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The Five Systems of Dysphagia: MCI to the AD Spectrum of Disorders

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Abstract

In order to swallow safely and effectively, there are five bodily systems that must work in coordination: Muscular, Respiratory, Neurological, Cognitive, and Gastrointestinal. Previously, these systems were established as the Five Systems of Dysphagia (5SysDys). Additionally, there exists an array of diseases/disorders that are linked to the development of Alzheimer's disease, and the current perspective proposes that these diseases/disorders can be referred to as the Alzheimer's Spectrum of Disorders (AD Spectrum). The current perspective proposes that the breakdown of the 5SysDys among patients suffering from the AD Spectrum is observable at the amnestic Mild Cognitive Impairment (aMCI) stage. Further, this perspective elucidates this relationship and distinguishes among the AD Spectrum, as well as proposes, for the first time in the literature, what types of 5SysDys breakdown is observable at the aMCI stage; aMCI is subdivided into the single and multiple domain diagnoses (SDaMCI & MDaMCI, respectively). We propose literature-driven conclusions and illustrate the importance of considering effective Dysphagia Management in the aMCI and AD Spectrum populations.

Introduction

Between 2010 and 2030, the geriatric population will dramatically increase to ~70 million elderly residents, representing ~20% of the total American population. Among the elderly, 10–15 million Americans will be over the age of 85 and are likely to be afflicted by progressively deteriorating neurocognitive diseases. Neurocognitive impairment affects ~10% of individuals over the age of 65 and ~30% beyond 90 years. Not surprisingly, cognitive decline is the most feared of the chronic diseases in American seniors (Winchester & Winchester, 2015). To date, many types of dementia have been identified, but one type of dementia, Alzheimer's disease (AD), accounts for a majority of the worldwide dementia cases.

In the past, there have been many inconsistencies in the diagnosis of AD and a lack of consensus within the clinical and scientific communities on what characterized the AD population. Neuroimaging and neuropsychological studies in vivo had conflicted with the diagnosis of AD postmortem. Additionally, in each type of study, inconsistences could be found. Neuroimaging studies

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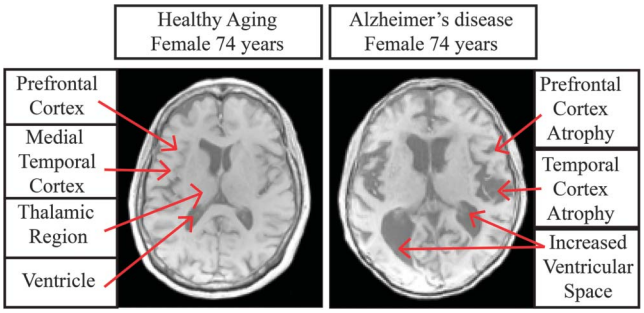
did not agree on which areas of cortical atrophy are seen in the earliest stages of AD. However, hippocampal deterioration in the medial temporal lobe was found consistently among researchers. After more than 20 years of research, the community came together to update the diagnostic criteria for AD, and left room for further discussion (Albert et al., 2011). For example, in the updated criteria, AD dementia continues to be considered a separate from the type of dementia that is observed when individuals suffer from prolonged cardiovascular and/or metabolic dysfunction.

To that end, we propose an evolution of the criteria for AD dementia and the types of dementia observed when patients suffer from age-related degeneration due to cardiovascular and/or metabolic dysfunction. Further, we relate this evolution of thought to the breakdown among the Five Systems of Dysphagia (5SysDys) known to be prevalent in the aging population. The present perspective will draw from the literature and will demonstrate significant gaps in the current research, with the intention of pushing the discussion of 5SysDys and AD-related dementia. Finally, we utilize this approach to discuss the relationship of 5SysDys to the type of cognitive decline seen in the Mild Cognitive Impairment (MCI) population, a prodromal phase between healthy aging and AD.

Alzheimer's Pathology

Half of all AD cases show signs of strictly AD pathology (e.g., amyloid plaques and neurofibrillary tangles that degenerate neurons, myelin, synapses, and larger cortical regions; Braak & Braak, 1991; Clifford, 2008). Others have mixed-dementia pathology (Alzheimer's Association, 2015) such as Vascular Dementia (VasD), one of the most common AD mixed-dementia pathologies (Alzheimer's Association, 2015). Amyloid plaques accumulate on the axons, dendrites, myelin, and exterior of neurons, as well as within the synapses between neurons. Neurofibrillary tangles degrade the neurons from the inside out (Alzheimer's Association, 2015; Braak & Braak, 1991). Primarily, AD cortical deterioration begins in the medial temporal lobe. However, deterioration in the inferior parietal, prefrontal, and near the tempo-occipital-parietal junction has been noted (See Figure 1). The cognitive symptoms of AD can vary among patients; though the gradual worsening of remembering new or recently acquired information is often a primary symptom (Alzheimer's Association, 2015). As the neuropathology of AD progresses, patients have issues with memory, communication, neuropsychiatric disturbances, sleep, planning, problem solving, activities of daily living, and visuospatial relationships (Alzheimer's Association, 2015).

Figure 1. Axial view of 3T Hi-Resolution Magnetic Resonance Imaging of Healthy Aging and AD Females of 74 Years.



In healthy aging, some overall reduction in cortical volume is apparent (Left). This differs from the deterioration due to AD, where prefrontal and temporal cortical atrophy combined with increased ventricular space is observable (Right). Images obtained from original academic research, provided by Jeanna Winchester, PhD.

