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The potential roles of excitatory-inhibitory imbalances and the repressor element-1 silencing transcription factor in aging and aging-associated diseases

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ABSTRACT

Disruptions to the central excitatory-inhibitory (E/I) balance are thought to be related to aging and underlie a host of neural pathologies, including Alzheimer's disease. Aging may induce an increase in excitatory signaling, causing an E/I imbalance, which has been linked to shorter lifespans in mice, flies, and worms. In humans, extended longevity correlates to greater repression of genes involved in excitatory neurotransmission. The repressor element-1 silencing transcription factor (REST) is a master regulator in neural cells and is believed to be upregulated with senescent stimuli, whereupon it counters hyperexcitability, insulin/insulin-like signaling pathway activity, oxidative stress, and neurodegeneration. This review examines the putative mechanisms that distort the E/I balance with aging and neurodegeneration, and the putative roles of REST in maintaining neuronal homeostasis.

1. Introduction

The spatial organization of neuronal inputs, which can be either excitatory or inhibitory, is critical for neuronal network function (Branco et al., 2010; Ju et al., 2020). By means of regulated, reproducible processes, individual neurons receive a relatively invariant ratio of excitatory/inhibitory (E/I) inputs (Iascone et al., 2020). Similarly, in larger-scale networks, the ratio of E/I neurons is regulated by multiple processes involving homeostatic plasticity (Hengen et al., 2013). This results in an overall E/I balance in the nervous system and is thought to represent a neuronal homeostatic determinant of cortical activity (Roudi and Latham, 2007; Shew et al., 2011). Maintenance of the balance is important as it is optimal for information processing and neural health (Shew et al., 2011). E/I imbalances are suspected to underlie a host of pathologies ranging from neuropsychiatric disorders to neurodegenerative diseases in aging (Gao and Penzes, 2015; Lee et al., 2017; Lopatina et al., 2019; Penzes et al., 2013; Ren et al., 2018). However, aging-associated processes can skew the balance towards excessive excitation, which has been implicated in the development of several comorbidities concomitant with aging, such as hearing and memory loss (Caspary et al., 2008; Richardson et al., 2013; Rozycka and Liguz-Lecznar, 2017). Processes that restore and maintain homeostatic regulation of the E/I balance in aging are therefore important for healthy longevity.

The repressor element-1 (RE1) silencing transcription factor (REST, also called neuron-restrictive silencing factor (NRSF)) is a conserved zinc-finger transcription factor that plays a master role in neural cells (Ballas et al., 2005; Chong et al., 1995). REST recruits several cofactors, most importantly CoREST, N-CoR, and mSin3A, forming a REST-repressor complex which epigenetically represses the expression of

Abbreviations: RE-1, Silencing transcription factor; REST, Excitatory/inhibitory balance; E/I Balance, Insulin/insulin-like growth factor signaling; IIS, Forkhead box transcription factor-1; FOXO, Abnormal Dauer formation; DAF, Lipid peroxidation product 4-hydroxynonenal; HNE, Cannabinoid receptor type-1-CB1R.

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thousands of genes containing specific binding sequences of which RE1 is the best characterized (Baldelli and Meldolesi, 2015; Chong et al., 1995; Otto et al., 2007). Approximately 1/3 of human RE1-sites are recently evolved and specific to primates, suggesting a role in primate-specific cognitive evolution and development (Mozzi et al., 2017). REST is active during neurodevelopment within embryonic and neural stem cells (ESCs and NSCs, respectively) after which it is progressively downregulated permitting crucial processes such as axon guidance, synaptogenesis, and the establishment of membrane excitability to occur, forming the mature nervous system (Baldelli and Meldolesi, 2015; Palm et al., 1998). Subsequent global neuronal nuclear REST levels remain low until senescent stimuli facilitate nuclear-entry in late life (Kawamura et al., 2019). However, the trajectory of REST levels varies between regions and species. In the cerebellar cortex, levels decline throughout life after development but in the prefrontal cortex (PFC), there is a steady increase after adolescence in primates (Mozzi et al., 2017). Evidence suggests that overall levels peak during cognitively healthy aging in humans but not other primates (Mozzi et al., 2017). Due to the vastness and variation of its regulatory network across species through evolution, the diversity of its functionality continues to be studied and it is thought to play critical roles in neurodevelopment, neuroprotection, as well as, if dysregulated, neurodegeneration.

Zullo et al. linked excessive excitation in old age with a shorter lifespan and increased aging-associated health problems such as cognitive decline, oxidative stress, and neurodegeneration (Zullo et al., 2019). Studies that have analysed REST-modulated gene expression in aging human cortical tissues revealed the most downregulated genes to be involved in excitatory neurotransmission and produce mRNAs inversely correlated with REST mRNA levels (Lu et al., 2014; Zullo et al., 2019). Indeed, REST may be the most activated transcription-factor in cognitively healthy aging (Lu et al., 2014). REST is able to combat neural excitation in aging and maintain neuronal viability with the activation state of REST helping differentiate neuroprotection from neurodegeneration in the aging brain (Garcia-Manteiga et al., 2015; Zullo et al., 2019). This review will comprehensively analyze and discuss putative cellular mechanisms associated with E/I imbalances in aging, including age-dependent GABAergic deficits, impaired metabolic and insulin pathways, oxidative stress, and how they may be modulated by REST. Lastly, we will examine how those processes coalesce to contribute to the pathogenesis of Alzheimer's disease (AD) and the combative role REST may play against AD neuropathology.

2. Methods

A comprehensive literature search using the following databases was performed: MEDLINE (Medical Literature Analysis and Retrieval System Online; National Library of Medicine, Bethesda, MD, USA), Embase (Excerpta Medica Database; Elsevier, Amsterdam, the Netherlands), and PsycINFO (American Psychological Association, Washington, DC). The search was conducted between August 2020 and September 2021 and focused on research that investigated the E/I balance, REST, or both, and specifically in relation to aging. Search terms included “aging”, “Alzheimer's Disease”, “aging brain”, “insulin/insulin-like growth factor (IGF) signaling (IIS)”, “lifespan”, “oxidative stress”, “hyperexcitation”, and “(neuronal) network dysfunction” cross-referenced with “REST”, “NRSF”, “E/I balance”, and “E/I imbalance.”. All articles used were limited to original publications published in the English language.

3. Results

3.1. Normal REST functionality

REST is essential for the repression of neuronal target genes in non-neural tissue and neural precursors (Chen et al., 1998). Disturbing REST activity in the developing embryo results in expression of those target genes in non-neural tissue and embryonic lethality (Chen et al., 1998). REST and CoREST can epigenetically induce long-term silencing of target (neural) genes in non-neural tissue (Ballas and Mandel, 2005; Dallman et al., 2004). The REST-repressor complex is loosely bound to RE1 sequences in ESCs suppressing expression of target genes without disabling them, which allows neurodifferentiation to occur (Ballas and Mandel, 2005). Unlike in NSCs or non-neural tissues, REST forms a part of an autoregulatory network, consisting of octamer-binding transcription factor 4, SOX2, and nanog, which controls the differentiation and pluripotency of ESCs (Johnson et al., 2008). A chromatin immunoprecipitation microarray assay revealed that REST regulates an ESC-specific set of genes related to the signaling and transcriptional regulation of pluripotency (Johnson et al., 2008). In NSCs, REST represses a subset of the genes that are also repressed in ESCs (Ballas and Mandel, 2005; Johnson et al., 2008). Interestingly, a comparison of mice and human ESC REST-binding profiles revealed many human-specific targets that were enriched for memory and learning functions (Rockowitz and Zheng, 2015).

During the transition from NSCs to postmitotic neurons, REST is downregulated, de-repressing genes critical for establishing axon guidance, synaptogenesis, and membrane excitability (Mucha et al., 2010; Ooi and Wood, 2007; Paquette et al., 2000). These include tubulin, neuron-glia cell adhesion molecules, and potassium voltage-gated channels 2/3 (Mucha et al., 2010; Paquette et al., 2000). After embryonic development and during terminal cortical differentiation, REST is post-translationally degraded and the REST gene is transcriptionally inactivated greatly decreasing REST levels (Ballas et al., 2005; Ballas and Mandel, 2005). REST levels are partly regulated by beta-catenin, huntingtin interacting protein 1, and SP1 transcription factors which also see decreased activity and thereby diminish REST expression and transcription (Nishihara et al., 2003; Willert et al., 2002). Concomitantly, REST is targeted for proteolytic degradation by a REST-specific ubiquitinating enzyme, skp1-cullin1-f-box transducin repeat-containing protein, which undergoes rapid overexpression (Westbrook et al., 2008). This activity greatly increases REST turnover during this critical period. Overexpression of REST during later stages of development can cause irregularities in axon pathfinding, radial migration, and greatly delay neurodifferentiation (Mandel et al., 2011; Paquette et al., 2000), suggesting that REST downregulation serves as a critical timer for terminal neurodifferentiation.

