REVIEW ARTICLE

Early Life Stress and Epigenetics in Late-onset Alzheimer's Dementia: A Systematic Review

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Abstract: Involvement of life stress in Late-Onset Alzheimer's Disease (LOAD) has been evinced in longitudinal cohort epidemiological studies, and endocrinologic evidence suggests involvements of catecholamine and corticosteroid systems in LOAD. Early Life Stress (ELS) rodent models have successfully demonstrated sequelae of maternal separation resulting in LOAD-analogous pathology, thereby supporting a role of insulin receptor signalling pertaining to GSK-3beta facilitated tau hyperphosphorylation and amyloidogenic processing. Discussed are relevant ELS studies, and findings from three mitogen-activated protein kinase pathways (JNK/SAPK pathway, ERK pathway, p38/MAPK pathway) relevant for mediating environmental stresses. Further considered were the roles of autophagy impairment, neuroinflammation, and brain insulin resistance.

For the meta-analytic evaluation, 224 candidate gene loci were extracted from reviews of animal studies of LOAD pathophysiological mechanisms, of which 60 had no positive results in human LOAD association studies. These loci were combined with 89 gene loci confirmed as LOAD risk genes in previous GWAS and WES. Of the 313 risk gene loci evaluated, there were 35 human reports on epigenomic modifications in terms of methylation or histone acetylation. 64 microRNA gene regulation mechanisms were published for the compiled loci.

Genomic association studies support close relations of both noradrenergic and glucocorticoid systems with LOAD. For HPA involvement, a *CRHR1* haplotype with *MAPT* was described, but further association of only *HSD11B1* with LOAD found; however, association of *FKBP1* and *NC3R1* polymorphisms was documented in support of stress influence to LOAD. In the brain insulin system, *IGF2R*, *INSR*, *INSRR*, and plasticity regulator *ARC*, were associated with LOAD. Pertaining to compromised myelin stability in LOAD, relevant associations were found for *BIN1, RELN, SORL1, SORCS1, CNP, MAG,* and *MOG*. Regarding epigenetic modifications, both methylation variability and de-acetylation were reported for LOAD. The majority of up-to-date epigenomic findings include reported modifications in the well-known LOAD core pathology loci *MAPT, BACE1, APP* (with *FOS, EGR1*), *PSEN1, PSEN2*, and highlight a central role of *BDNF*. Pertaining to ELS, relevant loci are *FKBP5, EGR1, GSK3B*; critical roles of inflammation are indicated by *CRP, TNFA, NFKB1* modifications; for cholesterol biosynthesis, *DHCR24*; for myelin stability *BIN1, SORL1, CNP*; pertaining to (epi)genetic mechanisms, *hTERT, MBD2, DNMT1, MTHFR2*. Findings on gene regulation were accumulated for *BACE1*, MAPK signalling, *TLR4, BDNF*, insulin signalling, with most reports for miR-132 and miR-27. Unclear in epigenomic studies remains the role of noradrenergic signalling, previously demonstrated by neuropathological findings of childhood nucleus caeruleus degeneration for LOAD tauopathy.

1. INTRODUCTION

1.1. Psychological Stress as a Risk Factor for Late Onset Alzheimer Disease (LOAD)

The last decade has brought about a profound reorganisation of knowledge on the age-related senile dementia of the Alzheimer type (LOAD). It has nowadays become broadly accepted that life stresses must play a mediatory role [1] in the complex genotype-environmental interaction which precedes clinical manifestation of the fatal Alzheimer endo-phenotype [2]. In contrast to all other neurodegenerative disorders, sporadic late-onset dementia of the Alzheimer type is a condition, which is almost probabilistically related to increasing age: it is increasing to almost 50% among those ≥90 years old (2.78% at 65 with almost linear increase to 56.13% at 95 per 1000 person years, slightly peaking at 85) [3].

The demographic change in combination with extending life expectancies is a major sociological risk for increasing

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incidences of LOAD in developed ageing societies. It has been stipulated that its aetiopathophysiology should accordingly adopt a life-span developmental perspective [4, 5]. The 2014 World Alzheimer Report estimates a worldwide prevalence of 44 million sufferers from this fatal disease, and expects that this number is to triple by the year 2050 [4]. For the US alone, an incidence rate of one million new patients per year is forecasted by the Alzheimer's Association [6], and the total expected prevalence 2050 is 13.8 million [6]. A proportion of 75% of all dementia cases have LOAD pathology (adding to a co-morbidity with vascular dementia towards 90% of all *post-mortem* dissected and thus histologically verified cases) [4], with highest prevalence figures in North America and Europe [1], where the life-time prevalence risk is currently 17% for females, and 9% for males [7]. Several European population-based cohort studies have provided evidence in the past five years that the age-specific incidence of dementia has decreased in the past 20 years [8], but incidences increased in China and threshold countries, a fluctuation possibly attributable to life-style factors.

The main difference to familial presenile AD (Morbus Alzheimer proper) is based on autosomal dominant mutations in the highly homologous presenlin 1 (*PSEN1* 14q24.1), presenilin 2 (*PSEN2* 1q42.13), and amyloid precursor protein (*APP* 21q21.3) genes. Up to date, there is still too little knowledge about the exact function and disorders of Amyloid Precursor Protein (APP) [9]. In the mutations linked to early-onset AD, pathogenic presenilin isoforms become part of the enzyme gamma-secretase responsible for the neurotoxic 42-aminoacid isomer of the cleaved APP [10]. In addition, the presenilins interact with Notch1 receptors and are involved in the Notch signalling pathways related to neuronal differentiation and neuritic outgrow. Specifically, in the notch pathway, gamma secretase releases the intracellular domain of the notch receptor protein 1 (*NOTCH1* 9q34.3), a relative of the epidermal growth factor (EGF), regulating nuclear gene expression, and synaptic stability through synaptic plasticity protein Arc (Section 3.2.). Notch signalling is also involved in oligodendrocyte differentiation and upregulation of myelin-associated glycoprotein MAG [11], thus constituting a direct biochemical link to myelination integrity and late-life myelin breakdown in LOAD. The further main commonality then shared with LOAD is the general pathophysiology (amyloid beta cascade and tau pathologies, in particular), which is the focus of the following sections.

In LOAD, the major genetic risk is the apolipoprotein E (*APOE* 19q32.13) epsilon4 allele, specifically in heterozygotic genotype with Odds Ratios (ORs) 2.6~3.2 [12, 13]. Apolipoprotein E is crucial for cholesterol transport and metabolism, and in the brain synthesised by astrocytes and microglia. In LOAD, the *APOE* epsilon4 allele is present in 40% [12, 13] -50% [8] of cases, and therefore constitutes the largest known single genomic risk, however, in 15-fold probability (OR 14.9) [13] for homozygotic carriers. Amongst these *APOE* epsilon4 carriers, the growth factor receptor-bound protein 2 associated binder protein 2 (*GAB2* 11q14.1) has been found to have an interaction with tangle bearing neurons leading to an overexpression of *GAB2* [14, 15] (however not replicated in all ethnicities). GAB2 ad-dresses PI3K/Akt/mTOR and ERK/MAPK (Section 2.2.) pathways and interacts with APP [16].

Several other rare genetic variants have been encircled by Genome Wide Association Studies (GWAS) [15, 17], Whole Exome Studies (WES) [18, 19], and family/twin studies (adjusted h^2=0.32-0.42 for memory) [20], (57-78% for onset time) [21, 22], (h^2=0.67-0.74 for liability) [23] (Table **1**: confirmed candidate genes, Section 4.1.). However, the lack of single large genomic bases lead to the conclusion that other mechanisms, such as epigenetic modification, transcriptional regulations and/or gene-environment interactions could play a substantial role in pathogenesis. Whereas global genetic expression rates (within age correlations) increase only slightly from 0.089 in the 4th towards 0.23 in the 7th decade [24], the major GWAS risk genes (Section 4.1.) showed marked methylation changes in LOAD over age as compared to a control population [25, 26]. Polygenic risk associations for cerebral substrates of LOAD, as well as amyloid-beta (Abeta) levels, prove significant only in younger ages, but not in higher ages [27, 28], suggesting that ageing *per se* is an independent process leading to cognitive decline. Hence, these authors led by Mormino conclude that "genetic risk may begin in early life and make an individual more susceptible to cognitive impairment in late life" (p. 481) [27].

Ageing is the single largest known risk in LOAD pathophysiology, but LOAD onset is mainly dependent on premorbid intactness of the cerebral neuropil [5]. Age specifically contributes to LOAD progression due to myelin content loss [29] associated with intra-neuronal agglomeration of hyper-phosphorylated tau protein (h-tau$_{181}$). Clinical manifestation of open LOAD is preceded by 20 years or more [30] latent prodromal phase, with no or few mnestic signs, but onset of Abeta plaques. A phase with subtle subjective memory problems, called Mild Cognitive Impairment (MCI), specifically in declarative and autobiographic memory systems, is a typical transition period, until with executive disturbances the capability for self-governance is lost. According to clinical literature, MCI and manifest LOAD states may switch forth and back before terminal neurodegeneration fully overrides executive functions. Although Abeta plaque precipitation also occurs within normal ageing, preclinical MCI is associated with more Abeta deposition [31], which is in turn related to global cognition, verbal and arithmetic memory, and executive functioning.

Several other risk factors were identified by epidemiological studies, including a meta-analysis of 18 British cohorts [32], once age effects were excluded:

- Sociological: social class, educational attainment, gender, family history, occupation, intellectual activities.

- Medical: small birth weight [33], concussion and contusion, traumatic encephalopathy, cerebrovascular diseases, Metabolic Syndrome (MetS) components (*e.g.* insulin resistance, hypertension, total cholesterol, BMI), sedentary lifestyle.

- Nutritional: dietary habits (*e.g.* cholesterol rich nutrition), vitamin D3 depletion, toxic environmental factors (*e.g.* metals, electromagnetic fields, traffic proximity) [7, 34-37], oestrogen supplementation [2].

- Protective (*i.e.* reducing risks): higher education with high cognitive function at baseline [3], regular physical exercise, non-steroid anti-inflammatory agents (*e.g.* aspirin, diclofenac), regular coffee and wine consumption [38].

In summary, several of these factors are strongly pointing towards a role of (early) life stress [7, 35] and of MetS (which is at 38% itself cortisol-level related [39]). In fact, available evidence also suggests that (a) major medical risk factor exposure was present in early adulthood, and (b) that present cognitive peculiarities date back to childhood [30, 33].

Looking at a closer connection of cognitive functioning and psychosocial stresses, the key pathogenic protein tau is a plausible target of Early Life Stress (ELS), because interference in its expression in early ontogeny [40] may leave genomic imprinting effects in neuropil structures increasing late-life LOAD susceptibility [41]. Phosphorylation of tau is regulated by protein kinase N1 (*PKN1* 19p13.12) and other kinases [42], being disruptive of neuronal microtubule organisation: Hyper-phosphorylation of protein tau produces inclusions in microtubules, later resulting in the formation of paired helicoidal filaments, and in a further stage to assembly of neurofibrillary tangles (NFT). Hyper-phosphorylation and formation of paired helicoidal filaments occurs with all six isoforms of the tau protein. Phosphorylation of tau occurs already during embryonic CNS development, where it is developmentally induced [40], thus making it a likely candidate for ELS effects in ontogeny: abnormalities in microtubule associated *h*-tau may therefore transport early developmental risks.

Further mechanisms related to brain neuropil involve anatomical alterations as an impact of stress psychophysiology. Hippocampal atrophy is a common consequence of exaggerated glucocorticoid action, being the main structural biomarker in LOAD (as well as *e.g.* in Post-Traumatic Stress Disorder, PTSD). But also in more subtle ways is chronic psychological stress inducing neuronal oxidative stress and thus accelerating biological ageing [43]. Further clinical arguments indicate a role of distress with high sympathetic arousal states in transition to LOAD. Here, late-life depression, which is discussed as one possible precursor [31] of LOAD, is regularly associated with high anxiety levels. The resulting state of so-called 'pseudo-dementia' with mnestic disorder in MCI, linking depression to dementia [44] includes vascular disease, alterations in glucocorticoid steroid levels and hippocampal atrophy, increased deposition of Abeta plaques, inflammatory changes, and depletion of neural growth factors [45]. A two-fold to five-fold increased risk of dementia was found to be associated with late-life depression, whilst another study found that even one additional depressive symptom increased dementia risk by 20% (odds ratios, ORs 1.4~4.6) [45]. Thus, the detrimental complex role of stress to LOAD may be present at several developmental time points.

1.2. Epidemiological Evidence for a Role of Stress in LOAD

Although many clinical researchers and the major scholarly societies now acknowledge roles of stresses in its patho-

physiology, a direct linkage between stress and LOAD is still not firmly established [46], partly because of a lack of *post-mortem* autopsy data pertaining to stress biomarkers. In epidemiology, effect sizes for direct concurrent links in humans are modest, and have best supported inflammatory causations, also by inclusion of other diseases. Still, however, a vast majority of prospective epidemiological evidence demonstrates that an active and socially integrated lifestyle is protective against LOAD [47], which suggests in reverse conclusion negative influences of psychological stresses. Nonetheless, there is classical evidence existing in support of life stress to manifestation of LOAD.

The best-known evidence is the Wilson study of catholic clergy utilising retrospective autobiographic data. Nuns with highest levels of distress measure had 2.7 times the risk of being specifically diagnosed with AD [46], but generally with a 10-fold more rapid cognitive decline [48]. In the Johansson study in Swedish women, life stress escalated Hazard Ratios (HRs) specifically for LOAD in over 35 years from 1.6 through 2.51 [49, 50], and in the Deng five-year prospective study of Chinese, a HR 1.5 was found for personal life adversities on the Folstein MMSE (Mini Mental State Examination, a neuropsychological test discriminative for MCI and AD) [51]. In the normative Leng prospective Norfolk study, there was an OR up to 1.24 for each score unit in self-perceived stress and MMSE scores after ten years [52]. In 77.9% of a Greek risk-sample, incident life stresses were found concrete triggers of clinical LOAD manifestation [53]. Findings in the Helsinki birth cohort study [54] support the notion of alteration of physiological functioning due to ELS particularly with cardiometabolic risk including Type 2 Diabetes Mellitus (T2DM), and also intellectual functioning. As meta-analyses show, T2DM has a specific LOAD-Relative Risk (RR) of 1.46 [55]. The classic Helsinki study found that those subjects with ELS had -0.28 SD units lower verbal ability, -0.13 SD units lower visuospatial ability, -0.18 SD units lower arithmetic ability scores as compared to non-separated with strongest relationship between ELS and lower scores on verbal reasoning [56] (these domains being early cognitive markers of LOAD).

Age as a risk factor is based on alterations in myelin content in white matter (evident as WM lesions) as recent MRI research revealed [57]. The longitudinal data from the Lothian birth cohort further indicated: There are also relations of early cognitive capacities and late-life cortical thickness (GM volume) [58]. The linkage of later white matter MR hyperintensities (indicating WM lesions, myelin vulnerability or myelin breakdown) with LOAD [59, 60], are assumed to be caused by neuropil disintegrities originated in early life, specifically related to myelination cycles in early childhood [57]. Findings from several approaches increasingly support the notion that early regional neuropil dysfunctions may be conducive to late life LOAD susceptibilities [57, 61, 62].

The World Alzheimer Report [4] acknowledges direct influence of ELS in terms of early life adversities, orphanage, divorce, foster care, evacuation, poverty, and other hazards to be related to later AD diagnosis. Having experienced socioeconomic hardship in early life increases the risk to developing MCI, the precursor of LOAD (OR 1.68) [63].

Table 1.   **Confirmed risk gene loci.**

Locus	Gene	Function	References
9q31.3	*ABCA1*	ATP-binding cassette transporter subfamily A member 1: regulates cholesterol efflux to forming HDL	[476, 604]
19p13.3	*ABCA7*	ATP binding cassette subfamily A member 7: lipid homeostasis of immune cells, efflux of phospholipids, phagocytosis	[541, 542, 557, 558, 569, 605-608]
15q23.3	*ADAM10*	A-disintegrin and metalloproteinase domain-containing protein 10: excitatory hippocampal synapses	[556, 559]
8p11.21	*ANK1*	Ankyrin 1: integral membrane protein in the spectrin-actin cytoskeleton, neuron motility, activation, proliferation, contact	[476, 569, 570]
19q13.32	*APOE*	Apolipoprotein E: neuronal cholesterol and triglyceride transport shuttle	[605, 606]
21q21.2	*APP*	Amyloid precursor protein: cell surface receptor, cleavage products binding acetyltransferase complex APBB1/TIP60, promoting transcriptional activation	[124, 211, 545, 546]
9q33.1	*ASTN2*	Neuronal protein astrotactin 2: neuron migration and connectivity	[578]
17q25.1	*ATP5H/KCTD2*	Mitochondrial ATP synthase H$^+$ transporting: catalyses ATP synthesis, involved in OXPHOS, mitochondrial energy and cellular stress	[541]
11q23.3	*BACE1*	Beta-secretase 1: transmembrane protease performing first cleavage step for amyloid beta	[547]
2q14.3	*BIN1*	Myc box-dependent-interacting protein 1: involved in synaptic vesicle endocytosis, endosomal vesicle cycling, clathrin-mediated endocytosis, related to tauopathy	[540, 542, 546, 557, 563, 564, 569, 572, 605-607]
19q13.32	*BLOC1S3*	Biogenesis of lysosomal organelles complex1, subunit 3: autophagy and apoptosis	[572]
22q13.1	*CARD10*	Caspase recruitment domain family, member 10: NFkappaB signalling pathway, hippocampal volume, hippocampal neurodegeneration with *PARP1* in *APOE* epsilon3 carriers	[541, 609]
20q13.31	*CASS4*	Cas scaffolding protein family member 4: cytoskeletal stabilisation, axonal transport, binding to CD2AP, involved in APP pathology, tauopathy	[542, 557, 605, 606]
6p12.3	*CD2AP*	CD2 associated protein: endosomal vesicle movement/cycling, cytoskeletal reorganisation, modulating with *GRB2* metabolism of APP	[540, 542, 546, 557, 558, 566, 605-607]
19q13.41	*CD33*	CD33 molecule: microglial/immune/inflammatory response, cell-cell interactions, related to cognitive decline, Abeta clearance	[541, 542, 557, 605-607, 610]
10q23.1	*CDH23*	Cadherin related 23: calcium dependent cell-cell adhesion glycoprotein, neuronal differentiation, neuronal transmission	[543, 569]
11p11.2	*CELF1*	CUGBP Elav-like family member 1: regulating pre-mRNA alternative splicing, editing, translation, including *MADD* MAPK–activating death domain, affecting long-term neuronal viability	[542, 557, 605, 606, 611]
16q13	*CETP*	Cholesteryl ester transfer protein: transfer of cholesteryl ester from HDL to other lipoproteins, related to myelination, white matter integrity, MetS components	[541, 612, 613]
1q31.1	*CFHR1*	Complement factor H related 1: controlling complement, facilitating tissue invasion, neuroinflammation with IL-6, neurodegeneration	[541, 614]
8p21.1	*CLU*	Clusterin: molecular chaperone, clearing cellular debris and apoptosis, cholesterol and lipid metabolism, regulation of cell proliferation	[541, 542, 546, 567, 605-608]
1q32.2	*CR1*	Complement receptor 1: membrane glycoprotein binding immune complexes, immune response, regulation of complement activation, neuroinflammation	[540, 541, 542, 546, 557, 562, 605-607]

Locus	Gene	Function	References
15q21.1	*CYP19A1*	Enzyme aromatase: oestrogen pathway, involved in tauopathy, Abeta cascade, interaction with IL-10	[544, 615, 616]
14q32.2	*CYP46A1*	Cholesterol 24S-hydroxylase (CYP46A1) promoter: monooxygenase related to synthesis of cholesterol hydroxylase, steroids and other lipids, cholesterol transport through BBB	[617-619]
1p23.3	*DHCR24*	24-dehydrocholesterol reductase: oxidoreductase catalysing cholesterol biosynthesis, cholesterol efflux	[476, 620, 621]
21q22.3	*DIP2A*	Disco interacting protein 2 homolog A: CNS axon patterning	[569]
18q12.1	*DSG2*	Desmoglein 2: calcium-binding transmembrane glycoprotein component of desmosomes, cell-cell junctions, glycoprotein generation, involved in APP processing	[606, 622]
1p36.12	*ECE-1b promoter*	Endothelin converting enzyme 1: related to Abeta degradation	[573, 574]
18q12.2-q21.1	*EPG5*	Ectopic P-granules autophagy protein 5 homologue: autophagy	[551, 623]
7q34-35	*EPHA1*	Ephrin receptor: mediating CNS development, modulating cell migration, axon guidance, synapse development and plasticity, cerebral glucose levels, atrophy, endosomal vesicle cycling, immune system	[542, 546, 557, 565, 567, 605-607]
2q33.3	*FASTKD2*	Fas-associated serine/threonine kinase domains 2: mitochondrial inner compartment protein, COX signalling, memory performance	[541, 624-626]
14q22.1	*FERMT2*	Fermitin family member 2: cytoskeletal function and axonal transport, actin assembly and cell shape modulation, cell matrix adhesion structures, activates integrins, related to tauopathy	[542, 557, 605, 606]
9p24.2	*GLIS3*	GLI-similar family zinc finger 3: repressor and activator of transcription, development of pancreatic beta cells, tauopathy, APP metabolism	[19, 541, 627]
3q28	*GMNC*	Geminin coiled-coil domain containing: involved chromosomal DNA replication, preferentially expressed in proliferating neurons, related to tauopathy	[19]
6p21.31	*HLA-DRB5/DRB1*	Major histocompatibility complex class II, DRbeta5 and DRbeta1: immunocompetence, encoding human leukocyte antigen, neuroinflammation	[542, 557, 605, 606]
14q32.33	*IGHV1-67*	Immunoglobulin heavy variable 1-67: neuroinflammation	[628]
2q37.1	*INPP5D*	Inositol polyphosphate-5-phosphatase: Immune response, gene regulation, posttranslational modification of proteins, microglial and myeloid function, interacting with *CD2AP*, neuroinflammation	[542, 557, 605, 606]
17q21.31	*KANSL1*	KAT8 regulatory NSL complex subunit 1: involved with histone acetylation, related to *MAPT* expression	[629]
12q24.31	*KDM2B*	Lysine demethylase 2B: phosphorylation-dependent ubiquitination, posttranslational modification	[630]
9q34.12	*LAMC3*	Laminin subunit gamma 3: extracellular matrix glycoprotein related to cellular morphogenesis, in interaction with *LRRK2* and *MADD* related to age-of-onset	[577]
12q12	*LRRK2*	Leucine rich repeat kinase 2: Ras-Raf signalling, cytoplasm and mitochondrial outer membrane, related to age-of-onset	[577]
11p11.2	*MADD*	MAP kinase activating death domain: TNFalpha signalling with the death domain of TNFalpha receptor 1, MAPK apoptotic signal transduction, related to age-of-onset	[577, 631, 632]
17q21.31	*MAPT*	Microtubule-associated protein tau: neuron stabilisation, transcript undergoes complex, regulated alternative splicing, producing several mRNA species	[546, 629]

(Table 1) contd….

Locus	Gene	Function	References
5q14.3	*MEF2C*	Myocyte enhancer factor 2C: immune response, neural development, synaptic connectivity and plasticity, limiting excessive activity-dependent synapse formation, facilitating hippocampal-dependent learning and memory, neuroinflammation	[557, 605, 606]
3p25.2	*MME/NEP*	Membrane metalloendopeptidase/neprisylin: glycoprotein neutral endopeptidase, related to WM hyperintensities, related to cleavage of peptides, related to Abeta degradation, covariation with WM disintegrity	[573, 633, 634]
11q12.2	*MS4A4/MS4A6E*	Membrane spanning 4-domains: involved in signal transduction as a component of a multimeric receptor complex, IgE receptor, immune response, neuroinflammation	[540, 542, 546, 605-608, 635]
20q13.33	*MYT1*	Myelin transcription factor: zinc finger transcription factor expressed on neurons, myelination onset, binding to the significant promoter *CYP46A1* polymorphism, in haplotypes with *CYP46A1*, related to *REST*, *MECP2*	[617]
20p11.21	*NANP*	N-acetylneuraminic acid phosphatase: implicated in insulin signalling, glycation, related to brain atrophy in neurodegeneration	[630]
20p11.21	*NINL*	Ninein-like protein: implicated in dynein-dynactin-interaction, related to stabilisation of microtubuli, tauopathy, related to brain atrophy in non-*APOE* epsilon4 carriers in haplotype with *NANP*	[630]
7p14.1	*NME8*	Thioredoxin domain-containing protein 3: implicated in dynein-related microtubular transport function, related to cognitive decline, neurodegeneration	[542, 557, 605, 606]
10q23.1	*NRG3*	Neuregulin 3: EGF-related ligand to transmembrane receptors, implicated in neuroblast proliferation, migration, differentiation, and survival or apoptosis, related to age-of-onset	[579]
12q22	*NTN4*	Netrin 4: EGF-related, responsible for axon guidance, neurite growth, neuron migration, angiogenesis, in haplotype with common variants	[577]
1p35.3	*OPRD1*	Delta-opioid receptor: small cerebral volume, implicated with APP processing	[541, 636-638]
3q28	*OSTN*	Osteocrin: primate-specific regulator of synapse formation, restricting activity-dependent dendritic growth, related to transcription factor MEF2 in the SASP (Section 1.4.)	[19, 541, 639]
1q42.12	*PARP1*	Poly(ADP-ribose) polymerase 1: neuron proliferation, hippocampal volume, hippocampal neurodegeneration in *APOE* epsilon3 carriers	[541, 609]
11q14.2	*PICALM*	Phosphatidylinositol binding clathrin assembly protein: membrane recycling, autophagy, endosomal vesicle cycling, trafficking of synaptic vesicle proteins	[7, 540, 541, 542, 546, 557, 561, 606, 607, 640]
19q13.2	*PLD3*	Enzyme phospholipase D: catalysis of membrane phospholipids, influence to processing of APP	[19, 540, 542, 557, 558, 568]
7q31.32	*POT1*	Protection of telomeres protein 1: hyper-phosphorylated tau, inflammatory response IL-6, ventricular dilation, cognitive decline	[541, 575]
2p14	*PPP3R1*	Protein phosphatase 3 regulatory subunit B alpha: calcineurin gene, implicated in cytokine release, TLR4 signalling, related to tauopathy	[567, 607, 641, 642]
8p21.2	*PTK2B*	Protein tyrosine kinase 2 beta: related to MAPK signalling, ionotropic receptors, neuron migration, synaptic function, LTP in hippocampal CA1 neurons, implicated in tauopathy	[542, 543, 557, 569, 605, 606, 632]
4q12	*REST*	RE1-silencing transcription factor: non-autonomous Wnt signalling, neuroprotection against OS and Abeta, autophagy, longevity	[541, 643]

Locus	Gene	Function	References
17q25.1	*RHBDF2*	Rhomboid 5 homolog 2: intramembrane serine protease, related to EGF receptor signalling, age-of-onset	[569]
19q13.33	*RPL13A*	60S ribosomal protein L13a: protein synthesis, close to *BAX* and *IRF3* loci, component of the IFNgamma-activated inhibitor of translation (GAIT) complex, repression of inflammatory genes	[569]
14q32.12	*SCL24A4*	Solute carrier family 24 member 4: Na$^+$/Ca^{++} exchanger, involved in neural development, hypertension	[542, 557, 605, 606]
14q32.13	*SERPINA3*	Alpha-1 antichymotrypsin: pro-inflammatory protein, related to amyloid plaques	[545]
17p13.1	*SERPINF1*	Pigment epithelium-derived factor: serpin F1 gene, neurotrophic functions, related to hypoxic stress, increases gamma-secretase activity, apoptotic signaling through p38 MAPK pathway	[569]
17p13.3	*SERPINF2*	Alpha 2-antiplasmin: serine protease inhibitor, involved in protein degradation, anti-inflammatory	[569]
2q36.2	*SLC19A3*	Solute carrier family 19 member A3: biotin-thiamine transporter, related to *HIF1A*, hypoxic stress	[577]
14q24.2	*SLC8A3*	Solute carrier family 8 member A3: Na$^+$/Ca^{++} exchanger, based in intracellular organelle membranes, related to oligodendrocyte maturation, myelination, involved in memory and sensory pathways	[577, 644]
15q22.31	*SNX1*	Sorting nexin 1: regulating the cell-surface expression of EGF receptor, lysosome formation, autophagy	[546, 645]
6q21	*SNX3*	Sorting nexin 3: involved in intracellular trafficking, regulating phagocytosis, interacting with cargo-selective retromer complex, involved in APP processing	[546, 645]
11q24.1	*SORL1*	Sortilin related receptor 1: neuronal LDL receptor, VPS10 receptor, endosomal vesicle cycling, vesicle trafficking, APP pathology	[1, 542, 546, 548-551, 605, 606, 646]
11p15.2	*SPON1*	Spondin 1: related to reelin signalling, involved in axon guidance, neural cell adhesion and neurite extension, formation of anatomical connectivity, involved in Abeta cleavage	[541, 647, 648]
5p15.33	*TERT*	Telomerase reverse transcriptase: serving as template for the telomere repeat, chromosome repair, age-of-onset	[203, 649, 650]
19q13.32	*TOMM40*	Translocase of outer mitochondrial membrane 40: outer mitochondrial membrane protein, protein import, mitochondrial dysfunction	[541, 555]
8q22.1	*TP53INP1*	Tumor protein p53 inducible nuclear protein 1: autophagy, caspase signalling	[628]
6p21.1	*TREM2*	Triggering receptor expressed on myeloid cells 2: microglial cytokine signalling, related to TYRO protein, autophagy, Abeta clearance, neuroinflammation, interacting with *IL4* and *TYROBP*	[540-542, 557, 560, 571, 606, 651]
15q22.31	*TRIP4*	Thyroid hormone receptor interactor 4: containing tetrameric nuclear activating signal co-integrator 1 (ASC-1) complex, associating with transcriptional coactivators, related to intrinsic histone acetyltransferase activity	[557, 650]
2p22.3	*TTC27*	Tetratricopeptide repeat domain 27: scaffolding protein-protein interactions, related to myelin formation, white-matter integrity	[652]
19q13.12	*TYROBP*	TYRO protein tyrosine kinase binding protein: transmembrane signalling polypeptide, tyrosine-based immunoreceptor, related to cerebral myelination, neuroinflammation, interacting with *CD33, MS4A4A, MS4A6A, TREM2, IL4*	[540, 542, 571, 651]

(Table 1) contd….

Locus	Gene	Function	References
8p12	*WRN*	Werner syndrome RecQ like helicase: DEAH family of DNA and RNA helicases, involved in DNA metabolism, transcription, replication, recombination, repair, age-of onset	[577]
7q22.1	*ZCWPW1*	Zinc finger CW-type and PWWP domain containing 1: early embryonic development, regulating chromatin methylation, regulating epigenetic modification	[8, 542, 557, 605, 606, 611]
6q14.3	*ZNF292*	Zinc finger protein 292: transcription factor, binding GH promoter, steroid receptor, posttranscriptional modifications, brain atrophy, neurodegeneration	[640]
19q13.42	*ZNF628*	Zinc finger protein 628: transcription regulator	[541, 653]
4q31.21-q31.22	*ZNF827*	Zinc finger protein 827: transcription regulator, related to tauopathy, haplotype block with *NANP* and *NINL*	[630]

Note: Tabulated are gene loci from GWAS, WES, case-control studies, and pathway analysis studies.

Four major prospective cohort studies include reports of ELS and LOAD:

A. Gothenburg Study with 9-year follow-up: RR 6.3 [64]

B. Cache County population study: OR 2.3 [65]

C. Israel Ischaemic Heart Disease study: ORs 2.15~4.22 [66]

D. Scottish Lothian 1932 birth cohort: threefold risk increase [67]

It is furthermore likely that the majority of ELS conditions are conducive to mid-life appearance of other psychopathological problems and/or increased mortality. Specifically, ELS programming predisposed towards later PTSD in a tenfold order [68] (see other contributions on this topic in the Special Section of this journal). And, further, PTSD increased LOAD risk considerably: PTSD had a 7-year cumulative incident dementia rate of 10.6% [46], as compared to 7% in age-matched controls. And, also, the degree of stress has a measurable impact: AD was increased in veterans who were POWs (HR 1.61) compared to those who suffered PTSD only (HR 1.52) [69]. Taken together all findings, available evidence suggests that ELS and/or later severe psychological life stresses can increase incidence risk for LOAD to a degree of major genetic risks.

1.3. Experimental Evidence for ELS Effects on LOAD

The notion of cognitive reserves as decisive for LOAD manifestation dates back to 1960s [70]. From an epidemiological perspective, Borenstein reviewed several lines of evidence pointing towards intrauterine, perinatal or postnatal factors influencing the early childhood cerebral growth spurt at 94% largely determinative for final brain size and, therefore, for such cognitive reserves [71]. The majority of studies indicated that head circumference (reflecting cerebral myelin content) as index of intracranial volume is predictive of MMSE status and later LOAD, but dependent on genetic risk status, vascular health and educational attainment [71, 72]. The summary of these findings let neuroepidemiologists conclude that those factors in neural differentiation, which are determinative for brain volume [33], are also critical for structural abnormalities in memory networks [73], and so could likely be conducive to late-life LOAD.

The prevalence of adversities leading to Early Life Stress (ELS) is estimated between 11-35% [74, 75]. Beyond dispute is the correlation of ELS with psychiatric morbidity in general: ELS is found in 44.6% of all childhood-onset disorders and with 25.9% to 32.0% in later-onset disorders [76]. The study of prenatal adverse effects is based on the well-known Barker hypothesis of "fetal programming" of diseases. There is furthermore accumulating evidence for a transgenerational transmission of fetal stress programming [77]. Besides adverse foetal programming, the most common ELS results from adverse parental care [78, 79], maternal separation [73, 80] or childhood physical or sexual abuse [81], neglect, or maltreatment [75]. Much of the human research is based on the Early Life Stress Questionnaire (ELSQ) [82], which assesses the occurrence of 17 Adverse Childhood Experiences (ACEs) (*e.g.* physical abuse, sexual abuse, neglect, family conflict, bullying). However, the core postnatal risk for toxic ELS is inconsistent caretaking [79], whereas, in contrast, attachment security resulting from contingently sensitive parenting is the "critical buffer" for the integrity of the HPA axis [78]. Attachment insecurity, the result of inconsistent caretaking, is associated with heightened sympathetic output, and elevated cortisol levels [83, 84].

Adverse Childhood Experiences (ACE) are well established in attenuating global physiological functioning [85], specifically cardiovascular health [33]. Recent studies have substantiated further epigenetic programming between methylation changes in stress and cardiometabolic candidate genes (Sections 3.1. and 3.2.) for lipid transport *ABCA1* (9q31.1), read-through insulin-like growth factor *INS-IGF2* (11p15.5), leptin *LEP* (7q32.1), cortisol converter *HSD11B2* (16q22.1), and glucocorticoid receptor *NR3C1* (5q31.3) due to early life adverse circumstances, independent of confounds [5]. Intrauterine cortisol excess has been shown to result in low birthweight, which, in turn, has been found a dementia risk [86]. Adverse early socioeconomic (SES) conditions were found to exert hypomethylation of the serotonin transporter (*SERT*/*SLC6A4* 17q11.2) resulting in amygdalar hyperreactivity in adolescence [87]. Specifically, glucocorticoid resistance, chronic latent inflammation, increased central corticotropin-releasing hormone (CRH) activity and de-

creased activity of the protective prosocial neuropeptide oxytocin [75] (an endocrine attachment-related counterweight for glucocorticoids) were found related to ELS. Available evidence also supports further interactions of ELS with nutrition, metabolic hormones, and epigenetic mechanisms [88, 89] therein. Animal studies found ELS CpG modification effects in the promoter of cortisol converter enzyme gene *HSD11B2*, and those greater in the hypothalamus than the cortex [90]. *HSD11B2* modification also showed interaction with sugar, fat and protein diets [91].

1.3.1. Long-term ELS Effects

Review of ELS in animal models reveals that its sequelae result in anxiety/depression behaviours, and memory deficits on the cognitive side [79, 92]. Alterations of gene expression patterns were observed in amygdala, hippocampus, hypothalamus, and frontal cortices. These resulted in amygdalar hyperreactivity, as in PTSD, as well as alterations of neurogenesis [79, 80, 93]. Additionally, long-term dynamic methylation may suppress synaptic plasticity in the hippocampus [94]. Specific long-term sequelae of ELS next to amygdalar hyperreactivity and psychopathology were seen in higher order, complex cognitive abilities, with heteromodal brain regions undergoing protracted postnatal development, which are particularly vulnerable to the deleterious effects of ELS [68] (see below).

1.3.2. Cortisol-related Consequences

Human ELS studies investigated fetal programming effects on hypothalamic-pituitary adrenocortical (HPA) axis-related genes in *post-partum* placenta as index of embryonic environment. In this approach, adversity effects have been documented for the DNA methylation of the cortisol converter enzyme 11-beta-dehydrogenase 2 (*HSD11B2* 16q22.1) (Section 3.1.) locus [95, 96]. Maternal stress levels indicated by elevated plasma cortisol levels [97] predicted increased activation of the regulatory promoter region exon 1F of the glucocorticoid receptor (1F *NR3C1* 5q31.3) (Section 3.1.) [98], and decreased brain derived neurotrophic factor exon IV promoter (*BDNF* IV 11p14.1) methylation. A further consequence of fetal *HSD11B2* modification has been found in programming towards obesity, MetS and T2DM, specifically insulin resistance mediated by gluconeogenesis controller phosphoenolpyruvate carboxykinase (PEPCK) (*PCK1* 20q13.31) (Section 3.2.) mRNA and activity [99]. The short-term ELS model assumes an impact on stress neurobiology, the emotion appraisal system, and emotion regulation [78], producing a specific vulnerability in the early postnatal years. Short-term effects of ELS on HPA functioning consisted in a lack of or in blunted cortisol secretion in rodent pups [74, 100, 101]. Long-term consequences in human infants to prenatal glucocorticoid exposure consisted in HPA-axis alterations with prolonged cortisol secretion [102]. In rats, chronic ELS resulted in specific amygdalar pro-convulsive cortisol releasing hormone (in humans: *CRH1* 8q13.1) (Section 3.1) secretion and infantile spasms [103]. In mice, HPA-alterations due to maternal separations result in diminished capabilities for coping of stress in adulthood [101]. ELS associated with later CRH hypersecretion was observed leading to six times greater ACTH in response to external stressors [81].

1.3.3. Brain Structural Growth and LOAD

Recent review on early-life predictors identified factors related to brain growth [33, 104]: early life adversity, early body growth and differentiation, socioeconomic status, to which adult risk factors accumulate to pacing abnormal neurodevelopmental trajectories. Low birthweight and small head circumference, indicators of poor myelination, were found related to later LOAD [4, 33]. Experience-expectant and experience-dependent mechanisms determine early brain maturation with simultaneous neuropil growth spurt, neuron differentiation, migration, synaptic pruning, and selective stabilisation of circuitries [105]. Myelination patterns are genetically triggered cycles following exercise-induced utilisation of effective connectivity [106, 107] in the context of experience-dependent development [108]. In this general frame, studies on structural brain growth in 2-25 month-old infants suggested differences in white matter myelin water fraction and grey-matter volume between *APOE* epsilon4 carriers and non-carriers [109]. This may suggest that differences in lipoprotein metabolism could influence myelin protein expression and storage of lipid content, and thus increase vulnerability for late-life WM lesions by decreased myelin stability.

Effects on cerebral structures established are amygdalar enlargement, hippocampal volume reduction and of adjacent medial temporal cortex, decreases in volume of orbital-frontal cortex [75]. Besides susceptibility for hippocampal atrophy, ELS is characterised by enlargement of the amygdalae, with blunted reactivity, and clinically, with depression, anxiety, and alexithymia [110]. Also, blunting of reward processing in terms of abnormal ventral striatum [111], and differences in corticostriatal circuitry, have been described with ELS, with lower activity after exposure to early social deprivation [112]. Genome-wide association of ELS through maternal care [113] showed highest correlations with clusters of protocadherins alpha, beta, and gamma involved in synaptogenesis [114], and related to gamma-secretase [115], by DNA methylation, histone acetylation, and transcriptional changes in humans and animals [114]. Accelerated age-related cognitive decline and neurodegeneration can thus be primed by ELS [116]. According to threshold theory [117, 118], LOAD onset depends (a) on previous white matter lesions acquired during life span, and (b) whether a basic reserve of normal functioning can be maintained. LOAD entry, according to this theory, then occurs once plaque deposition finally hampers this memory functioning reserve, as classic findings of Roth and colleagues [70] suggest.

Evidence suggests that, whilst some early effects are reversible in enriched environments, specifically structural hippocampal deficits are likely to persist [119], presumably maintained by profound alterations in the hippocampal neurogenesis structure dentate gyrus [100]. Hippocampal neurogenesis itself has been shown dependent on maternal separation/and or care [120, 121]. Experimental manipulations of high *vs.* low stress prone rodent pups suggest that ELS experiences have lasting effects also for adult neurogenesis [93, 122]. This would provide an explanation, why adult neurogenesis could not compensate for late-life neurodegenerative processes in ELS individuals.

1.3.4. Neurotrophic and Growth Factors

Next to glucocorticoid action, neurotrophin signalling pathways critical for neuronal differentiation, dendrite outgrowth, axon guidance, and synaptic integrity [123], are subject to ELS. Glucocorticoid and neurotrophin pathways converge specifically in the hippocampus, harming *BDNF* and its receptor, tropomyosin-related kinase receptor B (TrkB) (*NTRK2* 9q21.33) [124] expression. The majority of ELS paradigms (*e.g.* maternal separation, restraint, cold shock) report decreases in BDNF levels, and concomitant decreases in *p*-GSK-3beta, *p*-ERK1, *p*-ERK2 in the hippocampus, and overexpression of stress response protein dual specificity phosphatase 1 (*DUSP1* 5q35.1) [123]. The MAPK pathway is considered the linking mechanism between glucocorticoid and BDNF systems, where over-activation of *DUSP1* is inhibitive of neural differentiation and suppressing axonal outgrowth [123]. But there is also a direct effect of BDNF signalling on the GRs, where BDNF *via* its receptor TrkB enhanced the transcriptional activity of a synthetic GR reporter [124]. BDNF signalling thus modulates the effect of GRs on gene expression in primary neurons by modulating *NC3R1* posttranslational modifications through phosphorylation [124]. Other ELS studies showed a down-regulation of *Bdnf* expression, associated with hypermethylation of CpG sites in the gene regulatory region, whereby epigenetic changes were found within the CREB-binding region (CpG1B) [125] There has also a relation of ELS been observed, in terms of restraint stress, with an enhancement of *BDNF* promoter activity in hippocampal *cornu ammonis* subfield CA3, based on transcription co-activator CREBBP (*CREBBP* 16q13.3) signalling triggered through ERK1/2, dependent on glucocorticoid receptor activation [126]. BDNF depletion is therefore considered a biomarker of LOAD, since progression from MCI towards LOAD is accompanied with a significant decline in peripheral baseline BDNF levels [127], which then persists.

1.3.5. ELS Animal Models for LOAD

Of the three transgenic strains of murine models typically used in Alzheimer research (Tg2576, APPswe/PS1dE9, and 3xTg-AD) [7, 128], the preferred animal model for the isolation stress ELS paradigm is the Tg2576 mouse model of AD. This ELS paradigm resulted in an 59% increase of soluble Abeta$_{40}$ and Abeta$_{42}$ [7], accompanied by hippocampal and neocortical neuritic plaques. Moreover, this stress exposure paradigm caused a rise in basal plasma corticosterone levels, paralleled with an increased expression of the *Gr* and *Crh* [7]. Later adaptations were, however, reported resulting in reduced gluco- and mineralcorticoid receptor expression [129]. Animal evidence suggests that lacking maternal caregiving behaviours increase *Gr* expression in the offspring [114] *via* increased hippocampal serotonergic tone accompanied by increased histone acetylase transferase activity, histone acetylation and DNA demethylation mediated by the early growth response protein EGR-1/NGFI-A (*EGR1* 5q31.2) [130]. In a murine model of ELS by *Crh* (*CRH1* 8q13.1) overexpression, it was observed that MCI-analogous memory problems develop already in midlife [131]: These were caused by hippocampal tau phosphorylation based on activation of the type-1 corticotropin-releasing factor receptor (*CRHR1* 17q21.31) (Section 3.1.) *via* increased GSK-3beta activation. Furthermore, the mitogen-activated protein kinases (MAPKs) (Section 2.1.) p38 MAPK, CDK5 activator protein, p35, and ERK1/2 kinases, and also JNK [154], were robustly upregulated.

ELS murine studies pertaining to LOAD were pioneered by work of Nasser Zawia and co-workers, who found in the context of early lead exposure that early toxic impact bears consequences in structural growth in cortex, cerebellum, and hippocampus [132], mediated by EGR-1/NGFI-A and NGF altering synapsin gene expression. With respect to neonatal environmental impact, it was observed that toxic exposure transiently stimulated *APP* overexpression [133], which later returned in aged animals after a latency period [134]. These early insights were seminal to trigger the assumption of gene expression and regulation abnormalities in LOAD [135]. It was found that oxidative damage introduced by environmental influences during brain development inhibited DNA methyltransferases, thus altering methylation profiles in promoters of LOAD core pathology genes [136, 137]. Stress generally induces tau hyper-phosphorylation [138], for which a structural time course has been observed in the dentate gyrus neurons, wandering from somata to dendrites. In this context, it had been suggested that repeated stresses induce a dysregulation [139] of protein tau through phosphorylation of protein kinase GSK-3beta (Section 2.1) and of calmodulin kinase (CaMKII) (Section 2.1) (*CAMK2A* 5q32) during memory encoding in hippocampus and amygdala. It is furthermore suggested that, in later life, oxidative stresses in form of protein oxidation and lipid peroxidation then accelerate Abeta deposition, tau phosphorylation, and gliosis [140], leading to insults that cause memory dysfunctions. In addition, metabolic stresses contributed to vascular inflammation, astrocyte reactivity, and cerebral glucose metabolism in APP/PS1 mice [141].

Maternal stress proneness can be transmitted by methylome through gametic programming to the offspring [142], thus providing a stress diathesis phenotype. Furthermore, even mild stresses are conducive to programming of a LOAD phenotype [143]. The type of memory deficits induced by ELS was particularly found in recognition memory [73], as mediated by prefrontal, hippocampal and perirhinal oscillatory electrophysiological coupling. Differential results for Abeta deposition in the hippocampus [144] and amygdalar and MFC dendritic structure, but not for other cortices, were seen for ELS *vs.* caringly handled animals. ELS animals developed LOAD pathology earlier and fewer life expectancies. In contrast, increased levels of maternal care during the early life period delayed Abeta deposition and cognitive decline in the APPswe LOAD mouse model, involving the hippocampus, but not the amygdala [145]. Maternal separation studies yielded evidence that early and later stresses mainly alter cognitive function in memory tasks, with underlying impairment of neurogenesis in the hippocampal dentate gyrus [120]. This was accompanied by early rises, but long-term depletions, of Brain-Derived Neurotrophic Factor (BDNF), TrkB, Insulin-like Growth Factor-1 (IGF-1), and type 1 IGF receptor (IGF-1R) ligands and receptors [146]. Decreased *Bdnf* expression was found related to both increased histone acetylation and methylation of H3K9 in cortical neurons [147], as compared to wild-type animal neurons, where epigenomic modifications tend to decrease over age.

Lesion studies in maternal separation rats implied greater impairment in the cholinergic system [148], along with alterations of the HPA in increased CRF mRNA expression and a reduction of GR densities. Decreases in NGF and increases in NGF-p75NTR expression were correlated with memory impairments and learning deficits. The impairments in HPA feedback signalling involved both noradrenergic and glucocorticoids [80, 149], particularly mediated by hypothalamic PVN, and resulting in HPA hypersensitivity. HPA axis is activated in 3xTG-AD mice from early life [150], with exaggerated mRNA levels of *Mr* and *Gr* in the hippocampus, *Gr* and *Crh* in the PVN, *Gr* and *Crh* in the central nucleus of the amygdala, and *Crh* in the bed nucleus of the stria terminalis. This suggests that LOAD neuropathology is intrinsically connected with central HPA activation and neuroendocrine dysregulation. Related to HPA bias towards exaggerated reactivity reflected in glucocorticoid levels, c-fos expression was found enhanced [151]. This neuronal activity marker interacts with c-jun/AP-1 transcription markers (*FOS* 14q24.3), associated with the JNK signalling pathway [152]. The HPA bias and glucocorticoid levels interacted with the brain insulin system, inducing phosphorylation of insulin receptors, and so modifying downstream signalling of *p*-Akt, *p*-GSK-3beta, p-tau, and *p*-ERK1 [153], resulting in a shift towards amyloidogenic processing. The activation of JNK signalling pathway, upregulating *BACE1* expression with increased Abeta levels, was shown directly related to glucocorticoid increases, and mediated by hypomethylation of the CpG7 site of the BACE promoter [154].

1.3.6. ELS and Tau Pathophysiology

There is a clear direct link of stress response to the LOAD pathophysiological mechanism of tau phosphorylation. Murine models lacking one or both corticoid releasing hormone receptors *CRHR1* (17q21.31) and *CRHR2* (7p14.3) (Section 3.1.) receptors enabled the demonstration that tau hyper-phosphorylation specifically in the hippocampus, is dependent on CRHR1 and CRHR2 signalling [155]. CRH expression in the paraventricular nucleus [77] of the hypothalamus (PVN) is attenuated by ELS [156], mainly by cAMP response element (CRE), transcription factor AP-1, and Glucocorticoid Response Element (GRE) (Section 3.1.). In addition, methyl CpG-binding protein 2 (MeCP2) [96] and a functional restrictive silencing sequence of the element-1/neuron restrictive silencing element (RE-1/NRSE) (*REST* 4q12) connect to a sequence on the *CRH1* locus, which regulates CRH expression [156]. Other stress hormones than glucocorticoids have also been linked to inducing tau hyper-phosphorylation [86] (Sections 1.4. and 3.1.).

ELS related gene methylation changes have been observed in the hippocampus, but not in other cerebral regions. Szyf has hypothesised that three mechanisms are in specific pertaining to transport of epigenomic changes responsible for life-long ELS effects in animals in induced by ELS-neuronal activation: (a) Neuronal activity leads the calmodulin kinase II (CamKII, above) into changing the affinity of MeCP2 by phosphorylation, and thus induces demethylation of *BDNF* promoter [157]. (b) Furthermore, the methyl-CpG binding protein 2 MeCP2 (*MECP2* Xq28) has been found regulating the expression of arginine vasopressin (AVP) neurons in the hypothalamic PVN [158] following

ELS. This process has been identified being responsible for the loss of noradrenergic neurons in the locus caeruleus (Section 3.1.) [159]. (c) The interaction of the *AVP* (20p13) promoter with MeCP2 and CamKII induces hypomethylation of the *AVP* gene [157]. EGR-1/NGFI-A is likely to induce histone acetylation triggered by CREB binding protein CREBBP (*CREBBP* 16p13.3), and the methyl-CpG domain binding protein 2 MBD2 (*MBD2* 18q21.2) facilitates demethylation of *NC3R1* exon 1₇ promoter [157] (see below). Other loci such as the human GABA_A receptor (*GABRA1* 5q34) promoter within the frontopolar cortex and the tropomyosin-related kinase B receptor *TRKB* (for BDNF) have, however, not yet been investigated for ELS effects [157]. The hypophysiotropic stress neuropeptide pituitary adenylatecyclase-activating polypeptide (*ADCYAP1* 18p11.32) and its receptor PAC1 [160, 114] playing a role in PTSD was found to exert neuroprotective effects in murine AD models by supporting BDNF signalling [161].

1.3.7. ELS and Methylation Findings

A meta-analysis of human ELS studies confirmed methylation of five CpG sites preceding promoter region exon 1F *NR3C1* coding for GR in children, here resulting from maternal chronic psychosocial stress as experienced during pregnancy [162]. Animal studies have demonstrated that there are causal relations amongst epigenomic states based on DNA methylation, early growth response protein EGR-1 (an ERK transcription factor) binding, GR expression and hypothalamic-pituitary-adrenal (HPA) responses to stress in the offspring [163]. Environmental cues become effective on methylation by means of transcription factors [164], and for maternal care this is early growth response protein EGR-1/ Nerve Growth Factor-Inducible Protein A (NGFI-A) [163, 165]. *EGR1* initiates, by means of serotoninergic activation, and as a ligand to the promoter on exon 1F for the GR locus *NC3R,* the transcription of the latter [74, 165]. Involved in this mechanism are transcription factors TFIID complex (*TBP* 6q27), and coactivator CREBBP (see above) entailing histone acetyltransferase activity [74, 157]. ELS is generally mediated by the methyltransferases: Activity of DNA methyltransferase 1 (*DNMT1* 19q13.2), usually responsible for methylation stability, results in DNA demethylation in postmitotic neurons [113]. *De novo* methyltransferases DNMT3A (2p23.2) and DNMT3B (20q11.21) induce methylation, also in mature neurons [157]. DNMT3A was found responsible for maintenance of cognitive abilities during ageing [166]. Activity of these methyltransferases and of the MBD2 demethylase [167] was observed in LOAD animal models in methylation of the *PSEN1* locus.

1.3.8. ELS and Adult Neurogenesis

It is currently concluded [168] that environmental influences in early neurogenesis are dynamic, and change over time, and also that their relations with adult neurogenesis are still unclear. ELS in terms of maternal neglect has been found to increase the methylation of EGR-1-binding sequences, causing lower expression of EGR-1 target genes later in adult life on CpGs overlapping with the *EGR1*(*NGFI-A*)/Zif268/Krox-24-binding sequence that is positioned close to the putative binding sites of neurogenins (*NEUROG1* 5q23-31, *NEUROG2* 4q25, *NEUROG3* 10q21.3) [169, 39], the transcription factors involved in

specifying neuronal differentiation. Current views on ageing assume methylation relaxation effects due to losses in chromatin modifiers resulting in increasing genome instability [170]. In the brain, however, this effect is assumed to be dependent of neuronal activity, mediated by Wnt signal transduction. Wnt signalling globally mediates external environmental cues, by means of signal transduction in the GSK-3beta pathway, and is crucial for both embryonal and adult neurogenesis stimulated by astrocytes (with Wnt3, Wnt10b, and Wnt2), involving GSK-3beta and beta-catenin participating in the Wnt signalling pathway. Rats exposed to prenatal stress had accelerated, age-related decline in spatial and working memory [171], however, no primate data are available on this subject. Furthermore, both human and animal studies suggest in summary, that early stress can also improve cognitive functioning. However, if there is a deprivation of early maternal care, effects show impaired juvenile neurogenesis and increased adult apoptosis [172].

Epigenetic changes throughout ageing has been studied in a variety of species [173], indicating either globally decreasing or locally increasing methylation patterns. However, only two studies have yet focused on cerebral structures, and therefore, no universally reliable information is present to date. ELS may have direct effects on ageing as indexed by shorter telomere length in adulthood in leukocytes thus predisposing to generally poorer health outcome [174, 175]. Telomere length shortening has been observed in CVD, T2DM, MetS [176], and all dementias [175], in this context.

1.4. Core Processes in LOAD Pathophysiology

Aetiological mechanisms in LOAD remain unexplained in exact detail, as most experts agree, but the basic neuropathological features in the AD brain currently accepted are (a) widespread axosomatic and neuritic extracellular amyloid plaques leading to dystrophic neurites, (b) intracellular neurofibrillary tangles (NFTs) consisting of previously soluble tau proteins, (c) reduced cytochrome c oxidase (COX) activity in mitochondria, (d) reactive microgliosis, (e) impairment in autophagy related to neurons, and (f) oxidative stress combined with abnormal neuroendocrine signalling (*e.g.* acetylcholine, BDNF). These hallmarks eventually terminate in synapse atrophy, neuron loss, and widening of pre-existing white matter disintegrities.

1.4.1. APP Cleavage and Abeta Deposition

In contrast to presenile, familial AD, there is typically no genotypic APP pathology present in LOAD [177], and also no *PSEN* mutations (Section 1.1.). Normally, mature APP (whose exact physiological function remains unknown) becomes cleaved successively by alpha- or beta-, and then gamma-secretases in the late protein secretory pathway and the plasma membrane. The still immature APP is stored in the early secretory pathway such as Endoplasmic Reticulum (ER) or Golgi apparatus, where for imAPP no cleavages take place [178]. Whereas alpha-secretase cleavage does not result in amyloid pathogenic for LOAD, there are two relevant aberrant cleavage steps: (a) beta-site amyloid precursor protein cleaving enzyme 1 (*BACE1* 11q23.3) [179, 180], (b) gamma secretase (triggered by the gamma secretase activating protein pigeon homolog, *PION* 7q11.23) [8], and (c)

through mediation of delta-opioid receptor [10]: The extracellular APP-cleavage through BACE1 produces the soluble cell membrane-bound fragment C99. Gamma-secretase cuts the transmembrane domain of C99, thus releasing intracellular Abeta. Dependently on three possible cleavage sites, where the enzyme gamma secretase acts on the cleavage products of beta-secretase, are the products either $Abeta_{38}$ through $Abeta_{43}$ [181] isoforms, dependent on additional 15 known mutations [35, 180]. The insoluble isoform $Abeta_{42}$ constitutes the extracellular precipitate on neuron somata and axons. Extracellular $Abeta_{42}$ neuritic plaque deposition, then, occurs only at late neuropathological Braak amyloid-stage C, once the intracellular Abeta has caused neuron leakage and atrophy [182]. Soluble $Abeta_{40}$, in contrast, will deposit earlier in arterioles resulting into vascular angiopathy [183]. Oligomeric $Abeta_{40-42}$ is likely to spread from one neuron to another in similarity to prion diseases [184], which is promoted by impaired autophagy and clearance. Gamma-secretase is specifically activated by pro-inflammatory interferon-gamma, IL-1beta, or TNFalpha, and cytokine-induced gamma-secretase activity was found to be blocked by a JNK (Section 2.4.) inhibitor [185]. Animal evidence suggests that childhood physical exercise normalizes APP physiology, and in reverse, that early sedentary lifestyle may foster early Abeta deposition [186]. Recent prospective PET-imaging in MCI patients has recently supported the assumption that it is the cerebral Abeta deposit in basal and mesial temporal, orbitofrontal, and anterior and posterior cingulate cortices interacting then with total CSF *p*-tau [187].

1.4.2. Abeta Cascade

LOAD is generally assumed to be the result of a cascading process starting with stronger Abeta deposition (which also occurs in "normal" ageing, but to lesser amounts), with the accession of further pathogenic elements such as tauopathy, mitochondrial dysfunction, and microgliosis (Section 3.3.). Abeta is matured in the Golgi, ER and endosomal/lysosomal system [188], and in the secretory pathway, were beta- and gamma-secretases are to originate neurotoxic $Abeta_{42}$ and $Abeta_{40}$ monomers (the amyloidogenic pathway), which subsequently polymerise into oligomers, and finally aggregate into amyloid plaque aggregates. However, the quantity of $Abeta_{42}$ is not related to cognitive decline [35] *per se*, as its aggregation also occurs in healthy ageing, and in 20-40% *post-mortem* dissected cases to a degree also seen in AD, but without respective pathognomonic memory impairment present *ante-mortem*.

The prevailing theory, that only neurons carry the pathogenic agents $Abeta_{42}$ and NFT, had to be extended by findings of involvement of astrocytes and oligodendrocytes [189, 190]. Recent studies have shown that $Abeta_{42}$ oligomers are produced by cooperative activities of both neurons and its associated astrocytes [190]. In this context, are adjacent myelin-producing oligodendrocytes particularly vulnerable to h-tau_{181} and $Abeta_{42}$ [29]. Activation of alerted microglia (Section 3.3.) results in production and release of pro-inflammatory cytokines, including IL-1beta, IL-6, TNFalpha, and IFNgamma [191]. In turn, these cytokines stimulate the nearby astrocyte-neuron pairs to produce further amounts of $Abeta_{42}$ oligomers, thus activating even more $Abeta_{42}$ production and dispersal [190]. By means of exocytosis of oli-

gomeric Abeta$_{42}$ (Section 3.3.), associated astrocytes and oligodendrocytes can be infected, and in turn become themselves producer cells of Abeta and tau oligomers [190].

Unclear also remains the actual Abeta$_{42}$ residue induction in LOAD, but it is believed to be triggered from Reactive Oxidative Species (ROS) (see below). OS may result from several cellular processes such as ageing, hypoxia (mitochondrial dysfunction, HIF-1alpha), hyperglycaemia (advanced glycation endproducts, AGEs; Section 3.2.), NFkappaB), and hypercholesterolemia (oxysterols, sterol regulatory elements, *SREBPs* activation) [192]. Accordingly, it is the incidence of known risk factors for LOAD (Section 1.1.), which are ultimately inductive of gamma-secretase and *BACE1* activation through JNK/DUSP signalling. Evidence of lipid peroxidation and protein peroxidation appears very early in LOAD pathogenesis (corresponding to Braak tau-stages I and II) [192]. It has been shown recently, that cellular cholesterol transduction is associated with APP mis-cleavage by gamma-secretase, so increasing Abeta$_{42}$ deposition [193]. In specific, cholesterol sequestration is related to an impairment of lyosomal autophagy, with Abeta accumulation leading to oxidative stress and vulnerability for H_2O_2 toxicity. Abeta$_{42}$ reduces neuron-specific endophilin-B1 (*SH3GLB1* 1q22), a protein involved in beclin-2 mediated apoptosis, autophagy and mitochondrial function, which in turn enhances Abeta$_{42}$ accumulation and neuronal vulnerability to stress [194].

1.4.3. Tauopathy in LOAD

Protein tau is a physiological stabiliser of microtubuli in neuron cells, and hence present very early in ontogeny. Besides its role in cytoskeleton formation and functioning, a second neurophysiological role of tau has been detected in neuron nuclei [195]: In healthy neurons, tau has a function in posttranslational histone modification (associated with heterochromatin proteins H3K9me and HP1alpha), resulting in dense chromatin packaging, which is lost under stress conditions in LOAD brains, resulting in disordered heterochromatin organisation [195]. Tau is therefore also itself directly involved in epigenetic modification, although a tau gene (*MAPT* 17q21.31) alternate splicing variant is present in, but not specific to LOAD: The haplotype H1-specific expression of *MAPT* exon 10 [196] is active also in other tauopathies, and caused no signal in LOAD GWAS [197]; however, supported has been an epigenetic abnormal hypermethylation of *MAPT* in *post-mortem* LOAD neurons [198] (Section 4.3.). (Table **2**).

Tau kinases are activated already through fetal development and been detected in AD brains: cyclin-dependent kinases (*CDK5* 7q36.1), MAP kinases (MAPK) and GSK-3 proteins phosphorylate protein tau [199-201]. Tau, once hyper-phosphorylated, is no longer capable of docking to microtubuli, but accumulating in neurons, whilst forming paired helicoidal filaments. These paired helicoidal filaments formed as consequence of the hyper-phosphorylation of immunoreactive microtubule-associated tau destabilise neuronal microtubules [188], instead. *H*-tau is truncated in its N-terminal and impairs axonal transport of organelles, specifically mitochondria, to synaptic terminals forth and back. The N-terminal fragment of tau induces abnormal mitochondrial dynamics, defective mitochondrial function

with increased ROS, decreased cytochrome c oxidase (COX), and decreased ATP production, conducive to synapse deprivation and loss [202]. Hence is it the *h*-tau contributing through synaptic suffocation to neuron dysfunction and apoptosis [203].

No unequivocal relation between Abeta cascade and tauopathy has yet been registered in biomedical research. CDK5, however, is suspected to be the key link between Abeta and tau pathologies [204], possibly due to a correlation still unknown. Although It is still unexplained how tau pathology could exactly relate to amyloid pathology, however, as has been suggested, tau aggregation is caused by post-translational modifications [35, 198]. However, there is also a clinical phenotype with NFT formation only (Tangle-Only Dementia (TOD) and a Primary Age-Related Tauopathy (PART)) [205]. Recently, the neuropathologist Braak detected primary diffuse tauopathy early in childhood brains from four years onwards into early adolescence, with histologically confirmed *post-mortem* starting points in locus caeruleus, further subcortical relays of the noradrenergic system, and the transentorhinal region [206]. This discovery may suggest a close relation of tauopathy with the stress-related catecholaminergic system (Section 3.1.), and can support an early developmental origin of LOAD.

1.4.4. Neuropathological Braak Staging, LOAD Latency and Clinical Manifestation

Early in the disease course, diffuse Abeta plaques are seen in the frontal and parietal lobes, including the praecuneus [207], followed by hippocampi, basal ganglia, brainstem, and cerebellum. The synergistic interaction in early Braak stage regions was then related to subsequent overall 24-month metabolic decline. A localisation of phospo-MEK1 preceding ERK (for MAPKs see Section 2.) phosphorylation in neuronal nuclei was detected in Braak tau-stages I-II, indicating abnormal nuclear trafficking of this normally cytosolic kinase [208]. This Braak stage I-II is consistent with an onset of hyper-phosphorlyation of protein tau, however, not yet conglomerated as tangles [209]. The extracellular Abeta$_{42}$ neuritic plaque deposition occurs only at late Braak amyloid-stage C once the intracellular Abeta$_{40}$ has caused neuron leakage and atrophy [182]. The Braak stage III corresponds to MCI, termed the "limbic stage" [209] of cerebral neuropathy. In the Braak stages V/VI for tau NFTs and Braak stage C for senile Abeta plaques, there is the extracellular Abeta deposition as neuritic plaques [182], and the intracellular NFT [209] formation. In the clinical manifestation of LOAD, the main risk genes that were found to be associated with the MCI-AD transition (interacting with Abeta deposition) are amylin (*IAPP* 12p12.1) SNP rs73069071 and the neighbouring hepatic solute carrier organic anion transporter family member 1A2 SLCO1A2 (*SLCO1A2* 12p12.1) [210], the latter responsible for the uptake of bile acids, bromosulphophthalein, and steroidal compounds. Amylin is a calcitonin family peptide hormone synthesised in pancreatic beta cells together with insulin. It is the main component of amyloid deposition caused by T2DM in Langerhans islets. This may suggest that metabolic processes pertaining to T2DM could also play a role in LOAD manifestation (Section 3.2.).

Table 2.   Epigenetic modification findings in risk genes for late-onset Alzheimer disease.

Locus	Gene	Findings	References
12p13.31	*A2M*	negative	-
9q31.3	*ABCA1*	negative	-
19p13.3	*ABCA7*	ABCA7 methylation was associated with paired helicoidal filament tau tangle density. ABCA7 methylation was associated with density of neuritic plaques. Index SNP (rs3764650) was associated with neuritic plaque burden, no association with the level of methylation at cg02308560	[26, 569, 787]
21q22.3	*ABCG1*	negative for LOAD, confirmed for CHD	-
15q23.3	*ADAM10*	negative	-
18p11.32	*ADCYAP1*	negative	-
10q25.2	*ADRA2A*	negative	-
10q25.3	*ADRB1*	negative	-
5q31-32	*ADRB2*	negative	-
8p11.23	*ADRB3*	negative	-
6p21.32	*AGER*	negative	-
10q11.21	*ALOX5*	Consistent reduction in DNA methylation at 5-LOX gene promoter in LOAD	[788]
8p11.21	*ANK1*	Methylation level at cg11823178 associated with LOAD neuropathology	[569]
4p14-p13	*APBB2*	negative	-
19q13.32	*APOE*	*APOE* CGI is differentially demethylated in LOAD *post-mortem* probes	[789]
21q21.2	*APP*	Aberrant CpG methylation in non *APOE* epsilon4 carriers	[198]
8q24.3	*ARC*	negative	-
12q23.2	*ASCL1/MASH1*	negative	-
9q33.1	*ASTN2*	negative	-
22q13.1	*ATF4*	negative	-
17q25.1	*ATP5H/KCTD2*	negative	-
20p13	*AVP*	negative	-
11q23.3	*BACE1*	negative *in vivo*	-
19q13.33	*BAX*	negative	-
3q26.1	*BCHE*	negative	-
11p14.1	*BDNF*	Hypo- and hypermethylation of CpG islands *BDNF* promoter region. Methylation in four CpG sites in the promoter of the *BDNF* were elevated, and correlated negatively with *APOE*, glucose level, positively with *CRP* in peripheral blood. Significantly increased hippocampal HDAC2 relates to promoter region of *BDNF* exon VI; contributing to the histone H3 deacetylation and BDNF suppression in hippocampal CA1. Aberrations in histone acetylation related to ApoE epsilon4 increase nuclear translocation of HDACs in neurons, thereby reducing *BDNF* exon IV expression, mediated by *LRP1*, specifically in hippocampus	[790-793]
17q21.31	*BECN1*	negative	-
2q14.3	*BIN1*	Two CpG sites showed associations with LOAD, three with Abeta, and five with NFTs. Association of cg22883290 in the *BIN1* with LOAD	[26, 569]
19q13.32	*BLOC1S3*	negative	-

Locus	Gene	Findings	References
5q32	CAMK2A	negative	-
22q13.1	CARD10	negative	-
20q13.31	CASS4	negative	-
17q12	CCL2	negative	-
17q12	CCL3	negative	-
17q4	CCL4	negative	-
6p12.3	CD2AP	negative	-
19q13.41	CD33	negative	-
10q23.1	CDH23	Altered methylation at cg23968456, but unclear if not confounded by enhanced astrocyte activation indicated by GFAD expression	[569]
10q21.2	CDK1	negative	-
7q36.1	CDK5	negative	-
11p11.2	CELF1	Methylation change not directly *in loco*	[794]
16q13	CETP	negative	-
1q31.1	CFHR1	negative	-
8p21.1	CLU	negative	-
17q21.2	CNP	Reduced cortical and allocortical expression of *CNP* RNA not attributable to DNA methylation at *CNP* promoter	[672]
22q11.2	COMT	negative	-
1q32.2	CR1	negative	-
2q33.3	CREB1	Hypermethylation of *DUSP22* inhibiting PKA and CREB1 activity, thereby determining tau phosphorylation status	[795]
9p13.3	CREB3	negative	-
11p11.2	CREB3L1	negative	-
7q33	CREB3L2	negative	-
19p13.3	CREB3L3	negative	-
1q21.2	CREB3L4	negative	-
7p15.1-p14.3	CREB5	negative	-
16p13.3	CREBBP	Hyper- and hypomethylated CpG islands in promoter regions for *CREBBP*	[793]
8q13.1	CRH1	negative	-
5q13.3	CRHBP	negative	-
17q21.31	CRHR1	negative	-
7p14.3	CRHR2	negative	-
1q23.2	CRP	Methylation in four CpG sites in the promoter of the *BDNF* were elevated, and correlated negatively with *APOE*, glucose level, positively with *CRP* in peripheral blood	[790]
18q21.1	CTIF	negative	-
16q21	CX3CL1	negative	-
3p22.2	CX3CR1	negative	-
15q21.1	CYP19A1	negative	-

(Table 2) contd….

Locus	Gene	Findings	References
14q32.2	*CYP46A1*	negative	-
9q34.2	*DBH*	negative	-
16p12.1	*DCTN5*	negative	-
1q23.3	*DDR2*	negative	-
1p23.3	*DHCR24*	Study identified GC-rich element in the *DHCR24* promoter, which was shown to determine DHCR24 expression levels, also includingnacetylation of histones H3 and H4 to the enhancer region	[796]
21q22.3	*DIP2A*	Altered methylation at cg00621289 related to LOAD, interrelation with *SORL1* and *PLD3*	[569]
17p13.1	*DLG4*	negative	-
19q13.2	*DNMT1*	General DNA hypermethylation in LOAD by higher DNMT1 expression. Interindividual variation in *DNMT1* modification	[597, 788]
2p23.2	*DNMT3A*	Tested but no LOAD-specific results reported	[797]
20q11.21	*DNMT3B*	Tested but no LOAD-specific results reported	[797]
18q12.1	*DSG2*	negative	-
5q35.1	*DUSP1*	negative	-
21q22.13	*DYRK1A*	negative	-
11p13	*EAAT2/SLC1A2*	negative	-
1p36.12	*ECE-1b promoter*	negative	-
6p24.1	*EDN1*	negative	-
4q31.22-23	*EDNRA*	negative	-
13q22.3	*EDNRB*	negative	-
5q31.2	*EGR1*	H4 acetylation at *EGR1* and *FOS* promoters regulated by APP	[798]
2p22.2	*EIF2AK2*	negative	-
15q15.1	*EIF2AK4*	negative	-
14q23.3	*EIF2S1*	negative	-
18q12.2-q21.1	*EPG5*	negative	-
7q34-35	*EPHA1*	negative	-
2q33.3	*FASTKD2*	negative	-
14q22.1	*FERMT2*	negative	-
12p13.33	*FKBP4*	negative	-
6p21.31	*FKBP5*	FKBP51 levels increased relative to age and LOAD, corresponding with demethylation of the regulatory regions in the *FKBP5* gene. Higher FKBP51 levels were associated with LOAD progression. Age-associated increases in FKBP51 levels show interaction with Hsp90 promoting neurotoxic NFT accumulation	[686]
14q24.3	*FOS*	H4 acetylation at *EGR1* and *FOS* promoters	[798]
11q14.1	*GAB2*	negative	-
6p21.3	*GABBR1*	negative	-
9q22.33	*GABBR2*	negative	-
5q34	*GABRA1*	Tested but no LOAD-specific results reported	[797]

Locus	Gene	Findings	References
2q31.2	*GAD1*	Tested but no LOAD-specific results reported	[797]
10p12.1	*GAD65*	negative	-
5p13.2	*GDNF/GDNFOS*	negative	-
9p24.2	*GLIS3*	negative	-
1p35.3	*GMEB1*	negative	-
20q13.33	*GMEB2*	negative	-
3q28	*GMNC*	negative	-
12p13.31	*GNB3*	negative	-
5q33.1	*GRIA1*	negative	-
4q32.1	*GRIA2*	negative	-
Xq25	*GRIA3*	negative	-
11q22.3	*GRIA4*	negative	-
12p12	*GRIN2B*	negative	-
6q24.3	*GRM1*	negative	-
11q14.2-3	*GRM5*	negative	-
17q21.31	*GRN*	negative	-
19q13.2	*GSK3A*	negative	-
3q13.33	*GSK3B*	Aberrant CpG methylation *GSK3B* in LOAD non *APOE* epsilon4 carriers. PI3K/Akt/GSK-3beta inhibits leucine-309 demethylation of protein phosphatase-2A modulating phosphorylation of tau	[198, 799-801]
2q31.1	*HAT1*	negative	-
6q21	*HDAC2*	negative	-
7p21.1	*HDAC9*	negative	-
14q23.2	*HIF1A*	negative	-
7q34	*HIPK2*	negative	-
6p21.31	*HLA-DRB5/DRB1*	Methylation in cg17606183 was associated with Abeta load (3 CpG sites) and NFT density (9 CpG sites)	[26]
13q12.3	*HMGB1*	negative	-
5q13.3	*HMGCR*	negative	-
20q13.12	*HNF4A*	negative	-
1q32-q41	*HSD11B1*	negative	-
16q22.1	*HSD11B2*	negative	-
6q21.31	*HSPA1A*	negative	-
12p12.1	*IAPP*	negative	-
12q23.2	*IGF1*	negative	-
15q26.3	*IGF1R*	negative	-
11p15.5	*IGF2*	negative	-
6q25.3	*IGF2R*	negative	-
7p12.3	*IGFBP1*	negative	-

(Table 2) contd….

Locus	Gene	Findings	References
14q32.33	*IGHV1-67*	negative	-
1q32.1	*IL10*	negative	-
3q25.33	*IL12A*	negative	-
11q23.1	*IL18*	negative	-
2q14.1	*IL1A*	negative	-
2q14.1	*IL1B*	negative	-
9p24.1	*IL33*	negative	-
5q31.1	*IL4*	negative	-
7p15.3	*IL6*	negative	-
2q37.1	*INPP5D*	negative	-
11p15.5	*INS*	negative	-
11p15.5	*INS-IGF2*	negative	-
19p13.2	*INSR*	negative	-
1q23.1	*INSRR*	negative	-
19q13.33	*IRF3*	negative	-
2q36.3	*IRS1*	negative	-
13q34	*IRS2*	negative	-
17q21.31	*KANSL1*	negative	-
12q24.31	*KDM2B*	negative	-
9q34.12	*LAMC3*	negative	-
7q32.1	*LEP*	negative	-
12q13.3	*LRP1/APOER*	negative	-
2q31.1	*LRP2*	negative	-
12q12	*LRRK2*	negative	-
11p11.2	*MADD*	negative	-
19q13.12	*MAG*	negative	-
2q21.1	*MANI*	negative	-
5q13.2	*MAP1B*	negative	-
16q24.2	*MAP1LC3A/B*	negative	-
6q23.3	*MAP3K5*	negative	-
22q11.22	*MAPK1*	negative	-
22q13.11	*MAPK11*	negative	-
22q13.3	*MAPK12*	negative	-
6p21	*MAPK13*	negative	-
6p21.31	*MAPK14*	negative	-
16p11.2	*MAPK3*	negative	-
10q11.22	*MAPK8*	negative	-
11p11.2	*MAPK8IP1*	negative	-

Locus	Gene	Findings	References
16p13.3	*MAPK8IP3*	negative	-
5q35.3	*MAPK9*	negative	-
17q21.31	*MAPT*	Aberrant CpG methylation in *APOE* epsilon4 non-carriers. MMSE performance correlated with methylation level. Hypoacetylation of KXGS motifs enables phosphorylation of tau, reversed by HDAC6. Total histone H3 and total histone H4 protein levels significantly increased in *post-mortem* LOAD temporal cortices	[198, 802-804]
18q21.2	*MBD2*	In entorhinal cortex layer II, *DNMT1*, *MBD2*, and p66 with rRNA was nearly absent: loss of methylation markers and methylation stabilisers in LOAD neurons may cause deficits in rRNA gene expression, rRNAs, ribosomes, and ribosomal protein synthesis	[805]
18q23	*MBP*	negative	-
18p11.2	*MC2R*	negative	-
Xq28	*MECP2*	negative	-
5q14.3	*MEF2C*	negative	-
22q13.1	*MGAT3*	negative	-
3p25.2	*MME/NEP*	negative	-
6p22.1	*MOG*	negative	-
7q22	*MPO*	negative	-
11q12.2	*MS4A4/MS4A6E*	negative	-
8p22	*MSR1*	negative	-
1p36.22	*MTHFR*	*MTHFR* showed methylation levels ranging from 5% to 75% in LOAD, expressing large interindividual variation	[597, 806]
11q12.2	*MYRF*	negative	-
20q13.33	*MYT1*	negative	-
20p11.21	*NANP*	negative	-
17q21.1	*NBR1*	negative	-
8q13.3	*NCOA2*	negative	-
16q12.2	*NET*/SLC6A2	negative	-
5q23-31	*NEUROG1*	negative	-
4q25	*NEUROG2*	negative	-
10q21.3	*NEUROG3*	negative	-
4q24	*NFKB1*	Hyper- and hypomethylated CpG islands in promoter regions for NFkappaB frontal cortex	[793]
10q24.32	*NFKB2*	negative	-
14q13.3	*NFKBIA*	negative	-
2q37.1	*NGEF*	negative	-
20p11.21	*NINL*	negative	-
17p13.2	*NLRP1*	negative	-
1q44	*NLRP3*	negative	-
7p14.1	*NME8*	negative	-
7q36.1	*NOS3*	negative	-

(Table 2) contd….

Locus	Gene	Findings	References
9q34.3	*NOTCH1*	negative	-
4q32.2	*NPY1R*	negative	-
5q31.3	*NR3C1*	negative	-
9q33.3	*NR5A1*	negative	-
7q32.2	*NRF1*	negative	-
2q31.2	*NRF2*	negative	-
10q23.1	*NRG3*	negative	-
12q22	*NTN4*	negative	-
9q21.33	*NTRK2*	negative	-
Xq23	*NXT2*	In promoter region of *NXT2*, one CpG site located at -432 was differentially unmethylated in APP-sw cells	[675]
1p35.3	*OPRD1*	negative	-
3q28	*OSTN*	negative	-
12q24.31	*P2RX7*	negative	-
1q42.12	*PARP1*	negative	-
20q13.31	*PCK1*	negative	-
2p11.2	*PERK*	negative	-
11q14.2	*PICALM*	negative	-
7q11.23	*PION*	negative	-
19p13.12	*PKN1*	negative	-
19q13.2	*PLD3*	negative	-
Xq22.2	*PLP1*	negative	-
7q31.32	*POT1*	negative	-
11q13	*PP1*	negative	-
3p25.2	*PPARG*	negative	-
4p15.1	*PPARGC1A*	negative	-
5q32	*PPARGC1B*	negative	-
2p14	*PPP3R1*	negative	-
1p36.33	PRKCZ	negative	-
17p13.1	*PSD95/DLG4*	negative	-
14q24.1	*PSEN1*	Methylation markers changed. Methylation increased or decreased in peripheral blood cells. Methylation increased in promoter regions in LOAD. Deacetylation of H4 reported from animal models	[167, 807]
1q42.13	*PSEN2*	Methylation increased in promoter regions in LOAD	[807]
14q22.1	*PTGER2*	negative	-
1p31.1	*PTGER3*	negative	-
5p13.1	*PTGER4*	negative	-
9q33.2	*PTGS1*	negative	-
1q31.1	*PTGS2*	Hypo- and hypermethylation of CpG islands in COX-2 promoter region	[793]

Locus	Gene	Findings	References
8p21.2	*PTK2B*	negative	-
11p15.1	*PTPN5*	negative	-
16p11.2	*PYCARD*	negative	-
6p23	*RANBP9*	negative	-
21q22.1	*RCAN1*	negative	-
7q22.1	*RELN*	negative	-
4q12	*REST*	negative	-
17q25.1	*RHBDF2*	*RHBDF2* centered on cg13076843 associated CpG was found in close proximity to two genes, and RNA expression was altered relative to LOAD; *RHBDF2* related to *PTK2B*	[569]
19q13.33	*RPL13A*	*RPL13A* related to cg03169557 found associated to LOAD diagnosis	[569]
12q24.31	*SCARB1*	negative	-
4q21.1	*SCARB2*	negative	-
7q11.2	*SCARB3*	negative	-
14q32.12	*SCL24A4*	negative	-
14q32.13	*SERPINA3*	negative	-
17p13.1	*SERPINF1*	*SERPINF1* related to cg19803550 found associated to Abeta cascade network	[569]
17p13.3	*SERPINF2*	*SERPINF2* related to cg19803550 found associated to Abeta cascade network	[569]
17q11.2	*SERT/SLC6A4*	negative	-
6q23.2	*SGK1*	negative	-
1q22	*SH3GLB1*	negative	-
1q21.2	*SHC1*	negative	-
2q36.2	*SLC19A3*	negative	-
14q24.2	*SLC8A3*	negative	-
12p12.1	*SLCO1A2*	negative	-
4q22.1	*SNCA*	*SNCA* mRNA expression in AD subjects was significantly higher. mRNA expression and methylation rate of *SNCA* intron 1 was lower in LOAD at seven CpG sites	[808]
15q22.31	*SNX1*	negative	-
6q21	*SNX354654552331*	negative	-
1q25.2	*SOAT1*	negative	-
21q22.1	*SOD1*	negative	-
10q25.1	*SORCS1*	negative	-
11q24.1	*SORL1*	Methylation at 4 CpG sites (cg15241519, cg08441314, cg11606444, and cg22136098) were associated with both Abeta and tauopathy	[26]
11p15.2	*SPON1*	negative	-
17q21.2	*STAT3*	negative	-
Xp11.23	*SYP*	negative	-
6q27	*TBP*	negative	-
5p15.33	*TERT*	*hTERT* methylation frequency was associated with the aging process in LOAD	[809]

(Table 2) contd….

Locus	Gene	Findings	References
10q21.1	*TFAM*	negative	-
12q13.12-13	*TFCP2*	negative	-
6p21	*TFEB*	negative	-
19q13.2	*TGFB1*	negative	-
9q33.1	*TLR4*	negative	-
6p21.33	*TNFA*	Hypomethylation of the TNFA promoter was found in LOAD brains	[810]
8p21.2	*TNFRSF10A*	negative	-
8p21.2	*TNFRSF10B*	negative	-
12p13.31	*TNFRSF1A*	negative	-
1p36.22	*TNFRSF1B*	negative	-
13q14.11	*TNFSF11*	negative	-
19q13.32	*TOMM40*	negative	-
8q22.1	*TP53INP1*	negative	-
6p21.1	*TREM2*	negative	-
15q22.31	*TRIP4*	negative	-
Xq22.3	*TSC22D3*	negative	-
2p22.3	*TTC27*	negative	-
19q13.12	*TYROBP*	negative	-
12q24.33	*ULK1*	negative	-
5q31.1	*VDAC1*	negative	-
6p21.1	*VEGFA*	negative	-
9p24.2	*VLDLR*	negative	-
8p12	*WRN*	negative	-
7q22.1	*ZCWPW1*	Methylation change not directly *in loco*	[794]
6q14.3	*ZNF292*	negative	-
19q13.42	*ZNF628*	negative	-
4q31.21-q31.22	*ZNF827*	negative	-

Method remarks: Eligible for inclusion were human studies published until May 2017. PubMed was searched using the search terms "Alzheimer human" and gene locus and "epige-nomics" or "DNA methylation" or "histone acetylation" or "ubiquitination". Reported are only positive findings from LOAD patients, "negative" means here that no such results were available for this locus.

1.4.5. Oxidative Stress and Cognitive Impairment

Several studies also revealed that, relating to the Abeta cascade, chronic oxidative stress is the *conditio sine qua non* for the development of tau pathology [211]. The Abeta cascade involves excitotoxity, Abeta aggregation, inflammation, tau hyperphosphorylation, microglial activation [212], increased GSK-3beta activity, and deregulation of the neuronal calcium metabolism [188]. Oxidative stress appears triggered by free ROS such as the hydroxyl radical, the superoxide anion, and hydrogen peroxide, and also as ER stress [185]. Oxidative stress leading to lipid peroxidation precede the appearance of Abeta plaques due to Abeta oligomerisation. Resende [213] also observed increased activity of the antioxidant enzymes glutathione peroxidase (family 1-8) and superoxide dismutase (*SOD1* 21q22.1) as indicators of ROS. The final steps in oxidation stress consist in in lipid peroxidation, glutamatergic excitotoxicity, inflammation, and activation of the cascade of apoptotic cell death [212]. Neither Abeta nor intracerebral NFT themselves were found clearly related to cognitive decline. Yet in contrast, onset of cognitive decline was associated with increased markers of oxidative stress, caspase-9 activation, an index of neuron death, and decreased hippocampal synaptophysin levels, a synaptic vesicle glycoprotein [214] expressed by the *SYP* gene (Xp11.23). Cognitive impairments were associated with praecuneus, subcallosal cortex, cingulum, posterior to

Table 3.   Extracted risk genes for late-onset Alzheimer disease.

Locus	Gene	Function	References
12p13.31	*A2M*	Alpha$_2$-macroglobulin: cytokine transporter, Abeta degradation with LRP1, interaction with *MPO*	[654]
21q22.3	*ABCG1*	ATP binding cassette subfamily G member 1	[275, 276, 655, 656]
18p11.32	*ADCYAP1*	Adenylate cyclase activating polypeptide 1: proprotein increasing cyclic adenosine monophosphate (cAMP) levels, stress response	[656]
10q25.2	*ADRA2A*	Adrenoceptor alpha 2A: sympathetic transmission	[657, 658]
10q25.3	*ADRB1*	Adrenoceptor beta 1: sympathetic transmission	[376]
5q31-32	*ADRB2*	Adrenoceptor beta 2: sympathetic transmission	[381]
8p11.23	*ADRB3*	Adrenoceptor beta 3: sympathetic transmission	[659]
6p21.32	*AGER*	Advanced glycosylation endproduct (AGE) receptor: neuroinflammation	[660]
10q11.21	*ALOX5*	Arachidonate 5-lipoxygenase: regulator of gamma-secretase	[661]
4p14-p13	*APBB2*	Amyloid beta precursor protein binding family B member 2: Abeta cascade	[275, 276, 662]
21q21.3	*APP*	Amyloid beta precursor protein: Abeta cascade	[663]
8q24.3	*ARC*	Activity-regulated cytoskeleton-associated protein: synaptic plasticity, regulator of Notch	[664]
12q23.2	*ASCL1/MASH1*	Achaete-scute family bHLH transcription factor 1: ANS neurogenesis, noradrenergic neurons	[665]
22q13.1	*ATF4*	Activating transcription factor 4: neurodegenerative signal	Not tested
20p13	*AVP*	Arginine vasopressin: neuropeptide implicated in stress	Not tested
11q23.3	*BACE1*	Beta-secretase 1: Abeta cascade	[666, 667]
19q13.33	*BAX*	BCL2 associated X apoptosis regulator: interacting with mitochondrial voltage-dependent anion channel (VDAC)	[668]
3q26.1	*BCHE*	Butyrylcholinesterase: cholinergic transmission, acetylcholine catabolism	[275, 276]
11p14.1	*BDNF*	Brain-derived neurotrophic factor: age of onset	[669, 670]
17q21.31	*BECN1*	Beclin 1: autophagy	Not tested
5q32	*CAMK2A*	Calcium/calmodulin dependent protein kinase II alpha: synaptic plasticity, LTP	[671]
17q12	*CCL2*	C-C motif chemokine ligand 2: immune	Negative finding
17q12	*CCL3*	C-C motif chemokine ligand 3: immune	Negative finding
17q4	*CCL4*	C-C motif chemokine ligand 4: immune	Negative finding
10q21.2	*CDK1*	Cyclin-dependent kinase: cell cycle control, haplotype with p38α, JNK1-3, MEK2, and ERK2 loci	[671]
7q36.1	*CDK5*	Cyclin-dependent kinase: brain development	[275, 276, 612]
17q21.2	*CNP*	2',3'-Cyclic-nucleotide 3'-phosphodiesterase: oligodendrocyte differentiation, microtubule formation	[672]
22q11.2	*COMT*	Catechol-O-methyltransferase: catecholamine regulation	Negative finding
2q33.3	*CREB1*	cAMP response element binding protein 1: transcription induction	Not tested
9p13.3	*CREB3*	cAMP response element binding protein 3: transcription induction	Not tested
11p11.2	*CREB3L1*	cAMP responsive element binding protein 3 like 1: ER stress	Not tested
7q33	*CREB3L2*	cAMP responsive element binding protein 3 like 1: ER stress	Not tested

(Table 3) contd….

Locus	Gene	Function	References
19p13.3	*CREB3L3*	cAMP responsive element binding protein 3 like 1: ER stress	Not tested
1q21.2	*CREB3L4*	cAMP responsive element binding protein 3 like 1: ER stress	Not tested
7p15.1-p14.3	*CREB5*	cAMP response element binding protein 5: trans-activator	Not tested
16p13.3	*CREBBP*	CREB binding protein: chromatin remodelling to transcription factor recognition	Not tested
8q13.1	*CRH1*	Corticotropin releasing hormone: HPA	Not tested
5q13.3	*CRHBP*	Corticotropin releasing hormone binding protein: CRH inactivation	Not tested
17q21.31	*CRHR1*	Corticotropin releasing hormone receptor 1: HPA regulation, association with *MAPT* H1 haplotype	[673]
7p14.3	*CRHR2*	Corticotropin releasing hormone receptor 2: HPA regulation	Not tested
1q23.2	*CRP*	C-reactive protein: inflammation	[674]
18q21.1	*CTIF*	Cap binding complex dependent translation initiation factor: translation	[675]
16q21	*CX3CL1*	C-X3-C motif chemokine ligand 1: fractalkine	Not tested
3p22.2	*CX3CR1*	C-X3-C motif chemokine receptor 1	Not tested
9q34.2	*DBH*	Dopamine beta-hydroxylase: noradrenalin converter, interaction with *IL1A* and *IL6*	[386]
16p12.1	*DCTN5*	Dynactin subunit 5: vesicle transport	Not tested
1q23.3	*DDR2*	Discoidin domain receptor tyrosine kinase 2: cell-environment communication	[675]
1p32.3	*DHCR24*	24-dehydrocholesterol reductase: cholesterol biosynthesis	[275, 276, 620]
17p13.1	*DLG4*	Discs large MAGUK scaffold protein 4: postsynaptic density protein 95	[676]
19q13.2	*DNMT1*	DNA methyltransferase 1: maintaining methylation patterns	[92, 677]
2p23.2	*DNMT3A*	DNA methyltransferase 3A: *de novo* methylation	[678]
20q11.21	*DNMT3B*	DNA methyltransferase 3B: *de novo* methylation	[679]
5q35.1	*DUSP1*	Dual specificity phosphatase 1: cellular response to environmental stress	Not tested
21q22.13	*DYRK1A*	Dual specificity tyrosine phosphorylation regulated kinase 1A: brain maturation	[275, 276, 680]
11p13	*EAAT2/SLC1A2*	Excitatory amino acid transporter 2/glial high affinity glutamate transporter: synaptic glutamate clearance	[583, 681]
6p24.1	*EDN1*	Endothelin 1: vasoconstrictor	[682]
4q31.22-23	*EDNRA*	Endothelin receptor type A: vasoconstriction	Not tested
13q22.3	*EDNRB*	Endothelin receptor type B: vasoconstriction	Not tested
5q31.2	*EGR1*	Early growth response 1: transcriptional regulator	[683]
2p22.2	*EIF2AK2*	Eukaryotic translation initiation factor 2 alpha kinase 2: translation initiation	[253, 684]
15q15.1	*EIF2AK4*	Eukaryotic translation initiation factor 2 alpha kinase 4: protein synthesis	[602]
14q23.3	*EIF2S1*	Eukaryotic translation initiation factor 2 subunit alpha: protein synthesis initiation	Not tested
12p13.33	*FKBP4*	FK506 binding protein 4: steroid receptor signalling, immunoregulatory gene expression, tauopathy	[685]
6p21.31	*FKBP5*	FK506 binding protein 5: immunosuppression, calcineurin inhibition, tauopathy, LOAD progression	[686]
14q24.3	*FOS*	Fos proto-oncogene AP-1 transcription factor subunit: proliferation, apoptosis	[687]
11q14.1	*GAB2*	Growth factor receptor-bound protein 2 associated binding protein 2: interaction receptor tyrosine kinases, PI3K/ERK/Akt pathway, brain growth	[688-690]

Locus	Gene	Function	References
6p21.3	*GABBR1*	Gamma-aminobutyric acid type B receptor subunit 1: inhibitory neurotransmission	Not tested
9q22.33	*GABBR2*	Gamma-aminobutyric acid type B receptor subunit 2: inhibitory neurotransmission	Not tested
5q34	*GABRA1*	Gamma-aminobutyric acid type A receptor alpha1 subunit: inhibitory neurotransmission	Not tested
2q31.2	*GAD1*	Glutamate decarboxylase 1: GABA synthesis	Negative
10p12.1	*GAD65*	Glutamate decarboxylase 2: GABA synthesis	[691]
5p13.2	*GDNF/GDNFOS*	Glial cell derived neurotrophic factor: activation of SMAD family transcription factors, neuroprotection	[692]
1p35.3	*GMEB1*	Glucocorticoid modulatory element binding protein 1: transactivation of GRs bound to GREs	[12]
20q13.33	*GMEB2*	Glucocorticoid modulatory element binding protein 2: transactivation of GRs bound to GREs	[12]
12p13.31	*GNB3*	Guanine nucleotide-binding protein subunit beta 3: regulators of signal transduction receptors, interacting with ADRB1/MAPK signalling in LOAD	[376]
5q33.1	*GRIA1*	Glutamate ionotropic receptor AMPA type subunit 1: excitatory neurotransmission	Not tested
4q32.1	*GRIA2*	Glutamate ionotropic receptor AMPA type subunit 2: excitatory neurotransmission	[693]
Xq25	*GRIA3*	Glutamate ionotropic receptor AMPA type subunit 3: excitatory neurotransmission	Not tested
11q22.3	*GRIA4*	Glutamate ionotropic receptor AMPA type subunit 4: excitatory neurotransmission	[694]
12p12	*GRIN2B*	Glutamate ionotropic receptor NMDA type subunit 2B: ROS, excitotoxicity, excessive Ca^{++} influx, interacting with *ADRA1A*	[695]
6q24.3	*GRM1*	Glutamate metabotropic receptor 1: glutamatergic neurotransmission, activation of ERK1/2, LTD/LTP	Not tested
11q14.2-3	*GRM5*	Glutamate metabotropic receptor 5: glutamatergic neurotransmission, receptor for cellular prion protein PrP^C bound soluble $Abeta_{42}$ oligomers	[696, 697]
17q21.31	*GRN*	Granulin precursor progranulin: regulating cell growth	[698, 699]
19q13.2	*GSK3A*	Glycogen synthase kinase 3 alpha: regulating transcription factor JUN, Wnt/PI3K/signalling, Abeta cascade	Not tested
3q13.33	*GSK3B*	Glycogen synthase kinase 3 beta: regulating transcription factor JUN, Wnt/PI3K/signalling, energy metabolism, neuronal cell development, Abeta cascade	[275, 276, 700, 701]
2q31.1	*HAT1*	Histone acetyltransferase 1: rapid acetylation of newly synthesised cytoplasmic histones	[586, 589]
6q21	*HDAC2*	Histone deacetylase 2: deacetylation of lysine residues at histones, transcriptional repression, transcription factor activation	[702]
7p21.1	*HDAC9*	Histone deacetylase 9: recruitment of multi-component co-repressor complexes	[586, 589]
14q23.2	*HIF1A*	Hypoxia inducible factor 1 alpha subunit: regulating cellular response to hypoxia, Abeta cascade	[233, 703]
7q34	*HIPK2*	Homeodomain-interacting protein kinase 2: transcription factor, interaction with *HIF1A*, Abeta cascade	[704]

(Table 3) contd….

Locus	Gene	Function	References
13q12.3	*HMGB1*	High mobility group box 1: regulating transcription, neuroinflammation, interaction with *AGER*, Abeta cascade	[705]
5q13.3	*HMGCR*	3-hydroxy-3-methylglutaryl-CoA reductase: rate-limiting enzyme for cholesterol synthesis	[541, 706-708]
20q13.12	*HNF4A*	Hepatocyte nuclear factor 4 alpha: nuclear transcription factor, insulin signalling	Negative finding
1q32-q41	*HSD11B1*	Hydroxysteroid 11-beta dehydrogenase 1: cortisol converter enzyme	[12]
16q22.1	*HSD11B2*	Hydroxysteroid 11-beta dehydrogenase 2: cortisol converter enzyme	Negative finding
6q21.31	*HSPA1A*	Heat shock protein family A (Hsp70) member 1A: chaperone heat shock protein, trigger of neuronal apoptosis, caspase activation	[346]
12p12.1	*IAPP*	Islet amyloid polypeptide amylin: regulating blood glucose levels, brain insulin resistance, rs73069071 related to *SLCO1A2*	[210]
12q23.2	*IGF1*	Insulin like growth factor 1: mediating growth and development	[709]
15q26.3	*IGF1R*	Insulin like growth factor 1 receptor: anti-apoptotic agent, enhancing cell survival signaling neuroprotection, healthy ageing	[710, 711]
11p15.5	*IGF2*	Insulin like growth factor 2: mediating growth and development, overlap with *INS-IGF2*	[712]
6q25.3	*IGF2R*	Insulin like growth factor 2 receptor: activation of TGFbeta, degrading IGF2, covariation with WM disintegrity	[634]
7p12.3	*IGFBP1*	Insulin like growth factor binding protein 1: binding both IGFs, mediating interaction with cell surface receptors	[712]
1q32.1	*IL10*	Interleukin 10: anti-inflammatory cytokine produced by monocytes, anti-inflammatory reflex, interaction with *TNFA* and *CYP19A1*	[713, 714]
3q25.33	*IL12A*	Interleukin 12A: cytokine receptor, induction of IFNgamma	[715, 716]
11q23.1	*IL18*	Interleukin 18: pro-inflammatory cytokine, augmenting killer cell, stimulation IFNgamma	[716]
2q14.1	*IL1A*	Interleukin 1A: pro-apoptotic proprotein, interaction with *DBH* and *IL6* attributed to LC neuron loss	[386]
2q14.1	*IL1B*	Interleukin 1B: pro-inflammatory response cytokine, mediated by caspase-1, induction of COX-2	[716]
9p24.1	*IL33*	Interleukin 33: induction of T_{H2}-cells, activation of NFkappaB and MAPK pathways, histone binding	[717]
5q31.1	*IL4*	Interleukin 4: adaptive immunity, chronic inflammation, mediating neurodegeneration, regeneration cascade through effector STAT6, interacting with *TREM2* and *TYROBP*	[651, 718]
7p15.3	*IL6*	Interleukin 6: cytokine both pro- and anti-inflammatory, activating PI3K pathway, targeting PKB, activating DNMT1/DNMT3A/DNMT3B/HDAC1	[716, 718]
11p15.5	*INS*	Insulin: binding to the insulin receptor stimulates glucose uptake, overlap with *INS-IGF2*	[719, 720]
11p15.5	*INS-IGF2*	INS-IGF2 read-through: activating ERK and MAPK pathways	[712]
19p13.2	*INSR*	Insulin receptor: activating insulin signalling pathway, covariation with WM disintegrity	[634]
1q23.1	*INSRR*	Insulin receptor related receptor: activating insulin signalling pathway, covariation with WM disintegrity	[634]
19q13.33	*IRF3*	Interferon regulatory factor 3: transcription factor, forming complex with *CREBBP*	[721]

(Table 3) contd….

Locus	Gene	Function	References
2q36.3	*IRS1*	Insulin receptor substrate 1: signal transduction from INSR and IGF1R to PI3K/Akt and ERK/MAPK pathways, related to Beclin-1	[462]
13q34	*IRS2*	Insulin receptor substrate 1: mediating effects of insulin, insulin-like growth factor 1, cytokines, interacting with *IL4*	Not tested in humans
7q32.1	*LEP*	Leptin: secreted by white adipocytes, regulation of immune functions and inflammatory responses, interaction with *IAPP*	Not tested
12q13.3	*LRP1/APOER*	LDL receptor related protein 1: alpha 2-macroglobulin-mediated clearance of Abeta, reducing LOAD risk in *APOE* epsilon4 carriers	[722, 723]
2q31.1	*LRP2*	LDL receptor related protein 2 megalin: reuptake of lipoproteins and hormones, MAPK signalling and JNK interacting proteins	[724]
19q13.12	*MAG*	Myelin-associated glycoprotein: mediating certain myelin-neuron interactions, myelination process	[682, 725, 726]
2q21.1	*MANI*	Family with sequence similarity 168 member B: myelin-associated neurite-outgrowth inhibitor, differentiation into catecholaminergic neurons	[726]
5q13.2	*MAP1B*	Microtubule associated protein 1B: microtubule assembly, neurogenesis, tauopathy	[727]
16q24.2	*MAP1LC3A/B*	Microtubule associated proteins 1 light chain 3 alpha/beta: cytoskeleton interaction, neurogenesis, tauopathy	[728]
6q23.3	*MAP3K5*	Mitogen-activated protein kinase kinase kinase 5: activation of JNK/SAPK	[729]
22q11.22	*MAPK1*	Mitogen-activated protein kinase 1 ERK2: neuronal proliferation, differentiation, transcription regulation	[671]
22q13.11	*MAPK11*	Mitogen-activated protein kinase 11 p38beta: neuronal development	Not tested
22q13.3	*MAPK12*	Mitogen-activated protein kinase 12 p38gamma: signal transducer	Not tested
6p21	*MAPK13*	Mitogen-activated protein kinase 12 p38delta: microtubule dynamics regulator	[271]
6p21.31	*MAPK14*	Mitogen-activated protein kinase 12 p38alpha: stress related transcription, genotoxic stress response	[349, 671]
16p11.2	*MAPK3*	Mitogen-activated protein kinase 3 ERK1: neuronal proliferation	Not tested
10q11.22	*MAPK8*	Mitogen-activated protein kinase 8 JNK1: mediating immediate-early gene expression, co-induction of apoptosis with TNFalpha	[671, 730]
11p11.2	*MAPK8IP1*	Mitogen-activated protein kinase 8 interacting protein 1 JIP1: regulator of JNK1 mediated activation of transcription factors	[302, 303, 731]
16p13.3	*MAPK8IP3*	Mitogen-activated protein kinase 8 interacting protein 2 JIP2: regulator of JNK1 mediated activation of transcription factors	Not tested
5q35.3	*MAPK9*	Mitogen-activated protein kinase 2 JNK2: mediating immediate-early gene expression	[730]
18q21.2	*MBD2*	Methyl-CpG binding domain protein 2: mediator of the biological consequences of the methylation signal	Not tested
18q23	*MBP*	Myelin basic protein: major myelin constituent	[725, 732]
18p11.2	*MC2R*	Melanocortin 2 receptor: ACTH signalling	[12]
Xq28	*MECP2*	Methyl-CpG binding protein 2: binding to methylated DNA	Not tested
22q13.1	*MGAT3*	Mannosyl (beta-1,4-)-glycoprotein beta-1,4-N-acetylglucosaminyltransferase: glycosyltransferase, Abeta phagocytosis	[733]
6p22.1	*MOG*	Myelin oligodendrocyte glycoprotein: oligodendrocyte surface and outermost of myelin sheath surface, maintenance	[725, 726]

(Table 3) contd….

Locus	Gene	Function	References
7q22	*MPO*	Myeloperoxidase: myeloid differentiation, interacting with A2M	[654]
8p22	*MSR1*	Macrophage scavenger receptor 1: mediating endocytosis of LDLs	[734]
1p36.22	*MTHFR*	Methylenetetrahydrofolate reductase: rate-limiting enzyme in the methyl cycle, methylation homeostasis	[92, 735]
11q12.2	*MYRF*	Myelin regulatory factor: directly promoting myelin gene expression	Not tested
17q21.1	*NBR1*	Autophagy cargo receptor: autophagic degradation of peroxisomes	Not tested
8q13.3	*NCOA2*	Nuclear receptor coactivator 2: transcriptional coactivator for nuclear hormone receptors	[736]
16q12.2	*NET*/SLC6A2	Solute carrier family 6 member 2: noradrenaline reuptake	[737, 738]
5q23-31	*NEUROG1*	Neurogenin 1: regulating neuronal differentiation, interacting with *CREBBP*	Not tested
4q25	*NEUROG2*	Neurogenin 2: controlling cortical neuron migration	[739]
10q21.3	*NEUROG3*	Neurogenin 3: transcription factor involved in neurogenesis, determinative for pancreatic islet cell phenotype	Negative finding
4q24	*NFKB1*	Nuclear factor kappa B subunit 1 p50: transcription regulator, neuroinflammation	[740, 741]
10q24.32	*NFKB2*	Nuclear factor kappa B subunit 2: transcription regulator, neuroinflammation	[741]
14q13.3	*NFKBIA*	NFKB inhibitor alpha: anti-inflammatory reflex protein	[740, 741]
2q37.1	*NGEF*	Neuronal guanine nucleotide exchange factor ephexin: Abeta cascade	[742]
17p13.2	*NLRP1*	NLR family pyrin domain containing 1: neuronal inflammasome, mediating apoptosis, interaction with caspase-2 and caspase-9	[509, 743, 744]
1q44	*NLRP3*	NLR family pyrin domain containing 3: neuronal inflammasome, mediating apoptosis, upstream activator of NFkappaB signalling	[266, 509, 744]
7q36.1	*NOS3*	Nitric oxide synthase 3: reactive free radical, neurotransmission	[745]
9q34.3	*NOTCH1*	Notch 1: EGF-related, neuropil development	[711]
4q32.2	*NPY1R*	Neuropeptide Y receptor Y1: mobilisation of intracellular calcium, neuroprotection	Not tested
5q31.3	*NR3C1*	Nuclear receptor subfamily 3 group C member 1 glucocorticoid receptor: transcription factor, binding to glucocorticoid response elements	[746]
9q33.3	*NR5A1*	Nuclear receptor subfamily 5 group A member 1: transcription factor	Not tested
7q32.2	*NRF1*	Nuclear respiratory factor 1: mitochondrial biogenesis pathway, transcription factor, neurite outgrowth, correlation with PGC-1a	[296, 747]
2q31.2	*NRF2*	Nuclear respiratory factor 2: transcription factor, oxidative stress	[748]
9q21.33	*NTRK2*	Neurotrophic receptor tyrosine kinase 2: binding neurotrophins, signalling in MAPK pathway, neuronal differentiation	[749]
Xq23	*NXT2*	Nuclear transport factor 2 like export factor 2: mRNA nuclear export	[675]
12q24.31	*P2RX7*	Purinergic receptor P2X 7: formation of membrane pores	[750]
20q13.31	*PCK1*	Phosphoenolpyruvate carboxykinase 1: regulation of gluconeogenesis through insulin, glucocorticoids	[751]
2p11.2	*PERK*	Eukaryotic translation initiation factor 2 alpha kinase 3: modulating mitochondrial function, ER stress	[602]
7q11.23	*PION*	Gamma-secretase activating protein: increasing Abeta production, interaction with gamma-secretase and APP-CTF	[752]

(Table 3) contd….

Locus	Gene	Function	References
19p13.12	*PKN1*	Protein kinase N1: mediating insulin signalling, tauopathy	[753]
Xq22.2	*PLP1*	Proteolipid protein: transmembrane protein, myelin compaction, maintenance, interacting with *EDN1*	[682, 725]
11q13	*PP1*	Protein phosphatase 1: hepatic blood-glucose levels, glycogen metabolism	[754]
3p25.2	*PPARG*	Peroxisome proliferator activated receptor gamma: adipocyte differentiation, T2DM	Negative
4p15.1	*PPARGC1A*	PPARG coactivator 1 alpha: regulation of CREB and NRFs, neuronal cholesterol homeostasis	[296, 747]
5q32	*PPARGC1B*	PPARG coactivator 1 beta: non-oxidative glucose metabolism, regulating transcription factors and glucocorticoid receptor	[755]
1p36.33	*PRKCZ*	Protein kinase zeta: stabilisation of LTP, atypical isoform: insulin stimulated glucose transport, consistent with memory loss	[459, 460]
17p13.1	*PSD95/DLG4*	Postsynaptic density protein 95, LTP	[756]
14q24.1	*PSEN1*	Presenilin 1: regulating APP processing, cleavage of Notch receptor	Negative
1q42.13	*PSEN2*	Presenilin 2: regulating APP processing, cleavage of Notch receptor	Negative
14q22.1	*PTGER2*	Prostaglandin E receptor 2: glial cells, neuroinflammation, GSK-3beta, beta-catenin signalling, COX-2 induction	[757]
1p31.1	*PTGER3*	Prostaglandin E receptor 3: reducing cAMP-dependent signalling, COX-2 induction	[515]
5p13.1	*PTGER4*	Prostaglandin E receptor 4: activating transcription factor CREP signalling, EGR-1 expression through ERK, p38, PI3K/Akt/mTOR pathways	[758]
9q33.2	*PTGS1*	Prostaglandin-endoperoxide synthase 1 COX-1: catalysing prostaglandin biosynthesis	[759]
1q31.1	*PTGS2*	Prostaglandin-endoperoxide synthase 1 COX-2: inducible isozyme, prostanoid biosynthesis, neuroinflammation	[760, 761]
11p15.1	*PTPN5*	Protein tyrosine phosphatase, non-receptor type 5 STEP: dephosphorylation of ERK1/2, p38, internalisation of NMDARs, synaptic strength	[762]
16p11.2	*PYCARD*	PYD and CARD domain containing: apoptotic signalling pathway, activation of caspase	[763]
6p23	*RANBP9*	RAN binding protein 9: translocation of RNA, Abeta cascade	[764]
21q22.1	*RCAN1*	Regulator of calcineurin 1: inhibiting calcineurin-dependent signalling pathways, CNS development, activation of caspase-3, linking tau and Abeta	[765]
7q22.1	*RELN*	Reelin: neurogenesis, synaptic positioning, LTP, interaction with CDK5, GSK-3b, interaction with APP	[766]
4q12	*REST*	RE1 silencing transcription factor: neuron-restrictive silencer element, master negative regulator of neurogenesis	Not tested
12q24.31	*SCARB1*	Scavenger receptor class B member 1: HDL receptor	Negative
4q21.1	*SCARB2*	Scavenger receptor class B member 2: lyosomal membranes	Not tested
7q11.2	*SCARB3*	Scavenger receptor class B member 3 CD36: fatty acid transport	[767]
14q32.13	*SERPINA3*	Serpin family A member 3: plasma protease inhibitor	[768]
17q11.2	*SERT/SLC6A4*	Solute carrier family 6 member 4: serotonin transporter	Negative
6q23.2	*SGK1*	Serum/glucocorticoid regulated kinase 1: anti-apoptotic cellular stress protector, Akt homologue	[769]

(Table 3) contd….

Locus	Gene	Function	References
1q22	*SH3GLB1*	Endophilin-B1: Bax-interacting factor 1 Bif-1	[194]
1q21.2	*SHC1*	SHC adaptor protein 1: mitochondrial matrix, ROS regulator	[770]
12p12.1	*SLCO1A2*	Hepatic solute carrier organic anion transporter family member 1A2: uptake bile acids, steroidal compounds, interacting with IAPP	[210]
4q22.1	*SNCA*	Alpha synuclein: presynaptic terminals	[771]
1q25.2	*SOAT1*	Sterol O-acyltransferase 1: cholesterol acyltransferase, endoplasmic reticulum, cholesterol equilibrium, Abeta cascade	[275, 276]
21q22.1	*SOD1*	Superoxide dismutase 1: ROS converter	[772]
10q25.1	*SORCS1*	Sortilin related VPS10 domain containing receptor 1: covariation with WM disintegrity	[634, 773]
11q24.1	*SORL1*	Sortilin related receptor 1: neuronal LDL receptor, covariation with WM disintegrity	[634, 773]
17q21.2	*STAT3*	Signal transducer and activator of transcription 3: respondent to cytokines and growth factors	[741]
Xp11.23	*SYP*	Synaptophysin: binding cholesterol, targeting of vesicle-associated synaptobrevin	Not tested
6q27	*TBP*	TATA-box binding protein: element of transcription factor IID (TFIID)	[774]
10q21.1	*TFAM*	Mitochondrial transcription factor A: mitochondrial DNA replication and repair	[296, 775]
12q13.12-13	*TFCP2*	Transcription factor CP2: binding the alpha-globin promoter, inflammatory response	[776]
6p21	*TFEB*	Transcription factor EB: lyosomal biogenesis, autophagy, activated by PGC-1alpha	Not tested
19q13.2	*TGFB1*	Transforming growth factor beta 1: regulating cell proliferation, and growth, covariation with WM disintegrity	[634, 777]
9q33.1	*TLR4*	Toll like receptor 4: activation of innate immunity	[778]
6p21.33	*TNFA*	Tumor necrosis factor alpha: cytokine, cell proliferation, apoptosis, neuroinflammation	[779]
8p21.2	*TNFRSF10A*	TNF receptor superfamily member 10A: inducing cell apoptosis	[780]
8p21.2	*TNFRSF10B*	TNF receptor superfamily member 10B: transducing apoptosis signal	[780]
12p13.31	*TNFRSF1A*	TNF receptor superfamily member 1A: inhibiting inflammation	[781]
1p36.22	*TNFRSF1B*	TNF receptor superfamily member 1B: mediating anti-apoptotic signals, anti-oxidative pathways, neuroprotection	Negative finding
13q14.11	*TNFSF11*	TNF superfamily member 11 RANKL: regulation of cell apoptosis	[782]
Xq22.3	*TSC22D3*	TSC22 domain family member 3: anti-inflammatory protein glucocorticoid (GC)-induced leucine zipper, immunosuppression through NFkappaB	Not tested
12q24.33	*ULK1*	Unc-51 like autophagy activating kinase 1: autophagy regulator	Not tested
5q31.1	*VDAC1*	Voltage dependent anion channel 1: metabolite exchange in mitochondria	[217, 783]
6p21.1	*VEGFA*	Vascular endothelial growth factor A: embryonic blood vessel formation, metabolic abnormalities	[784]
9p24.2	*VLDLR*	Very low density lipoprotein receptor: VLDL-triglyceride metabolism, reelin signalling pathway	[785, 786]

Method remarks: This table contains suspected gene loci extracted from preceding text sections, based on animal research, and suspected risk genes from additional literature. These loci were tested for associations in human LOAD genetic studies in PubMed and/or AlzGene databases. If not available, human pathophysiology studies are reported instead.

anterior frontal regions [207], and adjacent to these regions, white matter hyperintensities in periventricular regions and callosal fascicles predicted cognitive impairment at >0.8 [207]. Hence, these associations with cognitive decline point towards underlying structural WM alterations and general oxidative status.

Oxidative stress is thus a common component of the neurodegenerative process. OS has been shown to induce serum glucocorticoid regulated kinase SGK1 (*SGK1* 6q23.2) involved in neurodifferentiation and neurodegeneration. SGK expression through a p38 MAPK-dependent pathway, inhibits apoptosis [215]. *SGK1* expression is mainly regulated by glucocorticoids (Section 3.1.), and glucocorticoids were demonstrated to enhance exercise-related memory consolidation in a range of in animals. Whilst chronic glucocorticoid excess impairs hippocampal neurogenesis by *NR3C1* activation, this mechanism is perpetuated by kinase SGK1.

1.4.6. Mitochondrial Dysfunction

Mitochondrial dysfunction is increasingly in focus as associated with tauopathy [203, 211, 216]. Available evidence suggests that tau hyper-phosphorylation is accompanied by multiple factors, including intraneuronal Abeta-oligomers, chronic oxidative stress, reduced insulin-like growth factor 1 (*IGF1* 12q23.2), and astrocytically mediated Abeta and caspase activation [211]. Pertaining to this ensemble is the observation that LOAD patients carry systemic mitochondrial dysfunction that causes brain pathology [177, 216]. COX reduction is already present at the MCI stage of LOAD pathogenesis, and also shows co-localisation with $Abeta_{42}$ generation [216]. $Abeta_{42}$, in turn, and *h*-tau interacted with the mitochondrial outer membrane protein VDAC1 (*VDAC1* 5q31.1) [217]. Of the three isoforms, only VDAC1 is expressed in neurons and may thus be relevant for neurodegeneration. VDAC forms the mitochondrion, maintains the mitochondrial permeability transition pore (mPTP, Section 2.6.), binds to apoptosis regulator beclin, and is thus important for apoptotic signalling. Reddy established that Abeta interacts with VDAC1, to the effect of mitochondrial dysfunction, with reduction of ATP and COX activity, lipid peroxidation, free radical production, and mitochondrial fission-linked GTPase activity [217], indicating ROS activation. Dysfunctional mitochondria contribute to malignant APP processing by (a) excess production of ROS, (b) releasing proteins ASK1 (*MAP3K5* 6q23.3) and glutathione *S*-transferases (GSTs), (c) thus leading to JNK release, and (d) deacetylation of histones and demethylation of *APP* and *BACE1* gene promoters, which trigger Abeta production [177, 216].

Mitochondrial dysfunctions, however, appear to be a function of normal ageing as well. Evidence indicates age-related mtDNA changes associated with CVD risks also occurring within the human brain basal ganglia. Ageing increases transcription of a 5-kilobase deletion that particularly affects mtDNA COX genes [218]. Overexpression of COX genes is present very early in ontogeny in murine AD models [211]. Heteroplasmic mutations in the COX-1 gene (*PTGS1* 9q32-q33.2), specifically a COX gene subunit located on the mtDNA, were increased during ageing, but doubled in LOAD subjects [219]. Multiple mutations were detected and the mutation frequency increased with age [216]. The mitochondrial dysfunction cascade assumes that such genomic variability is at the baseline of mitochondrial activity. Age-related perturbed mitochondrial function loss, which influences brain ageing and initiates compensatory responses with Abeta production, tau phosphorylation, and synaptic degeneration [216]. It has been shown that Fus1, a tumor suppressor protein residing in mitochondria, is crucial in regulating inflammatory and stress responses by cytokine and NFkappaB activation [220]. Early signs of LOAD are produced by Fus1 knock-out murine models [220]. Mitochondrial dysfunction and cognitive abilities have been shown improved by blockade of *shc1* (in humans *SHC1* 1q21.2) and its p66shc isoform regulating life-span, ROS production, and apoptosis [221]. Triggered through growth and insulin receptors, sirtuin-1 related p66SHC activates the Ras-ERK pathway but inhibiting ERK1/2 activity. p66SHC promotes stress induced apoptosis, mediating steroid action through the redox signalling pathway [222].

1.4.7. Mitochondrial Oxidative Phosphorylation (OXPHOS)

According to this current insight, mitochondrial damage therefore marks LOAD disease onset. The mitochondrial dysfunction onset early in manifest LOAD seems to be a result of molecular defects in OXPHOS [223], where expression of COX-1 gene *PTGS1*, for redox coenzyme NADH [224], and for ATPase delta-subunit, were up- or downregulated [224]. Mitochondrial overproduction of ROS energy in the form of ATP is efficiently produced *via* OXPHOS in the mitochondrial respiratory chain [203], but in LOAD, the mitochondrial surface membrane produces free radicals *via* H_2O_2. With $Abeta_{42}$ deposition, ROS are produced and become virulent, whilst in addition, LOAD patients appear to have a deficient antioxidant defence system, which may allow for excessive oxidative damage in mitochondrial DNA [203].

1.4.8. Reactive Microgliosis

Another hypothesis on LOAD is based on age-dependent alterations in microglial number, their cytotoxic activation, and related TGFbeta-SMAD (TGF ligands, transcription regulators) signalling [225] in the context of neuroinflammation (Section 3.3.). Phosphorylation of MAPKs and the activation of the nuclear factor kappa B (NFkappaB) pathway, which cause the release of inflammatory cytokines, activate astrocyte and microglia hyperfunctionalities. MAPKs comprise three pathways (Section 2.1.), (a) extracellular signal-regulated protein kinases (ERKs), (b) stress activated protein kinases c-Jun-NH2-terminal kinase (JNK), and (c) the p38 pathway. The age-related changes in elevation of pro-inflammatory cytokines, and microglial cell production of ROS, combined with the mitochondrial dysfunction are currently strongly hypothesised as triggering LOAD neurodegeneration. The decline of lysosomal and mitochondrial functions thus would result in an exacerbated generation of ROS by microglia. Ageing effects are further present in the resulting microglial incapability to phagocytise Abeta [225].

1.4.9. Role of APOE Uptake and Removal

Apolipoprotein (APO) E is used by neurons for repair following oxidative damage [201], however, becomes cytotoxic if not cleared by autophagy. *APOE* epsilon4 genotype is a risk probably due to the APOE epsilon4 isoform being less efficient in Abeta clearance than the APOE epsilon2 and APOE epsilon3 isoforms [201]. The *APOE* allele epsilon4 isoform utilises the very low-densitiy lipoprotein (VLDL) receptor (*VLDLR* 9p24.2) [226, 227] instead of LDL receptor related protein *LRP1/APOER* (12q13.3), as used by epsilon2 and epsilon3 allele isoforms, for removal of Abeta-APOE epsilon4 particles through the BBB, thus slowing Abeta clearance. In addition, the *LRP1*, which is central in the cholesterol import by apolipoprotein E critical for neuron functioning, is gradually lost in LOAD progression. *VLDLR* is otherwise used in the cerebral triglyceride metabolism [227], and plays a crucial role for gyrification in early brain development. APOE epsilon4 thus effects on the lipid metabolism in decelerating or precluding Abeta autophagy, in disinhibiting cyclophilin A signalling in the pericytes of the cerebral vasculature, in accelerating neurodegeneration, and in causing leakages of the blood-brain barrier (BBB) [8] (Section 3.3.).

However, the *APOE* epsilon4 genotype is only present in 40-50% of LOAD cases [12, 13, 109] and, because of its relatively rare allele frequency of 13.7% [13], it not considered a common variant of risk genes. Clinical studies revealed that *APOE* epsilon4 carrier status did not influence CSF levels of $A\beta_{42}$, and cortical $A\beta$ accumulation is in fact independent of *APOE* genotype [228]. However, when in coincidence, their interaction produces most rapid cognitive decline in MCI patients [229, 230]. *APOE* epsilon4 status revealed malignancy in the Baltimore ageing study when combined with higher cortisol levels, depression, and chronic illnesses, such as diabetes, and hypercholesteinaemia [231]. Normative data from a prospective longitudinal study on CSF Abeta$_{42}$, *p*-tau$_{181}$, gliosis markers including a Pittsburgh Compound B (a radioactive neuroimaging contrast label of Abeta) PET neuroimaging study [232] indicate that, early in midlife, CSF Abeta$_{42}$ levels decrease, whereas cerebral Abeta$_{42}$ increase, as part of normal ageing. CSF NFT and gliosis neuroinflammation marker YKL-40 increased then in later adulthood to a stronger degree if a *APOE* epsilon4 allele genotype was present.

1.4.10. Role of Alpha-synuclein

An alpha-synuclein fragment is known as the non-Abeta component (NAC) of AD amyloid, and synuclein aggregation was confirmed for familial AD. The alpha-synuclein protein (*SCN* 4q22.1) interacts with tau, inducing its phosphorylation and aggregation while, simultaneously in reverse, tau enhances alpha-synuclein aggregation [233]. Protein alpha-synuclein, which is relevant for presynaptic vesicles and dopamine regulation, is thought to be pivotal to Lewy body pathologies PD, LBD, and TDP-43, thought to be central in non-dementive neurodegeneration, but is likely also present in LOAD [234], and is conceived to possibly play a certain role in its aetiopathogenesis [235]. Specifically, alpha-synuclein aggregation has been observed to be involved in neuroinflammatory processes in LOAD [236] and subsequent autophagy impairment.

2. NEURODEVELOPMENTAL DIFFERENTIATION AND LATE-LIFE NEURODEGENERATION

2.1. Introduction to Stress and Cerebral Plasticity

Enduring stress-provoking early-life experiences may influence childhood and adolescent cognitive and emotional outcomes by disrupting the maturation of the underlying brain networks [79]. Particularly, this leads to alterations of SMA and HPA stress networks with an impairment of attachment learning essential for respective mental representations [84]. Modest empirical support yet exists for disruptions in neurogenesis, myelination, and synaptic pruning as underlying structural changes [237]. Thereby, it is believed that ELS interferes with the critical waves of neurogenesis, synaptic overproduction, and stabilisation of synaptic connections [238]. Specifically, ELS was found leading to 4.2%-6.3% volume reductions in hippocampal *cornu ammonis* subfields CA2-CA4 and subiculum [239]. Multiple meta-analyses [240-242] have confirmed reductions of hippocampal tissue and reduction of total cerebral white matter volume in adults who experienced ELS.

Another key player (next to protein tau, Section 1.1.) in early neural development are the Glycogen Synthase Kinase (GSK) proteins: GSK-3 proteins play a pivotal role in controlling neuronal progenitor proliferation and neuronal migration [243, 244], and specifically also cytoskeletal organisation. It has been found that upstream and downstream signals modulating neuronal GSK-3 function are critical for neuroplasticity and cognitive functioning across the life-span [243]. In the differentiation of neuropil, GSK-3 proteins are activated downstream to growth factor triggered activation of the tyrosine kinase RTK family of receptors (including *e.g.* growth factor receptor classes, cytokine and hormone receptors) and the PI3K/Akt/p38 pathway, and are engaged in neurogenesis, neuron orientation, polarisation, axonal and possibly dendritic outgrowth, and synaptogenesis [244]. In the function of stabilisation of microtubule dynamics, GSK-3s interact with the microtubule activated protein 1B (*MAP1B* 5q13.2) and tau, as well as MEK and ERK. In the coordination of microtubule dynamics, there is interaction with Wnt, mTor, and stress-related MAP kinases [244, 245], with beta-catenin, c-myc, c-jun, and CREB at the transcriptional level.

2.1.1. GSK-3 and MAP Kinases in LOAD

Whilst GSK-3 proteins have been implicated in early neurodevelopmental disorders including neuropsychiatric conditions [244], its late-life roles make it a central focus of LOAD pathology. It has been assumed that, while GSK-3 kinases induce tau hyperphosphorylation [246, 247], the stress kinases SAPK/JNK and p38/MAPK are triggered by Abeta$_{42}$ in such a way that there is a parallel precipitation of *h*-tau, Abeta, JNK and p38 in neurites [248] or co-localisation with tau deposits in astrocytes [249, 250]. But in addition, Akt/GSK-3beta, MAPK and NFkappaB activity can be elicited by oxidative stress induction [251]. JNK and p38 MAPK, and NFkappaB are the key mediating links with environmental stresses, ROS production to transcriptional regulation of *BACE1,* and *APP* genes [252]. For translational regulation of *BACE1*, the key players are the eukaryotic translation initiation factor-2 alpha subunit 1 (eIF2alpha,

EIF2S1 14q23.3) and protein kinase R PKR (*EIF2AK2* 2p22.2), a double-stranded RNA dependent protein kinase [252]. The PKR stress signalling pathway was hereby contributing to activation of JNK, and insulin receptor substrate for the metabolic inflammasome in T2DM and LOAD [253] (Sections 3.2. and 3.3.).

2.1.2. The MAPK Family of Mitogen-activated Kinases

Three pathways of MAPK are established [254, 255]: ERK1/2 signalling pathway, c-jun NH_3-terminal kinases SAPK, and p38 MAPK. All three are characterised generically as the "three-tiered" MAPK pathways [256, 257], where MAPKKKs are receivers of a variety of inputs and their "gatekeepers", the mediators MAPKKs for input signals, and the core of kinases MAPKs as functional effectors of phosphorylation. To a certain degree, the three pathways can share phosphorylation activity and be dephosphorylated by dual-specificity phosphatases (DUSPs) (Section 2.3.) [256, 257].

Each of the MAPK pathways have established roles in neuronal differentiation and development, (b) functional neuroplasticity including learning and memory (long-term potentiation, LTP), (c) in neuronal injury and repair, and (d) in apoptosis in the context of neurodegeneration [249, 250, 255]. Each of these enzymes exists in several isoforms: ERK1 to ERK8; p38alpha, -beta, -gamma, and -delta; and JNK1 to JNK3 [185]. All three MAP kinases, ERK1/2, c-Jun NH_3-terminal kinases and p38 MAPK are involved in LTP and long-term depression (LTD) in the hippocampus, but by separate mechanisms [258]. In complement to NFkappaB, the three MAPK pathways trigger innate and adaptive immune responses upon activation by MAPKKK [256]. In LOAD, the three MAPK kinases dynamically interact with CREB and calmodulin-dependent protein kinase (CaMKII) in oxidative stress-mediated abnormal hyper-phosphorylation of tau and "exclusively" promote the pathogenesis of LOAD [259]. It has been concluded that conjoint activation of all three MAPK kinase pathways together is essential for LOAD, since (a) ERK and JNK are present in early Braak stages, whilst p38 is not, and (b) because healthy subjects can exhibit activation of each single pathway without signs of dementia pathology [260].

2.2. Glycogen Synthase Kinase 3 (GSK-3)

The glycogen synthase kinase 3 (GSK-3) is involved in the canonical Wnt/beta-catenin signalling pathway [217], where it acts, dependent on Wnt signals, in a proliferative manner; alternatively, in pro-apoptotic decision, it phosphorylates transcription factors. Of the GSK-3 proteins, the major two isoforms exist in GSK-3beta (*GSK3B* 3q13.33) and GSK-3alpha (*GSKA* 19q13.2), are encoded by 85% homologous separate genes, which produce additional splice variants [244]. GSK-3beta activity, regulated by alpha-globin transcription factor CP2 (*TFCP2* 12q13.12-13) [261], is dependent of Akt [262], which plays a key role in switching GSK-3beta between active and passive forms [263]. In neurodifferentiation, GSK-3beta signalling antagonises the PI3-K/Akt/mTOR signalling pathways [264] and CREB signalling [265]. Psychological stress-induced activation of GSK-3beta leads to activation of the NLRP3/IL-1beta pathway [266] involved in inflammasome regulation (Section 3.3.).

GSK-3beta has been shown to be the main link to neuroinflammation by targeting inflammasome receptor genes *NLRP3* and *TLR4* [267, 268] (Section 3.3.), NFkappaB, and inversely, with anti-inflammatory IL-10 activation [266]. In addition, it exerts in parallel immune functions by regulating T-cells and macrophages [266].

GSK-3beta is the key enzyme in the regulation of the cell cycle; it fulfills major roles in early brain development, energy metabolism, neuronal cell development, and body pattern formation. A lacuna of human GSK-3 studies for LOAD has been stated by De Paula [188], but recently it has been shown that both GSK-3alpha and GSK-3beta are also essential in plasticity of dendritic spines, and thus for reliability of neuronal signal transmission [269]. GSK-3alpha is responsible for short-term spine structural plasticity *via* LTD [269], whereas long-term GSK-3beta depletion (but also its overactivity, see below) generally reduces synaptic spine densities. In LOAD, GSK-3beta plays in neurons a pivotal role in the regulation of tau phosphorylation (*i.e.,* overactive GSK-3beta leads to hyper-phosphorylation of tau - alone [270] and together with CDK5 [200]): GSK-3alpha, GSK-3beta, and MAPK13 were found to be the most active tau kinases in phosphorylating tau at all epitopes tested [271]. There is a direct link between APP, beta-secretase activity, with GSK-3beta and tau phosphorlylation [272]. Abeta$_{42}$, however, triggers GSK-3beta only by means of interruption of Akt signalling [273], which induces NFT formation by tau hyperphosphorylation [246, 247]. If tau phosphorylation is reduced by GSK-3beta inhibitors, Abeta$_{42}$ neurotoxicity is curtailed [234]. Moreover, it has been demonstrated that GSK-3alpha is involved in the preparatory steps of Abeta synthesis [274]: GSK-3alpha inhibitor lithium blocks the production of Abeta$_{42}$ isomers by interfering with APP cleavage at the gamma-secretase step. GSK-3beta activity itself is negatively regulated by several signal transduction cascades that protect neurons against apoptosis [259]. In response to oxidant stress, GSK-3beta translocates to the mitochondria, increases cytotoxic ROS from mitochondria [259], and GSK-3beta is proposed to activate VDAC1 (Section 1.4.) phosphorylation that ultimately leads to mitochondrial dysfunction and synaptic damage in AD [217]. Activation of GSK-3beta, even in the absence of Abeta produces dendritic spine loss in neurons *in vitro*, whilst pharmacological inhibition of GSK-3beta prevents spine loss and increases expression of CREB-target genes like *BDNF* [217, 247].

There is also an epistatic genetic expression interaction between the genes: *GSK3B* is proposed to activate VDAC1 phosphorylation that ultimately leads to mitochondrial dysfunction and synaptic damage in AD [275, 276]. The interaction between *GSK3B* (rs334543) and Abeta precursor binding protein *APBB2* (4p14-p13) (rs2585590) was confirmed in a *post-mortem* LOAD autopsy sample [275]. Also, epistatic effects for genetic interactions have been found for *GSK3B* and the tau *MAPT* gene in LOAD, which determine beta-catenin levels [277].

2.3. The Extracellular Signal-related Kinases (ERK)

Extracellular signal-related kinases are one of three specific subsets of the MAPK family and have neurodevelopmental functions in meiosis, mitosis and post-mitosis of neu-

rons, activated by growth hormones, cytokines, and G-coupled receptors. The Ras-Raf-MEK-ERK [254] pathway is involved in the regulation of growth and cell differentiation pathways through phosphorylation cascades. Once the signalling cascade is activated by receptors or ion channels, signals are transduced by MAPKK to adaptors which activate Raf, MEK1/2 and ERK, the core components of the pathway [254]. Downstream, ERKs activate nuclear transcription factors NFkappaB, ELK1, c-fos, c-myk, GSK-3 and CREB *via* phosphorylation. Their main inhibitor is cAMP [254]. As with the GSK-3s, the two major isoforms are overlapping at 85%, are ERK2 (*MAPK1*=p42 22q11.22) involved in developmental growth, and ERK1 (*MAPK3*=p41 16p11.2) essential for T-cell development, and roles in enhanced neuron proliferation, and differentiation.

ERK and Akt are two major intracellular signalling pathways activated by BDNF involved in neuron survival [278, 279]. In LOAD, however, Abeta-induced OS was aligned with an increment of the activation of Akt and ERK1/2, and activity of GSK-3 [214]. Abeta$_{42}$ presence reduces Akt, while increasing GSK-3beta [217]. However, in contrast to GSK-3beta, ERK1/2 are not themselves involved in tau phosphorylation [280], but have been found early in NFT appearance preceding Abeta deposition [209, 281]. It has been shown that a brief signal involving Akt/PTB inhibiting ERK1/2 activation may have neuroprotective survival effects, whereas sustained ERK1/2 signalling with p38 and JNK co-activation could exert pro-apoptotic death signal effects [279]. In LOAD, aberrant expression of ERK and other MAP kinases has been observed [255]. Furthermore, there is growing evidence for the assumption that the neuroprotective effects of ERK are reversed in the context of peroxidation [255]. It is likely that phosphorylated ERKs become inhibited in neurons or are sequestrated in mitophagy (Section 2.6.) of defunct mitochondria [255]. Abeta$_{42}$ docks to the MAPK/ERK cascade, binds to alpha$_7$ nicotinic acetylcholine receptors (nAChRs) [208, 282], and downregulates both CREB and ERK2. Memory impairments are induced by direct Abeta$_{42}$ infusion to the hippocampus [283], which affects the NMDA/ERK/CREB pathway. These memory impairments are reversible by MEK inhibitors [284], making clear that ERK over-activation is responsible for memory defects in LOAD.

Memory formation is mediated by acetylcholine release and uptake by ACh-receptors, where LTP in the postsynaptic membrane activates ERK thus enabling neuronal plasticity. Plasticity-related protein synthesis is regulated by mTOR controlling LTM-related translation of synaptic scaffold proteins PSD-95 (*DLG4* 17p13.1) [257], and insulin receptor substrates IRS1/2 (Section 3.2), specifically in hippocampus and prefrontal cortex [285]. A co-activation of muscarinic ACh and beta-adrenoceptors facilitates the conversion of short term into long term synaptic plasticity through an ERK- and mTOR-dependent translation initiation [286]. In LOAD, mTOR and GSK-3 have been found interrupted by Abeta$_{42}$, precluding synaptic plasticity [287], which explains anterograde amnesia in LOAD. Microgliosis (Sections 1.4. and 3.3.) in LOAD is also induced by ERK, by involvement of the MAPK pathway through phosphorylation of MARCKS, a kinase involved in phagocytosis, expressed by microglia to Abeta plaques [288]. Phosphorylation of

ERK1/2 and p38 in Abeta$_{42}$-activated microglia triggers production of pro-inflammatory cytokines TNFalpha, IL-6 and IL-1beta, amongst others, from microglia [191] (Section 3.3.).

Kamat and colleagues [259] have proposed that ionotropic glutamate receptor (NMDAR) dysfunction with OS and reduction of free influx of Ca$^+$ is critical for LOAD development, because NMDARs are central to cerebral development. NMDAR are glutamate receptors decisive for strengthening or weakening synaptic responses. Synaptic activations by glutamate input and cell depolarisation changes determine circuit maintenance, which is crucial for mnestic encoding and storage of memory content [289]. However, it was shown that NMDAR is also a receptor for Abeta$_{42}$ oligomers, and the interaction of NMDAR and Abeta is neurotoxic [290]. Hence, NMDARs contribute to excitotoxicity in LOAD pathology caused by NMDAR dysfunctions under stress conditions. NMDARs induce ERK and CREB activation, and limit Ca^{++} influx [259, 291], whereby Abeta$_{42}$ promotes NMDAR dysfunction. In turn, improves and restores the stimulation of the ERK pathway NMDAR functioning and LTP in the hippocampus [292]. Aberrant Ca^{++}-flow in neurons affected by Abeta is associated with loss of dendritic spines and neuritic dystrophy, mediated in part by the Ca^{++}-dependent protein phosphatase calcineurin [259]. RCAN1 (*RCAN1* 21q22.1), the regulator of calcineurin, is involved in adaptive responses to OS induced by soluble oligomeric Abeta [201]. RCAN1 inhibits calcineurin, a *p*-tau phosphatase, leading to tau hyperphosphorylation [201], as triggered by GSK-3beta.

2.4. The c-jun N-terminal Kinases (JNK) Pathway

The c-jun N-terminal kinases (JNK, also termed Stress-Activated Protein Kinases, SAPK) consist of 16 isoforms derived from three closely related [257] genes: JNK1/SAPK-gamma (*MAPK8* 10q11.22) (four splice isoforms), JNK2/SAPK-alpha (*MAPK9* 5q35.3) (four splice isoforms) and JNK3/SAPK-beta (*MAPK10* 4q21.3) (eight isoforms), each with nine or ten exons (6a/b, and alternative translation initiation site for JNK3) [257, 293]. Generally, JNK activity regulates several important cellular functions including cell growth, differentiation, survival and apoptosis, and is triggered by a multiplicity of both biotic and abiotic stressors [257, 294]. JNK activating kinases (the so-called MAPK Kinases (MAPKKs)), MKK4 and MKK7 [293]. JNK serves as a "primer" or "master kinase" for GSK-3beta phosphorylation activity on tau [257], and putatively, a role in chromatin remodelling and transcription effect on many targets [257]. Here, JNK has recently been implicated in the regulation of histone H3 acetylation in trigeminal neurons following their exposure to an environmental neurotoxin and neuroinflammatory agent [293].

During early development, JNK1 is critical for neurogenesis, cell differentiation, proliferation, migration, early brain development, apoptosis and neurodegeneration [257], metabolic homeostasis, but also inflammatory conditions and cytokine production mediated by activation protein 1 AP-1, IL-8 and GM-CSF. JNK2 is critical for regulation of fibroblast regulation, macrophage and T cell activity, other immune functions, and wound repair [257]. JNK3 is later only

present in the CNS [257] and related to neurodegeneration [293]. Their central function is revealed by the localisation of JNKs in the mitochondria and microtubule network in addition to their roles in the nucleus to regulate gene transcription [293]. Here, JNK is a link between various divergent functions [257], such as interactions with nuclear transcription factors (*e.g.* c-myc, ELK1, sirtuin, beta-catenin, histone H3.1, runx2), hormones (glucocorticoid receptor GR, glutamate receptors, lipoprotein receptor LSR, Wnt co-receptor LRP6, lipid sensor SREBP1, nuclear hormone receptor PPAR-gamma), cytoskeleton proteins (*e.g.* tau, MAP2), vesicular transport adaptors (JIP1, JIP3), cell membrane receptors (BMPR2), and mitochondrial pore proteins (Section 2.6.) (*e.g.* beclin targets apoptosis regulators Bcl2, Mcl1, Sab).

2.4.1. Pro-apoptotic vs. Pro-survival Functions

JNK activity is responsible for cell cycle arrest and caspase recruitment initiated by Tumor Necrosis Factor (TNF)-related apoptosis [293]. In LOAD, the specific pathogenic role for JNK consists in priming phosphorylation of the Bcl2-related protein family member Mcl-1 to allow subsequent phosphorylation by GSK-3beta. Stress-induced Mcl-1 degradation therefore requires the coordinated activity of JNK and GSK-3beta [293]. The presence of oligomeric Abeta$_{42}$, then in turn, increased the levels of phospho-JNK [295] in hippocampal neurons. In reverse, the inhibition of *p*-JNK decreased Abeta-induced ER stress, and increased pro-survival mitochondrial proteins [296], suggesting that JNK is mainly responsible for detrimental effects of Abeta$_{42}$. This is further supported by the observation that pro-survival mitochondrial proteins including nuclear respiratory factor-1 (NRF-1), peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PPARGalpha), PGC1-alpha, and mitochondrial transcription factor A (TFAM) are suppressed by JNK [296], suggesting a negative correlation of JNK and CREB activation. JNK regulates *NC3R1* (Section 3.1.) by means of phosphorylation, thus inhibiting GR-mediated transcription. The biological effect of the GR phosphorylation consists of enhancement of its nuclear export [297].

2.4.2. Axonal Swellings and Vesicle Transport Proteins

Yearly appearing new reports have encircled that c-jun N-terminal kinase-interacting protein 1 (JIP1) (*MAPK8IP1* 11p11.2) has crucial importance for fast axonal transport of APP and tau in coaction with kinesins [298-301]. Cargo transport proteins exert a strong feedback function for JNK signalling, supported by the notion that JIP1 can bind several MAP3Ks (MLKs and DLK) as well as MKK7 [257]. JIP4, in contrast, is related to and specific for the p38 pathway [257-301]. Recent evidence confirmed a role of *MAPK8IP1* and its mutations in pathological APP transport due to affinity for 42-residue APP protein [302, 303]. The inclusion of soluble *h*-tau into the neuron soma and its aggregation by JIP1 has been identified as one key neurotoxic event in LOAD pathogenesis [304, 305]. Margevicius have in *jip1-ko*-mice shown that JNK signalling is critical for tau hyper-phosphorylation, loss of synapses and memory decline, even under conditions of Abeta overexpression [306]. In addition, APP is also phosphorylated by JNK [299, 300]. JNK can itself hyper-phosphorylate JIP1 and other JIPs [257-294], however, only part of its binding regions were affected by

the post-translational modifications, amongst them, those for JNK, MAP kinase kinase, and RAC-Ser/Thr protein kinase, but not those for kinesin or Abeta [294]. JIP1 has been identified linking APP protein and reelin receptor ApoER2, by docking to AID terminals on APP [294, 307]. This mechanism is, however, not confirmed in human *post-mortem* brains [307]. Cytokine-induced gamma-secretase activity is mediated by JNK and to be enhanced by the expression of a constitutively active form of MEKK1, implicating the JNK signalling pathway in the regulation of gamma-secretase activity [185]. JIP1-kinesin linkage in the JNK pathway includes MAPKKK and MAPKK [294, 307-309]. Kinesin light-chain subunits of kinesin-I (KLC) related to JIP3 (*MAPK8IP3* 16p13.3), were shown related to kinesin-1 and choline acetyltransferase accumulation indicative of axonal swellings were present in early Braak stages I-III before Abeta deposition [310].

2.5. P38 Mitogen-activated Protein Kinases (p38 MAPKs)

The p38 mitogen-activated protein kinases characterise the third MAP kinase pathways pertaining neuronal cell differentiation, apoptosis, and autophagy. Four p38 MAP kinase isoforms, p38alpha MAPK (*MAPK14* 6p21.31), p38beta MAPK (*MAPK11* 22q13.11), p38gamma MAPK (*MAPK12/ERK6* 22q13.3), and p38delta MAPK (*MAPK13/SAPK4* 6p21), have been identified. Analogous to the JNK/SAPK pathway, p38 MAP kinase is activated by a pleiotropy of cellular and extracellular stresses including excitotoxic shock, inflammatory cytokines, and endotoxins. In neurodifferentiation, p38 MAPK signalling antagonises the PI3K/Akt/mTOR signalling pathway [264] and CREB signalling [265]. p38 is one of the major oxidative stress sensors triggered by its upstream activator, Mitogen-Activated Protein Kinase Kinase 6 (MAPKK6) [201]. New evidence implies that also p38 will induce tau hyper-phosphorylation in presence of oxidative stress [311], and antioxidants will inhibit this mechanism [201]. Specifically, the formation of paired helicoidal filaments with microtubule-associated *h*-tau, which impairs intracellular traffic, is induced by p38 [312]. In neurons, the upstream activators of p38 consist of MLK and MAPKK3/6 [313]. Once activated, this pathway initiates production of the pro-apoptotic transcription factors c-myc, Pax6, neuronal transcription factor MEF2, p53, Elk1, CREB, NFkappaB, and inflammatory cytokines, termed the Senescence-Associated Secretory Phenotype (SASP) [314, 315]. The SASP is mainly released from aged astrocytes in the LOAD brain [315], induced by the p38 MAPK pathway causing DNA damage by strand breaks [316]. *Via* its substrate MSK1/2, p38 MAPK is also related to the histone H3 [317].

2.5.1. Neuroinflammation and Synaptic Impairment

P38alpha MAPK, but not the other isoforms, shape the pro-inflammatory response (Section 3.3.) in the brain, released from microglia [317] and astrocytes [301, 318], including IL-1beta and TNFalpha release [319, 320]. There is evidence that also p38delta MAPK may play roles in inflammatory processes, TD2M and neurodegeneration [321]. Another cytokine, IL-33 released by oligodendrocytes, and its receptor ST2 on microglia, are involved in enhancement of Abeta phagocytosis by microglia [322]. Microglial activa-

tion on neurons have been found mediated by activation of p38alpha MAPK, because activated microglia stimulated p38-MAPK phosphorylation in neurons, thus influencing IL-1beta towards tau phosphorylation and increasing synaptophysin levels [323], the presynaptic synaptic vesicle protein [324] encoded by *SYP* (Xp11.23), as well as presynaptic synapsin I and postsynaptic glutamate receptor I [325]. Thereby, p38 MAPK contributes to microstructural alterations in synapses, increased neurotransmitter release and loss of plasticity [325]. Also in astrocytes, p38 MAPK has functions in glutamate excitotoxicity involved in AD pathophysiology [318]. P38 MAPK activity suppresses BDNF signalling [326], upregulated by IL-1beta [318]. BDNF signal transduction is dependent on phosphorylation of insulin receptor substrate 1 (IRS-1, Section 3.2.), a protein coupling activation of the BDNF receptor TrkB BDNF/NT-3 neurotrophic factor receptor (encoded by *NTRK2* 9q21.33), to downstream signalling pathways regulating CREB [326]. This mechanism can, however, be prevented by preceding BDNF activation [327].

In the inflammatory response following high-fat diet induced insulin resistance (Section 3.2.) by p38 MAPK, together with JNK pathway, and with the inflammatory NFkappaB pathways (Section 3.3.); this is accompanied by Abeta deposition, NFT formation and decrease in synaptic plasticity [328]. P38 and JNK develop neurotoxic properties under anaesthetic influence of isoflurane, whereas ERK1/2 are more neuroprotective [329].

2.5.2. P38 in LOAD Pathogenesis

As mentioned, p38 is one of the proteins involved in hyper-phosphorylating tau [201] but in combination with MEK3/MAPKK3 [271]. As a sensor for neuroinflammation, p38 MAPK expression reduced the lysosomal degradation of BACE1, enhanced BACE1 protein activity, and also inhibited autophagy [330]. At an early stage of LOAD pathogenesis, p38gamma MAPK located postsynaptically at scaffold protein PSD-95 sites was found to induce tau phosphorylation, which was found protective against Abeta$_{42}$ action [324]. Although only *in vitro*, this finding may suggest that, initially, tau phosphorylation may have a self-repair quality at postsynaptic locations. Clinical studies have shown that p38 and JNK increase with LOAD illness duration, which is related to memory performance decline [331].

The receptor for advanced glycosylation specific products (*AGER* 6p21.32) (Section 3.2.) activates p38 MAPK phosphorylation brought about by Abeta, resulting in LTP impairment [332]. p38 facilitates hippocampal gamma and theta EEG oscillations through ionotropic NMDAR [333], and is therefore pivotal for synaptic functioning. This is related to post-synaptic density protein PSD-95 (*DLG4* 17p31.1) [320], a marker of synaptic integrity [334, 335]. From observations in murine AD models it was inferred that synaptic impairment in LOAD consists of suppression of LTP and enhancement of LTD [336]. LTD in the dentate gyrus and entorhinal cortex [332] is induced by p38 MAPK under soluble Abeta$_{42}$, and is facilitated by metabotropic group I receptors GluR1/5 (*GRM1* 6q24.3, *GRM5* 11q14.2-3) [313, 336, 337] and ionotropic AMPA-type subunits GluR1-4 (*GRIA1* 5q33.1, *GRIA2* 4q32.1, *GRIA3* Xq25, *GRIA4* 11q22.3) [338], striatal enriched protein tyrosine

phosphatase STEP (*PTPN5* 11p15.1), and caspase-3 activation.

Recently it has been found that p38 MAPK and ERK1/2 play a pivotal role in the regional distribution of Abeta$_{42}$ into hippocampus and parietal cortex [229, 339]. The regional distribution of Abeta$_{42}$ is accompanied by intensified nAChRalpha$_7$ expression [339, 340]. By interacting of p38 with LDL receptor protein 1 (*LRP1/APOER* 12q13.3), Abeta$_{42}$ was internalised into cortical neurons and astrocytes, and distributed into mitochondria, lysosomes, and endoplasmic reticula [339]. This LDL/APOE receptor is crucial for the alpha$_2$-macroglobulin-mediated clearance of Abeta plaques. Expression of this gene decreases with age and has been found to be lower than controls in brain tissue from LOAD patients. However, this clearing mechanism is missing in *APOE* epsilon4 homozygosity (Section 1.4.).

2.6. Role of (Macro-)autophagy Impairment in LOAD Pathophysiology

Escalation of cytoplasmic protein aggregation is a common feature of neurodegenerative disorders. By means of their lysosomes, cells self-digest protein aggregates and damaged organelles [341], and impairment of this autophagic process accelerates ageing specifically in microglia [342]. Neurons in LOAD suffocate from swellings induced by immature autophagic vacuoles leading to dystrophic and degenerating neurites, caused by physical impairment of retrograde transport by lyosomes to cell somata [343, 344]. The key trigger of autophagic clearance is release of mTOR signalling in response to growth factor sensing indirectly activating PKB/PI3K/Akt activating the mTOR activator Ras homolog enriched in brain (Rheb) [236]. Closely tied to neuroinflammatory processes (Section 3.3.) [236], autophagy is genetically triggered from autophagy genes orchestrated by the identified master regulators *NFE2L2/NRF2* (2q31) (nuclear factor, erythroid 2 like 2) [224, 345] and transcription factor EB (*TFEB*) (6p21) for lysosomal pathways [346, 347], where *NFE2L2* is related to both *APP*/Abeta and *MAPT*/tau expression in LOAD. Under physiological conditions, stress-responsive transcription factors including p53, NFkappaB and transcription master activator STAT3 (*STAT3* 17q21.2) have been found regulating the autophagic response [348], and the p53, TNFalpha, mTOR pathway have been described central to LOAD [236, 341]. Specifically, the interplay between p38alpha MAPK14 and the Akt/mTOR pathways is decisive for pro- *vs.* anti-inflammatory direction in response to environmental stress [349], where a disturbance leads to impairment of plaque macroautophagy. The resulting insufficient clearance of Abeta oligomers of all isoforms causes cell-to-cell transmission of Abeta oligomers [184], which promotes propagation of neurotoxic elements.

The role of autophagy in neurodegeneration has been described [236, 350, 351] in the context of mitochondrial dysfunction [236]: A reduction of autophagic flux leads to a persistence of dysfunctional mitochondria and mitochondrial fissures [352], which generate ROS and are vulnerable to apoptotic and inflammatory agents. One such agent, regulator beclin-2, induces mitochondrial rupture-induced apoptosis [353], where the mitochondrial permeability transition

pore (mPTP) results in influx of solutes and water, as well as inner membrane swelling. Destruction of the outer membrane releases cytotoxic proteins into the cytosol and produces necrotic neuron death.

In LOAD, ER stress inducing autophagy is triggered by aggregated Abeta$_{42}$ [354-356] and decreased solubility of parkin, an E3 ubiquitin ligase involved in autophagy [357] and mitophagy [351]. Expression of parkin, in turn, ubiquitinates both intracellular and extracellular Abeta, stimulating the autophagy process initiating regulator beclin-1 (ATG6) (*BECN1* 17q21.31), while attenuating caspase activity [358]. GSK-3beta inhibits mTOR by activating the autophagosome enzyme ULK1 (*ULK1* 12q24.33). GSK-3beta modulates protein aggregation through the phosphorylation of the macroautophagy cargo receptor NBR1 (*NBR1* 17q21.1) [359]. Activation of the *ULK1* phosphorylates beclin-1, which regulates the activity of transcription factor vps34 [360] normally leading to autophagosome formation [351]. Loss of *BECN1* hampers the phagocytic function and induces inflammatory responses [361] in microglia and disruption of trophic support from astrocytes [291, 354]. The completion of the autophagosome is marked by the release of LC3beta-II (microtubule-associated protein-light chain 3 beta 2, ATG8, *MAP1LC3A/B* 16q24.2) from the autophagosome membrane [236], a marker found related to cognitive decline [342]. Abeta$_{42}$ was found hyperactivating the phosphoinositide3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) axis, which plays a central role in proteostasis, already at MCI/"limbic" Braak stage III [362]. mTOR activation reduces autophagy and induces insulin resistance. Activation and deactivation of mTOR, a kinase implicated in ageing and nutrition [352], is in mutual dependence of autolyosomal substrate digestion [350].

3. ENDOCRINOLOGICAL, METABOLIC, AND NEUROINFLAMMATORY PROCESSES IN LOAD

3.1. Stress Hormones and LOAD Pathology

Amyloid pathology is assumed causative for apoptosis in neurotransmitter producing neuron groups. Their cellular dysfunction is held responsible for disturbances in acetylcholine, noradrenaline, and serotonin transmitter systems [212]. However, the focus is kept here on cortisol, noradrenaline, and neuropeptide Y (NPY), which characterise stress systems; all three have been shown to trigger release of pro-inflammatory cytokines (Section 3.3.), and to bias thyroid hormones and immune reactions [363-365]. It is commonly accepted that at least noradrenaline and glucocorticoid systems are mutually interrelated [366, 367].

3.1.1. Noradrenaline Signalling

The sympathetic branch of the ANS is triggered from the amygdala (central and basolateral nuclei) in the presence of external stress signals [368]. Noradrenaline is considered the principle neurotransmitter of the SNS branch. In the CNS brainstem, the main conversion (from dopamine) site in the rostral pons for noradrenaline is the locus caeruleus (formerly coeruleus, LC) besides the adrenal medulla. Their projections to the major midbrain and cortical regions are exerted by noradrenergic neurons, and specifically target transentorhinal memory structures [289]. Abeta$_{42}$ deposition is

increased in these noradrenaline projection areas from locus caeruleus [367]. It is hypothesised that CRH afferents from the central amygdaloid nucleus into the locus caeruleus mediate the conveyance of environmental stresses [367].

Catecholamine release is directly related to SNS hyperreactivity, primarily mediating short-term stress response (also termed sympatho-medullo-adrenal (SMA) axis). SMA mediation of stress is under regulation by the catechol-o-methyltransferase (*COMT* 22q11.2) gene [369]. During normal ageing, COMT and brain-derived neurotrophic factor (BDNF) showed additive effects on decline in executive functioning in interaction with apolipoprotein E metabolism [370]. The *COMT* SNP rs4680 has also been found associated with LOAD, with its Met allele interacting with *APOE* epsilon4 status [371, 372]. Stress reactivity mediated by noradrenaline signalling is also involved in insulin release *vs.* inhibition from pancreatic beta cells. This mechanism ensures that blood glucose levels rise in stress states, but may also be causative for abnormal cerebral insulin signalling and insulin resistance in LOAD (Section 3.2.). Insulin release is stimulated by beta-adrenoceptors, and inhibited by adrenoceptor alpha$_{2A}$ [373]. These receptor types are also associated with LOAD.

3.1.2. Adrenoceptor Gene Loci and LOAD

There are overall nine subtypes of adrenoceptors, the majority of which have proven functions in spatial and emotional memory, and specifically in STM [374]. The known implications of adrenoceptors for LOAD are currently confined to alpha$_{2A}$, beta$_1$, beta$_2$, and beta$_3$-adrenoceptor subtypes. Adrenoceptor alpha$_{2A}$ (*ADRA2A* 10q25.2) has been shown to mediate the interaction between *SORL1* (11q24.1) (the neuronal APOE receptor, Section 1.4.) and the sortilin-related vaculuolar protein sorting VPS10 domain containing receptor 1 (*SORCS1* 10q25.1). Stimulation of the alpha$_{2A}$ adrenoceptor increases APP redirection into endosomes and miscleavage by beta-secretase [375]. Adrenoceptors beta$_{1-3}$ are more specifically involved in metabolic processes, their binding triggers intracellular concentrations of cAMP as second messenger. In their genomic bases, *ADRB1* (10q25.3) releases heterodimers that influence BMI, body weight regulation, blood pressure, and basic metabolic rate. Beta$_1$-adrenoceptor gene *ADRB1* interacts with guanine nucleotide-binding protein subunit beta$_3$ (*GNB3* 12p13.31) to increase LOAD pathophysiology [376]: the *GNB3* T allele increases risk for homozygosity of the *ADRB1* C allele. The co-expression of *GNB3* T and *ADRB1* C alleles produced increased cAMP levels and MAPK signalling.

Specifically, adrenoceptors beta$_2$ and beta$_3$ have in murine models been observed to interact with core LOAD pathophysiological processes (Section 1.4.) [374, 377]: Abeta can bind to the beta$_2$-adrenoceptors, and their activation triggers the protein kinase A (PKA)-JNK pathway [378], resulting in tau hyper-phosphorylation. However, a restoring effect for memory functions has, in contrast, also been found for beta$_2$-adrenoceptor [379]. Different polymorphic forms, other variants, and epigenetic modification of the *ADRB2* (5q31-32) gene are related to its mediation of hepatic blood flow with glycogenolysis and gluconeogenesis, and insulin secretion from the pancreas. Murine *ko*-studies indicated that β$_2$-adrenoceptors expressed on astrocytes are es-

sential in LTP and spatial memory [380]. Polymorphisms Gly16, Glu27 and the beta$_2$-adrenoceptor haplotype Gly16 Glu27 have been associated with LOAD, but dependent on *APOE* epsilon4 status [381]. Specifically, blockade of beta$_2$-adrenoceptors reduced Abeta production induced by acute stress in mice [377]. The haplotype of both the 16Gly allele and the 27Glu allele of *ADRB2* exhibited increased risk for LOAD, and a significant interaction with *APOE* epsilon4 [381]. Activation of beta$_2$-adrenoceptors with presenilin-1 increased gamma-secretase activity [382] in lysosomes, upregulating Abeta$_{42}$ cleavage, and subsequent plaque deposition. *ADRB3* (8p11.23) is mainly expressed in brown and white adipose tissue, and becomes activated in energy expenditure, thermogenesis and lipolysis. Hypermethylation of the *ADRB3* gene promoter in blood and visceral tissue is associated with metabolic disturbances [383], such as dyslipidaemia. Reductions of all adrenoceptor subtypes have been observed in LOAD pathology [374].

3.1.3. Noradrenaline Transporter Gene

The noradrenaline transporter gene *SLC6A2* (*NET* 16q12.2) is central to noradrenaline homeostasis and presynaptic reuptake. Its SNP *rs2242446* has been correlated to anxious arousal and PTSD [384]. *SLC6A2* expression is restricted to noradrenergic neurons that innervate the adrenal medulla. An epigenetic mechanism (hypermethylation of CpG islands in the *NET* gene promoter region) that results in reduced expression of the noradrenaline has been implicated in stress-related disorders [385]. Oxidoreductase dopamine-beta-hydroxylase (*DBH* 9q34.2) converts dopamine into noradrenaline, and may therefore influence noradrenaline levels. In combination with cytokines, a SNP (allele rs1611115) of *DBH* and polymorphisms of the pro-inflammatory cytokine genes, *IL1A* and *IL6* (Section 3.3.), were observed associated with LOAD [386].

