Published in final edited form as:
Top Geriatr Rehabil. 2011 ; 27(4): 257–267.

Plasticity in Early Alzheimer's Disease: An Opportunity for Intervention

Nikki L. Hill, MS, RN,
Doctoral Candidate, School of Nursing, 201 Health & Human Development East, The Pennsylvania State University, University Park, PA 16802, Phone: (814) 404-0932, Fax: (814) 865-6625, nln101@psu.edu

Ann M. Kolanowski, PhD, RN, FGSA, FAAN, and
Elouise Ross Eberly Professor in the School of Nursing, 106 Health & Human Development East, The Pennsylvania State University, University Park, PA 16802, Phone: (814) 863-9901, Fax: (814) 865-6625, amk20@psu.edu

David J. Gill, M.D.
Penn State Milton S. Hershey Medical Center, Penn State College of Medicine, Department of Neurology, H037, 500 University Drive, P.O. Box 850, Hershey, PA 17033-0850, Phone: (717) 531-0003 ext. 283934, Fax: (717) 531-4694, dgill2@hmc.psu.edu

Abstract

The scientific evidence of plasticity, or the brain's dynamic ability to alter its organization and activation throughout one's lifetime, has increased significantly over the last decade. This analytic review evaluates selected evidence regarding the persistence of plasticity in people with early-stage Alzheimer's disease (AD). Functional neuroimaging provides persuasive evidence of plasticity throughout aging as well as the early stages of dementia, including the possibility of a heightened response during the prodromal period of AD. Behavioral outcomes research demonstrates the ability of people with early-stage AD to relearn previously forgotten information or otherwise improve cognitive abilities following a cognition-focused intervention. Both of these bodies of evidence support the existence of compensatory processes at work, even in the presence of dementia-related pathology. This retained ability of the brain to adapt to neurodegenerative disease in an attempt to maintain function may provide a valuable opportunity for intervention, particularly in the prodromal or earliest stages of AD.

The maintenance of cognitive functioning is a major determinant of healthy aging in older adults. However, many elders are at risk for debilitating cognitive decline due to age-related neurodegenerative disease such as Alzheimer's disease (AD) or other dementias. Dementia is a significant threat to the health and well-being of older adults, currently affecting an estimated 3.4 million individuals in the United States, or 13.9% of those 71 years and older,[1] and projected to affect 7.7 million by 2030.[2] The progressive cognitive decline associated with dementia is devastating for those diagnosed as well as their family members who frequently assume caregiving responsibilities. Although dementia is degenerative and progressive, utilizing a rehabilitation approach in people with dementia may maximize function, including cognitive function, and minimize excess disability.[3] In this paper, we propose that compensatory brain mechanisms likely underlie improved cognitive function among individuals with early-stage AD.

The brain's ability to adapt in response to a lifetime's experience, often termed "neuroplasticity" or "cognitive plasticity", is thought to be maintained to a certain extent throughout the aging process.[4] It can be induced by a variety of motor and cognitive experiences including aerobic exercise[5] and repeated engagement in cognitively stimulating

activities.[6] Plasticity processes are believed to provide some compensation for brain damage such as functional recovery after acute injury[7] and maintenance of cognitive abilities during aging.[8] Recently, there has been interest in utilizing retained plasticity mechanisms to delay the progression of dementia.

The purpose of this analytic review is to evaluate the current evidence regarding the persistence of plasticity in dementia, particularly in regard to prodromal and early-stage AD. We begin with a brief review of age changes commonly seen in the brain and discuss these changes in light of the pathological changes that occur in dementia. The concept of plasticity is then described, followed by a discussion of observational and experimental research supporting the existence of plasticity in normal aging, the prodromal period, and early-stage dementia. It is hoped the evidence presented here is useful to clinicians interested in developing early dementia interventions.

Normal Brain Aging and Changes in Dementia

A widely held view is that subtle cognitive changes occur in normal aging including declines in attentional ability, episodic memory function, working memory function, and processing/psychomotor speed.[9] These changes have been felt to be inevitable and to reflect continuation of age-related structural changes, including enlargement of the cerebral ventricles and sulci with commensurate decreases in grey and white matter volumes.[10] Because the cognitive profile as much as ten years prior to the diagnosis of AD can accurately predict whether a person will develop AD,[11] it is felt that the cognitive profile seen in “normal” brain aging is different from that of prodromal AD or other dementia. However, a significant number of cognitively normal elderly have similar neuropathologic changes to those seen in AD.[12] A recent autopsy study investigated this concept further and found that in their cohort, healthy elderly without the neuropathologic changes seen in the common causes of dementia had little to no cognitive decline with age.[13] These lines of evidence raise the possibility that the “normal” cognitive decline seen with aging actually reflects the effects of neuropathologic changes that cause dementia. Further research is needed to resolve whether there is “normal” brain aging in the absence of the neuropathologic changes seen in AD and other dementias.

Because of the possibility that the cognitive changes associated with “normal” brain aging may actually represent prodromal stages of dementia, it may be somewhat difficult to dichotomously distinguish cognitive and anatomic changes due to “normal” brain aging and those seen with dementia. This has led some to consider “normal” cognitive aging and dementia as parts of a continuum.[14] Along this continuum there is thought to be a prodromal stage of dementia in which a level of cognitive impairment is evident beyond what would be considered “normal” cognitive aging, but does not meet the diagnostic criteria for AD or other dementias. Controversy exists regarding the characterization of this period, but it is frequently referred to in the literature as Mild Cognitive Impairment (MCI).

MCI is characterized by the following criteria: cognitive complaint that is preferably corroborated by an informant; objective cognitive decline; preserved general cognitive function; intact activities of daily living; and, absence of dementia.[15] The MCI diagnosis is further divided into one of four clinical subtypes based on characterization of the cognitive impairment. The presence of memory impairment indicates amnestic MCI; impairment in other cognitive domains (such as language or visuospatial skills) with the relative preservation of memory indicates the non-amnestic subtype. Further distinction is made based on whether single or multiple cognitive domains are affected. The four MCI subtypes are described in Table 1. Amnestic MCI subtypes are associated with a high risk for dementia, particularly AD.[16, 17] When individuals with amnestic MCI were followed

longitudinally, they demonstrated primarily AD pathology on autopsy.[18] MCI may represent a transitional stage between "normal" changes associated with aging and the neuropathology associated with very early AD;[19] however, a consensus regarding the utility of the MCI diagnosis has yet to be reached in the scientific community.