For a description of the types of dementias affecting the aging population and the mechanisms by which they deteriorate neurocognitive functioning, see Alzheimer's Facts & Figures, 2015,

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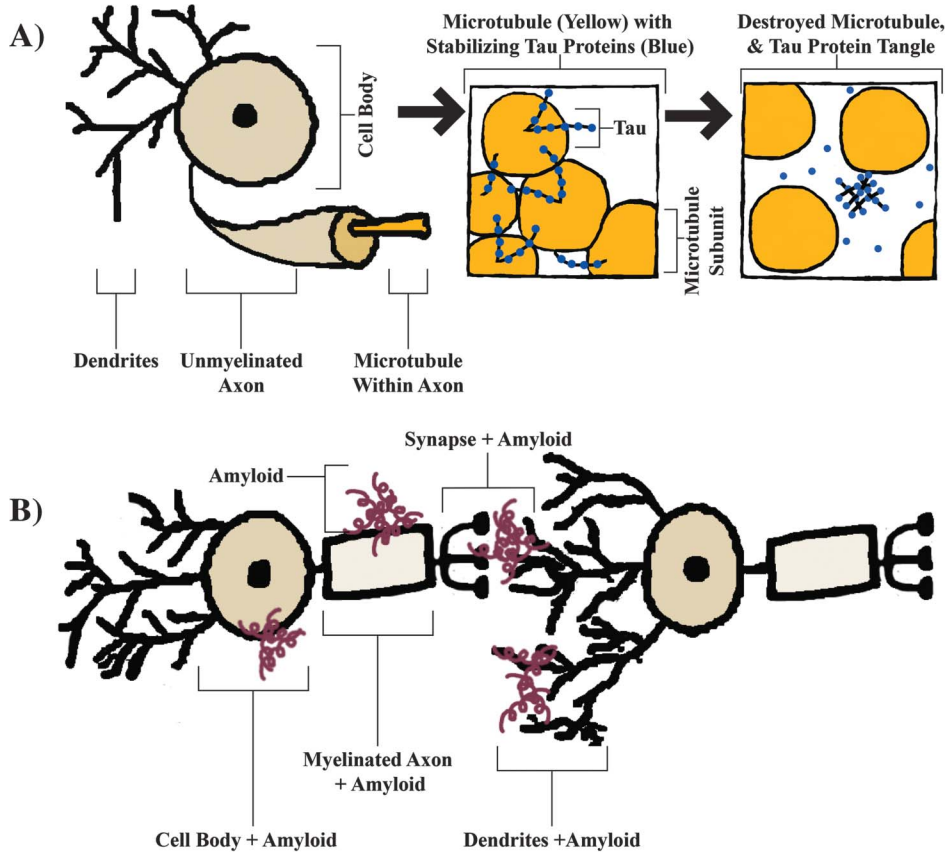
a publication of the Alzheimer's Association of America (Alzheimer's Association, 2015). Brief overviews of the fundamentals of amyloid plaque and neurofibrillary tangle formation have been illustrated, here (See Figure 2A & 2B).

Figure 2. The Fundamentals of AD Neuropathology.



(A) Within a single neuron's axon exist microtubules. In the microtubule subunit (yellow) exists the tau protein (blue), an integral part of neuronal integrity and supporting the neuron's overall structure. In AD, the tau protein aggregates accumulate into "tangles," and disrupts the overall integrity of the microtubule, which destroys the integrity of the neuronal structure. (B) Amyloid (purple) is a naturally occurring phenomenon in human physiology, and amyloid serves a purpose in healthy human functioning. In AD, the length of the amyloid proteins has been altered, and this affects the body's processing of amyloid in healthy functioning. As a result, the longer amyloid proteins accumulate in "plaques" which deposit in areas on the exterior of neurons and within synapses. Original artwork provided by Jeanna Winchester, PhD.

For the purposes of the current literature review, a detailed account of the mechanisms by which amyloid plaques and neurofibrillary tangles grow and propagate in the nervous system will not be recounted in detail. Instead, the current perspective will discuss topical aspects of cardiovascular and metabolic components in AD and its prodromal stage, MCI, then relate these topical discussions to dysphagia. Several research groups have established the cardiovascular mechanisms associated with AD (Craft 2009; Iadecola, 2013; Jellinger, 2007; Moorhouse et al., 2010; Ravaglia et al., 2005). Additionally, a plethora of investigators have established the relationship among metabolic dysfunction, insulin resistance, and AD neuropathology (Baker et al., 2011; Craft

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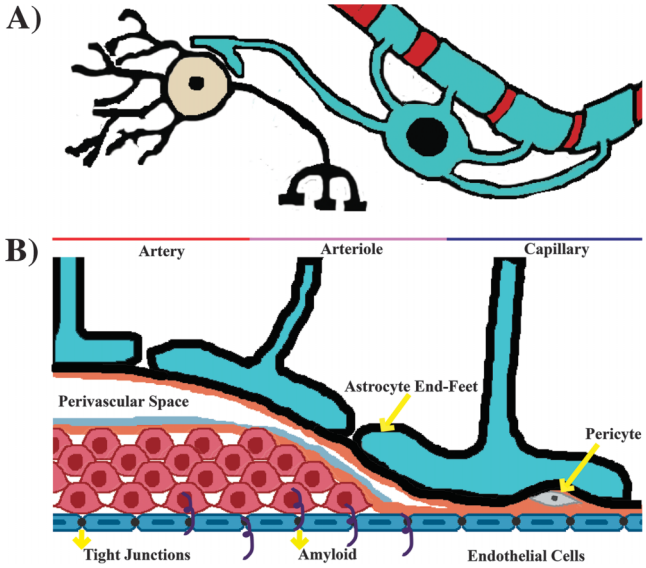
et al., 1998; Deeny et al., 2012; den Heijer et al., 2003; Messier, 2003). Cardiovascular and metabolic contributions to the growth of amyloid plaques and neurofibrillary tangles significantly relate to neuronal and synaptic dysfunction (Alzheimer's Association, 2015; Braak & Braak, 1991). Further, widespread ischemic and vascular lesions (e.g., microinfarcts and lacunes) are known to be prevalent in crucial brain networks supporting cognition, memory, behavior, and executive functioning; key brain networks deteriorating in both AD and VasD (Iadecola, 2013). For this reason, the relationship of AD neuropathology and vascular lesions in AD patients will be the first topical discussion of the present perspective.

