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Review

Gender-Specific Degeneration of Dementia-Related Subcortical Structures Throughout the Lifespan

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Abstract. Age-related changes in brain structure are a question of interest to a broad field of research. Structural decline has been consistently, but not unambiguously, linked to functional consequences, including cognitive impairment and dementia. One of the areas considered of crucial importance throughout this process is the medial temporal lobe, and primarily the hippocampal region. Gender also has a considerable effect on volume deterioration of subcortical grey matter (GM) structures, such as the hippocampus. The influence of age × gender interaction on disproportionate GM volume changes might be mediated by hormonal effects on the brain. Hippocampal volume loss appears to become accelerated in the postmenopausal period. This decline might have significant influences on neuroplasticity in the CA1 region of the hippocampus highly vulnerable to pathological influences. Additionally, menopause has been associated with critical pathobiochemical changes involved in neurodegeneration. The micro- and macrostructural alterations and consequent functional deterioration of critical hippocampal regions might result in clinical cognitive impairment–especially if there already is a decline in the cognitive reserve capacity. Several lines of potential vulnerability factors appear to interact in the menopausal period eventually leading to cognitive decline, mild cognitive impairment, or Alzheimer's disease. This focused review aims to delineate the influence of unmodifiable risk factors of neurodegenerative processes, i.e., age and gender, on critical subcortical GM structures in the light of brain derived estrogen effects. The menopausal period appears to be of key importance for the risk of cognitive decline representing a time of special vulnerability for molecular, structural, and functional influences and offering only a narrow window for potential protective effects.

Keywords: Aging, cognitive decline, gender, hippocampus CA1 region, subcortical grey matter

INTRODUCTION

Age-related changes in brain structure are a question of interest to a number of different fields of research including neuroendocrinology, neurobiology, and neuroimaging, to just name a few. The

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growing body of research evidence has linked structural alterations to certain functional and clinical manifestations, including dementia-related disorders. Dementia has become a major health and public concern worldwide with an increasing prevalence in the aged population. The most common cause of dementia in the general population above 60 years of age is Alzheimer's disease (AD) [1]. AD is characterized by progressive behavioral, affective, social, and cognitive impairment [2]. The neuropathological changes presumed to stand behind the functional impairment are primarily the amyloid depositions and the neurofibrillary tangles [3, 4]. These histopathological alterations have been described in several brain regions involving widespread frontal, parietal, and temporal cortical and subcortical structures. Among these, medial temporal subcortical structures are typically considered the most commonly emphasized areas affected [5]. The most important risk factor of developing AD that cannot be influenced is age itself [6]. The most recent systematic review and meta-analysis on prevalence and incidence of dementia, and dementia due to AD found that increasing age was significantly associated with increasing prevalence and incidence rates of dementia [7] and AD [8]. Thus it appears crucial to understand the age-related changes occurring in brain structures of potential key importance. Large sample epidemiological studies show that women have a significantly higher risk of developing AD for various reasons (e.g., longer lifespan) [9–11]. Interestingly, incidence rates appear to show and age-dependent relationship between sex and likelihood of developing AD. Incidence of AD has been reported to increase with age for both sexes until about 85–90 years but to continue to increase among women only [12]. Therefore, gender is also considered a crucial unmodifiable factor in AD pathology with clear differences in structural and functional decline of specific brain areas.

This review will be focusing on age and gender dependent changes in grey matter (GM) micro- and macrostructures–and especially subcortical GM formations—and related cognitive alterations as a functional representation in AD pathology.

GREY MATTER ALTERATIONS IDENTIFIED IN AD

A number of studies have addressed the neuroanatomical changes in the background of clinical symptoms presenting in AD. A recent large sample meta-analysis has used anatomic likelihood estimation aiming to identify more robust and consistent alterations [5]. GM atrophy has been found to primarily affect bilateral medial temporal lobe (MTL) structures, involving the amygdala, hippocampus, parahippocampal gyrus, uncus, and entorhinal cortex, as well as the thalamus, caudate, and cingulate cortices [13]. Strikingly, one significant cluster in the left MTL has been identified as a potential anatomical marker for AD development and progression. A robust GM loss has frequently been documented in regions of the MTL bilaterally [14, 15]. Furthermore, the microstructure of the white matter fibers in the close vicinity of the mediotemporal structures are also affected by the disease [16]. Hypometabolism as measured by PET studies and hypoactivation as revealed by functional MRI have also been reported [17]. Disrupted functional connectivity in these regions further supports the critical role of MTL structures in the pathophysiology of AD [18, 19]. A main question of debate remains as to what extent these changes reflect the course of the disease. Research evidence indicates that relevant alterations are present primarily in areas of the MTL several years before the clinical signs of AD [20]. Moreover, morphological abnormalities and atrophy have been detected in the left MTL specifically as the most consistent structure to predict conversion from mild cognitive impairment (MCI) to AD [21]. Thus, based on the pattern of structural atrophy, the left MTL has been suggested as a marker of disease progression in AD [5] (for a summary of referenced findings please see Table 1).