Considering the insidious, progressive nature of dementia, it is intuitive to view dementia development as a continuum of decline, even in prodromal stages when diagnostic criteria are not met. At this time it is not known whether "normal" cognitive aging is, indeed, typical and expected, or rather indicative of emergent pathology which will eventually lead to overt dementia symptomatology.

Neuropathologic Changes in Dementia and Clinical Presentation

Dementia is a syndrome of gradual and progressive cognitive decline due to a variety of underlying pathologies. AD is the most common cause of dementia, although it is now recognized that up to half of all cases of AD demonstrate mixed pathologies on autopsy, such as vascular components.[20, 21] Therefore, reports of the prevalence of dementia subtypes are varied in the literature. Although neuropathologic features may overlap in some individuals, typical cognitive profiles and structural changes are found in each subtype. These are summarized in Table 2.

The clinical presentation and progression of dementia symptoms varies considerably among people with the same underlying level of pathology. Although two people may have the same amount of dementia-related brain damage, one may experience debilitating effects while the other demonstrates few symptoms. The observation of this phenomenon led to the conceptualization of cognitive reserve: the hypothetical ability of the brain, at varying individual capacities, to withstand a certain level of injury before the clinical manifestation of dementia.[22]

The level of cognitive reserve capacity is due to both innate protective effects as well as the ability of the brain to actively compensate for injury.[23] It is believed that some compensatory mechanisms are able to counteract symptoms until this ability is overwhelmed.[24] In this model, once an individual reaches his or her maximal premorbid cognitive ability, different factors are at play which either support maintenance of cognition or impair cognitive ability. The plasticity of the brain is thought to be a factor that contributes significantly to the ability to build cognitive reserve.[7, 23] There is support for this concept, beginning with the seminal paper by Katzman, et. al.[25]

Reserve includes both passive and active processes that modify risk for the clinical expression of disease. Passive reserve is accounted for by brain size and synapse density.[22] Individuals with larger brains and greater synapse density can tolerate more extensive pathology before they reach the threshold at which symptoms become clinically evident. Active reserve refers to the efficiency with which an individual can use alternate networks or cognitive strategies to cope with the brain pathology. Cognitive reserve is related to the brain's metabolic activity[26] and can be modified by mental activity. Brain reserve and cognitive reserve are not mutually exclusive. Mental activity is a strong signal for the generation of neurons and synapses.[27] Individuals are thought to possess innate cognitive reserve that allows dementia-related pathology to accumulate before symptoms are demonstrated, but also have the ability to actively build reserve as a compensatory mechanism for brain damage. Although individuals with higher cognitive reserve take longer to exhibit dementia symptoms, ongoing damage will eventually exhaust the brain's protective and compensatory abilities, leading to dementia manifestation and progression.[28]

In summary, while the neuropathologic changes associated with dementia are responsible for the ultimate manifestation of symptoms, there is wide variability in level of brain pathology and its association with clinical presentation. The cognitive reserve model attempts to explain these inconsistencies, including the possibility that plasticity mechanisms actively build reserve, leading to delay or reduction in dementia symptoms when neuropathology is present.

A Primer on Plasticity

Scientists and clinicians long believed that a damaged brain is unable to repair, reorganize, or regenerate under any circumstances.[29] Brain development was considered to occur during an organism's very early development, with little or no ability for neuronal tissue to change with injury or aging. However, the last decades of neuroscience research paint a radically different picture of the brain's ability to change its structure and function. It is now widely believed that new neurons and synapses are generated throughout life[30] and neural pathways continually remodel in response to changes in the organism's internal and external environment.[31] Although these phenomena appear to be more pronounced during early development, research suggests the brain maintains its ability to change its structure and function throughout life and well into old age. Evidence suggests that older adults have been shown to utilize additional or altogether different brain areas, presumably as a compensatory mechanism for age-related cognitive decline, and may employ unique strategies for storing and recalling information as they age.[8] The extent to which these capabilities are maintained in the presence of dementia pathology holds important implications for developing evidence-based interventions.

The ability of the brain to change its architecture and function is referred to broadly as *plasticity*.[32] Plasticity implies a degree of malleability; brain organization is altered during the course of maturation, adaptation to environmental changes, or post-injury compensation. The mechanisms of plasticity are plentiful and include neurogenesis, synaptogenesis, and angiogenesis, to name but a few.[33] Changes may occur at the cellular level through adaptation of neurons and supporting cells[34] or through adaptation of dendrites and synapses due to environmental stimuli.[35] In the damaged brain, it is thought that these changes occur in response to the limitations imposed by brain pathology in an attempt to maintain functional ability.

Several terms are often used interchangeably in relation to the broad concept of plasticity including neuronal plasticity (or neuroplasticity), brain plasticity, or cognitive plasticity. While neuronal plasticity implies structural modifiability at the synaptic level[36] and brain plasticity refers to alterations in the activation of brain networks,[37] cognitive plasticity refers to the ability of an individual to improve performance after training.[38] More broadly, plasticity herein may be conceptualized as brain adaptation in response to stressors induced by aging or neuropathology.

Evidence for Plasticity in the Aging Brain and Dementia

The persistence of plasticity throughout old age and the dementia trajectory has been studied primarily through the use of neuroimaging research; however, intervention studies, such as measuring the ability of people with dementia to relearn forgotten skills, also provide support.

Neuroimaging and Investigations of Plasticity

Functional neuroimaging studies examine brain activity patterns during the performance of a memory or other cognitive task. These investigations provide the opportunity to view the

brain regions which are activated during specific tasks and to compare these patterns of brain activity between groups. Both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are utilized for this purpose. PET and fMRI measure changes in the magnitude of blood flow in brain areas relative to others. In short, increased neuronal activity requires higher oxygen levels to support function; therefore, cerebral blood flow increases in areas of increased brain activation. Measures of regional cerebral blood flow provide an indirect measurement of brain activation patterns. Although both PET and fMRI infer brain activity by examining cerebral blood flow, units of measurement differ. PET measures regional cerebral blood flow (rCBF) while fMRI measures blood-oxygen-level dependence (BOLD) signals. Both are measures of hemodynamic response and can be performed while a subject engages in a memory or other cognitive task. Patterns of functional brain activity are evidenced by increased rCBF or BOLD signals in the areas under the highest task-related demand.