3.1.4. Noradrenaline, Tauopathy and Locus Caeruleus Degeneration

Findings from the Lund Longitudinal Dementia Study [387] suggest that pontine locus caeruleus (LC) degeneration is common in and typical for LOAD. Relations of the degree of LC degeneration with white matter lesions, LOAD severity, nor duration have not yet been substantiated [387], however, this could be based on the scoring method used. Whether there are age-related changes in the LC is currently undecided, as small databases prohibit any conclusions [289]. *Post-mortem* findings in LOAD indicate that the amount of LC neuron loss is about 50% [289], and its level coincides with NFT deposition found in children from 6 years onwards [289], thus possibly providing a direct neuropathological link with ELS. Noradrenaline converted in the 15k LC neurons has additional anti-inflammatory functions on neuron membrane surfaces, glial cells and blood vessels in the neocortex and hippocampus [388, 389]. Noradrenaline induces microglia to suppress Abeta-induced production of cytokines and their phagocytosis of Abeta [389]. It is therefore likely that NFT deposition in LC and loss of its neuronal projections could promote increased Abeta deposition in LOAD brains [389]. In addition, have noradrenaline depletion studies resulted in impairments of working memory and social memory [374]. It is furthermore suspected that noradrenergic hypofunction is an impairment to effective

neuron-glia interaction, finally resulting into abnormal glial reaction, and fostering neuron degeneration [388]. Nucleus Basalis of Meynert (NBM) degeneration is also ubiquitous in LOAD, however NBM neuron loss not unique to LOAD, but also present in Parkinson's, Pick's disease (FTD), and Lewy body dementia. Acetylcholine depletion is also common amongst those neurodegenerative diseases, and thus not specific to LOAD.

3.1.5. Glucocorticoid System Involvement in LOAD

Cortisol secretion is a physiological response to cope with repeated anxiety triggers resulting from chronic stress [390-392]. Glucocorticoid excess has implications for ageing by reducing life-spans [393]. Cortisol levels in LOAD are directly related to hippocampal sizes, and hippocampus size predicts cognitive performance with increasing age [394]. In addition, CSF cortisol levels increase from MCI progression to LOAD, suggesting an increase during pathogenesis [395, 396], where cortisol increases amyloid neurotoxicity [397]. Cortisol serum levels are elevated in LOAD patients, where they are believed to contribute to a neuroprotective effect, as inverse correlations with *p*-tau and tau-Abeta relations, and positive association in CSF with Abeta$_{42}$, suggest [398]. Similar effects were found for non-demented *APOE* epsilon4 carriers [228]. In the Baltimore Memory Study [231], cortisol levels tended to negatively associate with memory domains language, visuospatial, visuomotor, executive *etc.*; however, two alleles of epsilon4 showed strong negative predictions in all memory domains.

3.1.6. Corticotropin-releasing Hormone Gene

Long-lasting stress effects are maintained through secretion of the Corticotropin-Releasing Hormone (CRH) resulting in HPA axis bias. In contrast to SMA activation, however, cortisol release in response to repeated stress habituates more quickly [399], but leads eventually into immunodeficiency by impairing CD19-promoted B-cell generation [400]. Synthesised in the hypothalamic paraventricular nucleus (PVN), CRH release is also triggered by TNFalpha and IL-6 resulting from inflammatory states, thus dampening the immune response, and controlling the inflammatory response. Environmental stress activates PVN CRH neurons resulting in a repertoire of stress-related coping behaviours [401]. The expression of *CRH1* (8q13.1) is normally inhibited by a negative feedback loop consisting of peripheral glucocorticoid signalling through GRs in hippocampus, hypothalamus and pituitary to the HPA [130, 365]. A second vertebrate corticotropin-releasing hormone gene *CRH2* has recently been discovered, but there is still a lacuna in human research [402]. Significant reduction in *CRH1* expression has been observed in association with Alzheimer's disease [403].

The glucocorticoid cascade hypothesis holds that LOAD and co-morbid depression being caused by accumulation of free cortisol responsible for age-related hippocampal tissue damage [397]. Strong co-morbidity of depression and LOAD exists at 50%. *Post-mortem* studies (although with small *N*) show that the PVNs of LOAD patients have significantly more CRH mRNA than healthy controls, but less than depressed [397]. Cortisol effects consist in (a) modulating neuroplasticity, circuitry and neurotransmitter systems, (b) regulating neuron death or survival, (c) releasing of structural

proteins from glia, and (d) suppressing myelin content [404]. LOAD is associated with profound changes in HPA, with chronic hyperactivation of CRH neurons and plasma hyper-cortisolaemia [397], which is related to MMSE scores and *APOE* epsilon4 presence. Correlational studies indicate that, in LOAD, hypercortisolism is associated with disease severity, disease progression and accelerated cognitive decline, as indicated by hippocampal atrophy [404].

3.1.7. Interactions of Glucocorticoid Receptor with MAPK and Cytokines

In humans, the glucocorticoid receptor protein is encoded by the *NR3C1* (5q31-32) gene. *NR3C1* has a function as nuclear transcription factor [405], whereby glucocorticoids induce mitochondrial DNA transcription, and so bias mitochondrial physiology in the hippocampus. The *NR3C1* gene consists of 9 exons, where alternative splicing in exon 9 generates mainly two highly homologous receptor isoforms, labelled alpha and beta [406]. It is bound in inactive state in the cytoplasm until glucocorticoid transgresses the membrane and the ligand-receptor conglomerates dock to Glucocorticoid-Response Elements (GREs) in the promoter regions of glucocorticoid-regulated genes [215]. These GREs are either facilitative or inhibitive, dependent on positive or negative binding, to transcription and transactivation [406], respectively. As floating monomers, the interaction with other transcription factors such as NFkappaB and CREB is repressive for dependent genes, such as those of cytokines IL-1beta, IL-2, TNFalpha and inducible NO-synthase (iNOS) [407, 408].

As mentioned, alternative splicing of *NR3C1* generates two main splice variants, the GRalpha and the minor isoform GRbeta [409], with three other isoforms [410]. GRbeta retains the ability to bind DNA and has been observed acting as negative inhibitor of GRalpha [409, 410]. GRalpha has at least 8 different translation initiation sites resulting in isoforms A, B, C1, C2, C3, D1, D2, and D3, which may be restricted to specific cell types, thus resulting in highly individual susceptibility patterns [411] in specific tissues. Loss of GR is observed during both normal ageing and LOAD, and more pronounced in presence of NMDARs [404], and similar processes were observed under stress.

There exists interference of GR with signalling pathways of MAPKs: ERK1/2, p38 MAPK, and JNK, GSK-3/Wnt signalling. Specifically, GR induced the expression of MAP stress protein DUSP1, presumably *via* the binding of GR to putative GREs in regulatory regions of the *mkp-1* promoter [412]. Equivocal results were, however, found on the role of GSK-3beta. There is a reciprocal interaction of GRE with CREB, activator protein AP-1, NFkappaB, and NGFI-B [409, 411, 412]. Transactivated genes through GREs include the insulin-like growth factor binding protein 1 (*IGFBP1* 7p12.3) FK506 binding protein 5 (*FKBP5* 6p21.31) (see below), NFkappaB inhibitor alpha (IkBa, *NFKBIA* 14q13.3), anti-inflammatory interleukin 10 (IL-10) receptor activator of nuclear factor kappa-B ligand (*RANKL* 13q14.11) [409]. Transrepressed genes through tethering include pro-inflammatory TNFalpha, IL-6, IL-8, IL-11 [409]. Transrepression has been reported also for a growing list of immune-regulating transcription factors, including NFkappaB, AP-1, CREB [410], of transcription coactivators such as interferone

regulatory factor IRF3 (*IRF3* 19q13.33) [410, 412]. Epigenetic modifications have been observed in *NC3R1* with interference with histone tail modifications on H3 [412], and for *HDAC2* (6q21) in association with NFkappaB [410] activation. The HPA deregulation typically present in manifest LOAD can be targeted by selective synthetic GR regulating agents [413]; their application in murine models resulted in Abeta clearance, restoration of hippocampal vesicle protein synaptotagmine, and reduction of caspases.

3.1.8. Corticotropin Receptors and ACTH Signalling

There are two subtypes of CRH receptors, mainly located in the anterior pituitary, also in amygdala, hippocampus and locus caeruleus. Their activation product, ACTH, is synthesised in basophile neurons of the anterior pituitary under regulation by CRH, and triggers release of glucocorticoids from the adrenal medulla [365]. Like free cortisol, ACTH levels are therefore increased in LOAD. The HPA signalling pathway is mainly dependent on corticotropin-releasing hormone receptor type 1 (CRHR$_1$) polymorphism on exon 6 of *CRHR1* (17q21.31) [414]. CRHR1s are most abundant within the hippocampus, but also present in liver tissue. *CRHR1* activation has been demonstrated to introduce hippocampal tau hyper-phosphorylation [403]; stress-induced *h*-tau accumulations were observed specifically in dendritic and axonal processes, with an increase of axonal mitochondrial transport, but with CREB and BDNF downregulation, which was reversible by GSK-3beta inactivation [403]. The *CRHR2* (7p14.3) gene has been described involved in cardiovascular homeostasis, PTSD, and susceptibility towards stress [415].

3.1.9. Cortisone-cortisol Interconversion HSD-11β Gene Loci

The protein encoded by the *HSD11B1* (1q32-q41) gene is a microsomal enzyme that catalyses the conversion of the stress hormone cortisol to the inactive metabolite cortisone and reverse. Because of its amplificatory action of active glucocorticoids, isoform 1 HSD-11β, has been assumed being a pathogenic factor in MetS, T2DM, and age-related cognitive decline [416]. Isoform 11β-HSD-2 has been implicated in neurodevelopmental susceptibility for the programming of diathesis towards chronic stress [417]. Too much cortisol can lead to central obesity, and several variations (*rs*10082248, *rs*2298930, and *rs*4545339) in the *HSD11B1* gene have been associated with obesity and insulin resistance in children [418]. The regulation of both 11β-HSD isoform-genes is dependent on NFkappaB [419] in adipose tissue. *HSD11B2* (16q22.1) protects cells from the growth-inhibiting and/or pro-apoptotic effects of cortisol, particularly during embryonic development. Mutations in this latter locus cause the syndrome of apparent mineralocorticoid excess and hypertension. Polymorphisms can regulate maternal cortisol levels *in utero* and regulate postnatal weight gain [420].

Of eleven genes tested from the glucocorticoid system (corticotropin-releasing hormone *CRH* (8q13.1), corticotropin-releasing hormone binding protein *CRHBP* (5q13.3), ACTH receptor 2 *MC2R* (18p11.2), 11β-hydroxysteroid dehydrogenase type 1 and 2 (*HSD11B1* 1q32.2, *HSD11B2* 16q22.1), glucocorticoid receptor *NR3C1* (5q31.3), gluco-

corticoid modulatory element binding protein 1 and 2 *GMEB1* (1p35.3), *GMEB2* (20q13.33), steroidogenic factor 1 *NR5A1* (9q33.3), nuclear receptor coactivator 2 *NCOA2* (8q13.3)), only *HSD11B1* SNPs rs846911 and rs860185, representing a rare T-A and a frequent C-A haplotype were found directly related to LOAD [12]. However, the significance level of this association was comparable to the significance of the *APOE* epsilon4 allele, but the effect size with an OR=6.2 was more than doubled [12].

3.1.10. FKBP5 and EGR1 in LOAD

Two other genes have gained considerable interest for their stress programming capabilities through epigenetic mechanisms. The co-chaperone FK506 binding protein 5 (*FKBP5* 6p21.31) in the cytoplasm is part of the GR-inactivating immunophilin proteins preventing and reducing affinity of GR to its ligand glucocorticoid [406]. GR and HPA [421] co-regulator *FKBP5* negatively regulated glucocorticoid function pertaining to PTSD [422]. Four SNPs significantly interacted (rs9296158, rs3800373, rs1360780, rs9470080) with ELS in childhood and later PTSD [423]. The functional *FKBP5* risk T-allele (rs1360780), which is related to HPA axis hyperreactivity, showed demethylation at intron 7 of the *FKBP5* gene [424]. This activation effect has been found being ageing-related and having impact on brain structure [425-427]: the T-allele carriers were found deficient in cognitive-attentional functioning, based on GM volume in the dorsal anterior cingulate and WM disintegrities. Yet, up to date, no clear associations with LOAD were reported in humans for calcineurin (Section 1.4.) inhibitor *FKBP5*. However, the binding proteins 51 (*FKBP5* 6p21.31) and 52 (*FKBP4* 12p13.33) [74, 428] are initiators of *NC3R* activation, and these proteins have been found regulative for (a) tau oligomerisation, and (b) Abeta toxicity [429].

Its downstream target, the early growth response 1 EGR-1, is a nerve growth factor-inducible protein (NGFI-A) and member of a family of immediate-early gene-encoded transcription factors. Its binding site located in the hippocampal *NR3C1* gene exon 1F (1_7 in animals) promoter has become of interest due to hypermethylation as a result of ELS [406], related to PTSD and depression. The exon 1F nuclear receptor *NR3C1* gene promoter, with at least 14 splice variants [406], has come to focus of neuropsychiatry because of ELS mediation (Section 1.3.). Brains of suicide victims who experienced ELS by childhood abuse, revealed reduced GR mRNA and increased levels of methylation of the *NR3C1* exon 1F, which regulates GR expression in the hippocampus [98]. Anacker and colleagues describe that *EGR1* also mediates compensatory activation to early stress responses [422] by maternal licking and grooming, which then increases EGR-1 binding in hippocampal *NR3C1* exon 1_7. In parallel, glutamate decarboxylase Gad1 (*GAD1* 2q31.2) [422], related to insulin signalling, increases. In result of both activations, histone code H3K9 acetylation stabilises GR promoter initiation in the hippocampus. Histone code H3K9ac was found critical for the recruitment of TFIID at the IFNgamma locus, and is hence considered important in eliciting immune responses. Negative ELS long-term effects are further mediated by the neuronal transcriptional repressor REST [169] (Section 1.3.), the expression of which is reduced in LOAD. However, *EGR1* itself is not methylated in the hippocampus, yet, is believed relating indirectly to expression of the *PSEN2* locus.

3.1.11. NPY and Interactions with Growth Factors

Properties of NPY in CNS consist of neuroprotection, stimulation of neurogenesis, inhibition of neuroinflammation, stimulation of autophagy, and increase of trophic metabolism [103]. In LOAD, severely altered structure of NPY neurons exist in cortex and hippocampus, reduction of NPY binding sites, and lower NPY CSF and plasma concentrations [103]. NPY neurons have been found damaged at early stages of LOAD, suggesting NPY system may have a role in pathogenesis [430], but which is not yet characterised. NPY has a resilience function in ELS through moderation of contextual fear learning, possibly exerted though *NPY1R* (4q32.2) in the amygdala and prefrontal cortex [431]. A resilience function has also been postulated for NPY in LOAD [430], based on *in vitro* studies. It is speculated that anxiolysis mediated by NPY2/NPY5 receptors may prevent excitotoxicity by inhibiting glutamate release. However, in humans, have genomic association studies hitherto failed to find respective effects. In rat experiments, pharmacologically induced LOAD-simulations were counteracted in terms of protective effects for spatial memory encoding and retention [431], mediated by NPY1R. NPY administration reduced Abeta$_{40}$ in neurons, consistent with the observed loss of NPY neurons in LOAD [431]. NPY interacts with ERK1/2 and JNK/SAPK pathways through NPYR1, 2 and 5 [103], mutual upregulation of NPY and BDNF expression. NPY might induce BDNF upregulation through CREB phosphorylation, because BDNF and its receptor TrkB are CREB-target genes.

3.2. Indirect Metabolic Long-term Mediation of Stress

3.2.1. Interaction of Metabolic Factors with Stress and ELS Programming

A considerable part of the GWAS-confirmed risk genes (Section 4.1.) points towards engagement or alterations of metabolic processes as essential for LOAD abnormalities. Such metabolic processes as the moderators of cognitive function include inflammatory mediators, rheological factors, and dysregulation of the HPA axis [432]. Many of the long-term ELS effects induced by *e.g.* maternal separation and isolation cause programming towards weight gain, glucose intolerance, insulin resistance, and other MetS components [92] (Section 1.3.). There exists direct longitudinal evidence of ELS effects by maternal separation into senescence related to LOAD symptoms demonstrated by Solas and colleagues [153] in a rat model: ELS induced altered HPA axis reactivity evincing persistent cognitive impairments. Ageing effects there consisted in reductions in insulin receptors, phosphorylated insulin receptors, in MAPK-related signalling pathways (*p*-Akt, *p*-GSK-3beta, *p*-tau, and *p*-ERK1/2 levels), and in the plasticity marker Arc, the regulator of Notch signalling [433] (Section 1.1.). The activity-regulated cytoskeleton protein Arc (*ARC* 8q24.3) [153] is a CREB binding [434] synaptic protein responsible for stabilisation of neural circuits arising from mnemonic encoding, in the MAPK signalling cascade under regulation of BDNF and other neurotrophins. *ARC* expression is reduced in animal models of Alzheimer, and subject to posttranslational modification by CpG methylation, or histone ubiquitination [433]. Probably in concert with PSD-95, Arc is the master regulator

of *de novo* experience-dependent plasticity through LTP and LTD, and this function becomes disrupted by Abeta [434]. Directly related to LOAD core pathophysiology (Section 1.4.) were in the Solas study increased C99 ratio, Abeta$_{42}$ level, and BACE1 level in the hippocampus of ELS rats [153].

In human epidemiology, obesity and nutrition-related ELS programming effects were described in the 1958 British National Child cohort [85], where early life adversities contributed to MetS in 37.5% prevalence for males and 19.8% for females. Co-morbidities with MetS-related diseases (*e.g.* CVD, T2DM) sum up to 74% [6]-81% [267, 435, 436] of all LOAD cases. Increased risk of insulin resistance for LOAD was first reported in the Rotterdam ageing study [437] with RRs 1.9~4.3. Other epidemiological studies also revealed that T2DM is associated with a 1.5-2.5-fold increased risk of dementia [432]. Elevating fasting glucose levels increased LOAD risk also in nondiabetic elders at HR=1.19 per 0.9 nmol/L difference [438]. Epigenomic modifications, *e.g.* in *IGF2* methylation, are by now particularly well documented for obesity [439] and subsequent conditions like MetS and T2DM. Such investigation also showed concurrent epigenomic modifications in loci relevant to stress processing (*NR3C1*, *HSD11B2*, *SCL4A6*), and immune functions (*PI3KCD*, *TNFA*, *IL6* promoter) thus connecting ELS and later obesity [439], with late-life LOAD.

3.2.2. Insulin Signalling and Glucose Transport in LOAD as Sequelae of ELS

Deceleration in cerebral glucose transport is characteristic of LOAD. This glucose transportation abnormality and the dysfunction of intracellular glucose catabolism [440] is already present in MCI and predictive to clinical manifestation of LOAD. It is partly responsible for cognitive deficits and neuronal degeneration, and (a) altered functional status of thiamine metabolism, and (b) brain insulin resistance were conjectured as major pathogenic mechanisms in LOAD [440]. Moreover, abnormal glucose metabolism induces oxidative stress and mitochondrial dysfunction [440]. Programming towards glucose intolerance is also a known effect of low birthweight commonly attributed to glucocorticoid excess exposure. This has been found to modify insulin sensitivity of tissues, and altered insulin-secreting capacity of the endocrine pancreas [99]. Modification of *HSD11B2* increasing foetal glucocorticoid load in rodents, resulted in permanent hyperglycaemia and hyper-insulinaemia in the offspring with life-long elevations in phosphoenolpyruvate carboxykinase (*PEPCK*) (Section 1.3.) mRNA and activity [99]. The hepatocyte nuclear factor 4 alpha *HNF4A* (20q13.12) and GR regulate *PEPCK* by binding its promoter in the liver [99]. Also, 11beta-HSD type 1 (*HSD11B1*) methylation, providing reinforcement of local tissue glucocorticoid levels, was identified mediating ELS effects in MetS [39].

Insulin has further to glucose transport essential functions in the CNS, in neural development, dendritic arborisation, synaptic stability, and cognitive functioning [441], which are mediated by insulin receptor expression in diencephalon and telencephalon. However, insulin permeability across the BBB is restricted to hypothalamus, hippocampus and parietal cortex, whereas occipital and other midbrain regions lack

permeability. Impairment of the insulin signalling pathway IR/PI3K/Akt is assumed to be responsible for insulin resistance in the brain [441]. There is a strikingly reduced CNS expression of genes encoding insulin (*INS* 11p15.5), IGF-1 (*IGF1* 12q23.2), and IGF-2 (*IGF2* 11p15.5), as well as the insulin and IGF-1 receptor (*IGF1R* 15q26.3) coinciding with abnormalities in insulin, and IGF-1/IGF-2 signalling diminished in LOAD [442]. Correspondingly, levels of insulin mRNA, IGF, and their receptors are typically reduced in *post-mortem* LOAD brains [436] (but see [443]), in proportion to progression with neuropathological Braak staging [436]. This progression coincides with reduced levels of insulin receptor substrate (*IRS1* 2q36.3) mRNA, tau mRNA, IRS-associated PI3K/*p*-Akt, GSK-3beta activity [436], and increased amyloid precursor protein mRNA expression. In addition to the PI3K/Akt/GSK-3beta pathway, decreased insulin levels activate also the other MAPK pathways [444] early in LOAD pathogenesis, thus both contributing to NFT aggregation. The IGF-1 in the brain is transported through BBB from the serum by LDL receptors megalin/LRP2 (2q31.1) and LRP1 (Secton 2.5.). IGF-1 binds to megalin/LRP2 on the endothelial cell surface; IGF-1 import can also be facilitated by LRP1, which is regulated by neuronal activity [443].

There are reduced brain glucose levels reported generally in LOAD brains [441], which have been found accompanied by reduction of the state of O-GlcNAAcylation [445], in turn increasing tau phosphorylation. Hereby, the monosaccharide beta-N-acetylglucosamine (GlcNAc) attaches to serine/threonine residues *via* an O-linked glycosidic bond in human brain tau. This finding suggests that abnormal hyper-phosphorylation of tau also results from decreased tau O-GlcNAcylation, which is probably induced by deficient brain glucose uptake/metabolism in AD [445]. Reduced glucose metabolism in LOAD is attributable to significant reductions of glucose transporters GLUT-1 and GLUT-2, responsible for neuronal glucose uptake, and to down-regulation of hypoxia-inducible factor 1 alpha subunit (*HIF1A* 14q23.2), the regulator of *GLUT1* and *GLUT3*, coinciding with decreased O-GlcNAcylation, with hippocampal atrophy, hyper-phosphorylation of tau protein, and density of NFTs [446]. GLUT-4 is only present in hippocampal neurons, but not responsible for glucose transport [447]. All four GLUTs are regulated by *IGF1* and *IGF1R* [443, 447]. The reduction in glucose metabolism, in turn, promotes OX-PHOS (Section 1.4.) malfunctions, mitochondrial dysfunctions, and impairment of cyclo-oxygenase COX-2 (*PTGS2* 1q25.2-q25.3) activity [166, 448].

Neurotoxic Advanced Glycation Endproducts (AGEs) indicate accelerated Maillard reactions due to ageing in T2DM, and are found in LOAD hippocampal neurons [449, 450] and glial cells. AGEs and their receptor RAGE (*AGER* 6q21.31) resulting from chronic hyperglycaemia provide critical links between diabetes and LOAD [451]. The RAGE gene *AGER* produces number of splice variants, and resulting protein isoforms of RAGE, including a secreted extracellular form and a N-truncated form [450]. In LOAD, AGEs co-localise with both NFT and Abeta$_{42}$ plaques [436], thereby increasing oxidative stress through generation of ROS interactions with NFT. Because AGE albumin is syn-

thesised and secreted by microglia, and in turn induced the expression of RAGE, which is also a receptor for Abeta$_{42}$ [451], and high mobility group protein B1 (*HMGB1* 13q12.3) (see below), AGEs and RAGEs become critically co-involved in LOAD core pathophysiology [436, 442]. Abeta$_{42}$ interaction with RAGE, in turn, triggers downstream interaction of the JNK/SAPK pathway [192], in analogy also to MetS [293].

3.2.3. Insulin Receptor-related Receptors, Insulin Receptor Substrates and Insulin Degrading Enzyme

Transport of insulin involves not only insulin (*INS* 11p15.5), insulin-like growth factors IGF-1 (*IGF1* 12q23.2), IGF-2 (*IGF2* 11p15.5), the insulin/IGF-1 receptor (*IGF1R* 15q26.3), and the myelin-related IGF-2 receptor (*IGF2R* 6q25.3) [435], but also further regulators such as the insulin receptor-related receptor (*INSRR* 1q23.1) and the family of insulin receptor substrates, with four members [452, 453], two of which are relevant to LOAD. IRS act as docking sites for adaptor regulators and enzymes [452]. Both insulin receptor substrate 1 (*IRS1* 2q36.3) [447] and IRS-2 (*IRS2* 13q34) are decisive for early structural brain growth and functioning, glucose uptake and insulin transport [452]. Specifically, IRS-1 can induce tau phosphorylation through (a) the PI3K/Akt/GSK-3 pathway and (b) through Ras/Mek/MAPK pathways [452]. Also for the IGF-1R, downstream targets include activation of the MAPK/ERK and PI3K/Akt pathways [443]. Insulin/IGF-1 signalling defects pertain to PI3K/Akt pathway through malignant cascades in glucose metabolism, reduction in their expression correlated with *GSK3B* activation [440]. This association is covaried with BDNF signalling in charge of maintenance of axonal transport [454]. However, of positive associations with metabolic risk factors [455] for LOAD tested, survived only JNK1 (*MAPK8* 10q11.22) the analysis in *post-mortem* study, but not IKK-beta, IRS1, or PKR [455] associations.

Insulin degrading enzyme (*IDE* 10q23-q25) is correlated to hippocampal Abeta$_{42}$, with general relations to MAPK signalling in pathophysiology. Insulysin aka insulin-degrading enzyme, which promotes the cleavage catabolism of insulin, is also the major Abeta$_{42}$ degrading enzyme [436, 456], however only in its monomeric form [457]. Sequestration of insulysin due to hyperinsulinaemia therefore hampers Abeta autophagy [451]. Several of the physiological functions of protease IDE have not yet been elucidated, but are suggested by different locations in cytosol, peroxisomes, endosomes, proteasome complexes. On outer cell surfaces, IDE was found down-regulating the levels of secreted Abeta extracellularly in oligomeric form [458]. PKMzeta, an alternative splice product of the protein kinase Czeta gene (*PRKCZ* 1q36.33), has been identified important for stabilisation of LTP thus subserving long-term memory engrammes. As one of two atypical isoforms of PKMzeta, it is important in insulin stimulated glucose transport, and its lack consistent with memory loss [459, 460]. Insulin induces phosphorylation of Serine$_{831}$ GluR1 subunit of AMPAR and induces over-expression of PKMzeta [461]. Insulin-dependent PKMzeta over-expression and MAPK/ERK1/2 phosphorylation is negatively correlated with Abeta$_{42}$ aggregates, suggesting in conclusion, that Abeta interrupts insulin turnover in LOAD.

3.2.4. Commonalities Between LOAD and T2DM

Glucose hypo-metabolism is an invariant biomarker in LOAD [440], as had become evident from (radioactively labelled glucose) PET neuroimaging, and because it is herein different from all other dementias, LOAD has been termed "T3DM" [435]. Moreover, insulin resistance was found *post-mortem* also in those LOAD sufferer brains [462], who were not diabetic, specifically in the hippocampi with reduced IGF-1 responsivity in the IGF-1R/IRS-2/PI3K signalling pathway. Brain insulin resistance reduced expression insulin receptor (IRs) and lead to defects in Akt/Foxo3a insulin signalling. Reduced levels of *p*-Akt and increased levels of Foxo3a were found in the nuclei of neurons with pro-apoptotic genes activated [463]. Insulin resistance is now generally accepted of being induced by TNFalpha (*TNFA* 6p21.3) as part of cytokine release. It has been proposed that the common pathogenic link between T2DM/T3DM and LOAD thus consists in the key innate immune receptor TLR4 (*TLR4* 9q33.1) signalling, activating the JNK/SAPK pathway (Section 2.1.) [268], thereby triggering NFkappaB. Exciting TNFalpha and IL-6 will act into a pro-inflammatory state, whereas chronic TLR4 activation may activate the PI3K/Akt signalling pathway ultimately leading into insulin insensitivity [268, 442]. Further to NFkappaB, TLR4 triggers DUSP1, STAT1, and IRF3, which mediates pro-inflammatory cytokine release [464]. In the cerebrum, TLR4s are expressed mainly in microglia, astrocytes and neurons, where TLR4 contributes to Abeta-induced microglial neurotoxicity, and upregulation of cytokines TNFalpha, IL-1, IL-10 and IL-17 [436, 465]. In the presence of Abeta$_{42}$, TLR4 converts microglia towards neurotoxicity.

There may be further parallelisms between LOAD and T2DM in amyloid plaque deposition, by the presence of insoluble amyloid protein oligomers in brain and pancreas, respectively [436, 442]. The physiological function of pancreatic amylin appears to be in regulation of insulin secretion from pancreatic beta cells [436]. Amylin (Section 1.4.) (hIAPP) aggregation is associated with pancreatic beta-cell loss, whilst Abeta aggregation is associated with neuronal and synaptic dysfunction [166]. T2DM increases Abeta deposition in hippocampal neurons, and decreases autophagy as indexed by lysosome markers LAMP1 and LAMP2 [466]. Voltage-dependent anion-selective channel 1 (*VDAC1* 5q31.1) on the outer mitochondrial membrane is responsible for Ca^{++} transport and ATP efflux into neuron cytosol (Section 1.4.). The interaction of VDAC1 with Abeta$_{42}$ was found cytotoxic due to conductance increase and resulted in mitochondrially induced apoptosis [467] or mitochondrial dysfunction and neuroinflammation through APP/hIAPP catabolism [468]. Autophagy impairment exacerbates insulin resistance *via* reductions of insulin secretion in pancreatic beta cells of Langerhans islets [166, 469]. Wang and colleagues observed elevation in the expression of histone deacetylases (HDACs) class IIa in T2DM brains *pari passu* with altered expression of synaptic proteins, associated with increased susceptibility to oligomeric Abeta$_{42}$ deposition leading to synaptic dysfunction in the hippocampal formation [470].

It has been proposed that T2DM and LOAD are further characterised by common metabolic factors in the glia-

neuron "cholesterol shuttle" constituting one single pathway [261]: (a) lipoproteins APOA1, APOA4, APOC1, APOC2, APOC3, APOD, APOE and LPA, (b) cholesterol transporters ABCA1, ABCA2, CETP, (c) lipoprotein receptors LDLR, LRP1, LRP8 and VLDLR, (d) metabolising enzymes CYP46A1, CH25H, SOAT1, LIPA whose oxysterol products activate APP. APP metabolises cholesterol to 7-betahydroxycholesterol, a substrate of SOAT1 and cortisol converter *HSD11B1*, tethering to LRP1. BACE1 then cleaves both APP and LRP1. Gamma-secretase cleaves LRP1, LRP8, APP, so regulating transcription factor TFCP2, which controls *GSK3B* expression responsible for hyper-phosphorylation of microtubular protein tau (MAPT) [261].

A further link between T2DM and LOAD is the heat shock protein Hsp72 (*HSPA1A* 6p21.33), which is a stress-related chaperone with correction, DNA repair and degradation functions [471]. Being essential to neurodifferentiation during embryonic development, it is also related to involution by regulating caspase activation stimulating the JNK pathway, and inhibiting insulin signalling through NFkappaB and protein kinase C (PKC).

3.2.5. Cholesterol and Lipid Metabolism in LOAD

Lipid traits are important to healthy brain functions equally for neurons and glia. Cholesterol is required by neurons for axonal growth and functioning, and for the synaptic membrane, and there is respective depletion in LOAD *post-mortem* cases. Cholesterol and triglycerides are necessary ingredients and metabolic precursors of myelin phospholipids. *Ko*-studies revealed that cholesterol accounts for >70% of myelin lipid bilayer growth [472]. Consequently, cholesterol depletion increases risk for LOAD, as myelin breakdown is accelerated. Lipidomics studies reviewed by Trushina [473] revealed but further group differences between healthy, MCI and LOAD cases: Specifically, in systems phospholipids, phosphatidylinositol, sphingomyelin, ceramide, triacylglycerol, and cholesterol esters. These findings indicate substantial pathological changes in brain myelin content referring to role of myelin breakdown. Related is the deterioration of lipid metabolism in LOAD, and the myelination breakdown tied to apolipoproteins E, C1, J [474], with midlife plasma cholesterol transport. The common cardiovascular and metabolic conditions are therefore at the same time also risk factors for later LOAD manifestation.