Vascular Dysfunction & Alzheimer's Disease

Vascular lesions often coexist with AD pathology, because the accumulation of amyloid can occur in the cortex and along the blood-brain-barrier (Craft, 2009; Iadecola 2013). Therefore, a simplified illustration of the blood-brain-barrier (Figure 3A), cerebral amyloid angiopathy (Figure 3B), and cerebral vascular lesions in AD (See Figure 4) is provided here. Specifically, amyloid plaques deposit in the parenchyma and the media/adventitia of cerebral vessels (Craft, 2009; Iadecola, 2013), leading to degeneration of smooth muscle cells and pericytes (Iadecola, 2013; Jellinger, 2007). Dysfunction of the blood-brain-barrier may affect amyloid expulsion from the cerebrovasculature to the periphery, thereby increasing amyloid deposition in the cortex and cerebrovasculature (Craft, 2009). Minor cerebrovascular lesions, except for severe amyloid angiopathy, appear non-essential to the cognitive decline in progressed stages of AD, but both AD pathology and small vessel disease seem to interact, synergistically (Moorhouse et al., 2010). AD pathology may cause vascular injury due to amyloid-induced inflammation and dysfunction of the blood-brain-barrier may affect amyloid expulsion from the cerebrovasculature to the periphery, causing parenchymal and neurovascular amyloid deposition (Craft, 2009). Furthermore, prefrontal cortical deterioration with corresponding executive dysfunction is found in both AD and VasD. Individuals who demonstrate both AD and VasD pathologies seem to have the greatest impairments in these areas when compared to either disease alone (Moorhouse et al., 2010).

Figure 3. Blood-Brain-Barrier (A) and Cerebral Amyloid Angiopathy (B).



Astrocytes (blue) protect the neuron by filtering the materials obtained from the bloodstream and provide a supporting role in the nervous system by acting as the immune system. Compromised Arteries/Capillaries (red) can be found in individuals with AD, as amyloid (purple) is able to penetrate and accumulate. Original Figure by Jeanna Winchester, PhD, adapted from Iadecola (2013).

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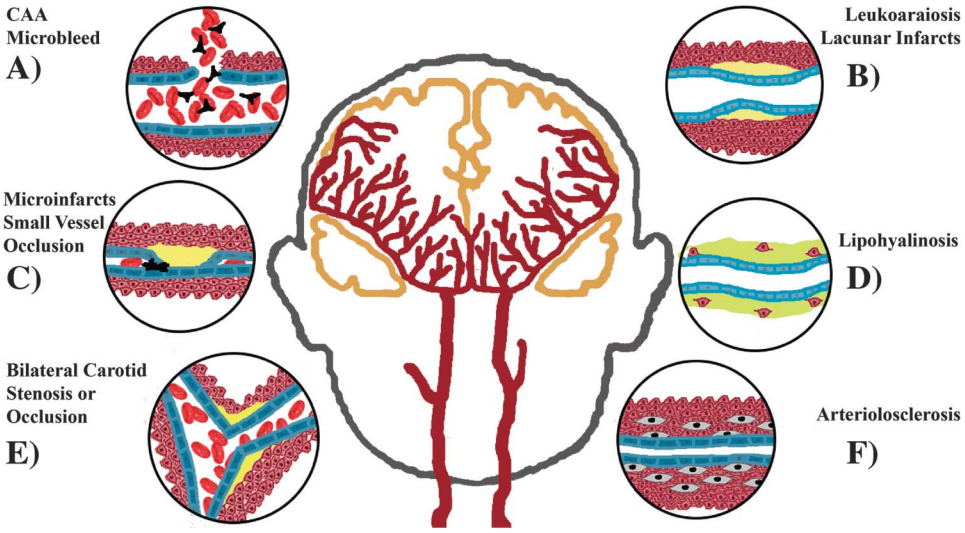
Figure 4. Vascular Lesions in Vascular Dementia and Alzheimer's Disease.



This Figure shows cardiovascular muscle tissue (red, A-F), endothelial cells (blue), red blood cells (A, C & E), inflammation (yellow, B, C & E), and hyaline substance growth (yellow, D) throughout. (A) Cerebral amyloid angiopathy (CAA) and Microbleed. Amyloid accumulation deteriorates the smooth muscle cells and pericytes. (B) Leukoaraiosis & Lacunar Infarcts. Leukoaraiosis is the imaging correlate to deterioration of myelinated nervous system tissue. Lacunes are small (<1.5cm) white matter lesions. Both are commonly associated with hypertension, diabetes mellitus and hyperlipidemia. (C) Microinfarcts and Small Vessel Occlusion. Microinfarcts are lesions not visible to the naked eye and an occlusion has occurred when the flow of a blood vessel has been blocked. (D) Lipohyalinosis. Deposits of a hyaline substance are found in the vascular wall. (E) Bilateral Carotid Stenosis. Stenosis or occlusion of the carotid arteries correlates with chronic ischemia and can independently cause cognitive impairment. (F) Arteriolosclerosis. Fibrotic changes in the vessel wall result in a stiffening and a microvascular distortion of the artery, arteriole or capillary. Original Figure by Jeanna Winchester, PhD, adapted from Iadecola (2013).

VasD can be difficult to diagnose. Currently, the clinical community considers VasD a heterogenous construct corresponding to cerebral and cardiovascular pathology that presents with multiple macroinfarcts (See Figure 4B), small vessel ischemia (See Figure 4A & 4C) or microvascular injury (O'Brien et al., 2003). However, the community refers to this as a "narrowed" definition. Interestingly, research has shown that "Pure" VasD, which has neuropathology related to arteriosclerosis and microangiopathies, differs from that shown in the mixed-type of dementia where AD pathology is combined with vascular encephalopathy, resulting in large infarcts (Iadecola, 2013; Jellinger, 2007). That research, then, conceptualized "Pure" VasD as a cognitive profile including preserved memory functioning, but with impairments in the attention and executive functioning domains (O'Brien et al., 2003). In contrast, the mixed-type of VasD/AD dementia has diagnostic criteria that accounts for a greater proportion of the dementia population (O'Brien et al., 2003).