Compensatory activation of brain regions may include increased use of nearby brain areas during a task or the use of brain areas not typically associated with the task. These responses are thought to demonstrate plasticity of neural networks, which are altered presumably in response to cognitive demand. In individuals with damage to the brain, such as those with AD pathology, differences in magnitude or patterns of brain activation when compared to cognitively normal adults are often interpreted as evidence of a plasticity response.

Plasticity and Normal Aging

Multiple studies have explored age differences in memory tasks during functional neuroimaging. In one study,[39] Cabeza et al. examined prefrontal cortex activity in younger adults, cognitively low performing older adults, and cognitively high performing older adults using PET during word recall and recognition tasks. When subjects were asked to recognize whether a word had been presented during a study phase in either auditory or visual format (source recognition), younger adults exhibited activation of the right prefrontal cortex. Low performing older adults recruited similar brain regions as the younger group during the task, but high performing adults demonstrated bilateral prefrontal cortex activation. Therefore, older adults who had better cognitive performance recruited additional brain areas, perhaps as a compensatory response to cognitive aging.

In another study,[40] Park et al. examined both frontal cortex and hippocampal activations using fMRI in younger and older adults during a working memory task that involved picture recall and recognition. The younger adults demonstrated increased brain activation in the hippocampus compared to older adults, while older adults showed increased bilateral frontal cortex activation. A similar fMRI investigation by Gutchess et al.[41] examined scene encoding in younger and older adults. Older adults demonstrated decreased parahippocampal activity and increased frontal cortex activity. Furthermore, there was a negative correlation between these activation patterns such that those who had the least parahippocampal activity also had the highest increases in frontal cortex activity. Therefore, greater frontal cortex activity may be a compensatory response for age-related declines in the activity of the hippocampus and surrounding structures.

Plasticity and Early Alzheimer's Disease

Due to the degenerative nature of AD and other dementias, the ability of the brain to compensate for such progressive injury is significantly impaired. However, the early preservation of certain functions in dementia as well as individual variation in disease progression highlights the beneficial potential of plasticity, particularly early in the disease. The evidence supporting this retained ability includes neuroimaging studies as well as investigations of cognitive plasticity in individuals with AD.

Neuroimaging evidence of plasticity in dementia.

Early studies of plasticity in dementia utilized Positron Emission Tomography (PET) to compare individuals with early-stage AD to matched controls during memory tasks. Becker et al.[42] compared functional brain activity patterns using PET in subjects with probable early-stage AD and normal older adult controls matched to age, education, and gender. All participants completed a series of verbal memory tasks at varying levels of difficulty with PET scans completed for each condition (including rest). The inclusion of different difficulty levels among the tasks permitted the examination of responses in both the AD and control groups when cognitive processing demands increased. Compared to rest conditions, AD subjects demonstrated a larger increase in rCBF magnitude than controls during a three word recall task; brain regions associated with phonologic storage and processing of information were activated in AD subjects as in controls, but to a greater extent. Activation of brain regions associated with verbal working memory and lower-level processing of information to-be-remembered occurred in both AD and control subjects. However, AD subjects did not activate brain regions typically involved in episodic memory processing as did the controls. During an eight word recall task, AD subjects demonstrated increased activity in the lateral dorsolateral prefrontal cortex, rather than the lateral frontal cortex. Therefore, the AD group showed increased activation (e.g., greater rCBF) in the same brain regions as controls during less demanding tasks, but demonstrated alternate region activation when cognitive processing demands were higher.

Similarly, Backman et al.[43] used PET to examine cerebral blood flow in eight subjects with probable early-stage AD and eight cognitively normal older adult subjects. Memory tasks performed under PET included both study of words (encoding) and cued recall of those words when presented with word stems (retrieval). Patterns of activation were generally similar for the AD and control groups during cued recall, indicating that the frontal, parietal, temporal, and cerebellar regions maintained relatively normal functioning in the early stages of AD. However, some increases in left inferior prefrontal activity were seen in the AD group, which the authors interpreted as compensatory activity in response to information retrieval difficulty.

The Becker et al. and Backman et al. studies provide intriguing evidence that in the presence of AD pathology, the brain may adapt to processing demands by increasing activity in regions typically associated with the particular task or may utilize alternate brain regions as a compensatory response. Reallocation of brain function in response to limitations imposed by AD pathology may be considered a demonstration of plasticity: the brain's ability to adapt in response to damage. However, in order to consider plasticity responses compensatory, corresponding maintenance or improvement in functional ability must accompany these brain adaptations.

More recent research addressed the relationship between activation alterations and actual memory performance, demonstrating similar results with both PET[44] and fMRI[45] techniques. Grady et al.[44] explored the relationship between increased prefrontal rCBF using PET and successful task performance in normal older adults and individuals with probable early-stage AD. The AD and control groups differed in the magnitude of brain activation when completing semantic and episodic memory tasks. Specifically, the AD group demonstrated a more extensive recruitment of brain regions in response to task demands including the prefrontal and tempoparietal cortices bilaterally. Most importantly, this greater degree of activation correlated with improved task performance such that individuals with AD who demonstrated increased brain activation in these regions were able to perform both semantic and episodic memory tasks with more accuracy than those who demonstrated less brain activation.

Pariente et al.[45] compared fMRI results during a face-name recognition task in people with mild AD compared to cognitively intact controls. In addition to BOLD signal patterns, successful encoding and retrieval of each face-name pair was determined to allow for comparison with patterns of brain activation. Compared to the control group, subjects with AD demonstrated decreased activation in the hippocampus and simultaneously increased activation in the parietal and frontal lobes during successful encoding and retrieval of information. This response was interpreted as effective compensation; the use of additional cognitive resources, unique to cognitively intact controls, was associated with better task performance.

Age-related vs. dementia-related plasticity.

Although advances in neuroimaging provide some evidence of compensatory responses, it is important to distinguish between age-related and dementia-related plasticity. The question arises as to whether differential activation of brain networks is an illustration of plasticity in response to dementia pathology or the preserved ability of the brain to compensate for normal age-related changes. Individuals with dementia find memory tasks more difficult, for example, and therefore plasticity responses may occur in response to an increase in task difficulty rather than the presence of dementia pathology.

