Neurobiology of Stress 8 (2018) 172–185

Contents lists available at ScienceDirect

Neurobiology of Stress

journal homepage: www.elsevier.com/locate/ynstr

A preclinical perspective on the enhanced vulnerability to Alzheimer's disease after early-life stress

Lianne Hoeijmakers, Sylvie L. Lesuis, Harm Krugers, Paul J. Lucassen, Aniko Korosi*

Brain Plasticity Group, Center for Neuroscience, Swammerdam Institute for Life Sciences, University of Amsterdam, Science Park 904, Amsterdam, The Netherlands

A B S T R A C T

Stress experienced early in life (ES), in the form of childhood maltreatment, maternal neglect or trauma, enhances the risk for cognitive decline in later life. Several epidemiological studies have now shown that environmental and adult life style factors influence AD incidence or age-of-onset and early-life environmental conditions have attracted attention in this respect. There is now emerging interest in understanding whether ES impacts the risk to develop age-related neurodegenerative disorders, and their severity, such as in Alzheimer's disease (AD), which is characterized by cognitive decline and extensive (hippocampal) neuropathology. While this might be relevant for the identification of individuals at risk and preventive strategies, this topic and its possible underlying mechanisms have been poorly studied to date. In this review, we discuss the role of ES in modulating AD risk and progression, primarily from a preclinical perspective. We focus on the possible involvement of stress-related, neuro-inflammatory and metabolic factors in mediating ES-induced effects on later neuropathology and the associated impairments in neuroplasticity. The available studies suggest that the age of onset and progression of AD-related neuropathology and cognitive decline can be affected by ES, and may aggravate the progression of AD neuropathology. These relevant changes in AD pathology after ES exposure in animal models call for future clinical studies to elucidate whether stress exposure during the early-life period in humans modulates later vulnerability for AD.

1. Introduction

Alzheimer's disease is the most prevalent neurodegenerative disease among elderly and a major burden to society (Prince et al., 2013; Wimo et al., 2013). AD patients are characterized by progressive cognitive decline, that starts with mild cognitive impairments (MCI) and develops over time in full blown dementia. The brains of AD patients are characterized by the abundant presence of amyloid plaques, that are located extracellularly and contain various β-amyloid (Aβ) peptides, and by neurofibrillary tangles that are made up of hyper-phosphorylated tau inside of neurons (Querfurth and LaFerla, 2010; Scheltens et al., 2016). Neurodegeneration in the hippocampus, as the results of these neuropathological changes, is one of the key features of AD and in concert to the hippocampus other brain regions involved in the medial temporal lobe memory circuit are affected too (Weiner et al., 2015).

A small percentage of the demented population suffers from familial AD, in which the disease results from genetic mutations and/or specific gene variants. For the majority of patients with sporadic, late-onset AD, however, no genetic or heritable causes have been identified. These patients have been reported to show a high degree of heterogeneity in the progress of clinical symptoms, hippocampal plasticity and neuropathological characteristics (Komarova and Thalhauser, 2011; Mufson et al., 2015; Weiner et al., 2015). It is suggested that the etiology of sporadic AD relates to an interaction of specific genetic risk variants with various environmental and lifestyle factors, potentially leading to a dysregulated epigenome (Andrieu et al., 2015; Gatz et al., 2006; Haaksma et al., 2017; Maloney and Lahiri, 2016).

One of these environmental factors is stress. The frequency of lifetime distress has repeatedly been associated with accelerated cognitive decline, enhanced incidence of MCI and increased risk for late-onset AD (Aggarwal et al., 2014; Johansson et al., 2014; Sindi et al., 2016; Wilson et al., 2006, 2003; 2007). Particularly stress occurring during the sensitive period of early-life may additionally aggravate the later vulnerability to AD (Lahiri and Maloney, 2012, 2010). Individuals with a history of early-life stress (ES) have been shown to age less “successful” (Kok et al., 2017) and have an increased probability to develop diseases in old age (Dong et al., 2004; Ferraro et al., 2016; Schafer and Ferraro, 2012). Interestingly, the occurrence of parental death between the age

* Corresponding author. Brain Plasticity Group, Center for Neuroscience, Swammerdam Institute for Life Sciences, University of Amsterdam, Science Park 904, 1098XH, Amsterdam, The Netherlands.

E-mail address: a.korosi@uva.nl (A. Korosi).

https://doi.org/10.1016/j.ynstr.2018.02.003

Received 21 November 2017; Received in revised form 17 February 2018; Accepted 20 February 2018

Available online 23 February 2018

of 0 and 18 years has been associated with a higher risk for AD (Norton et al., 2011; Ravona-Springer et al., 2012). Also, childhood neglect and traumatic events have been associated with an augmented risk to develop early MCI with age (Wang et al., 2016a) and childhood stress have been associated with dementia and AD in Australian aboriginals (Radford et al., 2017). On the other hand, early-life adversity was not associated with aging-related cognitive decline in Caucasians, and may even be protective against cognitive decline in an aging African American population (Barnes et al., 2012). Importantly, these retrospective studies may contain bias as the variation in the later-life questionnaires on (self-reported) childhood maltreatment in elderly can be a potential confounder in these study designs (Ayalon, 2015; Jivraj et al., 2017). Whereas prospective longitudinal studies in humans would be an important addition, they are difficult from a logistic point of view, given the long interval between the early-life period and the age at which clinical AD symptoms appear.

Animal studies, however, provide a great opportunity to gain further insight into the ES-mediated modulation of aging-related cognitive decline and AD development. Notably, various specific AD characteristics are modeled in mice, i.e. by transgenic (over) expression of mutant genetic variants that underlie familial AD (Box 1). These transgenic models develop transgene driven AD-related neuropathological features such as amyloid plaques, and portray at least some of the associated cognitive deficits. This provides a useful approach to study whether and how risk factors, like ES, can modulate later neuropathological hallmarks, cognitive decline and related impairments in neuroplasticity.

Here, we discuss whether stress in early-life acts as a vulnerability factor for AD. We summarize the available pre-clinical literature and focus on the biological substrates that might mediate such vulnerability. Finally, we highlight the outstanding questions that can help bring the field forward.

2. Early-life experiences affect AD neuropathological hallmarks and cognition

In recent years, the vulnerability to develop AD after ES was investigated with the use of different ES rodent models (Box 2). These studies demonstrate that both positive and adverse early-life experiences can modulate disease severity and AD pathology (Cañete et al., 2015; Hoeijmakers et al., 2017; Hui et al., 2017; Lesuis et al., 2016, 2017; Martisova et al., 2012, 2013; Sierksma et al., 2012, 2013; Solas et al., 2010, 2013).

Interestingly, ES triggered Aβ formation in non-transgenic rats; MS from P2 to P21 induced an elevated ratio of the amyloid precursor protein (APP)-derived fragments C99 and C83, and an increased expression of Aβ40 and Aβ42 peptides in the hippocampus of adult (Martisova et al., 2012, 2013; Solas et al., 2010, 2013) and aged rats (Solas et al., 2010). While it is interesting to learn that ES enhances amyloidogenic processing in the brain of wild type rodents, these rats do not develop the pathological oligomeric or fibril forms of Aβ. ES experiments performed in transgenic AD models that do express these pathological Aβ species help to uncover if ES advances or accelerates these specific features of AD pathology with age.

Perinatal stress was shown to affect the later development of amyloid neuropathology in transgenic AD models in an age- and thus intrinsically pathological stage-dependent manner. In fact, both prenatal maternal-restraint stress (PS) from embryonic day (E)1 to E7 as well as chronic ES from postnatal day (P)2-P9 reduced Aβ in the hippocampus of 4-month-old APPswe/PS1dE9 mice, a relatively early pathological stage. Specifically, Aβ plaque load in the hippocampus of female, but not male, APPswe/PS1dE9 mice was decreased after PS, while no effects were found on intracellular Aβ immunoreactivity, nor on hippocampal soluble Aβ40 and Aβ42 peptide levels (Sierksma et al., 2012, 2013). Chronic ES from P2 to P9 also reduced intraneuronal Aβ levels in the dentate gyrus of male APPswe/PS1dE9 mice (Hoeijmakers et al., 2017). On the other hand, 4-month-old bigenic (BiAT) mice, which express both amyloid and tau mutant genes, exposed to the same chronic ES design showed an elevation of Aβ peptide levels (Lesuis et al., 2016). Interestingly, at a later pathological stage in 9- and 10-month-old APPswe/PS1dE9 mice, hippocampal plaque load was aggravated after exposure to chronic ES from P2-P9 or after 3 weeks of MS (Hoeijmakers et al., 2017; Hui et al., 2017), while cortical plaque load was affected by MS at this age as well (Hui et al., 2017). This shows that although in some models Aβ is initially reduced in young adulthood, the pathology is exacerbated by ES exposure at later ages.

In contrast to the modulation of Aβ peptides, tau pathology received very little attention in ES studies so far. Interestingly, tau protein in the hippocampus undergoes specific isoform switches and phosphorylation

Box 1
Modeling AD-related neuropathology in mice.

AD is characterized by the accumulation of Aβ and tau neuropathology, that is comprised of β-amyloid peptides and hyperphosphorylated tau (Buerger et al., 2006; Hardy, 2002). Aβ peptides are generated from the amyloid precursor protein (APP) that is cleaved by β- and γ-secretases. They accumulate firstly in cells, but ultimately end-up in fibrillar amyloid plaques in the extracellular space. The neuropathological progression of Aβ involves the presence of different Aβ species (i.e. soluble/insoluble Aβ peptides, Aβ oligomers, intraneuronal/cell-associated Aβ or Aβ plaques). Next to this, tau pathology develops by an increased phosphorylation of the protein tau. Tau hyperphosphorylation destabilizes neuronal microtubules, ultimately leading to the formation of neurofibrillary tangles. Similar to the rate-determining factors for amyloidogenic processing, expression of total tau protein and (the activity of) kinases mediate tau phosphorylation and pathological progression.

Aβ and tau pathology can be modeled in mice by transgenic (over)expression of human genetic mutations that drive the neuropathology in familial AD. Many different transgenic lines have been developed over the last decade, overexpressing (a combination of) genes carrying familial AD mutations (Götz et al., 2004). As examples, the Tg2576 and APPswe transgenic lines both overexpress the Swedish familial APP mutations KM670/671NL (Borchelt et al., 1997; Hsiao et al., 1996). The inclusion of mutated presenilin 1 (PSEN1 or PS1), one of the proteins of the γ-secretase complex, accelerates Aβ onset and progression in the APPswe/PS1dE9 and APPswe/PS1M146L models. The APPswe/PS1dE9 model for instance develops the first Aβ plaques around 4 months of age and cognitive deficits occur between 4 and 6 months (Edwards et al., 2014; Jankowsky et al., 2004).

Similar to Aβ models, the microtubule associated protein tau (MAPT) gene is overexpressed to generate tau neuropathological characteristics in mice. The JNPL3 transgenic model overexpresses MAPTP301L to drive an age-related increase in hyperphosphorylated tau with the first tangles around 6 months of age (Lewis et al., 2000). Lastly, several models express APP as well as MAPT variants. An example is the so-called bigenic (BiAT) mice expressing APP.V717I and MAPTP301L, and 3xTgAD mice that harbor three mutant genes (APPswe, PS1M146L and MAPTP301L variants). These 3xTgAD mice firstly display cognitive impairments at 3 months, Aβ plaque pathology by 6 and tau pathology by 10 months of age (Oddo et al., 2003).

Box 2
Rodent models of early-life stress.

In rodents, the early-life environment can be modulated during the prenatal period by manipulation of the pregnant females, and during the postnatal period via manipulation of the mother's interaction with her offspring. This can lead to immediate and later-life consequences for the offspring's brain structure and function. Several extensive reviews summarize and describe the different prenatal and postnatal ES models (Lucassen et al., 2013; Schmidt et al., 2010). We here highlight some relevant models in detail.

Prenatal maternal-restraint stress (PS) generally consists of restraining the pregnant mouse or rat for 1–3 times a day during a number of consecutive days, which can take place during different gestational phases. As an example, Sierksma et al. restrained mothers from embryonic day (E)1 to E7 for 3 daily 45-min periods (Sierksma et al., 2012, 2013).

Postnatal stress models in both rats and mice include for example maternal separation (MS), maternal deprivation (MD), or chronic ES/limiting bedding and nesting material (LBN). MS consists of a daily separation of mother and her pups for several hours, for up to 3 weeks (Hui et al., 2017; Martisova et al., 2012, 2013; Solas et al., 2010, 2013). MD consists of one prolonged (up to 24 h) period of separation, typically on postnatal day (P)3 or P4 (Oitzl et al., 2000). The chronic ES model or LBN model requires the mother and her offspring to be placed in an impoverished environment from P2-9 (Hoeijmakers et al., 2017; Lesuis et al., 2016; Walker et al., 2017).

Early-life handling (EH) is, in contrast to the other models, a positive manipulation, consisting of brief (± 15 min) separation of the mother and pups on a daily basis, which enhances maternal care upon reunion (Korosi and Baram, 2010; Meaney et al., 1988). Such an EH model can be employed from P2 to P9 with the usual 15-min daily separation (Lesuis et al., 2016, 2017), or for instance from P1 to P21 for only 8 min per day (Cañete et al., 2015).

changes during the early-life period, which have been suggested to contribute to neuronal development and function (Sennvik et al., 2007; Boekhoorn et al., 2006). Although interference of such processes by stress in early-life can potentially have detrimental impact, based on the only study available on this topic to date, ES does not seem to impact phosphorylated tau in 4-month-old BiAT mice (Lesuis et al., 2016). At 4 months of age, BiAT mice do however not normally develop tau pathology, possibly preventing detection of any ES modulation in this study and highlighting the need for future investigation on the topic.

Interestingly, ES exposure also seemed to affect the cognitive performance of APPswe/PS1dE9 mice. The reduced Aβ plaque load in PS-exposed APPswe/PS1dE9 mice at 4 months and the MS-induced increased Aβ plaque load in the same transgenic mice at 9 months were associated with, respectively, improved and impaired performance in hippocampus-dependent cognitive tasks (Hui et al., 2017; Sierksma et al., 2013). Such ES-induced cognitive modulation was not detected in 4-month-old BiAT mice as both control and ES-exposed BiAT mice were unimpaired at this age (Lesuis et al., 2016).

In contrast to ES, and in support of the important role for the (quality of the) early-life environment, a 'positive' early-life experience attenuated Aβ pathology and cognitive decline. For instance, early handling (EH) from P2 to P9, which was associated with improved care by the mother, reduced Aβ levels in 4-month-old BiAT mice and in 11-month-old APPswe/PS1dE9 mice (Lesuis et al., 2016, 2017). This reduction in amyloid levels in APPswe/PS1dE9 mice after EH was further accompanied by an improved cognitive performance at 11 months of age (Lesuis et al., 2017). In addition, prolonged EH exposure from P1-P21 prevented spatial learning impairments at a pre-pathological stage, in 4-month-old male and female 3xTgAD mice (Cañete et al., 2015).

These initial studies strongly suggest that perinatal experiences can shape the later progression of Aβ neuropathology and cognitive performance. In general, it appears as if stress experienced in early-life reduces Aβ pathological hallmarks at an early pathological stage, while it ultimately aggravates Aβ pathology at more advanced pathological stages. These alterations are associated with parallel changes in cognition. So far, these conclusions are based on only a few studies, which focus on Aβ rather than on tau neuropathology. This highlights the need to extend our knowledge of the consequences of ES at different pathological stages. Moreover, with the exception of the EH study in APPswe/PS1dE9 mice (Lesuis et al., 2017), these studies addressed cognition only in transgenic mice and not in age-matched wild type mice exposed to the early-life paradigm (Cañete et al., 2015; Hui et al., 2017; Sierksma et al., 2013). The inclusion of these control groups would be relevant in order to assess whether AD pathology accelerates or aggravates the onset of cognitive impairments relative to unstressed transgenic as well as stressed wild type groups. It is also important to understand which mechanisms are involved and which pathways might mediate such late consequences. This is addressed in the following sections.

3. Stress in early-life modulates regulators of Aβ and tau neuropathological progression

So far, most of the aforementioned ES studies have not fully addressed the possible mechanisms mediating the later neuropathological changes. It is interesting to speculate whether mechanisms involved in the effects of adult stress on AD neuropathology might also be important to consider in the context of early-life experiences. In fact, the impact of adult stress exposure on Aβ and tau hallmarks has been more extensively studied in various AD models (Machado et al., 2014; Marcello et al., 2015).