Although global REST levels decline after early neurodevelopment, REST expression is essential for non-neuronal cells such as glia and contributes to a diversity of functions including gliogenesis (Abrajano et al., 2009a; Ballas et al., 2005). REST expression is also elevated in NSCs and hippocampal granule and pyramidal neurons, playing a master role in adult neurogenesis (Palm et al., 1998; Sun et al., 2005) as a transcriptional repressor and activator, mediating genetic activity through stage-specific neuronal gene expression (Gao et al., 2011; Kuwabara et al., 2004). REST is critical for maintaining NSCs in a quiescent state in mice, and if ablated from the hippocampus, a net decrease in neurogenesis will be observed over time, resulting in fewer hippocampal granule neurons (Gao et al., 2011). Thus, REST is responsible for maintaining the pool of NSCs available for differentiation in the mature nervous system. Postmitotic neurons also retain the ability to increase REST expression in response to certain noxious stimuli such as hyperexcitability or oxidative stress (see Sections 3.2 and 3.4.2, respectively) (Hwang and Zukin, 2018; Jessberger et al., 2007). Postmitotic neurons can also elevate REST expression for physiological functions such as synaptic homeostasis (see Section 3.2) (Rodenas-Ruano et al., 2012). REST is known to ensure neuronal subtype specificity during development (Tang, 2009), but Abrajano et al. found REST and CoREST also maintain the subtype throughout a neuron's lifespan by repressing genes specific to different subtypes (i.e. Smad2, Dlx2, Ctnnd2, etc.) (Abrajano et al., 2009b). REST and CoREST likely perform maintenance functions which maintain the postmitotic subtype (Abrajano et al., 2009b; Qureshi et al., 2010). Those findings demonstrate that despite the decline in neuronal REST after development, REST continues

to play an important and active role in the mature nervous system.

3.2. What are E/I imbalances?

Disturbances to the E/I balance are broadly defined as changes in E/I sufficient to alter the overall level of cortical activity at which neuronal homeostasis is achieved (Sohal and Rubenstein, 2019). This can result in impaired information processing and aberrant network behaviour (Sohal and Rubenstein, 2019). Excitatory imbalances are more common and often arise due to impaired GABAergic signaling, especially diminished $GABA_A$ receptor (GABAAR) activity (Heise et al., 2013; McQuail et al., 2015; Sohal and Rubenstein, 2019). However, hypo-/mal-function of *N*-methyl-D-aspartate receptors (NMDARs), in certain regions such as the PFC can also significantly affect the E/I balance (Gao and Penzes, 2015; Moghaddam and Javitt, 2012). These effects are exacerbated when the NMDARs on cortical interneurons are impaired (Gonzalez-Burgos and Lewis, 2008). Inhibitory signaling is key for the spatiotemporal coordination of global network activity (neural coding and processing (Buzsáki et al., 2007; Isaacson and Scanziani, 2011; Wood et al., 2017)) and hence, the maintenance of the physiological state in the CNS. Inhibitory dysfunction may enable behavioural and cognitive deficits to manifest, such as anxiety, aggression, agitation, and cognitive decline (Lanctôt et al., 2004; Zhu et al., 2019), and have been linked to the pathogenesis of neuropsychiatric disorders like major depressive disorder (MDD), autism spectrum disorder, and schizophrenia, as well as neurodegenerative diseases (Palop et al., 2006; Sohal and Rubenstein, 2019; Uhlhaas and Singer, 2012). Yizhar et al. used optogenetics to manipulate the E/I balance in the mouse medial PFC. The authors found that non-specific excitation of pyramidal neurons in the mPFC resulted in cognitive (impaired information processing) and social (avoidance) aberrance. However, excitation of inhibitory interneurons rescued those deficits (Yizhar et al., 2011). Conversely, increasing inhibitory function improved social behaviour which was also rescued by increasing excitation (Yizhar et al., 2011). There are two homeostatic pathways employed to combat disturbances: synaptic homeostasis (also called synaptic scaling/remodeling) and intrinsic homeostasis (Chowdhury and Hell, 2018; Sohal and Rubenstein, 2019). Synaptic homeostasis involves regulated, concerted molecular and functional changes to all components of the synapse while intrinsic homeostasis involves modulation of neural excitability and is not as well characterized (Chowdhury and Hell, 2018; D'Angelo, 2010; Pozzi et al., 2013). The pathways function to restore the E/I balance along with physiological network activity.

Electroencephalogram (EEG) recordings of aged mice revealed REST conditional-knockout (cKO) mice are more prone to epileptiform discharges, indicating significant E/I imbalances, which can precede AD – see Section 3.6 (Zullo et al., 2019). REST is a vital actor in intrinsic homeostatic mechanisms that counter hyperexcitable aberrance in network cultures (Mou and Zhao, 2016; Pozzi et al., 2013). Inducing chronic hyperactivity in primary neuronal cultures resulted in a globally reduced excitable state with a key mechanic being a dramatic (~75%) REST-mediated reduction in Nav1.2 channel density (which is a major REST target and quite responsible for membrane excitability, Chong et al., 1995) (Pozzi et al., 2013). Pozzi et al. also observed reductions in action potential (AP) firing rate, amplitude, and calcium transient spike amplitude; all levels were restored by shRNA-based prohibition of REST expression (Pozzi et al., 2013). REST function was noted to be minimal at baseline conditions (Pozzi et al., 2013), suggesting that REST primarily acts as a compensatory mechanism to combat E/I imbalances. Researchers created identical cultures and treatments as Pozzi et al. and found hyperexcitation induced REST-dependent synaptic homeostatic control of vesicular glutamate transporter-1 density (Pecoraro-Bisogni et al., 2018). REST also downregulated synaptosome associated protein-25, synapsin-1, and synaptotagmin-2, which are essential for presynaptic vesicular release (Pecoraro-Bisogni et al., 2018; Ramakrishnan et al., 2012). This finding demonstrates REST's ability to also influence synaptic homeostasis. The authors noted that this was the first time a protein was observed to influence both homeostatic pathways to restore the E/I balance and implicates REST as a mutual transcriptional hub (Pecoraro-Bisogni et al., 2018). Those data suggest that REST serves an essential role in maintaining the E/I balance and neuronal homeostasis.

3.3. REST and adulthood-associated/related pathology

REST expression is strongly influenced by aging. Western blot analysis on post-mortem human hippocampal tissue revealed increased REST levels starting from age 40 (McGann et al., 2021). Schiffer et al. (2014) observed elevated cytoplasmic REST levels in various brain regions including the hippocampus in ages 44–60, without nuclear staining. Staining in similarly aged dopaminergic neurons of the substantia nigra revealed no nuclear presence and minimal cytoplasmic accumulation (Kawamura et al., 2019). However, increased REST was observed in the nucleus and cytosol of older (72–81 years) substantia nigra samples. This suggests the nature of REST upregulation is region-dependent and it is nuclear-entry that is most influenced by aging. This relationship potentially serves to combat the noxious stimuli alluded to in 3.1 which naturally increase in severity with age. REST does this by regulating a gene network mediating stress resistance, apoptosis, and hyperexcitability. However, in certain aging-associated diseases such as various neurodegenerative diseases, REST expression is greatly impaired, dysregulating its network and causing significant widespread effects. Hence, it may be instructive to examine REST in relation to predisposing conditions as explored in Fig. 1. Poor physical health increases one's risk for developing neurodegenerative diseases and cognitive decline (Falck et al., 2017; Jedrziewski et al., 2007; Lee et al., 2012). Dallagnol et al. studied two groups of physically active and sedentary mice and found that increased REST levels are upregulated with age, as mentioned above, but REST levels were also with upregulated in the hippocampus with physical activity in the active mice compared to the sedentary group (Dallagnol et al., 2017). Physiological, chronic stress involves E/I imbalances and disposition towards mental disorders and AD (Bisht et al., 2018; Dong and Csernansky, 2019; Justice, 2018; Wang et al., 2019). Several studies show that REST is neuroprotective against social stress, downregulates corticotrophin-related factors, and can confer a lasting resilience to chronic stress (Korosi et al., 2010; Singh-Taylor et al., 2018; Soga et al., 2021). MDD is another condition involving aberrant network activity and AD predisposition (Otsuki et al., 2010). Performing quantitative reverse transcription polymerase chain reaction on a group of patients with MDD, remissive MDD, and healthy controls revealed that REST mRNA is significantly decreased in patients with MDD compared to the other two groups (Otsuki et al., 2010). Similarly, a study examined REST levels in patients aged 81 and older with elevated neuropsychiatric risk factors for AD (depression and anxiety) before and after performing mindfulness-based stress reduction techniques (MBSR) (Ashton et al., 2017). After performing MBSR, REST levels increased considerably compared to the control group; simultaneously, their depression and anxiety scores decreased (Ashton et al., 2017). Thus, poor adulthood physiological conditions may interfere with the senescent stimuli that induce REST upregulation and increase the risk of aging-associated pathology.