This possibility was examined in a study[46] designed to determine whether individuals with AD were actually altering typical patterns of brain activation rather than responding in a typical way to a task that, for them, was more difficult. This was accomplished by matching task difficulty across all control and probable early-stage AD subjects. During PET scanning, subjects performed a verbal recognition task (word study and retrieval) under both low demand and titrated demand conditions. The titrated demand condition was determined for each subject by adjusting the size of a word list to be remembered such that the subject accurately recognized 75% of words on the list. The titrated word list was determined one day prior during practice sessions. This process provided for equal task difficulty across both control and AD subjects. The task itself was selected due to its demands on encoding, storage, and retrieval of information which would require interactions among multiple brain networks in cognitively normal adults. They found that increased task difficulty in controls was associated with recruitment of the left anterior cingulate and anterior insula, and three of the AD group demonstrated the same response in rCBF. However, the remainder of the AD group utilized an alternate brain network during the titrated condition. In response to increased task difficulty, these individuals recruited an alternate network including the left posterior temporal cortex, calcarine cortex, posterior cingulate, and the vermis. Those with network activation similar to cognitively intact elders were hypothesized to possess normal networks which had not yet been irreversibly damaged by AD pathology. Alternatively, those who recruited alternate brain networks were presumed to have reached a point at which brain function was significantly altered.

An evolving body of evidence supports the maintenance of brain plasticity throughout aging as well as in the presence of AD pathology. It appears that the brain is able to adapt to age-related or dementia-related changes by altering the utilization of brain networks. This occurs in older adults when compared to younger adults, but also in older adults with AD when compared to cognitive intact older adults. Plasticity responses to dementia-related or other brain damage may be unique to what is found during normal aging. However, it is likely that intra-individual variability in plasticity processes exist, even between individuals in the same stage of AD.

Differences in Prodromal vs. Early-Stage AD

AD pathology is insidious, beginning years before the manifestation of symptoms.[47] Therefore, the study of plasticity as it relates to prodromal AD is extremely important for intervention considerations. Research examining plasticity during this period has focused on MCI as a prodromal phase of AD. Recent fMRI evidence of compensatory brain processes during the dementia trajectory has compared the activation of brain networks in individuals with MCI to those with AD. Interestingly, a distinctive trend has emerged: increased network activity in some brains areas of those with MCI (presumably a compensatory response), compared to decreased network activity response in those with AD.[48] For example, one study[49] compared brain activation during a memory task in cognitively intact older adults, those with mild MCI, and those with probable AD. Findings demonstrated significantly increased hippocampal activity in the MCI group and significantly decreased hippocampal activity in the AD group compared to controls. Those with MCI performed comparably to the control group, but those with AD had poorer performance. More recently, a study[50] compared activation patterns using fMRI in cognitively intact, MCI, and AD groups during a memory task. Prefrontal brain activity in the AD group was significantly decreased compared to controls, but the MCI group demonstrated significantly increased activity compared to both the AD and cognitively intact groups.

The overall hypothesis arising from these and similar studies is that in those with preclinical AD or MCI, an initial period of increased brain activation in response to cognitive demand is followed by decreased activation as disease progression continues, eventually exhausting the compensatory response. However, not all studies support this hypothesis. The temporal lobe, which includes the hippocampus, was examined in another fMRI study[51] during a memory task. Results demonstrated no significant differences in activation between the MCI and AD groups, and both groups showed decreased activation when compared to a cognitively intact group. These conflicting results are likely due to the heterogeneity of the MCI diagnosis, which includes individuals who will progress to AD as well as some who will not.[52] The accurate identification of these individuals in future studies will further our understanding of plasticity processes in response to dementia pathology.

The ability to maximize the potential of plasticity in a clinical context may depend on the selection of best candidates for intervention. In order for interventions targeting plasticity to be effective, the brain must still be capable of compensation for deficits that maintains functional ability or performance. If individuals with MCI are indeed exhibiting a highly compensatory response to advancing dementia pathology, interventions may target this group in order to maximize or prolong this response before a threshold is exceeded that results in severe cognitive impairment. Although a degree of plasticity seems to be maintained throughout the early stages of AD, the critical period for treatment maybe prior to AD diagnosis.

Evidence of Plasticity in Learning and Performance Improvements

Beyond neuroimaging evidence of brain plasticity, it is also possible to explore plasticity mechanisms indirectly, with less focus on neurobiological processes in favor of evidence regarding cognitive plasticity. Cognitive plasticity is referred to in the literature as learning potential or changes in behavioral performance after training.[37] In other words, the maintained ability of people with early-stage dementia to learn, to regain abilities they have lost throughout the dementia process, or to improve their cognitive abilities. Therefore, although neurodegenerative changes including hippocampal atrophy are occurring in early AD, cognitive performance improvements including the ability to remember new or

previously forgotten information is possible. This body of research supports the maintenance of cognitive plasticity throughout the early stage of AD.

Engagement in cognitively stimulating or challenging activities is thought to promote plasticity and specific techniques such as the use of cognitive strategies may improve performance.[6] It is not yet known what mechanisms are involved in the activation of plasticity-related events; however, it is believed that cognitive activity stimulates and strengthens neural connections. Actual programs may include multiple components of different approaches as well as additional elements such as aerobic exercise or physical therapy.

Cognitive training is most frequently used to illustrate plasticity since it involves structured practice on tasks targeting areas such as memory, reasoning, and information processing speed.[53] Improvements in memory performance of individuals with dementia over time, with repeated practice, may be interpreted as evidence of cognitive plasticity. The benefits of training on cognitive plasticity are evident in older adults without dementia,[54] and although improvements are more limited with increasing age, significant benefits after practice are possible.[55]

A meta-analysis[56] of randomized controlled trials (RCTs) of cognitive training in cognitively intact older adults as well as those with MCI explored the effectiveness of such training on cognitive plasticity. Outcome measures including improvement in cognitive functioning, sustainability of effects, and transfer of training effects were considered markers of plasticity. The authors report that while most interventions improved performance in the treatment group after training, most differences were not significant between the active control, which included non-specific treatments, and the treatment groups. It appears difficult to determine the unique cognitive plasticity effects of a cognitive training program. A comprehensive review[53] of RCTs of cognitive training in early-stage dementia found similar results: no significant differences between experimental and control groups; however, many methodological limitations exist in the interpretation of these findings. Most notably, intervention protocols vary considerably across studies including differences in intervention length, number of treatments, testing procedures, implementation of training, and variation in outcome measures. There is also considerable confusion in the literature regarding the distinction between cognition-focused approaches; the term cognitive training is often used interchangeably with cognitive rehabilitation, for example.

