Stress and memory in health and disease

Impact on Alzheimer's disease and memory mechanisms

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General Introduction

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Vulnerability and resilience to Alzheimer's disease: Early life conditions modulate neuropathology and determine cognitive reserve

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Introduction

The period during peri- and early postnatal life is a critical developmental phase that plays an important role in shaping adult health, a concept that has been widely described in the context of the so called Developmental Origins of Health and Disease (DOHaD) hypothesis[1,2]. This hypothesis centres around the notion that the early life environment impacts later health and the vulnerability to develop diseases throughout the entire lifespan, for instance in relation to mental health[3,4], obesity, diabetes, coronary heart disease (e.g.[5,6]). Indeed, accumulating preclinical and clinical evidence highlights the association between early life adversity and impaired cognitive function, the predisposition to develop psychopathology, and neurological disorders such as Alzheimer's disease.

1. Early life experiences and cognitive function later in life

During early postnatal development, the brain undergoes an impressive growth that involves a massive growth and migration of glia and the proliferation of stem cells and their differentiation into young neurons, that are guided by migration along glia, their formation of early axonal connections and the functional maturation of these neural connections into (early) neuronal networks. These developmental phases involve a carefully controlled orchestration of numerous specific genes being expressed in a well-defined spatiotemporal pattern, allowing complex neuronal networks to be formed.

This delicate, developing brain is very sensitive to external influences and environmental factors, particularly during stages when massive proliferation and migration of neurons occur. As such, stressful experiences and the presence of elevated levels of glucocorticoid hormones (cortisol in humans; corticosterone in rodents) during the early life period have been reported to interfere with ongoing brain development and can exert long-lasting effects on adult brain function and behaviour. Indeed, adverse events during prenatal and early postnatal life (early life stress, ELS) are associated with stress exposure and an increased vulnerability to subsequent stressors and compromised physical and mental health later in life, both in humans and rodents[7–12]. In contrast, more positive and 'stimulating' experiences during early life are, at least in rodents, associated with an apparent resilience to later-life challenges, with a good physical and mental health, as well as with decreased chances to develop later anxiety- and depressive-like behaviour[13–17].

The vulnerability of the brain, and in particular the hippocampus (**box 1**),

Box 1. Brain regions most relevant to the studies in this thesis

While the stress response starts in the hypothalamus, in this thesis, the main focus will be on the **hippocampus**, an extremely plastic brain region with high relevance for cognition[205] and regulation of the stress response[32]. The hippocampus is highly relevant for processing contextual information and spatial learning. The hippocampus continues to develop postnatally, until two years of age in humans and up to two weeks after birth in rodents[206, 207], making it particularly sensitive to events early in life. This is supported by clinical evidence showing that early life adversity results in decreased cognitive functioning in adulthood[208–210], and correlates with reduced hippocampal volume[211–213]. Furthermore, hippocampus dysfunction is among the first presentation of Alzheimer's disease. Different hippocampal subfields each exert their distinct roles in information processing, among which processing of spatial (CA1[214]; CA3[215]) or temporal information[216,217], novelty (CA1[218]), and social memory (CA2[219]). The **dentate gyrus** (DG), another hippocampal subregion, is critically involved in separation, the ability to independently represent and store similar experiences[220].

The **amygdala** plays a key role in the circuitry underlying emotional learning and memory[221–223], with a crucial role in auditory fear conditioning[224–226]. Specific subregions have further been associated with encoding cues (basolateral amygdala (BLA)[227]), in mediating the effects of stress hormones on memory consolidation (BLA[226]), and with fear memory extinction (BLA[228]; central amygdala[229]; lateral amygdala[230]).The amygdala further interacts closely with the **medial prefrontal cortex** (mPFC), which is involved in appraisal of threat or safety and through which, together with other brain regions, many emotional and cognitive processes are affected[231–234]. The mPFC is also involved in planning, behavioural flexibility and inhibitory behaviour[235,236].

to an age-related loss of function seems to parallel the effects of negative or positive early life experiences on cognitive performance. For example, prenatal stress increases, while neonatal handling (which increases maternal care) decreases the rate of brain and/or hippocampal aging and plasticity[18–20]. This has, in part, been attributed to lasting alterations in hypothalamic-pituitary-adrenal (HPA) axis activity that occurs following such early life experiences. The changes in reactivity of the adult life HPA axis e.g., play a major role in determining the rate of brain and body aging[21–29].