3.4. Putative mechanisms associated with E/I, REST, and aging

3.4.1. Glucose and metabolic dysfunction

Glucose and lipid metabolism change in the brain with aging, reducing aerobic glycolysis (Goyal et al., 2017; Peters, 2006). These changes contribute to cognitive decline and ictogenic mechanisms with age (Schauwecker, 2012). Glucose metabolism is critical for neurotransmitter synthesis and homeostasis, especially in glutamatergic and GABAergic systems (d'Almeida et al., 2020), and therefore, is directly connected to the E/I balance. Insulin resistance is a lack of responsiveness to insulin and is also related to poor cognitive function and is a risk

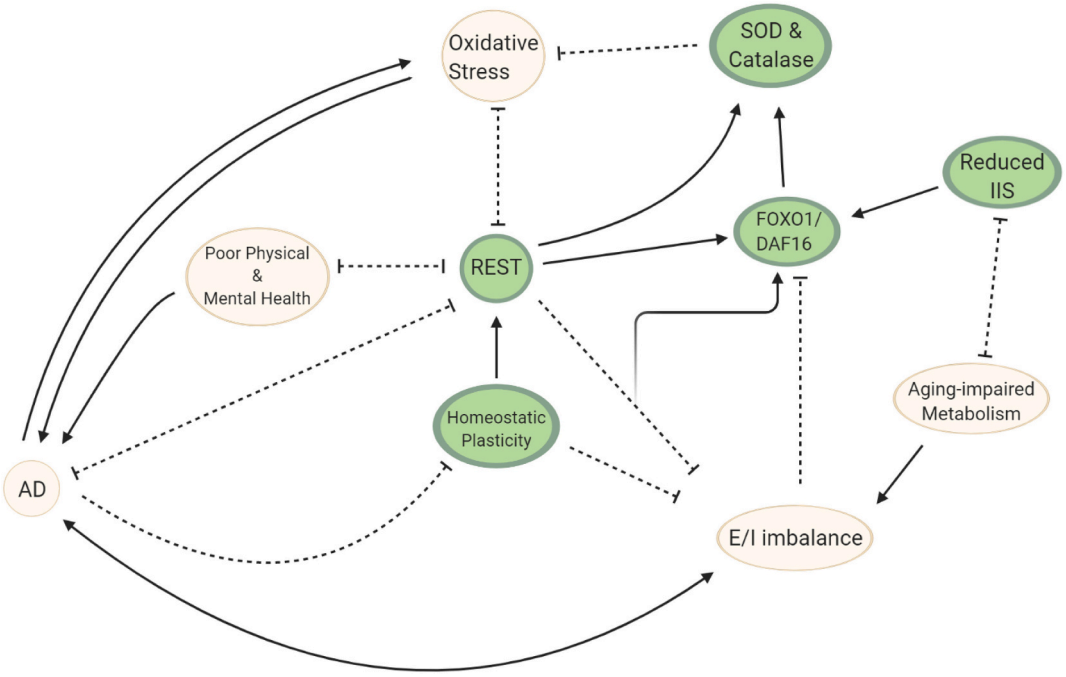

Fig. 1. Putative relationship between E/I imbalance and REST in AD
AD – Alzheimer's Disease; DR – Dietary Restriction; E/I – Excitatory/Inhibitory; FOXO1 – Forkhead box transcription factor-1; IIS – insulin/insulin-like growth factor signaling; REST – Repressor element-1 silencing transcription factor; SOD – superoxide dismutase. Elements encircled in green improve/maintain neural health with aging while elements in pale worsen aging-related health.

factor for AD (Neth and Craft, 2017; Thambisetty et al., 2013). Aging-associated insulin resistance depletes the neuronal glucose supply causing glucose hypometabolism as well as amyloid-β (Aβ) aggregation (Meusel et al., 2014; Willette et al., 2015). Low neural insulin levels can exacerbate Aβ and tau pathology – hallmarks of AD (Meusel et al., 2014). Although diabetes-mediated insulin resistance is milder than in AD, the underlying mechanisms are similar and AD has been suggested to be a form of brain selective diabetes (de la Monte and Wands, 2008; Steen et al., 2005). Studies found that rodents fed high fat/sugar diets exhibited elevated markers of oxidative stress in the hippocampus and their cognitive performance was significantly poorer compared to mice fed low/moderate fat/sugar diets (Beilharz et al., 2014). Furthermore, older obese and diabetic rodents displayed impaired hippocampal synaptic plasticity and neurogenesis (Farr et al., 2008; Greenwood and Winocur, 1990; Stranahan et al., 2008). Similarly, humans who are obese in midlife are more prone to cognitive decline and neurodegeneration later in life and people with cardiometabolic risk factors or diabetes display cognitive and structural deficits similar to the neurodegeneration and aberrant network behaviour observed in AD (Kullmann et al., 2015; Mazon et al., 2017). Patients with diabetic neuropathy can display significant E/I imbalances in several brain regions with elevated glutamate and diminished GABA levels (Petrou et al., 2012). It is possible that diminished GABA signaling causes hyperexcitability and contributes to the pathogenesis of diabetic neuropathy (Wang et al., 2011). With age and pathology, certain neuronal populations (dependent on the pathology), become more active, elevating the E/I balance and requiring a greater energy supply (Muddapu et al., 2020). However, the diminished aging-associated metabolic capabilities instead induce greater calcium influxes and E/I imbalances (Amigo et al., 2017; Muddapu et al., 2020). Furthermore, mitochondria become increasingly defective with age at providing neurons with the means to address their bioenergetic demands (Mattson and Arumugam, 2018). Under such energy deficient conditions, overexcitation leads to accumulation of calcium and reactive oxygen species (ROS) within the cell, glutamate in the synaptic cleft, and increased amounts of excitotoxicity (Muddapu et al., 2020). The loss of neurons under excitotoxic conditions renders entire networks more vulnerable to E/I imbalances (Staley, 2015). Therefore, the aging-associated trajectory of neural metabolism is intractably connected to the aging-associated trajectory of E/I imbalances.

Metabolically-mediated alterations of E/I ratios ameliorate several of the above-mentioned deficits and improve cognitive health. The ketogenic diet (KD) is a carbohydrate-minimum diet and works by replacing glucose throughout the body as an energy source with B-hydroxybutyric acid (Sen et al., 2016). The KD has been shown to reduce cortical network excitability, confer resilience to anxiety (which relates to E/I imbalances, see Section 3.2 and (Wang et al., 2016)), and improve cognitive performance across the lifespan but especially in older age (Cantello et al., 2007; Hernandez et al., 2018). The KD works in part by lowering reliance on glucose which mitigates glutamatergic excitotoxicity and reduces IIS activity (Newman et al., 2017) and increasing inhibitory drive (Smith et al., 2016). Studies have found increased GABA levels following KD administration in rats (Calderón et al., 2017; Hartman et al., 2007; Smith et al., 2016). This demonstrates how metabolic alterations can directly influence the E/I balance and suggests that glucose-based diets and IIS activity can negatively skew the balance.