Cholesterol transport is mediated by apolipoprotein E (APOE). APOE in the brain maintains BBB integrity and regulates the lipid shuttle between lipoproteins [227] (see above). The circumstance that epsilon4 processed Abeta$_{42}$ utilises VLDLRs (Section 1.4.) affects healthy BBB functioning in the metabolisms of insulin, triglycerides, free fatty acids (FFAs), and other metabolites involved in cognitive processes [227]: There is initial evidence suggesting that *APOE* epsilon4 carriers (a) are less effective in insulin utilisation, and (b) are less able to utilise triglycerides in lipoprotein transport [227]. Receptors that can bind APOE, which is also generated by astroglia and neurons, are [475]: the LDLR, very-low-density lipoprotein receptor (VLDLR), LDLR-related protein 8 (LRP8, also known as APOE recep-

tor 2), LRP1 (also known as LRP), and the sortilin-related receptor SORL1 (*SORL1* 11q24.1). Receptors LRP1, LRP1B, and SORL1 regulate endocytosis of APP, trafficking, and trapping into the Golgi [475] in physiological condition. Other LDL receptor family members, which are not capable binding APOE, include LRP4 (also known as multiple EGF-repeat-containing protein 7 MEGF7), LRP5 and LRP6 [475]. Lipid receptors are essential for embryonic neural development [475], and may therefore be potential candidates for ELS susceptibilities. Astrocytes and neurons participate in cholesterol synthesis through 3-hydroxy-3-methylglutaryl coenzyme A reductase (*HMGCR* 5q13.3), mobilisation through ATP-binding cassette transporter types A1 and G1 (ABCA1/ABCG1), and transport through BBB by neuron-specific enzyme cholesterol 24S-hydroxylase, encoded by *CYP46A1* (14q32.2). The genes related also to cholesterol biosynthesis, *DHCR24*, and to cholesterol efflux, ATP-binding cassette transporter (*ABCA1*) [476], have furthermore been related to LOAD.

Signalling through the isoprenoid cascade provides a biochemical chain through which cholesterol synthesis can indirectly modulate production of *p*-tau in the CNS: from geranylgeranyl diphosphate (GGPP) to cyclin-dependent kinase 5 (CDK5); to GSK-3beta, to protein kinase A (PKA) [474]. As central receptors involved in LOAD [477] were identified: Apolipoprotein E receptor 2 (ApoER2/LRP8) and very-low-density lipoprotein receptor (VLDLR), and low-density lipoprotein receptor-related protein 1 (LRP1) have central roles in lipid clearance of APOE (Section 1.4.) The receptors of the LDL receptor family VLDLR, LRP4, LRP5 and LRP6 are involved in Wnt signalling and are implicated in synaptic plasticity, adult neurogenesis and LOAD pathogenesis [477]. Neuronal stress, *e.g.* through ER stress or ROS, specifically upregulates *VLDLR* expression (also known to be preferentially used in *APOE* epsilon4 allele genotype, Section 1.4.). As memory performance in T2DM is moderated by *APOE* epsilon4 status [478], this mechanism, together with loss of LRP1s during disease progression, is central to LOAD pathophysiology. Stress impact herein was found accompanied by transiently increased stabilisation and decreased expression of hypoxia-inducible factor 1 alpha subunit (HIF-1alpha, involved in glucose transport, Section 3.2.) and decreased beta-catenin levels affecting the Wnt pathway through GSK-3beta phosphorylation [477]. This mechanism is also promoted by nutritional factors such as excessive LDL intake (see below).

Deficient insulin signalling and glucose metabolism has been widely shown to be influenced by nutritional factors [328]. High-fat plus high sucrose diet triggers expression of insulin receptor, decreasing its tyrosine phosphorylation and, increasing serine phosphorylation of IRS-1. In parallel, inflammatory response by NFkappaB and activations of stress kinase pathways p38 MAPK and JNK/SAPK (Section 2.1.) in whole brain lysate were registered [328]. These changes primed the murine brains towards deposition of Abeta, formation of NFTs, and decreased synaptic plasticity. High fat diet alone increased *p*-tau levels, microglial activation and induced cognitive impairment, but preferentially in aged animals [479]. Unsaturated fatty acids (PUFAs omega-3 and omega-6) enable in contrast more fluent and effective cholesterol metabolism [183].

3.3. Neuroinflammation in LOAD

3.3.1. *Reciprocal Relations of Sympathetic Arousal and Inflammation*

Neuroinflammation in LOAD is increasingly discussed as revealed by rising publication numbers. A proportion of GWAS candidate genes pertaining to immune functions (Table **1**; Section 4.1.) indicate a strong role for neuroinflammation in LOAD. These findings will be presented as to their specific relevance for the systematic review as tied to ELS: A principle relation consists of the psychophysiological coupling of inflammatory response and noradrenergic signalling. This provides a direct and reciprocal relation of the SNS stress response and cytokines [39].

There is consensus that chronic low-level neuroinflammation in LOAD [480, 481] drives exacerbating neuron degeneration. It is still not conclusively resolved if neuroinflammation is cause or consequence of LOAD [181], but current views [481, 482] increasingly emphasise that neuroinflammation is the driving force for the progression of MCI to clinical manifestation of LOAD. Neuroinflammation alone is sufficient to excite neurodegeneration essential in LOAD pathophysiology [481]. However, neuroinflammation is (such as tauopathy) not specific to LOAD, but exists in a variety of neurodegenerative and autoimmune-related conditions [483]. Suggested by microglial physiology (below) is that early life inflammation is related to late life morbidity, and epidemiology data suggest that LOAD manifestation can be postponed or even prevented by anti-inflammatory agents [484].

3.3.2. *Essential Role of Neuroinflammation in LOAD*

As inflammatory processes also appear in healthy ageing, their differentiation against LOAD is a matter of dispute [181]. However, neuroinflammatory processes in LOAD are predominant in vulnerable regions with Abeta and NFT deposition [485], where plaques provide stimulation [485] for pro-inflammatory agents such as acute phase proteins and cytokines. Such circumscribed lesion regions are present early in LOAD pathogenesis in dispersed, micro-localised, and enduring manner [485]. When astrocytes and microglia tend to accumulate at such inflammation sites, a process termed 'reactive gliosis' [486] appears, which coincides with persistent microglial activation.

Reactive microgliosis (Section 1.4.) is accompanied by processes involving classical complement and alternative complement pathways of the innate immune response [181, 487]. Findings of Abeta$_{42}$ in and on microglia and astrocytes may suggest that both cell types can be involved in phagocygotic processes [487]. In microglia and astrocytes [488-490], the plaque-associated cytokines interleukin-1(IL-1), IL-6, IL-8, tumor necrosis factor alpha (TNFalpha), interferon gamma (IFNgamma), transforming growth factor beta (TGFbeta), major histocompatibility complex (MHC) class I&II complex proteins [489, 490], and macrophage inflammatory protein-1 alpha and beta (*CCL3* 17q12 upstream, *CCL4* 17q4 downstream) [448] and chemokine ligand MCP-1/CCL2 (17q12 cluster) [491], are upregulated in LOAD, a process controlled by the neuroprotective chemokine fractalkine (*CX3CL1* 16q21) [492]. Free radical generation by activated microglia has been demonstrated by a wide range of *in vitro*

experiments using monocytes/macrophages and microglia, notably ROS, COX-2 [448], increased astrocytic NO [493], and inducible nitric oxide synthase iNOS [488], prostaglandin E2 (PGE-2, the major enzymatic product of COX-2) [448], lipophilic amines [480]. Heneka and colleagues have concluded that Locus Caeruleus (LC) and Nucleus Basalis of Meynert (NBM) (Section 3.1.) degeneration are induced by COX-2 activity [448, 491]. Cytokine release is accompanied directly by CDK5 and JNK/SAPK overexpression increasing with age [494]. In LOAD patients, tumor necrosis factor receptor TNF-R1 (*TNFRSF1A* 12p13.31) levels are increased, whereas anti-apoptotic TNF-R2 (*TNFRSF1B* 1p36.22) levels are decreased [495].

3.3.3. *Priming and Activation of Microglia in LOAD*

Microglia are leukocytes and the brain's myeloid cells [482], occurring as both free migrating monocytes and tissue bound macrophages [483]. Activated microglia at the inflammation site change their morphology (polarisation), express increased levels of Major Histocompatibility Complex (MHC) antigens, and become phagocytic [236]. Four microglial forms according to stage of activation are known in the literature: (a) the amoeboid stage during early brain development, contributing to cerebral morphology, as freely moving phagocytes; (b) a ramified stage, with provision of stable immune function and as macrophages; (c) a polarised neuroinflammatory stage, with retraction of branches, antigen presenting, production of chemokine and complement component proteins [496]; (d) the dystrophic microglia as a result of the ageing process [483], and related to cerebral neurodegeneration.

Neuroinflammation in LOAD is characterised by innate immune responses and monocyte activation (and in contrast to other neuroinflammatory diseases, with adaptive immune responses), whereby monocytes retain these capabilities also under Abeta burden [497]. Microglia-depleted rodent models revealed that dystrophic microglia are involved in propagation of *h*-tau *via* exosomes [498], and thus transregional spreading of NFTs. Tau interacts with *APOE* epsilon4 allele [499] to boost cytokine release from microglia involved in neuroinflammation [483]: Deficiency of microglial-specific fractalkine receptor (*CX3CR1* 3p22.2) was observed leading to increased microglial IL-1beta release thus increasing tauopathy through p38 MAPK activation [500]. Progranulin expressed on microglia (*GRN* 17q21.31) is important for microglial [483] complement expression and lysosome maturation, may in LOAD be protective for synapse functioning [501], and inhibitive of plaque deposition [502]. *GRN* polymorphisms were found associated with LOAD risk [502].

Inflammatory priming of microglia is a further possible link between ELS and LOAD pathology. It was found that a prenatal pro-inflammatory environment decreases adult neurogenesis by persisting microglial activation and by downregulated expression of Transforming Growth Factor beta-1 (TGFbeta1) [503]. Important for this state is the so-called priming phase, when microglia are first stimulated towards cytokine release [100, 482]. Such microglial priming can occur as an early life event, including stressful events or infections, and be suppressed by epigenetic programming of microglial histone deacetylase inhibitors [100], and also being mediated by nutrition. Ageing or other insult can then

simply reactivate the suppressed inclination towards neuroinflammation [100]. Once activated, microglia differentiate in phenotypes M1 and M2 [504]: M1 classically activated, respond to LPS in combination with IFNgamma in pro-inflammatory profiles, whereas M2, or alternatively activated microglia, respond to IL-4 and IL-13 with anti-inflammatory profile. Dependent pro-inflammatory profiles are inhibitive of adult neurogenesis, whereas anti-inflammatory microglia phenotype stimulates hippocampal neurogenesis and oligogendrogenesis through immune modulators such as TGFbeta1 [505].

3.3.4. Role of Microglial Action in LOAD

The microglial involvement consists of a dual contribution [480]: (a) microglia help eliminating Abeta aggregation *via* phagocytosis; and (b) microglia reinforce Abeta accumulation through the release of neurotoxic proteases and IFN Regulatory Factor 1-dependent (IRF1-dependent) inflammatory response [506]. Control of neuroinflammation is exerted through the anti-inflammatory reflex (see below) cytokines IL-4, IL-10, IL-13 [480]. However, if polarised, microglia present pro-inflammatory cytokines and chemokines, and this will result in self-harm, whereby 'burnt-out' microglia become dystrophic [482]. Microglia are furthermore the source of the heme enzyme myeloperoxidase (*MPO* 7q22) in LOAD brains [507]. Increased expression of *MPO* mRNA is detected in microglial cells upon treatment with aggregated Abeta peptide, and MPO immunoreactivity has been observed in microglia co-localised with neuritic plaques [507]. High-mobility-group-protein B1 *(HMGB1* 13q12.3) was found the missing link between neuroinflammation and NFT tauopathy in LOAD [508], where it has a cytokine-like function. Its main receptor is TLR4/2, and its most important signalling pathways are p38 MAPK and NFkappaB. The *HMGB1* locus is known for posttranslational modifications by acetylation, methylation, ADP-ribosylation, phosphorylation, and glycosylation.

3.3.5. Inflammasome Participation in LOAD Neuroinflammation

Several studies suggested that inflammasome activation may be linked to disease severity in LOAD by increasing memory deficits. Involvement of inflammasome, a multiprotein oligomer consisting of caspase 1, caspase 5, pattern recognition NOD-like receptor NALP, and apoptosis associated protein PYCARD with its adaptor ASC (*PYCARD* 16p11.2), is usually a defence against external infection. Abeta is probably acknowledged as such, as it is known to trigger the activation of the cryopyrin gene (*NLRP3* 1q44), a sensor protein playing a critical role in microglial activation and hence LOAD initiation [509, 510]. Inflammasome activation is triggered by autophagy impairment (Section 1.4.), mediated by beclin-1 and the interacting anti-apoptotic Bcl-2 family members [360]. These are ageing-related, but still overexpressed in LOAD brains [360, 361]. The core complex beclin-1/Atg14L/Vps34/Vps15 is under regulation of CDK5, and inversely related to Abeta$_{42}$ deposition [361].

The NLR ('Nod-like receptor') family *NLRP3* gene provides instructions for synthesis of the protein cryopyrin (NALP3), the activation sensor of the inflammasome [511], an intracellular oligomeric organelle consisting of the pro-

teins caspase-1/5, PYCARD, and NALP. Cryopyrin interacts with the apoptosis-associated speck-like protein PYCARD and its inflammasome adaptor ASC, which contains a caspase recruitment domain (CARD), and is a member of the NALP3-inflammasome complex. Psychological stress-induced activation of GSK-3beta leads to activation of the NLRP3/IL-1beta pathway [266], thus enhancing active caspase-1 expression [511, 512]. This NALP-inflammasome complex functions as an upstream activator of NFkappaB signalling thereby triggering the NACHT, LRR and PYD domains-containing protein 3 (*NLRP3*); the inflammasome induces mitochondrial apoptotic signalling by beclin-2, stimulating the production of interleukin-1beta (IL-1beta) [513]. Oxidised mitochondrial DNA released into the cytosol induces the formation of the *NLRP3* inflammasome. Autophagy, in contrast, has been found to be essential for restoring mitochondrial dynamics during *NLRP3* inflammation [451]. In addition to *NLRP3*, also *NLRP1* (17p13.2) and its polymorphisms, have been implicated in LOAD [512].

Four prostaglandin E receptors (EP1-EP4) are present on microglia [448], of which EP2 (*PTGER2* 14q22.1) expression is regulated by methylation, and OS related [506, 514]; also EP3 (*PTGER3* 1p31.1) with at least eight isoforms [515, 516], and EP4 (*PTGER4* 5p13.1) [517], were found related to LOAD. Their activation of ERK induces expression of *EGR1/NGFI-A* (an ERK transcription factor, 5q31.2) (Sections 1.3. and 3.1.), and suppresses the activation of cytokines by inhibiting the NFkappaB pathway. Recent murine studies [506] have demonstrated that inhibition of the COX-2/PGE2/EP2 immune pathway by deletion of the microglia-specific *ptger2* restored microglial chemotaxis and Abeta clearance, suppressed toxic inflammation, and increased cytoprotective Insulin-like Growth Factor 1 (IGF1) signalling [506].

3.3.6. Leakage of Blood-brain Barrier and Exacerbation of Neuroinflammation in LOAD

The key process in LOAD neuroinflammation consists probably in RAGE (Section 3.2.) malfunction-caused leakage of the inflammation BBB [100, 480, 518], accompanied by *LPR1* expression downregulation (thus pathogenic irrespective of *APOE* allelic status) (Section 1.4.) [181], and dysregulation of enzymatic degradation (such as zinc matrix metalloprotease MMP-9 involved in learning and memory [*MMP9* 20q13.12]) [480, 519]. Whereas Abeta clearance by autophagy is more effective in younger age ranges, in higher ages, RAGEs tend to interact with glycated adducts on endothelial cells leading into diabetic vascular injury. Production of pro-inflammatory cytokines and vasoconstrictor endothelin-1 (*EDN1* 6p24.1) then reduces cerebral blood flow and induces mutually malignant potentiation of Abeta influx and RAGE expression [518]. Of four known isoforms, the endothelin receptor genes *EDNRA* (4q31.22-23), and *EDNRB* (13q22.3), were found involved in BBB leakage. The increased BBB permeability gives rise to age-dependent progressive BBB breakdown, by activating the pro-inflammatory cyclophilin A and the NFkappaB-dependent matrix MPP-9 pathway [181], resulting in general cerebral vulnerability to peripheral immune processes [181].

It has been suggested that increased LOAD risk of HR 1.07-1.12 due to proximity to major roads may be associated

with disruption of BBB and activation of microglia [37]. The effects of increased NFkappaB activation, mitochondrial dysfunction and cytoskeletal disintegration causing death of oligodendrocytes give rise to myelin lesions and terminal myelination breakdown in LOAD [181]. Likely is a co-action of brain insulin resistance (Section 3.2.), with ROS generation, and with neuroinflammation [447]. Another potential mechanism of neurotoxicity potentiation consists in the blockade of intracellular insulin actions, thus by downstream inhibition of insulin signalling events, through pro-inflammatory cytokine action on *p*-IRS1. In parallel, were markers of ER stress p-ERK, and eIF2alpha, observed elevated in LOAD brains [447].

3.3.7. Abeta Phagocytosis by Microglia

In manifest LOAD is Abeta phagocytosis mediated by scavenger receptors and modified LDL-clearance performed by polarised microglia [520]. Scavenger receptors, part of innate immunity, are expressed by microglia, related to atherosclerotic lesions, with secreting cytokines [496]. There are currently ten classes (A-J) encompassing 19 receptor types with highly divergent domain structures [496, 520], four of which have been described relevant to LOAD [480]: Class-A scavenger receptor/CD204 gene (*MSR1* 8p22, 3 isoforms) expresses the SR-A isoform1, which is related to ROS production and microglial interaction with Abeta. SR-A isoform2 promotes phagocytosis by binding fibrillar Abeta and AGEs. SR-A isoform 3 is inhibitive of types 1 and 2. SR-B2/CD36 (*SCARB3* 7q11.2) is also relevant to LOAD, as activated SR-B2 signal transduction involves the tyrosine kinase Fyn, p38 MAPK and JNK [520]. SR-B1 (*SCARB1* 12q24.31) is the microglial Abeta receptor and promoting cerebrovascular oxidative dysfunction. SR-B3 (*SCARB2* 4q21.1) mediates post-Abeta binding activation and lyosomal transport [480]. Activation by ligand Abeta on CD36 triggers p38 MAPK, ERK1/2, JNK, and NFkappaB pathways and stimulates production of pro-inflammatory cytokines and of pro-apoptotic signals [496]. Specifically, the pathogenic interaction of Abeta with engagement of CD36–TLR4-TLR6 receptor complexes on microglia results in neuroinflammation and consequent damage to local tissues at sites of Abeta accumulation [496].

Abeta may itself act as a pro-inflammatory agent [236], and microglia can also be activated by Abeta$_{42}$ oligomers upon mediation by the scavenger receptor SR-A, and the activated potassium channel KCa3.1, before fibrillary deposits are formed [510]. Several Abeta-degrading enzymes such as neprysilin NEP, insulysin IDE, endothelin converting enzymes ECE-1 and ECE-2, angiotensin converting enzyme ACE, cathepsin B, and plasmin are involved in neuroinflammation, which inhibit their microglial activity to degrade and clear Abeta [480, 519]. Mononuclear cells (PBMC's) stressed with Abeta upregulated the glycosyltransferase MGAT-III (*MGAT3* 22q13.1) by a factor of 327. The gene product of *MGAT3* may have a critical role in phagocytosis [519]. In addition, microglial-expressed purinergic ionotropic receptor P2X$_7$ (*P2RX7* 12q24.31) participates in phagocytosis, however, a role in LOAD remains to be clarified [482].

It was shown that neuroinflammation upregulates *BACE1* expression, and that knock out of the *mapk14* gene encoding p38alpha MAPK enhanced *BACE1*-induced lysosomal degradation and autophagy [330]. TGFbeta1 decreased Abeta burden in an AD mouse model by promoting microglial Abeta clearance. However, blocking TGFbeta1 and downstream SMAD2-SMAD3 signalling specifically in CD11c-positive myeloid cells also reduced Abeta-like pathology [225]. TGFbeta1 is secreted by astrocytes, and binding of TGFbeta1 to its receptor activates the SMAD3 pathway, as well as MAPKs and PI3K signalling in microglia. Thus, TGFbeta1 regulates the inflammatory activation of microglia, but this capability is lost in ageing or chronic activation, in contrast to MAPK signalling [225].

3.3.8. Proinflammatory Cytokines in LOAD Memory Impairment

Ageing promotes infiltration of immune cells into the brain owing to damage to the Blood Brain Barrier (BBB), thus leading to the exacerbation of central inflammation [451], a process greatly accelerated in LOAD. *In vivo*, microglia express pro-inflammatory cytokines IL-1, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-12 and IL-23, and TNFalpha [482]. These directly impair hippocampal LTP [521], and for IL-1, IL-6, TNFalpha, and alpha1-antichymotrypsin (*SERPINA3* 14q32.13), genomic polymorphisms have been documented for LOAD [491]. The ratio of the pro-inflammatory cytokine IL-1 to the anti-inflammatory cytokine IL-10 is greatly elevated in the serum of AD patients, resulting in a chronic neuroinflammation state [236]. Novel evidence supports the notion that tau hyper-phosphorylation can be induced by C-reactive protein (*CRP* 1q23.2) a pro-inflammatory marker *via* the Akt/GSK-3beta signalling pathway [522], and thereby priming neuronal apoptosis. Other cytokines such as TNFalpha, IL-1beta, IL-6 were shown involved in a previous study [523], but only increased in the hippocampus, when CRP application *in vitro* triggered APP expression and Abeta$_{42}$ cleavage. In contrast, phosphorylation of Akt (Ser473) and GSK-3beta (Ser9) were decreased by CRP treatment, whereas phosphorylation of ERK and p38 were not affected [522]. Taken together, the experiments demonstrate that also the acute-phase protein CRP is capable of triggering key pathogenic mechanisms in AD *in vitro*.

The arachinodate 5-lipoxygenase (5LO) (*ALOX5* 10q11.21) is a pro-inflammatory enzymatic pathway widely distributed within the central nervous system and is upregulated in LOAD [524] in regions of progressed neurodegeneration. Through mediation of CDK5 [524], GSK-3beta, MAPK, and as part of innate immunity, it subserves chronic neuroinflammation, known to modifying tau hyper-phosphorylation and inhibiting postsynaptic marker PSD-95 (Section 2.1.) [524]. The multiplicity of splice variants from this gene suggest susceptibility for environmental influences.

The enzyme endothelial nitric oxide synthase eNOS (*NOS3* 7q35-36), an important vasodilator, has been shown to be inhibitive of microglial activation and the pro-inflammatory phenotype [525]. eNOS-deficient mice showed increased expression of *APP* and *BACE1*, therefore *NOS3* is a modulator of LOAD pathophysiology. *NOS3* is extensively documented for multiple epigenetic modifications und has been shown to be related to early uterine longitudinal conditions [526], where 5-hydroxymethylcytosine, H3K9ac and histone 2A (H2A) interact.

3.3.9. Polymorphisms for Cytokines Related to LOAD

TNFalpha [527], which has partly neuroprotective effects [528], when interacting with NFkappaB and IL-1beta [529], and binding tumor necrosis factor receptor 1 TNF-R1 [530]. TNF-R2 signalling mediates most of the protective and regulatory effects of TNFalpha in the CNS [528]. Recent analyses have shown that neuroprotective effects of NFkappaB are exerted by p65 dimers, whereas p50 dimers are pro-apoptotic [531, 532]. Therefore the p65:p50 ratio is decisive for direction of NFkappaB action. Anti-inflammatory and immunosuppressive protein glucocorticoid induced leucine zipper GILZ (*TSC22D3* Xq22.3), which is a p65-binding protein that sequesters activated p65, and thereby inhibits transactivation of inflammatory and apoptotic factors. In contrast is Abeta$_{40}$ synthesis related to p50-preferential signalling [531]. GILZ regulates multiple signal transduction pathways involved in cell growth, cell differentiation, and cell survival. Reviewed for transethnic LOAD association [533] were the following cytokine loci: *IL1A* (2q14.1), *IL1B* (2q14.1), *IL6* (7p15.3), *TNFA* (6p21.33), *VEGFA* (6p21.1), *IL18* (11q23.1), *IL33* (9p24.1), *IL12A* (3q25.33), *IL12B* (5q33.2), *IL4* (5q31.1), *IL10* (1q32.1), *TGFB1* (19q13.2). The cytokine SNPs have often divergent risks, showing decreased *vs.* increased risk, dependent on the population [533] tested.

3.3.10. Anti-inflammation Reflex

Inflammatory action of NFkappaB and ERK pathways is inhibited by peroxisome proliferator-activated receptor gamma (*PPARG* 3p25.2) activation, and many intervention address this mechanism [489, 534] or its regulator transcription coactivator PGC-1alpha [535] (*PPARGC1A* 4p15.2). *PPARGC1A*, a regulator of metabolic genes, OXPHOS (Section 1.4), and mitochondrial biogenesis, activates CREB and is involved in mitochondrial ROS generation, the reason why it was recently nominated to be a master regulator of neuroinflammation in LOAD [536]. It has been demonstrated that receptor PGC-1alpha action regulates *BACE1* expression and is downregulated in LOAD patients [535]. *PPARGC1A* and MetS-related *PPARGC1B* (5q32), which stimulates expression of glucocorticoid receptors, is furthermore involved in T2DM; both genes are transcriptionally and post-transcriptionally regulated [536].

3.3.11. Apoptosis Related to Neuroinflammation

It has been shown that neuronal cell death in LOAD is causally induced by the proto-oncogene c-myc [537], whose overexpression is counter-regulated and apoptosis is induced [538]. This occurs when neurons are (a) deprived of NGF and (b) exposed to Abeta$_{42}$ cytotoxicity. Consequently, myc expressions are preferentially located at diffuse plaques, dystrophic neurites, synaptosomes, and in astrocytes [539], apparently interacting with NFkappaB. The death receptors DR4 (*TNFRSF10A* 8p21.2) and DR5 (*TNFRSF10B* 8p21.2) were shown to mediate cerebral microvascular endothelial cell apoptosis that was induced by oligomeric Abeta [236]. RNA translocation protein RanBP9 (*RANBP9* 6p23) is a scaffold protein that is increased in brains of AD patients [236]. Heightened activation of inflammatory responses produces phosphorylation of p38 MAPK, JNK, and NFkappaB pathways [488, 493] thus inducing apoptosis. Neurotoxic elements are conducive to apoptotic signalling through acti-

vator protein AP-1-dependent beclin-associated protein BAX (*BAX* 19q13.33) and caspase-9 in oligodendrocytes and astrocytes [488], thus accelerating myelination breakdown in LOAD. Abeta$_{42}$ also directly induces cell death in oligodendrocyte cell cultures [490].

4. EPIGENETICS OF RISK GENES AND GENE REGULATION

4.1. Summary of LOAD Risk Genes in the Reviewed Literature

In sporadic AD, there is no Mendelian heritability, and also familial transmission showed variable concordance rates. There is no single genetic risk for LOAD [540], therefore network analyses of genes are currently considered most promising. A growing number of GWAS in the past two decades have confirmed candidate genes, where common variants, such as *ABCA7* [541] or *CR1* [542], typically account only for 3-4% variance [8, 543]. It has been suspected that *APOE* epsilon4 masking effects have hitherto precluded the detection of other genetic risk loci [544]. Studies of gene expression and neuronal activity have, however, been scarcely done [540], a promising combination, which could identify neuroimaging patterns in relation to epigenetics.

Risk genes derived from core pathophysiological processes (Section 1.4.), such as *APP* [545, 546], *MAPT* [546], and *BACE1* [547] have been found transcriptionally downregulated in LOAD [545], possibly to maintain protein homeostasis. For APP processing, to date >160 mutations in *APP* have been reported, most of which increase the production of the amyloidogenic Abeta$_{42}$ isoform of Abeta [475]. *APOE* epsilon4 allele and *APP* [211] are, however, classified rare variants in LOAD [546] due to their allele frequencies. The *MAPT* H1 haplotype, then, is characteristic of several late-onset neurodegenerative disorders [211]. The neuronal receptor of apolipoprotein E (*SORL1* 11q24.1) is the only firmly established risk gene further to *APOE* epsilon4 [1, 475, 542, 548-553]. The sortilin-related receptors *SORCS1* (10q25.1), *SORCS2* (4p16.1) and *SORCS3* (10q25.1) (vacuolar protein sorting 10 [VPS10] domain-containing receptors 1-3) are inhibitive of APP processing [554]. The channel-forming subunit of mitochondrial translocase (*TOMM40*, 19q13.32) [541] is critical for general protein precursor import into mitochondria, and is considered a common variant. The risk status of its SNP rs2075650 was confirmed in a recent meta-analysis although not for all populations [555]. The clusterin gene (*CLU* 8p21.1) [183, 188, 541, 542] is a molecular Golgi chaperone, but under stress involved in intracellular clearing, lipid transport and apoptosis. The cytochrome P450 enzyme *CYP19A1* [92, 544] (15q21.1) aromatase or oestrogen synthase showed association likely due to the neuroprotective effects of oestrogen.

Further GWAS-confirmed candidate genes (Table **1**) (additional suspected genes extracted from preceding review sections listed in Table **3**) are the ABC1 transporter gene *ABCA7* [542] (19p13.3), the A-disintegrin and metalloproteinase domain-containing protein gene *ADAM10* [556] (15q23.3)*,* the bridging integrator protein gene, involved in axonal ensheathment by oligodendrocytes and white matter tracts, *BIN1* [546] (2q14.3), the CD2-associated protein gene *CD2AP* [542, 557] (6p12.3)*,* the complement C3b/C4b re-

ceptor type 1 gene *CR1* [542, 546] (1q32.2), the ephrin type-A receptor 1 *EPHA1* [542, 546, 557] (7q34-35)*,* the membrane-spanning 4-domains subfamily A member 4 *MS4A4A/ MS4A6A* [542] (11q12.2), the phosphatidylinositol binding clathrin assembly protein *PICALM* [542] (11q14.2)*,* the phospholipase D family member 3 gene *PLD3* [542, 557] (19q13.2)*,* and triggering receptor expressed on myeloid cells 2 *TREM2* [542] (6p21.1)*,* which have been found associated specifically with LOAD [540]. The *ABCA7* transporter is known affecting the production and clearance of Abeta [557, 558]. The *ADAM10* encodes a proteolytic enzyme at the alpha secretase cleavage stage, accumulating in hippocampal synapses [556, 559]. The *TREM2* encodes microglial cytokine signalling elements related to chronic inflammation, autophagy and Abeta clearance [541, 542, 557, 560]. The *PICALM* [7, 541, 542, 546, 557, 561] gene produces a clathrin protein involved in membrane recycling and autophagy. The *CR1* complement receptor 1 gene [8, 541, 542, 546, 557, 562], a membrane glycoprotein binding to immune complexes. *BIN1* [542, 546, 557] produces a nucleocytoplasmic adaptor protein important for synaptic functioning and myelination [563, 564]. The *EPHA1* gene product was found regulating cerebral glucose levels, and brain atrophy [565]. The *CD2AP* encodes a cytoplasmic protein implicated in membrane trafficking, related to Abeta$_{40/42}$ levels [566]. The *MS4A4A/MS4A6A* was found significantly related to CSF Abeta$_{42}$ [567]. The *PLD3* enzyme phospholipase D is described catalysing membrane phospholipids, thereby exerting influence upon processing of APP [568]. *ABCA7* and *BIN1*, *ANK1*, *CDH23*, *DIP2A*, *RHBDF2*, *RPL13*, *SERPINF1* and *SERPINF2* [569]*, ANK1*, a well-known susceptibility gene for T2DM [476]*, RPL13* and *RHBDF2*, are biologically linked to *PTK2B*, a known LOAD-associated gene. The fourth, the cadherin gene *CDH23*, is involved in neuronal differentiation [543]. The *ANK1* gene was associated with neuropathology in the entorhinal cortex, and was confirmed as being substantially hypermethylated in superior temporal gyrus and prefrontal cortex [570].

Additional rare variants were also detected in *APP*, *TREM2*, *PLD3* [542, 571]. The SNP rs597668 near *BLOC1S3* (19q13.32) biogenesis of lysosomal organelles complex1 subunit 3 is responsible for functioning of the lyosomal system [572]. The highly polymorphic *ECE*-1b (1p36.12) promoter [573] was found relevant for *APOE* epsilon4 non-carriers: endothelin converting enzyme 1 is the key enzyme in endothelin biosynthesis and crucial for receptor recycling and Abeta degradation [574]. The protection of telomeres protein 1 gene *POT1* (7q31.32, rs4728029) was detected as related to *h*-tau, inflammatory response cytokine IL-6 [575], ventricular enlargement and cognition. The TYRO protein tyrosine kinase-binding protein gene *DAP12/TYROBP* (19q13.12) encodes a transmembrane signalling polypeptide containing an immunoreceptor, and is crucial for brain myelination, inflammation and causal regulation of microglial genes [576]. In LOAD, genetic variants in sortilin related receptor 1, clusterin, complement component receptor 1, *CD2AP*, *CD33* [541], *EPHA1*, and *MS4A4/MS4A6E* [542, 546] genes contribute to late-onset age. Further common variants identified for age-of-onset are: *WRN*, *NTN4*, *LAMC3* [577], and *HMGCR* [541]; rare vari-

ants for age-of-onset are *SLC8A3*, *SLC19A3*, *MADD* and *LRRK2* [577].

