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DOI
10.1016/j.biopsych.2024.11.007

Publication date
2025

Document Version
Final published version

Published in
Biological Psychiatry

Biological Psychiatry

Review

How Can Early Stress Influence Later Alzheimer's Disease Risk? Possible Mediators and Underlying Mechanisms

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ABSTRACT

Alzheimer's disease (AD) is a progressive, age-related neurodegenerative disorder to which genetic mutations and risk factors contribute. Evidence is increasing that environmental and lifestyle-related factors, such as exercise, nutrition, education, and exposure to (early-life) stress modify the onset, incidence, and progression of AD. Here, we discuss recent preclinical findings on putative substrates that can explain or contribute to the effects of stress early in life on the risk of developing AD. We focus in particular on stress hormones, neural networks, synapses, mitochondria, nutrient and lipid metabolism, adult neurogenesis, engram cell ensembles, and neuroinflammation. We discuss the idea that stress exposure early in life can alter these processes, either combined or in isolation, thereby reducing the capacity of the brain to resist deleterious consequences of, for example, amyloid-β accumulation, thereby accelerating cognitive decline and progression of Alzheimer-related changes in model systems of the disease. A better understanding of whether experiences early in life also modify trajectories of cognitive decline and pathology in AD and how the substrates discussed translate to humans may help develop novel preventive and/or therapeutic strategies to mitigate the consequences of stressors early in life and increase resilience to developing dementia.

https://doi.org/10.1016/j.biopsych.2024.11.007

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive, age-related impairments in cognition that impacts many people worldwide. Next to classical hallmarks, such as amyloid-β (Aβ) plaques and neurofibrillary tangles, brain atrophy, angiopathy, astro-/microgliosis, neuronal hyperexcitability, and synapse loss characterize the AD brain. Mutations in the amyloid precursor protein (*APP*) and *PSEN1* and *PSEN2* genes, which cause familial AD, comprise only a small percentage of all dementia cases. Most patients suffer from sporadic AD, a multifactorial disorder, with *APOE* ε4 as the best-known genetic risk factor. Large AD genome-wide association studies (1,2) have identified additional genetic risk factors at 108 genomic loci, each with limited prevalence and penetrance, apart from the APOE locus (3,4). Expansion of these studies captures more rare variants with larger effects (5). Interestingly, genome-wide association study loci aggregate in specific disease pathways [related to Aβ plaque and neurofibrillary tangle formation, cholesterol metabolism, endocytosis/phagocytosis, and the innate immune system (3,6)].

Epigenetic mechanisms, such as DNA methylation, histone modifications, and noncoding RNAs, can exacerbate or rescue dysregulation of these pathways, and while results of recent studies were not always consistent, global increases in methylation/hydroxymethylation have been described in AD, and hypomethylation of the APP gene has, e.g., been linked to increased APP expression (7,8). Also, epigenetic alterations in APOE or insulin signaling can cause insulin resistance and increase AD risk. Thus, epigenetic changes may alter susceptibility, but their exact role in AD requires more study.

The aberrant processing of the APP gene and/or the gradual accumulation of Aβ with age has been associated with neuronal spine loss, neurofibrillary tangles, vascular changes, and glial activation that together may underlie the behavioral and cognitive deficits in AD (9). Between patients with AD, there is substantial heterogeneity in disease onset, progression, and neuropathology, variation that is often discussed in the context of brain/cognitive reserve (10–15). This may be related to early-life factors (16–19) (see below) and helps conceptualize why some individuals are more prone to developing AD than others.

ENVIRONMENTAL FACTORS

Besides age and (epi)genetic factors, environmental factors, including stressful experiences, modulate dementia risk. In the Framingham Heart Study, temporal trends were described in the incidence of dementia over 3 decades, and a consistent reduction was found in the cumulative hazard rates for dementia among participants, while the incidence rate steadily declined during the second, third, and fourth epochs (20).

ISSN: 0006-3223

Because genetic changes were unlikely to be involved, these studies highlight lifestyle as a potential contributor to AD heterogeneity and risk. Nevertheless, which aspects of lifestyle, such as nutrition, exercise, smoking, stress, and education, are critical remains poorly understood (4,18,21). In individuals with higher educational attainment, IQ, or occupational attainment, a reduced risk for dementia has been found; reduced risk for dementia has also been found in those engaged in more social and leisure activities, bilingualism, and lifelong learning (although such conditions cannot be separated from differences in income and health care). Also, postmortem studies have substantiated links between a higher education level and/or participation in cognitively stimulating activities and a reduced risk of AD neuropathology (14,22–25).