Distinguishing between "Pure" VasD and the VasD/AD mixed pathology is key in the present discussion. To that end, VasD will be discussed only as it relates to the AD Spectrum, and discussions of the "Pure" VasD dementia symptomology can be found in other literature reviews (Craft, 2009; Iadecola, 2013; Jellinger, 2007). Viewing the symptomology of VasD and AD as more of a continuum assists the clinical community in diagnostic accuracy and affords a broader

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avenue of treatment possibilities. Evaluating the cardiovascular components in AD is important to successful patient outcomes, but focusing on those symptoms by themselves would result in an incomplete picture. To get the full view of the variety of AD patients, the following discussion includes an investigation of the metabolic dysfunction, possible insulin resistance, and likelihood for a diagnosis of diabetes mellitus (DM) as an AD comorbidity.

Metabolic Dysfunction, Insulin Resistance, & Alzheimer's Pathology

Cerebral metabolic dysfunction is a complicated and multifactorial interaction (Strachan, Reynolds, Marioni, & Price, 2011), a major component to the development of AD pathology and is noted in DM patients. Insulin is involved in a number of factors associated with late-life neurodegeneration, and AD pathology, such as cerebral glucose metabolism, vascular function, synaptic maintenance, amyloid regulation, and tau phosphorylation (Baker et al., 2011). Accordingly, DM patients have a similar type of medial temporal cortical atrophy to that noted in the amnestic forms of MCI and AD (Deeny et al., 2012; den Heijer et al., 2003; Gold et al., 2007; Manschot et al., 2006).

The AD Spectrum is heavily influenced by key genetic factors (Deeny et al., 2012), and in the present perspective, we will focus our discussion on one gene that has been correlated with all dementias along the AD Spectrum: The Apolipoprotein Epsilon-4 allele (APOE4). For example, future AD/VasD onset, a greater likelihood for developing congestive heart failure and many forms of insulin resistance are significantly predicted by the presence of at least 1 copy of APOE4 in a patient's genome, known as an APOE4 carrier (Vogels, Scheltens, Schroeder-Tanka, & Weinstein, 2007). APOE4 carriers with normal cognitive functioning demonstrate impaired cerebral glucose metabolism in the medial temporal, parietotemporal, and frontal cortices, similar to patients with DM, AD, and the amnestic forms of MCI (Baker et al., 2011; Deeny et al., 2012; Luchsinger et al., 2007; Ward et al., 2015; Yau, Kluger, & Convit, 2014).

APOE4 carriers seem to convert to a status of AD at an earlier onset than APOE4 non-carriers (Mosconi et al., 2005). APOE4 carriers with adult-onset DM have an increased likelihood of developing AD than APOE4 carriers without DM (Messier, 2003). All DM patients, regardless of APOE4 status, have a 1.5–2.5 fold higher likelihood of developing AD than those patients without DM (Strachan et al., 2011). This interaction may be due to the relationship of insulin resistance to the formation of amyloid plaques (Ryan, Fine, & Rosano, 2014). AD patients have abnormal insulin levels in their cerebrospinal fluid and plasma, when compared with healthy aged adults, a relationship that is modulated by the presence of the APOE4 genotype (Craft et al., 1998). The APOE4 genotype also modulates the amount of AD neuropathology in patients with DM, thereby influencing DM cognitive decline across the following domains: information processing, psychomotor efficiency, attention, memory, learning, problem solving, motor speed, vocabulary, general intelligence, visuoconstruction, visual perception, somatosensory examination, mental flexibility, and executive function (Alzheimer's Association, 2015; Kodl & Sequist, 2008; Malek-Ahmadi et al., 2013; Ryan et al., 2014).

Importantly, glucose hypometabolism confirmed via Positron Emission Tomography (PET) in the medial temporal lobe, the location of the hippocampus and memory function, is a defining characteristic of AD diagnosis in vivo (Alexander, Chen, Pietrini, Rapoport, & Reiman, 2002; Deeny et al., 2012; Ryan et al., 2014). Given the key feature of reduced medial temporal cortical glucose metabolism in diagnosing AD, a discussion of AD without metabolic dysfunction is simply incomplete.

A New Approach to the Concept of Alzheimer's Disease

Taken together, metabolic and cardiovascular dysfunctions are found among the amnestic forms of MCI and among AD, VasD, and DM dementias (Craft, 2009; Exalto, Whitmer, Kappele, & Biessels, 2012; Schmidtke & Hermeneit, 2008). When the diseases are conceptualized separately,

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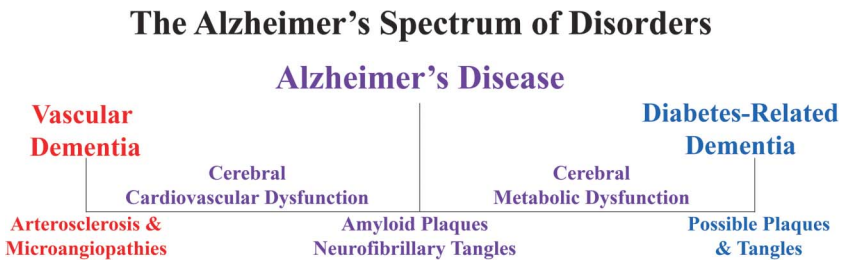
confusion and misdiagnosis are increased. Additionally, treating the diseases as separate entities narrows one's treatment options. When the diseases are seen as more of a spectrum of related, but distinct, metabolic and vascular dementia disorders that broaden the diagnostic definition of AD, the clinical community can better serve the aging population. These areas of overlap and distinction will only be briefly reviewed, here. For the purposes of the current discussion, these dementias will be referred to as the AD Spectrum (See Figure 5). Understanding the cognitive and neurological bi-directional breakdown among the AD Spectrum is critical in the fight against dementia in the elderly, because VasD accounts for fewer than 20% of cases (Iadecola, 2013; Ravaglia et al., 2005) and AD accounts for 60–80% of all dementia cases (Alzheimer's Association, 2015).

Figure 5. The Alzheimer's Spectrum of Disorders.