Other cognition-focused approaches to intervention have demonstrated outcomes supporting the ability of people with dementia to improve cognitive performance. Improvements in cognitive function have been demonstrated in individuals with dementia compared to control groups after a cognitive stimulation program,[57] most notably in regard to language function.[58] Although cognitive abilities decrease with the progression of dementia, the ability to learn and to employ cognitive strategies is retained in some capacity in early AD.[59] In a recent study[60] of individuals with mild-moderate dementia, subjects were able to learn face-name associations in less than four sessions, on average. Previously known associations that were forgotten prior to intervention were learned significantly faster than new associations. Although degree of cognitive impairment was significantly related to learning of new information, there was no significant relationship between degree of impairment and the relearning of previously known information.

Multi-component interventions may include cognitive approaches as well, such as the successful example of the Experience Corps (EC). The EC places older adult volunteers into elementary schools within a program designed to enhance physical, social, and cognitive activity while also providing benefits to students. Memory and executive functioning

abilities are targeted through reading comprehension activities with students, problem-solving skill experience and training, and other interactions with fellow volunteers, students, and teachers. Multiple studies,[61, 62] including a RCT,[63] have demonstrated the potential of the EC model to improve memory, executive function, social activity, and cognitive activity in elders. The most recent study[64] investigating EC outcomes used fMRI at pre- and post-intervention to determine whether an EC group (n=8) demonstrated increased prefrontal cortex activity when compared to controls (n=9). Subjects were considered cognitively at risk due to low education, income, and Mini-Mental Status Exam (MMSE) scores. In addition to improvement in executive functioning after the intervention, the EC group demonstrated increased brain activity during a task designed to measure executive function in older adults.

Due to the multiple components of the EC program which includes cognitive activity embedded within a social environment as well as physical activity, it is difficult to discern the contribution of each aspect of the intervention on outcomes. However, preliminary evidence supports the ability of the EC to promote plasticity in individuals at risk for dementia. Additionally, the use of multiple components thought to promote plasticity, including cognitive and physical activity, is an important consideration for the design of rehabilitation interventions aiming to maximize overall function and minimize disability in people with dementia.

Decline in Plasticity as a Hallmark of the Dementia Process

In contrast to evidence supporting the maintenance of plasticity throughout early-stage dementia, a decrease in plasticity has been considered as an actual indicator of dementia onset.[65] In multiple studies,[66, 67] measures of cognitive plasticity have been used to detect early cognitive changes that may progress to dementia, perhaps leading to early identification of at risk individuals. These studies use changes in scores on instruments such as the Auditory Verbal Learning Test of Learning Potential or Figural Relations tests to assess cognitive plasticity (improvement in cognitive performance over time). Healthy older adults, those with MCI, and those with probable AD have been shown to demonstrate significant differences in plasticity such that decreases in plasticity are indicative of cognitive decline leading to dementia.[37, 68] Evidence supports that lack of cognitive plasticity is predictive of cognitive decline, including the ability to potentially predict a progression to dementia. These findings imply that individuals with dementia inherently possess a lower degree of plasticity, even prior to dementia onset.

Reconciling the Evidence of Plasticity Maintenance with that of Plasticity Decline

Evidence from both neuroimaging and behavioral outcomes research supports the ability of the brain to adapt, modify, and learn throughout, at a minimum, the early stages of dementia. There is evidence supporting a decrease in plasticity in the early stages of dementia; however, many of the same studies that demonstrate plasticity decreases as a hallmark of the dementia trajectory also include findings that could be considered supportive of plasticity-focused interventions. Although performance improvement (i.e., cognitive plasticity) was less in individuals with MCI or AD when compared to cognitively intact older adults, it still improved significantly after intervention.[66, 68] Therefore, although a decrease in plasticity as a result of dementia pathology may be expected, even to the point of being diagnostic, individuals in the early stages dementia may retain the ability to improve their cognitive performance. Undoubtedly, this capability gradually declines to the point of little utility, but nevertheless, a window of opportunity for interventions that provide at least a short-term benefit does exist.

Conclusion

AD leads to gradual and irrevocable damage of neural networks, and as a consequence, neuronal plasticity progressively declines. However, individuals with prodromal or early-stage AD may be capable of a compensatory response to this decline that optimizes cognitive function within the confines of advancing pathology. Neuroimaging evidence indicates brain activation differences in individuals with early-stage AD when compared to normal controls during cognitive tasks. These alterations in magnitude or location of brain activity have been associated with functional improvements (i.e., improved performance on cognitive tasks) and appear to be unique to age-related plasticity responses although much remains to be learned regarding the heterogeneity of responses among individuals. MCI, particularly the amnestic subtypes, may indicate a period on the AD continuum in which plasticity processes are able maintain cognitive performance by increasing brain activity as a compensatory response to AD-related pathology.

Future research is needed in order to understand the mechanisms of plasticity as well as the conditions under which they are optimally triggered. Although evolving use of neuroimaging studies have contributed to our understanding of brain network usage in response to cognitive demands, much is still unknown. Longitudinal functional neuroimaging studies examining patterns of brain activation in cognitively normal older adults, individuals with MCI, and persons with early-stage AD are necessary in order to determine if and how these patterns change with disease progression. Use of neuroimaging techniques in controlled intervention trials is also crucial in order to determine whether improvements in performance are indeed the result of structural or functional brain changes.

The investigation of plasticity in persons with AD holds important implications for intervention development and testing. Multiple intervention studies have demonstrated the ability of individuals at risk for AD or in the early stages to learn, improve cognitive performance, and employ cognitive strategies, although intervention approaches are highly varied and results are inconsistent across studies. Combining this research with functional neuroimaging in the future may provide a link between specific treatment approaches and the triggering of plasticity processes.