Thus, whereas positive lifestyle factors may contribute to resilience to AD (26,27), adverse environmental experiences in contrast have been linked to earlier development of AD. Poor nutrition, obesity, smoking, sleep deprivation, and heavy alcohol use have been associated with increases in neuroinflammation, neurodegeneration, and a higher risk of developing AD (6,28). Also, stressful life events may lower the age of onset in patients with familial AD, while major depression, a disorder with a strong stress-related component, can increase sporadic AD risk (29,30). Furthermore, hypothalamic-pituitary-adrenal axis activity and glucocorticoid levels are commonly elevated already early in AD, highlighting an interaction between stress and AD risk (31,32). In addition, elderly individuals who are prone to psychological distress are more likely to develop AD than age-matched, non-stressed individuals (29–34). This is supported by preclinical studies in rodents that have shown that glucocorticoids may enhance AD pathology (29,35–38), while targeting glucocorticoids can mitigate AD pathology (35,39).

AIM OF THIS REVIEW

Many aspects of adult brain function are determined early in life (40), and the early perinatal period represents a sensitive time window during which pronounced effects on later cognition and disease risk can be exerted (18,41). While the outcome of negative early-life experiences may depend on the match/mismatch with the context later in life (42–45), early adversity is commonly linked to deleterious consequences for brain function and higher risk for psychopathology (46). However, surprisingly little is known about the early-life period as risk factor for AD. Because early prevention of AD is critical, it is important to understand the substrates affected by stress early in life (early-life stress [ELS]) and how they contribute to AD risk.

Here, we discuss recent preclinical findings on putative mediators of ELS effects on later AD risk. We acknowledge that none of the existing AD mouse models encompasses the full complexity of human AD pathology. However, these models remain indispensable because they allow us to study how ELS modulates specific cellular and neuropathological features in the context of AD. Because some of them can be manipulated experimentally, they are of considerable value for future therapeutic/preventive approaches (see Figure 1).

ELS: CLINICAL STUDIES

The long time window between early-life and AD manifestation is challenging for (prospective) clinical studies. Consequently,