During the early postnatal period, the dam is a critical factor for her pups and a disturbance of the mother-pup interaction can have lasting effects on the HPA axis and memory of her offspring later in life (see section 1.1). In rodent models (see **box 2** for a summary of the different rodent models of early life stress or enrichment), perinatal stress impairs cognitive performance at an adult age, while generally increasing emotionality and reactivity of the HPA axis and autonomic nervous system in the offspring, effects that generally also last throughout life[1,2].

1.1. Hypothalamic-pituitary-adrenal (HPA) axis

Experiences early in life can change HPA axis responsiveness in a long-lasting manner, thereby programming the (cumulative) extent of glucocorticoid exposure over life[30]. Activation of the HPA axis drives glucocorticoid hormone secretion from the adrenal cortex, both in a circadian manner and in response to stress[3,4]. HPA axis activity is initiated by internal and external signals that trigger the hypothalamus to release corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to secrete adrenocorticotropic hormone (ACTH). ACTH acts on the adrenal cortex to stimulate the synthesis and secretion of glucocorticoids. In turn, glucocorticoids also target the hypothalamus and anterior pituitary to inhibit the production and release of CRH and ACTH and thereby GCs control their own release via a negative feedback loop[31]. Elevations of basal corticosterone levels and a reduced capacity to adapt to and recover from stressors are an inherent part of aging[5,6], and an acceleration or delay of these processes may directly influence brain and cognitive aging.

Glucocorticoid hormones can bind to the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). The MR has a high affinity for glucocorticoid hormones, is occupied under basal conditions, and is involved in the initial rise of the endocrine stress response[32]. GRs, which have a tenfold lower affinity to glucocorticoids, are occupied when glucocorticoid levels are high in response to a stressor. They are involved in terminating the stress response[7–12]. Both receptors are present in the cytosol and activate or suppress nuclear gene expression upon the binding of the ligand[32], important for adaptation and termination of the stress response as well as the storage of information for future use. In addition, activation of these receptors can also exert rapid, non-genomic effects[13–17]. These rapid effects affect neuronal excitability and are important for the initial stress response and rapid behavioural effects[22]. Combining non-genomic and genomic actions, MRs and GRs can affect behaviour over a wide time range[18–20].

Box 2. Rodent models of early life stress and enhancement

In the early life period, the brain shows massive development and is highly sensitive to environmental factors that can disturb this process and affect brain function for life. The consequences of the interferences depend on the maturity of the brain at the moment of birth. For instance, the rat brain at birth is about as mature as the human brain at mid-gestation. This programming is critically determined by, amongst others, interactions between the mother and her offspring. In animal models, the critical components shaping the local environment are; the intrauterine environment, that can be affected by specific medication or e.g. stress hormones that reach the pregnant dam and her fetus(es), as well as postnatal interactions between the dam and her offspring. This involves elements like tactile stimulation, nutrition and warmth. Both time windows can be manipulated experimentally to study the consequences of such early life experiences. We will here highlight some relevant models.

Prenatal stress[20] is a model most commonly induced in pregnant rodents by a single or repeated session of maternal restraint stress and/or defeat during specific gestational periods (mostly during the last week of gestation, sometimes earlier).

Models in which the **naturally occurring variation in maternal care** is used to select for pups that received high amounts of maternal care compared to pups receiving low amounts of maternal care (**low vs. high licking and grooming**). This represents a model to test the consequences of 'negative' and stressful vs. a 'positive' early life environment for later brain structure and function[94,96].