AGE-RELATED CHANGES OF RELEVANT GM STRUCTURES

A great body of research evidence confirms that aging is associated with decrease in total whole-brain volume [22–24], overall GM and white matter (WM) volume [25–29], as well as cortical thickness [30]. It seems evident to state that, parallel to total brain volume, the volume of subcortical brain structures in general decreases with age. However, evidence indicates that the changes are very different in specific brain areas [31, 32]. Even studies reporting no overall significant effect of aging on WM volume did reveal a decline with age in some areas [26, 33].

In order to understand the relevance of the structural loss, we have to decipher their complex neurobiological background and their effect

Table 1
Age- and gender-related changes of medial temporal lobe, with the major focus on the hippocampus

Golomb et al., [160]	Size of hippocampal formation predicts longitudinal alterations of performance on memory tests.
Murphy et al., [50]	Larger age-related total GM volume loss and atrophy in frontal and temporal areas in males than in females, Greater atrophy in females than in males in hippocampus and parietal cortices. Hemispheric metabolic asymmetry in temporal and parietal cortices, Broca's area, thalamus, and also in hippocampus.
Raz et al., [43]	Largest age-related decline: volume of the prefrontal cortices. Slighter age-related alterations: volume of the fusiform gyri, inferior temporal, superior parietal areas. Weak effects of age on hippocampus and postcentral gyrus. Larger total brain volume and the hippocampus in males than in females.
Jack et al., [161]	Annual decline in hippocampal volume, increase in temporal horn volume was identified in the elderly. 2.5 times greater rates in patients with AD than in age- and gender-matched controls.
Xu et al., [60]	Larger atrophy with aging in right frontal lobe posteriorly in males compared to females. Age-related atrophy in right temporal lobe medially, in parietal cortices, cerebellum + left basal ganglia in males, but not in females. Smaller left thalamus, parietal, occipital cortices + cerebellum volume compared to the right hemisphere. No age- and gender-related difference in this asymmetry.
Good, et al., [26]	Linear global GM volume loss with age, steeper decline in men. Accelerated loss bilaterally in the insula, superior parietal gyrus, central sulcus + cingulum. Little or no age effect in amygdala, hippocampus + entorhinal cortex.
Ge et al., [25]	Constant GM volume loss, linearly with age throughout adulthood, whereas delayed WM volume loss until midlife. No effect of sex.
Scahill et al., [24]	Acceleration in atrophy with age in all analyses, prominently after the age of 70, particularly in the ventricles and in the hippocampus.
Wang et al., [162]	Distinct patterns of hippocampal shape alteration with age, different patterns of hippocampal volume loss may distinguish mild dementia from healthy aging.
Sullivan et al., [52]	Linear thalamic volume loss with age in a similar pace in males and females, whereas more steep cortical GM volume decline during aging in men than in women.
Fleisher et al., [80]	Greater deleterious effect of APOE*E4 genotype status on gross hippocampal pathology and memory functions in women as compared to men.
Lemaitre et al., [55]	Between the ages of 63 and 75 years, largest GM atrophy in primary cortices + in angular gyri, superior parietal gyri, orbitofrontal cortex + in hippocampus. No sex × age interaction.
Ahsan et al., [42]	Larger left caudate, nucleus accumbens + putamen, and larger globus pallidus in men.
Smith et al., [29]	Relative regional differences in GM volume frontal, parietal + temporal cortices, no volume loss in medial temporal lobe and in posterior cingulate. No gender effects.
Sowell et al., [30]	Thicker right inferior parietal + posterior temporal cortices in females. Gender differences in these areas are detectable from late childhood and are maintained throughout life.
Curiati et al., [35]	Selective focus of accelerated GM reduction only in men, including temporal neocortices, prefrontal cortices, and medial temporal areas.
Neufang et al., [65]	Larger GM volumes of left amygdala in males, larger right striatal GM volumes and hippocampal GM volumes bilaterally in females. Independently of gender, volumes of amygdala and hippocampus are associated with levels of circulating testosterone.
Ostby et al., [36]	From childhood until adulthood: non-linear decrease in GM in cerebral cortex, linear decrease in caudate, putamen, pallidum, nucleus accumbens, and cerebellum. Small, non-linear increase in amygdala and hippocampal GM volume.
Ystad et al., [163]	Hippocampal volumes are important predictors for memory function in elderly women. Hemispheric asymmetry in hippocampal volumes during aging. In females, volume of left hippocampus has predictive value. Gender and left hippocampal volume may predict verbal memory performance in healthy elderly.
Erickson et al., [82]	Limited time window for hormone replacement therapy to positively influence hippocampal volume.
Fjell and Walhovd, 2010 [38]	Heterogeneous pattern in the atrophy of specific brain areas during aging: largest shrinking in frontal and temporal cortices + in putamen, thalamus, and nucleus accumbens.
Mukai et al., [77]	Important role of hippocampus-derived estradiol in the modulation of synaptic plasticity.
Goto et al., [83]	Reduced GM volume in bilateral hippocampus in females in their fifties (most of them experiencing menopause) compared to females in their forties (most of them not experiencing menopause). → Menopause may correlate with reduction of hippocampal volume.
Skup et al., [45]	Different patterns of decline with age in males and females in AD group and MCI group compared to healthy controls in precuneus and caudate nucleus bilaterally, right entorhinal gyrus, thalamus bilaterally, left insula, and also in right amygdala.
Takahashi et al., [51]	More retained GM concentrations in females during aging in inferior frontal gyri bilaterally, cingulate gyrus anteriorly, hypothalamus and in medial thalamus.