Overall, there are several pathways in which stress exposure can regulate Aβ progression. These include; 1) driving Aβ synthesis via the modulation of APP expression and the APP-cleaving secretases, or 2) by modulating clearance of Aβ, for instance by changes in transportation to the periphery or by altering the rate of phagocytosis by immune cells (Chesser et al., 2013; Deane et al., 2009; Martin et al., 2013; Ries and Sastre, 2016). The propagation of tau neuropathology on the other hand, is similarly modulated by tau expression, tau mutations, and activity of specific kinases and phosphatases. These factors are driving tau neuropathology and also 'prion-like' tau propagation is of relevance in this respect (Sanders et al., 2014). Alternatively, tau can be cleared through degradation pathways, halting the progression of pathology. We will here discuss the existing literature on these proposed regulators of AD neuropathology following (early-life) stress exposure.

3.1. Stress-related factors modulate AD neuropathology

Stress-related factors are certainly important to consider as possible modulators of AD pathology. Not only were stress hormone levels shown to be dysregulated in AD patients (Arsenault-Lapierre et al., 2010; Csernansky et al., 2006), but stress was also associated with an acceleration of the course and duration of MCI and with AD progression in general (Johansson et al., 2014; Sindi et al., 2016; Wilson et al., 2007). This effect is mostly thought to be mediated by stress-related hormones and neuropeptides, such as glucocorticoids (cortisol in human and corticosterone in rodents) and corticotropin releasing hormone/factor (CRH; CRF). Interestingly, ES exposure has been described

to alter later hypothalamic pituitary adrenal (HPA) axis functioning, leading to an increased responsiveness to stressors and overexposing body and brain to elevated levels of glucocorticoids (reviewed in Frodl and O'Keane, 2013; Heim and Nemeroff, 2001). Such changes in HPA axis functioning could be considered a plausible mediator of accelerated AD pathology (Herbert and Lucassen, 2016).

3.1.1. Glucocorticoids

Various clinical studies have implicated elevated glucocorticoid levels in the cognitive decline that followed (cumulative life-time) stress experiences in elderly and AD patients (Arsenault-Lapierre et al., 2010; Comijs et al., 2010; Csernansky et al., 2006; Lupien et al., 1999; Popp et al., 2015). This supports an important role for glucocorticoids as possible mediators of AD vulnerability after exposure to stress and indeed several mechanistic, pre-clinical studies implicated glucocorticoids in the pathological processing of enhancing tau and amyloid levels after (adult) stress exposure (Baglietto-Vargas et al., 2015; Catania et al., 2009; Green et al., 2006; Joshi et al., 2012, 2013; Sotiropoulos et al., 2008, 2011).

As an example, glucocorticoid exposure and chronic stress in wild type rats enhanced phosphorylation of tau protein in the hippocampus and prefrontal cortex, likely through the elevated expression of kinases, and these alterations were associated with cognitive deficits in the rats (Sotiropoulos et al., 2011). Tau knockout mice further showed resilience for (part of) the stress-induced hippocampal abnormalities and cognitive deficits (Lopes et al., 2016), indicating a mechanism through which stress-induced tau alterations can enhance neuropathological hallmarks as well as vulnerability for cognitive deficits.

With respect to Aβ pathology, the expression of APP and the APP cleaving enzyme β-secretase 1 (BACE1) was increased by exposure to corticosterone or to the glucocorticoid receptor (GR) agonist dexamethasone, both in neuronal cell cultures as well as in 3xTgAD mice. These changes increased expression of APP-derived fragments (C99, C83), and notably, they further steered APP processing towards the amyloidogenic pathway, ultimately increasing Aβ levels (Green et al., 2006). A similar amyloidogenic potential of glucocorticoids was found after adult stress exposure, which also increased expression of BACE1 and APP-derived fragments in the hippocampus and frontal cortex of non-transgenic rats (Catania et al., 2009).

In addition, blocking the GR with the antagonist mifepristone attenuated both Aβ and tau pathology in 12-month-old 3xTgAD mice, after 3 weeks of treatment, while restoring cognitive performance in various behavioral tasks (Baglietto-Vargas et al., 2013). In contrast to the glucocorticoid-mediated elevation of Aβ, the neuropathological reduction after mifepristone treatment was not mediated by BACE1 activity, but through a still unknown APP protease that steered APP processing to the non-amyloidogenic pathway (Baglietto-Vargas et al., 2013).

Interestingly, ES modulated amyloidogenic pathways in non-transgenic rats via the same mediators as reported for adult stress and glucocorticoid exposure. BACE1 expression was elevated in MS-exposed, adult non-transgenic rats and accompanied by an increased C99/C83 ratio (Martisova et al., 2012, 2013; Solas et al., 2010, 2013). This elevated BACE1 expression was further associated with reduced DNA methylation of the BACE1 promotor (Martisova et al., 2012). On an additional note, the methylation levels of for example APP might also be instrumental in the processing of amyloid after ES, in a similar manner as discussed for BACE1 (Lahiri et al., 2009). It still remains to be determined when this epigenetic mark arises, but GR activity might possibly contribute to the induced BACE1 expression and DNA hypomethylation when considering that MS-exposed rats exhibit heightened corticosterone levels in adulthood (Aisa et al., 2007; Martisova et al., 2013). On the other hand, BACE1 DNA hypomethylation can also be a programmed epigenetic mark that arises directly after ES exposure and lasts into adulthood, and it will be interesting to study whether this or an ES-mediated rise in glucocorticoid levels and subsequent GR activation in adulthood affected methylation and the eventual BACE1 expression pattern. Chronic ES exposure did not induce an increase in basal corticosterone in adult mice (Naninck et al., 2015, 2017) and, thus, not all ES models induce elevated basal or stress-induced corticosterone levels. Whether glucocorticoid levels in chronic ES-exposed mice affect BACE1 expression, APP or other factors in the amyloid processing pathway to mediate the increased Aβ pathology in APPswe/PS1dE9 mice remains thus to be determined.

3.1.2. Corticotropin releasing factor/hormone

Next to glucocorticoids, clinical data have also pointed to abnormal CRF signaling in AD patients (De Souza et al., 1987; Hatzinger et al., 1995; May et al., 1987; Raadsheer et al., 1995). CRF levels were reported to be reduced in the cerebrospinal fluid and cortical tissue of (sporadic) AD patients (De Souza et al., 1987; May et al., 1987) and AD patients also responded less to stimulation of the HPA axis with exogenous CRF (Hatzinger et al., 1995). Next to this, CRF mRNA expression was elevated in postmortem tissue of the hypothalamic paraventricular nucleus of AD patients (Raadsheer et al., 1995). On the functional level however, CRF expression was reported to exert a neuroprotective response to Aβ toxicity (Pedersen et al., 2001) and to favor non-amyloidogenic APP cleavage (Lezoualc'h et al., 2000), which would both be beneficial in a context of Aβ accumulation.

In contrast to these observations, multiple studies have indicated that stress exposure aggravated Aβ neuropathology in close association with elevations in CRF. Enhanced CRF signaling in 3xTgAD mice subjected to chronic adult stress was associated with enhanced Aβ neuropathological progression (Baglietto-Vargas et al., 2015). Kang and colleagues have further shown that exogenous administration of CRF, but not corticosterone, mimiced the acute stress-induced increase in Aβ40 and Aβ42 (Kang et al., 2007), and central CRF administration similarly enhanced these peptide levels (Dong and Csernansky, 2009). Such an Aβ-enhancing potential of CRF can be mediated through γ-secretase activity, showing a mechanistic link between (stress-induced) CRF and Aβ (Park et al., 2015). In addition, the modulating role of CRF in stress-induced Aβ was confirmed by a deficiency in CRF signaling, either via a CRF receptor 1 (CRFR1) knockout line or antagonist treatment, respectively, showing a blockage of the stress-induced aggravation in Aβ pathology after post-traumatic stress-like exposure in APPswe/PS1M146V mice (Justice et al., 2015), and after acute stress in Tg2576 mice (Kang et al., 2007), Next to this, several studies have also attributed the potential of stress to enhance tau pathology to CRF (Carroll et al., 2011; Rissman et al., 2007). Tau phosphorylation was enhanced in CRF overexpressing mice compared to wild type mice and treatment with a CRFR1 antagonist restored the phosphorylation of tau to wild type levels at some but not all epitopes (Campbell et al., 2015). Adult stress exposure increased tau hyperphosphorylation through the activity of specific kinases mediated by CRFR1 activation (Rissman et al., 2007). Similar to adult stress, ES in rodents led to enhanced CRF signaling in the hippocampus (Ivy et al., 2010) and frontal cortex (Wang et al., 2011). This implicates that altered CRF signaling after ES exposure may contribute to AD-related tau hyperphosphorylation and Aβ aggravation, but further evidence is needed to test this hypothesis.

To summarize the role of (early-life) stress-related factors in the later vulnerability to develop AD, both glucocorticoids and CRF have been implicated in the progression of AD neuropathology. This supports the possibility that the enhanced AD vulnerability after ES might be mediated by the alterations in the stress system. Intervention studies that modulate the consequences of ES on stress signaling should help to clarify these cause-or-effect aspects and further elucidate this relationship. In addition, it will be interesting to investigate if ES has the potential to also (epigenetically) program expression of AD neuropathological modulators, such as tau, APP, or BACE1 expression, possibly via GR activation.

3.2. Regulation of the inflammatory response to amyloid neuropathology by ES

Over the recent years, attention for the role of neuroinflammation in AD etiology has strongly increased (Heneka et al., 2015; Mhatre et al., 2015; Wyss-Coray and Rogers, 2012). Clearance of Aβ can be mediated by microglia, the innate immune cells of the brain, and/or by infiltrating myeloid cells. The latter are still debated as to whether they just assist, or rather overtake microglial functions in AD (Bates et al., 2009; Fu et al., 2012; Hickman et al., 2008). The accumulation of Aβ in the brain has been shown to elicit a chronic inflammatory response, both in terms of microglial and complement activation (Rodríguez et al., 2010; Veerhuis et al., 2003; Zhang et al., 2012), depending on the pathological stage (Sudduth et al., 2013). The potential of neuroinflammatory modulation of AD progression was further illustrated by studies that change the neuroinflammatory response using genetic tools to, depending on the specific type of modulation, either aggravate (Griciuc et al., 2013; Mass et al., 2017; Wang et al., 2015, Wang et al., 2016b) or ameliorate Aβ neuropathology (Guo et al., 2015; Hjorth et al., 2013; Lee et al., 2010).

Despite these relevant findings, a possible role for inflammation in the interaction between (early) stress and AD has so far been addressed only in a few studies. First, an adult stress-induced increase in plaque pathology in Tg2576 mice was found to coincide with a reduction in plaque-associated microglia (Carroll et al., 2011), indicating a reduced microglial response to Aβ deposits. A comparable reduction in plaque-associated Iba1 immunoreactivity, a marker for microglia, was observed in chronic ES-exposed 10-month-old APPswe/PS1dE9 mice (Hoeijmakers et al., 2017). However, an opposite phenotype was observed at an earlier age in the 4-month-old APPswe/PS1dE9 mice, since ES enhanced the expression of microglial CD68, a lysosomal protein and phagocytic marker in 4-month-old APPswe/PS1dE9 mice (Hoeijmakers et al., 2017).

One can speculate that the changes in neuropathology between 4 (reduced Aβ in ES group) and 10 months (increased Aβ in ES group) in the ES-exposed mice were not due to differences in Aβ production, but may rather result from a differential clearance mediated through microglia. An outstanding question in that respect is, whether the microglial response to inflammatory challenges like Aβ is intrinsically (epigenetically) programmed by ES in the microglia, and then evoked by Aβ exposure in adulthood. Other ES studies in rats have indeed shown that the microglial response in adulthood was primed or sensitized when stimulated by secondary inflammatory challenges, leading to an enhance (pro-)inflammatory response from microglia (Diz-Chaves et al., 2012; Szczesny et al., 2014). On the other hand, other cell types, such as neurons and astrocytes, release factors that can regulate microglia and thereby modulate their inflammatory response. As an example, fractalkine signaling between neurons and microglia was found to be diminished in PS-exposed rats by the reduced expression of the (neuron-derived) chemokine CX3CL1 and the microglial CX3CR1 receptor (Ślusarczyk et al., 2016), indicating that neurons might influence the microglial phenotype after ES exposure.

Together, these data show that ES affects microglia and their neuroinflammatory responses, and that this in turn might modulate Aβ neuropathological progression. It still needs to be elucidated if an altered microglial phenotype after ES exposure might contribute to aggravated Aβ pathology in APPswe/PS1dE9 mice via a change in Aβ clearance. In addition, it will be important to further investigate if the microglial phenotype in ES APPswe/PS1dE9 mice results from an intrinsic, primed, or sensitized microglial response to Aβ. Alternatively, the Aβ accumulating in ES-exposed mice might have elicited impairments in other cell types in the brain, which may then stimulate the microglia to respond more or less strongly.

3.3. Metabolic factors can play a role in progression of AD neuropathology after ES

Other factors that can modulate AD vulnerability after ES exposure relate to the metabolic aspects of AD. Over the last years, the abnormal metabolic profile of AD patients (Bedse et al., 2015; Dineley et al., 2014) and the beneficial or aversive effects of nutrients on AD progression have received considerable attention (Luchsinger et al., 2007; Ramesh et al., 2010; Solfrizzi et al., 2017). In fact, a recent study also provided evidence that early-life nutritional deficiency during the Great Chinese famine elevated the incidence of MCI in later life (Kang et al., 2017) and it has been suggested that metabolic and nutritional factors during early-life might indeed modulate the onset and progression of cognitive decline and AD (Lahiri et al., 2007).

The topic of nutritional deficiency is of particular interest as improving eating habits represent a non-invasive and relatively cheap tool for intervention in order to prevent or delay AD. Adversities in early-life, and stress in particular, have been well-described to affect metabolism and the nutritional profile (reviewed in among others Lucassen et al., 2013; Yam et al., 2015). Such metabolic changes after ES included among others fat deposition and altered signaling of the fat-derivative leptin (Yam et al., 2017a), reduced insulin signaling (Solas et al., 2013), elevated cholesterol levels (Paternain et al., 2016) and altered poly-unsaturated fatty acid plasma levels, including reduced omega-3 fatty acids (Clarke et al., 2009). We next discuss two of these important metabolic regulators, i.e. insulin signaling and fatty acid levels, that might contribute to AD neuropathological progression after exposure to ES.

3.3.1. Insulin resistance in AD

Hyperinsulinemia leads to a deficiency in insulin signaling, or insulin resistance, that can ultimately develop into type II diabetes. Type II diabetes is highly prevalent world-wide and a well-recognized risk factor that potentiates AD progression (Baker et al., 2011; Biessels et al., 2014; Steen et al., 2005). The involvement of insulin in AD progression was further demonstrated by studies of APP overexpression models that developed insulin resistance with age, and normalizing such abnormal signaling ameliorated cognitive deficits and Aβ peptide levels (Pedersen et al., 2006). But how could hyperinsulinemia promote AD progression? One of the mechanisms via which hyperinsulinemia has been suggested to promote Aβ accumulation is via the insulin-degrading enzyme (IDE) that degrades not only insulin, but also Aβ. An impairment in IDE might thus lead to both high insulin and Aβ levels, and because of the higher affinity for insulin, IDE might degrade less or even no Aβ peptides under conditions of high insulin (Qiu and Folstein, 2006). Moreover, hyperinsulinemia has also been associated with AD vulnerability via other pathways, as discussed in various excellent reviews (Craft, 2005; Diehl et al., 2017; De la Monte, 2009).

Interestingly, both adult stress and ES have been shown to affect insulin levels and insulin signaling. The suppression of insulin signaling in 6-month-old APPswe/PS1dE9 mice was potentiated by exposure to chronic unpredictable mild adult stress and therewith aggravated the Aβ phenotype (Han et al., 2016). Amyloidogenic processing in PS-exposed adult non-transgenic rats was similarly accompanied by decreased expression of various factors involved in insulin signaling pathways (Solas et al., 2013). Together, these studies suggest that adult stress and ES can induce amyloidogenic processing through altered insulin signaling (Han et al., 2016; Solas et al., 2010). Furthermore, chronic ES exposure increased insulin levels in P9 mice (Yam et al., 2017b) as well as adult rats (Maniam et al., 2015), which is thus consistent with the concept that ES increases the risk for hyperinsulinemia and insulin resistance. Altogether, there is evidence for insulin-mediated AD hallmarks after ES exposure, but additional investigation to directly tackle the effect of ES-modulated insulin signaling in transgenic AD models are needed to gain insight into this topic.