Box continues on next page

Persistent increases in HPA axis activity can result in higher basal glucocorticoid levels, and in a stronger and more prolonged exposure to glucocorticoid levels following a stressor. Chronic early life stress, induced by housing dams and pups with limited nesting and bedding material (LBN, see **box 2**) results in elevated corticosterone level, increased adrenal gland weight[33], as well as reduced glucocorticoid receptor (GR), mineralocorticoid receptor (MR) and CRH expression[21–29]. The MR is involved in the appraisal of stressful situations and in the maintenance of basal corticosterone levels, while GR regulates the stress response when endogenous GC levels are

Box 2 (continued)

Alterations in the postnatal mother-pup interaction can also be induced experimentally. Postnatally, early life stress is e.g. induced by a single, prolonged separation of dam and pups, called **maternal deprivation**[99], which usually lasts for 24 hours and is conducted at postnatal day (PND) 3 or 4. Alternatively, with **maternal separation**[97], the dam and pups are separated repeatedly for 2-5 hours/day. To introduce chronic early life stress[54], a reduction in the available nesting and bedding material (**limited nesting and bedding material**, LBN) triggers erratic and fragmented maternal care and stress in the dam which is transmitted to her offspring.

In contrast, a 'positive' early life environment is typically installed by separating the dam and her pups for a brief period of up to 15 minutes on a daily basis, during a time window from PND 2-9 or until weaning. This model is generally called postnatal or **neonatal handling**[19,56,237] and, results in increased levels of maternal care of the dam towards her pups upon reunion.

high by regulating the negative feedback of the HPA axis to stress. Naturally occurring low levels of maternal care also result in increased corticosterone levels and enhanced CRH release in response to a stressor[34–37] and in a lower expression of hippocampal GRs[30]. Maternal separation increases corticosterone levels in response to a stressor[38,39], which is accompanied by reduced GR[31] and increased CRH levels[40–46]. Maternal deprivation also increases basal and stress induced corticosterone levels but decreases expression of GR[32]. Finally, prenatal stress in rats, applied during the last week of gestation, increased HPA axis responsiveness to subsequent stressors in the adult offspring[45,47–49]. Also, the maintenance of basal levels of HPA axis activity is altered, possibly due to a reduced hippocampal MR expression[32], thus highlighting the sensitivity of the HPA axis for early life adverse experiences.

Conversely, increased levels of maternal care early in life, e.g. introduced experimentally by subjecting animals to neonatal handling (see **box 2**), exerts opposite effects; both corticosterone and ACTH levels are reduced following stress exposure[36,50], accompanied by higher hippocampal GR[22], lower MR[33], and changes in CRH levels[51–55]. Even studies in which both prenatal stress and cross-fostering were combined, which can also be considered a form of neonatal handling as it involves intense licking of the pups upon the return of the mother[34–37], show that the effects of prenatal stress on HPA axis activity can

be reversed by cross-fostering the pups to new mothers[56,57]. This emphasises the strong protective effect of positive early life experiences on HPA-axis responsiveness.

Alterations in glucocorticoid hormone levels and changes in HPA axis feedback have often been associated with hippocampal aging and accelerated cognitive decline[38,39], although exceptions exist as well[58–60]. In humans, those aged individuals who exhibited elevated basal cortisol levels, were the ones who displayed impaired explicit memory performance and selective attention deficits[40–46]. Their hippocampus was also found to be 14 % smaller than that of age-matched controls who did not show progressive cortisol increases and who were not cognitively impaired[59]. Rats with increased HPA-reactivity show an earlier age-related decline of several hippocampus-dependent cognitive functions[45,47–49], while older, cognitively impaired animals also display higher HPA axis activity[61]. Besides the deleterious effects of prolonged glucocorticoid hormone exposure, early life stress also affects the CRH and CRH receptor 1 system (see below), resulting in functional and behavioural impairments in adult life[36,50]. Together, the specific effects of glucocorticoid hormones on neural development and HPA axis reactivity may change qualitatively as the nervous system matures and ages[61], indicating that the timing of the applied procedure and the stress hormone exposure, relative to the developmental stage of the different brain regions, is important for its later effects.

1.2. Behaviour

Early life experiences have also been correlated to behavioural alterations later in life, which may be related to HPA axis activity. Chronic early life stress (see **box 2** for details) e.g. increases adult anxiety-like behaviour in the elevated plus maze[51–55], in the open field and in the light/dark box[62]. Furthermore, various types of chronic early life stress induce memory deficits in the Morris Water Maze[56,57], novel object recognition test[63] and Y-maze[58–60], while conditioned fear responses are increased[31,64]. Offspring that received low amounts of maternal care also shows impaired spatial memory and object recognition performance[59] and increased conditioned fear responses[64,65]. Impaired spatial memory was also reported following maternal separation[61], and maternal deprivation[17,19,61,66–68]. Furthermore, maternal separation results in more anxious animals in the light/dark exploration test[61] and after fear conditioning[14,61]. Finally, prenatal stress has been found to increase anxiety in an open field test[62], and to impair spatial learning at adulthood[61]. Neonatal handling on the other hand, has been associated with a slower rate of cognitive aging and a reduced loss of hippocampal function throughout life[63]. It also results in improved behavioural

performance in different learning and memory paradigms[69] and a reduction in conditioned and unconditioned fear responses[31,64].

