

# Estrogen pendulum in schizophrenia and Alzheimer's disease: Review of therapeutic benefits and outstanding questions

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## ABSTRACT

Although produced largely in the periphery, gonadal steroids play a key role in regulating the development and functions of the central nervous system and have been implicated in several chronic neuropsychiatric disorders, with schizophrenia and Alzheimer's disease (AD) most prominent. Despite major differences in pathobiology and clinical manifestations, in both conditions, estrogen transpires primarily with protective effects, buffering the onset and progression of diseases at various levels. As a result, estrogen replacement therapy (ERT) emerges as one of the most widely discussed adjuvant interventions. In this review, we revisit evidence supporting the protective role of estrogen in schizophrenia and AD and consider putative cellular and molecular mechanisms. We explore the underlying functional processes relevant to the manifestation of devastating conditions, with a focus on synaptic transmission and plasticity mechanisms. We discuss specific effects of estrogen deficit on neurotransmitter systems such as cholinergic, dopaminergic, serotonergic, and glutamatergic. While the evidence from both, preclinical and clinical reports, in general, are supportive of the protective effects of estrogen from cognitive decline to synaptic pathology, numerous questions remain, calling for further research.

## 1. Introduction

For many decades, sex differences in behavior were assumed to reflect the function of the hypothalamus and its role in reproduction and stress—controlling the production of reproductive and stress hormones and regulating hunger, thirst, and other metabolic mechanisms. Thus, sex differences in brain function have been viewed largely in connection with biological factors associated with reproduction, regulation, and metabolism. However, since the 1980s, emerging evidence suggests much broader sex-related variations in brains, from molecular to systems levels, and has led to the notion of true neural dimorphisms, based on mechanisms and degrees of sexual differentiation, inferring two types of brains in the same species [1,2]. These differences concern not only substructures of the hypothalamic and limbic regions related to sexual function, but extend to areas involved in higher brain functions such as cognition, memory, and affective circuits, as well as reward systems and basal ganglia function [2]. A growing number of animal and human studies, including post-mortem analysis as well as brain imaging data, have found considerable sex-related brain differences, rendering them an integral part of physiological dimorphism [3,4].

While the fundamental differences related to sex contribute to normal brain functions, without doubt, they also manifest under pathological conditions, shaping the response of neural processes and mechanisms to environmental and homeostatic challenges, including stress and brain disorders, contributing to differential susceptibility, developmental onset, and progression of a range of diseases. Indeed, numerous reports suggest that several common and devastating brain diseases differ markedly in their rate, progression, and severity between sexes, with schizophrenia and Alzheimer's disease (AD) among the most widely discussed [1,2]. While the former is prevalent in men of old ages, the latter occurs at significantly higher rates in postmenopausal women [5,6]. As key gonadal hormones, estrogens have been implicated in differential susceptibility of both sexes to these disorders, protecting women from schizophrenia and AD. The decline of estrogens after the onset of menopause, or menstrual cycle-related estrogen fluctuations, on the other hand, is thought to enhance the risk of the onset and progression of these diseases. Although there is an ongoing debate over the efficacy of these gonadal hormones as adjuvant treatment, with neuroprotective effects of estrogen considered as replacement therapy

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(ERT) [7,8], the field remains ~~is full of controversy and~~ requires in-depth research.

In AD, for instance, a significant decline of estrogens linked with menstrual pause is acknowledged as a risk factor for higher susceptibility to the disease, although until recently, there was a lack of agreement if levels of estrogens in the peripheral circulation of AD subjects differ from that in age-matched controls. The level of brain estrogens, on the other hand, is significantly lower in AD women, as compared to that of healthy [9]. Of note, the expression of aromatase, which is a key enzyme converting testosterone into estrogen in the brain, is also lower in AD brains [10,11], with a single nucleotide polymorphism in the CYP19 (aromatase) gene viewed as a major risk factor [12]. These and many other studies suggest the possibility that the protective activity of estrogens in the AD brain but not in the periphery may be compromised, leading to pathological changes. In schizophrenia, the alleged relationship of estrogen with the onset and manifestation of the disease and protective effects are even more complex. As discussed throughout this review, in females, the age of the onset of schizophrenia is 4-5 years later than that of men. Also, unlike men with a single onset peak between 18 and 24 years of age, in women, the peak of age-at-onset falls at 45-50 years and coincides with the beginning of menopause. Intriguingly, in brain imaging studies, women reveal fewer structural abnormalities, including ventricles size changes and lower temporal lobe volume [13]. As a final point, there is increasing evidence that schizophrenia, in general, has a less severe course of illness in women as compared to men, with the former showing a more favorable response to the antipsychotic treatment.

Notwithstanding the fundamental difference of etiology, pathobiology, and as well as differences in clinical manifestations between AD and schizophrenia, the alleged buffering effects of estrogen imply shared molecular targets with potential mechanistic overlap. With growing recognition of the mechanistic intersection between these two major brain disorders [14,15], the rising evidence for protective effects of estrogen warrants critical review and analysis, with the view of future experimental studies and prospective therapeutic translation.

## 2. Estrogen in the brain: A brief overview

Estrogens ((estrone (E1), estradiol (E2), and estril (E3)) exert their actions in the brain via binding to specific estrogen receptors (ERs). ERs comprise two general classes of receptors - genomic and non-genomic, which upon activation alter housekeeping, neurochemical, and electrophysiological properties of neurons in different regions of the brain. Nuclear receptors for <sup>3</sup>H-estradiol were discovered originally in the mediobasal forebrain, largely in the preoptic area and hypothalamic nuclei, but also within limbic structures such as the amygdala, and brainstem regions, including the ventral tegmentum and central grey [16-19]. The use of <sup>125</sup>I-labelled estradiol subsequently revealed binding sites in other regions as well, such as the cortex and striatum [20], some of which were found on neuronal membranes. Later, two isoforms of nuclear ERs were isolated, known as ER $\alpha$  and ER $\beta$  [21]. When bound, these receptors dimerize and activate their DNA-binding domains with palindromic estrogen response elements (EREs) or other transcription factors that ultimately induce gene transcription and subsequent protein translation. The latter can act slowly as regulatory enzymes, neurochemicals, or receptors, that alter both the local neuronal response to stimulation and the global response of neural systems that the hormone-activated neurons are part of. For example, protein-synthetic actions of estradiol that lead to ovulation and sexual behavior begin days before those events [18,22]. In contrast, binding of estradiol to the surface membrane ERs (mERs) can activate G-protein coupled ER GPER30 [23], which produce rapid changes in specific second messengers such as cAMP, inositol trisphosphate (IP3), and Ca<sup>2+</sup>, and activates the mitogen-activated protein kinases (MAPKs) ERK 1 and 2. These rapid, non-genomic effects occur within several seconds to minutes and

alter the membrane potential of neurons, thus creating neurotransmitter-like effects of estradiol. Due to excellent lipid-solubility, estrogens can have a chain of actions, first at mERs to induce short-term changes in membrane potential, followed by its effects at nuclear ERs, causing long-term changes in protein synthesis and neuronal function (Fig. 1).

In females, the main source of brain estradiol is ovaries. Upon release in the bloodstream, estradiol is transported through the circulation via steroid hormone binding globulins (SHBGs), which also bind the androgens testosterone and dihydrotestosterone. In reproductive women, circulating estradiol levels vary between 130 and 400 pg/ml depending on the menstrual cycle phase and individual differences. Approximately 20 to 40% of circulating ovarian estradiol is taken to the brain by SHBGs, with the rest having peripheral actions in muscle, skin, bone, uterus, clitoris, etc. In both females and males, however, circulating androgens can be metabolized into estradiol by the enzyme aromatase, which is enriched in neurons of the preoptic area, bed nucleus of the stria terminalis, thalamus, ventromedial hypothalamus, medial amygdala, and hippocampus, and appears critical for local synthesis of estradiol from androgens of systemic and neuronal origin. Peripheral levels of estradiol and testosterone in both sexes are critically dependent upon age (Fig. 2A). Estradiol output from ovaries changes dynamically across the ovulatory/menstrual cycle. In women, the cycle begins with a progressive rise in estradiol during the follicular phase and peaks a few days before ovulation. Estradiol dips through ovulation, then rises during the luteal phase, followed by fall off before menstruation. A similar pattern is observed in female rats, albeit compressed into a 4-day cycle.

Although the role of estradiol via both genomic and nongenomic effects have been studied most extensively in the context of female sexual behavior [18,22], sexual differentiation [24], and cognition in aging [25-27], there is considerable evidence for its general neuroprotective effects, with relevance to the treatment of AD and schizophrenia. Despite its ability to mobilize intracellular Ca<sup>2+</sup>, estradiol has overall protective effects on neurons, by preventing the formation of reactive oxygen species (thus reducing oxidative stress) in mitochondria, maintaining mitochondrial membrane integrity, and averting the apoptotic release of cytochrome *c* [28]. Additionally, two convergent intracellular signaling pathways used by estradiol and IGF-1, the MAPK/ERK and phosphatidylinositol-3-kinase/Akt (PI3K/Akt) systems, are neuroprotective [29]. Moreover, functions of different transmitter systems of the brain can be altered by fluctuating estradiol concentrations during the ovulatory—menstrual cycle. These include oxytocin, vasopressin, melanocortins, opioids, dopamine, noradrenaline, serotonin,  $\gamma$ -aminobutyric acid (GABA), cannabinoids (and other arachidonic acid metabolites), and muscarinic cholinergic systems [22]. In the context of the pathobiology of AD and schizophrenia, estrogen-induced enhancement of the expression of tyrosine hydroxylase, the rate-limiting enzyme in the production of the catecholamines dopamine and noradrenaline [30], and allosteric association of membrane-bound ER $\alpha$  with metabotropic glutamate receptors (mGluRs) [31], and modulation of cholinergic activity [7] are of direct relevance.

## 3. Estrogens and schizophrenia

### 3.1. Sex and disease prevalence

Although affecting only up to 1% of the world population, schizophrenia belongs to the most burdensome and costly diseases [32]. It is a chronic, severe, and debilitating condition, with no cure available. Only about a minority of all affected (~14%) recovers fully within the first five years after the disease onset [33]. Epidemiological analysis shows that the disease is more prevalent in men than women, with the predominant age of onset in men ~ 18-25 years, ~~ie~~ on average ~ 7 years earlier than in women with the age of onset ~ 25-35 years [34]. Also, the course of the disease as well as its prognosis in men are less favor-

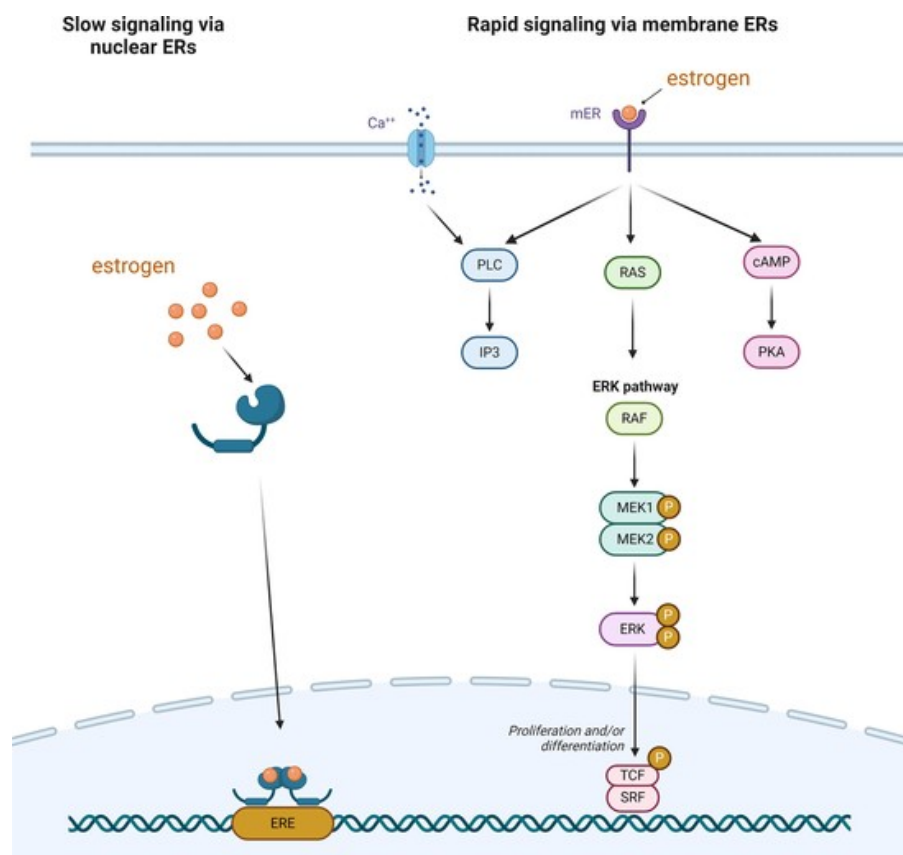


Fig. 1. Signaling pathways via nuclear and membrane estrogen receptors. The slow (genomic) signaling pathway is mediated via nuclear estrogen receptors and rapid (second messenger) signaling pathways via membrane estrogen receptors. Membrane receptors can also mediate slow genomic events via the MAPK pathway. (Figure created with BioRender.com).

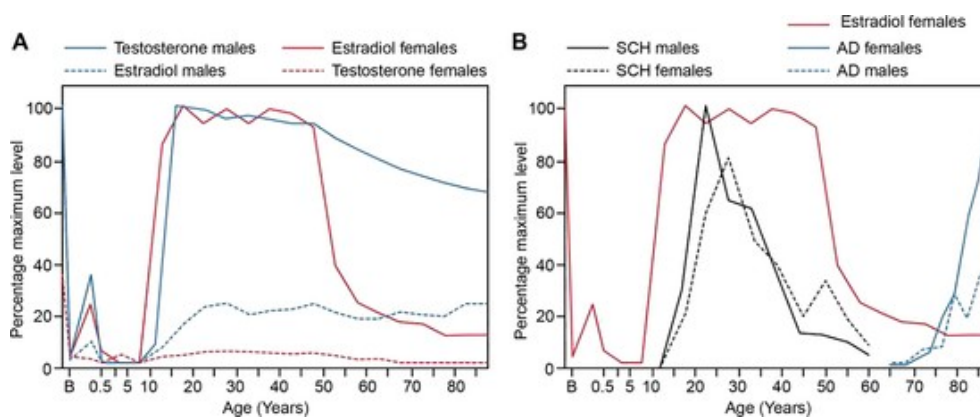


Fig. 2. Sex steroids throughout the lifetime and the disease onset and prevalence. On pane A, blood levels of estradiol and testosterone in men and women throughout the lifetime are depicted. Pane B shows the prevalence of schizophrenia and Alzheimer’s disease by age in men and women, in relation to estradiol levels during and post-reproductive periods. Note. Pane B: SCH – schizophrenia; AD – Alzheimer disease. The figure is based on data in [113].

able than in women, manifested via greater social, cognitive, and neuro-behavioral deficit [35]. Importantly, only women show a second age peak of schizophrenia onset, typically after 45 years, corresponding to the pre-menopausal period with the onset of hormonal decline [36] (Fig. 2). Based on the gender differences in susceptibility to schizophrenia and onset timing, a hypothesis of the protective role of estrogen has been proposed, which suggests that “...oestrogens raise the vulnerability threshold for the outbreak of the disease” [37]. This view is in general agreement with the observation that psychotic symptoms worsen during physiological states with low estradiol levels, i.e. after childbirth, pre- or during menstruation, as well as in women of post-reproductive age [38,39]. In men diagnosed with schizophrenia, on the

other hand, elevated levels of free testosterone and DHEA-S during the first episode of psychosis were reported in a meta-analysis [40].

While the hormonal imbalances in schizophrenic patients can be partly attributed to antipsychotic medications, changes in estrogen level and activity occur also in drug-naïve cohorts [36]. Further evidence suggests that sex steroid imbalances might not only exist before the antipsychotic medication but also well before the onset of the disease. For example, Riecher-Rössler (2002) [37] reported later onset of menarche, greater loss of hair, mid-cycle bleeding, light bleeding, hirsutism, and tendency to infertility, all before the disease onset. At a neuro-behavioral level, reports suggest prominent socio-sexual difficulties (e.g. opposite-sex involvement) in young people at high risks of

schizophrenia, long before the disease onset [41,42]. It is of note that these aspects are crucially connected to hormonal surges in puberty and sexual maturation.

### 3.2. Putative mechanisms of estrogen involvement in schizophrenia

Schizophrenia is currently conceptualized as a disturbance to the complex dopaminergic and glutamatergic interactions within the ventral tegmental area, limbic structures, and prefrontal cortex, manifested by mesolimbic dopaminergic hyperfunction, mesocortical dopaminergic hypofunction, and mesocortical glutamatergic hyperfunction [43, 44]. Besides these traditional schizophrenia pathways, recent neuroimaging studies suggest a crucial role of the nigrostriatal dopaminergic system [45] and bilateral atrophy of subcortical structures such as the hippocampus, amygdala, thalamus, and nucleus accumbens [46]. Serotonergic and muscarinic cholinergic systems are also of relevance to schizophrenia, being involved in perception/sensory gating abnormalities [47] and cognitive deficit [48], respectively. Importantly, the topographic mosaic of ER distribution in the brain aligns conspicuously with all the major structures and networks implicated in the neurobiology of schizophrenia [49] (Fig. 3), further implicating the involvement of ER in the disease. Furthermore, a high degree of co-localization of ER with D2 receptor in neuronal bodies in the arcuate nucleus of the hypothalamus, which projects to the anterior pituitary, constituting the so-called tuberoinfundibular pathway implicates the involvement of these circuits as well. Of note, functional dysregulations in these systems, together with supra-normal prolactin release, which causes amenorrhea, galactorrhea, gynecomastia, and sexual dysfunction, have been reported in antipsychotic-medicated as well as in drug-naïve schizophrenia patients [50]. Finally, a pioneering postmortem study [51] has shown a disease-specific reduction in ER $\alpha$  expression in the dorsolateral prefrontal cortex and dentate gyrus of the hippocampus in men and women, with follow up reports demonstrating differential regulation of arrays of genes associated with lower expression of ER not only in animal models but also in schizophrenia patients [52].

### 3.3. Estrogen as adjuvant therapy for schizophrenia

The positive modulation of estrogen signaling in schizophrenia patients can have a therapeutic impact. Polymeropoulos et al. [53] sug-

gested that some antipsychotics might exert their therapeutic effects via enhancement of the estrogen signaling system. To date, several well-controlled clinical trials confirmed the ameliorative effects of estrogens and selective ER modulators (SERMs) in women and men with schizophrenia [54,55]. Patients who received estrogen adjunct therapy required lower dosages of antipsychotics for symptomatic relief and showed better functional and clinical outcomes. It is of special importance that, unlike current antipsychotics targeting primarily positive symptoms, estrogens appear to improve also negative symptoms and social-cognitive aspects of patients.