(*Continued*)

Table 1
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Devanand et al., [164]	Differences in volumes of hippocampus, entorhinal cortex, and parahippocampal gyrus between MCI and healthy controls.
	In patients converting from healthy to MCI: larger atrophy in the head of hippocampus, specifically in CA1 and subiculum, in entorhinal cortex, especially in bilateral pole of EC.
Borghesani et al., [165]	Improvement of midlife memory positively correlates with larger hippocampal volume in the elderly, compared to those who had decline or no change in their episodic memory in their midlife.
Ooishi et al., [78]	Crucial role of hippocampus-derived estradiol, T, and DHT in modulating synaptic plasticity.
Rijpkema et al., [53]	No gender difference in caudate nucleus and nucleus accumbens.
	Larger globus pallidus and putamen volume.
Spencer-Segal et al., [79]	In females, important role of estrogen receptor signaling in hormone's influence regarding hippocampal synaptic plasticity.
Fjell et al., [34]	Faster estimated decline in the elderly in hippocampus.
Taki et al., [166]	Positive correlations between yearly regional GM volume alterations and age: temporal pole bilaterally, caudate nucleus, insula, hippocampus.
	Negative correlations between age and changes in cingulate gyri bilaterally + cerebellum.
	Age × gender interaction between annual ratio of regional GM volume change in hippocampus bilaterally.
Crivello et al., [167]	Higher GM decline in females compared to males (persistent throughout age ranges)
	Hippocampus: similarly accelerated decline with age in males and females.
Li et al., [58]	Age-related atrophy in basal ganglia and thalamus.
	Hippocampus atrophy in males only, and no decline in the amygdala.
Perlaki et al., [57]	No sexual dimorphism in the size of hippocampus.
Kiraly et al., [56]	Larger hippocampus volume in females.
	Age-related decrease of caudate nucleus, putamen and thalamic volumes in males.
	Thalamic volume loss in females.
	Faster decrease in total GM volume in males as compared to females.

on functionality. Fjell and his co-workers have done tremendous work in an effort to characterize cross-sectional and longitudinal changes in brain aging and to compare healthy normal aging to pathological alterations (i.e., the Alzheimer Disease Neuroimaging Initiative) [34]. Fjell et al. have used a nonparametric smoothing spline approach to assess age trajectories of anatomical structures in a large sample of healthy adults. Cross-sectional as well as longitudinal, follow-up data has been analyzed identifying certain critical age periods. These critical ages would account for a more significant rate of change within the estimated range of volume loss. Latter has been described for total brain volume with a stronger correlation above the age of 60, as well as for the cerebral cortex, and, interestingly the pallidum, with the age of around 25 years correlating most with structural decline. A linear reduction with age has been identified for a number of subcortical structures, i.e., the amygdala, nucleus accumbens, putamen, and the thalamus, also supported by several previous findings [31, 35]. The hippocampus has been previously characterized by a nonlinear pattern of estimated change through adulthood. This might be explained by a prolonged phase of development [36], a longer stable period and, critically, an accelerated volume loss starting around the age of 50 and an even more robust negative relationship above 60 [37–39]. Indeed, in the longitudinal analysis, the hippocampus showed the fastest rate of volume reduction (–0.83% per year) among subcortical structures [34]. Changes in brain volume constitute a truly dynamic process with a great number of potential influencing factors, which should be ideally monitored by using longitudinal approaches with a high density of assessments. Nevertheless, more complex and sophisticated methods of analysis as well as large volume data could yield more insight into targeted questions [40].

Another highly dynamic process throughout the human lifespan is considered the interaction with and accommodation of constant endogenous and exogenous influences. The view of lifespan trajectories of change in brain structure and function might serve as a base of understanding vulnerability to certain age-related disorders such as MCI and AD. It might be crucial to emphasize the potential significance of life course effects which, in a complex interaction, will eventually separate dementia and cognitive decline from normal aging-related mechanisms. However, it also appears that the relationship between different exogenous and endogenous events and their impact on brain structure and function varies in importance in the light of the time of their occurrence [41].

