imaging studies have also shown reduced glucose uptake and availability in the brain (via positron emission tomography [PET]), and atrophy of the brain (via structural MRI) in some regions, especially the hippocampus, frontal lobe, and temporal lobe [16–19]. Post-mortem indices of hallmark pathologic lesions in the brain include neurofibrillary tangles and senile plaques made of hyperphosphorylated tau protein and Aβ peptides, respectively [20].

Structure often dictates function, hence, the pathology of AD results in a marked disease presentation. The onset of MNCD in AD is characterized not only by well-known memory loss, but

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other cognitive impairments such as problems with word-finding ability, impaired judgement, visual and spatial problems, and agraphia (an impairment of graphic motor patterns) [21–23]. The diagnostic criteria for AD were updated in 2011 to establish a sense of continuous progression rather than definitive staging [24]. Although these criteria are immensely helpful, their accuracy is limited only to official post-mortem diagnoses; hence a standardized set of clinical manifestations are required to diagnose living patients with AD.

3. Motor Impairments in Alzheimer's Disease

APOE allele status has been implicated as a risk factor that may predict age-related motor decline, especially related to a dramatic reduction in motor strength [25]. In a study that measured global motor functions over 8 years, subjects with even one copy of the abnormal ε4 allele experienced a decrease in muscle function when performing motor function tests, even after controlling for factors such as body mass index (BMI), race, diseases, and vascular aberrations [25]. Since motor networks, which regulate motor planning and execution, extend from interconnected cortical regions to subcortical regions and the spinal cord, AD may present some pathologic deficiencies in the motor pathway because the protein deposits may subserve movement, affecting motor strength and function [26,27]. By connecting motor impairments with APOE allele status, the relationship between AD and motor coordination symptoms can be assessed.

Muscle strength and function are related to AD incidence. Decreased muscle strength (in the form of grip and axial muscle strength) is associated with decreased grip function and global cognition [28]. Furthermore, motor performance assessments test wider functions of body movement, from central processing centers of sensation and perception to the cognitive understanding of movement [28]. For those with AD, motor performance tasks (e.g., finger tapping, gait, and balance) are significantly reduced compared to healthy controls, even when controlled for other disease factors [28]. The onset of muscular decline may occur prior to any significant cognitive decline [28]. For those who exhibit parkinsonism, the risk of AD development increases significantly [28]. Although only correlational in longitudinal studies, increased physical frailty relates to a decrease in global cognitive skills, which may progress into AD [28]. Interestingly, the rate of increased frailty poses a risk for a subsequently faster rate of cognitive decline [28]. Because of the association between motor impairments and AD diagnoses, an understanding of the progression of muscular impairments can help in developing a therapeutic intervention that targets these motor dysfunctions.

In addition to muscle strength and frailty, studies have explored the association between broader health measures and AD. Muscular atrophy, as indicated by declining BMI, may also point to a systemic loss of nervous system function [29]. Although BMI may be sensitive, it is far from specific to AD, therefore alternate motor function biomarkers must be enlisted. Current methods of identifying motor function in stroke patients are motor unit number index, compound muscle action potential, and motor unit size index [30]. By considering alternate motor function data, more specific and sensitive diagnostics can be collected to understand the motor changes that occur with the progression of AD. With further study and adaptation of these non-cognitive biomarkers in AD, they can be used in conjunction with or even preceding cognitive impairment tests in clinical diagnoses.

4. Noradrenergic and Dopaminergic Dysfunction in Alzheimer's Disease

Norepinephrine (NE) and dopamine are important monoamine neurotransmitters in the sympathetic nervous system. The noradrenergic system consists of NE binding to alpha- and beta-adrenergic receptors, which subsequently bind to alpha and beta receptors of adipose and smooth muscle somatic cells [31,32]. NE plays a role in cognition and motivation, and is primarily released by the LC [32]. The LC works in conjunction with multiple brain regions such as the amygdala, insula and hypothalamus [33], and controls catecholamines, including NE, via direct and indirect pathways, which can impact autonomic, motor, sensory, and cognitive functions [32]. Atrophy of the LC can lead to significant global cognitive decline because of the lack of crucial NE-driven communication

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between brain regions [33]. AD is documented by substantive LC atrophy [34]. The decrease in LC volume suggests a decrease in NE release, which may not only hinder noradrenergic function but also impact autonomic and motor processes.

Furthermore, NE pathways interplay with dopamine pathways, even in the LC, allowing for normal control of a variety of cognitive and non-cognitive functions [35]. In parkinsonism, the loss of dopaminergic neurons causes neurodegenerative motor symptoms [36]. Due to the complex ways in which the noradrenergic and dopaminergic neurons functionally interplay, dopaminergic neurons may indirectly affect AD as well [36]. By exploring this avenue of research, the interaction of these two catecholamines can lead to a better understanding of the sensorimotor dysfunction associated with AD.