The spectrum ranges from dementia due to arteriosclerosis/ microangiopathies and other cerebrovascular insults (red) to the "mixed" form of dementia seen in Alzheimer's disease (purple) to the type of decline noted from insulin resistance and other types of metabolic dysfunction such as diabetes mellitus (blue). The "mixed" forms of dementia may include both plaque/ tangle formation combined with cerebrovascular insults (Left) or this may both plaque/ tangle formation combined with insulin resistance/ metabolic dysfunction (Right). Ultimately, patients diagnosed with Alzheimer's disease are likely to present with symptomology that falls somewhere on this spectrum, but are still considered patients suffering from an Alzheimer's-related disorder. Taken together, these types of dementia are not completely distinct from one another, and have many areas of overlap that fall on a spectrum of relatedness.

The Five Systems of Dysphagia & The Alzheimer's Spectrum of Disorders

The next topic of discussion will expand on the established foundation of the Alzheimer's Spectrum of Disorders, and take into account the deterioration of 5SysDys. Previously, we discussed the role of 5SysDys on deglutition (Winchester & Winchester, 2015). Cognitive strategies for executing neurological functions, adapting behaviors for safe deglutition under various conditions, adjusting body positions, perceiving the body as a unit, and perceiving the entire eating experiences as a unit are just a few of the necessary cognates involved in safe deglutition (Winchester & Winchester, 2015). The muscular system of dysphagia (MuscDys) has strong physical and mechanical components in deglutition that interact with the individual's neurological, respiratory, and gastrointestinal systems (NeuroDys, RespDys, & GIDys, respectively). There is a complex interaction among 5SysDys in terms of nutrition, nourishment, healthy functioning, and patient safety (Winchester & Winchester, 2015). The type of cognitive functioning seen in MCI puts the individual at risk for Cognitive Dysphagia (CogDys). Shockingly, no investigations exist in the literature, which specifically elucidate the relationship between 5SysDys and MCI, or its subtypes. Further patient-oriented clinical research is crucially needed in this area.

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Given the established relationship of cognitive and neurological decline with dysphagia, it is no surprise that many MCI and early-to-moderate AD patients experience an impairment in all four basic taste sensations, a loss of appetite, and a change in food preference. These changes can correlate with decreased body weight and deglutition changes that put them at risk for malnutrition, dehydration, and/or a common cause of death in AD patients, aspiration pneumonia (Humbert et al., 2010; Kai et al., 2015; Wada et al., 2001). Upwards of 80% of AD patients suffering from cognitive dysfunction and neuropsychiatric disturbances, such as hallucinations and clinical depression, have dysphagia and significant changes in eating habits (Kai et al., 2015). The overall rates of eating disturbances are as much as 24.5% in moderate to severe AD patients, 15.2% in mild AD patients, and 19.8% in MCI patients, but only 6% in healthy aged adults, respectively (Kai et al., 2015). AD patients require greater assistance with feeding, such as partner-initiated or subject-initiated cues and/or direct assistance, corresponding to prolonged swallow duration for the oral transit duration of food as well as pharyngeal respond duration and total swallow duration of liquids (Priefer & Robbins, 1997).

Evidence from the literature shows a clear relationship between AD decline and 5SysDys (Humbert et al., 2010; Kai et al., 2015; Priefer & Robbins, 1997; Wada et al., 2001). What remains unclear is how 5SysDys vary among the AD Spectrum, and how a breakdown of 5SysDys develops during the MCI stage. In the following sections, this perspective will further elucidate the relationship between 5SysDys and the AD Spectrum.

Alzheimer's Disease Dysphagia

AD dysphagia includes delayed pharyngeal swallow onset, reduced lingual movement, difficulty with oral preparation of the bolus, pharyngeal clearance, upper esophageal sphincter opening, and visible aspiration on instrumentation evaluations, corresponding to breakdown in the NeuroDys, MuscDys, RespDys and GIDys (Winchester & Winchester, 2015). AD-related degeneration occurs in the antero-medial temporal cortices; a region involved in the swallow reflex and memory functioning. When AD patients had swallow trials of varying bolus consistencies, they had decreased hemodynamic responses (i.e., BOLD responses which are an MRI correlate of neuronal activity) bilaterally in the precentral gyri (Humbert et al., 2010). Further, during transition of a water bolus from the oral to the pharyngeal stages of the swallow, AD patients had decreased BOLD responses in the right hemisphere's inferior and middle temporal gyri, right superior parietal gyrus, right rolandic operculum as well as in the left supramarginal gyri and both the pre and postcentral gyri, bilaterally (Humbert et al., 2010). These regions are involved in tongue elevation during the swallow in healthy adults (Martin et al., 2004), and their decreased cortical functioning found in AD patients may contribute to AD-related breakdown of 5SysDys.

AD patients, during saliva-only swallow trials, had greater BOLD activation bilaterally in the supplementary motor area, left hemisphere's precentral gyrus, inferior and middle temporal gyri, inferior frontal gyrus pars opercularis, and right hemisphere's middle cingulate gyrus. Each of these regions has been associated with cortical activation during tongue propulsion when a bolus is transited from the oral to the pharyngeal stages of the healthy/functioning swallow (Martin et al., 2004). One explanation may be that when tongue elevation is decreased due to 5SysDys breakdown in AD patients, they are attempting to transit the bolus more quickly to compensate. Further evidence on the relationship of tongue propulsion to tongue elevation during the swallow of AD patients is warranted. Finally, significantly greater BOLD activity was noted in the right hemisphere's postcentral gyrus when AD patients swallowed water compared with swallowing saliva, possibly because water elicits sensory stimulation when compared to one's own saliva, and this area is important in sensory function during the swallow (Humbert et al., 2010).

