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# Non-Demented Individuals with Alzheimer's Disease Neuropathology: Resistance to Cognitive Decline May Reveal New Treatment Strategies

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## Abstract

Alzheimer's disease (AD) is a terminal neurodegenerative disorder that is characterized by accumulation of amyloid plaques and neurofibrillary tangles in the central nervous system. However, certain individuals remain cognitively intact despite manifestation of substantial plaques and tangles consistent with what would be normally associated with fully symptomatic AD. Mechanisms that allow these subjects to escape dementia remain unresolved and understanding such protective biological processes could reveal novel targets for the development of effective treatments for AD. In this review article we discuss potential compensatory mechanisms that allow these individuals to remain cognitively intact despite the typical AD neuropathology.

### Keywords

Alzheimer's disease; Non-Demented with Alzheimer's Neuropathology; compensatory mechanisms in AD; resistance to cognitive decline

## 1. INTRODUCTION

Alzheimer's Disease (AD) is the most common form of dementia, affecting more than 47 million people woldwide [1]. AD is a multifactorial disease that is characterized by cognitive decline and unique neuropathology. Microscopic changes in the brain begin long before memory loss [2]. Synapse loss is believed to occur at early stages of the disease [2, 3], while overt cell death occurs at later stages and is directly related to cognitive decline [2]. Two main neurodegenerative processes in the AD brain are amyloidogenesis and neurofibrillary degeneration [4]. Amyloidogenesis leads to deposition of extracellular amyloid beta (Aβ) peptide, while aggregation of hyperphosphorylated tau protein is known as neurofibrillary degeneration.

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**CONFLICT OF INTEREST**

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Several research groups, including ours, have described individuals that remain cognitively intact in spite of having accumulation of Aβ and neurofibrillary tangles (NFTs) to an extent comparable to that normally observed in fully symptomatic Alzheimer's disease [5–8]. We refer to these individuals as "Non-Demented with Alzheimer's Neuropathology" (NDAN) [9]. Thus, NDAN individuals manifest AD-like pathology, however they remain cognitively intact. Due to the fact that AD-like pathology is observed in the brain of these individuals, they have also been termed "cognitively successful aging", "pathological aging", "asymptomatic AD", "resilient AD" and "preclinical AD" [8, 10–13]. In this article we aim to review the current literature about non-demented subjects that manifest AD-like pathology.

## 2. DISCUSSION

### 2.1. Classification of AD and NDAN

Latest progress in neuroimaging and advancement of other laboratory assays have allowed to effectively monitor the progression of AD neuropathology *in vivo*. Presence of Aβ aggregates in the brain of affected individuals can be correlated with structural and functional alterations in mild cognitive impairement (MCI) and AD patients [14]. It is also recognized that a certain cohort of individuals with AD-like neuropathology do not become symptomatic during their lifetime. As we continue to learn more about early stages of AD, the need to redefine the disease emerges. At the same time we still need to discover more biomarkers that will help us define the severity of the disease and predict development of clinical symptoms, as well as define the individuals that will not progress to AD dementia. We will need to develop a set of biomarkers which allows to detect the degree of synaptic loss, Aβ and NFT accumulation, inflammation and other markers that could aid in more accurate diagnosis and prognosis of AD. In 2012 Alzheimer's Association workgroup in the diagnostic guidelines for Alzherimer's Disease, part of National Institute on Aging, suggested that during diagnosis we should separate those individuals that present with dementia and AD pathology from cognitively intact indivuals with typical AD neuropathology. The latter group of individuals can be described as "asymptomatic at risk for AD dementia", or "not normal, not MCI" [14]. It remains unknown, however, if these individuals would have developed AD should they have lived longer. Several studies describe the presence of Aβ aggreagates and other biomarkers in 20–40% of older individuals that are cognitively intact [15–23]. However, multiple studies demonstrate that these cognitively normal individuals have disrupted functional networks [24–26] and some brain atrophy [27]. Sperling *et al.* suggest that aberrant neural activity is associated with Aβ deposits and appears before cognitive impairment [24]. The same group has also noticed increased hippocampal activity which could indicate existence of compensatory mechanism.

It is clear that more longitudinal studies are needed in order to describe different stages of asymptomatic and clinical AD.