5. Gait Issues in Alzheimer's Disease

Gait is a complex movement that involves not only motor areas such as the basal ganglia and cerebellum, but also extra-motor regions, including the central executive network, that processes working memory and attention control [37,38]. Therefore, creating movement not only requires autonomic processes but also a highly synchronized pattern of behavior with the use of the central executive network [38]. Hence, the severity of MNCD due to cognitive and motor impairments can be assessed using gait [37,38]. To further understand the progression of AD, an assessment, dementia-related gait changes (DRGC), can be utilized to measure stride velocity, stride length, and the support necessary for movement [38]. Decreases in DRGC are associated with progressive sensorimotor dysfunction that accompanies AD [38]. For patients with vascular and Lewy body dementias, DRGC indicated a decrease in stride velocity and length [38]. By examining gait-related impairments in conjunction with cognitive assessments used to monitor AD, there is an opportunity to potentially improve diagnostic capabilities, allowing more sufficient time for preventative measures to be taken.

Decreased NE, resulting from the loss of noradrenergic neurons in the LC, may lead to the "freezing of gait" [38]. Gait alterations are characteristic of another dementia-related disease, Parkinson's disease [38,39]. The severe muscular impairment is indicative of a combination of muscular, cognitive and affective deficits [37]. With further research, a similar relationship could be determined between decreased NE in those with pre-clinical AD and rapid muscular decline.

6. Alzheimer's Disease Motor Pathology Beyond Supratentorial Structures

Motor signals from the cortex are relayed to the peripheral nervous system (and somatosensory signals in the opposite direction) through the brainstem and spinal cord, which are mediated by the cerebellum [40]. Since these infratentorial structures play an important role in the sensorimotor system, a suggestive dysfunction may occur locally prior to any global cognitive decline, leading to impaired motor and somatosensory function [40]. These motor impairments are frequently attributed to age progression; however, they may also be early markers of the preclinical stage of AD. Those diagnosed with AD have an increased susceptibility to apraxia, which is when learned motor movements are not executed properly because of an impairment of the sensory, motor, or cerebellar networks [41]. Apraxia presence and severity has been shown to increase with the progression of AD as compared to other dementias, such as frontotemporal dementia and diffuse Lewy body disease [41]. The presence of apraxia in AD further necessitates the need to research the causal relationship between motor pathology and histopathology to improve preclinical detection of AD. Furthermore, early AD symptoms include fine motor impairment that can progress to agraphia, a lexical impairment with altered motor system function whereby the individual is unable to write [42]. Although agraphia involves both central and peripheral components of the nervous system, mainly the cognitive aspects of this complex motor movement have been studied [42,43]. Focusing research on the key peripheral pathways impacted in agraphia via imaging could help identify pre-symptomatic AD.

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Since the spinal cord is the highway for signal transduction to/from the periphery, it is important to consider the effect of AD on motor functions carried out by direct innervation of skeletal muscle, and by cranial, vagal, and sacral innervation [44]. Those with MNCD are at increased risk of gastroparesis, constipation, dysphagia and excessive sweating [45]. Dysregulation of acetylcholine, the chief mediator of parasympathetic innervation, plays a significant role in the degeneration of synaptic neurons in the progression of AD [46]. Hence, many drugs used for attenuating the progression of AD, such as donepezil and rivastigmine, are cholinesterase inhibitors which prevent acetylcholine degradation at neural synapses and neuromuscular junctions [46]. Moreover, it has been hypothesized that Aβ plaques are neurotoxic to cholinergic synapses, leading to dysregulated processing of neural and motor networks [47]. Aβ pathology can lead to a chronic blockade of muscarinic transmission of impulses, affecting parasympathetic activity by inhibiting the synaptophysin/synaptobrevin complexes [48]. When these complexes are impaired, signal transduction via the release of neurotransmitters by exocytosis are dysregulated [48]. Thus, studying chemical messenger networks can help to better isolate the motor deficits present in AD symptomatology.

Another crucial neurotransmitter is NE, whose role is to mediate neuroprotection, inflammation, and plasticity, not just in supratentorial regions, but in neural connections throughout the body [49] – thus involved in motor dysfunction. Further research is warranted in characterizing the clinical progression of AD along this aspect [50]. In Parkinson's disease, decrease in the production of NE is associated with tremors at rest, bradykinesia and rigidity, likely due to the degeneration of substantia nigra, LC, and even the cerebellum [50]. Motor deficits occur similarly in AD's course progression, including difficulties in facial expressions, gait and posture changes, bradykinesia, and tremors [51]. NE signaling in AD is redirected by Aβ oligomerization, which activates the glycogen synthase kinase 3β leading to tau hyperphosphorylation [52]. Yet, the study of NE signaling in AD has largely focused on supratentorial structures, with a primary focus on the LC [53]. Studying the shared pathogenesis of infratentorial structures in AD can help better characterize associated motor impairments.