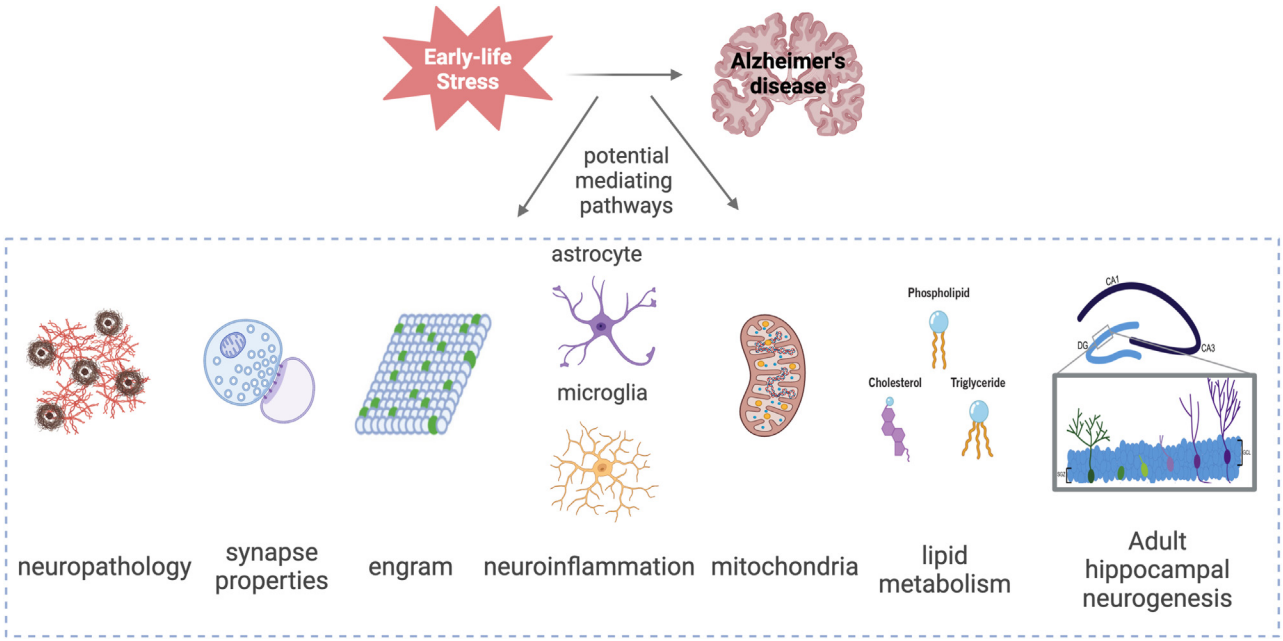

Figure 1. Summary of the different mechanisms through which early-life stress may alter development of later Alzheimer's pathology. Rodent studies provide evidence that early-life stress alters the progression and severity of Alzheimer's-related Aβ as well as tau pathology and cognitive dysfunction. At the cellular level, these changes may be mediated by alterations in synaptic function, stress responsivity, neural networks (and the excitation/inhibition balance within neural networks), neuroinflammation (including priming of microglia), mitochondrial function, lipid metabolism, and hippocampal neurogenesis. DG, dentate gyrus. (Figure created with BioRender.com.)

the clinical evidence that ELS affects AD risk is limited to retrospective studies on early exposure to trauma that was associated with compromised physical and mental health later in life (47–49). Studies on exposure, during early gestation, to the Dutch famine in 1944 to 1945 is associated with poorer cognitive function later in life. In particular, exposed men have shown evidence of advanced brain aging (16,50,51). Also, prenatal exposure to the Chinese famine has been associated with a higher prevalence of dementia (52). Adverse childhood events, such as losing a parent at a young age, increase dementia risk (48,53–55), and AD risk for people who experienced 3 or more adverse childhood events doubled (56). In addition, early social deprivation, sexual/physical abuse, and living in an orphanage have all been linked to a higher AD risk or impaired cognition as an adult (47,57–59). Recent systematic reviews have also linked the prenatal environment and childhood experiences to increased dementia risk (18,53,60).

ELS: PRECLINICAL STUDIES

While human studies underscore the relevance of focusing on early life, animal models provide mechanistic insight. Some of the most frequently found consequences of stress exposure during early life are accelerated development and altered stress responsivity (61–63). Notably, ELS is associated with accelerated maturation of brain regions involved in memory, from the synaptic to the network level (62,64–66). While such accelerated maturation may be beneficial in the short run, it may come at a cost for longevity (67), and increased stress sensitivity can modulate specific (epi) genetic programs (11) and/or render the brain more susceptible to AD-related pathology (18,39,54,68).

Cognitive decline is an important readout altered during the course of AD and is relatively easy to measure. In wild-type mice, exposure to ELS from postnatal days 2 to 9 induced prominent cognitive decline (62,69) but did not cause amyloid or tau pathology per se. The fact that no such accumulations occurred might have depended on genetic background, which was not taken into account here. When exposing AD transgenic mice to ELS, aggravated amyloid accumulation was observed in APPswe/PS1dE9 (APP/PS1) mice (38,70,71), and cognitive flexibility and memory were impaired (18,39,68,72). Furthermore, hippocampal Aβ plaque load, soluble Aβ levels, and BACE1 levels were increased in the hippocampus of 6- and 12-month-old APP/PS1 mice exposed to ELS, while, surprisingly, the opposite was found after postnatal handling (71).

In 12-month-old APP/PS1 mice, the impaired cognitive flexibility could be rapidly rescued by a brief treatment with a glucocorticoid receptor antagonist, indicating an important role for stress hormones in these deficits (39). The same ELS paradigm further decreased hippocampal cell–associated (i.e., not plaque-related) Aβ levels in APP/PS1 mice at 4 months old, an age at which APP/PS1 mice start to show cognitive deficits (65,68,73); however, ELS exacerbated hippocampal Aβ plaque load at 10 months of age (68), demonstrating that ELS affects different forms of Aβ load in an age-dependent manner.