Although the consideration and investigation of plasticity in AD is relatively new, emerging evidence supports the potential of compensatory processes in individuals with prodromal or early-stage AD. Effective compensation for advancing pathology is likely limited, but the optimization of cognitive functioning may be achieved by targeting preserved plasticity. It is well-accepted that factors influencing plasticity after acute brain injury may be manipulated for therapeutic benefit,[69] and employing a rehabilitation perspective to people with AD may be similarly effective in maximizing cognitive function. The public health significance of slowing cognitive decline could be enormous given the projected numbers of people who may develop AD in the next 20 years. The possible delay in institutionalization and the resultant cost savings have the potential to improve quality of life for older adults and their families who care for them.

Acknowledgments

Nikki Hill is a John A. Hartford Foundation Building Academic Geriatric Nursing Capacity (BAGNC) Scholar and acknowledges support from the BAGNC Award Program. Ann Kolanowski acknowledges support from the National Institute of Nursing Research, The National Institutes of Health, grant number R01 NR012242. NINR had no role in the writing of the manuscript or in the decision to submit the manuscript for publication. David Gill acknowledges support from the National Institutes of Health, grant number RO1 AG027771-01A2 and the Michael J. Fox foundation. The NIH and Michael J. Fox Foundation had no role in the writing of the manuscript or in the decision to submit the manuscript for publication.

References

1. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007; 29(1-2):125–132. [PubMed: 17975326]
2. Alzheimer's Association. [Accessed March 29, 2010] Alzheimer's Disease Factors and Figures. 2010. http://www.alz.org/documents_custom/report_alzfactsfigures2010.pdf
3. Clare L, Woods B. Editorial: A role for cognitive rehabilitation in dementia care. Neuropsychol Rehabil. 2001; 11(3/4):193–196.
4. Sapolsky R. Stress and plasticity in the limbic system. Neurochem Res. 2003; 28(11):1735–1742. [PubMed: 14584827]
5. Osborne H, Simpson J, Stokes G. The relationship between pre-morbid personality and challenging behaviour in people with dementia: A systematic review. Aging Ment Health. May 14.2010 :1–13. [PubMed: 20155517]
6. Vance DE, Webb NM, Marceaux JC, Viamonte SM, Foote AW, Ball KK. Mental stimulation, neural plasticity, and aging: directions for nursing research and practice. J Neurosci Nurs. Aug; 2008 40(4):241–249. [PubMed: 18727340]
7. Bach-y-Rita P. Theoretical basis for brain plasticity after a TBI. Brain Inj. Aug; 2003 17(8):643–651. [PubMed: 12850949]
8. Meade, ML.; Park, DC. Enhancing cognitive function in older adults. In: Chodzko-Zajko, W.; Kramer, AF.; Poon, LW., editors. Enhancing cognitive functioning and brain plasticity. Aging, exercise, and cognition series. Human Kinetics; Champaign, IL: 2009. p. 35-47.
9. Grady CL, Craik FI. Changes in memory processing with age. Curr Opin Neurobiol. Apr; 2000 10(2):224–231. [PubMed: 10753795]
10. Raz N, Gunning-Dixon FM, Head D, Dupuis JH, Acker JD. Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging. Neuropsychology. Jan; 1998 12(1):95–114. [PubMed: 9460738]
11. Tierney MC, Yao C, Kiss A, McDowell I. Neuropsychological tests accurately predict incident Alzheimer disease after 5 and 10 years. Neurology. Jun 14; 2005 64(11):1853–1859. [PubMed: 15955933]
12. Davis DG, Schmitt FA, Wekstein DR, Markesbery WR. Alzheimer neuropathologic alterations in aged cognitively normal subjects. J Neuropathol Exp Neurol. Apr; 1999 58(4):376–388. [PubMed: 10218633]
13. Wilson RS, Leurgans SE, Boyle PA, Schneider JA, Bennett DA. Neurodegenerative basis of age-related cognitive decline. Neurology. Sep 21; 2010 75(12):1070–1078. [PubMed: 20844243]
14. Richards M, Deary IJ. A life course approach to cognitive reserve: a model for cognitive aging and development? Ann Neurol. Oct; 2005 58(4):617–622. [PubMed: 16178025]
15. Petersen R, Negash S. Mild cognitive impairment: an overview. CNS Spectr. 2008; 13(1):45–53. [PubMed: 18204414]
16. Rosenberg PB, Lyketsos C. Mild cognitive impairment: searching for the prodrome of Alzheimer's disease. World Psychiatry. 2008; 7(2):72–78. [PubMed: 18563204]
17. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004; 256(3):183–194. [PubMed: 15324362]
18. Markesbery W, Schmitt F, Kryscio R, Davis D, Smith C, Wekstein D. Neuropathologic substrate of mild cognitive impairment. Arch Neurol. 2006; 63(1):38–46. [PubMed: 16401735]
19. Petersen R, Parisi J, Dickson D, et al. Neuropathologic features of amnestic mild cognitive impairment. Arch Neurol. 2006; 63(5):665–672. [PubMed: 16682536]
20. Armstrong RA, Lantos PL, Cairns NJ. Overlap between neurodegenerative disorders. Neuropathology. Jun; 2005 25(2):111–124. [PubMed: 15875904]
21. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. Ann Neurol. Aug; 2009 66(2):200–208. [PubMed: 19743450]
22. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. JINS. 2002; 8(3):448–460. [PubMed: 11939702]