4.1.1. Myelin Structural and Neuronal Plasticity Genes in LOAD

Stability of myelin and integrity of WM tracts are critical for the functioning cognitive reserve during ageing, and disruptions are structural biomarkers of neurodegeneration. GWAS have supported a central role of myelin maintenance by revealing indirect myelination markers such as *SORL1*, *SORCS1*, *BIN1*, *TYROBP*. However, traditional myelin protein genes, such as myelin basic protein *MBP*, myelin oligodendrocyte protein *MOG*, myelin associated glycoprotein *MAG*, have rarely been studied in the context of LOAD. Genes crucial for onset of white matter myelination and myelin transcription factor *MYT1*, myelin regulatory factor *MYRF*, 2',3'-cyclic-nucleotide 3'-phosphodiesterase *CNP*, and cholesteryl ester transfer protein *CETP* [541] have not been studied systematically in LOAD. More interest have, in contrast, raised synaptic plasticity and anatomical connectivity genes, such as neuronal protein astrotactin 2 *ASTN2* [578], neuregulin 3 *NRG3* [579], spondin *SPON1* [541] and reelin *RELN*. The mammal-specific factors osteocrin *OSTN* and the related *MEF2C* are highly expressed in human cortices, here contributing to cognition. For these genes, it has been shown that epigenetic mechanisms exist, where HDACs deacetylate targets indicated by lysine histone codes H3K9 and H4K12, to regulate downstream genes important for neuroplasticity (*BDNF*, *EGR1/NGFI-A*, *CDK5*, *SYT1*, *SYP*, and *GRN*).

The plasticity marker activity-regulated cytoskeleton-associated protein Arc (*ARC* 8q24.3) (Section 3.1.) belongs to a class of genes transcribed in presence of protein synthesis inhibitors, and localised to NMDARs [580] in the synaptic cleft, there stabilising learning-related plastic changes as a Synaptic Activity Response Element (SARE) essential for associative learning and conditioning. Arc is also related to glutamatergic signalling *via* AMPA receptors [581], dopamine receptor 1, and LTP, responsive to neurotrophic signals including epidermal growth factor EGF, nerve growth factor NGF, and brain-derived neurotrophic factor BDNF [581]. Its gene is regulated by CREB, dependent of the MAPK [580] pathway following ERK1/2 phosphorylation [580], and the microtubular mRNA transport locally translated at dendritic spines and activated synapses [582].

Overall, brain growth is a LOAD risk-factor, and the delta-opioid receptor *OPRD1* was related to small cerebral volume [541] (and to amyloidogenic processing, Section 1.4.). Glutamate transporter *EAAT2* is overactive in LOAD leading to excess glutamate in synaptic functioning [583]. The fas-associated serine/threonine kinase domains 2 *FASTKD2* was associated with memory performance [541]. Poly(ADP-ribose) polymerase 1 *PARP1*, and caspase recruitment domain family, member 10 *CARD10* genes correlated with hippocampal volume [541], whereas astrotactin 2 *ASTN2*, and ionotropic glutamate receptor, N-methyl D-aspartate 2B, *GRIN2B* correlated with hippocampal and temporal atrophy [541]. The biological ageing-related gene *POT1* (protection of telomeres 1) has been observed in correlation with ventricular dilation [541], whereas neuroprotection was promoted by expression of RE1-silencing transcription factor *REST* [541].

4.1.2. Immune System Genes in LOAD

Under physiological conditions, triggering receptor expressed on myeloid cells 2 (*TREM2*) pairs with the adaptor protein DNAX-activating protein (*DAP12/TYROBP*) to induce phagocytosis of apoptotic neurons without inflammatory responses, and to regulate toll-like receptor (*TLR4/2*) mediated inflammatory responses, and microglial activation [584]. It has been detected recently that its natural ligands consist of stress-related mitochondrial heat shock proteins [584]. Further GWAS-genes associated with neuroinflammation [482, 504] were summarised with *CR1* complement receptor, *CFHR1* [541] complement receptor, immunoreceptor *CD33*, membrane-spanning proteins *MS4A6A/MS4A4E*, interleukin-6 receptor *IL6R* [541], geminin coiled-coil domain containing *GMNC,* transcription repressor GLIS family zinc finger *GLIS3* [541], and mitochondrial energy and cellular stress genes *ATP5H/KCTD2* [541]. Genes associated with microglial function [498] were summarised as *TREM2*, *CD33*, *CR1*, *CLU*, *CD2AP*, *EPHA1*, *ABCA7*, and *INPP5D*. Genes relating to neuroinflammation [510] were summarised in *MRP14*, *MS4A6A, MS4A4AE*. Autophagy genes identified: (a) *ULK1, ULK2, BECN1*, (b) *ATG13, ATG2A, ATG2B, ATG4C, ATG4D* (c) *MAPLC3A, MAPLC3B2* (d) *LAMP1* [341, 345, 352]. Mitophagy genes identified are: *PINK, PARK1, MAPLC3A, MAPLC3B2, HDAC6* [351, 352], and ectopic P-granules autophagy protein 5 homologue *EPG5* [551].

Table **3** lists the candidate genes extracted from the previous sections of pathophysiological mechanisms in LOAD, mainly from animal studies, with their loci and brief functional descriptions. The references then pertain to human association, case-control, or pathophysiology studies in LOAD patients, where the genes have been reported involved. For 60 of 224 gene loci, no positively confirming results were reported in humans.

4.2. Meta-analytic Evaluation of Genes Nominated from the Collection of Studies

Because known LOAD risk genes are not sufficient in explaining the heritability estimates (Section 1.1.), epigenetic mechanisms are increasingly assumed to playing a key role in LOAD aetiopathology [1]. It is herein supposed that epigenetic modification mechanisms are typically associated to SNPs [1] occurring in risk loci. It has been proposed for LOAD pathogenesis, that Lahiri's "Latent Early Associated Regulation" (LEARn) theory, which was formulated for all neurodegenerative disorders, provides a sufficient theoretical framework for the contribution of epigenomics towards clinical manifestation. Consistent with the notion of ELS priming of stress for brain functioning, the LEARn model posits that early environmental exposures can change gene expression for long-lasting developmental time periods. Alterations of gene expression would hence be conducive to neuropathology that only becomes apparent later in life. As an example, the concept of a fetal basis of amyloidogenesis [133] assumes that the regulatory regions of the genes involved in amyloid processing, become biased specifically through changes in methylation and oxidation status within the promoter of specific genes [585], and therefore epigenetically programmed towards late-life neurodegeneration.

Whilst a variety of currently known post-translational modifications can occur: acetylation, methylation, ubiquitylation, phosphorylation, sumoylation, crotonlylation and numerous less well-studied modifications [586, 587], the probes yet examined for LOAD have included only the two main mechanisms DNA methylation and histone acetylation.

4.2.1. Previous Epigenomic Findings in LOAD

Best cues to epigenetic modification currently stem from histone deacetylases (HDAC) in model systems of AD and in off-label treatments of LOAD patients with HDAC inhibitors [569]. HDAC (isoforms 1, 2 and 3) can also be PET-neuroimaged in humans, and in normals showed greatest variability in cortical grey matter [588]. Epigenetics is specifically relevant in cognitive disturbances [586, 589], and enzymes responsible for histone acetylation (HAT) and deacetylation (HDAC) here act as the regulators of synaptic plasticity and memory. Disrupted epigenetic regulation is suspected in LOAD [586, 589] with respect to memory-related genes such as *CREB*, *CREBBP*, *FOS*, *ARC*, *PSD95*, *CDK5*, *GLUR*, *GABBR*, *PP1*, NFkappaB, *MECP2*, alpha-synuclein, Ephexin5, ERK/MAP, reelin *RELN* [589]. But HDACs furthermore epigenetically control Abeta expression, beta/gamma secretases, and the Abeta degradation enzyme Mmp2 [590]. The parallel downregulation of HDACs and upregulation of histone acetyltransferases at the p300/CREB-binding protein locus (*CREBBP*) was observed with concurrent DNA methyltransferase reduction [591]. Epigenetic regulations of Abeta$_{42}$ processing are therefore exerted jointly by DNA methyltransferase DNMT, histone acetyltransferase HAT, and histone deacetylase complex HDAC genes. *In vivo* and *post-mortem* findings suggest also that soluble polymeric Abeta can itself trigger epigenetic regulation of transcriptional activation and inhibition [592], specifically of histone H3 homeostasis [591-593].

Histone deacetylase 2 (HDAC2) associates with and reduces the histone acetylation of genes important for learning and memory. Overexpression of *HDAC2*, but not that of *HDAC1*, decreased dendritic spine density, synapse number, synaptic plasticity and memory formation. However, this was found reversible, which suggests that cognitive capacities following neurodegeneration are not entirely lost, but merely impaired by this epigenetic blockade [594, 595]. The *HDAC2* exhibited a relation with chronic stress experience and reward related plasticity in the ventral striatum [596]. Chronic stress resulted there in significant increase in the level of HDAC2 and in its binding to the promoter region of glial cell-derived neurotrophic factor (GDNF), thereby causing down-regulation of *Gdnf* expression in the mesolimbic nucleus accumbens (NAcc).

Methylation studies in twelve LOAD patients revealed evidence for an "epigenetic drift" with interindividual variabilities in *APOE* promoter; *DNMT1*, *MTHFR* and *TFAM* were hypermethylated compared to the norm [92]. Controls did not exhibit notable epigenetic distances from the norm in cerebral methylation for LOAD candidate genes. Similar results pertaining to large interindividual variation in candidate genes are reported by a number of studies (Table **2**). Epigenetic drifts were substantiated in LOAD for genes involved in amyloid processing (*PSEN1*, *APOE* promoter) and methylation homeostasis (*MTHFR*, *DNMT1*) [597]. Fur-

thermore, regulations of Abeta$_{42}$ are exerted by DNA methyltransferase DNMT genes. While it remains difficult to measure impact of early life adversity over the entire lifespan, available evidence suggests that environmental influences tend to inhibit DNA methyltransferases during brain development, which results *e.g.* in hypomethylation of APP gene [136]. It is therefore plausible that analogous alterations are leading to genomic imprints for late-life susceptibility of LOAD (corresponding to the Lahiri LEARn model):

Both hypermethylation and hypomethylation were found to be involved in oxidative stress damage induced by Abeta miscleavage [136]. In hypermethylation of AD genes, methylcytosines restrict repair of adjacent hydroxyguanosines, thus increasing susceptibility to oxidative stress [136]. Recent studies isolated methylation and hydroxymethylation as putative key epigenetic mechanisms in LOAD [598]. The respective markers 5-methylcytidine (5-mC) and 5-hydroxymethylcytidine (5-hmC) were decreased in a magnitude of 20% in LOAD-hippocampi and negatively correlated with Abeta plaques [598]. One further mechanism related to ER stress is the homocysteine metabolism known to be altered during ageing. Hepatic S-adenosylmethionine (SAM) metabolism [599, 600] is also reduced in AD and found to cause hypomethylation in *APP* and *PSEN1* promoter genes [600], thus leading to increased Abeta expression [600].

In vitro results demonstrate that environmental stress MAPK pathways p38 and JNK are activators of Abeta by means of an ensemble of epigenetic modulations: demethylation in three gene promoters responsible for reduction of methyltransferases (DNMTs) enhanced expression of *APP*, *BACE1*, and *PSEN1* [591]. Histone H3 hyperacetylation in concord with DNMT-dependent hypomethylation inducing Abeta overexpression are thus the putative consequence of MAPK stress signalling [591]. Another putative mechanism for JNK activation in stress signalling is the pro-apoptotic kinase PKR (double-stranded RNA dependent protein kinase) phosphorylating eIF2alpha (eukaryotic translation initiation factor-2 alpha) [601] in translational regulation of *BACE1*. The two kinases related to eIF2alpha, PERK and GCN2, were found responsible for impairments in spatial memory and synaptic plasticity [602], and are dependent of phosphorylation of eIF2alpha. Phosphorylated eIF2alpha generally stops protein translation in response to cellular stress. AD genes, in contrast, including *BACE1*, are activated by eIF2alpha [252, 544].

For the evaluation presented in Table **2**, the 313 candidate risk genes of Tables **1** and **3** were combined. It was searched for results from human studies. 35 studies were identified containing human epigenomics findings. In addition, gene regulation studies pertaining to candidate genes were compiled. In this literature, 64 separate gene regulation mechanisms were described. Fig. (**1**) illustrates the extraction of genes and analysis steps.

4.2.2. Summary of Present Findings on Epigenomics in LOAD

The meta-analysis on epigenetic modification of risk genes (Table **2**) is mainly extending the lines of the literature detailed above. Special care in generalisation of findings should be at hand, as the relative small amount of studies tend to cluster to relative few well-known gene loci. Previous reports of findings tend to attract further studies in the same loci, whereas the less well-known risk genes remain unresearched. Given the fact that epigenomics is assumed to be crucial in LOAD pathophysiology for more than a decade, little research effort has been invested up to date in comparison. An explanatory reason for this slow progression is that epigenomic studies of *post-mortem* tissue are difficult to accomplish. For these reasons, the compiled findings are likely to reflect a certain sampling bias. In addition, the studies have mostly small sample sizes. Epigenomic findings encompass seven groups:

(a) Genes relevant to familial EOAD *APP, PSEN1, APOE, MAPT*;

(b) Central role of *BDNF*;

(c) Myelin-related genes *BIN1, CNP, SORL1*;

(d) ELS-related genes: *FKBP5, EGR1/NFI-A, GSK3B;*

(e) Lipid metabolism: *ABCA7, ALOX5, DHCR24;*

(f) Gene modification itself: *CREB, CREBBP, FOS, MBD2, MTHFR2, DNMT1;*

(g) Neuroinflammation: *NFKB1, TNFA, ANK1, CRP.*

Given the large number of candidate genes, it is likely that the research field in epigenomics of LOAD is only in its initial stage.

4.2.3. Summary of Present Findings on Gene Regulation by MicroRNA

The compilation of microRNA resulting from candidate genes is listed in Table **4**. Search for microRNA biomarkers has been conducted since 2007, but without reaching consensus yet [560]. Special areas were gene regulation during neurogenesis [116] and microRNAs related to memory impairments as implicated in LOAD [603]. It is likely that only a small proportion of LOAD-related microRNA has been identified.

With respect to frequency of the target, 10 microRNAs relate to BACE1, 7 to MAPK signalling, 5 to APP, 5 to TLR4, 4 to BDNF, and 3 to insulin signalling. Most mechanisms are related to microRNA-132 and microRNA-27. It must be stated that in this research domain no tentative conclusions can be reached yet.

4.3. Evaluation with Respect to Possible Impact of Early Life Stress

Returning to the initial question of ELS effects in LOAD, the present state of research permits the conclusion that rodent studies have indeed demonstrated such effects. Gaining direct evidence from human studies remains difficult for the larger life-spans, and the greater genomic complexity of the organism *homo sapiens*.

The summary of findings from the genome level supports an involvement of SMA and HPA in LOAD. The accumulated evidence from association studies includes support for the assumption of strong role of structural brain growth factors. This relates to the microtubule associated protein tau gene *MAPT* and further neuronal cell stabilisers. Association studies also suggest a strong role of genes related to myelin
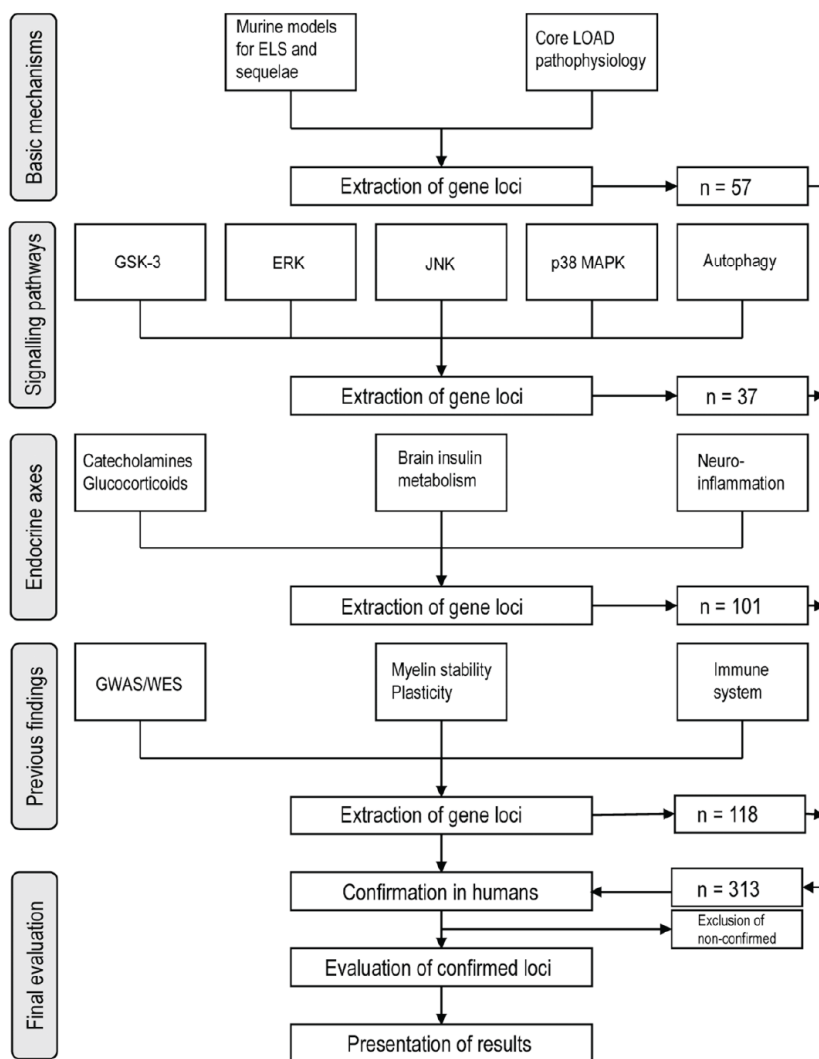
Fig. (1). PRISMA flowchart depicting levels of data extraction and meta-analysis.

Table 4.   Gene regulation.

Number of micro-RNA	Target/Function	References
miR-106b	ABCA1	[476, 546]
miR-107	BACE1	[811]
miR-124	CREB, APP, BACE1	[546]
miR-124	Neurogenesis (*e.g.* SOX9, Jag1 and Dlx2)	[799]
miR-125b	Tau hyperphosphorylation, p35, p44/42, CDK5, MAPK signalling	[812-814]
miR-128b	CREB1, ROS, Abeta	[546, 815]
miR-132	Morphological rearrangements of neurons, memory formation	[546, 813]
miR-132	MeCP	[546]
miR-132	TLR4	[268]
miR-132	NBM degeneration, cholinergic system, related to *EGR1*	[683]
miR-132/107	-	[560]

(Table 4) contd….

Number of micro-RNA	Target/Function	References
miR-132/128	-	[560]
miR-132/132	-	[560]
miR-132/138	-	[560]
miR-132/191	-	[560]
miR-132/206	-	[560]
miR-132/212	Tau expression, tau hyperphosphorylation, tau aggregation, GSK-3beta, PP2B	[816]
miR-132/384	-	[560]
miR-134	BDNF, MCI	[546]
miR-135a/-193b/-200b/-384	APP/BACE1	[817-819]
mir-135b	Hippocampal cell proliferation, neuroprotection, memory capacities	[820]
miR-138	RARA/GSK-3b pathway	[551]
miR-144	Negatively related to ADAM10, regulated by AP-1	[821]
miR-146a	TLR4, microglia, NRF2	[268, 822]
miR-153	APP	[823]
miR-155	JNK pathway, B-cell maturation and immunoglobulin production	[293]
miR-155	TLR4	[268]
miR-16/101	APP	[546]
miR-181c	*SIRT1*, stress, inflammation	[813]
miR-182	Cortactin	[546]
miR-186	BACE1	[824]
miR-188-3p	PPARgamma, MAGL	[825]
miR-193b	APP	[819]
miR-195	BACE1	[826]
miR-200	APP, *PSEN1*	[817]
miR-206	IGF1	[827]
miR-206	BDNF	[828]
miR-20a	APP	[546]
miR-26b	IGF1	[829]
miR-26b	Aberrant cell cycle entry (CCE), CDK5 kinase activity, tau-phosphorylation	[814, 830]
miR-27-3p	Adipocyte differentiation, extracellular signal related kinase 5 (ERK5), peroxisome proliferator-activated receptor gamma (PPARgamma), CCAAT/enhancer binding protein (C/EBP)	[476]
miR-27a	-	[560]
miR-27b	TNFalpha, IL-6, PPARgamma	[831]
miR-298/328/195	BACE1	[546]
miR-299-5p	Suppression of autophagy, neuroprotection, attenuation of caspase-mediated apoptosis	[832]
miR-29a/20b-1/9b	BACE1, SPTLC2	[546]
miR-29b	BACE1	[813, 833]
miR-29c	Positively to DNMT3, negatively to BDNF	[834]

Number of micro-RNA	Target/Function	References
miR-29c	BACE1, increasing CREBBP	[835, 836]
miR-33	Cholesterol homeostasis	[476]
miR-33	ABCA1 expression, Abeta reduction, APOE lipidation	[837]
miR-339-5p	BACE1	[838]
miR-34	Tau aggregation	[170, 546, 814]
miR-34a	TREM2, NFkappaB	[839]
miR-511	FKBP5 interaction	[840]
miR-512	cFLIP, MCL1, *h*-tau	[841]
miR-574	Neuritin	[842]
miR-603	LRP1	[843]
miR-613	BDNF	[844]
miR-758	ABCA1	[476]
miR-9	Abeta, orphan receptor TLX, expressed in neural progenitors, neuronal differentiation	[546, 813]
miR-922	Ubiquitin carboxyterminal hydrolase L1 (UCHL1), tau hyperphosphorylation	[845]
miR-98	IGF-1, autophagy, GSK-3beta, tau hyperphosphorylation	[546, 846]

Index of gene loci in the text

ABCA1 9q31.1, 11; *ADCYAP1* 18p11.32, 16; *ADRA2A* 10q25.2, 35; *ADRB1* 10q25.3, 35; *ADRB2* 5q31-32, 36; *ADRB3* 8p11.23, 36; *AGER* 6p21.32, 32; *ALOX5* 10q11.21, 52; *APBB2* 4p14-p13, 26; *APOE* 19q32.13, 6; *APP* 21q21.3, 6; *ARC* 8q24.3, 42; *AVP* 20p13, 16; *BACE1* 11q23.3, 18; *BAX* 19q13.33, 54; *BDNF* 11p14.1, 12; *BECN1* 17q21.31, 33; *CAMK2A* 5q32, 14; *CCL2* 17q12, 48; *CCL3* 17q12, 48; *CCL4* 17q4, 48; *CDK5* 7q36.1, 20; *COMT* 22q11.2, 35; *CREBBP* 16p13.3, 16; *CREBBP* 16q13.3, 13; *CRH1* 8q13.1, 12, 37; *CRHBP* 5q13.3, 39; *CRHR1* 17q21.31, 15, 39; *CRHR2* 7p14.3, 15, 39; *CRP* 1q23.2, 52; *CX3CL1* 16q21, 48; *CX3CR1* 3p22.2, 49; *CYP46A1* 14q32.2, 46; *DBH* 9q34.2, 36; *DLG4* 17p13.1, 27; *DLG4* 17p31.1, 32; *DNMT1* 19q13.2, 16; *DNMT3A* 2p23.2, 16; *DNMT3B* 20q11.21, 16; *DUSP1* 5q35.1, 13; *EDN1* 6p24.1, 51; *EDNRA* 4q31.22-23, 51; *EDNRB* 13q22.3, 51; *EGR1* 5q31.2, 14; *EIF2AK2* 2p22.2, 24; *EIF2S1* 14q23.3, 24; *FKBP4* 12p13.33, 40; *FKBP5* 6p21.31, 38; *FOS* 14q24.3, 15; *GAB2* 11q14.1, 7; *GABRA1* 5q34, 16; *GAD1* 2q31.2, 40; *GMEB1* 1p35.3, 39; *GMEB2* 20q13.33, 39; *GNB3* 12p13.31, 36; *GRIA1* 5q33.1, 32; *GRIA2* 4q32.1, 32; *GRIA3* Xq25, 32; *GRIA4* 11q22.3, 32; *GRM1* 6q24.3, 32; *GRM5* 11q14.2-3, 32; *GRN* 17q21.31, 49; *GSK3A* 19q13.2, 26; *GSK3B* 3q13.33, 26; *HDAC6* 6q21, 38; *HIF1A* 14q23.2, 43; *HMGB1* 13q12.3, 44; *HMGCR* 5q13.3, 46; *HNF4A* 20q13.12, 43; *HSD11B1* 1q32-q41, 39; *HSD11B2* 16q22.1, 11; *HSPA1A* 6p21.33, 45; *IAPP* 12p12.1, 20; *IDE* 10q23-q25, 44; *IGF1* 12q23.2, 21, 43; *IGF1R* 15q26.3, 43, 44; *IGF2* 11p15.5, 43; *IGF2R* 6q25.3, 44; *IGFBP1* 7p12.3, 38; *IL10* 1q32.1, 53; *IL12A* 3q25.33, 53; *IL12B* 5q33.2, 53; *IL18* 11q23.1, 53; *IL1A* 2q14.1, 53; *IL1B* 2q14.1, 53; *IL33* 9p24.1, 53; *IL4* 5q31.1, 53; *IL6* 7p15.3, 53; *INS* 11p15.5, 43; *INS-IGF2* 11p15.5, 11; *INSRR* 1q23.1, 44; *IRF3* 19q13.33, 38; *IRS1* 2q36.3, 43; *IRS2* 13q34, 44; *LEP* 7q32.1, 11; *LRP1/APOER* 12q13.3, 23; *LRP2* 2q31.1, 43; *MAP1B* 5q13.2, 24; *MAP1LC3A/B* 16q24.2, 33; *MAP3K5* 6q23.3, 22; *MAPK1* 22q11.22, 27; *MAPK10* 4q21.3, 29; *MAPK11* 22q13.11, 31; *MAPK12* 22q13.3, 31; *MAPK13* 6p21, 31; *MAPK14* 6p21.31, 31; *MAPK3* 16p11.2, 27; *MAPK8* 10q11.22, 29; *MAPK8IP1* 11p11.2, 30; *MAPK8IP3* 16p13.3, 30; *MAPK9* 5q35.3, 29; *MAPT* 17q21.31, 19; *MBD2* 18q21.2, 16; *MC2R* 18p11.2, 39; *MECP2* Xq28, 16; *MGAT3* 22q13.1, 52; *MPO* 7q22, 50; *MSR1* 8p22, 51; *NBR1* 17q21.1, 33; *NCOA2* 8q13.3, 39; *NET* 16q12.2, 36; *NEUROG1* 5q23-31, 17; *NEUROG2* 4q25, 17; *NEUROG3* 10q21.3, 17; *NFKBIA* 14q13.3, 38; *NLRP1* 17p13.2, 50; *NLRP3* 1q44, 50; *NOS3* 7q35-36, 53; *NOTCH1* 9q34.3, 6; *NPY1R* 4q32.2, 40; *NR3C1* 5q31.3, 11; *NR3C1* 5q31-32, 38; *NR5A1* 9q33.3, 39; *NRF2* 2q31, 33; *NTRK2* 9q21.33, 13; *P2RX7* 12q24.31, 52; *PCK1* 20q13.31, 12; *PION* 7q11.23, 18; *PKN1* 19p13.12, 8; *PPARG* 3p25.2, 53; *PPARGC1A* 4p15.2, 53; *PPARGC1B* 5q32, 53; *PSEN1* 14q24.1, 6; *PSEN2* 1q42.13, 6; *PTGER2* 14q22.1, 50; *PTGER3* 1p31.1, 50; *PTGER4* 5p13.1, 50; *PTGS1* 9q32-q33.2, 22; *PTGS2* 1q25.2-q25.3, 43; *PTPN5* 11p15.1, 32; *PYCARD* 16p11.2, 50; *RANBP9* 6p23, 54; *RANKL* 13q14.11, 38; *RCAN1* 21q22.1, 28; *REST* 4q12, 15; *SCARB1* 12q24.31, 51; *SCARB2* 4q21.1, 51; *SCARB3* 7q11.2, 51; *SCN* 4q22.1, 23; *SERPINA3* 14q32.13, 52; *SERT/SLC6A4* 17q11.2, 11; *SGK1* 6q23.2, 21; *SH3GLB1* 1q22, 19; *SHC1* 1q21.2, 22; *SLCO1A2* 12p12.1, 20; *SOD1* 21q22.1, 21; *SORCS1* 10q25.1, 35; *SORL1* 11q24.1, 35; *STAT3* 17q21.2, 33; *SYP* Xp11.23, 21; *TBP* 6q27, 16; *TFCP2* 12q13.12-13, 26; *TFEB* 6p21, 33; *TGFB1* 19q13.2, 53; *TLR4* 9q33.1, 45; *TNFA* 6p21.33, 53; *TNFRSF10A* 8p21.2, 54; *TNFRSF10B* 8p21.2, 54; *TNFRSF1A* 12p13.31, 49; *TNFRSF1B* 1p36.22, 49; *TSC22D3* Xq22.3, 53; *ULK1* 12q24.33, 33; *VDAC1* 5q31.1, 21, 45; *VEGFA* 6p21.1, 53; *VLDLR* 9p24.2, 23*

stability *BIN1*, *CNP*, *MOG*, *MAG*, *RELN*, *SORL1*, *SORCS1*. Structural MRI studies have previously demonstrated WM loss in LOAD.

SNPs in genes of adrenoceptors alpha and beta providing noradrenergic signalling were found associated with LOAD. However, genomic research have no clues yet for the connection between noradrenaline systems and LC degeneration in LOAD. Unclear also remains the physiological regulation between noradrenaline and disrupted cerebral insulin signalling present in LOAD. Association studies for genes related to HPA functioning and LOAD have ruled out most loci for steps of glucocorticoid processing. The sole surviving sig-

nificant gene *HSD11B1* for association with LOAD is, however, a strong argument for ELS effects in LOAD. Further support for the assumption of ELS effects in LOAD are also associations of the trauma-related genes *FKBP5* and *NR3C1* in glucocorticoid signalling. Because rat models implicated insulin signalling abnormalities, and altered levels of the protein Arc related to active neurites and synapses, and activated by MAPK signalling, insulin metabolism was specifically included. The finding of genomic associations for genes involved in cerebral insulin signalling *IGF2R*, *INSR*, *INSRR*, and the related plasticity marker *ARC*, is therefore also supportive for ELS in LOAD. Generally, were meta-

bolic biases as consequence of ELS, as conducive to LOAD, well supported animal and human studies.

The summary of findings on the epigenomic level is also able to extend these conclusions. On the epigenomic level, the present state of the literature suggests that the assumption of priming influences of environment in terms of epigenetic mechanism may be supported for core pathology genes of the Abeta cascade *APP*, *BACE1*, *PSEN1*, *PSEN2*, and of tauopathy *MAPT*. Mutations of these genes were found relevant for EOAD, but not LOAD. Findings of epigenetic modifications can now provide explanations as to their analogous pathophysiologies. As LOAD is dependent on ageing effects, epigenetic mechanisms in lipid metabolism genes *ABCA7*, *ALOX5*, *DHCR24*, *APOE* promoter are explanative. Modification in major neuroinflammation markers *NFKB1*, *TNFA*, *ANK1*, *CRP* extend recent analogous findings from GWAS. Metabolic and inflammatory processes are likely related to modifications in myelin-related genes *BIN1*, *CNP*, *SORL1*. ELS effects are assumable through modifications in ELS-related genes *FKBP5*, *EGR1/NGFI-A*, *GSK3B*. Finally, modifications in *CREB*, *CREBBP*, *FOS*, *MBD2*, *MTHFR2*, *DNMT1* suggest alterations of synaptic functioning, transcription, and epigenetic gene modification itself in LOAD.

CONCLUSION AND FURTHER DIRECTIONS

In conclusion, it is noteworthy to say that the present analysis supports plausibility for an assumption of trauma-related ELS effects in LOAD, specifically *FKBP5* and *EGR1* mediated, and early life stress effects through glucocorticoid converter *HSD11B1*. The state of research suggests a coupling of the glucocorticoid receptor to the *MAPT* gene. Therefore, it is plausible that early tau neuronal mechanisms could be affected. This is also suggested by findings of early childhood LC degeneration and tauopathy. It is also possible, and also paediatric findings of a relation between reduced early cerebral growth and LOAD support this assumption, that early myelin formation could be compromised. Lesser myelin stability could be conducive to WM disintegrities as a structural biomarker of LOAD in old age. Similarly, early microglial priming towards an inflammatory phenotype, and early metabolic priming towards insulin resistance are plausible consequences of ELS effects. Unclear remains the functioning of the noradrenaline system in the context of locus caeruleus degeneration-related neuropathology.

Directions for further research must point to the interaction of neuroinflammation, cerebral lipid metabolism, brain insulin resistance, and myelin disintegration, which is suggested by the genomic and epigenomic findings accumulated. Currently, there is not enough knowledge in each of these domains available to answer the questions raised by abnormal cerebral insulin metabolism, myelin genes and maintenance of white matter, under the impact of chronic neuroinflammation.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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