The evidence demonstrates that although there is clear 5SysDys breakdown in AD, particularly in the neurological domain, some preserved sensory function is apparent despite documented changes in gustatory function (Kai et al., 2015). AD patients have significantly less hyoid and laryngeal elevation than healthy aged adults that is paired with longer durations of laryngeal vestibule closer (Humbert et al., 2010). The areas of the pre and postcentral gyri are

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commonly active during the normal swallow, regardless of age group or disease state, but they are not generally deteriorated in the early stages of AD. They receive input from the insula, an area involved in swallow preparation (Humbert et al., 2010; Martin et al., 2004) and the insula is an area that deteriorates in the early AD stages. Input to the pre and postcentral gyri via the insula can affect their functioning and result in NeuroDys/CogDys in AD patients. The insula also receives active input from areas of the temporal cortices during swallowing, and temporal cortical atrophy in AD may further impede insular function and its functionally connected regions. Insular and medial temporal cortical impairments may affect the AD patient's ability to initiate and execute an effective swallow (Humbert et al., 2010); demonstrating AD-related 5SysDys breakdown.

The literature supports the claim that cortical deterioration due to amyloid plaque and neurofibrillary tangle accumulation, combined with cardiovascular and metabolic dysfunction in AD, results in 5SysDys breakdown. In the subsequent sections, we will parse and elucidate the 5SysDys breakdown for VasD and DM.

Vascular Dementia Dysphagia

While there is an established foundation for the interaction of 5DysSys and AD, some variability among the AD Spectrum is apparent. For example, there are different patterns of swallowing disorders in AD vs. VasD. AD patients are significantly more impaired in oral transit delay over 5 seconds with liquids (e.g., NeuroDys and MuscDys), whereas VasD patients show more difficulty in bolus formation and mastication of semisolid food, hyolaryngeal excursion, epiglottic inversion, and silent aspiration (e.g., MuscDys and RespDys, respectively). It is possible that AD-related dysphagia results from sensory impairment in relation to dysfunction in the temporparietal areas. However, VasD dysphagia is primarily caused by motor impairments due to disruptions in the corticobulbar tract, a tract involved in breathing mechanisms (Suh, Kim & Na, 2009) and represents CogDys, NeuroDys, MuscDys, and RespDys. Though, both AD and VasD can lead to significant breakdown of the 5SysDys, each kind of disorder within the AD Spectrum may demonstrate overlapping, yet distinct, patterns of 5SysDys breakdown.

Previously, it was established that patients along the AD Spectrum could have impaired taste sensations. We propose that this impairment may contribute to additional aversions to bolus textures and temperatures. It may be that the impaired taste sensation indirectly contributes to a heightened sense of textures and temperatures. The multidisciplinary team must take into account the texture preference of the patient, but not confuse this with consistency. Here, we refer to texture preference as what the patient considers pleasurable as a sensation on the tongue, because this sensation may be heightened due to other impaired sensations. Not taking texture consistencies into account could increase the patient's dysphagia and aspiration risks if the patient were to spit the food back out due to a food aversion. To avoid increasing patient risk, the multidisciplinary team may consider engaging the patient in one or two sessions where pleasurable food texture trials are presented. This process may be broken up into a session that is coupled with instrumentation, to ensure that safe consistencies are utilized, and a session following therapeutic interventions.

For this purpose, the multidisciplinary team may consider the incorporation of therapeutic techniques, which specifically target MuscDys, RespDys, and NeuroDys in VasD patients. Subsequent therapy should include functional interventions to prolong independence and increase patient safety. The speech-language pathologist (SLP) may consider the use of comprehensive instrumentation to ensure that safe food consistencies are evaluated to reduce silent aspiration risk in VasD patients, and this is consistent with previous research in early AD patients where alterations in bolus consistency have been successful in increasing patient safety (Humbert et al., 2010).

The SLP may also consider deep pharyngeal stimulation or other electrical stimulation techniques that could strengthen the musculature or heighten the patient's awareness of the bolus in one or more domains. Oral exercises that focus on tongue strengthening, range of motion, and/or the use of an assistive feeding device such as a sip cup or straw could be useful in this population. Finally, cueing exercise and caregiver education could increase patient success, especially if the VasD is more advanced. Ultimately, the VasD population has more difficulties

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along the motor dimension when compared other patients long the AD Spectrum, and therapeutic recommendations must take this into account.

Diabetes Mellitus Dysphagia

The interaction of 5SysDys and the AD Spectrum varies depending on where the patient falls along the Spectrum. However, one similarity among AD, VasD, and DM is the correlation with an increased risk of 5SysDys breakdown resulting in aspiration pneumonia (Zhao, Frokjaer, Drewes, & Ejskjaer, 2006). Particular to DM, white matter tract deterioration between the prefrontal and medial temporal cortices have been identified, which correspond to progressively deteriorating memory function (Ryan et al., 2014). Many of the cognitive domains that deteriorate in DM are highly dependent on the white matter connectivity between the prefrontal and medial temporal cortices (Ryan et al., 2014), affecting NeuroDys and CogDys in this population.

DM deterioration of prefrontal cortical connectivity can have widespread effects on deglutition. Several studies demonstrate the connectivity of the prefrontal and motor cortices via thalamic relays and the functional connectivity of the motor and thalamic relays to the execution of the swallow (Babaei et al., 2013; Behrens et al., 2003; Martino et al., 2008; Mosier & Bereznaya, 2001; Zhang et al., 2008). The prefrontal cortex, then, plays an additional role of orchestrating thoughts and actions in accordance with internal goals of the individual, possibly through the maintenance of activation patterns that represent goals and the means to achieve them. In doing so, the prefrontal cortex acts as a way to bias signals to other areas of the cortex that, in turn, affect the flow of neural pathway activity in establishing mappings among inputs, internal states, and needed outputs in task performance (Miller, 2001). The functional and anatomical connectivity of the prefrontal, medial temporal, thalamic, and motor cortices interact with the brainstem during the swallow.

All types of dementia along the AD Spectrum have GIDys, but DM is associated with a significant level of GI dysfunction that may be due to the particular type of autonomic neuropathy commonly found in DM patients (Lluch et al., 1999; Zhao et al., 2006). DM GIDys includes impaired sensation and motor function, gasteroesophageal reflux disease (GERD), esophagus, small/large bowel and stomach dysmotility, and delayed transit/emptying (Bytzer et al., 2001; Lluch et al., 1999; Zhao et al., 2006). GIDys, here, may further disrupt the already impaired CogDys, NeuroDys, MuscDys, and RespDys of DM patients.