Elevated IIS activity downregulates forkhead box protein O/ abnormal Dauer formation-16 (FOXO/DAF16) levels (DAF16 being the *Caenorhabditis Elegans* orthologue to the mammalian FOXOs) (El-Ami et al., 2014; Zullo et al., 2019). FOXO/DAF16 are both also upregulated by REST (and the orthologous SPR3/4 in *C. elegans*) (Zullo et al., 2019). FOXOs regulate catalase and superoxide dismutase (SOD) (important antioxidants involved in neuronal homeostasis - see Section 3.4.2) expression in addition to mediating growth, metabolism, and aging (Doonan et al., 2008; Tothova et al., 2007). FOXO activity also regulates genes essential for gluconeogenesis and glycolysis, representing a metabolic switch akin to low glucose and fasting conditions (Gross et al., 2009). Dietary restriction and reduced IIS are among the most robust methods of lengthening lifespan in yeast, worms, flies, fish, mice, and primates (Anderson et al., 2009; Bareja et al., 2019; Fontana et al., 2010; Pan and Finkel, 2017; Partridge et al., 2011; Santos et al., 2016) displaying remarkable evolutionary conservation. DAF2 is the sole IIS

receptor in *C. elegans* and is orthologous to the mammalian IGF-1R; DAF2 analogously downregulates DAF16 as IGF-1R does to FOXO1 (Holzenberger et al., 2003; Kimura et al., 1997). Heterozygous deletions of IGF-1R in mice confer increased oxidative stress resistance and cognitive competence compared to littermate controls (Cohen et al., 2009). IGF-1R mutations and lower IIS activity are more abundant in certain centenarian human populations. Mutations which hyperactivate FOXO have been linked with extreme longevity in Japanese-Hawaiian and German centenarians (Cohen, 2011). Wolkow et al. manipulated DAF2 pathway function in cells most related to metabolic aging: neuronal, intestinal, and muscular (Wolkow et al., 2000). Lifespan extensions in DAF2 mutants were rescued when DAF2 expression was restored in neurons but not the other cell types (Wolkow et al., 2000). The finding is significant as the intestine and muscles are major sites of metabolic activity. This points to an important connection between the nervous system, metabolism, and aging.

Given that diabetes is a risk factor for AD and that diabetic patients are capable of developing AD cognitive phenotypes, it is perhaps not surprising that REST dysregulation in alpha and beta cells can provoke diabetes in mice and potentially humans (Martin and Grapin-Botton, 2017). The relationship between REST levels in those cells and neurons is unclear, as is the trajectory of REST within non-neuronal cells over aging. Moreover, analysis of gene ontology enrichment has revealed that metabolism-related genes are enriched for REST-binding sites (McGann et al., 2021; Otto et al., 2007). Given that an adverse midlife metabolic profile allows for incipient dementia (MacIntosh et al., 2020), and that REST can also be dysregulated during this time (see Section 3.3), investigating this link may shed further light on the connection between diabetes, aging, and AD. When Zullo et al. increased Suppressor of Presenilin defect-4 (SPR4 – REST orthologue) levels moderately in *C. elegans*, there was a significant increase in lifespan and robust decrease in neural excitation (Zullo et al., 2019). Through calcium fluorescent imaging, they also found that the SPR4-mediated suppression of excitation activated DAF16 (Zullo et al., 2019). Treatment of mouse cortical cultures with NMDAR and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonists significantly increased global FOXO1 levels (Zullo et al., 2019). That the regulation of excitatory activity negates IIS function points to a conserved connection between the E/I balance and metabolic activity. Gene transcriptome profiling of DAF2 mutants revealed that the most downregulated genes related to excitation, neurotransmission, and synaptic function (like the older adults described in 3.5) (Zullo et al., 2019). Suggesting that REST's repression of excitation and the connection of IIS pathways to E/I balance are conserved regulatory features. REST demonstrably regulates FOXO1 expression in human-derived cells (Lu et al., 2014). In the aging human brain, REST mRNA expression correlates positively with FOXO1 mRNA expression, co-localising in PFC neurons (Zullo et al., 2019). Nuclear levels of both factors correlated strongly in all age groups (Zullo et al., 2019). In REST-cKO mice, age-dependent FOXO1 induction was abolished (Lu et al., 2014; Zullo et al., 2019), further establishing the conserved nature of REST's involvement with metabolic activity. As seen in Fig. 1, FOXO1 may also be a mutual factor between neural activity and metabolism with REST serving as a potential integrator.

3.4.2. Oxidative stress

Oxidative stress is most damaging when there is an imbalance between ROS and antioxidant defences (Mattson and Arumugam, 2018). During aging, neurons accumulate dysfunctional, clustered proteins because of this imbalance (Gladyshev, 2014; Mattson and Arumugam, 2018). Aged dog brains reveal accumulated lipid peroxidation product 4-hydroxynonenal (HNE), associated with amyloid deposits and neurofibrillary tangles – hallmarks of AD (Papaioannou et al., 2001). HNE can severely impair neurons by diminishing their metabolic and survival capabilities (Mattson, 2009; Perluigi et al., 2014). Considerable evidence suggests that impaired antioxidant defences and ROS damage greatly accelerate brain aging (Mattson and Arumugam, 2018). Genetic oxidative damage is more profound in brain regions affected by AD (where nuclear REST is absent, see Section 3.6.1) compared to healthy controls (Camandola and Mattson, 2011; Mattson, 2004). The damage especially affects genes related to neuronal excitability and likely contributes to the excitatory-induced network dysfunction and impaired calcium homeostasis observed in AD (see Section 3.6) (Camandola and Mattson, 2011; Lu et al., 2004). Indeed, major ROS are generated during elevated intracellular calcium concentrations (Halliwell, 2001). Oxidative stress affects the E/I balance distorting the signal-to-noise ratio in fly olfactory neurons such that they are among the earliest sensory systems to succumb to age-related neurodegeneration (Hussain et al., 2018). Inhibition of oxidative stress in excitatory pathways fully rescues this aging-associated degeneration (Hussain et al., 2018).

HNE impairs proteins involved in ion transport, neurotransmission, disrupts calcium homeostasis, and inflicts hyperexcitability and metabolic failure (Mark et al., 1997; Mattson, 2009; Mattson et al., 1992). Additionally, calcium-induced after-hyperpolarisations are impaired in aged-hippocampal pyramidal neurons and result in significantly higher calcium influxes (Camandola and Mattson, 2011; Gant et al., 2015; Gant et al., 2006). Such neurons are more vulnerable to calcium-mediated excitotoxic degeneration and death (with ROS being an important actor) (Gant et al., 2006). This creates a positive feedback loop wherein oxidative stress can impair the E/I balance by distortion of regular neuronal signaling and calcium homeostasis which results in increased production of oxygenated molecules and further network destabilization. As mentioned in Section 3.3.1, unstable networks are prone to global E/I imbalances (Staley, 2015). SOD and catalase are vital for breaking down oxygenated molecules into innocuous counterparts (Fukai and Ushio-Fukai, 2011; Tovmasyan et al., 2015). Genetic reduction of SOD induces aging phenotypes in mice and drosophila: neurodegeneration, aberrant network activity, impaired DNA repair, among other deleterious effects (Duttaroy et al., 2003; Lebovitz et al., 1996; Paul et al., 2007). REST promotes expression of SOD and catalase (Lu et al., 2014). Reversible ROS DNA damage occurs naturally with aging but is exacerbated following excitatory synaptic activity (Yang et al., 2010). Alleviating E/I imbalances by chelating intracellular calcium or increasing SOD expression prevents this DNA damage; unabated, unrepaired DNA damage can cause hyperexcitation (Yang et al., 2010). Administering calcium chelators to worms substantially reduces excitatory activity and extends lifespan (Zullo et al., 2019). REST upregulates SOD but is absent in regions of extensive AD-induced oxidative damage, particularly the hippocampus. Oxidative DNA damage may occur in response to excitatory transmissions involved in learning and memory (Huang et al., 2015). SOD is generated during normal, spontaneous glutamatergic synaptic activity and potentially nullifies ROS damage caused by physiological levels of glutamate receptor activation, playing a relevant role in synaptic plasticity and nullifying the negative effects of excitatory activity (Hongpaisan et al., 2004; Thiels et al., 2000). Fig. 1 demonstrates how REST, directly and indirectly, inhibits oxidative stress.