23. Stern Y. Cognitive reserve and Alzheimer disease. Alzheimer Dis Assoc Disord. 2006; 20(2):112–117. [PubMed: 16772747]
24. Palop J, Chin J, Mucke L. A network dysfunction perspective on neurodegenerative diseases. Nature. 2006; 443(7113):768–773. [PubMed: 17051202]
25. Katzman R, Terry R, DeTeresa R, et al. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. Ann Neurol. Feb; 1988 23(2):138–144. [PubMed: 2897823]
26. Perneczky R, Haussermann P, Drzezga A, et al. Fluoro-deoxy-glucose positron emission tomography correlates of impaired activities of daily living in dementia with Lewy bodies: implications for cognitive reserve. Am J Geriatr Psychiatry. Mar; 2009 17(3):188–195. [PubMed: 19454846]
27. van Praag H, Kempermann G, Gage FH. Neural consequences of environmental enrichment. Nat Rev Neurosci. Dec; 2000 1(3):191–198. [PubMed: 11257907]
28. Desmurget M, Bonnetblanc F, Duffau H. Contrasting acute and slow-growing lesions: a new door to brain plasticity. Brain. 2007; 130(4):898–914. [PubMed: 17121742]
29. Rakic P. Limits of neurogenesis in primates. Science. Mar 1; 1985 227(4690):1054–1056. [PubMed: 3975601]
30. Galvan V, Bredesen DE. Neurogenesis in the adult brain: implications for Alzheimer's disease. CNS Neurol Disord Drug Targets. Oct; 2007 6(5):303–310. [PubMed: 18045158]
31. Duffau H. Brain plasticity: from pathophysiological mechanisms to therapeutic applications. J Clin Neurosci. 2006; 13(9):885–897. [PubMed: 17049865]
32. Flicker L. Life style interventions to reduce the risk of dementia. Maturitas. 2009; 63(4):319–322. [PubMed: 19631480]
33. Feldman DE. Synaptic mechanisms for plasticity in neocortex. Annu Rev Neurosci. 2009; 32:33–55. [PubMed: 19400721]
34. Mattson MP, Duan W, Chan SL, et al. Neuroprotective and neurorestorative signal transduction mechanisms in brain aging: modification by genes, diet and behavior. Neurobiol Aging. Sep-Oct; 2002 23(5):695–705. [PubMed: 12392775]
35. Greenwood PM. Functional plasticity in cognitive aging: review and hypothesis. Neuropsychology. Nov; 2007 21(6):657–673. [PubMed: 17983277]
36. Berlucchi G, Buchtel HA. Neuronal plasticity: historical roots and evolution of meaning. Exp Brain Res. 2009; 192(3):307–319. [PubMed: 19002678]
37. Fernández-Ballesteros, R.; Zamarron, MD.; Calero, MD.; Tarraga, L. Cognitive plasticity and cognitive impairment. In: Fernández-Ballesteros, R., editor. Geropsychology: European perspectives for an aging world. Hogrefe & Huber Publishers; Ashland, OH: 2007. p. 145-164.
38. Baltes M, Raykov T. Prospective validity of cognitive plasticity in the diagnosis of mental status: A structured equation model. Neuropsychology. 1996; 10:549–556.
39. Cabeza R, Anderson N, Locantore J, McIntosh A. Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage. 2002; 17(3):1394–1402. [PubMed: 12414279]
40. Park DC, Welsh RC, Marshuetz C, et al. Working memory for complex scenes: age differences in frontal and hippocampal activations. J Cog Neurosci. Nov 15; 2003 15(8):1122–1134.
41. Gutchess AH, Welsh RC, Hedden T, et al. Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. J Cog Neurosci. Jan; 2005 17(1):84–96.
42. Becker JT, Mintun MA, Aleva K, Wiseman MB, Nichols T, DeKosky ST. Compensatory reallocation of brain resources supporting verbal episodic memory in Alzheimer's disease. Neurology. Mar; 1996 46(3):692–700. [PubMed: 8618669]
43. Backman L, Andersson JL, Nyberg L, Winblad B, Nordberg A, Almkvist O. Brain regions associated with episodic retrieval in normal aging and Alzheimer's disease. Neurology. 1999; 52(9):1861–1870. [PubMed: 10371535]
44. Grady CL, McIntosh A, Beig S, Keightley M, Burian H, Black S. Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. J Neurosci. 2003; 23(3):986–993. [PubMed: 12574428]

45. Pariente J, Cole S, Henson R, et al. Alzheimer's patients engage an alternative network during a memory task. Ann Neurol. Dec; 2005 58(6):870–879. [PubMed: 16315273]
46. Stern Y, Moeller JR, Anderson KE, et al. Different brain networks mediate task performance in normal aging and AD: Defining compensation. Neurology. 2000; 55(9):1291–1297. [PubMed: 11087770]
47. Arendt T. Synaptic degeneration in Alzheimer's disease. Acta Neuropathol. 2009; 118(1):167–179. [PubMed: 19390859]
48. Dickerson BC. Advances in functional magnetic resonance imaging: technology and clinical applications. Neurotherapeutics. Jul; 2007 4(3):360–370. [PubMed: 17599702]
49. Dickerson BC, Salat DH, Greve DN, et al. Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. Neurology. 2005; 65(3):404–411. [PubMed: 16087905]
50. Li C, Zheng J, Wang J, Gui L, Li C. An fMRI stroop task study of prefrontal cortical function in normal aging, mild cognitive impairment, and Alzheimer's disease. Curr Alzheimer Res. 2009; 6(6):525–530. [PubMed: 19747163]
51. Machulda MM, Ward HA, Borowski B, et al. Comparison of memory fMRI response among normal, MCI, and Alzheimer's patients. Neurology. 2003; 61(4):500–506. [PubMed: 12939424]
52. Johnson KA, Moran EK, Becker JA, Blacker D, Fischman AJ, Albert MS. Single photon emission computed tomography perfusion differences in mild cognitive impairment. J Neurol Neurosurg Psychiatry. 2007; 78(3):240–247. [PubMed: 17056633]
53. Clare L, Woods RT, Moniz Cook ED, Orrell M, Spector A. Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia. Cochrane Database Syst Rev. 2003; (4):CD003260. [PubMed: 14583963]
54. Willis S, Tennstedt S, Marsiske M, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. JAMA. 2006; 296(23):2805–2814. [PubMed: 17179457]
55. Yang L, Krampe RT, Baltes PB. Basic forms of cognitive plasticity extended into the oldest-old: retest learning, age, and cognitive functioning. Psychol Aging. Jun; 2006 21(2):372–378. [PubMed: 16768581]
56. Zehnder F, Martin M, Altgassen M, Clare L. Memory training effects in old age as markers of plasticity: a meta-analysis. Restor Neurol Neurosci. 2009; 27(5):507–520. [PubMed: 19847073]
57. Spector A, Thorgrimsen L, Woods B, et al. Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. Br J Psychiatry. Sep. 2003 183:248–254. [PubMed: 12948999]
58. Spector A, Orrell M, Woods B. Cognitive Stimulation Therapy (CST): effects on different areas of cognitive function for people with dementia. Int J Geriatr Psychiatry. 2010; 25(12):1253–1258. [PubMed: 20069533]
59. Bier N, Van Der Linden M, Gagnon L, et al. Face-name association learning in early Alzheimer's disease: a comparison of learning methods and their underlying mechanisms. Neuropsychol Rehabil. 2008; 18(3):343–371. [PubMed: 18569747]
60. Hopper T, Drefs S, Bayles K, Tomoeda C, Dinu I. The effects of modified spaced-retrieval training on learning and retention of face-name associations by individuals with dementia. Neuropsychol Rehabil. 2010; 20(1):81–102. [PubMed: 19513931]
61. Fried L, Carlson M, Freedman M, et al. A social model for health promotion for an aging population: initial evidence on the Experience Corps model. J Urban Health. 2004; 81(1):64–78. [PubMed: 15047786]
62. Glass T, Freedman M, Carlson M, et al. Experience Corps: Design of an intergenerational program to boost social capital and promote the health of an aging society. J Urban Health. 2004; 81(1):94–105. [PubMed: 15047788]
63. Carlson M, Saczynski J, Rebok G, et al. Exploring the effects of an "everyday" activity program on executive function and memory in older adults: Experience Corps. Gerontologist. 2008; 48(6): 793–801. [PubMed: 19139252]
64. Carlson M, Erickson K, Kramer A, et al. Evidence for neurocognitive plasticity in at-risk older adults: the experience corps program. J Gerontol A Biol Sci Med Sci. 2009; 64(12):1275–1282. [PubMed: 19692672]