Behavioral characterization of young adult APP/PS1 mice exposed to ELS showed an impairment in reversal learning already at 3 months of age, particularly when the task criteria were increased (65). Also, hippocampal spatial learning was impaired at 15 weeks of age (74). Although no plaques were observed at this age in these studies, some amyloid deposition has been reported by others in the neocortex at 6 weeks of age and at very low levels in the hippocampus at 3 months of age. Thus, relatively subtle cognitive impairments might have gone undetected with previously used behavioral paradigms and suggest that it is the preplaque Aβ deposition and/or soluble Aβ levels that may be involved in impaired cognitive flexibility. This may, to some extent, mimic the mild cognitive impairment that precedes the onset of full-blown AD. Thus, the early-life period modulates later cognition (69,75,76), with ELS enhancing pathological features characteristic of AD (18,25,38,39,53,59,77).

SYNAPSES

Next to these effects of ELS on Aβ and cognition in young APP/PS1 mice, ELS increased the synaptic strength of dentate gyrus granular cells and decreased the population of calretinin-expressing interneurons in the dentate gyrus at this age (65,66). This suggests that ELS could potentially change excitatory/inhibitory (E/I) balance in the hippocampus at an early age, thereby contributing to later cognitive decline. Parvalbumin-positive (PV^+) interneurons are particularly sensitive to (neonatal) stress, and their maturation depends on synapse formation, axon myelination, and the acquisition of fast-spiking properties during the first postnatal weeks in mice (78).

In mouse models of AD, several studies have highlighted PV^+ neuron dysfunction as a causal contributor to cognitive impairment. Hypoactivity of PV^+ cells has been observed at relatively late disease stages in these mice, when Aβ plaques are present and optogenetic stimulation of PV^+ cells, PV^+ cell transplantation, or polysensory stimulation at 40 Hz (the typical firing frequency of PV^+ cells) rescue cognitive deficits (78,79).

Interestingly, in 3- to 4-month-old APP/PS1 mice, i.e., before Aβ plaque deposition, hippocampal hyperexcitable PV^+ cell states are observed that precede the hypoactivity at 6 months of age (74,80). Early chemogenetic inhibition of hippocampal PV^+ cells also resulted in long-lasting restoration of E/I balance and cognitive performance and reduced the accumulation of Aβ plaques. Conversely, inducing an early hyperexcitable cell state of PV^+ cells in wild-type mice increased sensitivity toward the neuronal network-disrupting effects of Aβ, and subthreshold concentrations of Aβ oligomers that are normally not toxic induced PV^+ cell dysfunction, E/I imbalance, and cognitive impairment (74,80). Together, this suggests that early changes in hippocampal PV^+ cell maturation, which is sensitive to ELS, could enhance AD pathology at an earlier age.

Hippocampal Aβ production is promoted by excitatory synaptic transmission. Hippocampal E/I balance disturbed by ELS can thereby accelerate Aβ accumulation and render APP/PS1 mice more vulnerable to later AD pathology, consistent with the disturbed network activity and symptoms of epilepsy frequently observed in several amyloid-based models (78,79,81–84) and in people developing AD (85,86). Long-term potentiation is suppressed by Aβ (87) and after ELS (70), which is mitigated by postweaning administration of the glutamate release inhibitor riluzole, consistent with the hypothesis that hyperexcitability may play a crucial role in ELS effects on later network disturbances relevant for AD.

Hippocampal synaptic dysfunction and spine loss are early features of AD neuropathology (88) and correlate well with cognitive decline. These changes are thought to be mediated by excess Aβ triggering hippocampal synaptic depression and loss in AD models (89,90). Notably, not all synapses appear equally vulnerable to Aβ. In the hippocampus, at the postsynaptic site, Aβ oligomers interact with NMDA receptors (87), particularly those that contain subunit GluN2B (91). Upon exposure to Aβ, mainly GluN2B-containing synapses are lost or weakened (92). GluN2B-containing NMDA receptors that bind scaffolding protein PSD-95 are thereby protected from synaptic depression (92). Although speculative, because ELS reduces PSD-95 and GluN2B content in synaptosomes (66), the resulting decreases in GluN2A/GluN2B ratio may thus render synapses more vulnerable to Aβ toxicity.