### 2.2. Potential Compensatory Mechanisms

It has been established that Aβ deposition in cognitively normal individuals can be observed. Bjorklund *et al.* report that NDAN vs AD individuals have comparable levels of Aβ plaques

and NFTs, low molecular weight Aβ oligomers and $A\beta_{1-42}$ levels in their brains [9]. Also the pattern of distribution of plaques and tangles has been reported to be the same in AD and NDAN [21]. However, it is not yet clear if presence of Aβ plaques in NDAN should be interpreted as an early event in AD pathogenesis (preclinical AD) or if there are mechanisms that are present in these people allowing them to counteract the toxicity of Aβ and therefore remain cognitively intact. Multiple groups report the results of PET imaging using Pittsburg Compound B (PiB) in healthy aged individuals, including those older than 85 years of age [15], which indicates that these subjects may indeed be resistant to Aβ toxicity. Understanding the protective mechanisms at play in these resistant individuals would be of great importance for the development of effective therapies. Here we review some of the proposed protective mechanisms that could be responsible for resistance to AD or significant delay of clinical symptoms in NDAN individuals.

**2.2.1. Hippocampal Volume—**The volume of the hippocampus is a well-established criterion that allows for discriminating healthy and AD subjects. Gosche *et al.* performed a study involving 56 brains of nuns of the School Sisters of Notre Dame congregation and concluded that hippocampal volume correlates well with the AD neuropathology [28]. In their study, they also looked at brains of nuns who had significant AD neuropathology (44% of total number of cases), but were non-demented during their life. These non-demented subjects with Alzheimer's neuropathology had some brain atrophy, which allowed the authors to conclude that hippocampal atrophy is not AD specific.

One of the hypotheses is that the presence of AD lesions in the brain may be insufficient to cause cognitive decline in these individuals due to larger brain reserve [6]. Some reports show that total brain and hippocampal volume are greater in cognitively intact subjects with high load of Aβ plaques and NFTs [2]. Additionally, higher number of synapses and enlargement of neuronal nuclei are hypothesized to correlate with preserved cognitive function [6–8]. In the study by Chetelat *et al.* the healthy individuals with high Aβ loads presented larger global and regional grey matter volumes when compared to cognitively impaired subjects with high Aβ [29].

Regulation of apoptosis has been suggested as one of the potential explanations for larger brain volume [6, 30]. Large neuronal loss is typical for late stages of AD and is thought to be intitiated by the presense of plaques and tagles, however the execution of apoptosis may be different in NDAN. Indeed, one can argue that Aβ plaques and NFTs do not cause neuronal death, which is supported by phenomena observed in NDAN.

Other research groups find brain atrophy in non-demented individuals with high pathology. They report that even though the atrophy is present, the progression rate is consistent with normal aging [27]. Some studies report that hippocampal atrophy is not significant when compared to no pathology control [17]. And other studies do not find any difference in hippocampal volume [31]. The discrepancies in the results discussed here could be due to different participant inclusion/exclusion criteria, the assessment being done ante- or postmortem and/or the acquisition parameters used in the MRI studies.

**2.2.2. Cognitive Reserve—**"Cognitive reserve" represents the ability of the brain to engage alternate networks or cognitive strategies to manage the effects of pathology [14]. This hypothesis leads to two predictions: aged individuals with more education are expected to demonstrate less cognitive impairment when compared to people with less education, and, on the other hand, comparison of subjects with similar cognitive status would reveal more severe changes in brain structures in those subjects who have higher education due to the fact that original cognitive reserve can provide a "buffer" that will allow these individuals to resist dementia [32–35]. This can explain why there are several studies reporting higher atrophy in cognitively intact individuals who have AD neuropathology.

In several studies, high socioeconomic status has been associated with resistance to AD [36]. Fotenos *et al.* report that individuals with higher socioeconomic status are able to withstand the typical AD pathology for extended time due to unknown mechanisms [37]. Even though the non-demented people with AD pathology demonstrated reduced brain volume when followed in this longitudinal study, they did not manifest cognitive decline. Some participants began to show early signs of dementia, however individuals with higher socioeconomic status remained non-demented throughout the study [37].

Ngandu *et al.*, based on their study of a Finnish cohort, conclude that level of education is not associated with other risk factors for dementia and less education correlates with higher risk for dementia [38]. It is, however, hard to determine if the cognitive reserve is innate, or if it is set during childhood years or later during adulthood. Another possibility is that more years of education allow people to make better choices regarding their lifestyle, thus leading to better overall health and decreased risks for dementia [38].

**2.2.3. Brain Reserve—**The hypothesis of greater brain reserve refers to the ability of the brain to resist the pathological insult, possibly due to greater synaptic density or larger number of healthy neurons. High brain reserve can be associated with up to 50% reduction in prevalence of dementia [39].