1.3. Synaptic plasticity

Cognitive and memory impairments may be related to deficits in synaptic plasticity[58]. The capacity to display long-term potentiation (LTP) is one of the major cellular mechanisms thought to underlie learning and memory[64,65]. Indeed, chronic early life stress results in a reduced capacity to trigger LTP in the hippocampal CA3[70,71] and CA1 area[17,19,61,66–68]. Similarly, pups that received low amounts of maternal care failed to show LTP induction in the dentate gyrus[21–29] or hippocampal CA1 area[14,61]. Maternal separation further impaired LTP in the prefrontal cortex (PFC)[72–77], whereas maternal deprivation impaired LTP in the dentate gyrus[61] and CA1 area[78]. In line with this, exposure to prenatal stress was found to impair the induction of LTP in hippocampal areas at a young adult age[69]. Interestingly, neonatal handling paradigms, which lower corticosterone exposure, have also been shown to prevent age-related hippocampal and cortical neuronal atrophy and dysfunction[79], and to enhance LTP in the CA1 area of adult rats[58] (more extensively reviewed by[18]).

1.4. Dendritic morphology

Various studies have shown that pre- and neonatal experiences cause persistent morphological changes to individual neurons in specific limbic brain regions and the PFC[70,71]. For example, following early life stress, dendritic atrophy of CA1 pyramidal cells and expansions in the CA3 mossy fibres were observed, while the number of granule cells in the hippocampal CA1 area and its innervation of CA3 pyramidal neurons was reduced[28], possibly via stress-induced increases in CRH neurons[21–29]. Furthermore, exposure to chronic early life stress reduces the number of dendritic spines, i.e. the anatomical substrate for memory storage and synaptic transmission, in both CA1 and CA3 areas. Also, a reduced inhibitory synaptic density was found in the CA1 area and in parallel, a reduction in excitatory synaptic density in the hippocampal CA1 and CA3 areas[80,81].

Although less well described, also other brain regions are affected, and chronic early life stress hampers dendritic development and spine density in the PFC[72–77], whereas it increases spine density in the basolateral amygdala (see **box 1**)[82,83]. In addition, pups that received low amounts of maternal care early in life show reduced dendritic complexity in the CA1 area and dentate gyrus at adulthood, compared to pups that received high amounts of maternal care[78].

Also, the number of spines in hippocampal neurons is higher in pups that received high compared to low amounts of maternal care[79]. Finally, maternal separation caused atrophy of the basal dendritic tree and reduces spine density on both the apical and basal dendrites in layer II/III of the PFC[84,85]. Maternal deprivation reduced the number of granule cells and dendritic complexity in the dentate gyrus[18], but had no effects in the amygdala[86].

1.5. Adult neurogenesis

Aging is a prominent inhibitor of adult hippocampal neurogenesis, a form of structural plasticity referring to the continued production of new hippocampal neurons throughout adulthood. These adult-generated neurons are derived from stem cells present in the adult hippocampal dentate gyrus that go through distinct developmental stages before they become fully functional and well integrated within the hippocampal tri-synaptic circuitry[28]. The process of adult neurogenesis is regulated by various hormonal and environmental factors, including a stimulation by enriched environmental housing or exercise[52,81,87,88] and in general an inhibition by stress[80,81]. Some exceptions exist as well, but in these cases, stress was often predictable, controllable and/or mild, and may actually have resulted in enrichment and could thus have been perceived as positive and rewarding experiences[52,54,81,88]. Neurogenesis plays a role in stress regulation[82,83] and is involved in various forms of (hippocampus-dependent) learning and memory[87], including pattern separation[84,85].