The evidence for the relationship between dysphagia and the AD Spectrum, as well as the variability of this relationship among AD Spectrum patients, is apparent. For aMCI patients with metabolic dysfunction, insulin resistance, and/or DM, the multidisciplinary team must focus on controlling the GERD and accounting for fatigue in all therapeutic recommendations. Many of the symptoms described in the previous sections are observable at earlier stages in the progression from MCI to the AD Spectrum. Therefore, the present perspective will discuss the relationship of 5SysDys and MCI in the subsequent sections.

Mild Cognitive Impairment & The Five Systems of Dysphagia

A detailed account of the recommendations on the clinical criteria for the diagnosis of MCI have been published previously and can be resourced for further background information on MCI (Albert et al., 2011). The current perspective assumes a fundamental understanding of MCI. We take the discussion further by focusing on the relationship of dysphagia with the type of MCI likely to convert to one of the dementias in the AD Spectrum within a short time period, Amnestic MCI (aMCI). aMCI is considered a prodromal phase between healthy aging and AD because upwards of 80% of all aMCI patients progress to AD status within an average of 6 years (Karas et al., 2008; Whitwell et al., 2007). Biomarkers of AD pathology are found in aMCI patients and predicts 95% MCI to AD conversions (Ewers et al., 2012; Fleisher et al., 2007; Hansson et al., 2006). Adults with aMCI have reduced cerebral glucose metabolism in the posterior cingulate, precuneus,

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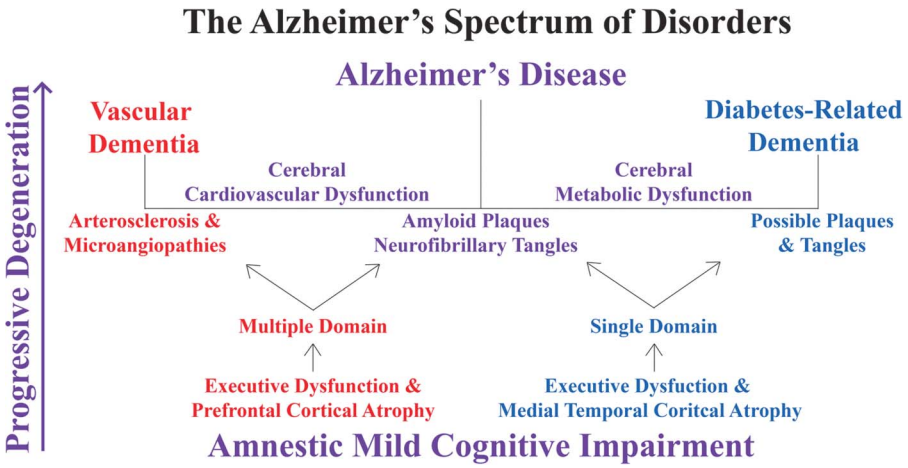
parietotemporal, and frontal cortices; have poorer memory performance; and exhibit signs of amyloid plaque accumulation (Baker et al., 2011).

The subcategories of aMCI are Single Domain Amnestic (SaMCI) and Multiple Domain Amnestic (MDaMCI), respectively (Fischer et al., 2007). A portion of patients with SaMCI will convert to a status of AD within a short number of years (Ewers et al., 2012; Landau et al., 2010). Patients with MDaMCI are highly likely to convert to a status of AD or VasD (Fischer et al., 2007; Petersen et al., 2006; Rasquin, Lodder, Visser, Lousberg, & Verhey, 2005; Whitwell et al., 2007).

Individuals with SDaMCI are more likely to progress to a status along the AD Spectrum that includes amyloid plaque and neurofibrillary tangle formation, with possible insulin resistance, DM, and/or metabolic dysfunction. SDaMCI patients are likely to present with memory dysfunction that corresponds to deterioration in the medial temporal lobe, particularly in the hippocampal region. Individuals with MDaMCI are more likely to present with other cardiovascular-based complications, and may or may not present with amyloid plaques and/or neurofibrillary tangles. Additionally, they are likely to have executive dysfunction that correlates with prefrontal cortical atrophy (See Figure 6).

Figure 6. Amnestic Mild Cognitive Impairment (MCI) Progressively Degenerates to the Alzheimer's Spectrum of Disorders.



Among patients with amnestic MCI (bottom), individuals with multiple-domain MCI are likely to convert to a status of vascular dementia or the "mixed" vascular/Alzheimer's-type dementia (red, left). Those individuals with a single-domain MCI diagnosis are likely to convert to a status of the "mixed" metabolic dysfunction/Alzheimer's-type of dementia or the type of dementia noted in diabetes mellitus and other metabolic disorders (blue, right). Original Figure by Jeanna Winchester, PhD.

The question that remains is the degree to which one can expect the dysphagia severity to be when a patient presents at the SDaMCI and MDaMCI stages. It is possible that SDaMCI patients without the presence of a DM diagnosis, who present with amyloid plaque and neurofibrillary tangle neuropathology and cerebral glucose impairments in the medial temporal lobe, would demonstrate notable alterations in BOLD response that is dependent on the bolus consistency presented, such as that found in AD. SDaMCI patients can possibly convert to a status of DM-related dementia, depending on the extent of their glucose metabolism dysfunction.

We propose that this population may experience altered taste sensations. The severity of the dysphagia symptoms at this stage would largely be dependent on the amount of AD pathology accumulation in the cortex, their activity levels in their daily lives, and the relationship of 5SysDys

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breakdown known to be common among non-dementia co-morbidities found in community-dwelling elderly residents. In the absence of other possible co-morbidities, a high level of daily activity and a low amount of AD neuropathology accumulation, the patient's 5SysDys breakdown may be relatively mild. For individuals with more increasing severity in any of those aspects of living with SDaMCI, the ramifications among 5SysDys could be quite severe. It is unknown whether or not SDaMCI patients would have documented alterations in hyoid/laryngeal elevation and duration of laryngeal vestibule closer at the MCI stage, because only prospective, clinical research utilizing fMRI, neuropsychological, neurocognitive, dysphagia instrumentation, and comprehensive MCI diagnostic criteria could illuminate that relationship.