In 1988 Katzman *et al.* have described a group of individuals "nondemented with Alzheimer's changes" which have higher number of large neurons when compared to age-matched healthy control and AD brains; they also reported higher brain weight when compared to control and AD [23]. They find these individuals to be intermediate between control and AD and they hypothesized that "nondemented with Alzheimer's changes" subjects are able to escape shrinkage of large neurons that usually occurs during aging. A possible explanation for these results is that larger brains and greater number of neurons since early in the life of these protected individuals would provide a "reserve" allowing them to cope with age-associated losses.

SantaCruz *et al.* report non-demented individuals to have heavier brains when compared to demented AD patients [40]. Interestingly, individuals with higher socioeconomic status or those with larger brains are less likely to develop dementia, whereas, having both high education and larger brain does not provide an advantage to lower the risk of dementia [41].

It may require more pathology for the individuals with greater brain reserve to manifest clinical dementia [42, 43]. By the time the dementia is detectable in those with higher brain reserve, most likely the brain has already accumulated substantial pathology, which results in the observation that those individuals with greater brain reserve die sooner after AD diagnosis [44]. Along these lines, there is also some evidence that people with higher education and IQ experience quicker cognitive decline [45–47].

In concordance with the reserve theory, higher levels of leisure activity prior to the manifestation of clinical symptoms of AD are linked to more severe neuropathology and progression of the disease [48].

**2.2.4. Insulin Responsiveness—**The link between insulin resistance and progression of AD has been established [49]. Insulin resistance is a characteristic of type II diabetes mellitus and it is also present in AD [50, 51]. Insulin, a key player in CNS signaling, has been proposed as a therapeutic target for AD. Insulin prevents binding of Aβ oligomers to the synapse thus improving cognitive performance in patients with early AD [52, 53]. Aβ oligomer binding ability to synapses decreases due to insulin-dependent reduction of binding sites [52]. By preventing the binding, insulin provides protection from Aβ-induced synapse retraction, oxidative stress and insuin receptor loss [52]. When used *in vivo*, the insulin-sensitizing drug rosiglitazone has shown some promising results in mouse models of AD and some clinical trials in early AD patients [54–56]. In a small preliminary clinical trial, rosiglitazone showed beneficial effects in terms of cognitive improvement during the treatment period; however, the effect was short-lived, ceasing as soon as the treatment was withheld [54]. This suggests that insulin-sensitizing medications can affect the symptoms of AD, but not the underlying pathology. Unfortunately, phase III clinical trials with insulin-sensitizing drugs have returned negative results [57, 58].

Insulin signaling increases the levels of insulin-degrading enzyme (IDE), which can degrade insulin and also monomeric Aβ [59, 60]. IDE was found to be increased in AD when compared to NDAN, which suggests that degradation of insulin is increased in AD and, consequently, glucose metabolism impaired in affected brain cells [13].

Levels of key insulin signaling elements downstream of activated insulin receptors that are decreased in AD [51, 61], are maintained in NDAN hippocampi, and in some cases even higher than control (Taglialatela, unpublished). Using Western blotting we have measured several markers of the insulin signaling pathway, including insulin receptor, insulin receptor substrate 2, pAkt and pGSK-3β in post-synaptic densities (PSDs) in control, AD and NDAN hippocampi. We observed a high degree of activation of all four proteins in NDAN that was significantly greater than AD and exceeded the levels observed in controls. Silva *et al.* reported higher pAkt in NDAN when compared to AD, which is consistent with our findings [30]. Collectively these results suggest that NDAN individuals have increased insulin sensitivity at the PSD when compared to AD.

**2.2.5. Synaptic Health—**The number of synapses has been shown to be positively correlated with cognitive testing results, while Aβ oligomers have been suggested as a potent cause of synaptic loss in AD [62]. The mechanism of Aβ synaptotoxicity is not fully

understood, but it is hypothesized that Aβ oligomer association with the PSD results in disturbed $Ca^{2+}$ signaling in dendritic spines, which can affect multiple downstream pathways [63]. Aβ oligomers can interact with multiple proteins and receptors at the PSD, including α7-nAChR (α7-nicotinic acetylcholine receptor), AChE (acetylcholinesterase), PrPc (prion protein), NMDAR (N-methyl-D-aspartate receptor), TNF-R (tumor necrosis factor receptor), α2β1 and αVβ1 integrins, NL-1 (neuroligin-1) and others [64]. Association of Aβ oligomers with the PSD implicates dephosphorylation (deactivation) of CREB (cAMP response element-binding protein factor), which in turn affects transcription of genes regulating long-term changes in synaptic strength [65].