65. Baltes MM, Kuhl KP, Sowarka D. Testing for limits of cognitive reserve capacity: a promising strategy for early diagnosis of dementia? J Gerontol. 1992; 47(3):165–167.

66. Calero MD, Navarro E. Relationship between plasticity, mild cognitive impairment and cognitive decline. Arch Clin Neuropsychol. 2004; 19(5):653–660. [PubMed: 15271409]

67. Raykov T, Baltes M, Neher K, Sowarka D. A comparative study of two psychometric approaches to detect risk status for dementia. Gerontology. 2002; 48(3):185–193. [PubMed: 11961374]

68. Fernández-Ballesteros R, Zamarron MD, Tarraga L, Moya R, Iniguez J. Cognitive plasticity in healthy, mild cognitive impairment (MCI) subjects and Alzheimer's disease patients: A research project in Spain. European Psychologist. 2003; 8(3):148.

69. Moucha R, Kilgard MP. Cortical plasticity and rehabilitation. Prog Brain Res. 2006; 157:111–122. [PubMed: 17167905]

70. Price BH, Gurvit H, Weintraub S, Geula C, Leimkuhler E, Mesulam M. Neuropsychological patterns and language deficits in 20 consecutive cases of autopsy-confirmed Alzheimer's disease. Arch Neurol. 1993; 50(9):931–937. [PubMed: 8363447]

71. Metzler-Baddeley C. A review of cognitive impairments in dementia with Lewy bodies relative to Alzheimer's disease and Parkinson's disease with dementia. Cortex. Jul; 2007 43(5):583–600. [PubMed: 17715794]

72. Ballard C, Ziabreva I, Perry R, et al. Differences in neuropathologic characteristics across the Lewy body dementia spectrum. Neurology. Dec 12; 2006 67(11):1931–1934. [PubMed: 17159096]

73. Desmond DW, Moroney JT, Paik MC, et al. Frequency and clinical determinants of dementia after ischemic stroke. Neurology. Mar 14; 2000 54(5):1124–1131. [PubMed: 10720286]

74. Gold G, Bouras C, Canuto A, et al. Clinicopathological validation study of four sets of clinical criteria for vascular dementia. Am J Psychiatry. Jan; 2002 159(1):82–87. [PubMed: 11772694]

75. Cairns NJ, Bigio EH, Mackenzie IR, et al. Neuropathologic diagnostic and nosologic criteria for frontotemporal lobar degeneration: consensus of the Consortium for Frontotemporal Lobar Degeneration. Acta Neuropathol. Jul; 2007 114(1):5–22. [PubMed: 17579875]

Table 1

Subtypes of Mild Cognitive Impairment[a]

Mild Cognitive Impairment (MCI)

Presents with:

- Cognitive complaint
- Cognitive decline not normal for age
- No dementia
- Preservation of functional activities

MCI Subtypes

1. **Amnestic MCI Single Domain:** Memory impairment only
2. **Amnestic MCI Multiple Domain:** Impairment in memory and other cognitive domains
3. **Non-Amnestic MCI Single Domain:** No memory impairment; impairment in one non-memory cognitive domain
4. **Non-Amnestic MCI Multiple Domain:** No memory impairment; impairment in multiple non-memory cognitive domains

[a] Petersen R, Negash S. Mild cognitive impairment: an overview. CNS Spectr. 2008;13(1):45

Table 2

Dementia Subtype Features

Category	Approximate % of cases	Subtypes	Cognitive profile	Structural changes
Alzheimer's disease	50-70%	• Alzheimer's disease • Posterior cortical atrophy	Early episodic memory impairment with subsequent impairment in visuospatial, language and executive function impairments.[70]	Neuronal and synaptic loss along with neuronal shrinkage resulting in cortical atrophy. Ultrastructurally, extraneuronal senile/neuritic plaques containing β-amyloid protein and intraneuronal neurofibrillary tangles containing hyperphosphorlyated tau protein.
Lewy body dementias	20%	• Dementia with Lewy bodies • Parkinson's disease with dementia	Parkinsonism with more severe visuospatial, attentional and executive function impairments than in Alzheimer's disease.[71]	Lewy bodies, neuronal aggregates of α-synuclein, in subcortical and cortical regions. More than half of patients have neuritic plaques as well.[72]
Vascular dementia	10-30%	• Strategic infarct • Multi-infarct dementia • Lacunar state • inswanger's disease • cadasil[a]	Varies based on location of infarct. Impairments in abstraction, mental flexibility, information processing speed, and working memory are common.[73]	Complete or incomplete infarcts, microinfarcts, selective neuronal loss, and/or leukoencephalopathy (CADASIL) in the setting of atherosclerosis. Concomitant Alzheimer's disease pathology is often present.[74]
Frontotemporal degeneration	2-15%	• Frontotemporal dementia • Primary Progressive aphasia • Progressive supranuclear palsy • Corticobasal degeneration	Progressive symptoms of behavioral symptoms, language disturbances, and/or parkinsonism.	Either presence of tau protein positive inclusions within neurons (frontotemporal dementia, primary progressive aphasia, and corticobasal degeneration) or neuronal inclusions of TAR DNA-binding protein 43 (frontotemporal dementia and primary progressive aphasia).[75]

[a] CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy