Chapter 4

Gender Differences in Frontotemporal Lobar Degeneration (FTLD) Support an Estrogenic Model of Delayed Onset

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Abstract

Gender differences in frontotemporal lobar degeneration (FTLD) have been reported in the literature but not well characterized or explored. In the present work, we propose that steroid hormone estrogens delay the onset of FTLD in pre-menopausal women compared to age equivalent men, and may provide neuroprotection in the early post-menopausal period. We present a model wherein estrogens serve a regulatory role in attenuating the microglia conversion from the benign to active form in response to cell stress that might otherwise trigger an inflammatory response. Via microglia stabilization, estrogens preserve the homeostasis of both the ubiquitin-proteosome degradation system and lysosome-autophagy recycling system. Both systems have been implicated in the genetic forms of FTLD, with the latter system recognized to be associated with the majority of them.

Keywords: frontotemporal lobar degeneration (FTLD), gender differences, estrogens, autophagy, microglia, neuroprotection

1. Introduction

FTLD is second only to Alzheimer's disease as a leading cause of primary degenerative dementia in those under age 65 [1, 2]. Researchers estimate that it is responsible for one out of six cases of pre-senile dementia in post-mortem confirmed cases of individuals under age 70 [3]. FTLD symptoms range from motor and language impairment to profound behavioral changes and deficits [4, 5], including severely attenuated initiative to profound impulsivity

[6]. FTLD is characterized by three subtypes: behavioral variant frontotemporal dementia (bvFTD), semantic dementia (SD), and primary progressive aphasia agrammatic variant (PPA-agrammatic), although there remains ongoing discussion about their classification [5, 7]. As the most prevalent form of pre-senile dementia after early onset Alzheimer and vascular dementia [8], gender differences in onset and characteristics of FTLD have received little attention in comparison to older onset Alzheimer's dementia. The initial conclusions of the Women's Health Initiative Memory Study (WHIMS) associated long-term estrogen replacement in women ≥65 years of age with increased risk of senile dementia but not mild cognitive impairment (MCI) [9]. MCI, as the Alzheimer's dementia prodrome, is known to remain stable in 1/2 to 2/3 of patients, with stability largely dependent upon the absence of apolipoprotein E e4 (APOE e4) alleles [10]. Consistent with this, estrogen replacement risk of senile dementia has been shown to be dependent upon the presence of the APOE e4 gene. In their longitudinal evaluation of the cognitive status of 12,612 participants of the Nurses' Health Study (≥70 years old) over 4 years, Kang and Grodstein [11] found that participants on hormone replacement since menopause onset, who were carriers of the APOE e4 allele demonstrated a significantly worse rate of cognition decline than nonhormone users. In the absence of APOE e4, the cognitive status of participants was equivalent, regardless of hormone replacement status. While findings did not demonstrate any significant benefit from hormone replacement in this cohort, the authors point out that this was a relatively homogeneous population of highly educated female nurses. Cognitive reserve may have protected nonestrogen users from declines into dementia during the 4 year period of study.

With respect to FTD, Ratnavalli and colleagues [12] found that men were four times more likely than women to be affected by bvFTD. They posited that this may have been an artifact of their small sample size, but also referred to older research documenting higher rates of FTLD in men [13] and encouraged further exploration. Johnson and colleagues [14] also reported sex differences. They found that more men had bvFTD and SD, while more women had progressive nonfluent aphasia. They noted that this may be due to sex-specific vulnerability to neurodegeneration for women in the left frontal region and men in right frontal and bilateral temporal regions. Bede and colleagues [15] recently evidenced gender differences in amyotrophic lateral sclerosis (ALS), considered to be a motor variant of FTLD on a clinical continuum [16, 17] with characteristics of FTLD in the absence of dementia in up to 50% of cases [18].

2. The role of estrogen in the brain

Beyond their role as reproductive hormones, estrogens, specifically 17β estradiol, exert a neuroprotective role in the brain through estrogen receptors widely distributed in the male and female brain. Multiple estrogen signaling pathways are now recognized in the human brain that are involved in the protection of brain from cognitive decline, emotional dysregulation, and neurodegeneration [19]. Moreover, the neuroendocrine response to stress is gender-specific and associated with the presence of gender-specific gonadal steroids [20]. Estrogen has been shown to be involved in cortical and subcortical hypothalamic-pituitary-adrenal (HPA) function [21], with activation of HPA arousal circuitry evidenced to be regulated in adult women by the hormonal cycle [21, 22].

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All three subtypes of FTLD (bvFTLD, SD, and PPA-agrammatic) are associated with alterations in arousal, characterized by apathy. Our recent findings from a national, multicenter study of nondemented ALS with cognitive impairment and/or behavioral impairment were consistent with this, while evidencing a significantly greater incidence of impulsivity and jocularity in males, as well as personal neglect in females [23]. We contend that this distinction is due to the involvement of ventromedial natural reward and dominance circuitry in the emerging neurodegenerative disease process and the role of estrogen therein (**Figures 1** and **2**).

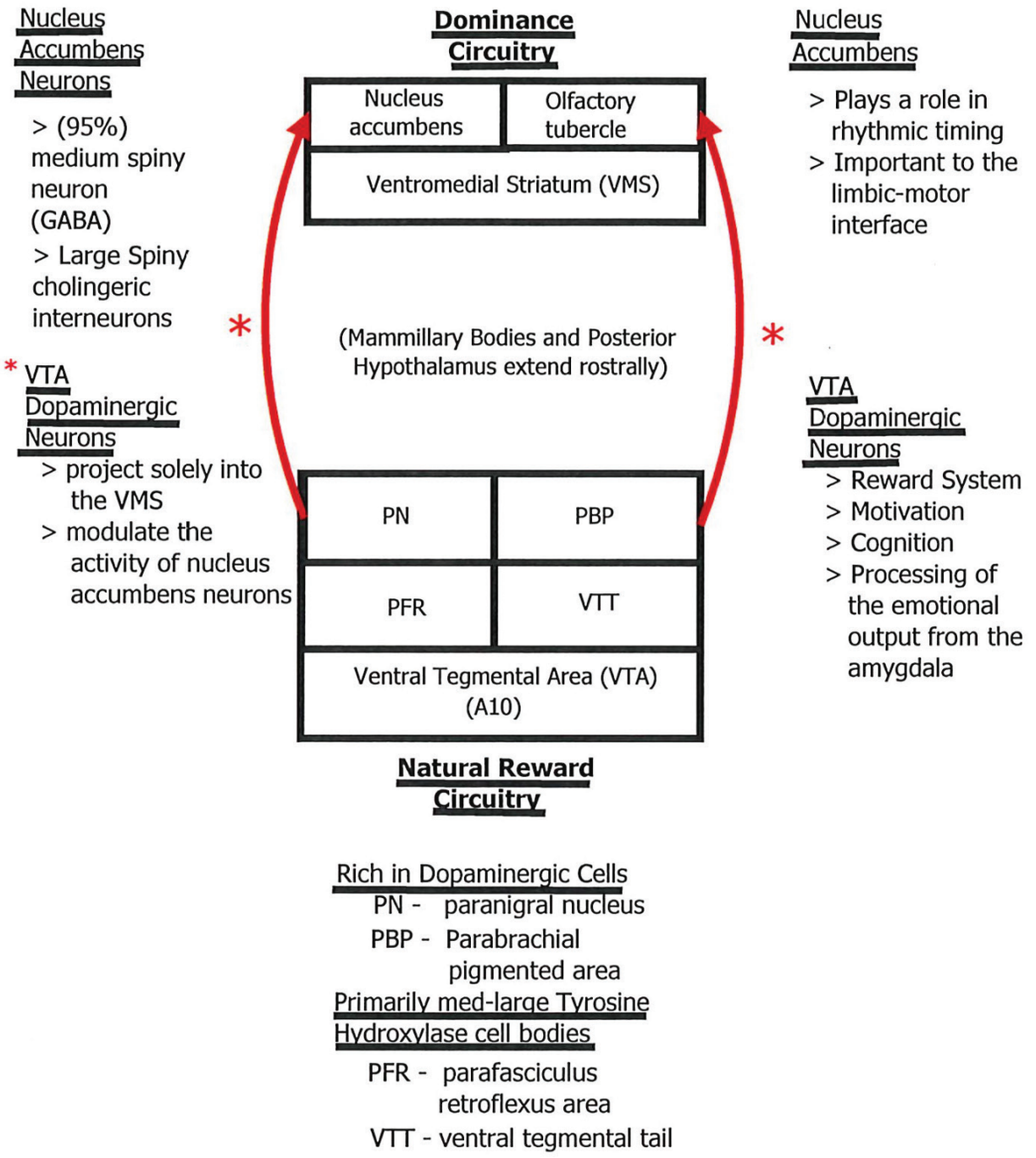

Figure 1. Mesostriatal pathway: natural reward–dominance neural system.

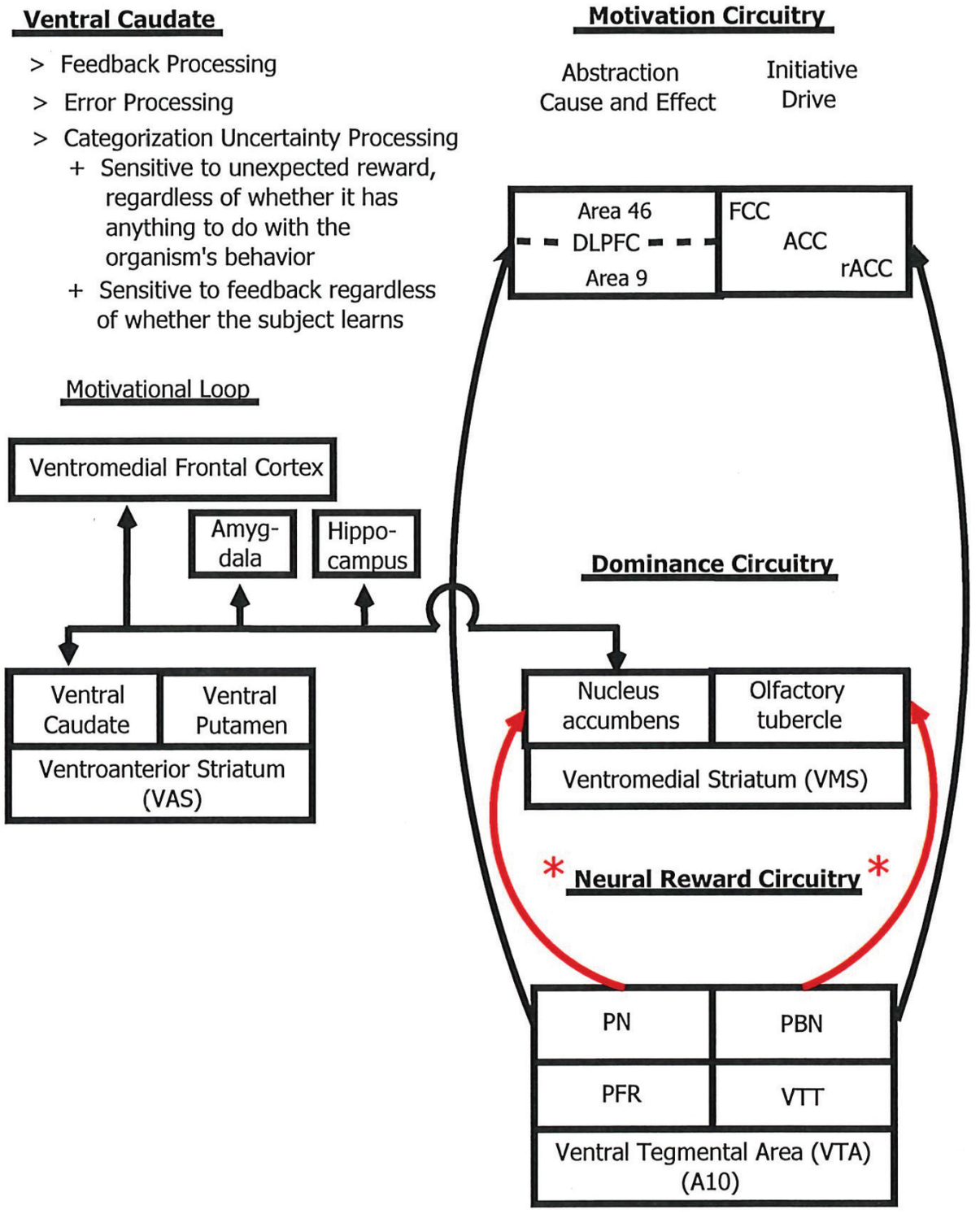

Figure 2. Mesocortical pathway: natural reward–dominance–motivation neural system; PN = paranigral nucleus, PBN = parabrachial pigmented area, PFR = parafasciculus retroflexus area, VTT = ventral tegmental tail, DLPFC = dorsolateral pre-frontal cortex, FCC = frontocingulate cortex, ACC = anterior cingulate cortex, and rACC = rostral ACC.

More recently, we evidenced greater cognitive and behavioral stability in 78 women from this cohort, based upon both site of disease onset (midbrain vs. spinal cord) and estrogen status (high vs. low).

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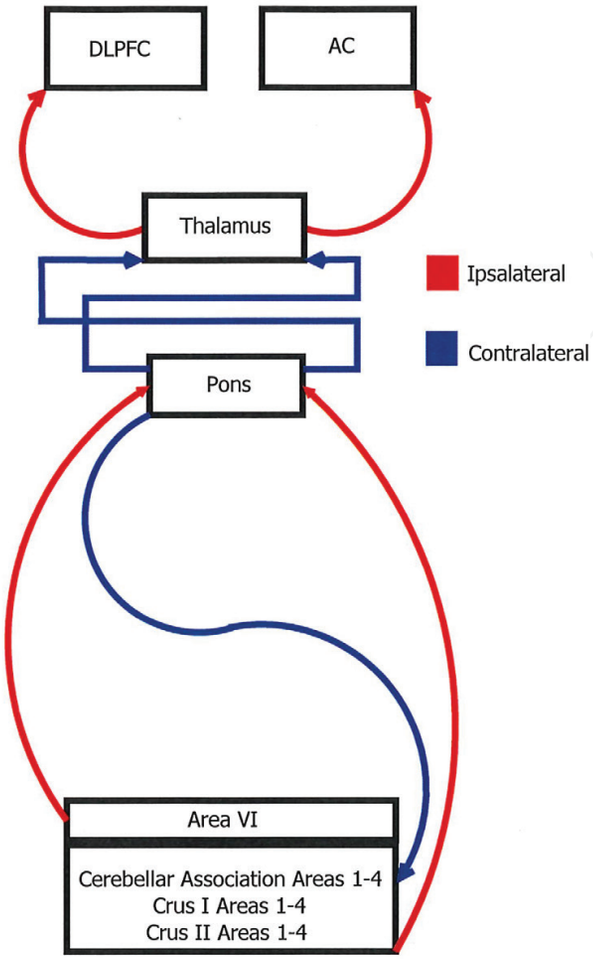

Figure 3. Cerebellar regulation of the mesocortical pathway: regulation of the natural reward-dominance-motivation neural system.

Given that midbrain onset females in our study demonstrated estrogen neuroprotection with respect to cognitive executive functions, we expanded our model of midbrain involvement in FTLD to involve the role of the cerebellum in executive functioning decline, based upon our own findings and recent imaging evidence [24] (**Figure 3**).

It has been widely established that ovarian gonadosteroidal hormones provide protection against brain injury and degeneration and provide cognitive maintenance [25–27]. Evidence of estradiol (the primary ovarian estrogen) neuroprotection comes from histopathological studies in rats [28] as well as healthy human females [29]. The release of neuroestradiol from the stalk median eminence (SME) of the hypothalamus in ovarectomized female monkeys has recently been evidenced [30]. Electrical stimulation of the medial basal hypothalamus resulted in release of both gonadotrophin releasing hormone (GnRH) and estrodial. This suggests its vital role as a neurotransmitter involved in regulation of GnRH release.

In recent neuroimaging data, the evidence of estrogen regulation of anterior cingulate cortex (ACC)-associated motivation in healthy human females was evidenced by examining the effects of estrogen on the neural correlates of emotional response inhibition. Applying an

in-subject design involving 20 right-handed female subjects of average age 25.4 years, Amin and colleagues [31] combined 3.0 T functional magnetic resonance imaging (fMRI) with quantitative analysis of ovarian hormones. All participants evidenced stability of mood across the menstrual cycle. Subjects were scanned during the early follicular phase, when levels of estrogen and progesterone were low, and during the mid-luteal phase, when levels of estrogen and progesterone were high. Subjects were scanned while they were engaged in a verbal go/no-go task involving positive, negative, and neutral stimuli. This task was chosen because it was already evidenced in the literature to activate the dorsolateral prefrontal cortex (DLPFC) and the ACC. Cycle phase and condition were within-subject independent variables, while mean reaction time and accuracy of response were independent variables. During the follicular phase (low hormones), women exhibited significantly decreased activation in the bilateral ACC and some portions of the left PFC in response to positive distracters, relative to positive targets. During the luteal phase (high hormones), however, women exhibited decreased activation in the ACC in response to negative distracters and increased activation in the DLPFC in response to positive distracters. The investigators noted that the luteal phase findings were consistent with literature associating human female estrogen levels with positive affect. They further noted that their findings of negative correlation between estradiol levels and activation in response to negative distractors, relative to negative targets, were consistent with previous research [21]. This contention is further supported by more recent findings from the KEEPS longitudinal clinical trial focused on the potential for estrogen neuroprotection in 693 younger post-menopausal women of average age 52.6 years old and 1.4 years past their last menstrual period [32]. Following 4½ years, the estrogen replacement subgroups (N = 693) evidenced significant improvements in depression and anxiety in comparison to a placebo subgroup (N = 262). Cognitive status remained stable with monitoring to assess dementia incidence with aging ongoing.

3. Estrogen regulation of the stress response as a model of neuroprotection

Goldstein and colleagues [21] applied an fMRI paradigm to examine the effect of estrogen on brain regions involved in the stress response by using aversive affective stimuli in a group of 12 right-handed women, ages 36–40. Their imaging data evidenced an association between the early follicular phase (low estrogen) and significantly increased activation to neutral stimuli, relative to negative targets, in the central amygdala nuclei, paraventricular hypothalamic nuclei, peripeduncular nuclei, orbital frontal cortex, and AC gyrus (ACG). In comparison to the early follicular phase, the luteal phase (high estrogen) was associated with decreased activation in the central amygdaloid, ventromedial hypothalamic, orbital frontal, and cingulate nuclei in response to negative vs. neutral stimuli. With respect to FTLD, we propose a model whereby estrogen provides neuroprotection by mediation of the neuroimmunological and neuroendocrinological stress response (i.e., release of anti-inflammatories and stress associated hormones) (**Figure 4**).

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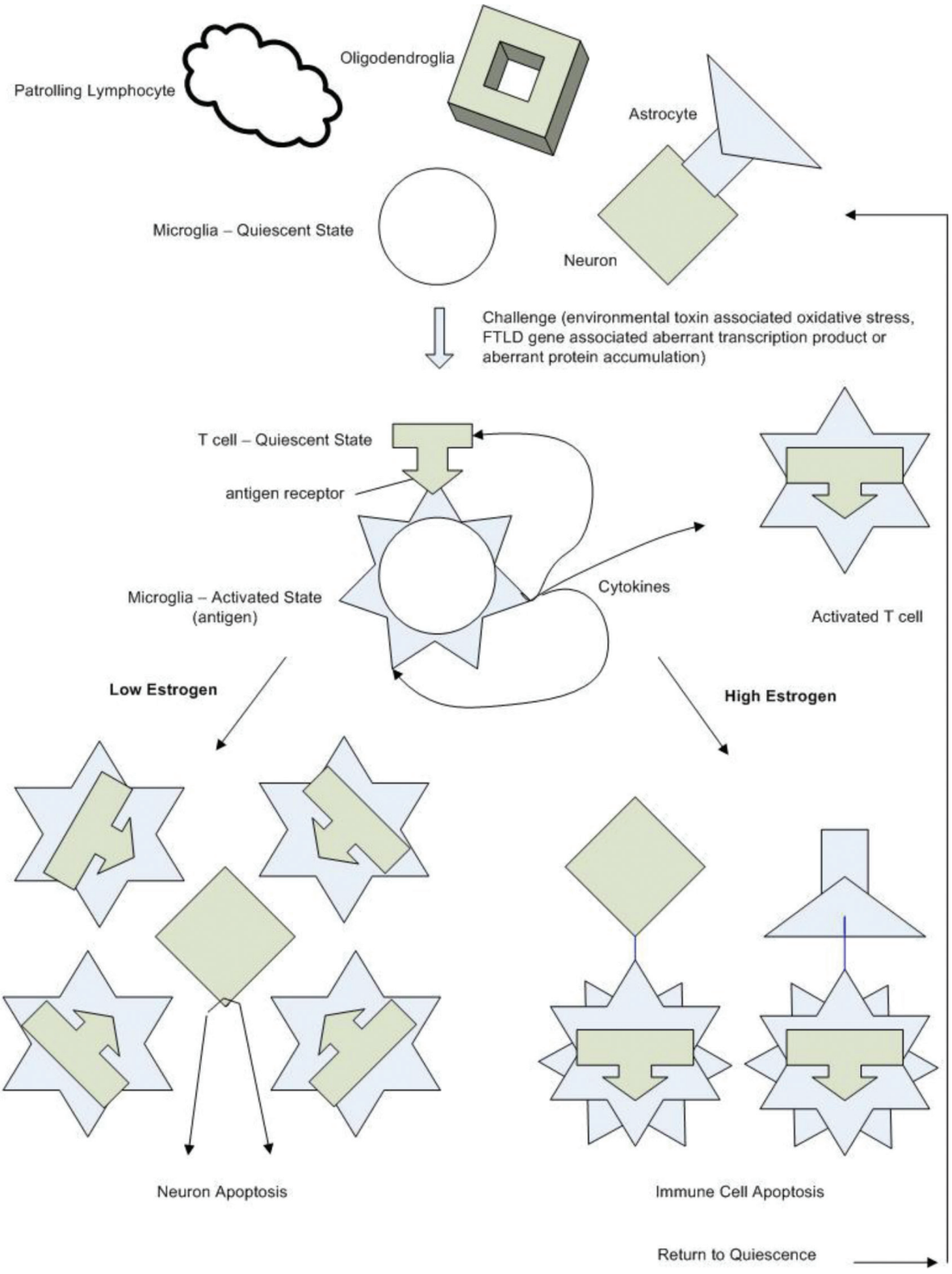

Figure 4. Estrogen binding to microglia induces feedback inhibition of the inflammatory cascade, resulting in neuroprotection. Mice models of toxic demyelination evidence estrogen induction of insulin-like growth factor 1 (IGF-1) expression by astrocytes. IGF-1 then promotes proliferation of oligodendrocyte precursors and their differentiation into mature remyelinating oligodendrocytes.

4. Lysosome and proteosome homeostasis: estrogen mitigation of the microglia inflammatory response in neurodegeneration

As disorders of aging, many neurodegenerative diseases demonstrate significant gender differences in their prevalence, symptomatology, and prognosis, implicating gonadal steroidal hormones in their pathophysiology [33, 34]. Parkinson's disease (PD) has for a long time been recognized to be more prevalent in males than in females, with a relative male to female ratio ranging from 1.4 to 3.7. Evidence suggests that levels of estrogens or progesterone or differences in their respective receptor levels could account for this gender difference [35, 36]. Particularly with respect to early onset dementia, emerging with onset of menopause or andropause, endogenous estrogen regulates brain physiology through a concerted action on diverse cell types and molecular targets [37]. Women who undergo surgical removal of the ovaries before menopause clearly demonstrate that oophorectomy is associated with an increased risk of cognitive impairment and dementia [38]. Women's Health Initiative (WHI) data, taking into consideration the time between menopause onset and hormone therapy initiation, showed beneficial effects of estrogens when therapy was initiated early after menopause, with detrimental effects associated with treatment started several years following menopause [39]. This supports the theory of estrogen as a neuroprotective agent while underscoring the limitations of the approach. Estrogen protection has a 'window-in-time': potentially effective if applied around the menopause period and maintained for a 5–10 year period of clinical effectiveness, given the absence of significant cancer or dementia risk factors [40], including the presence of the APOE e4 gene [11].

The neuroendocrine system is a powerful regulator of the inflammatory response in health and disease states [41]. In addition to regulating peripheral immune responses, steroid hormones, including glucocorticoids and gonadal steroids, support anti-inflammatory properties in the brain [42]. Steroid hormone protective actions in the nervous system range from stabilizing the blood brain barrier (BBB), alleviating brain edema, dampening pro-inflammatory/supporting anti-inflammatory processes, activating anti-apoptotic pathways, stimulating survival-promoting factors, counteracting oxidative stress, promoting respiratory chain function, and reducing glutamate excitotoxicity [43–48].

Estrogens are known to exert their actions through members of the nuclear hormone receptor superfamily, ERα [49], and the more recently identified estrogen receptor–ERβ [50–52]. Estrogen is recognized to exert an inhibitory response to neuroinflammation, with specificity of binding to microglia, resulting in the attenuation of the inflammatory response [53]. 17β-estradiol and progesterone have also been shown to mediate anti-inflammatory activity and improve neuronal survival [44, 54–56]. 17β-estradiol targets many pathways active in secondary injury; including oxidative stress, inflammation, apoptosis, and ischemia [57] (**Figure 4**).

Detecting the expression of the two estrogen receptors ERα and ERβ in cells of the monocyte-macrophage lineage, Vegeto and colleagues first evidenced the role that estrogens play in inflammatory diseases [58] with several laboratories later demonstrating that these gonadal steroid hormones act in a variety of macrophage-like cells to regulate the inflammatory response triggered by diverse inflammatory stimuli [59, 60]. In addition to having a

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regulatory role in the immune system, ERβ is involved in tumor suppression [61]. Thus, in recent years, pharmaceutical companies have generated selective agonists for ERα and ERβ, with ERβ research ongoing for ERβ development as a cancer preventative, as an anti-inflammatory drug and for the attenuation of neurodegenerative diseases [62].

Microglia are mediators of the innate immune defense, acting as antigens and scavenger cells during brain inflammation, acute central nervous system (CNS) injury, and neurodegeneration in the course of aging [63]. As such, they represent the resident macrophages of the CNS, comprising 5–15% of total cells in the brain [64]. As the brain-resident immunocompetent cells, microglia are critical for proper innate immune responses in the brain [42]. In the steady state, they perform housekeeping chores via autophagy [65] and may participate in postnatal neuronal development, whereas following trauma or pathogenic insult; they initiate the inflammatory response as part of the brain immune defense [66]. In the course of this, they increase their release of several inflammatory-associated substances, including reactive oxygen intermediates, nitric oxide (NO), and (inflammatory) cytokines [interleukin-1 and 6 (IL-1 and IL-6), interferon-g (IFN-g), and tumor necrosis factor-α (TNF-α)] [67].

Microglia cells express a set of classical and non-classical steroidal hormonal receptors, including ERα, ERβ, progesterone receptors (PR), glucocorticoid receptors (GR), and mineralocorticoid receptors (MR) [42, 68]. The central role of ERα and ERβ in the regulation of the microglia inflammatory response, in conjunction with the recent discovery of medial basal hypothalamic neuroestradiol, suggests the potential of estrogens to mitigate the pathogenesis and progression of neuroinflammation and neurodegeneration [69]. In particular, two gonadal steroid hormones, 17α-estradiol and progesterone, provide robust neuroprotection in a variety of experimental brain injury models [43, 54, 70, 71] and under neurodegenerative conditions [72–74]. It is possible that 17α-estradiol is an effective neuroprotective agent due to its actions as an anti-oxidant, anti-inflammatory, and anti-apoptotic steroid hormone [42, 57, 75–77].

Given the role of estrogenic steroids in modulating neurogenesis and the generation of dendritic spines and neuroprotection, Jellinck and colleagues [66] explored the question of whether microglia might serve as a regional *source* for estrogenic steroids. With respect to neuroprotection, dehydroepiandrosterone (DHEA) is considered to exert its positive influence via conversion to estrogen (estrone and estradiol). However, this conversion is slow and limited in brain cell cultures, with the exception of microglia [66]. These researchers were able to demonstrate the presence of the enzyme necessary for the rate limiting step of this conversion within microglia cells, supporting their contention that microglia are integral to regional regulation of adult estrogen-dependent brain plasticity and neuroprotection.

In the healthy CNS, microglia appear in a "resident state" with a ramified morphology (**Figure 4**). However, microglia are very susceptible to changes in the CNS milieu and become rapidly activated in response to CNS insult. Attracted by endogenous and other chemical messenger factors, microglial cells demonstrate the capacity to migrate toward the site of brain injury. Upon activation, microglia undergo morphological and functional changes such as hypertrophy and up-regulation of major histocompatibility complex (MHC) antigens. Activated cells secrete inflammatory mediators, including cytokines and chemokines [78, 79]. Microglia can also produce different types of free superoxide radicals and prostanoids [55].

As a first line of defense, activated microglia perform phagocytosis of apoptotic neuronal cell bodies via the lysozyme-autophagy recycling system. However, chronic activation of microglia with associated excess pro-inflammatory response in the aftermath of CNS insult may overwhelm this natural recycling system of the cell, resulting in cytotoxicity [80]. In the aftermath of stroke, for example, microglial activation is one of the earliest responses; requiring several hours to fully develop, while persisting for up to several days [81, 82]. The microglia inflammatory response, therefore, needs to be tightly controlled to avoid collateral damage within intact brain tissue. Estrogen appears to provide this level of regulation.

Microglia express steroid hormone receptors that include ER-α, with immunoreactivity evidenced by electron microscopy studies [35, 42, 68, 83–86]. Indeed, the neurodegenerative process of several CNS diseases, including amyotrophic lateral sclerosis, frontotemporal lobar degeneration, multiple sclerosis, Alzheimer's disease, and Parkinson's disease are associated with the activation of microglia cells, which drive the resident inflammatory response [17, 87–89]. In addition, a number of pro-inflammatory mediators are elevated in the CNS or cerebrospinal fluid of neurodegenerative disease patients [30]. Given this, it is particularly important to recognize that estrogen is understood to maintain microglia in the benign form, associated with suppression of the inflammatory response, suggesting its protective role in the aging brain against ubiquitin-proteosome mediated degradation.

Estrogen signaling is characterized by cell-specificity and dose dependent responsiveness. Divergent effects of estrogens have been reported for T cell activation [90], microglia modulation, and astroglia effects based upon different hormone concentrations [91, 92]. 17β-estradiol inhibits microglial activation following exposure to bacterial lipopolysaccharides [53], with estrogen-induced neuroprotection from autophagy lysis or proteasome degradation related to declines in TNF-α expression and NO production [43, 53]. NADPH oxidase represents one important source of free radicals in activated microglia [92], which catalyzes the reduction of oxygen to superoxide radical [93]. 17β-estradiol has been shown to decrease lipopolysaccharides-induced superoxide production and release in N-9 microglia cell lines [94].

ERα and ERβ are intracellular proteins, which activate a multitude of genomic as well as nongenomic effectors in neural cells [87]. Through the use of an estrogen receptor antagonist [ICI 182780], hormone action in microglia has been attributed to the activation of endogenous ERs, since antagonist binding was able to block the effect of estradiol, suggesting a receptor-mediated effect of the hormone [35, 53, 95, 96]. Using estrogen receptor knock out mutant mice, several investigators have described the selective involvement of ERα in the anti-inflammatory and neuroprotective activity of estradiol against neuroinflammatory and vascular pathologies of the brain [97–100]. In ICI 182780 studies, ERα appeared to be selectively involved in estradiol anti-inflammatory activity in microglia, a finding later confirmed by additional experimentation using primary cultures of microglia as well as cell lines [97, 101].

Estrogen-dependent attenuation of microglia activation has been demonstrated to involve reduced lysosome-phagocytic activity, production of reactive oxygen and nitrogen species and other factors of the inflammatory cascade [35, 94, 102–104]. The inhibitory activity of estrogens on microglia-associated neuroinflammation may prove to be a beneficial therapeutic

opportunity for delaying the onset and progression of early onset neurodegenerative diseases such as FTLD, with replacement offsetting menopause associated declines.

Importantly, estradiol does not alter the inflammatory signaling cascade in microglia if it is administered after inflammatory stimuli [94, 97, 101]. Moreover, prolonged hormonal deprivation has been evidenced to affect estrogen protective activity in ischemia; resulting in a null or even pro-inflammatory response following administration of exogenous hormone [105]. Collectively, the experimental evidence indicates that the efficacy of estrogenic molecules as anti-inflammatory agents is confined to a therapeutic window and that their use should be considered only as preventive pharmacological strategies. Applied during the pre-clinical or prodrome stage, estrogen represents a therapeutic opportunity to forestall the onset and mitigate the progression of pre-senile neurodegenerative disease processes, particularly those like FTLD that typically emerge in mid-life, prior to or throughout the course of menopause and andropause. With the advent of personalized medicine, it may eventually be possible to identify genotypically high risk individuals and intervene with hormone replacement therapy while the neurodegenerative disease process remains at the sub-clinical level.

5. Estrogen interaction with cellular signaling molecules

Estrogen exerts an indirect effect on microglia through specific interactions with cellular signaling molecules. Nitric oxide synthases, a family of enzymes catalyzing the production of NO from L-arginine, are important cellular signaling molecules. The inducible isoform, inducible nitric oxide synthase (iNOS), serves a number of roles, including involvement in the immune response, with production of NO as an immune defense mechanism, due to its free radical nature. It is the proximate cause of septic shock and may function in autoimmune disease [106, 107]. In rats and microglia cell lines, the expression of iNOS and release of reactive oxygen species is reduced in certain cell types through the action of estrogen, including microglia [53, 76, 94], while expression of endothelial and neuronal subtypes of iNOS are increased [108].

After immunostimulation by lipopolysaccharides, estrogen but not progesterone has been shown to attenuate microglial superoxide release and phagocytotic activity as well as iNOS expression [94]. These effects are transmitted through an estrogen receptor-dependent activation of the MAP-kinase signaling system. Using a transient focal ischemia animal model, investigators have shown that estrogen and progesterone prevent the hypoxia-induced attraction and activation of local microglia and their morphological transition into an activated phenotype in the cortical penumbra [109]. The reduced stimulation of microglia is considered to result from diminished cytokine and interleukin expression and release in local astroglia, consequent to the close concerted communication between these two glial cell types during tissue stress. Focal ischemic mouse model experiments further evidence diminution of the penumbra of estrogen/progesterone-treated animals, along with reduction in chemokine levels, central microglia, and recruited monocytes. Ischemic mouse model data are confirmed by several other studies, which have demonstrated that these steroid hormones affect local cytokine production during brain inflammation in microglia [53, 76, 110], in astroglia [111, 112], and in unidentified cell types [113].

Mitogen-activated protein kinases (MAPKs) are involved in directing cellular responses to a diverse array of stimuli, such as mitogens, osmotic stress, heat shock, and microglia generated pro-inflammatory cytokines (e.g., TNFα, IL-6, and IL-1β) [114]. MAPKs regulate proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis [115]. Several MAPK pathways, including p42/44 MAPKs, are known to be activated by 17β estradiol [116]. Moreover, studies have evidenced the importance of activated p42/44 MAPK pathways in estrogen-mediated neuroprotection and microglia homeostasis [117]. When activated in response to inflammation, microglia release large amounts of oxygen and nitrogen radicals. Proteosomes clear oxidized and damaged proteins from cells, serving as a microglia compensatory response to activation. In the mouse model, the p42/44 MAPK pathway participates in estrogen-mediated proteasome activation, with estrogen up-regulation of proteosome activity considered to be one way estrogen potentially promotes microglial viability [117, 118].

Calcium-dependent protease with papain-like activity, or calpain, is a cytoplasmic cysteine protease that is activated by calcium [119]. Calpain is involved in neurodegeneration in a variety of injuries and diseases [120]. Calpain cleaves many substrates, including cytoskeletal proteins, axonal, and myelin proteins, and pro-apoptotic Bax causing mitochondrial cytochrome c release, activation of caspase-3, and activation of microglia [121–123]. Studies indicate that estrogen attenuates Ca^{2+} influx via modulation of L-type Ca^{2+} channels and the Na^{+}/Ca^{2+} exchanger [124]. Estrogen has also been shown to reduce calpain expression and activity, resulting in reduced axon degeneration and neuronal apoptosis in vitro [125].

Finally, estrogen is involved in regulation of microglial matrix metalloproteinases [126]. Metalloproteases secreted from microglia mediate inflammation and tissue degradation through processing of pro-inflammatory cytokines and damage to the BBB [127]. Progestins and estrogens affect matrix metalloproteinase enzyme activity in microglial cells, reducing indications of microglial inflammation [97, 126, 128].

6. Evidence of estrogenic effects in FTLD

Although few studies known to-date have focused on estrogenic effects in FTLD, indirect evidence comes from physiological studies in both normal and genetically disordered individuals. In this regard, it is notable that FTLD is associated with over a dozen genetic mutations that include the ALS-associated X linked UBQLN2 variant [129]. Neuropathologically, FTLD is primarily represented by two subtypes: one involving aberrant inclusions of microtubule protein tau, and one involving inclusions of TAR DNA binding protein [130].

6.1. Appetite regulation

Both bvFTD and SD are associated with changes in appetite and eating habits, with overeating and a preference for sweets and excessive seasonings, including salt [131–133]. Appetite is recognized to be modulated by gonadal steroid hormones, including peripheral and central

mediating mechanisms [131, 134, 135]. In the healthy adult, sex differences in eating exist, regulated by the hypothalamic-pituitary-gonadal (HPG) axis. Little is known about the direct effect of testosterone on eating, while the effects of 17β-estradiol, the primary estrogen, have been well characterized. Hypothalamic centers are recognized to be intimately involved in the regulation of appetite, with extensive neuronal control reflected in their innervation by axons expressing all the major neurotransmitters [136, 137]. Hypothalamic centers are known to play a vital role in neuronal action of insulin and adipose tissue-secreted leptins. Estrogen binding (i.e., estradiol-triggered calcium influx) results in appetite suppression, with parvabumin potentially serving a protective role in the attenuation of calcium overload-associated neuronal degeneration (see Sinchack and Wagner for a detailed review) [138].

The posterior hypothalamus contains nuclei that play a critical role in regulating feeding behavior [136, 137]. Recent in vivo structural neuroimaging demonstrated a relationship between deterioration in the posterior hypothalamus and appetite disturbances in FTLD, an early sign of disease onset evident within 2 years of diagnosis [133]. Post-mortem analysis further evidenced sparse TDP-43-immunoreactive neurites within TDP-43 positive cases, with occasional intracytoplasmic inclusions in posterior hypothalamic neurons [133]. In their analysis of the differential effects of peripheral hormones vs. hypothalamic pathology on eating behavior in FTLD, Ahmed and colleagues [131] found higher levels of the hypothalamic derived satiation hormone agouti-related peptide in the serum of bvFTD and SD patients, with both groups having elevated scores on a questionnaire of eating behaviors. Atrophy of the posterior and total hypothlamus was found only for the bvFTD subgroup [131]. Interestingly, gender differences could not be examined, due to the relatively low numbers of females in both the bvFTD (4/15) and SD (8/18) subgroups, in comparison to gender matched controls (12/11).

6.2. Motivation regulation

As a bvFTD subtype, apathy is characterized by inertia and loss of volition, as well as apathy, in association with pathology within the dorsolateral convexities of the frontal lobe [139]. As an amotivational syndrome, apathy is also well recognized to be associated with disruptions to the ventral anterior cingulate cortex [139, 140]. In addition, regions known to be associated with Apathy include the medial dorsal nucleus of the thalamus, caudate nucleus, ventral medial striate (nucleus accumbens) and globus pallidus; with the cortical-striatal-thalamic-cortical circuit being the circuit most implicated in the Apathy syndrome [141]. Apathy neural circuitry is linked to the richly dopaminergic nonmotor limbic loop of the basal ganglia, with adaptive behaviors requiring a combination of reward evaluation, associative learning, and ability to develop appropriate action plans [142]. Dopamine deficiencies are often characteristic of FTLD. Clinical trials involving the use of dopaminergic psychostimulants have evidenced improvements in symptomology ranging from apathy to disinhibition and risk taking behaviors [143]. With respect to the potential for estrogen derivatives to mitigate apathy in FTLD, the responsiveness of dopamine neurons to estrogens has long been established, with inducement of dopamine synthesis and release, as well as dopamine neuron differentiation [144–147].

6.3. Turner syndrome

The overarching role of gonadal steroidal regulation of brain anatomy and physiology with respect to cognitive and affective executive functioning comes from studies of Turner syndrome, one of the most common sex chromosome-associated genetic disorders. Turner syndrome results in females from the complete or partial loss of one X chromosome, with partial loss involving the distal tip of its short arm [148, 149]. Turner syndrome individuals retain a healthy sense of desire for social interaction, while experiencing disruption in social salience in association with a right hemisphere learning disability. Turner syndrome is typically associated with early loss of ovarian function, leading to gonadal steroid deficiencies that result in pubertal delay and lack of developmental maturation. On a cognitive level, Turner Syndrome results in attentional deficits, disruptions to arithmetic reasoning, visuospatial processing, and executive functions. fMRI studies of Turner Syndrome adults provided with estrogen replacement to allow for physical maturation have implicated the parietal, amygdala and prefrontal areas in this condition, in association with tasks of working memory, as well as interpretation of facial emotional expressions, and mediation of arousal by affective stimuli. Provision of estrogen replacement to stimulate developmental maturation thus has the indirect effect of mitigating many cognitive and behavioral abnormalities also characteristic of cognitive and behavioral declines seen in emerging FTLD in females [23, 24, 150].

7. Summary

Early researchers found no evidence that FTLD affects men and women differentially [151, 152]. However, recent work has demonstrated hormonal differences in FTLD females not seen in either male FTLD or Alzheimer's patients [153]. Moreover, a multitude of genes have been identified associating FTLD characteristics with ALS, a motor variant of FTLD. ALS is known to have a greater percentage of males among patients who present with disease onset prior to mid-life and to have fMRI evidenced distinct patterns of neurophysiological change with ALS disease progression [15], up to half of whom potentially evidenced signs of FTLD associated cognitive and/or behavioral decline [18]. With respect to concerns about the association between estrogen replacement therapy and increased dementia risk in older women, raised by the results of the Woman's Health Initiative studies of the 1990s, estrogen replacement risk of senile dementia has been shown to be dependent upon the presence of the APOE e4 gene [11]. In the present effort, we present evidence that estrogen, in the absence of the APOE e4 genetic risk factor for Alzheimer's dementia, serves a neuroprotective role in females, including an association between female estrogen levels and cognitive and behavioral stability in emerging FTLD. The potential for estrogen replacement to delay disease onset in females vulnerable to FTLD, a condition typically emerging in midlife, is in need of further exploration.

Disclosure

The authors have no conflicts of interest to disclose.

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