Also, AMPA receptor (AMPAR) subunit composition determines whether synapses are sensitive to Aβ. AMPAR removal from synapses is a critical step through which Aβ oligomers mediate synaptic depression and synapse loss. Aβ oligomers weaken, or induce loss of, synapses from neurons that express the AMPAR subunit GluA3 (93). Whereas ELS affects AMPAR function (64), it initially decreases the GluA3 content at synapses, while increasing levels later in life (66). Consistent with this, increased GluA3 and GluN2B levels are associated with more severe cognitive dysfunction in people with mild cognitive impairment (94). Thus, ELS may render synapses even more vulnerable to synaptic Aβ toxicity by also altering their AMPAR subunit composition.

MITOCHONDRIA

Because synapses have high energy demands and are affected early in AD, there is growing interest in mitochondria and their oxidative phosphorylation capacity as possible substrates linking ELS to synaptic changes and AD pathogenesis (95–97). Genetic risk factors for AD, such as *APOE* ε4, have been linked to mitochondrial function (98–101), and clear connections exist between mitochondria and stress also in the human brain (102). In wild-type mice, ELS has been shown to alter hippocampal expression of genes involved in mitochondrial fission, mitophagy, and antioxidant defenses (103). Also, in young APP/PS1 mice, alterations in oxidative phosphorylation, electron transport, and mitochondrial mass occur, and recent proteomic studies of the synaptosome of AD mice have revealed a clear resemblance in protein expression profiles to those of AD samples. Furthermore, specific alterations were found in APP/PS1 mice after ELS at early (preplaque) or later stages of Aβ pathology (104).

ELS in wild-type mice also triggers a similar synaptosomal profile as the one that is induced by early Aβ pathology in nonstressed APP/PS1 mice at 4 months of age. At a later (10 months of) age, ELS strongly affected the synaptic proteome of APP/PS1 mice, particularly the expression of astrocytic and mitochondrial proteins (while having minimal effects in wild-type mice). Thus, ELS and amyloidosis may share pathogenic pathways that involve synaptic mitochondrial dysfunction (104), and mitochondria may represent a shared substrate through which both ELS and Aβ can act to disturb energy homeostasis, synaptic physiology, and cognition.

NEUROINFLAMMATORY CHANGES AND MICROGLIA

Neuroinflammation and astro- and microglia activation are hallmarks of AD (6,28,105,106). Notably, both human and preclinical studies have shown that ELS impacts the immune system, and in animal models, ELS impacts the immune system long-term (41,68,107,108). In human cohorts, ELS has been shown to trigger low-grade systemic inflammation and impact inflammatory markers, including higher C-reactive protein and altered cytokine profiles (109–111). In addition, early-life adversity, so far comprising studies using a poor diet or stress during early life, has been demonstrated to prime microglia, the main immune cells of the brain (17,112), and to increase their response to amyloid in the hippocampus (68). Reemst *et al.* (112) further characterized the long-term impact of ELS on microglia in the hippocampus of adult males and found that ELS affected microglial morphology and altered gene expression of 186 genes, most notably increasing tumor necrosis factor α–responsive genes and genes implicated in cytoskeleton dynamics. Administration of an additional inflammatory challenge led to distinct changes in microglia, either isolated from the adult hippocampus of ELS mice or from control conditions. ELS reduced their capacity to phagocytose synaptosomes ex vivo, both early and later in life.

This revealed priming and persistent effects of ELS on microglia function and on the microglial response to a secondary immunological challenge. Activation- and age-related changes have also been described for hippocampal astroglia after ELS (107), suggesting that alterations in neuroimmune function may mediate ELS effects on AD risk.

In support of this idea, blocking microglia in their activity by minocycline treatment affected various cognitive and functional measures in AD mice when provided from an early age on, i.e., before the onset of microgliosis (73). Soluble hippocampal Aβ levels or Aβ plaques deposition were not affected by minocycline treatment from 4 months of age, whereas these were reduced upon treatment at a later stage (6 months of age). A similar but different approach that selectively targets only plaque-associated microglia via systemic dendrimer administration is promising in this respect (113). Together, this highlights the need to intervene early with glial activation to reduce later Aβ pathology.