3.3.2. Involvement of omega-3 and omega-6 fatty acid profiles in AD vulnerability

Research on the essential omega-3 and omega-6 fatty acids have implicated the omega-3 variant to be beneficial for brain functioning (Fiala et al., 2017; Zárate et al., 2017). Omega-3 supplementation or deficiency in adult rodents, indeed, altered progression of Aβ neuropathology and cognitive decline in different APP mutant mouse models (Calon et al., 2005; Green et al., 2007; Lim et al., 2005; Oksman et al., 2006). This makes these poly-unsaturated fatty acid levels another interesting factor with respect to AD vulnerability. Interestingly, ES reduced omega-3 fatty acids in the plasma of adult rats exposed to MS during early-life (Clarke et al., 2009). In addition, when MS-exposed rats were fed an omega-3 deficient diet throughout adulthood, these rats showed a higher vulnerability for metabolic deficits when compared to unstressed rats fed with this deficient diet (Bernardi et al., 2013; Mathieu et al., 2008).

These studies thus suggest that the reduction in omega-3 fatty acids after ES can make ES-exposed mice more vulnerable to (progression of) AD neuropathology and cognitive decline. But how can fatty acids exert such modulatory effects on the brain? Dietary enrichment with omega-3 in adult unstressed mice showed that Aβ neuropathology was reduced in the cortex of 18-month-old Tg2576 mice after ± 3 months of dietary supplementation (Lim et al., 2005). This reduction could not be attributed to an altered expression of well-known drivers of the amyloidogenic pathway, including APP, BACE1, and ApoE (Lim et al., 2005). The beneficial effects of omega-3 fatty acids on Aβ accumulation seemed actually to be modulated by reduced PS1 expression and this was found to reduce γ-secretase activity, subsequent amyloidogenic processing and eventually even tau hyperphosphorylation in the 3xTgAD mice (Green et al., 2007). It still remains to be investigated if an ES-modulated omega-3 profile contributed to altered Aβ neuropathological progression. Next to this, it is of interest to mention that fatty acids can directly benefit other AD-related aspects, like neuroplasticity (Calon et al., 2004, 2005; Hashimoto et al., 2006), and inflammation (Hjorth et al., 2013), which might additionally contribute to the ES phenotype.

3.4. Interplay of the neuropathological regulators that are affected by ES

As discussed in the previous sections, AD might progress after ES exposure through the modulation of stress-related, neuroinflammatory and metabolic factors. Additional studies on the direct consequences of ES for each of these modulating pathways, at different time points in transgenic models of AD, should help to elucidate the determining factors. It must be noted in this respect that the different systems that can affect AD neuropathology after ES exposure are strongly interrelated and alterations in one system will likely elicit many changes in another. This makes it unlikely that ES would affect solely one of these systems while leaving others untouched (Hoeijmakers et al., 2015).

To further illustrate this subtle interplay between stress, neuroinflammation and metabolism, hyperinsulinemia was for instance found to enhance central inflammation and Aβ42 levels in the cerebrospinal fluid of healthy adults (Fishel et al., 2005). In addition, Tg2576 mice developed Aβ pathology next to impaired insulin levels, that in turn can drive a rise in fasting-induced corticosterone and hyperinsulinemia by 13 months of age (Pedersen and Flynn, 2004). This process could be prevented by modulating glucose and lipid metabolism through a dietary intervention, containing (among others) a peroxisome proliferator-activated receptor-γ (PPARγ) agonist (Pedersen and Flynn, 2004), that acts not only as a metabolic but also as an inflammatory mediator. Omega-3 fatty acids further modulated microglial phagocytosis of Aβ (Hjorth et al., 2013), while neuroinflammation is again regulated by stress mediators, like corticosterone (Espinosa-Oliva et al., 2011; Frank et al., 2012; Tynan et al., 2010), that can in turn induce insulin resistance (van Donkelaar et al., 2014).

These studies portray the interrelated characteristics of several pathways related to ES as well as AD. The interactions of these different factors at play have unfortunately not been studied in detail in AD yet, but such studies might shed light on the primary modulating pathways of ES in determining AD vulnerability. This interrelated character obviously makes it also difficult to tease out whether ES determines AD vulnerability through one common denominator or driving factor, or whether a synergistic action of all these pathways is involved. This awaits future studies.

4. AD vulnerability through ES-modulated neuroplasticity

Neuronal networks can be modified by selective pruning of synapses, formation of new, or strengthening of existing ones (Chattarji et al., 2015; Kim and Diamond, 2002; Martin et al., 2000). Next to this, the hippocampus exhibits the (unique) capacity to generate new, functional neurons, a process that was shown to be essential for hippocampus-dependent cognitive functioning (Kempermann et al., 2015; Leuner et al., 2006). Such neuronal plasticity forms are ultimately affected by the neuropathological progression in AD, as supported by the synapse loss, neuronal atrophy and selective cell death in the AD brain (Coleman and Flood, 1987; De Leon et al., 1997; Scheff et al., 1990), which is at least in part paralleled by pre-clinical research in rodent models of AD (for reviews, see Götz and Ittner, 2008; Götz et al., 2012; Jang and Chung, 2016; Marlatt and Lucassen, 2010; Pozueta et al., 2013; Selkoe, 2002). This close relation between pathology and neuroplasticity deficits as well as (aberrant) regenerative responses in AD (Kuhn et al., 2001, 2007) makes it relevant to discuss how ES affects neuroplasticity in AD models.

Next to this, ES-exposed wild type rodents have been reported to display reduced levels of hippocampal neurogenesis at an adult age (Hulshof et al., 2011; Naninck et al., 2015; Oomen et al., 2010; Suri et al., 2013), decreased in dendritic complexity (Huot et al., 2002; Ivy et al., 2008), reduced spine density and synaptic protein expression (Aisa et al., 2009; Wang et al., 2011), as well as impaired long-term potentiation of synaptic connections (Brunson et al., 2005; Herpfer et al., 2012; Ivy et al., 2008; Wang et al., 2011). Such impairments in neuroplasticity are thought to underlie the cognitive deficits in ES-exposed adults, and these neuroplasticity forms as well as cognition decline with aging (Barnes et al., 1997; Foster, 2012; Lindner, 1997). Considering this, we first discuss how ES intrinsically affects such aging-related alterations in cognition and neuroplasticity in wild type rodents, followed by the evidence for neuroplasticity alterations in AD models after ES exposure.

4.1. ES modulation of neuroplasticity with aging

Interestingly, the regulators of the ES-mediated impairments in neuroplasticity in adult offspring can be attributed to stress mediators, neuroinflammatory alterations and metabolic changes (for reviews see Hoeijmakers et al., 2015; Johnson and Kaffman, 2017; Korosi et al., 2012), implicating that similar pathways might be involved in stress-induced neuroplasticity changes in AD-related neuropathology. In addition, ES exposure in rodents was shown to induce several of the later-life (neuronal) consequences already early-on, lasting into adulthood, such as the ES-induced reduction in hippocampal volume in mice (Hoeijmakers et al., 2017; Naninck et al., 2015), whereas other consequences were actually age-dependent. As an example, chronic ES exposure in mice increased cell proliferation at P9, but reduced newborn cell survival in the adult hippocampus (Naninck et al., 2015). Although the consequences of ES have been extensively studied in adulthood, less attention has been given to how this phenotype is affected with aging.

With aging, the majority of elderly typically show a decline in cognition (Kirova et al., 2015; Langa and Levine, 2014) and cognitive functioning in rodents similarly diminishes with age (Barnes et al., 1997; Foster, 2012; Lindner, 1997). One can imagine that impairments

in the neuroplasticity after ES exposure can trigger a steeper decline with aging. Indeed, individuals with a history of childhood stress exhibited cognitive deficits already in (young) adulthood (Chugani et al., 2001; Kaplan et al., 2001; Mueller et al., 2010) and these deficits seem to further progress in a stronger manner with aging (Radford et al., 2017; Wang et al., 2016a).

In aged rodents, cognitive impairments were exacerbated in PS-exposed rats (Vallee et al., 1999), and a similar phenotype was confirmed in aged rats that underwent MS from P2-14 (Sousa et al., 2014) or from P2-P21 (Solas et al., 2010). In comparison to age-matched control rats, MD on P3 similarly led to a more cognitively impaired aged rats, but in addition it also led to more good performers during the learning task (Oitzl et al., 2000). This study thus indicated that ES did not impair all rats, but rather that the individual variation within the group was enhanced with aging after stress exposure early in life.

Altogether, the majority of these studies point to an aggravated age-related cognitive decline in ES-exposed rodents. Such impairments in cognitive performance were accompanied by impaired long-term potentiation in CA1-CA3 synapses of 16-month-old MS-exposed rats, when compared to age-matched controls (Sousa et al., 2014). A study of 30- to 32-month-old rats that were exposed to MD on P3 and classified as cognitively impaired or unimpaired, based on Morris water maze training in aging, revealed that 5-HT receptor 1 mRNA expression in the hippocampus was more strongly increased in impaired MD rats compared to the impaired control rats (Sibug et al., 2001). In addition, activity-regulated cytoskeleton-associated protein (ARC) mRNA expression, but not brain-derived neurotrophic factor (BDNF), was strongly reduced in aged rats with a history of MS, relative to unstressed aged rats and adult groups (Solas et al., 2013).

Other parameters of neuronal plasticity have, to our knowledge, so far not been studied in aged ES-exposed rodents and their age-matched controls. Nevertheless, based on the evidence for impaired cognitive performance of ES aged rats, it is to be expected that neuronal plasticity parameters will be impaired too. Additional studies are needed to further elucidate which factors are involved in the aggravated aging-related decline after ES.

4.2. ES might aggravate AD-related impairments in neuroplasticity

Next to a potential steeper decline with aging per se, it is plausible that ES exacerbates various neuroplasticity hallmarks in AD transgenic mouse lines. For example, dendritic complexity is altered by chronic ES in different brain regions of BiAT mice, with reduced complexity in the infralimbic frontal cortex and increased complexity in the prelimbic frontal cortex and amygdala (Lesuis et al., 2016). The expression of BDNF is reduced in the female, but not male hippocampus of PS-exposed APPswe/PS1dE9 mice relative to control APPswe/PS1dE9 (Sierksma et al., 2012). Both these studies of BiAT and APPswe/PS1dE9 were performed in 4-month-old mice, an age when no cognitive deficits are yet present. It will therefore be of particular interest to study the alterations in neuroplasticity also at an age when cognitive functioning of ES transgenic mice differs from control transgenic mice, such as for 9-month-old ES APPswe/PS1dE9. Interestingly, these 9-month-old ES-exposed APPswe/PS1dE9 mice showed an increased loss of cholinergic neurons in their forebrain, in close association with memory deficits (Hui et al., 2017). These 3 studies together indicate that neuroplasticity appears to be reduced by ES in AD transgenic mouse models.

Unfortunately, all 3 studies failed to include wild type littermates that are exposed to the same early-life paradigms. This hampers the possibility to address whether the ES phenotype is different or aggravated in mice with a transgenic background. Previous studies subjecting wild type mice to the same stress paradigms showed that at least prefrontal cortex dendritic arborization (Yang et al., 2015) and BDNF expression (Dong et al., 2015; Zheng et al., 2016) were similarly affected by chronic ES and PS. It is, therefore, at this point unclear if neuroplasticity markers in these studies are differently or more strongly affected when ES is applied in mutant APP mice when compared to wild type mice.

Several studies on chronic stress at an adult age interestingly point to a steeper decline in neuroplasticity hallmarks in AD transgenic models than in non-stressed transgenic or stressed wild type mice (Baglietto-Vargas et al., 2015; Grigoryan et al., 2014). Spine numbers in the stratum radiatium and stratum lacunosum moleculare of the CA are reduced by adult stress exposure in wild type mice, but more strongly so in the 3xTgAD mice (Baglietto-Vargas et al., 2015). When compared to wild type and control 3xTgAD mice, 6-month-old stress-exposed 3xTgAD mice additionally exhibited a stronger decrease in long-term potentiation, as was recorded in the CA1 stratum radiatium (Grigoryan et al., 2014). These studies suggest that adult stress can modulate neuroplasticity factors that in turn may accelerate impairments, either as a result of a faster progression of neuropathology, or by direct effects of adult stress regulation and stress hormone exposure on neuronal functioning.

To conclude, neuroplasticity seems to be impaired in ES-exposed AD transgenic mice compared to non-stressed transgenic mice. Such impairment appears in line with the stronger cognitive decline in ES-exposed AD transgenic mice, however, it remains unclear whether this impairment is similar for ES wild type and ES AD transgenic mice, or whether the neuroplasticity impairments are stronger in the transgenic models exposed to ES. To address this question, it is essential that future studies include both ES-exposed transgenic mice as well as wild type mice, and compare those to the unstressed transgenic and wild type controls. In addition, other synaptic plasticity-related molecules than those studied to date might be interesting future targets. As examples, ES has been reported to impact neural cell adhesion molecules (NCAMs; Aisa et al., 2009; Marco et al., 2013), polysialylated (PSA-)NCAM (Castillo-Gómez et al., 2017; Tsoory et al., 2008) and nectin-3 levels (Wang et al., 2013), which are also associated with AD-related neuropathological impairments (Leshchyns'ka et al., 2015; Maurin et al., 2013; Mikkonen et al., 1999). It will furthermore be of interest to investigate if the neuroplasticity impairments result from an altered progression of the neuropathology in the transgenic lines, or if these changes occur irrespective of neuropathology.

5. Development of AD through ES-mediated later-life risk factors

Next to ES-induced cognitive deficits in adulthood (Chugani et al., 2001; Kaplan et al., 2001; Mueller et al., 2010), childhood stress has been indicated to enhance the risk for other later-life adversities. The risk to experience later-life trauma or other adult stressful events was indeed enhanced in individuals with an ES history (Dich et al., 2015) and also the risk to develop psychopathologies in adulthood was associated with an ES history (McLaughlin et al., 2010). This feature brings forward another interesting aspect through which ES can potentially regulate AD vulnerability. Multiple recognized adult risk factors for AD were shown to be determined by ES, and these include but are not limited to a cumulative stress or allostatic (over)load (Barboza Solís et al., 2015; Bellis et al., 2015; McLaughlin et al., 2010; Tomasdottir et al., 2015), obesity (Barboza Solís et al., 2015; Ferraro et al., 2016) and depression (Hovens et al., 2012; Miller and Cole, 2012; Turner and Butler, 2003). ES might in this way be the first step to comorbidity as a cumulative factor increasing vulnerability for AD.

Given these later-life risk factors and the reduced cognitive functioning of ES-exposed individuals, it can be questioned whether also the 'cognitive reserve' of ES-exposed individuals is lower. Cognitive reserve can be seen as someone's ability to cope with emerging damage in the brain, until a certain threshold is reached and the loss of function becomes apparent (Stern, 2002). Also in AD patients, neuropathological hallmarks have been accumulating in the brain for many decades before the first clinical signs of AD arise as the manifestation of MCI (Jack et al., 2010, 2013). This suggests that individuals with lower cognitive abilities or less neuroplasticity capacities could be classified as having a

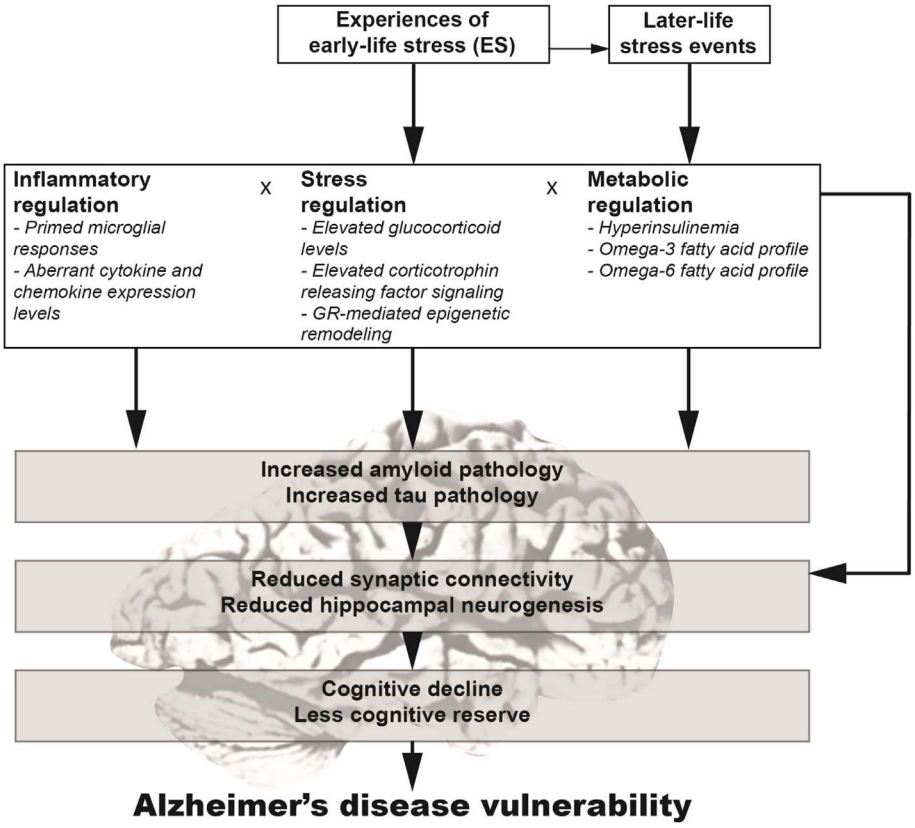

Fig. 1. Proposed model of how exposure to early-life stress could modify Alzheimer's disease vulnerability.
Early-life stress (ES) alters, either directly or through an enhanced sensitivity to later-life stress effects, neuroinflammatory, stress and metabolic regulation. Several potential candidate factors involved in such regulation have this far been identified to alter AD-related amyloid and tau pathological hallmarks and may therewith reduce neuroplasticity. These 3 systems can additionally impact neuroplasticity, irrespective of the development of AD neuropathology. Ultimately, the reduced neuroplasticity during this period may result in a lower cognitive reserve and finally in an earlier and possible more aggressive cognitive decline. These closely interrelated events may altogether determine AD vulnerability after exposure to stress in early-life.

lower cognitive reserve and might exhibit, irrespective of the neuropathological build-up, an earlier onset of MCI and AD.