It is believed that aging-related oxidative stress induces REST expression (Baldelli and Meldolesi, 2015; Hwang and Zukin, 2018; Lu et al., 2014). Since REST is also crucially relevant to neurogenesis and a stable E/I balance, it may be worthwhile to investigate REST functionality in the hippocampus in relation to SOD and learning and memory as the hippocampus is particularly vulnerable to oxidative stress and AD. Lu et al. created cortical cultures derived from REST-cKO mice and littermate controls and treated them with H_2O_2 to induce oxidative stress (Lu et al., 2014). They also placed mutant and wild-type (WT) worms on a medium with a superoxide generator to measure SPR4 expression (Lu et al., 2014). The REST-deficient subjects fared significantly worse in terms of survival and neurodegeneration than the controls but could be rescued by lentiviral-transduction of REST into the nucleus (Lu et al., 2014). The authors also observed REST-dependent FOXO1 expression; FOXO1 is known to be relevant for stress resistance and can also upregulate SOD and catalase (Lu et al., 2014).

Whether REST's upregulation of those antioxidant enzymes is independent of FOXO1 activity remains unknown. Prion diseases preferentially affect older adults and induce oxidative stress and neuronal apoptosis (Song et al., 2017). REST-KO results in significantly greater ROS release and cell death in prion disease mouse cortical cultures while overexpression can increase the survival rate from 65% to 78% (Song et al., 2017). Excessive exposure to manganese can induce a PD-phenotype in neurons; a key mechanism involves a significant oxidative stress-mediated degradation of the dopamine synthesis pathway and reduction of antioxidants catalase and Nrf2 (Pajarillo et al., 2020). REST overexpression attenuated oxidative stress and consistently improved neuronal survival in *in vitro* cultures and mice models (Pajarillo et al., 2020). However, severe oxidative stress in HCT116 cells promoted the proteasomal degradation of REST via polyubiquitination (Kwon et al., 2013), suggesting that oxidative stress can reduce REST levels. Oxidative stress can severely damage neurons and networks, destabilize the E/I balance, and create detrimental, positive feedback loops. By mitigating the extent of oxidative damage and conferring resilience, REST helps safeguard neuronal homeostasis and cognitive viability.

3.5. E/I-associated aberrant network activity in aging

Even in the absence of disease or obvious pathology, aging is associated with cognitive decline. E/I imbalances decrease the signal-to-noise ratio and induce impaired information processing and aberrant network behaviour (Sohal and Rubenstein, 2019). With age, the brain naturally atrophies, reducing cortical volume and compromising white matter integrity (Andrews-Hanna et al., 2007; Driscoll et al., 2009; Fjell et al., 2009; Salat et al., 2005). How much those changes affect the E/I balance remains unclear. Rodents are known to experience age-related declines in GABA concentration and synthesis (Caspary et al., 2013; Gao et al., 2013). Porges et al. used Mescher-Garwood point resolved spectroscopy and reported that lower concentrations of GABA in humans was associated with increased age and negatively correlated with cognitive performance (Porges et al., 2017). The authors further found that this decline was independent of atrophy and reflected a reduction in tissue GABA concentration (Porges et al., 2017). The medial geniculate body (MGB) of the thalamus, an important relay station for auditory information, experiences significant age-dependent deficits in inhibitory tone (Richardson et al., 2013). MGB GABAAR density and function reduce with age, resulting in increased excitability (Richardson et al., 2013). This E/I imbalance results in aberrant information processing and impaired hearing in older adults; reducing this excitability by increasing inhibitory tone enhances the signal-to-noise ratio improving coding fidelity and resultantly, hearing (Duguid et al., 2012; Richardson et al., 2011). It is possible that the lack of inhibition extends to the entire sensory thalamus and affects sensory processing during waking and sleeping states, as EEG studies have shown a broadband increase in neuronal activity in both healthy older adults and those with age-related neurodegenerative conditions (Crowley, 2011; Kahya et al., 2019). The primary visual cortex of healthy, aged non-human primates, mice, and cats display reduced GABAergic inhibition and directly relate to impaired vision (Ding et al., 2017; Hua et al., 2008; Leventhal et al., 2003). A magnetic resonance spectroscopy (MRS) study found significantly reduced GABA levels in older human visual cortices, compared to younger ones, as well and correlated the levels with visual task performance (Simmonite et al., 2019). Increasing GABA and applying GABA agonists partly improve some of those visual deficits in older primates (Leventhal et al., 2003). MRS studies have shown reduced GABA levels in the hippocampus and frontal and parietal cortices in older adults, suggesting aging impairs GABAergic inhibition (Gao et al., 2013; Huang et al., 2017). Zullo et al. performed gene transcriptome profiling on healthy older adults and divided the results into older (>85 years old) and younger (70–85) groups (Zullo et al., 2019). The most down-regulated genes in both groups were related to excitatory signaling and were enriched for the RE1 motif; their mRNA expression inversely correlated with REST mRNA expression (Zullo et al., 2019). Levels of the REST gene were significantly greater in the older group (Zullo et al., 2019). It is therefore plausible that the brain may attempt to compensate for the diminished inhibitory function by increasing REST to enforce the E/I balance with age.

3.6. E/I imbalances and associated mechanisms may contribute to AD pathogenesis

AD affects over 30% of people over 85 years old and is the most common cause of dementia and yet, only symptomatic treatments exist (Kawas and Corrada, 2006). The lack of disease-modifying treatments may be related to multiple pathological mechanisms that underlie dementia and continue to be investigated by researchers. Canonical AD neuropathology consists of accumulated Aβ plaques and tau neurofibrillary tangles, however, approximately 25% of diagnoses lack significant presence of those markers, and instead display substantial hippocampal and pyramidal neuronal loss (Mattson, 2015; Mattson and Arumugam, 2018). It is increasingly being questioned whether those hallmarks are sufficient to induce dementia; perturbed network activity and E/I imbalances are observed in early AD, preceding overt clinical symptoms (Vossel et al., 2017; Wang et al., 2015). Evidence suggests such imbalances may be causative factors. It is possible that early E/I imbalances trigger a cascade of reactions culminating in neurodegeneration and dementia (Ambrad Giovannetti and Fuhrmann, 2019). E/I imbalances are proposed to underlie epileptiform activity in AD mice (Palop et al., 2007). Epileptiform activity stimulates neuronal Aβ synthesis and release in hippocampal slices (Cirrito et al., 2008; Cirrito et al., 2005). A positive feedback loop can develop between this synthesis and hyperexcitability (Jang and Chung, 2016). Inhibiting hyperexcitation reduces memory loss in early AD model mice that exhibit epileptiform activity and seizures (Sanchez et al., 2012). It is important to note, however, that the relationship between E/I imbalances, Aβ and tau, and AD pathogenesis is not clear: Aβ plaques can accumulate even in healthy humans over long stretches of time without consequence. Moreover, AD pathology works in part by further disrupting E/I balances in various regions in the brain, as explored below. It is possible that early E/I imbalances relate to more general neuronal detriments, like dysregulated REST, which set the stage for AD-associated pathology. Functional magnetic resonance imaging revealed that several cortical regions display increased activation in AD patients compared to controls (Dickerson and Sperling, 2008). Multiple studies noted that important cortical structures related to memory and cognition, such as the entorhinal cortex, medial temporal lobe, and hippocampus, display greater levels of activation in mild-cognitive impairment (MCI) compared to controls (Dickerson et al., 2005; Dickerson and Sperling, 2008; Putcha et al., 2011). Further, the extent of clinical impairment and cognitive decline correlated with the intensity of activity or excitability within some of these structures (Dickerson and Sperling, 2008). Levetiracetam is an anticonvulsant that likely works by tempering excitatory neurotransmitter release (Vogl et al., 2012) and when administered to patients with amnestic MCI, there was a significant improvement in cognitive performance as well as normalization of fMRI-detected activity in the hippocampus (Bakker et al., 2015). Moreover, individuals with the greatest levels of hyperactivation also had the greatest subsequent deterioration in cognitive performance (Bakker et al., 2012). Aberrant excitability may stimulate the cognitive impairment preceding overt AD symptoms.