GENDER-RELATED CHANGES OF RELEVANT GM STRUCTURES

Sexual dimorphism of the human brain anatomy has gained increasing interest, with subcortical GM structures also being investigated more widely [42].

A number of studies have addressed the combined effects of age and gender on human brain structures. A more profound decline in GM volume has been described in males [33, 43, 44]. However, in patients with MCI and AD, GM volume has been found to decline faster in females as compared to males supporting the evidence of faster progression from MCI to AD [45]. This might be related to the main difference in brain anatomy between sexes, i.e., brain size. A larger brain might well have a greater reserve capacity to withstand pathology at the same level of functionalilty and cognitive abilities [46]. This has also been underlined by autopsy studies reporting women to have significantly higher odds of a clinical diagnosis of AD at the same level of neuronal pathology [47].

The effect of gender on the volume of these structures might be crucial, considering that basal ganglia possess a high density of sex steroid receptors [48]. However, neuroimaging results on the gender dependent volume of subcortical GM are somewhat contradictory. Some studies reported larger volumes of the caudate nuclei [49], hippocampus [50], and thalamus in females [51], while others had opposing results [52, 53]. The amygdala [54], pallidum, and the putamen [53] have been consistently found to be larger in males. Thus, research evidence appears inconsistent especially considering the subcortical GM structure [55]. This might also be due to the method of analysis, considering the difficulty to delineate subcortical GM using conventional voxel based morphometric methods. Our research group has applied a deformable surface model based segmentation approach to address volumetric alterations especially in regions with low tissue contrast [56]. While age, gender, and head size (intracranial volume) are the most commonly included 'nuisance' variables when performing neuroimaging analysis, studies vary as to which of these variables are included and which method is used for correction [57]. These factors might widely account for the great variability in the results. Accounting for skull size significantly influences results when it comes to GM volume and it might be of even greater importance when considering differences between males and females. Our results revealed larger cortical and subcortical GM volume for females as a result of correction for total intracranial volume in a study involving 103 participants in the age range of 21–58 years. The volume of the hippocampus was found significantly larger in the female group as compared to males. We also detected a significant effect of hemisphere in the male group only, with larger volumes of the right caudate and the left thalamus as compared to their contralateral structures.

Interestingly, we also found an age-dependent decrease in the volume of cortical as well as subcortical GM. Latter remained significant after correction for skull size in the caudate, putamen, and thalamus bilaterally for males and the thalamus bilaterally for females. Within the age range of 21 to 58 years, we found a linear decrease in GM volume with aging. Strikingly, this process proved to occur at a faster pace in males. Converging research evidence emphasizes the importance of considering age and sex interaction effects on the volumetric decline of subcortical structures. Li and his colleagues found this to be of key relevance for the hippocampus specifically, showing a linear negative correlation with age for males only [58]. Strikingly, for females, the pace of hippocampal volume decline has been found to occur at an even slower pace than whole brain volume loss. In contrast with this, a strong effect of aging on basal ganglia and thalamus volume changes has been observed primarily for females. The authors link these results to functional consequences involving predominantly psychomotor performance especially at later ages [59–61]. However, a number of studies did not find a significant effect of gender on cognitive performance or decline with age [62, 63]. While directly linking functional aspects to structural changes in brain anatomy might not be equivocal, elucidating effects of age $\times$ sex interaction on specific subcortical GM regions might well serve the investigation of related psychopathological alterations, such as MCI or AD.

The background of the disproportionate GM volume changes has not yet been elucidated, but the changes in hormone levels and the consequent sensitivity of the brain to hormonal effects are most certainly involved [64]. Sex hormones have been found to critically influence regional maturation of subcortical GM structures, e.g., higher circulating testosterone levels correlated positively with amygdala volume and negatively with hippocampal volume [65]. Estrogen among androgens has gained significant interest for its crucial role

during brain development. Females with endogenous estrogen deficiency have been found to have disproportionately reduced hippocampal volumes and increased amygdala volume as compared to age-matched controls [66]. This might be related to the complex distribution of estrogen receptors throughout the brain. Distinct estrogen receptor subtypes have been identified in nearly all cell types of the central nervous system, and importantly, in brain regions typically associated with cognitive function such as memory and affective processing, e.g., the amygdala and the hippocampus [67]. Strikingly, the estrogen-related volume deficiency evidenced by structural neuroimaging has also been associated with functional consequences revealed by cognitive assessment [68].