Besides protective effects countering excitotoxicity, oxidative stress, inflammation, and apoptosis, estrogens may also improve dopaminergic and glutamatergic signaling, as shown in animal models [52]. These effects include normalization of D1/D2 and mGluR expression, enhancement of the transporter availability and functions (DAT, EAAT 1, and EAAT 2), and restoration of levels of DA as well as its primary and secondary metabolites, DOPAC and HVA, respectively, in selected brain regions. Upregulated 5-HT1A and downregulated 5-HT2A in the prefrontal cortex have been also reported in schizophrenia patients [56]. Estradiol replacement therapy, as shown in studies with positron emission tomography (PET), increases 5-HT2A binding in postmenopausal women [57,58] but does not affect the expression of 5-HT1A [59]. Gogos et al. (2015) have reported that pre-treatment of female rats with 17 $\beta$ -estradiol prevents prepulse inhibition abnormalities caused by blockade of 5-HT1A [60]. Blockade of muscarinic cholinergic drive mediated via M1 and M4 receptors has been also shown to alleviate cognitive and positive symptoms of schizophrenia [48]. Finally, multiple reports in animal models have suggested that 17 $\beta$ -estradiol regulates the expression of various muscarinic acetylcholine receptor subtypes [61] and stimulates both, synthesis and activity of acetylcholine esterase [62]. Beneficial effects of estrogens on neuro-behavioral phenotypes of schizophrenia (sensory-motor gating via pre-pulse inhibition, cognitive functions via object recognition test, and locomotor hyperactivity) mediated by serotonergic system have also been documented [52]. It should be noted that reports of the role of estrogens in animal models have been primarily carried out after gonadectomy, which leads to compensatory upregulation of ERs in the brain. It remains unknown whether any such changes are in play in schizophrenia patients receiving ERT. Gogos et al. (2015) reasoned that a specific reduction in the expression of ER $\alpha$  in the prefrontal cortex of patients [51] is unlikely to result from the lower peripheral levels of steroids, as decrease of estrogens in circulation is known to upregulate central ER [52]. Other mechanisms should be considered as well in this context, including the adaptive response to chronic stress. Indeed, in a study related to endocannabinoid signaling, chronic stress was shown to downregulate CB1 receptor expression and also significantly reduce hippocampal 2-arachidonylglycerol, overwhelming compensatory mechanisms [63].

## 4. Estrogen and Alzheimer's disease

### 4.1. Epidemiological and phenomenological overview

With the projected > 90 million people affected worldwide by 2050 [64,65], AD is one of the major public health care priorities. Amongst the key challenges is the heterogeneity of disease manifestation and progression among patients, with cases greatly varying by the extent of amyloid pathology and cognitive decline [66]. These variations fueled an interest in the characterization of both, genetic and phenotypic traits which predict the disease onset and progression, which should help to decide on intervention response. Genetic and phenotypic characteristics are applied in stratification and clustering for AD diagnosis and treatment, with sex-related differences receiving much interest [1]. Nonetheless, current discussions of sex differences in AD focuses primarily on epidemiological aspects. It emerged recently, that sex differences are of key relevance to the pathobiology of AD, given

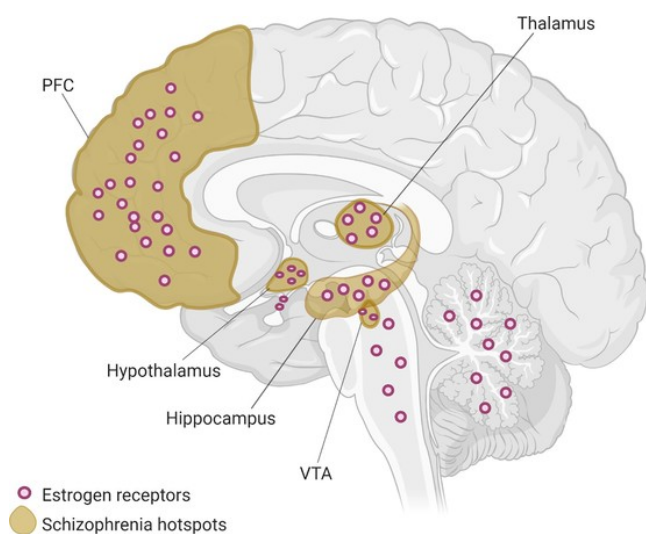


Fig. 3. Estrogen receptors topology in respect to schizophrenia. This figure shows topological overlaps between estrogen receptors' distribution in the brain and areas implicated in schizophrenia. The high degree of co-localization adds further credibility to hypotheses about the involvement of estrogen signaling in schizophrenia etiology. Note. (Figure created with BioRender.com).