Several studies indeed showed that the onset of AD was earlier and progressed stronger in individuals with lower intellectual and cognitive abilities (Osone et al., 2014; Pietrzak et al., 2015; van Veluw et al., 2012). In addition, the cognitive abilities at age 11 were associated with the cognitive level of 79-year-old non-demented elderly (Gow et al., 2008), indicating that childhood cognition may indeed be associated with cognition during aging. However, the decline of these non-demented elderly between age 79 and 83 was not associated with their childhood abilities (Gow et al., 2008), suggesting that the decline in aging was not related with childhood performance. Indeed, a large (prospective) study of Danish men (Osler et al., 2017) and a Scottish cohort (McGurn et al., 2008) associated lower cognitive abilities specifically with an increased risk for (vascular) dementia, and not AD, although the number of AD patients in these studies was very low. On a similar note, a higher social economic household was associated with higher cognitive abilities that were retained during aging, but neither higher nor lower social economic household were an indicator for AD development (Wilson et al., 2005).

On an additional note, there is current interest in the potentially transgenerational effects of ES. Several reports have provided evidence for inheritable effects across generations for at least some of the ES consequences, mediated by DNA methylation or other epigenetic mechanisms (Bohacek and Mansuy, 2015; Franklin et al., 2010; Gapp et al., 2014; Roth et al., 2009). The hypothetical latent early life associated regulation (LEARn) model furthermore proposes that later-life disease, such as sporadic AD, develops faster in individuals who might have inherited specific (epi)genetic trait and experienced an adverse, environmental early-life event (Lahiri et al., 2009; Maloney and Lahiri., 2016). Transgenerational effects of (early-life) stress might in such a way lead to higher risk for dementia in a heritable fashion.

Overall, the discussed studies show that childhood cognition is intrinsically associated with specific forms of dementia, while cognitive abilities in adulthood were specifically associated with a risk for AD. It will be of interest to further explore how general cognitive abilities throughout life determine AD risk and whether indeed a lower cognitive reserve will lead to an earlier onset of MCI and AD.

6. Mediators of ES vulnerability for AD; a model

The ES phenotype is suggested to be determined by the interplay of different systems (Hoeijmakers et al., 2015) and it is of interest that these same systems are implicated in neuroplasticity regulation and in the progression of AD neuropathology. We propose the following model of ES-mediated vulnerability for AD (Fig. 1). We hypothesize that ES modulates the inflammatory, stress and/or metabolic systems. The interplay of these systems will lead to aggravated AD-related neuropathology, which in turn can reduce hallmarks of neuroplasticity, such as synaptic connectivity and hippocampal neurogenesis, to ultimately diminished cognitive abilities. Alternatively, ES directly reduces neuroplasticity and its associated cognitive functions through inflammatory, stress and metabolic regulation as well, and may thereby potentially lower the cognitive reserve of ES individuals. Finally, ES is an important risk factor for the occurrence of later-life stress events and such cumulative stress again would induce a cumulative risk for deficits through the aforementioned pathways.

7. Conclusion

Childhood stress experiences are suggested to modify various aspects of healthy aging and the development of AD. The decades-long interval between such early-life experiences and the onset of aging-related diseases like AD is problematic for (prospective) studies on the association between ES exposure and AD vulnerability. A thorough discussion of the pre-clinical research on this topic is therefore crucial to improve our understanding of the topic. The studies on rodent models support a modulatory effect of stress experienced in early-life in

Box 3
Outstanding questions.

- Which factors mediate the ES-enhanced Aβ neuropathology? Can this be prevented with intervention studies targeting stress, neuroimmune or metabolic regulation?
- Are tau neuropathological hallmarks affected by ES exposure, and how is this mediated?
- How is the altered cognitive decline in ES-exposed aged individuals, without AD neuropathology, mediated and which neuroplasticity changes or other factors are involved?
- Do prospective studies support an earlier onset and progression of AD after childhood adversity? Is this associated with prevalence of later-life risk factors?

the progression of AD. Preclinical research has, however, not fully explored which factors are involved in this relation, and more controlled preclinical studies are thus essential to identify these factors, to unravel their interactions and to verify the current findings (Box 3). Such knowledge, supported by (prospective) clinical studies, will strongly benefit the identification of populations at elevated risk for AD, which can possibly allow to develop an early and targeted treatment during the many decades between ES exposure and AD (clinical) onset.

Funding

This work was supported by Alzheimer Nederland (AN) (WE.03-2012-41) and Internationale Stichting Alzheimer Onderzoek (ISAO; grant numbers 12536 and 12534).

References

Aggarwal, N.T., Wilson, R.S., Beck, T.L., Rajan, K.B., Mendes de Leon, C.F., Evans, D.A., Everson-Rose, S.A., 2014. Perceived stress and change in cognitive function among adults 65 Years and older. Psychosom. Med. 76, 80–85. http://dx.doi.org/10.1097/PSY.0000000000000016.

Aisa, B., Elizalde, N., Tordera, R., Lasheras, B., Del Rio, J., Ramirez, M.J., 2009. Effects of neonatal stress on markers of synaptic plasticity in the hippocampus: implications for spatial memory. Hippocampus 19, 1222–1231. http://dx.doi.org/10.1002/hipo.20586.

Aisa, B., Tordera, R., Lasheras, B., Del Rio, J., Ramirez, M.J., 2007. Cognitive impairment associated to HPA axis hyperactivity after maternal separation in rats. Psychoneuroendocrinology 32, 256–266. http://dx.doi.org/10.1016/j.psyneuen.2006.12.013.

Andrieu, S., Coley, N., Lovestone, S., Aisen, P.S., Vellas, B., 2015. Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions. Lancet Neurol. 14, 926–944. http://dx.doi.org/10.1016/S1474-4422(15)00153-2.

Arsenault-Lapierre, G., Chertkow, H., Lupien, S., 2010. Seasonal effects on cortisol secretion in normal aging, mild cognitive impairment and Alzheimer's disease. Neurobiol. Aging 31, 1051–1054. http://dx.doi.org/10.1016/j.neurobiolaging.2008.07.011.

Ayalon, L., 2015. Retrospective reports of negative early life events over a 4-year period: a test of measurement invariance and response consistency. J. Gerontol. B Psychol. Sci. Soc. Sci. 72, 901–912. http://dx.doi.org/10.1093/geronb/gbv087.

Baglietto-Vargas, D., Chen, Y., Suh, D., Ager, R.R., Rodriguez-Ortiz, C.J., Medeiros, R., Myczek, K., Green, K.N., Baram, T.Z., LaFerla, F.M., 2015. Short-term modern life-like stress exacerbates Aβ-pathology and synapse loss in 3xTg-AD mice. J. Neurochem. 134, 915–926. http://dx.doi.org/10.1111/jnc.13195.

Baglietto-Vargas, D., Medeiros, R., Martinez-Coria, H., LaFerla, F.M., Green, K.N., 2013. Mifepristone alters amyloid precursor protein processing to preclude amyloid beta and also reduces tau pathology. Biol. Psychiatr. 74, 357–366. http://dx.doi.org/10.1016/j.biopsych.2012.12.003.

Baker, L.D., Cross, D.J., Minoshima, S., Belongia, D., Watson, G.S., Craft, S., 2011. Insulin Resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch. Neurol. 68, 51–57. http://dx.doi.org/10.1001/archneurol.2010.225.

Barboza Solís, C., Kelly-Irving, M., Fantin, R., Darnaudéry, M., Torrisani, J., Lang, T., Delpierre, C., 2015. Adverse childhood experiences and physiological wear-and-tear in midlife: findings from the 1958 British birth cohort. Proc. Natl. Acad. Sci. Unit. States Am. 112, E738–E746. http://dx.doi.org/10.1073/pnas.1417325112.

Barnes, C.A., Suster, M.S., Shen, J.M., McNaughton, B.L., 1997. Multistability of cognitive maps in the hippocampus of old rats. Nature 388, 272–275. http://dx.doi.org/10.1038/40859.

Barnes, L.L., Wilson, R.S., Everson-Rose, S.A., Hayward, M.D., Evans, D.A., Mendes de Leon, C.F., 2012. Effects of early-life adversity on cognitive decline in older African Americans and whites. Neurology 79, 2321–2327. http://dx.doi.org/10.1212/WNL.0b013e318278b607.

Bates, K.A., Verdile, G., Li, Q.X., Ames, D., Hudson, P., Masters, C.L., Martins, R.N., 2009. Clearance mechanisms of Alzheimer's amyloid-beta peptide: implications for therapeutic design and diagnostic tests. Mol. Psychiatr. 14, 469–486. http://dx.doi.org/10.1038/mp.2008.96.

Bedse, G., Di Domenico, F., Serviddio, G., Cassano, T., 2015. Aberrant insulin signaling in Alzheimer's disease: current knowledge. Front. Neurosci. 9, 76. http://dx.doi.org/10.3389/fnins.2015.00204.

Bellis, M.A., Hughes, K., Leckenby, N., Hardcastle, K.A., Perkins, C., Lowey, H., 2015. Measuring mortality and the burden of adult disease associated with adverse childhood experiences in England: a national survey. J. Public Health 37, 445–454. http://dx.doi.org/10.1093/pubmed/fdu065.

Bernardi, J.R., Ferreira, C.F., Senter, G., Krolow, R., de Aguiar, B.W., Portella, A.K., Kauer-Sant'Anna, M., Kapczinski, F., Dalmaz, C., Goldani, M.Z., Silveira, P.P., 2013. Early life stress interacts with the diet deficiency of omega-3 fatty acids during the life course increasing the metabolic vulnerability in adult rats. PLoS One 8, e62031. http://dx.doi.org/10.1371/journal.pone.0062031.

Biessels, G.J., Strachan, M.W.J., Visseren, F.L.J., Kappelle, L.J., Whitmer, R.A., 2014. Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards targeted interventions. Lancet Diabetes Endocrinol. 2, 246–255. http://dx.doi.org/10.1016/S2213-8587(13)70088-3.

Boekhoorn, K., Terwel, D., Biemans, B., Borghgraef, P., Wiegert, O., Ramakers, G.J.A., de Vos, K., Krugers, H., Tomiyama, T., Mori, H., Joëls, M., Van Leuven, F., Lucassen, P.J., 2006. Improved long-term potentiation and memory in young tau-P301L transgenic mice before onset of hyperphosphorylation and tauopathy. J. Neurosci. 26, 3514–3523. http://dx.doi.org/10.1523/JNEUROSCI.5425-05.2006.

Bohacek, J., Mansuy, I.M., 2015. Molecular insights into transgenerational non-genetic inheritance of acquired behaviours. Nat. Neurosci. 16, 641–652. http://dx.doi.org/10.1038/nrg3964.

Borchelt, D.R., Ratovitski, T., van Lare, J., Lee, M.K., Gonzales, V., Jenkins, N.A., Copeland, N.G., Price, D.L., Sisodia, S.S., 1997. Accelerated amyloid deposition in the brains of transgenic mice coexpressing mutant presenilin 1 and amyloid precursor proteins. Neuron 19, 939–945.

Brunson, K.L., Kramár, E., Lin, B., Chen, Y., Colgin, L.L., Yanagihara, T.K., Lynch, G., Baram, T.Z., 2005. Mechanisms of late-onset cognitive decline after early-life stress. J. Neurosci. 25, 9328–9338. http://dx.doi.org/10.1523/JNEUROSCI.2281-05.2005.

Buerger, K., Ewers, M., Pirttilä, T., Zinkowski, R., Alafuzoff, I., Teipel, S.J., DeBernardis, J., Kerkman, D., McCulloch, C., Soininen, H., Hampel, H., 2006. CSF phosphorylated tau protein correlates with neocortical neurofibrillary pathology in Alzheimer's disease. Brain 129, 3035–3041. http://dx.doi.org/10.1093/brain/awl269.

Calon, F., Lim, G.P., Yang, F., Morihara, T., Teter, B., Ubeda, O., Rostaing, P., Triller, A., Salem Jr., N., Ashe, K.H., Frautschy, S.A., Cole, G.M., 2004. Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. Neuron 43, 633–645. http://dx.doi.org/10.1016/j.neuron.2004.08.013.

Calon, F., Lim, G.P., Morihara, T., Yang, F., Ubeda, O., Salem, N., Frautschy, S.A., Cole, G.M., 2005. Dietary n-3 polyunsaturated fatty acid depletion activates caspases and decreases NMDA receptors in the brain of a transgenic mouse model of Alzheimer's disease. Eur. J. Neurosci. 22, 617–626. http://dx.doi.org/10.1111/j.1460-9568.2005.04253.x.

Campbell, S.N., Zhang, C., Monte, L., Roe, A.D., Rice, K.C., Taché, Y., Masliah, E., Rissman, R.A., 2015. Increased tau phosphorylation and aggregation in the hippocampus of mice overexpressing corticotropin-releasing factor. J. Alzheimers Dis. 43, 967–976. http://dx.doi.org/10.3233/JAD-141281.

Cañete, T., Blázquez, G., Tobeña, A., Giménez-Llort, L., Fernández-Teruel, A., 2015. Cognitive and emotional alterations in young Alzheimer's disease (3xTgAD) mice: effects of neonatal handling stimulation and sexual dimorphism. Behav. Brain Res. 281, 156–171. http://dx.doi.org/10.1016/j.bbr.2014.11.004.

Carroll, J.C., Iba, M., Bangasser, D.A., Valentino, R.J., James, M.J., Brunden, K.R., Lee, V.M.Y., Trojanowski, J.Q., 2011. Chronic stress exacerbates tau pathology, neurodegeneration, and cognitive performance through a corticotropin-releasing factor receptor-dependent mechanism in a transgenic mouse model of tauopathy. J. Neurosci. 31, 14436–14449. http://dx.doi.org/10.1523/JNEUROSCI.3836-11.2011.

Castillo-Gómez, E., Pérez-Rando, M., Bellés, M., Gilabert-Juan, J., Llorens, J.V., Carceller, H., Bueno-Fernández, C., García-Mompó, C., Ripoll-Martínez, B., Curto, Y., Sebastiá-Ortega, N., Moltó, M.D., Sanjuan, J., Nacher, J., 2017. Early social isolation stress and perinatal NMDA receptor antagonist treatment induce changes in the structure and neurochemistry of inhibitory neurons of the adult amygdala and prefrontal cortex. eNeuro 4http://dx.doi.org/10.1523/ENEURO.0034-17.2017. ENEURO.0034–17.2017.

Catania, C., Sotiropoulos, I., Silva, R., Onofri, C., Breen, K.C., Sousa, N., Almeida, O.F.X., 2009. The amyloidogenic potential and behavioral correlates of stress. Mol. Psychiatr. 14, 95–105. http://dx.doi.org/10.1038/sj.mp.4002101.

Chattarji, S., Tomar, A., Suvrathan, A., Ghosh, S., Rahman, M.M., 2015. Neighborhood matters: divergent patterns of stress-induced plasticity across the brain. Nat.