Epidemiological results support the notion that age-related loss of steroid hormones is associated with an increasing risk to develop AD [69]. Above this, AD prevalence is higher in postmenopausal women as compared to age-matched men–not explained by the generally higher life expectancy for females [70, 71]. The crucial role of estrogen is supported by several lines of evidence, with early menopause having been associated with an increased prevalence of dementia [72]. Estrogen has been found to modulate neurogenesis and activation of new neurons in response to targeted cognitive demands in the hippocampus [73, 74]. This might be mostly dependent on brain derived estradiol concentration [75], suggesting the importance of neuronal, and especially hippocampal, estrogen production [76]. Estrogen has a potent effect on inducing neurogenesis, neuronal morphology, and plasticity in specific areas of the hippocampus, such as the CA1 region and the dentate gyrus [74, 77–79]. An association between estrogen deficiency and hippocampal volume loss in females with clinically diagnosed MCI [80] might well serve as a potential common course leading to AD. However, there might be another crucial aspect, which should be emphasized when considering neuronal estrogen related hippocampus structure and function. A significant sex hormone cycle related effect on specific cognitive performance has only been found during initial testing and disappeared with repeated examinations of the same parameter, controlling for other confounding factors [81]. This occurred during an 8-week long testing period, which raises interesting questions about a life course perspective of hippocampus-related cognitive performance and the risks of consequent dementia. Furthermore, hormone treatment effects on the hippocampus in post menopause detected a limited window of opportunity to influence hippocampal volume. However, the larger hippocampal volumes associated with hormone treatment initiated at the time of menopause did not translate to improved cognitive performance [82].

Hippocampal volume loss appears to become accelerated in the postmenopausal period [83], which, associated with brain estrogen production decline, might be due to a significant reduction in neuronal plasticity primarily in the CA1 region. While postmenopausal hormone replacement therapy might spare the total hippocampal volume in a limited window of action, this might not be effective on the key areas of neuroproliferation. Consecutively, cognitive performance is not affected beneficially, eventually leading to the development of MCI or AD, due to the impaired cognitive reserve abilities influenced by several other factors (Fig. 1).

FUNCTIONAL CONSEQUENCES OF GM CHANGES RELEVANT FOR DEMENTIA OCCURANCE

Above the structural differences, there is increasing evidence for the functional sexual dimorphism of subcortical structures. Hippocampus-related memory functions are differently affected by stress in males and females [84]. Peripartum hormonal changes are known to modulate the hippocampal function [85]. In addition to gender effects, recent evidence supports the influence of brain hemisphere showing lateralization of structure-function relationships, as well as more specific relationships between individual structures (e.g., left hippocampus) and functions relevant to particular aptitudes (e.g., vocabulary) [86]. Numerous differences between the cognitive patterns of the two sexes have been reported [87]. Estrogen and testosterone appear to play a significant and continuous role in cognition throughout the lifespan [58]. In puberty, adolescents who mature later have better visuospatial skills than those who mature earlier [88]. Furthermore, a longer reproductive period is associated with higher levels of verbal fluency later during adulthood [89]. In adulthood, certain differences between male and female cognitive features are well known, e.g., higher performance on visuospatial tasks in males and female advantage in verbal skills [90]. This characteristic pattern of different cognitive abilities appears to persist later in life [91]. Interestingly,