Individuals with the SDaMCI diagnosis and a DM co-morbidity diagnosis could see similar dysphagia symptom presentations, which may be compounded with GERD, esophageal/bowl/stomach dysmotility, and delayed transit/emptying. This may lead to additional RespDys, MuscDys, and exacerbated NeuroDys/CogDys due to nature of the interaction among these systems. Comprehensive dysphagia management evaluations that utilize instrumentation may be effective in designing a treatment plan that would address all 5SysDys and increase patient safety (Winchester & Winchester, 2015). Both types of SDaMCI patients, regardless of DM status, would likely have difficulties with rehabilitation, because comprehension of the risks to his or her safety may be compromised. Due to the breakdown of the medial temporal cortices and their role in effective memory functioning, the patient may not be able to learn or relearn safe deglutition techniques, and/or muscular training further impairing their ability to make safe judgments when it comes to eating/swallowing (Winchester & Winchester, 2015).

Depending on where the MDaMCI patient falls along the AD Spectrum (independent of documented insulin resistance, DM, or metabolic dysfunction), the patient may present with amyloid plaque and neurofibrillary tangle accumulation in conjunction with cerebrovascular disease. In this scenario, the patient would have probable atrophy of the prefrontal cortex and possible atrophy of the medial temporal cortex. MDaMCI patients are likely to convert to a status of AD within the next few years, and the severity of dysphagia-related complications is likely to be worse than those observed in the SDaMCI patients previously described. MDaMCI patients may have preserved taste sensations, but are more likely to have issues with bolus formation, mastication, hyolaryngeal excursion, epiglottic inversion, and, due to corticospinal tract dysfunction, have impaired oral/pharyngeal sensations that may contribute to silent aspiration. Depending on the number of domains impaired in MDaMCI patients, rehabilitation could be effective. Similar to the issues seen in SDaMCI patients, there will be issues with teaching compensatory strategies, impaired comprehension of patient safety, and difficulties with compensatory strategies. Comprehensive dysphagia management spanning MD, NSG, OT, PT, and ST has the highest likelihood of success for aMCI patients of either subtype (Winchester & Winchester, 2015).

Additionally, both subtypes of aMCI patients will have observable issues with the effective administration of medications. First, because of the amnestic nature of their deficits, caregiver and/or NSG oversight of medication administration is vital to patient safety. Patients may accidentally undertake or overtake medication that could further exacerbate the 5SysDys already in existence, and impaired deglutition would cause issues with safely ingesting the medication. Last, patients with neuropsychiatric disturbances may become apathetic, agitated, depressed, or may even hallucinate. The patient may not totally comprehend the reason(s) for medication administration and/or how their medication may improve quality of life. This would cause a dangerous and complicated scenario for the individual tasked with administering the medication to the patient (Winchester & Winchester, 2015). Both aMCI subtypes are likely to start to withdraw from social gatherings, particularly those that involved eating situations, and the seclusion may contribute significantly to increased decline within a short time period.

Intervening at the MCI stage can have broad sweeping benefits to cognitively impaired patients. Due to the neurocognitive plasticity of the human nervous system (Winchester & Winchester, 2015), interdisciplinary intervention and rehabilitation may halt neurocognitive

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decline. If these patients are also able to receive comprehensive dysphagia management that is based on effective instrumentation and thorough diagnostic criteria, then improvements in deglutition corresponding with improved patient outcomes spanning 5SysDys are likely (Winchester & Winchester, 2015). Comprehensive interventions may or may not thwart future conversions to dementia; however, they are likely to affect the time course of those conversions, in a beneficial way.

A Broader Perspective on Dementia of the Alzheimer's Type

The broader perspective of viewing dementia related to AD, VasD, and DM as a spectrum of AD Disorders opens possibilities that have never before been exploited in the clinical community. The perspective affords both distinction and relatedness. It does not "box" patients into a particularly confined diagnosis, but instead allows for the patient variability that is representative of the AD population. Further, the relatedness among the spectrum allows the clinical community to magnify the treatment options available to the patient. For example, the multidisciplinary approaches of dietary and environmental changes compounded with physical and cognitive interventions have shown significant improvements in AD patients (Winchester et al., 2013). The multidisciplinary approach may be combined with utilizing pharmacological options in a different way than previously conceptualized. To that end, perhaps incorporating more cardiovascular disease-controlling medications in patients with metabolic dysfunction, insulin resistance, and/or DM could offer greater patient success, and vice versa. The spectrum allows for these alternate approaches because it emphasizes the relatedness clearly evident in the AD literature. It accounts for the respiratory, muscular, gastrointestinal, neurological, and cognitive dimensions in the AD, VasD, and DM.

Additionally, proposing that the diseases should be considered as Disorders of the AD spectrum presents a situation where we can clearly see correlations between the spectrum and 5SysDys. In early AD patients, alterations in bolus consistency have been successful in increasing safety (Humbert et al., 2010), suggesting that therapeutic interventions and an effective multidisciplinary dysphagia management could be successful in patients along the AD Spectrum. This comprehensive, though brief, review of the evidence demonstrates that there is some overall consistency and distinction among dysphagia symptoms associated with a diagnosis of AD. Further, the literature demonstrates how the 5SysDys degrade in a varying fashion among the AD Spectrum depending on whether the AD-related breakdown is of a cardiovascular, metabolic, or mixed pathology, and takes into account the progression from the aMCI stage. Overall, the present perspective is multidisciplinary, innovative, and may spark an evolution of dialogue in the clinical community.

Conclusions

There is variability among the AD Spectrum with respect to disease pathology, cognitive decline, and dysphagia. 5SysDys breakdown in this population includes cortical/network atrophy, which in turn affects the swallow functioning via altered oral transit, taste sensations, hyoid/laryngeal elevation, and laryngeal vestibule closure. 5SysDys breakdown is apparent at the MCI stage, and likely varies according the MCI subtype. Further research elucidating the relationship of 5SysDys breakdown to the subtypes of MCI is critically needed.

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