Most AD mice models are based on genetic mutations which cause familial AD (FAD), however, FAD only accounts for 1–5% of human cases with the rest classified as sporadic AD (Ambrad Giovannetti and Fuhrmann, 2019). The apolipoprotein E4 (ApoE4) gene, as opposed to the neutral ApoE3 variant, is the most reliable predictor of sporadic AD (Li et al., 2009; Wang et al., 2014). ApoE4 is less efficient at clearing soluble Aβ than ApoE3 (Castellano et al., 2011). It is thought that before pathological accumulation, soluble Aβ further disrupts E/I imbalances,

alters network activity, and causes cognitive decline in AD (Busche and Konnerth, 2016; Palop and Mucke, 2016; Ren et al., 2018). Post-mortem studies link Aβ accumulation and excitotoxicity to significant losses in inhibitory interneurons in the entorhinal cortex (Ambrad Giovannetti and Fuhrmann, 2019). Interneurons in hippocampal slices of AD mice could not reliably generate APs, indicating hyperexcitability (Hazra et al., 2013). Aβ-induced hyperexcitability is observed in human cortical preparations as well (Amatniek et al., 2006; Palop and Mucke, 2010). ApoE4 knock-in expression reduced the number of GABAergic interneurons and synapses in the hippocampus (Li et al., 2009). It is possible that an impaired GABAergic system and elevated E/I balance mediate ApoE4-related AD. As described in Section 3.2.1, excitation of the mPFC yielded social and cognitive deficits in mice: the anterior cingulate cortex (ACC) is within the mPFC and is involved with memory, attention, and emotion – each of which are affected by age-related cognitive decline (Rolls, 2019). The ACC is one of the earliest affected areas in AD and an "epicentre" (Ren et al., 2018; Zhou et al., 2012). Accumulated Aβ promoted excessive dopaminergic firing which can contribute to epileptiform activity by increasing the E/I ratio (Krashia et al., 2019; Palop and Mucke, 2016). Ren et al. found, using ACC slices, Aβ treatment increased AP firing frequency and spontaneous EPSCs in excitatory neurons while decreasing mIPSC frequency and amplitude via diminished presynaptic GABA release (Ren et al., 2018). A D1 receptor antagonist reversed this hyperexcitability and points to Aβ-induced dopaminergic release onto interneurons as causative of the severe E/I imbalance in the ACC (Ren et al., 2018). This demonstrates how E/I imbalances and impaired inhibition are key mechanisms of AD pathology.

Insulin resistance is a risk factor for AD, resulting in impaired glucose metabolism in the temporal, parietal, and frontal lobes, and the motor cortex (Peters, 2006). Reduced metabolism in the temporal and parietal lobes is distinctly worse in AD patients than healthy age-matched controls (Kato et al., 2016). GLUT3, a glucose transporter, is quite vulnerable to damage from oxidative stress and HNE (Mattson, 2009). Positron emission tomography (PET) imaging studies show that reduced glucose utilization occurs in early AD pathogenesis: post-mortem follow-ups reveal a global decrease in glucose transporters (Ceravolo et al., 2008; Friedland et al., 1989; Kato et al., 2016). Brain regions displaying diminished glucose metabolism on PET scans in AD and MCI overlap with regions significantly vulnerable to conditions like diabetes and strongly relate to cognitive decline. Conditions like diabetes can indirectly promote Aβ accumulation, providing another avenue for E/I imbalances to develop. Given the convergence of metabolically detrimental effects in specific brain-regions, it may be interesting to explore REST activity there as REST is impaired in AD whereas RESTs relationship with diabetes is unclear. Mice with only once copy of Igf1r are protected from behavioural and pathological impairments stemming from Aβ accumulation (Cohen, 2011). Additionally, there were smaller Aβ plaques and lower neuronal and synaptic loss in those mice (Cohen, 2011). AD model mice with insulin receptor substrate-2 (IRS2) mutations had smaller Aβ plaques than control AD mice: overall fractions were equivalent but the IRS2-mutant mice possessed fewer plaques suggesting the mutation relates to enhanced Aβ disaggregation and clearance (Cohen, 2011; Romeijn et al., 2019). Those mice also performed significantly better on cognitive tests (Cohen, 2011). Late-life DAF2-RNAi protected worms from Aβ proteotoxicity suggesting it can attenuate AD progression (O'Neill et al., 2012). Overall, reducing IIS activity in mice, worms, and flies can alter Aβ and tau protein homeostasis towards less toxic conformations and improve cognition (O'Neill et al., 2012). Analysis shows overall IGF-1R levels are significantly increased in AD brains, specifically, in activated astrocytes (indicative of neuro-inflammation), degenerating synapses, and neurites within and surrounding Aβ plaques (O'Neill et al., 2012). AD-affected neurons can cause excessive excitation of the IIS pathway, which often leads to increased tau pathogenesis and neurodegeneration in flies (Cowan et al., 2011; Prüßing et al., 2013).

As Aβ accumulates, ROS and HNE are generated (Cheignon et al., 2018). HNE-damaged proteins accumulate with aging and HNE increases production of Aβ42, a toxic variant of Aβ proteins distinct from those arising physiologically (Arimon et al., 2015). HNE impairs proteins involved neurotransmission, disrupts calcium homeostasis, and inflicts hyperexcitability (Mattson, 2009; Mattson et al., 1992). The disrupted calcium homeostasis worsens stress resistance resulting in further Aβ accumulation (Mattson, 2009). Neurons attempt to combat this by expelling Aβ in extracellular vesicles which can propagate Aβ pathology across networks, progressing the disease (Eitan et al., 2016; Zhang et al., 2018). Thus, ApoE4, HNE, oxidative stress, and Aβ pathology can render neurons more vulnerable to hyperexcitation and cell death.

3.6.1. REST and AD

REST levels are significantly lower in hippocampal and cortical nuclei in AD brain samples compared to age-matched controls (Zullo et al., 2019). REST is also depleted in frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), Parkinson's disease (PD), and Huntington's disease (HD) (Kawamura et al., 2019; Lu et al., 2014; Rigamonti et al., 2009; Zullo et al., 2019). One reason for this may be due to a disease-related disruption of the nuclear lamina which inhibits nuclear translocation of REST (Kawamura et al., 2019; Meyer et al., 2019). Lu et al. found REST represses genes relating to Aβ generation (presenilin-2, p35, p39), tau phosphorylation (MAPT), and proapoptotic genes (Lu et al., 2014). The authors treated cultures of E16 cortical neurons from REST-cKO and littermate control mice with H_2O_2 and oligomeric Aβ42 (Lu et al., 2014). The REST-cKO culture underwent neurodegeneration and apoptosis far more readily than the control cultures (Lu et al., 2014). Lu et al. also approximately replicated those results with worms and SPR4, suggesting REST's neuroprotective role is a conserved regulatory feature. Induced pluripotent stem cell (iPSC) based models of sporadic AD and ApoE4 neural progenitor cells possess notably lower nuclear REST levels and undergo accelerated neurodifferentiation (see 3.1) (Meyer et al., 2019). Moreover, ApoE4 knock in expression resulted in a direct reduction of REST levels (Meyer et al., 2019). REST dysfunction and greater intrinsic excitability persisted after differentiation and may contribute to AD-onset (Meyer et al., 2019). Confirming Lu et al.'s results, MAPT was significantly upregulated in the SAD cells compared to controls (Meyer et al., 2019). Lentiviral-transduction of REST prevented precocious differentiation and MAPT function (Meyer et al., 2019). This supports the idea that aberrant network activity, accelerated neurodifferentiation, and dysregulated REST precede the canonical tau and Aβ-related AD pathology. This is also consistent with the fact that REST levels are diminished in MCI which in turn is connected to hyperexcitation in the hippocampus. Indeed, declining REST levels have been correlated with reduced hippocampal volumes and increasing cognitive decline (Ashton et al., 2017) Ashton et al. measured REST in blood levels in 4 different groups: health aged controls, a stable MCI (sMCI) group, an MCI group that later converted to dementia (cMCI), and an AD group. The AD group's blood REST levels were significantly lower than the healthy group; the cMCI levels were closer to those of the AD group while the stable MCI group resembled that of the healthy controls (Ashton et al., 2017). REST correlated with hippocampal, entorhinal, whole brain, and ventricular volumes (correlating with hyperactive regions discussed earlier). Taken together, those results point to a fundamental connection between REST, E/I balance, and CNS health.