Synapses are the most vulnerable neuronal structures in AD and, interestingly, the number of synapses and levels of synaptic markers are preserved in NDAN [13, 62, 66, 67]. Low molecular weight Aβ species are present at PSDs of AD brains, however they are rejected by NDAN synapses [9]. Absense of Aβ oligomers at the PSD of NDAN can be potentially explained by regulation of $Zn^{2+}$ homeostasis [9]. Aβ oligomers can be targeted to the synapses by synaptic $Zn^{2+}$ [68]. Bjorklund *et al.* report that AD brains have significantly higher $Zn^{2+}$ levels, while NDAN samples have more than control, but less than AD [9]. Additionally, levels of pCREB, an indicator of synaptic health, were similar in control and NDAN, however significantly reduced in AD [9]. This observation suggests that synaptic integrity is indeed preserved in NDAN. To further understand if the PSD of NDAN subjects possesses additional protective mechanisms, we have performed proteomic analysis of PSDs of control, AD and NDAN (Zolochevska *et al.*, in preparation). We have determined a set of proteins that are unique to PSD of NDAN subjects, further suggesting that critical structural/biochemical changes at the NDAN synapse can contribute to its resistance to Aβ impact.

**2.2.6. Neurogenesis—**Neurogenesis in adult human brain was first described in 1998 in cancer patients who had received BrdU for diagnostic purposes [69]. Proliferating progenitor neural cells were found in the subventricular zone of the lateral ventricles and the granule cell layer and subgranular zone of the dentate gyrus, which served as a confirmation of continuously active neurogenesis in humans [69]. The newly formed neurons have been shown to integrate into existing networks (reviewed in [70]). There are many factors that can alter neurogenesis. As reviewed by Farin *et al.*, aging, stress, antidepressants, exercise, neurotrophic factors can all play a role in neurogenesis in adult organism [71]. Levels of neurotrophic factors are altered in AD [72, 73], including brain-derived neurotrophic factor (BDNF), which is known to play a role in regulation of basal level of neurogenesis [74]. We found increased levels of BDNF (Baymon *et al.*, in preparation) and neurogenesis in NDAN (Briley *et al.*, in preparation), which could both contribute to preserved cognition in these resistant individuals.

Dysregulation of cell cycle (an important determinant in neurogenesis) has also been reported in AD [30]. Markers of cell cycle progression (Cdk4, cyclin D, pRb, E2F1, Cdk1 and Cyclin B) are elevated and those of cell cycle inhibition – decreased (Cdk5 and p27) in AD when compared to control and NDAN [30]. Cell cycle regulation in NDAN is similar to control, which suggests that NDAN individuals possess a compensatory mechanism that allows them to retain control of cell cycle and thus neurogenesis [30].

**2.2.7. Oxidative Stress—**Oxidative stress and damage induced by free radicals has been hypothesized to cause synaptic loss in AD brains [75–78]. It has been suggested that oxidative damage is a very early event, which can lead to neuronal dysfunction and AD independently or in conjunction with other factors [79]. Silva *et al.* have measured levels of oxidative DNA damage, DNA repair pathway activity, cell cycle and cell death in healthy aged population, as well as AD and non-demented subjects with AD pathology [30]. They have demonstrated that control and NDAN subjects cluster very closely together for all studied parameters, whereas in most cases AD manifests significant changes when compared to the other two groups. Furthermore, levels of oxidative DNA damage as measured by 8-hydroxyguanine and λ-H2AX (both established markers of DNA damage) were significantly higher in AD when compared to control [30]. DNA repair proteins (P53, BRCA1 and PTEN) were significantly elevated in control and NDAN when compared to AD, which indicates the DNA repair pathway is a possible compensatory mechanism in NDAN allowing these individuals to maintain proper cognitive functioning and, therefore, resist memory impairment [30]. Additionally, we have assessed in NDAN and AD brains levels of APE1 and XRCC1, proteins involved in DNA repair pathway (Taglialatela, unpublished). APE1 levels were higher in control and NDAN when compared to significantly lower levels in AD. XRCC1, on the other hand, was significantly increased in NDAN when compared to control however it was significantly lower that AD, which is in agreement with the findings by Silva *et al.* of activated DNA repair pathway in NDAN.