Depending on the animal model used, early life stress generally impairs hippocampal neurogenesis at adult ages[51,89], whereas 'positive' stimuli like (adult life) environmental enrichment or exercise increase the number of newborn cell numbers in the dentate gyrus[86], but this also depends on earlier treatments and experiences, possibly in a sex-dependent manner[90–93]. For instance, exercise, which enhances neurogenesis in males, failed to increase neurogenesis in middle-aged female mice that had been exposed to chronic early life stress in their first week of life[52,81,87,88]. Thus, early life experiences can modify the aging-associated decrease in neurogenesis as well as its subsequent sensitivity to environmental stimuli applied later in life[94–96].

2. Early life experiences and Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder that is highly prevalent among the elderly population. AD is characterised by progressive impairments in various behavioural and cognitive functions[52,54,81,88] that have a profound impact on AD patients, their families, caregivers, and society.

Prominent neuropathological hallmarks in the brains of AD patients include amyloid-β (Aβ)-peptide-containing plaques and neurofibrillary tangles (NFTs) containing hyperphosphorylated tau. In humans and rodents, the gradual accumulation of Aβ-containing plaques and NFTs has been associated a.o. with spine loss and glial activation. Together, they may trigger the age-related cognitive decline and behavioural symptoms characteristic for AD[87].

Seminal genetic studies have identified mutations in the amyloid precursor protein (APP), Presenilin-1, Presenilin-2 genes and variations in ApoE in relation to early and late-onset familial AD (see e.g.[97,98]). While these mutations explain a small percentage, the vast majority of AD cases likely has a multifactorial aetiology, in which both age and lifestyle factors play an important modulatory role[51,89]. Epidemiological studies have shown that factors like higher education, a more healthy diet, more social and physical activities, bilingualism, and measures for lifelong learning and mental stimulation correlate with a slower rate of memory decline during aging, a delayed onset of mild cognitive impairment (MCI) and/or a lower incidence of AD[99–102]. These positive lifestyle factors may therefore delay AD onset and increase the resilience to develop AD.

On the other hand, adverse environmental experiences such as prolonged stress, have been associated with a faster progression of AD symptoms and an earlier development of pathology[90–93]. Stressful life events have been reported to reduce the age of onset in familial AD[103], while major depression, which has a strong stress-related component, has been associated with an increased risk to develop AD earlier in life (e.g.[94–96]). Furthermore, glucocorticoid (GC) hormones, the main mediators of the stress response, are often increased in AD, notably already early in the disease[104] and dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis, i.e. the main neuro-endocrine axis controlling GC release and feedback, may increase the risk to develop AD[97,98]. Together, these studies highlight a possible interaction between genetic predisposition and lifestyle factors such as stress and/or low socio-economic status, in determining the vulnerability and resilience to develop AD.

In a recent study, Wang et al.[31,64] have identified in particular the early postnatal period in humans as a sensitive time window for lasting effects on brain structure and function and also on the risk to develop AD[105,106]. Indeed, stressful and traumatic experiences during the early life period have been strongly associated with an increased vulnerability to stressors, and compromised physical and mental health in later life, both in humans and rodents[99–102]. On the other hand, 'positive' or stimulating early life experiences in humans[83,107] and rodents[103] have been associated with an apparent resilience

Box 3. Rodent models of AD neuropathology

Preclinical studies have so far employed transgenic and non-transgenic approaches to model aspects of Alzheimer's Disease. These models generally reproduce various disease aspects; memory impairments, Aβ containing plaques, and/or tau/tangles, and neuronal loss (only in a few Aβ based models).

Transgenic models most frequently (over)express single or multiple mutations in the APP, presenilin (PS) and/or tau genes, or combinations of these genes, that relate to familial forms of AD. Non-transgenic models are generated by the injection of specific toxins into the brain, such as Aβ, tau or inflammatory-related compounds, or use naturalistic models of aging. Although none of these models fully captures the entire human disease profile and often model only one specific aspect of AD neuropathology, the existing models have made important contributions to our current understanding of AD pathophysiology. There are, however distinct differences in the presentation of neuropathology in transgenic models and the human presentation of dementia, in particular with regard to animal models of amyloid pathology which overall display severe hippocampal amyloidosis, which is different from the human presentation of plaque pathology. Also, no tau mutations have been identified that cause autosomal dominant AD, unlike mutations in Aβ -associated genes. Tau mutations in contrast, produce fronto-temporal dementia. The Aβ and tau-based models will be discussed in more detail in the second part of this box.