Most human risk genes for AD are highly, and several are selectively, expressed by microglia cells and astrocytes (2) that play key roles in neural circuit plasticity. Microglia can induce synapse loss and neuron loss in AD and contribute to impaired synaptic E/I balance, while astrocytes become reactive already early in AD and show impaired structural interactions with synapses (114) that may impair network activity. Remarkably, stimulation of hippocampal gamma oscillations, one of the indices of E/I balance, alters microglia activity, attenuates AD pathology, and improves cognition (115). Together, this positions microglia activation both upstream and downstream of E/I balance in AD pathology (see above).

LIPID METABOLISM

In addition to these physiological effects, increasing evidence highlights a possible role for lipid metabolism in neurodegeneration. Lipids are vital for brain structure, function, and metabolism, and the main lipids found in the brain

(phospholipids, polyunsaturated fatty acids [PUFAs], and cholesterol) show alterations in AD (116–119). Dysregulation of lipid metabolism has also been implicated in neuroinflammation and various aspects of AD (120), particularly regarding neuron-glia interactions (121). Moreover, polymorphisms of genes involved in lipid metabolism (like *APOE*) and in neuroinflammation (like *TREM2*) represent significant risk factors for AD, and the cognitive decline triggered by age-associated inflammation also involves specific lipids (122).

In particular, PUFAs from the n-6 and n-3 families and their derivatives, oxylipins, are important regulators of neuroinflammation (121). PUFAs are abundant in neurons and glial cells, including microglia, and decreased levels of n-3 PUFAs have been reported in the blood and brain of elderly participants with cognitive decline and AD (121,123). n-3 PUFA-derived specialized proresolving mediators, such as resolvins, maresins, and protectins, are crucial to resolve inflammation and enhance tissue restoration (121), and their levels are decreased in patients with mild cognitive impairment and AD (124) and in 5xFAD mice (125).

ELS alters various metabolic measures, including fat distribution and metabolic hormones like ghrelin and leptin, and changes brain lipid composition (76,112), which in the long-term can result in lipid dyshomeostasis. Interestingly, an early diet enriched in n-3 PUFAs could protect against ELS-induced cognitive deficits in wild-type mice, pointing toward opportunities for prevention (76). In fact, there is evidence that PUFA-based interventions can be effective in modulating AD-related pathologies in transgenic AD models (126–128) as well as in human trials (129). In addition, composite dietary interventions that include PUFA components have been promising (130,131). Additional investigation related to this exciting opportunity is needed to refine specific composition and optimal intervention times. Taken together, lipid dyshomeostasis may be a key biological substrate in mediating ELS-induced AD risk as well as a promising target for intervention.

NEUROGENESIS

The ELS-induced acceleration of brain development also affects structural plasticity, in particular neurogenesis, which is prominent during early brain development but persists into old age. Neurogenesis originates from stem cells that give rise to new neurons in the adult hippocampus and olfactory bulb. It is regulated by factors like exercise, inflammation, stress, and environment. Glucocorticoids are strong modulators (69,132–134) that, when they occur during early life, alter cortical and hippocampal neurogenesis and the response to stress for life (126,132,134,135). Exercise at later ages can in turn reduce stress, enhance learning, and promote neurogenesis, even in aged mice; however, no such rescue was reported after stress during early life (136,137).

Adult neurogenesis is involved in cognition and has been implicated in AD, based on both rodent and human studies (102,138). Reductions in neurogenesis occur notably already early in the disease process also in the human brain and in close correlation with cognitive status antemortem (102,138–140). The modulation of neurogenesis parallel to cognition by AD pathology as well as by ELS, exercise, and nutrients in various models (72,76,141) highlights a potential role for neurogenesis in hippocampal cognition and AD etiology and offers promise to promote resilience to AD (26,102,134,137–139,142).

ENGRAMS

ELS hampers later synaptic function and learning and memory (18). Recent studies suggest that memories are encoded in the brain by sparsely distributed, learning-activated cells and that synaptic properties of these engram cell ensembles are relevant for memory (143). Engram activation can restore memory retrieval in mouse models of AD (144,145) indicating that, at least in the earlier stages, mouse models of AD display in particular deficits in memory retrieval. In adult animals, stress and stress hormones enlarge the engram, which in turn influences memory expression. In contrast, ELS reduces neuronal activation after learning and hampers retrieval (146). Thus, memories for which the encoding and consolidation were weaker as a consequence of ELS may be harder to retrieve over time, making them more susceptible to forgetting and thus particularly relevant for AD.