**2.2.8. Neuroinflammation and Glial Activation—**Neuroinflammation is an important component of the events through which Aβ and NFTs manifest their detrimental neurodegenerative effects on the brain. Lue *et al.* report that, similar to controls, NDAN brains have significantly lower levels of inflammatory markers C5b-9 and LN3 when compared to AD [67]. Consistent with preserved cognitive ability, absence of inflammation in the brains of NDAN subjects can indicate a potential compensatory mechanism.

Maarouf *et al.* describe no differences in levels of inflammatory TNF-α cytokine and GFAP in AD *vs.* NDAN [13]. GFAP is elevated in regions with high pathology in AD brains, which is thought to indicate a response to trauma, chemical injury, neuroinflammation, and astrogliosis in dementia [80–82]. Interestingly, a significant increase in S100B level was found in NDAN when compared to AD [13]. S100B is produced by astrocytes and plays a role in protein degradation, cell movement, proliferation and differentiation, cytoskeleton assembly, regulation of transcription factors and enzyme activities and receptor functions [83–85]. S100B is considered to be a neuroprotective factor for cholinergic neurons during oxygen and glucose deprivation [86], and therefore the moderate increase in S100B levels observed by Maarouf *et al.* can be interpreted as a protective effect in NDAN.

AD brains are characterized by significant increases in the number of activated astrocytes and microglia when compared to control and NDAN [87]. Reactive glia in the brain of AD patients can be very toxic to neuronal function, and lack of such activation in NDAN might indicate the lack of synaptic and neuronal damage [87].

**2.2.9. Genetic Advantage—**Genetic mutations can provide an ability to resist a particular disease. Silva *et al.* describe significant changes in genes involved in energy

metabolism, cell cycle, DNA synthesis and repair, inflammatory signaling, and transcriptional regulation in AD and NDAN vs control [10]. While reporting that AD and NDAN subjects are overall transcriptionally similar, Silva *et al.* describe six genes which allowed them to distinguish these two groups, suggesting that differential expression of specific genes could represent a possible compensatory mechanism in NDAN to resist dementia [10]. Consistent with this possibility, multiple transcriptional changes were also observed in control vs AD and NDAN by Liang *et al.* [88]. Of these, several could be hypothesized as representing potential compensatory mechanisms underscoring NDAN resistance to dementia: inhibition of NFTs formation (changes in tau expression and tau kinases), inhibition of Aβ clearance pathway (lower levels of BACE1, presenilin 1 and 2), and changes in learning and memory processes [88].

Kramer *et al.* have utilized NDAN subjects to determine if there is a genetic mutation that promotes cognitive health in these individuals despite presence of AD neuropathology [5]. A genome-wide SNP (single nucleotide polymorphism) association study (GWAS) was conducted based on samples from non-demented subjects with and without NFT pathology [5]. There was no difference in education level and APOEε4 allele distribution between the two groups. Three reelin SNPs were found to be associated with higher AD pathology [5]. Reelin is an extracellular matrix protease that regulates microtubule function in neurons, plays a role in tau phosphorylation [89–91], and can protect against Aβ-induced decrease in long-term potentiation [92]. Reelin expression is elevated in hippocampal pyramidal neurons in AD and NDAN, which suggests that upregulation of reelin may be a compensatory mechanism in response to Aβ or tau-driven neuronal stress, even prior to dementia onset [5]. The same authors propose that SNPs in the reelin gene lead to disruptions in tau phosphorylation resulting in formation of NFTs [5].

## 3. CONCLUSION

Over the years, numerous studies have included non-demented individuals with Alzheimer neuropathology as a part of the control non-demented group when investigating Alzheimer's disease. NDAN subjects perform similar to healthy aged individuals that have no AD pathology. However, there are currently no biomarkers that can distinguish NDAN from healthy aged population with no AD pathology. NDAN individuals are able to preserve their cognitive function while maintaining normal levels of several biochemical and functional markers that are normally degraded in fully symptomatic AD. While several studies, including those described in the present review, report close clustering of biochemical and functional markers in control and NDAN, there are some discrepancies in the reported data which could be explained by different selection criteria used among different research groups to classify an individual as NDAN. Considering the clinical importance of understanding the involved mechanisms, there is still a pressing need for standardized inclusion criteria that would fully encompass the characteristics of NDAN subjects.

In the present review we have discussed potential mechanisms involved in preservation of cognitive function in NDAN individuals. Regardless whether NDAN are resistant to AD-related dementia, or whether they have extraordinarily delayed the onset of cognitive decline, understanding the involved molecular mechanisms would represent a significant

step toward developing a new therapeutic concept for AD centered on inducing cognitive resistance in spite of the occurrence of overt AD neuropathology.

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