Box continues on next page

to later-life challenges and a better later physical and mental health.

Together, several human studies suggest that stressful events early in life are associated with a higher chance to develop AD[104] whereas, in contrast, early life enrichment, longer education and more cognitive 'stimulation' during early periods, are correlated with a later presentation of AD symptoms[19,66–68,108]. While the association between early life experiences, HPA axis responsiveness, brain structure, synaptic plasticity and memory underscores the possible importance of the early postnatal period also for AD symptomatology and neuropathology, the long time lag in between the early environment and the onset of AD symptoms has so far hampered a deeper understanding of the underlying causes and possible mechanisms. To address this, animal models

Box 3. Continued

Aβ neuropathology: The amyloidogenic pathway of amyloid precursor protein (APP) processing occurs through APP cleavage by β– and γ-secretases, producing C83, C99 and Aβ fragments. Aβ peptides can aggregate to form oligomers, which exist in different forms (e.g. soluble/insoluble, oligomeric, fibrillary plaques) and have different pathogenic properties. The most commonly used mouse models overexpress a mutant form of APP (isoform 695) with the Swedish mutation (KM670/671NL) ("**Tg2576**" mice), resulting in elevated levels of Aβ and cognitive impairments by 1 year of age[238]. The introduction of an additional PSEN1 mutation, which increases γ-secretase activity, yields the widely used **APPswe/PS1dE9** mouse, which develop progressive Aβ deposits and cognitive impairments as early as 6 months[239,240].

Tau neuropathology: Tau proteins are the product of the microtubule-associated protein tau (MAPT)-gene, and mutations in this gene lead to hyperphosphorylation. Excessive levels of this protein, or its abnormal phosphorylation, both result in the formation of NFTs and pathogenic paired-helical filament-tau. The **PS19**[241], **Tau.P301L**[242] and **JNPL3**[243] models overexpress the MAPTP301L gene, and show progressive tangle-like pathology in the midbrain and brain stem, parallel to cognitive deficits (not reported in JNPL3 mice). Given the preferential targeting of the disease gene to these brain regions and the important role of tau for (large) motor neurons, many tau mutant mice develop motor problems prior to the onset of hippocampal and cognitive impairments, which is a drawback of these models.

Combined neuropathology: When multiple transgenes are combined, both Aβ and tau neuropathology is induced, for instance in the bi-genic model overexpression APPV717I and Tau.P301L mutation ("**biAT**")[244]. Other commonly used models are the **3xTg-AD**, harbouring the APP Swedish, the MAPT P301L, as well as the PSEN1 M146V mutations, displaying learning deficits from 6 months onwards[245]. The **5xFAD** model, harbouring the APP Swedish, Florida and London mutations, as well as the PSEN1 M146V, and PSEN1 L286V mutations show aggressive and early presentation of amyloid pathology, starting at 1.5 months of age[246]. Additional and related models have been generated as well[247–250].

allow for a more detailed investigation of these relationships that may help to identify the mechanisms by which environmental factors during the early life

period can affect AD symptoms and pathology. The ability to e.g. model specific genetic risk factors for AD and the precise control over (timing of) life events make such animal models highly suitable for investigating the mechanisms underlying the interactions between genes, the (early) environment and AD (see **box 3** for an overview of animal models of AD neuropathology).

3. Conclusion

In conclusion, lifelong patterns of adrenocortical function and (cumulative) stress hormone exposure, in part determined by changes in set point due to early life experiences, can contribute to the rate of brain aging, at least in experimental animals. Healthy aging is often characterised by a gradient elevation of glucocorticoid levels, a process that is also modulated by early life experiences and that may influence the vulnerability or resilience of the brain to additional insults. This may be mediated by (epi)genetic alterations in GR, MR and/or CRH expression[31,64], that can have persistent consequences for glucocorticoid feedback sensitivity and the function and structure of neurons in specific brain regions. This lifelong programming of the brain by early life experiences thus contributes to the vulnerability or resilience to develop cognitive impairment and psychopathologies later in life, and may further determine the onset, severity, and/or progression of Alzheimer's disease.

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