Neurosci. 18, 1364–1375. http://dx.doi.org/10.1038/nn.4115.
Chesser, A.S., Pritchard, S.M., Johnson, G.V.W., 2013. Tau clearance mechanisms and their possible role in the pathogenesis of Alzheimer disease. Front. Neur. 4, 122. http://dx.doi.org/10.3389/fneur.2013.00122.
Chugani, H.T., Behen, M.E., Muzik, O., Juhász, C., Nagy, F., Chugani, D.C., 2001. Local brain functional activity following early deprivation: a study of postinstitutionalized Romanian orphans. NeuroImage 14, 1290–1301. http://dx.doi.org/10.1006/nimg.2001.0917.
Clarke, G., O'Mahony, S.M., Hennessy, A.A., Ross, P., Stanton, C., Cryan, J.F., Dinan, T.G., 2009. Chain reactions: early-life stress alters the metabolic profile of plasma polyunsaturated fatty acids in adulthood. Behav. Brain Res. 205, 319–321. http://dx.doi.org/10.1016/j.bbr.2009.07.008.
Coleman, P.D., Flood, D.G., 1987. Neuron numbers and dendritic extent in normal aging and Alzheimer's disease. Neurobiol. Aging 8, 521–545. http://dx.doi.org/10.1016/0197-4580(87)90127-8.
Comijs, H.C., Gerritsen, L., Penninx, B.W.J.H., Bremmer, M.A., Deeg, D.J.H., Geerlings, M.I., 2010. The association between serum cortisol and cognitive decline in older persons. Am. J. Geriatr. Psychiatr. 18, 42–50. http://dx.doi.org/10.1097/JGP.0b013e3181b970ae.
Craft, S., 2005. Insulin resistance syndrome and Alzheimer's disease: age- and obesity-related effects on memory, amyloid, and inflammation. Neurobiol. Aging 26, 65–69. http://dx.doi.org/10.1016/j.neurobiolaging.2005.08.021.
Csernansky, J.G., Dong, H., Fagan, A.M., Wang, L., Xiong, C., Holtzman, D.M., Morris, J.C., 2006. Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. Am. J. Psychiatr. 163, 2164–2169. http://dx.doi.org/10.1176/ajp.2006.163.12.2164.
De la Monte, S.M., 2009. Insulin resistance and Alzheimer's disease. BMB Rep 42, 475–481.
De Leon, M.J., George, A.E., Golomb, J., Tarshish, C., Convit, A., Kluger, A., De Santi, S., Mc Rae, T., Ferris, S.H., Reisberg, B., Ince, C., Rusinek, H., Bobinski, M., Quinn, B., Miller, D.C., Wisniewski, H.M., 1997. Frequency of hippocampal formation atrophy in normal aging and Alzheimer's disease. Neurobiol. Aging 18, 1–11. http://dx.doi.org/10.1016/S0197-4580(96)00213-8.
De Souza, E.B., Whitehouse, P.J., Price, D.L., Vale, W.W., 1987. Abnormalities in corticotropin-releasing hormone (CRH) in Alzheimer's disease and other human disorders. Ann. N. Y. Acad. Sci. 512, 237–247. http://dx.doi.org/10.1111/j.1749-6632.1987.tb24964.x.
Deane, R., Bell, R., Sagare, A., Zlokovic, B., 2009. Clearance of amyloid-β; peptide across the blood-brain barrier: implication for therapies in Alzheimers disease. CNS Neurol. Disord. - Drug Targets 8, 16–30. http://dx.doi.org/10.2174/187152709787601867.
Dich, N., Hansen, Å.M., Avlund, K., Lund, R., Mortensen, E.L., Bruunsgaard, H., Rod, N.H., 2015. Early life adversity potentiates the effects of later life stress on cumulative physiological dysregulation. Anxiety, Stress, & Coping 28, 372–390. http://dx.doi.org/10.1080/10615806.2014.969720.
Diehl, T., Mullins, R., Kapogiannis, D., 2017. Insulin resistance in Alzheimer's disease. Transl. Res. 183, 26–40. http://dx.doi.org/10.1016/j.trsl.2016.12.005.
Dineley, K.T., Jahrling, J.B., Denner, L., 2014. Insulin resistance in Alzheimer's disease. Neurobiol. Dis. 72, 92–103. http://dx.doi.org/10.1016/j.nbd.2014.09.001.
Diz-Chaves, Y., Pernía, O., Carrero, P., Garcia-Segura, L.M., 2012. Prenatal stress causes alterations in the morphology of microglia and the inflammatory response of the hippocampus of adult female mice. J. Neuroinflammation 9, 71. http://dx.doi.org/10.1186/1742-2094-9-71.
Dong, M., Giles, W.H., Felitti, V.J., Dube, S.R., Williams, J.E., Chapman, D.P., Anda, R.F., 2004. Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. Circulation 110, 1761–1766. http://dx.doi.org/10.1161/01.CIR.0000143074.54995.7F.
Dong, H., Csernansky, J.G., 2009. Effects of stress and stress hormones on amyloid-β protein and plaque deposition. J. Alzheimers Dis. 18, 459–469. http://dx.doi.org/10.3233/JAD-2009-1152.
Dong, E., Dzitoyeva, S.G., Matrisciano, F., Tueting, P., Grayson, D.R., Guidotti, A., 2015. Brain-derived neurotrophic factor epigenetic modifications associated with schizophrenia-like phenotype induced by prenatal stress in mice. Biol. Psychiatr. 77, 589–596. http://dx.doi.org/10.1016/j.biopsych.2014.08.012.
Edwards, S.R., Hamlin, A.S., Marks, N., Coulson, E.J., Smith, M.T., 2014. Comparative studies using the Morris water maze to assess spatial memory deficits in two transgenic mouse models of Alzheimer's disease. Clin. Exp. Pharmacol. Physiol. 41, 798–806. http://dx.doi.org/10.1111/1440-1681.12277.
Espinosa-Oliva, A.M., de Pablos, R.M., Villarán, R.F., Argüelles, S., Venero, J.L., Machado, A., Cano, J., 2011. Stress is critical for LPS-induced activation of micrglia and damage in the rat hippocampus. Neurobiol. Aging 32, 85–102. http://dx.doi.org/10.1016/j.neurobiolaging.2009.01.012.
Ferraro, K.F., Schafer, M.H., Wilkinson, L.R., 2016. Childhood disadvantage and health problems in middle and later life: early imprints on physical health? Am. Socio. Rev. 81, 107–133. http://dx.doi.org/10.1177/0003122415619617.
Fiala, M., Kooij, G., Wagner, K., Hammock, B., Pellegrini, M., 2017. Modulation of innate immunity of patients with Alzheimer's disease by omega-3 fatty acids. Faseb. J. 31, 3229–3239. http://dx.doi.org/10.1096/fj.201700065R.
Fishel, M.A., Watson, G.S., Montine, T.J., Wang, Q., Green, P.S., Kulstad, J.J., Cook, D.G., Peskind, E.R., Baker, L.D., Goldgaber, D., Nie, W., Asthana, S., Plymate, S.R., Schwartz, M.W., Craft, S., 2005. Hyperinsulinemia provokes synchronous increases in central inflammation and β-amyloid in normal adults. Arch. Neurol. 62, 1539–1544. http://dx.doi.org/10.1001/archneur.62.10.noc50112.
Foster, T.C., 2012. Dissecting the age-related decline on spatial learning and memory tasks in rodent models: N-methyl-D-aspartate receptors and voltage-dependent Ca2+ channels in senescent synaptic plasticity. Prog. Neurobiol. 96, 283–303. http://dx.doi.org/10.1016/j.pneurobio.2012.01.007.
Frank, M.G., Thompson, B.M., Watkins, L.R., Maier, S.F., 2012. Glucocorticoids mediate stress-induced priming of microglial pro-inflammatory responses. Brain Behav. Immun. 26, 337–345. http://dx.doi.org/10.1016/j.bbi.2011.10.005.
Franklin, T.B., Russig, H., Weiss, I.C., Gräff, J., Linder, N., Michalon, A., Vizi, S., Mansuy, I.M., 2010. Epigenetic transmission of the impact of early stress across generations. Biol. Psychiatr. 68, 408–415. http://dx.doi.org/10.1016/j.biopsych.2010.05.036.
Frodl, T., O'Keane, V., 2013. How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. Neurobiol. Dis. 52, 24–37. http://dx.doi.org/10.1016/j.nbd.2012.03.012.
Fu, H., Liu, B., Frost, J.L., Hong, S., Jin, M., Ostaszewski, B., Shankar, G.M., Costantino, I.M., Carroll, M.C., Mayadas, T.N., Lemere, C.A., 2012. Complement component C3 and complement receptor type 3 contribute to the phagocytosis and clearance of fibrillar Aβ by microglia. Glia 60, 993–1003. http://dx.doi.org/10.1002/glia.22331.
Gapp, K., Jawaid, A., Sarkies, P., Bohacek, J., Pelczar, P., Prados, J., Farinelli, L., Miska, E., Mansuy, I.M., 2014. Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. Nat. Neurosci. 17, 667–669. http://dx.doi.org/10.1038/nn.3695.
Gatz, M., Reynolds, C.A., Fratiglioni, L., Johansson, B., Mortimer, J.A., Berg, S., Fiske, A., Pedersen, N.L., 2006. Role of genes and environments for explaining alzheimer disease. Arch. Gen. Psychiatr. 63, 168–174. http://dx.doi.org/10.1001/archpsyc.63.2.168.
Gow, A.J., Johnson, W., Pattie, A., Whiteman, M.C., Starr, J., Deary, I.J., 2008. Mental ability in childhood and cognitive aging. Gerontology 54, 177–186. http://dx.doi.org/10.1159/000118098.
Götz, J., Streffer, J.R., David, D., Schild, A., Hoerndli, F., Pennanen, L., Kurosinski, P., Chen, F., 2004. Transgenic animal models of Alzheimer's disease and related disorders: histopathology, behavior and therapy. Mol. Psychiatr. 9, 664–683. http://dx.doi.org/10.1038/sj.mp.4001508.
Götz, J., Ittner, L.M., 2008. Animal models of Alzheimer's disease and frontotemporal dementia. Nat. Rev. Neurosci. 9, 532–544. http://dx.doi.org/10.1038/nrn2420.
Götz, J., Matamales, M., Götz, N.N., Ittner, L.M., Eckert, A., 2012. Alzheimer's disease models and functional genomics - how many needles are there in the haystack? Front. Physiol. 3, 320. http://dx.doi.org/10.3389/fphys.2012.00320.
Green, K.N., Billings, L.M., Roozendaal, B., McGaugh, J.L., LaFerla, F.M., 2006. Glucocorticoids increase amyloid-beta and tau pathology in a mouse model of Alzheimer's disease. J. Neurosci. 26, 9047–9056. http://dx.doi.org/10.1523/JNEUROSCI.2797-06.2006.
Green, K.N., Martinez-Coria, H., Khashwji, H., Hall, E.B., Yurko-Mauro, K.A., Ellis, L., LaFerla, F.M., 2007. Dietary docosahexaenoic acid and docosapentaenoic acid ameliorate amyloid-β and tau pathology via a mechanism involving presenilin 1 levels. J. Neurosci. 27, 4385–4395. http://dx.doi.org/10.1523/JNEUROSCI.0055-07.2007.
Griciuc, A., Serrano-Pozo, A., Parrado, A.R., Lesinski, A.N., Asselin, C.N., Mullin, K., Hooli, B., Choi, S.H., Hyman, B.T., Tanzi, R.E., 2013. Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. Neuron 78, 631–643. http://dx.doi.org/10.1016/j.neuron.2013.04.014.
Grigoryan, G., Biella, G., Albani, D., Forloni, G., Segal, M., 2014. Stress impairs synaptic plasticity in triple-transgenic Alzheimer's disease mice: rescue by ryanodine. Neurodegener. Dis. 13, 135–138. http://dx.doi.org/10.1159/000354231.
Guo, H.B., Cheng, Y.F., Wu, J.G., Wang, C.M., Wang, H.T., Zhang, C., Qiu, Z.K., Xu, J.P., 2015. Donepezil improves learning and memory deficits in APP/PS1 mice by inhibition of microglial activation. Neuroscience 290, 530–542. http://dx.doi.org/10.1016/j.neuroscience.2015.01.058.
Haaksma, M.L., Vilela, L.R., Marengoni, A., Calderón-Larrañaga, A., Leoutsakos, J.M.S., Rikkert, M.G.M.O., Melis, R.J.F., 2017. Comorbidity and progression of late onset Alzheimer's disease: a systematic review. PLoS One 12http://dx.doi.org/10.1371/journal.pone.0177044. e0177044.
Han, B., Yu, L., Geng, Y., Shen, L., Wang, H., Wang, Y., Wang, J., Wang, M., 2016. Chronic Stress aggravates cognitive impairment and suppresses insulin associated signaling pathway in APP/PS1 mice. J. Alzheimers Dis. 53, 1539–1552. http://dx.doi.org/10.3233/JAD-160189.
Hardy, J., 2002. The amyloid hypothesis of alzheimer's disease: progress and problems on the road to therapeutics. Science 297, 353–356.
Hashimoto, M., Hossain, S., Shimada, T., Shido, O., 2006. Docosahexaenoic acid-induced protective effect against impaired learning in amyloid beta-infused rats is associated with increased synaptosomal membrane fluidity. Clin. Exp. Pharmacol. Physiol. 33, 934–939. http://dx.doi.org/10.1111/j.1440-1681.2006.04467.x.
Hatzinger, M., Z'brun, A., Hemmeter, U., Seifritz, E., Baumann, F., Holsboer-Trachsler, E., Heuser, I.J., 1995. Hypothalamic-pituitary-adrenal system function in patients with alzheimer's disease. Neurobiol. Aging 16, 205–209. http://dx.doi.org/10.1016/0197-4580(94)00159-6.
Heim, C., Nemeroff, C.B., 2001. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol. Psychiatr. 49, 1023–1039.
Heneka, M.T., Golenbock, D.T., Latz, E., 2015. Innate immunity in Alzheimer's disease. Nat. Immunol. 16, 229–236. http://dx.doi.org/10.1038/ni.3102.
Herpfer, I., Hezel, H., Reichardt, W., Clark, K., Geiger, J., Gross, C.M., Heyer, A., Neagu, V., Bhatia, H., Atas, H.C., Fiebich, B.L., Bischofberger, J., Haas, C.A., Lieb, K., Normann, C., 2012. Early life stress differentially modulates distinct forms of brain plasticity in young and adult mice. PLoS One 7, e46004. http://dx.doi.org/10.1371/journal.pone.0046004.
Herbert, J., Lucassen, P.J., 2016. Depression as a risk factor for Alzheimer's disease: genes, steroids, cytokines and neurogenesis - what do we need to know? Front. Neuroendocrinol. 41, 153–171. http://dx.doi.org/10.1016/j.yfrne.2015.12.001.
Hickman, S.E., Allison, E.K., Khoury, El, J., 2008. Microglial dysfunction and defective -amyloid clearance pathways in aging alzheimer's disease mice. J. Neurosci. 28, 8354–8360. http://dx.doi.org/10.1523/JNEUROSCI.0616-08.2008.

Hjorth, E., Zhu, M., Toro, V.C., Vedin, I., Palmblad, J., Cederholm, T., Freund-Levi, Y., Faxen-Irving, G., Wahlund, L.O., Basun, H., Eriksdotter, M., Schultzberg, M., 2013. Omega-3 fatty acids enhance phagocytosis of Alzheimer's disease-related amyloid-β42 by human microglia and decrease inflammatory markers. J. Alzheimers Dis. 35, 697–713. http://dx.doi.org/10.3233/JAD-130131.

Hoeijmakers, L., Lucassen, P.J., Korosi, A., 2015. The interplay of early-life stress, nutrition, and immune activation programs adult hippocampal structure and function. Front. Mol. Neurosci. 7, 1–16. http://dx.doi.org/10.3389/fnmol.2014.00103/abstract.

Hoeijmakers, L., Ruigrok, S.R., Amelianchik, A., Ivan, D., Van Dam, A.M., Lucassen, P.J., Korosi, A., 2017. Early-life stress lastingly alters the neuroinflammatory response to amyloid pathology in an Alzheimer's disease mouse model. Brain Behav. Immun. 63, 160–175. http://dx.doi.org/10.1016/j.bbi.2016.12.023.

Hovens, J.G.F.M., Giltay, E.J., Wiersma, J.E., Spinhoven, P., Penninx, B.W.J.H., Zitman, F.G., 2012. Impact of childhood life events and trauma on the course of depressive and anxiety disorders. Acta Psychiatr. Scand. 126, 198–207. http://dx.doi.org/10.1111/j.1600-0447.2011.01828.x.

Hsiao, K., Chapman, P., Nilsen, S., Eckman, C., Harigaya, Y., Younkin, S., Yang, F., Cole, G., 1996. Correlative memory deficits, abeta elevation, and amyloid plaques in transgenic mice. Science 274, 99–102.

Hui, J., Feng, G., Zheng, C., Jin, H., Jia, N., 2017. Maternal separation exacerbates Alzheimer's disease-like behavioral and pathological changes in adult APPswe/PS1dE9 mice. Behav. Brain Res. 318, 18–23. http://dx.doi.org/10.1016/j.bbr.2016.10.030.

Hulshof, H.J., Novati, A., Sgoifo, A., Luiten, P.G.M., Boer den, J.A., Meerlo, P., 2011. Maternal separation decreases adult hippocampal cell proliferation and impairs cognitive performance but has little effect on stress sensitivity and anxiety in adult Wistar rats. Behav. Brain Res. 216, 552–560. http://dx.doi.org/10.1016/j.bbr.2010.08.038.

Huot, R.L., Plotsky, P.M., Lenox, R.H., McNamara, R.K., 2002. Neonatal maternal separation reduces hippocampal mossy fiber density in adult Long Evans rats. Brain Res. 950, 52–63.

Ivy, A.S., Brunson, K.L., Sandman, C., Baram, T.Z., 2008. Dysfunctional nurturing behavior in rat dams with limited access to nesting material: a clinically relevant model for early-life stress. Neuroscience 154, 1132–1142. http://dx.doi.org/10.1016/j.neuroscience.2008.04.019.

Ivy, A.S., Rex, C.S., Chen, Y., Dubé, C., Maras, P.M., Grigoriadis, D.E., Gall, C.M., Lynch, G., Baram, T.Z., 2010. Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. J. Neurosci. 30, 13005–13015. http://dx.doi.org/10.1523/JNEUROSCI.1784-10.2010.

Jack, C.R., Knopman, D.S., Jagust, W.J., Shaw, L.M., Aisen, P.S., Weiner, M.W., Petersen, R.C., Trojanowski, J.Q., 2010. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 9, 119–128. http://dx.doi.org/10.1016/S1474-4422(09)70299-6.

Jack, C.R., Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw, L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., Lesnick, T.G., Pankratz, V.S., Donohue, M.C., Trojanowski, J.Q., 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 12, 207–216. http://dx.doi.org/10.1016/s1474-4422(12)70291-0.

Jang, S.S., Chung, H.J., 2016. Emerging link between Alzheimer's disease and homeostatic synaptic plasticity. Neural Plast. 2016, 1–19. http://dx.doi.org/10.1155/2016/7969272.

Jankowsky, J.L., Fadale, D.J., Anderson, J., Xu, G.M., Gonzales, V., Jenkins, N.A., Copeland, N.G., Lee, M.K., Younkin, L.H., Wagner, S.L., Younkin, S.G., Borchelt, D.R., 2004. Mutant presenilins specifically elevate the levels of the 42 residue beta-amyloid peptide in vivo: evidence for augmentation of a 42-specific gamma secretase. Hum. Mol. Genet. 13, 159–170. http://dx.doi.org/10.1093/hmg/ddh019.

Jivraj, S., Goodman, A., Ploubidis, G.B., de Oliveira, C., 2017. Testing comparability between retrospective life history data and prospective birth cohort study data. J. Gerontol. B. Psycho. Sci. Soc. Sci. http://dx.doi.org/10.1093/geronb/gbx042.

Johansson, L., Guo, X., Duberstein, P.R., Hällström, T., Waern, M., Östling, S., Skoog, I., 2014. Midlife personality and risk of Alzheimer disease and distress: a 38-year follow-up. Neurology 83, 1538–1544. http://dx.doi.org/10.1212/WNL.0000000000000907.

Johnson, F.K., Kaffman, A., 2017. Early life stress perturbs the function of microglia in the developing rodent brain: new insights and future challenges. Brain Behav. Immun. 1–10. http://dx.doi.org/10.1016/j.bbi.2017.06.008.

Joshi, Y.B., Chu, J., Praticò, D., 2013. Knockout of 5-lipoxygenase prevents dexamethasone-induced tau pathology in 3xTg mice. Aging Cell 12, 706–711. http://dx.doi.org/10.1111/acel.12096.

Joshi, Y.B., Chu, J., Praticò, D., 2012. Stress hormone leads to memory deficits and altered tau phosphorylation in a model of Alzheimer's disease. J. Alzheimers Dis. 31, 167–176. http://dx.doi.org/10.3233/JAD-2012-120328.

Justice, N.J., Huang, L., Tian, J.B., Cole, A., Pruski, M., Hunt, A.J., Flores, R., Zhu, M.X., Arenkiel, B.R., Zheng, H., 2015. Posttraumatic stress disorder-like induction elevates β-amyloid levels, which directly activates corticotropin-releasing factor neurons to exacerbate stress responses. J. Neurosci. 35, 2612–2623. http://dx.doi.org/10.1523/JNEUROSCI.3333-14.2015.

Kang, J.E., Cirrito, J.R., Dong, H., Csernansky, J.G., Holtzman, D.M., 2007. Acute stress increases interstitial fluid amyloid-beta via corticotropin-releasing factor and neuronal activity. Proc. Natl. Acad. Sci. Unit. States Am. 104, 10673–10678. http://dx.doi.org/10.1073/pnas.0700148104.

Kang, Y., Zhang, Y., Feng, Z., Liu, M., Li, Y., Yang, H., Wang, D., Zheng, L., Lou, D., Cheng, L., Chen, C., Zhou, W., Feng, Y., Li, X., Duan, J., Yu, M., Yang, S., Liu, Y., Wang, X., Deng, B., Liu, C., Yao, X., Zhu, C., Liang, C., Zeng, X., Ren, S., Li, Q., Zhong, Y., Zhang, Y., Kang, J., Yan, Y., Meng, H., Zhong, Z., Zhou, W., Wang, Y., Li, T., Song, W., 2017. Nutritional deficiency in early life facilitates aging-associated cognitive decline. Curr. Alzheimer Res. 14, 841–849. http://dx.doi.org/10.2174/1567205014666170425112331.

Kaplan, G.A., Turrell, G., Lynch, J.W., Everson, S.A., Helkala, E.L., Salonen, J.T., 2001. Childhood socioeconomic position and cognitive function in adulthood. Int. J. Epidemiol. 30, 256–263. http://dx.doi.org/10.1093/ije/30.2.256.

Kempermann, G., Song, H., Gage, F.H., 2015. Neurogenesis in the adult Hippocampus. Cold Spring Harb. Perspect. Biol. 7, a018812. http://dx.doi.org/10.1101/cshperspect.a018812.

Kim, J.J., Diamond, D.M., 2002. The stressed hippocampus, synaptic plasticity and lost memories. Nat. Rev. Neurosci. 3, 453–462. http://dx.doi.org/10.1038/nrn849.

Kirova, A.M., Bays, R.B., Lagalwar, S., 2015. Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. BioMed Res. Int. 2015, 748212–748219. http://dx.doi.org/10.1155/2015/748212.

Kok, A.A.L., Aartsen, M.J., Deeg, D.J.H., Huisman, M., 2017. The effects of life events and socioeconomic position in childhood and adulthood on successful aging. J. Gerontol. B Psychol. Sci. Soc. Sci. 72, 268–278. http://dx.doi.org/10.1093/geronb/gbw111.

Komarova, N.L., Thalhauser, C.J., 2011. High degree of heterogeneity in Alzheimer's disease progression patterns. PLoS Comput. Biol. 7http://dx.doi.org/10.1371/journal.pcbi.1002251. e1002251.

Korosi, A., Baram, T.Z., 2010. Plasticity of the stress response early in life: mechanisms and significance. Dev. Psychobiol. 52, 661–670. http://dx.doi.org/10.1002/dev.20490.

Korosi, A., Naninck, E.F.G., Oomen, C.A., Schouten, M., Krugers, H., Fitzsimons, C., Lucassen, P.J., 2012. Early-life stress mediated modulation of adult neurogenesis and behavior. Behav. Brain Res. 227, 400–409. http://dx.doi.org/10.1016/j.bbr.2011.07.037.

Kuhn, H.G., Palmer, T.D., Fuchs, E., 2001. Adult neurogenesis: a compensatory mechanism for neuronal damage. Eur. Arch. Psychiatr. Clin. Neurosci. 254, 152–158. http://dx.doi.org/10.1007/s004060170035.

Kuhn, H.G., Cooper-Kuhn, C.M., Boekhoorn, K., Lucassen, P.J., 2007. Changes in neurogenesis in dementia and Alzheimer mouse models: are they functionally relevant? Eur. Arch. Psychiatr. Clin. Neurosci. 257, 281–289. http://dx.doi.org/10.1007/s00406-007-0732-4.

Lahiri, D.K., Maloney, B., 2012. The “LEARn” (latent early-life associated regulation) model: an epigenetic pathway linking metabolic and cognitive disorders. J. Alzheimers Dis. 30 (Suppl. 2), S15–S30. http://dx.doi.org/10.3233/JAD-2012-120373.

Lahiri, D.K., Maloney, B., 2010. The “LEARn” (Latent Early-life Associated Regulation) model integrates environmental risk factors and the developmental basis of Alzheimer's disease, and proposes remedial steps. Exp. Gerontol. 45, 291–296. http://dx.doi.org/10.1016/j.exger.2010.01.001.

Lahiri, D.K., Maloney, B., Zawia, N.H., 2009. The LEARn model: an epigenetic explanation for idiopathic neurobiological diseases. Mol. Psychiatr. 14, 992–1003. http://dx.doi.org/10.1038/mp.2009.82.

Lahiri, D.K., Maloney, B., Basha, M.R., Ge, Y.W., Zawia, N.H., 2007. How and when environmental agents and dietary factors affect the course of Alzheimer's disease: the ‘LEARn’ model (latent early-life associated regulation) may explain the triggering of AD. Curr. Alzheimer Res. 4, 219–228. http://dx.doi.org/10.2174/156720507780362164.

Langa, K.M., Levine, D.A., 2014. The diagnosis and management of mild cognitive impairment: a clinical review. J. Am. Med. Assoc. 312, 2551–2561. http://dx.doi.org/10.1001/jama.2014.13806.

Lee, S., Varvel, N.H., Konerth, M.E., Xu, G., Cardona, A.E., Ransohoff, R.M., Lamb, B.T., 2010. CX3CR1 deficiency alters microglial activation and reduces beta-amyloid deposition in two Alzheimer's disease mouse models. Am. J. Pathol. 177, 2549–2562. http://dx.doi.org/10.2353/ajpath.2010.100265.

Leshchyns'ka, I., Liew, H.T., Shepherd, C., Halliday, G.M., Stevens, C.H., Ke, Y.D., Ittner, L.M., Sytnyk, V., 2015. Aβ-dependent reduction of NCAM2-mediated synaptic adhesion contributes to synapse loss in Alzheimer's disease. Nat Comms. 6, 8836. http://dx.doi.org/10.1038/ncomms9836.

Lesuis, S.L., Maurin, H., Borghgraef, P., Lucassen, P.J., Van Leuven, F., Krugers, H.J., 2016. Positive and negative early life experiences differentially modulate long term survival and amyloid protein levels in a mouse model of Alzheimer's disease. Oncotarget 7, 39118–39135. http://dx.doi.org/10.18632/oncotarget.9776.

Lesuis, S.L., van Hoek, B.A.C.E., Lucassen, P.J., Krugers, H.J., 2017. Early postnatal handling reduces hippocampal amyloid plaque formation and enhances cognitive performance in APPswe/PS1dE9 mice at middle age. Neurobiol. Learn. Mem. 144, 27–35. http://dx.doi.org/10.1016/j.nlm.2017.05.016.

Leuner, B., Gould, E., Shors, T.J., 2006. Is there a link between adult neurogenesis and learning? Hippocampus 16, 216–224. http://dx.doi.org/10.1002/hipo.20153.

Lewis, J., McGowan, E., Rockwood, J., Melrose, H., Nacharaju, P., Van Slegtenhorst, M., Gwinn-Hardy, K., Paul Murphy, M., Baker, M., Yu, X., Duff, K., Hardy, J., Corral, A., Lin, W.L., Yen, S.H., Dickson, D.W., Davies, P., Hutton, M., 2000. Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. Nat. Genet. 25, 402–405. http://dx.doi.org/10.1038/78078.

Lezoualc'h, F., Engert, S., Berning, B., Behl, C., 2000. Corticotropin-releasing hormone-mediated neuroprotection against oxidative stress is associated with the increased release of non-amyloidogenic amyloid β precursor protein and with the suppression of nuclear factor-κB. J. Mol. Endocrinol. 14, 147–159. http://dx.doi.org/10.1210/mend.14.1.0403.

Lim, G.P., Calon, F., Morihara, T., Yang, F., Teter, B., Ubeda, O., Salem, N., Frautschy, S.A., Cole, G.M., 2005. A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. J. Neurosci. 25, 3032–3040. http://dx.doi.org/10.1523/JNEUROSCI.4225-04.2005.

Lindner, M.D., 1997. Reliability, distribution, and validity of age-related cognitive deficits