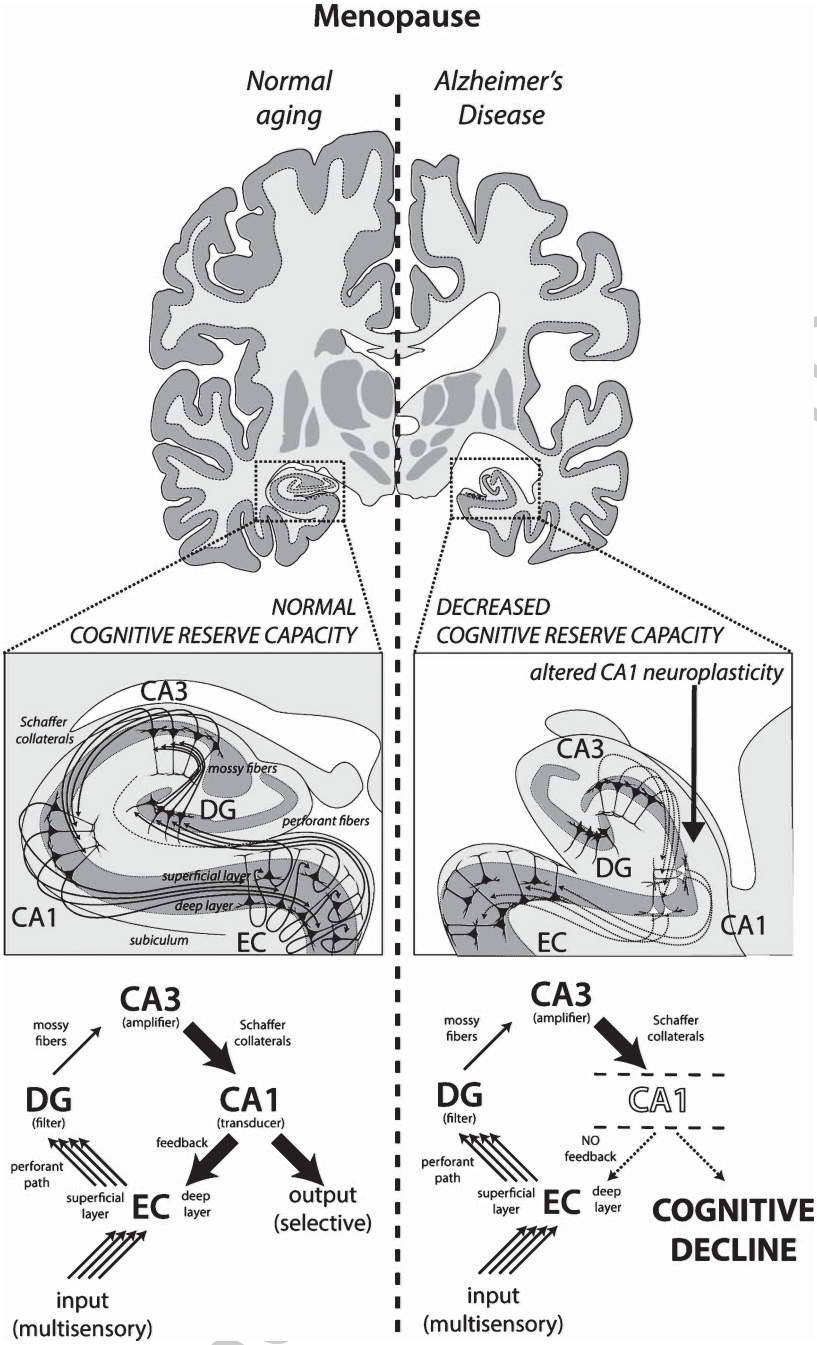

Fig. 1. According to major communication pathways of the hippocampal circuit multisensory input information enters primarily the entorhinal cortex (EC) then projecting towards the dentate gyrus (DG) and the CA3. Pyramidal cells of the CA3 send their axons to the CA1, which then projects to deep layers of the EC and sends the selected information along the output paths of the hippocampus. Additionally, feedback is being provided to the EC. The postmenopausal period and related estrogen loss might be associated with changes in the neuroplastic capacity of especially vulnerable regions of the hippocampus, such as the CA1 region. This region is rich in brain derived estrogen receptors and represents a key area for estrogen related neuronal manifestations. Molecular and pathobiochemical alterations might be present in the background of this deterioration, i.e., mitochondria-related inflammatory, oxidative effects. As a consequence, the selection of relevant information might become impaired or completely altered. In addition, the feedback source of the EC representing the major multisensory input area also becomes disturbed or even absent. In the presence of an impaired cognitive reserve capacity related to several previous internal and external factors, this might be an especially vulnerable time window for hippocampal structural and functional decline. This could result in an accelerated volume loss of the hippocampus and presumably, a consequent significant cognitive decline.

cognitive skills of women tend to decline slower than those of men [92]. Estrogen has been suggested as a protective factor against dementia through facilitating neurogenesis in the hippocampus and thus enhancing hippocampus-related spatial learning and aspects of memory [74].

Distinguished patterns of cognitive skills were confirmed not only in healthy aging, but also in patients with AD. Assessing AD patient's verbal skills, a meta-analysis revealed a difference in naming tasks and semantic fluency with lower performance in women [93]. As to visuospatial skills, no significant difference was found between women and men with AD [94]. Based on another meta-analysis assessing global dementia severity in men and women, it was found that women reached a significantly lower score compared to men with AD [95].

Apart from the individual's sex and its hormonal influences on cognition through the lifespan, other contributing factors might enhance or prevent cognitive decline and developing AD. According to a recent cohort study, lower performance in school during childhood may increase the risk for cognitive decline in later life [96]. Greater midlife stress is associated with a higher risk to develop dementia, especially AD among women [97]. Strongly negative life events such as losing a close relative can also increase vulnerability to enhance cognitive decline along with depression; however, milder but chronic stress factors may even stimulate cognitive functioning [98].

Brain areas typically affected in MCI and AD have a specific hierarchical order in which they become altered during the course of the disease based on Braak and Braak's neuropathological model [3]. According to this model, the first lesions can be detected in the MTL, including the hippocampus, parahippocampus, and crucial areas of the limbic circle, e.g., the amygdala, then in several areas of the temporal lobe, followed by other regions of the neocortex. The affected structures have their distinct roles in cognition; however, they contribute altogether to the characteristic clinical manifestation of AD. As an example of key importance, higher visual perception, including identification and recognition of faces and landmarks, as well as recognition of facial emotions, is dependent on the medial temporal lobe structures [99]. The impairment of these abilities might have an impact on behavioral disturbances in early AD and might even serve early identification of AD [100].