4. Discussion

Numerous aging-associated mechanisms disrupt the E/I balance, conferring vulnerability to neurodegenerative processes. Irrespective of pathology, brain atrophy occurs with aging, and has decreased GABAergic signaling and inhibitory tone, potentially compensating by upregulating REST which represses genes relating to excitatory signaling. Aging neuronal metabolic capabilities and physiological IIS

activity have broad but ill-defined effects on the nervous system that increase risks for cognitive impairment and dementia. Metabolically-oriented interventions ameliorate this, in part, by increasing inhibitory drive and GABA levels. SPR4-mediated suppression of excitation evidently runs counter to DAF2 function with reduced DAF2 activity supporting the E/I balance with age. This suppression activates DAF16 and together, they lengthen lifespan and delay aging-associated diseases in worms and potentially mice as well. Disrupted neuronal homeostasis and aberrant network behaviour worsen oxidative stress in the brain which can result in positive feedback loops between ROS and oxidative products and neuronal excitability. Oxidative stress occurs naturally but when the antioxidant defences are insufficient can become very damaging for network function, for instance if REST or FOXOs are impaired. Positive feedback loops between ROS and oxidative products and excitability can develop and greatly accelerate the aging process and increase the risk for AD. All these factors increase the likelihood of neurodegeneration and dementia which severely affect an already disrupted E/I balance and inhibit REST.

4.1. Questions to be answered

While the E/I balance is fundamentally tied to neural health and aging, this review has used a unidimensional definition of the concept wherein excitation/inhibition are treated as singular, diametric entities. It is difficult to quantitatively define the balance for several reasons: the balance is thought to be maintained over longer, indeterminate timescales with frequent transient imbalances; due to the variability and complexity of neural network configurations, the spatiotemporality of E/I ratios vary along different pathways (Litwin-Kumar and Doiron, 2012; Sohal and Rubenstein, 2019). Interneurons innervate excitatory and inhibitory neurons allowing for increases of inhibition along certain pathways to affect a net-increase of excitation (Sohal and Rubenstein, 2019; Tremblay et al., 2016). As such, multiple studies have noted a unidimensional approach can have counterproductive results (Antoine et al., 2019; Nelson and Valakh, 2015; Vogt et al., 2015). However, the concept of E/I balances remains fruitful and researchers would benefit from finer, quantitative definitions. Future studies should focus on quantifying the variability among E/I homeostases and how those relate to behaviour and cognition. Abnormal gamma waves, which inflict cognitive impairment, have been co-observed with E/I imbalances (Aron and Yankner, 2016; Sohal et al., 2009; Yizhar et al., 2011). Indeed, irregular gamma waves have been found to contribute to Aβ and tau accumulation in AD and FTD models (Aron and Yankner, 2016), similar to the effects hyperexcitability has on Aβ. Further, restoration of regular gamma waves reduced memory deficits in AD model mice as did restoring the E/I balance (Sanchez et al., 2012; Verret et al., 2012). Understanding the connection between E/I imbalances and gamma synchrony may provide a biomarker for better defining the mechanisms surrounding imbalanced disruptions and allow for more informed research.

REST counters hyperexcitability as an intrinsic feature of homeostatic plasticity and continues to suppress excitation when induced with age in a conserved fashion. REST is neuroprotective against oxidative stress and neurodegeneration and it is essential for maintaining neuronal viability and cognitive health with age. Individuals with significant AD pathology but high REST levels seemingly do not succumb to dementia. This raises the possibility of creating novel interventions targeted against dementia but also general aging. However, REST is sequestered in autophagosomes in AD, FTD, DLB, and PD with pathological misfolded proteins like Aβ, TDP-43, and α-synuclein (Kawamura et al., 2019; Lu et al., 2014; Rigamonti et al., 2009; Zullo et al., 2019). Severe oxidative stress can also target REST for proteasomal degradation (Kwon et al., 2013). Research should be directed towards understanding how REST can be overcome by those pathological processes before any therapeutic intervention can be developed. Adults with poor mental/physical health have diminished/dysregulated REST which may persist with age and weaken REST's neuroprotective abilities, potentially allowing for impairment. This is particularly pertinent as such conditions (poor health) relate to E/I imbalances and increased AD risk. Aberrant REST levels can cause impaired neurogenesis and excessive excitation setting the stage for aberrant network behaviour often observed before AD.

MCI typically precedes AD and Ashton et al. noted significantly lower REST levels in individuals with MCI who converted compared to stable MCI (Ashton et al., 2017). This points to the importance of understanding REST regulation prior to aging-onset. In contrast, some studies have noted increased REST levels to be damaging in certain conditions, notably ischaemia and epilepsy (Calderone et al., 2003; McClelland et al., 2014; Noh et al., 2012; Spencer et al., 2006); after the onset of either condition, dampening REST activity accelerated the healing process. REST's involvement in epilepsy is widely debated, however, as studies have also found REST to be antiepileptic (Carminati et al., 2019; Hu et al., 2011). It has been suggested that REST is neuroprotective under physiological conditions and does not induce harmful processes, rather strengthens them once pathology has set in (Pecoraro-Bisogni et al., 2018). Interestingly, a similar characterization has been suggested for homeostatic plasticity's function against hyperexcitation: it may be beneficial at local levels but disruptive on larger, pathological scales (Howard et al., 2014). Given REST's unique link between synaptic and intrinsic homeostases, investigation may help understand this maladaptivity which too is essential before any therapeutic interventions can be considered. Such an investigation may also shed light on the hippocampal and other regional hyperactivity that is observed in MCI before AD; recall that REST levels are elevated in the hippocampus. Is such hyperactivity a reflection of REST's maladaptation or is it the lack of REST influenced by pathology that permits the E/I imbalance?

The relationship between senescence and REST expression and its nuclear-entry is unclear. Cellular senescence is not a well-characterized process due to its extreme heterogeneity (Saez-Atienzar and Masliah, 2020). There is a dearth of bona-fide biomarkers and much of what is known derives from in vitro studies. With aging, the abundance of cellular senescence exceeds the immune system's capacity for eliminating senescent cells, and there is evidence this feeds back to accelerate aging (Saez-Atienzar and Masliah, 2020; Zhou et al., 2021). Baker et al. (2016) demonstrated that eliminating senescent cells in aged mice improved aging-associated cognitive decline and increased lifespan. The causality between senescence and AD is unclear: clearance of senescent cells reduces Aβ-deposition and neurofibrillary tangle formation, but deposition and formation themselves can induce neural senescence (Zhang et al., 2019; Bussian et al., 2018; Saez-Atienzar and Masliah, 2020). If senescent cells are not cleared by immune cells, they become chronically senescent and inflammatory (van Deursen, 2014). Sustained inflammation can cause a REST-mediated downregulation of excitatory signaling (Buffolo et al., 2021). However, the expression of inflammatory molecules was shown to be significantly higher in REST-deficient astrocytes compared to controls (Li et al., 2020). REST-deficient astrocytes and microglia significantly aggravate neurodegenerative pathology (Li et al., 2020). Microglia are prone to senescence and their senescent state may precede tau pathology (Streit et al., 2009). Thus, senescent/inflamed microglia (with potentially dysregulated REST) may trigger early events which increase the risk of AD (Saez-Atienzar and Masliah, 2020). Conversely, AD-pathology, spurned by diminished REST activity, can induce microglial senescence and activation which would further spread neuroinflammation and disease progression. The role of REST in glia is not well known. Therefore, investigating REST's relationship with glial cells may shed light on the causal relationship between senescence and AD as well as REST's overall ontogenetic trajectory.

The accumulation of damaged mitochondria is a hallmark of aging and several neurodegenerative conditions (Mattson and Arumugam, 2018). This occurs in large part due to impaired mitophagy, resulting in diminished degradation and recycling of those mitochondria.