in the Morris water maze. Neurobiol. Learn. Mem. 68, 203–220. http://dx.doi.org/10.1006/nlme.1997.3782.
Lopes, S., Vaz-Silva, J., Pinto, V., Dalla, C., Kokras, N., Bedenk, B., Mack, N., Czisch, M., Almeida, O.F.X., Sousa, N., Sotiropoulos, I., 2016. Tau protein is essential for stress-induced brain pathology. Proc. Natl. Acad. Sci. Unit. States Am. 113, E3755–E3763. http://dx.doi.org/10.1073/pnas.1600953113.
Lucassen, P.J., Naninck, E.F.G., van Goudoever, J.B., Fitzsimons, C., Joëls, M., Korosi, A., 2013. Perinatal programming of adult hippocampal structure and function; emerging roles of stress, nutrition and epigenetics. Trends Neurosci. 36, 621–631. http://dx.doi.org/10.1016/j.tins.2013.08.002.
Luchsinger, J.A., Noble, J.M., Scarmeas, N., 2007. Diet and Alzheimer's disease. Curr. Neurol. Neurosci. Rep. 7, 366–372. http://dx.doi.org/10.1007/s11910-007-0057-8.
Lupien, S.J., Nair, N., Briere, S., Maheu, F., Tu, M.T., Lemay, M., McEwen, B.S., Meaney, M.J., 1999. Increased cortisol levels and impaired cognition in human aging: implication for depression and dementia in later life. Rev. Neurosci. 10, 117–139. http://dx.doi.org/10.1515/REVNEURO.1999.10.2.117.
Machado, A., Herrera, A.J., de Pablos, R.M., Espinosa-Oliva, A.M., Sarmiento, M., Ayala, A., Venero, J.L., Santiago, M., Villarán, R.F., Delgado-Cortés, M.J., Argüelles, S., Cano, J., 2014. Chronic stress as a risk factor for Alzheimer's disease. Rev. Neurosci. 25, 785–804. http://dx.doi.org/10.1515/revneuro-2014-0035.
Maloney, B., Lahiri, D.K., 2016. Epigenetics of dementia: understanding the disease as a transformation rather than a state. Lancet Neurol. 15, 760–774. http://dx.doi.org/10.1016/S1474-4422(16)00065-X.
Maniam, J., Antoniadis, C.P., Wang, K.W., Morris, M.J., 2015. Early life stress induced by limited nesting material produces metabolic resilience in response to a high-fat and high-sugar diet in male rats. Front. Endocrinol. 6, 138. http://dx.doi.org/10.3389/fendo.2015.00138.
Marcello, E., Gardoni, F., Di Luca, M., 2015. Alzheimer's disease and modern lifestyle: what is the role of stress? J. Neurochem. 134, 795–798. http://dx.doi.org/10.1111/jnc.13210.
Marco, E.M., Valero, M., la Serna de, O., Aisa, B., Borcel, E., Ramírez, M.J., Viveros, M.-P., 2013. Maternal deprivation effects on brain plasticity and recognition memory in adolescent male and female rats. Neuropharmacology 68, 223–231. http://dx.doi.org/10.1016/j.neuropharm.2012.08.014.
Marlatt, M., Lucassen, P., 2010. Neurogenesis and alzheimers disease: biology and pathophysiology in mice and men. Curr. Alzheimer Res. 7, 113–125. http://dx.doi.org/10.2174/156720510790691362.
Martin, L., Latypova, X., Wilson, C.M., Magnaudeix, A., Perrin, M.L., Yardin, C., Terro, F., 2013. Tau protein kinases: involvement in Alzheimer's disease. Ageing Res. Rev. 12, 289–309. http://dx.doi.org/10.1016/j.arr.2012.06.003.
Martin, S.J., Grimwood, P.D., Morris, R.G., 2000. Synaptic plasticity and memory: an evaluation of the hypothesis. Annu. Rev. Neurosci. 23, 649–711. http://dx.doi.org/10.1146/annurev.neuro.23.1.649.
Martisova, E., Solas, M., Gerenu, G., Milagro, F.I., Campion, J., Ramirez, M.J., 2012. Mechanisms involved in BACE upregulation associated to stress. Curr. Alzheimer Res. 9, 822–829.
Martisova, E., Aisa, B., Guereñu, G., Ramírez, M.J., 2013. Effects of early maternal separation on biobehavioral and neuropathological markers of Alzheimer's disease in adult male rats. Curr. Alzheimer Res. 10, 420–432. http://dx.doi.org/10.2174/1567205011310040007.
Mass, E., Jacome-Galarza, C.E., Blank, T., Lazarov, T., Durham, B.H., Ozkaya, N., Pastore, A., Schwabenland, M., Chung, Y.R., Rosenblum, M.K., Prinz, M., Abdel-Wahab, O., Geissmann, F., 2017. A somatic mutation in erythro-myeloid progenitors causes neurodegenerative disease. Nat. Neurosci. 1–19. http://dx.doi.org/10.1038/nature23672.
Mathieu, G., Denis, S., Lavialle, M., Vancassel, S., 2008. Synergistic effects of stress and omega-3 fatty acid deprivation on emotional response and brain lipid composition in adult rats. Prostaglandins Leukot. Essent. Fatty Acids 78, 391–401. http://dx.doi.org/10.1016/j.plefa.2008.05.003.
Maurin, H., Seymour, C.M., Lechat, B., Borghgraef, P., Devijver, H., Jaworski, T., Schmidt, M.V., Kuegler, S., Van Leuven, F., 2013. Tauopathy differentially affects cell adhesion molecules in mouse brain: early down-regulation of nectin-3 in stratum lacunosum moleculare. PLoS One 8, e63589. http://dx.doi.org/10.1371/journal.pone.0063589.
May, C., Rapoport, S.I., Tomai, T.P., Chrousos, G.P., Gold, P.W., 1987. Cerebrospinal fluid concentrations of corticotropin-releasing hormone (CRH) and corticotropin (ACTH) are reduced in patients with Alzheimer's disease. Neurology 37http://dx.doi.org/10.1212/WNL.37.3.535. 535–535.
McGurn, B., Deary, I.J., Starr, J.M., 2008. Childhood cognitive ability and risk of late-onset Alzheimer and vascular dementia. Neurology 71, 1051–1056. http://dx.doi.org/10.1212/01.wnl.0000319692.20283.10.
McLaughlin, K.A., Conron, K.J., Koenen, K.C., Gilman, S.E., 2010. Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: a test of the stress sensitization hypothesis in a population-based sample of adults. Psychol. Med. 40, 1647–1658. http://dx.doi.org/10.1017/S0033291709992121.
Meaney, M.J., Aitken, D.H., van Berkel, C., Bhatnagar, S., Sapolsky, R.M., 1988. Effect of neonatal handling on age-related impairments associated with the hippocampus. Science 239, 766–768. http://dx.doi.org/10.2307/1700764.
Mhatre, S.D., Tsai, C.A., Rubin, A.J., James, M.L., Andreasson, K.I., 2015. Microglial malfunction: the third rail in the development of Alzheimer's disease. Trends Neurosci. 38, 621–636. http://dx.doi.org/10.1016/j.tins.2015.08.006.
Miller, G.E., Cole, S.W., 2012. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. Biol. Psychiatr. 72, 34–40. http://dx.doi.org/10.1016/j.biopsych.2012.02.034.
Mikkonen, M., Soininen, H., Tapiola, T., Alafuzoff, I., Miettinen, R., 1999. Hippocampal plasticity in Alzheimer's disease: changes in highly polysialylated NCAM immunoreactivity in the hippocampal formation. Eur. J. Neurosci. 11, 1754–1764.
Mueller, S.C., Maheu, F.S., Dozier, M., Peloso, E., Mandell, D., Leibenluft, E., Pine, D.S., Ernst, M., 2010. Early-life stress is associated with impairment in cognitive control in adolescence: an fMRI study. Neuropsychologia 48, 3037–3044. http://dx.doi.org/10.1016/j.neuropsychologia.2010.06.013.
Mufson, E.J., Mahady, L., Waters, D., Counts, S.E., Perez, S.E., DeKosky, S.T., Ginsberg, S.D., Ikonomovic, M.D., Scheff, S.W., Binder, L.I., 2015. Hippocampal plasticity during the progression of Alzheimer's disease. Neuroscience 309, 51–67. http://dx.doi.org/10.1016/j.neuroscience.2015.03.006.
Naninck, E.F.G., Hoeijmakers, L., Kakava-Georgiadou, N., Meesters, A., Lazic, S.E., Lucassen, P.J., Korosi, A., 2015. Chronic early life stress alters developmental and adult neurogenesis and impairs cognitive function in mice. Hippocampus 25, 309–328. http://dx.doi.org/10.1002/hipo.22374.
Naninck, E.F.G., Oosterink, J.E., Yam, K.Y., de Vries, L.P., Schierbeek, H., van Goudoever, J.B., Verkaik-Schakel, R.N., Plantinga, J.A., Plosch, T., Lucassen, P.J., Korosi, A., 2017. Early micronutrient supplementation protects against early stress-induced cognitive impairments. Faseb. J. 31, 505–518. http://dx.doi.org/10.1096/fj.201600834R.
Norton, M.C., Smith, K.R., Østbye, T., Tschanz, J.T., Schwartz, S., Corcoran, C., Breitner, J.C.S., Steffens, D.C., Skoog, I., Rabins, P.V., Welsh-Bohmer, K.A., Cache county investigators, 2011. Early parental death and remarriage of widowed parents as risk factors for Alzheimer disease: the Cache County study. Am. J. Geriatr. Psychiatr. 19, 814–824. http://dx.doi.org/10.1097/JGP.0b013e3182011b38.
Oddo, S., Caccamo, A., Shepherd, J.D., Murphy, M.P., Golde, T.E., Kayed, R., Metherate, R., Mattson, M.P., Akbari, Y., LaFerla, F.M., 2003. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. Neuron 39, 409–421.
Oitzl, M.S., Workel, J.O., Fluttert, M., Frosch, F., de Kloet, E.R., 2000. Maternal deprivation affects behaviour from youth to senescence: amplification of individual differences in spatial learning and memory in senescent Brown Norway rats. Eur. J. Neurosci. 12, 3771–3780. http://dx.doi.org/10.1046/j.1460-9568.2000.00231.x.
Oksman, M., Iivonen, H., Hogyes, E., Amtul, Z., Penke, B., Leenders, I., Broersen, L., Lütjohann, D., Hartmann, T., Tanila, H., 2006. Impact of different saturated fatty acid, polyunsaturated fatty acid and cholesterol containing diets on beta-amyloid accumulation in APP/PS1 transgenic mice. Neurobiol. Dis. 23, 563–572. http://dx.doi.org/10.1016/j.nbd.2006.04.013.
Oomen, C.A., Soeters, H., Audureau, N., Vermunt, L., van Hasselt, F.N., Manders, E.M.M., Joëls, M., Lucassen, P.J., Krugers, H., 2010. Severe early life stress hampers spatial learning and neurogenesis, but improves hippocampal synaptic plasticity and emotional learning under high-stress conditions in adulthood. J. Neurosci. 30, 6635–6645. http://dx.doi.org/10.1523/JNEUROSCI.0247-10.2010.
Osler, M., Christensen, G.T., Garde, E., Mortensen, E.L., Christensen, K., 2017. Cognitive ability in young adulthood and risk of dementia in a cohort of Danish men, brothers, and twins. Alzheimers Dement. http://dx.doi.org/10.1016/j.jalz.2017.04.003.
Osone, A., Arai, R., Hakamada, R., Shimoda, K., 2014. Impact of cognitive reserve on the progression of mild cognitive impairment to Alzheimer's disease in Japan. Geriatr. Gerontol. Int. 15, 428–434. http://dx.doi.org/10.1111/ggi.12292.
Park, H.J., Ran, Y., Jung, J.O., Holmes, O., Price, A.R., Smithson, L., Ceballos-Diaz, C., Han, C., Wolfe, M.S., Daaka, Y., Ryabinin, A.E., Kim, S.H., Hauger, R.L., Golde, T.E., Felsenstein, K.M., 2015. The stress response neuropeptide CRF increases amyloid-b production by regulating γ-secretase activity. EMBO J. 34, 1674–1686. http://dx.doi.org/10.15252/embj.201488795.
Paternain, L., Martisova, E., Campion, J., Martínez, J.A., Ramirez, M.J., Milagro, F.I., 2016. Methyl donor supplementation in rats reverses the deleterious effect of maternal separation on depression-like behaviour. Behav. Brain Res. 299, 51–58. http://dx.doi.org/10.1016/j.bbr.2015.11.031.
Pedersen, W.A., Flynn, E.R., 2004. Insulin resistance contributes to aberrant stress responses in the Tg2576 mouse model of Alzheimer's disease. Neurobiol. Dis. 17, 500–506. http://dx.doi.org/10.1016/j.nbd.2004.08.003.
Pedersen, W.A., McCullers, D., Culmsee, C., Haughey, N.J., Herman, J.P., Mattson, M.P., 2001. Corticotropin-releasing hormone protects neurons against insults relevant to the pathogenesis of alzheimer's disease. Neurobiol. Dis. 8, 492–503. http://dx.doi.org/10.1006/nbdi.2001.0395.
Pedersen, W.A., McMillan, P.J., Kulstad, J.J., Leverenz, J.B., Craft, S., Haynatzki, G.R., 2006. Rosiglitazone attenuates learning and memory deficits in Tg2576 Alzheimer mice. Exp. Neurol. 199, 265–273. http://dx.doi.org/10.1016/j.expneurol.2006.01.018.
Pietrzak, R.H., Lim, Y.Y., Neumeister, A., Ames, D., Ellis, K.A., Harrington, K., Lautenschlager, N.T., Restrepo, C., Martins, R.N., Masters, C.L., Villemagne, V.L., Rowe, C.C., Maruff, P., 2015. Amyloid-β, anxiety, and cognitive decline in preclinical Alzheimer disease: a multicenter, prospective cohort study. J. Am. Med. Assoc. Psychiatr. 72, 284–291. http://dx.doi.org/10.1001/jamapsychiatry.2014.2476.
Popp, J., Wolfsgruber, S., Heuser, I., Peters, O., Hüll, M., Schröder, J., Möller, H.J., Lewczuk, P., Schneider, A., Jahn, H., Luckhaus, C., Perneczky, R., Frölich, L., Wagner, M., Maier, W., Wiltfang, J., Kornhuber, J., Jessen, F., 2015. Cerebrospinal fluid cortisol and clinical disease progression in MCI and dementia of Alzheimer's type. Neurobiol. Aging 36, 601–607. http://dx.doi.org/10.1016/j.neurobiolaging.2014.10.031.
Pozueta, J., Lefort, R., Shelanski, M.L., 2013. Synaptic changes in Alzheimer's disease and its models. Neuroscience 251, 51–65. http://dx.doi.org/10.1016/j.neuroscience.2012.05.050.
Prince, M., Bryce, R., Albanese, E., Wimo, A., Ribeiro, W., Ferri, C.P., 2013. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimer's Dement 9, 63–75. http://dx.doi.org/10.1016/j.jalz.2012.11.007. e2.
Qiu, W.Q., Folstein, M.F., 2006. Insulin, insulin-degrading enzyme and amyloid-beta peptide in Alzheimer's disease: review and hypothesis. Neurobiol. Aging 27, 190–198. http://dx.doi.org/10.1016/j.neurobiolaging.2005.01.004.