Being a key structure of the MTL and its memory network, the integrity of the hippocampus is required not only in episodic and semantic memory, but also in spatial information processing and manipulation [101]. The reduced ability to retain new information is one of the earliest core features of dementia and constitutes a heavy burden on the daily life of patients and caregivers [102]. A significant correlation of reduced hippocampal volume combined with higher levels of cortisol and performance on auditory and verbal memory subtests of the Wechsler's Intelligence Scale and Block Design tests measuring visuospatial skills has also been reported [103]. A recent study describes decreased thickness of the hippocampal GM formation in AD as compared to healthy individuals or patients with MCI [104]. Considering that scores on the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog) correlate with baseline entorhinal cortex thickness, its atrophy might be a predictor of subsequent cognitive impairment. The atrophy of hippocampal areas has been associated with more severe deficits in several aspects memory (especially episodic memory) and executive function [105]. Associated with lower activity in these areas, AD patients have demonstrated poorer encoding and retrieval than healthy individuals [106]. Simultaneously, increased activation in ventral lateral prefrontal areas may be interpreted as a compensatory mechanism in AD.

When considering the broader picture of cognitive disturbances already detectable in early stages of dementia, several other areas need to be mentioned. The thalamus, as a key area of the limbic circuit and the episodic memory network, has also been reported to be affected in early stage AD [107]. Alterations of the amygdala appear to have a profound effect on emotional aspects of memory in AD [108, 109]. Emotional stimuli, especially those with negative valence, have altered influence on memory functions in AD patients [110] and amygdala atrophy has been correlated positively with emotional memory impairment severity [111]. Some recent studies even pointed out other complex functions of the MTL, including path integration, e.g., spatial representation, self-motion sensing, and temporal processing [112]. Lesions of the anterior areas of the hippocampus, parahippocampus, amygdala, and the anterior and lateral section of temporal gyrus are associated with poor performance on tests of delayed memory, long-term memory and spatial memory. Additionally, patients with alterations of these structures have difficulties in target-directed walking because of deficits of allocentric spatial information processing.

The picture is certainly much more complex and it becomes increasingly difficult to decipher a causal relationship. Nevertheless, the role of the hippocampal region appears to be crucial in the occurrence and progression of the cognitive impairment in MCI and AD.

It is debated whether the extent of MTL structural atrophy is a better predictor of clinical dementia as compared to the memory deficit. Some studies found that the ratio of amygdala volume loss and bilateral entorhinal cortex shrinkage predicted time until MCI symptom occurrence [113]. Others, for example Visser et al., reported scores on cognitive test batteries to serve as better predictors than MTL atrophy in a longitudinal study design [114].

Considering that the volume of subcortical GM critically impacts the size of neurons, glia cells, and number of synapses it entails, we might hypothesis that it affects the function and performance of these structures. While deducing cognitive or any other type of functional activity of subcortical GM solely from their structural characteristics would be inadmissibly simplified, observing changes in volume of subcortical GM influenced by gender and aging might yield better insight into several pathological conditions, e.g., MCI and AD [115].

TRANSITION FROM HEALTHY AGING TO MILD COGNITIVE IMPAIRMENT AND AD

MCI is considered a precursor stage of AD with an annual conversion rate of approximately 15% [116]. However, the clinical manifestation of MCI is still not considered a predestination of a future conversion to AD. One of the crucial biomarkers proposed in the aim of a more valid diagnostic construct is MTL atrophy [117]. A large number of studies have focused on hippocampal volume loss focusing on MCI conversion to AD reporting a non-uniform pattern of hippocampal shrinkage. Converging research evidence emphasizes the key role of the CA1 region and subiculum showing the most significant involvement throughout disease progression early on in the course of illness [118–124]. While hippocampus volume has been reported to hold the highest predictive accuracy for conversion to AD, the best multivariate model for AD prediction, interestingly, consisted of cognitive variables only [125].

A potential explanation for this seeming discrepancy might be related to methods of imaging analysis with more advanced techniques needed to ascertain reliable and accurate data processing. The radial atrophy technique used to investigate subtle changes in distinct regions of the hippocampus might be a useful method in addressing prominent volume loss prior to clinical pathology. Here, the CA1 region might be of crucial importance, considering its robust volumetric loss above the age of 60 also compared to other regions of the hippocampus. However, if this is true for the normal aging process, what could then be the key turning point that eventually leads to the outcome of dementia?