Mitophagy is fundamental for neuronal health and survival (Martinez-Vicente, 2017). Mitochondrial dysfunction induces ATP deprivation, oxidative stress, and cellular senescence (Guo et al., 2013; Chapman et al., 2019). Animal models and post-mortem hippocampal tissue from AD patients demonstrate severely impaired mitophagy (Fang et al., 2019; Palikaras et al., 2015). Neurons with mitochondrial dysfunction and bioenergetic deficits have exacerbated AB/tau pathology which in turn can promote further mitochondrial defects (Kerr et al., 2017; Pérez et al., 2018). Stimulating mitophagy in AD model mice tended their transcriptomic profile towards those of WT mice which involves upregulation of inhibitory signaling and neuroprotective pathways (Fang et al., 2019). A hallmark of PD is the α-synuclein-mediated destruction of dopaminergic neurons in the substantia nigra pars compacta (SNc). α-synuclein accumulation in those neurons induced significant mitochondrial damage, mitophagic impairment, oxidative stress, and REST sequestration compared to adjacent GABAergic neighbours who could upregulate REST and preserved mitochondrial function (Kawamura et al., 2019; Ryan et al., 2021). CRISPR-induced REST-KO in SHSY5Y cells significantly diminished mitophagy, mitochondrial health, antioxidant capabilities, and ATP production. Ryan et al. (2021) suggest REST modulates mitophagy by upregulating PGC-1a which is key to mitochondrial biogenesis. Diminished PGC-1a has been observed in PD and AD lines as well as neurodegenerative animal models. (Ryan et al., 2021; Lautrup et al., 2019). Kawamura et al. (2019) claimed that in PD, α-synuclein-oligomerization, and not mitochondrial dysfunction induces REST dysregulation. However, Ryan et al. (2021) claimed that GABAergic neurons of the SNc could upregulate REST against α-synuclein aggregation. Understanding why REST activity differs between neuronal subtypes is key to better understanding neurodegenerative pathology as well as REST functionality. Stimulating mitophagy is ameliorative against neurodegenerative pathology (Lautrup et al., 2019) – it is unclear whether these effects function independently of REST. Investigating the relationship between REST and mitophagy would further characterize the mechanisms underlying aging and neurodegeneration and may point to areas of therapeutic intervention.

It was recently discovered that REST hippocampal-binding profiles differed between humans and mice suggesting unique roles for REST-regulated genes in human neurodevelopment (McGann et al., 2021). A detailed bioinformatic study of REST-regulated genes in the brain is imperative to characterizing REST functionality. This would aid in developing knowledge of the molecular interactions and mechanisms through which REST modulates physiological responses. Such a study may be taken up in the near future. Unlike in humans, REST declines with age in mice implicating a difference in aging mechanisms. Gene-ontology enrichment analysis was significantly associated with innate immune response and inflammatory pathways. (McGann et al., 2021). In the absence of REST, some of those factors have been found to be significantly upregulated in AD (Derk et al., 2018; Firuzi et al., 2008; Rangaraju et al., 2018). Immune/inflammation related genes are upregulated with aging and can contribute to the progression of AD-pathology and neurodegeneration (Akiyama et al., 2000; Cribbs et al., 2012). The complement pathway is critical to the innate immune response and helps establish the E/I balance during development (Cribbs et al., 2012; Stephan et al., 2012). REST has been found to regulate expression of important complement genes like C1Q and clusterin which are associated with increased AD-risk and pathology (Bray et al., 2020; Hong et al., 2016; Kunkle et al., 2019; McGann et al., 2021). REST may finetune the expression of complement genes to regulate the aging-associated increase in innate immune responses. Aberrant REST levels can therefore induce dysregulated immune activity that contributes to AD pathology. Higher complement activity has been indicated in people with AD compared to healthy controls, however, its role remains unclear (Krance et al., 2019). Understanding REST's interactions with the complement pathway may elucidate the connection between immune system activity and AD pathogenesis.

4.2. Diagnostic REST

Lithium has shown promise in preclinical work against several aging-associated/neurodegenerative diseases including PD, AD, HD, and prion disease (Forlenza et al., 2014; Lazzara and Kim, 2015; Matsunaga et al., 2015). Primary mechanisms for lithium's neuroprotective effects involve the downregulation of glycogen-synthase kinase-3β, significant down-regulation of apoptotic proteins as well as inhibition of oxidative stress and excitotoxicity (Kim et al., 2011; Lazzara and Kim, 2015; Nonaka et al., 1998). Administration of lithium reduces tau phosphorylation in vitro and in vivo (Forlenza et al., 2014). Moreover, lithium has reduced Aβ production and plaque aggregation in AD model mice while also improving their memory and cognition (Zhang et al., 2011). Lithium improves neuronal survival and may delay the onset of dementia. It has been suggested that lithium may be an agonist for REST (Song et al., 2018). Song et al. found that lithium increased REST expression in prion-disease primary cultured cortical neurons and controls and restored nuclear REST function by augmenting its nuclear translocation (Song et al., 2018; Song et al., 2017). REST upregulation by lithium was independent of autophagic pathways (Song et al., 2017), highlighting the role of autophagy in disabling REST in neurodegenerative diseases and points to lithium as a point of intervention.

Intriguingly, knockdown of REST significantly diminished lithium's neuroprotective effects, suggesting REST may be vital for lithium-associated neuroprotective mechanisms (Song et al., 2017). Moreover, overexpression of REST in conjunction with lithium administration compounds lithium's neuroprotective effects under physiological and pathological conditions raising the possibility of an augmented lithium treatment (Song et al., 2017). Despite the promise of lithium, the few clinical trials involving humans have thus far yielded mixed results, however many studies indicate it improves cognitive performance with age and neurodegeneration (Kessing et al., 2010; Matsunaga et al., 2015; Trujillo-Estrada et al., 2013) – REST is likely essential for maintaining cognitive viability with age. One study posits that lithium may have benefits against AD if started early enough (Forlenza et al., 2014), potentially when REST has not yet been significantly dysregulated. Research that is dedicated towards understanding the interplay between aging, REST, and lithium may produce findings fruitful towards combating dementia and neurodegeneration.

There is also considerable interest into how the endocannabinoid system relates to nervous system pathology and E/I imbalances. Endocannabinoids are likely related to mechanisms underlying pyramidal excitability and are key regulators of cortical E/I tone (den Boon et al., 2015; Durieux et al., 2021; Worley et al., 2020). The cannabinoid receptor-1 (CB1R) has been observed to suppress GABA release in the PFC (Hill et al., 2011). A study found that transient CB1R activation in the PFC mitigated stress induced anxiety (which relates to E/I imbalances), but chronic activation exacerbated it (Worley et al., 2020). This demonstrates the difficulty of quantifying the effects of E/I balances as well as qualifying it since CB1R-KO has been associated with neurodegeneration (Blázquez et al., 2011). Interestingly, REST potentially downregulates CB1R as its gene may contain REST-binding sites (Blázquez et al., 2011; Luo et al., 2020), lending further support to Ren et al.'s (Ren et al., 2018) study on AD-induced E/I imbalances in the PFC. Researchers should investigate REST's relationship with the endocannabinoid system as pertaining to states of E/I imbalances and neurodegeneration/neuroprotection. Most of the REST studies reviewed in this paper used animal models or in vitro cultures and not live human participants. This could be problematic as REST has different expression profiles between mice and humans (McGann et al., 2021). Ashton et al.'s methodology for measuring peripheral REST in blood plasma correlated with disease markers and may provide a solution to the scarcity of human studies (Ashton et al., 2017). Whether those peripheral levels reflect central levels and the time course of how REST levels vary in plasma must be clarified before the technique can be widely adopted. However, if proven, measuring plasma REST may become a critical tool

in understanding cognitive vulnerability and the trajectory of healthy and pathological aging.

5. Conclusion

E/I imbalances are deeply connected to brain aging and yet are often overlooked by researchers when investigating aging or neurodegeneration. The effects imbalances have on aging are conserved and the downregulation of excitatory signaling was found to be strongest in the transcriptomes of cognitively healthy older adults, correlating positively with age (Zullo et al., 2019). E/I imbalances can develop detrimental feedback loops with harmful by-products of the aging process. Oxidative stress and metabolic dysfunction are both worsened by and themselves worsen hyperexcitation. Considerable evidence points to REST serving as a critical regulator of these processes and may be essential to preserving cognitive function in old age. Nowhere is this more evident than in the absence/dysregulation of REST, whereupon these processes coalesce to significantly increase the risk of neurodegeneration, especially AD.

REST dysregulation along with aging-associated pathology likely occur before Aβ-deposition, which by itself may be insufficient for inducing neurodegeneration. AD profoundly impairs inhibitory signaling which has further cascading effects that serve to strengthen disease progression. The remarkable evolutionary conservation displayed in REST's regulatory features in relation to neuroprotection, metabolism, and the E/I balance – which itself bears a conserved relationship with neural health – speaks to their importance and can guide us in understanding the processes differentiating typical from atypical aging and may reveal putative mechanisms to delay and treat neurodegeneration.

Declaration of competing interest

None.

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