Furthermore, ELS-activated cells are involved in stress sensitivity later in life, resulting in greater reactivation of ELS-activated ensembles during adult stress (147). This may increase susceptibility to adult-life stressors, thereby increasing cumulative, lifelong stress exposure and accompanying vulnerability to AD pathophysiology. Such effects may be due at least in part to changes in the synaptic properties of engram cell ensembles (148), and similar processes could be involved in relation to ELS and AD pathology (144). Additionally, PV^+ interneuron function and their critical ability to govern engram ensemble formation and memory processing are age dependent (149) and are notably impaired by ELS. Weakened PV^+ activity following ELS may thus disrupt engram ensemble formation and/or accessibility and thereby impair memory processing.

CONCLUSIONS

Various (pre)clinical lines of evidence suggest that negative experiences early in life can modulate the trajectory of cognitive decline and the onset, incidence, and progression of (aspects of) AD. This emphasizes the importance of better understanding the mechanisms by which ELS can alter AD features.

The substrates discussed help us understand how such long-lasting effects are mediated and can possibly be prevented. They include alterations in E/I balance, synapse function, mitochondria, lipid metabolism, neurogenesis, and neuroinflammation and may render brain cells and networks less able to adapt to AD pathology, thereby decreasing resilience and advancing AD onset.

Preclinical models have helped identify several putative substrates, but human data on similar mechanisms remain scarce. Whereas the importance of the early-life period for psychopathologies, such as depression, is generally recognized, research should also focus on this critical period for the brain in relation to AD.

ELS effects on brain health and AD risk involve different substrates and pathways. Therefore, a multifaceted and/or lifestyle-based approach is also likely required to target the early phase of AD. Also, the optimal timing of such interventions needs to be determined. Because there is evidence that early diet-based

Box 1. Outstanding Questions

- What are the critical periods in perinatal (human) development that are most sensitive to environmental alterations and bear relevance to increasing either resilience or vulnerability to Alzheimer disease (AD)?
- How does early-life stress affect AD pathology and cognitive decline? This may involve (epi)genetic factors, altered stress responsivity, amyloid clearance, glymphatics, neurogenesis, mitochondria, and (micro)glia priming. A better understanding is needed of how early-life stress changes (pro- and anti-inflammatory) properties of glia (subtypes) and how this can affect clearance and pruning of (excitatory and inhibitory) synapses and network function.
- Does early-life stress influence inhibitory neuron function and network imbalances in AD? Can restoring alterations in inhibitory neurons rescue network function and cognitive deficits in patients with AD?
- How is neurogenesis linked to AD, and can its stimulation, or its programming by early-life factors, modulate cognitive decline in AD?
- What is the link between lipid metabolism, neuroinflammation, and later cognition? Early nutritional interventions, focusing on, e.g., polyunsaturated fatty acids and specialized proresolving mediators, could be tested in relation to later AD features.
- Which of the substrates discussed exerts the largest contribution and to what extent are they interconnected? Also important is which positive lifestyle factors during early life can stimulate cognitive/brain reserve, mitigate cognitive decline, delay disease onset, and ultimately promote resilience to AD.

interventions can counteract later cognitive decline after ELS (94,111,112,123,125,128,129,142,150), future studies should assess whether later life dietary interventions are effective as well.

Next to identifying and targeting mechanisms that increase AD risk and/or reduce its age of onset (as summarized in Figure 1), more research should be devoted to identifying protective factors that can promote resilience to AD (12,14,18,22,26,42), preferably at the earliest age possible (see Box 1).

ACKNOWLEDGMENTS AND DISCLOSURES

PJL, HJK, AK, ABS, REVK, MHGV, SLL, and HWK are supported by the Mechanisms Of DEMentia (MODEM) Memorabel program of Zon-MW, the Netherlands, and by Alzheimer Nederland. A-MVD is supported by the Nationaal MS Fonds. PJL, SRdR, and HJK are supported by the Centre for Urban Mental Health of the University of Amsterdam. PJL, A-MVD, and AK are supported by the Gravitation grant "iCNS" funded by the Dutch Research Council (NWO) (Grant No. 024.006.009).

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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Received Jul 25, 2024; revised Nov 12, 2024; accepted Nov 14, 2024.

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