A view that gains increasing support offers an explanation relying on neuroplasticity. Brain regions characterized by high neuroplasticity have been found to be especially vulnerable to neurodegeneration as well [126–128]. The CA1 region of the hippocampus maintains its neuroplastic flexibility well into adulthood presumably serving cognitive capacity in interaction with external and internal demands. Converging evidence supports the finding that high level abilities of neuroplasticity are retained late in life [129–131], especially in areas with long axonal connections, such as the hippocampal region [127]. The neurons in these regions might be able to maintain their morphological and functional flexibility to serve cognitive processes, however, these abilities might on the other hand increase their vulnerability to neurotoxic effects eventually resulting in structural and functional decline [132, 133]. The hippocampal region is undoubtedly a key area for high-order cognitive processes, such as memory and learning, associated with high demands for neuroplasticity and neuronal flexibility [134, 135]. In addition to this, other neuronal morphological processes, such as dendritic spine plasticity, might also play a crucial role in cognitive flexibility throughout the lifespan [136]. This mechanism might be involved in cognitive processes related to the CA1 region of the hippocampus [137, 138]. However, this might also be a vulnerability component for pathological effects, i.e., disturbed neurogenesis and neuronal flexibility in the hippocampus has been suggested as a crucial early component in cognitive decline and even AD [139]. The relatively rapid structural decline observed in postmenopausal women in these vulnerable regions might further accelerate the deterioration resulting in a vicious circle [140]. This is supported by findings of an age × gender × subcortical structural dependent interaction with an impact on cognitive reserve abilities [141].

RELEVANT MICROSTRUCTURAL AND PATHOBIOCHEMICAL CHANGES IN THE BACKGROUND OF STRUCTURAL AND FUNCTIONAL DETERIORATION

In the light of the presumably impaired neuroplasticity consequently leading to macrostructural changes in the hippocampal formation, one has to certainly address the microstructural neuropathology behind it. Focusing on specific hormonal effects, it has been shown that neuronal substrates associated with cognitive decline are significantly impacted by estrogens [142]. Research evidence indicates that most of estrogens' neuronal effects are related to brain derived estrogen, synthetized within the central nervous system [143, 144]. While levels of brain estrogen might largely differ from that of circulating estrogen, female brain estrogen levels have been found to relate well with blood estrogen levels measurable on the periphery [145]. Strikingly, a significant decline in brain-derived estrogen characterizes the postmenopausal period. It has also been suggested that this decline occurs mainly around menopause and, paired with a significant reduction in brain derived estrogen synthesis, it might lead to consequent cognitive deterioration [146, 147]. One key neuronal substrate that integrates several estrogen regulated molecular pathways is the mitochondria [148–150]. Estrogen receptors have been found in the mitochondria and the key role of mitochondria in estrogen associated neuroprotection has been supported by several different lines of evidence involving anti-inflammatory actions, anti-oxidant effects, and glutamate-related mechanisms among others (for an excellent review, see [151]). New evidence also indicates that a mitochondrial estrogen receptor deficiency found in the female AD brain results in impaired anti-inflammatory and anti-oxidative capacity of the mitochondria indicating vulnerability for neurodegeneration [152]. Our research has focused on the mitochondrial disturbances critical in aging, neurodegeneration, and AD specifically also involving the kynurenine system [153–155], glutamatergic mechanisms [156], and bioenergetic effects [157]. The complex interaction of these processes might well serve as a pathobiochemical and molecular background for the structural and functional alteration described in neurodegeneration. This is also supported by the relationship between worse pathological changes (i.e., amyloid depositions and total tau levels) and a more rapid hippocampal atrophy and cognitive decline in females, marking a potentially increased vulnerability for the clinical manifestations of MCI and AD [158]. In the female brain, the menopausal period brings deterioration in the above mentioned bioenergetical balance with a potential lack of compensatory mechanisms representing a vulnerability to cognitive decline [159].

CONCLUDING REMARKS

AD is a growing healthcare issue worldwide demanding more and more precise characterization and identification of potential turning points from healthy aging to MCI and AD. An increasing body of research evidence has confirmed specific subcortical GM alterations in the brain during this process, evolving based on a hierarchical model. The firstly affected and most crucial areas are the components of MTL, especially the hippocampus. Endogenous and exogenous factors interacting with each other contribute to continuous alterations of these areas from our birth throughout adulthood. There are non-modifiable variables, such as age and gender, which have specific effects during aging, involving hormonal influence. In women, hippocampal volume loss appears to be accelerated in the postmenopausal period. This volume loss might be associated significantly and in a beginning stage with the neuroplasticity of the CA1 region in hippocampus, considering its high sensitivity to pathological alterations. The atrophy and consequent structural decline and functional impairment of this region evolving to other hippocampal and MTL areas might lead to the clinical manifestation of cognitive decline. This risk might be the greatest in the case of an already narrowed cognitive reserve capacity or subclinical cognitive impairment. Serving as a potential biomarker, specific structural hippocampal changes might be associated with consequent functional patterns of cognition, potentially supporting the identification of MCI and AD prior to the clinical symptoms of the disease. The interaction of age and gender combined with individual variables such brain-derived estrogen receptors, bioenergetical balance, and compensatory mechanisms should be taken altogether into consideration when assessing a potential occurrence of MCI and AD.

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