The symptoms that arise frequently in patients with AD suggest that there must also be histological evidence of motor dysfunction. Post-mortem histochemical autopsies have found that a higher proportion of tau tangles are present in the cervical spinal cord as compared to age-similar controls [54]. AD effects (i.e., Aβ plaques) can accumulate in the spinal cord concurrently with severe cord atrophy [54]. Tau pathology was also detected in the brainstem and the spinal cord via PET scans of transgenic mice [55]. Furthermore, Aβ plaque deposits in transgenic mice were found along the corticospinal tract; a suggested deposition pathway was via the neurons of the sensorimotor network [56]. Neurofibrillary analysis found that tau isoforms in the midbrain and pontine regions changed structurally and quantitatively along with disease progression even after initial production [57]. The two isoforms of tau (3R and 4R) help to inform the stage of AD [57]. However, the 3R isoform consistently remains elevated in pontine structures from an early phase [57]. This localized phenomenon in the pontine region of the brainstem is important due to its proximity to the LC, as the increase in the 3R isoform could be related to the aberrant NE signaling and subsequent motor impairments [58]. Due to limited research into the relationship between infratentorial CNS structures and AD, many questions about the physiological mechanisms of tau tangles, especially in the cerebellum and spinal cord, remain unanswered. For example: Do these depositions of tau tangles and Aβ plaques arise upon onset of disease, or do they manifest later? How and why do Aβ plaques present themselves in these regions? When do these senile plaques result in impairment of healthy neuronal networks and cause subsequent motor deficits? How do tau tangles and Aβ plaques impact the function of these infratentorial structures?

With the aid of transgenic mice and MRI scans, morphometric changes in infratentorial structures have also been demonstrated in AD [59]. Degeneration of white matter fiber tracts in the brain and spinal cord can occur due to inflammation, as evidenced by the upregulation of astrocyte and microglial production [56,60]. These inflammatory processes mediate axonal degeneration and

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neuronal loss in the spinal cord [61,62]. Moreover, AD patients present with reduced cross-sectional area in all vertebrae of the cervical spinal cord, and a reduced cross-sectional volume in spinal levels C1 and C2 [63]. Interestingly, brain volumes did not significantly correlate with these spinal cord anatomical metrics [63]. Further research into the inflammatory changes that mediate degeneration would aid in discerning the volumetric and atrophic changes prior to symptom onset.

Research on the role of the cerebellum in AD has only recently gained momentum. The cerebellum plays a unique role, as it functions to integrate both the motor and cognitive aspects needed for skilled behaviors [64]. Research in AD shows a lateralization of atrophy in regions corresponding to working memory and language processing [65]. As stated earlier, apraxia and agraphia are both presentations of deficits in these tasks [43,65]. Furthermore, cerebellar degeneration leads to decreased strength of the hands, dexterity of the fingers, stride time, stride length, and functional mobility [66]. Yet, the role of the cerebellum in AD has been understudied. Studies characterizing the role of the cerebellum in both cognitive and motor impairments are in conjunction with supratentorial structures, preventing the clear identification of pathology directly attributable to the cerebellum and surrounding infratentorial regions. By exclusively studying cerebellar changes through the course of AD, stronger diagnostic criteria can be developed.

The past decade has also seen a rise in research on how those with AD are more likely to experience cerebrovascular disease, which compounds the progression of AD because of poor blood circulation [67,68]. Accordingly, poor vascular circulation in the spinal cord could relate to the progression of AD [63,69,70]. Blood not only provides oxygen and nutrients, but it also helps ensure the health of neural and glial cells [71]. Examining the function of spinal cord vasculature in AD pathology will lead to an understanding of how motor impairments occur as a result of blood flow alterations. With electrical and magnetic stimulation of the cord, blood flow can be increased, which is hypothesized to slow disease progression [72,73]. Spinal cord stimulation is already used for treating cervical neck pain by increasing blood flow with electrical impulses [74]. Pursuing this line of research could form a similar viable therapy to prevent plaque and tangle depositions in AD pathogenesis.

7. Conclusions

A study of supratentorial structures (e.g., the LC) in relation to cognitive decline has been the dominant imaging narrative in AD. However, lately, we have seen a marked increase in studies on infratentorial structures (brain stem, cerebellum, and spinal cord) because of the prevalence of somatosensory and motor dysfunction in AD. By studying these structures in relation to clinical symptoms related to motor impairment, early detection and diagnosis of AD could potentially improve, allowing for the sufficient implementation of lifestyle changes and interventions to slow the progression of this disease. Motor dysfunction associated with preclinical stages of AD is generally passed off as symptoms of old age, indicating a need for changing societal perceptions, and subsequently improving disease detection and monitoring of cognitive and motor function in AD.

Over the past couple of decades, earlier detection of AD has risen in importance. An early diagnosis confers the advantage of more manageable symptoms, even if a cure is not possible. By delaying the progression of AD, a longer lifespan and a higher quality of life can be achieved. The use of different imaging techniques and modalities while expanding areas of imaging to include regions such as the spinal cord are avenues that should be explored to diagnose and assess the progression of AD quickly and more accurately.

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