Querfurth, H.W., LaFerla, F.M., 2010. Alzheimer's disease. N. Engl. J. Med. 362, 329–344. http://dx.doi.org/10.1056/NEJMra0909142.
Raadsheer, F.C., van Heerikhuize, J.J., Lucassen, P.J., Hoogendijk, W.J., Tilders, F.J., Swaab, D.F., 1995. Corticotropin-releasing hormone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. Am. J. Psychiatr. 152, 1372–1376. http://dx.doi.org/10.1176/ajp.152.9.1372.
Radford, K., Delbaere, K., Draper, B., Mack, H.A., Daylight, G., Cumming, R., Chalkley, S., Minogue, C., Broe, G.A., 2017. Childhood stress and adversity is associated with late-life dementia in aboriginal Australians. Am. J. Geriatr. Psychiatr. http://dx.doi.org/10.1016/j.jagp.2017.05.008.
Ramesh, B.N., Rao, T.S.S., Prakasam, A., Sambamurti, K., Rao, K.S.J., 2010. Neuronutrition and Alzheimer's disease. J. Alzheimers Dis. 19, 1123–1139. http://dx.doi.org/10.3233/JAD-2010-1312.
Ravona-Springer, R., Beeri, M.S., Goldbourt, U., 2012. Younger age at crisis following parental death in male children and adolescents is associated with higher risk for dementia at old age. Alzheimer Dis. Assoc. Disord. 26, 68–73. http://dx.doi.org/10.1097/WAD.0b013e3182191f86.
Ries, M., Sastre, M., 2016. Mechanisms of Aβ clearance and degradation by glial cells. Front. Aging Neurosci. 8, 715–719. http://dx.doi.org/10.3389/fnagi.2016.00160.
Rissman, R.A., Lee, K.F., Vale, W., Sawchenko, P.E., 2007. Corticotrophin-releasing factor receptors differentially regulate stress-induced tau phosphorylation. J. Neurosci. 27, 6552–6562. http://dx.doi.org/10.1523/JNEUROSCI.5173-06.2007.
Rodríguez, J.J., Witton, J., Olabarria, M., Noristani, H.N., Verkhratsky, A., 2010. Increase in the density of resting microglia precedes neuritic plaque formation and microglial activation in a transgenic model of Alzheimer's disease. Cell Death Dis. 1, e1. http://dx.doi.org/10.1038/cddis.2009.2.
Roth, T.L., Lubin, F.D., Funk, A.J., Sweatt, J.D., 2009. Lasting epigenetic influence of early-life adversity on the BDNF gene. Biol. Psychiatr. 65, 760–769. http://dx.doi.org/10.1016/j.biopsych.2008.11.028.
Sanders, D.W., Kaufman, S.K., DeVos, S.L., Sharma, A.M., Mirbaha, H., Li, A., Barker, S.J., Foley, A.C., Thorpe, J.R., Serpell, L.C., Miller, T.M., Grinberg, L.T., Seeley, W.W., Diamond, M.I., 2014. Distinct tau prion strains propagate in cells and mice and define different tauopathies. Neuron 82, 1271–1288. http://dx.doi.org/10.1016/j.neuron.2014.04.047.
Schafer, M.H., Ferraro, K.F., 2012. Childhood misfortune as a threat to successful aging: avoiding disease. Gerontol. 52, 111–120. http://dx.doi.org/10.1093/geront/gnr071.
Scheff, S.W., DeKosky, S.T., Price, D.A., 1990. Quantitative assessment of cortical synaptic density in Alzheimer's disease. Neurobiol. Aging 11, 29–37. http://dx.doi.org/10.1016/0197-4580(90)90059-9.
Scheltens, P., Blennow, K., Breteler, M.M.B., de Strooper, B., Frisoni, G.B., Salloway, S., Van der Flier, W.M., 2016. Alzheimer's disease. Lancet Neurol. 388, 505–517. http://dx.doi.org/10.1016/S0140-6736(15)01124-1.
Schmidt, M.V., Wang, X.D., Meijer, O.C., 2010. Early life stress paradigms in rodents: potential animal models of depression? Psychopharmacology 214, 131–140. http://dx.doi.org/10.1007/s00213-010-2096-0.
Selkoe, D.J., 2002. Alzheimer's disease is a synaptic failure. Science 298, 789–791. http://dx.doi.org/10.1126/science.1074069.
Sennvik, K., Boekhoorn, K., Lasrado, R., Terwel, D., Verhaeghe, S., Korr, H., Schmitz, C., Tomiyama, T., Mori, H., Krugers, H., Joëls, M., Ramakers, G.J.A., Lucassen, P.J., Van Leuven, F., 2007. Tau-4R suppresses proliferation and promotes neuronal differentiation in the hippocampus of tau knockin/knockout mice. Faseb. J. 21, 2149–2161. http://dx.doi.org/10.1096/fj.06-7735com.
Sibug, R.M., Oitzl, M.S., Workel, J.O., de Kloet, E.R., 2001. Maternal deprivation increases 5-HT(1A) receptor expression in the CA1 and CA3 areas of senescent Brown Norway rats. Brain Res. 912, 95–98.
Sierksma, A.S.R., Prickaerts, J., Chouliaras, L., Rostamian, S., Delbroek, L., Rutten, B.P.F., Steinbusch, H.W.M., van den Hove, D.L.A., 2013. Behavioral and neurobiological effects of prenatal stress exposure in male and female APPswe/PS1dE9 mice. Neurobiol. Aging 34, 319–337. http://dx.doi.org/10.1016/j.neurobiolaging.2012.05.012.
Sierksma, A.S.R., Vanmierlo, T., De Vry, J., Raijmakers, M.E.A., Steinbusch, H.W.M., van den Hove, D.L.A., Prickaerts, J., 2012. Effects of prenatal stress exposure on soluble Aβ and brain-derived neurotrophic factor signaling in male and female APPswe/PS1dE9 mice. Neurochem. Int. 61, 697–701. http://dx.doi.org/10.1016/j.neuint.2012.06.022.
Sindi, S., Hagman, G., Håkansson, K., Kulmala, J., Nilsen, C., Kåreholt, I., Soininen, H., Solomon, A., Kivipelto, M., 2016. Midlife work-related stress increases dementia risk in later life: the CAIDE 30-year study. J. Gerontol. B Psychol. Sci. Soc. Sci. 0, 1–10. http://dx.doi.org/10.1093/geronb/gbw043.
Solas, M., Aisa, B., Mugueta, M.C., Del Rio, J., Tordera, R.M., Ramirez, M.J., 2010. Interactions between age, stress and insulin on cognition: implications for Alzheimer's disease. Neuropsychopharmacology 35, 1664–1673. http://dx.doi.org/10.1038/npp.2010.13.
Solas, M., Aisa, B., Tordera, R.M., Mugueta, M.C., Ramirez, M.J., 2013. Stress contributes to the development of central insulin resistance during aging: implications for Alzheimer's disease. Biochim. Biophys. Acta 1832, 2332–2339. http://dx.doi.org/10.1016/j.bbadis.2013.09.013.
Solfrizzi, V., Custodero, C., Lozupone, M., Imbimbo, B.P., Valiani, V., Agosti, P., Schilardi, A., D'Introno, A., La Montagna, M., Calvani, M., Guerra, V., Sardone, R., Abbrescia, D.I., Bellomo, A., Greco, A., Daniele, A., Seripa, D., Logroscino, G., Sabbá, C., Panza, F., 2017. Relationships of dietary patterns, foods, and micro- and macronutrients with Alzheimer's disease and late-life cognitive disorders: a systematic review. J. Alzheim. Dis. 59, 815–849. http://dx.doi.org/10.3233/JAD-170248.
Sotiropoulos, I., Catania, C., Pinto, L.G., Silva, R., Pollerberg, G.E., Takashima, A., Sousa, N., Almeida, O.F.X., 2011. Stress acts cumulatively to precipitate Alzheimer's disease-like tau pathology and cognitive deficits. J. Neurosci. 31, 7840–7847. http://dx.doi.org/10.1523/JNEUROSCI.0730-11.2011.
Sotiropoulos, I., Catania, C., Riedemann, T., Fry, J.P., Breen, K.C., Michaelidis, T.M., Almeida, O.F.X., 2008. Glucocorticoids trigger Alzheimer disease-like pathobiochemistry in rat neuronal cells expressing human tau. J. Neurochem. 107, 385–397. http://dx.doi.org/10.1111/j.1471-4159.2008.05613.x.
Sousa, V.C., Vital, J., Costenla, A.R., Batalha, V.L., Sebastião, A.M., Ribeiro, J.A., Lopes, L.V., 2014. Maternal separation impairs long term-potentiation in CA1-CA3 synapses and hippocampal-dependent memory in old rats. Neurobiol. Aging 35, 1680–1685. http://dx.doi.org/10.1016/j.neurobiolaging.2014.01.024.
Steen, E., Terry, B.M., Rivera, E.J., Cannon, J.L., Neely, T.R., Tavares, R., Xu, X.J., Wands, J.R., la Monte de, S.M., 2005. Impaired insulin and insulin-like growild typeh factor expression and signaling mechanisms in Alzheimer's disease–is this type 3 diabetes? J. Alzheim. Dis. 7, 63–80. http://dx.doi.org/10.3233/JAD-2005-7107.
Stern, Y., 2002. What is cognitive reserve? Theory and research application of the reserve concept. J. Int. Neuropsychol. Soc. 8, 448–460. http://dx.doi.org/10.1017/S1355617702813248.
Sudduth, T.L., Schmitt, F.A., Nelson, P.T., Wilcock, D.M., 2013. Neuroinflammatory phenotype in early Alzheimer's disease. Neurobiol. Aging 34, 1051–1059. http://dx.doi.org/10.1016/j.neurobiolaging.2012.09.012.
Suri, D., Veenit, V., Sarkar, A., Thiagarajan, D., Kumar, A., Nestler, E.J., Galande, S., Vaidya, V.A., 2013. Early stress evokes age-dependent biphasic changes in hippocampal neurogenesis, BDNF expression, and cognition. Biol. Psychiatr. 73, 658–666. http://dx.doi.org/10.1016/j.biopsych.2012.10.023.
Szczesny, E., Basta-Kaim, A., Ślusarczyk, J., Trojan, E., Glombik, K., Regulska, M., Leśkiewicz, M., Budziszewska, B., Kubera, M., Lason, W., 2014. The impact of prenatal stress on insulin-like growild typeh factor-1 and pro-inflammatory cytokine expression in the brains of adult male rats: the possible role of suppressors of cytokine signaling proteins. J. Neuroimmunol. 276, 37–46. http://dx.doi.org/10.1016/j.jneuroim.2014.08.001.
Ślusarczyk, J., Trojan, E., Wydra, K., Głombik, K., Chamera, K., Kucharczyk, M., Budziszewska, B., Kubera, M., Lasoń, W., Filip, M., Basta-Kaim, A., 2016. Beneficial impact of intracerebroventricular fractalkine administration on behavioral and biochemical changes induced by prenatal stress in adult rats: possible role of NLRP3 inflammasome pathway. Biochem. Pharmacol. 113, 45–56. http://dx.doi.org/10.1016/j.bcp.2016.05.008.
Tomasdottir, M.O., Sigurdsson, J.A., Petursson, H., Kirkengen, A.L., Krokstad, S., McEwen, B., Hetlevik, I., Getz, L., 2015. Self reported childhood difficulties, adult multimorbidity and allostatic load. A cross-sectional analysis of the Norwegian HUNT study. PLoS One 10http://dx.doi.org/10.1371/journal.pone.0130591. e0130591.
Tsoory, M., Guterman, A., Richter-Levin, G., 2008. Exposure to stressors during juvenility disrupts development-related alterations in the PSA-NCAM to NCAM expression ratio: potential relevance for mood and anxiety disorders. Neuropsychopharmacology 33, 378–393. http://dx.doi.org/10.1038/sj.npp.1301397.
Turner, H.A., Butler, M.J., 2003. Direct and indirect effects of childhood adversity on depressive symptoms in young adults. J. Youth Adolesc. 32, 89–103. http://dx.doi.org/10.1023/A:1021853600645.
Tynan, R.J., Naicker, S., Hinwood, M., Nalivaiko, E., Buller, K.M., Pow, D.V., Day, T.A., Walker, F.R., 2010. Chronic stress alters the density and morphology of microglia in a subset of stress-responsive brain regions. Brain Behav. Immun. 24, 1058–1068. http://dx.doi.org/10.1016/j.bbi.2010.02.001.
Vallee, M., Maccari, S., Dellu, F., Simon, H., Le Moal, M., Mayo, W., 1999. Long-term effects of prenatal stress and postnatal handling on age-related glucocorticoid secretion and cognitive performance: a longitudinal study in the rat. Eur. J. Neurosci. 11, 2906–2916. http://dx.doi.org/10.1046/j.1460-9568.1999.00705.x.
van Donkelaar, E.L., Vaessen, K.R.D., Pawluski, J.L., Sierksma, A.S., Blokland, A., Cañete, R., Steinbusch, H.W.M., 2014. Long-term corticosterone exposure decreases insulin sensitivity and induces depressive-like behaviour in the C57BL/6NCrl mouse. PLoS One 9, e106960. http://dx.doi.org/10.1371/journal.pone.0106960.
van Veluw, S.J., Sawyer, E.K., Clover, L., Cousijn, H., De Jager, C., Esiri, M.M., Chance, S.A., 2012. Prefrontal cortex cytoarchitecture in normal aging and Alzheimer's disease: a relationship with IQ. Brain Struct. Funct. 217, 797–808. http://dx.doi.org/10.1007/s00429-012-0381-x.
Veerhuis, R., Van Breemen, M.J., Hoozemans, J.M., Morbin, M., Ouladhadj, J., Tagliavini, F., Eikelenboom, P., 2003. Amyloid beta plaque-associated proteins C1q and SAP enhance the Abeta1-42 peptide-induced cytokine secretion by adult human microglia in vitro. Acta Neuropathol. 105, 135–144. http://dx.doi.org/10.1007/s00401-002-0624-7.
Walker, C.D., Bath, K.G., Joëls, M., Korosi, A., Larauche, M., Lucassen, P.J., Morris, M.J., Raineki, C., Roth, T.L., Sullivan, R.M., Taché, Y., Baram, T.Z., 2017. Chronic early life stress induced by limited bedding and nesting (LBN) material in rodents: critical considerations of methodology, outcomes and translational potential. Stress 16, 1–28. http://dx.doi.org/10.1080/10253890.2017.1343296.
Wang, L., Yang, L., Yu, L., Song, M., Zhao, X., Gao, Y., Han, K., An, C., Xu, S., Wang, X., 2016a. Childhood physical neglect promotes development of mild cognitive impairment in old age - a case-control study. Psychiatr. Res. 242, 13–18. http://dx.doi.org/10.1016/j.psychres.2016.04.090.
Wang, X.-D., Su, Y.-A., Wagner, K.V., Avrabos, C., Scharf, S.H., Hartmann, J., Wolf, M., Liebl, C., Kühne, C., Wurst, W., Holsboer, F., Eder, M., Deussing, J.M., Müller, M.B., Schmidt, M.V., 2013. Nectin-3 links CRHR1 signaling to stress-induced memory deficits and spine loss. Nat. Neurosci. 16, 706–713. http://dx.doi.org/10.1038/nn.3395.
Wang, X.D., Rammes, G., Kraev, I., Wolf, M., Liebl, C., Scharf, S.H., Rice, C.J., Wurst, W., Holsboer, F., Deussing, J.M., Baram, T.Z., Stewart, M.G., Müller, M.B., Schmidt, M.V., 2011. Forebrain CRF_1 modulates early-life stress-programmed cognitive deficits. J. Neurosci. 31, 13625–13634. http://dx.doi.org/10.1523/JNEUROSCI.2259-11.2011.
Wang, Y., Cella, M., Mallinson, K., Ulrich, J.D., Young, K.L., Robinette, M.L., Gilfillan, S.,

Krishnan, G.M., Sudhakar, S., Zinselmeyer, B.H., Holtzman, D.M., Cirrito, J.R., Colonna, M., 2015. TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease Model. Cell 160, 1061–1071. http://dx.doi.org/10.1016/j.cell.2015.01.049.

Wang, Y., Ulland, T.K., Ulrich, J.D., Song, W., Tzaferis, J.A., Hole, J.T., Yuan, P., Mahan, T.E., Shi, Y., Gilfillan, S., Cella, M., Grutzendler, J., DeMattos, R.B., Cirrito, J.R., Holtzman, D.M., Colonna, M., 2016b. TREM2-mediated early microglial response limits diffusion and toxicity of amyloid plaques. J. Exp. Med. 213, 667–675. http://dx.doi.org/10.1084/jem.20151948.

Weiner, M.W., Veitch, D.P., Aisen, P.S., Beckett, L.A., Cairns, N.J., Cedarbaum, J., Green, R.C., Harvey, D., Jack, C.R., Jagust, W., Luthman, J., Morris, J.C., Petersen, R.C., Saykin, A.J., Shaw, L., Shen, L., Schwarz, A., Toga, A.W., Trojanowski, J.Q., Alzheimer's disease neuroimaging initiative, 2015. 2014 Update of the Alzheimer's Disease Neuroimaging Initiative: A review of papers published since its inception. Alzheimers Dement 11, e1–120. http://dx.doi.org/10.1016/j.jalz.2014.11.001.

Wilson, R.S., Arnold, S.E., Schneider, J.A., Kelly, J.F., Tang, Y., Bennett, D.A., 2006. Chronic psychological distress and risk of Alzheimer's disease in old age. Neuroepidemiology 27, 143–153. http://dx.doi.org/10.1159/000095761.

Wilson, R.S., Evans, D.A., Bienias, J.L., de Leon, C.F.M., Schneider, J.A., Bennett, D.A., 2003. Proneness to psychological distress is associated with risk of Alzheimer's disease. Neurology 61, 1479–1485. http://dx.doi.org/10.1212/01.WNL.0000096167.56734.59.

Wilson, R.S., Scherr, P.A., Hoganson, G., Bienias, J.L., Evans, D.A., Bennett, D.A., 2005. Early life socioeconomic status and late life risk of Alzheimer's disease. Neuroepidemiology 25, 8–14. http://dx.doi.org/10.1159/000085307.

Wilson, R.S., Schneider, J.A., Boyle, P.A., Arnold, S.E., Tang, Y., Bennett, D.A., 2007. Chronic distress and incidence of mild cognitive impairment. Neurology 68, 2085–2092. http://dx.doi.org/10.1212/01.wnl.0000264930.97061.82.

Wimo, A., Jönsson, L., Bond, J., Prince, M., Winblad, B., Alzheimer disease international, 2013. The worldwide economic impact of dementia 2010. Alzheimers Dement 9, 1–11. http://dx.doi.org/10.1016/j.jalz.2012.11.006. e3.

Wyss-Coray, T., Rogers, J., 2012. Inflammation in Alzheimer disease-a brief review of the basic science and clinical literature. Cold Spring Harbor Perspect. Med. 2http://dx.doi.org/10.1101/cshperspect.a006346. a006346–a006346.

Yam, K.Y., Naninck, E.F.G., Schmidt, M.V., Lucassen, P.J., Korosi, A., 2015. Early-life adversity programs emotional functions and the neuroendocrine stress system: the contribution of nutrition, metabolic hormones and epigenetic mechanisms. Stress 18, 328–342. http://dx.doi.org/10.3109/10253890.2015.1064890.

Yam, K.Y., Naninck, E.F.G., Abbink, M.R., la Fleur, S.E., Schipper, L., van den Beukel, J.C., Grefhorst, A., Oosting, A., van der Beek, E.M., Lucassen, P.J., Korosi, A., 2017a. Exposure to chronic early-life stress lastingly alters the adipose tissue, the leptin system and changes the vulnerability to western-style diet later in life in mice. Psychoneuroendocrinology 77, 186–195. http://dx.doi.org/10.1016/j.psyneuen.2016.12.012.

Yam, K.Y., Ruigrok, S.R., Ziko, I., De Luca, S.N., Lucassen, P.J., Spencer, S.J., Korosi, A., 2017b. Ghrelin and hypothalamic NPY/AgRP expression in mice are affected by chronic early-life stress exposure in a sex-specific manner. Psychoneuroendocrinology 86, 73–77. http://dx.doi.org/10.1016/j.psyneuen.2017.09.006.

Yang, X.D., Liao, X.M., Uribe-Mariño, A., Liu, R., Xie, X.M., Jia, J., Su, Y.A., Li, J.T., Schmidt, M.V., Wang, X.D., Si, T.M., 2015. Stress during a critical postnatal period induces region-specific structural abnormalities and dysfunction of the prefrontal cortex via CRF1. Neuropsychopharmacology 40, 1203–1215. http://dx.doi.org/10.1038/npp.2014.304.

Zárate, R., Jaber-Vazdekis El, N., Tejera, N., Pérez, J.A., Rodríguez, C., 2017. Significance of long chain polyunsaturated fatty acids in human health. Clin. Transl. Med. 6, 25. http://dx.doi.org/10.1186/s40169-017-0153-6.

Zhang, W., Bai, M., Xi, Y., Hao, J., Zhang, Z., Su, C., Lei, G., Miao, J., Li, Z., 2012. Multiple inflammatory pathways are involved in the development and progression of cognitive deficits in APPswe/PS1dE9 mice. Neurobiol. Aging 33, 2661–2677. http://dx.doi.org/10.1016/j.neurobiolaging.2011.12.023.

Zheng, Y., Fan, W., Zhang, X., Dong, E., 2016. Gestational stress induces depressive-like and anxiety-like phenotypes through epigenetic regulation of BDNF expression in offspring hippocampus. Epigenetics 11, 150–162. http://dx.doi.org/10.1080/15592294.2016.1146850.