the larger number of women than men affected worldwide (2:1 women:men ratio) [1,67] (Fig. 2B). While there is data suggesting that these differences could be due to environmental trends and domestic conditions, i.e. socio-economic, occupation, education, and other factors [68], considerable evidence suggests that differences in biology are also at play. The general notion is that sex differences in AD frequency are due to complex factors, which determine the longer life expectancy of women, especially after a diagnosis of AD, contributed by the low survival of men with the prevalent co-morbidities of old age [69]. This view, however, is waiting for systematic analysis.

Sex-related differences are of key relevance to differences in cognitive aging and AD, manifesting at multiple levels across the full spectrum of tests. In verbal and cognitive tests, for instance, healthy women score consistently higher in all age groups and display slower cognitive decline. This trend is typically maintained during the prodromal and amnesic mild cognitive impairment (aMCI) stage of AD but fades away with the progression of the disease [70,71]. Cognitive data from a majority of studies indicate that in clinical AD, women score lower than men in verbal memory and fluency tasks, particularly confrontation naming tasks. Hence, the lack of sex differences in memory performance observed in early stages of clinical AD indicates substantial sex-related reversal effects, with mounting data inferring faster cognitive deterioration in women over the early 2 years of the disease, with disease progression twice as fast over the next 8 years [72]. These findings however need to be interpreted with caution given recent evidence obtained with the use of sex-specific cut-offs in which women, on average, score higher on verbal memory tasks [73,74]. Sundermann et al. (2019) reported recently that when sex-specific scores and cut-offs were used for MCI diagnosis, the number of women diagnosed increased by over 30%, whereas the number of men diagnosed decreased to a similar extent [73]. Importantly, in women diagnosed with MCI, but only when sex-specific cut-offs were used, imaging biomarkers of AD showed more advanced pathology than in those who were not diagnosed with MCI. On the other hand, in men diagnosed with MCI using the non-specific cut-offs but not sex-specific cut-offs, AD brain imaging biomarkers were similar to men without MCI, compared to men with MCI. It is important to note that fast-progressing cases of AD are also more prevalent in women [75]. The use of these new methods not only improves the assessment of cognitive decline in MCI, but also allows the selection of a more effective approach for differential treatment of men and women.

Finally, a comparison of neuropsychiatric symptoms among individuals with sporadic AD and related behavioral dysfunctions and mood components showed women being affected more severely than men [1]. The specific biological underpinnings of sex-related differences with greater sensitivity of women to AD remain a matter of research, with divergence in synaptic biology and mechanisms of neuromodulation, neurotrophic signaling, immune responses, and others contributing to the observed effects.

#### 4.2. Estrogen, brain, and Alzheimer disease

Neurochemical tests with functional studies showed significantly reduced levels of circulating 17 $\beta$ -estradiol and testosterone in women and men with AD, respectively [76,77]. Due to the major decline of endogenous estrogen after menopause and increase in human longevity, women on average spend almost a third of their life in deficiency of estrogen, with related disabilities. As a neuroactive steroid, estrogen has protective effects with its decline causing impairment of brain functions and mechanism [78]. Estrogen is known as a potent stimulant of neurogenesis and plasticity, with changes in its level and activity related to impairments of neuroplasticity and deficit of renewal of neurons of the dentate gyrus of the hippocampus, contributing to memory and learning deficit. In women with MCI, hippocampal atrophy has been correlated with a decline in mnemonic and cognitive function [79]. Another widely discussed mechanism that also contributes to cognitive impair-

ments during estrogen decline is the deregulation of cholinergic drive and related plasticity mechanisms. Endogenous acetylcholine plays a key role in regulating synaptic plasticity induction threshold as well as synchrony of hippocampal and cortical circuits [80,81]. Accordingly, loss of cholinergic neurons is recognized as one of the key hallmarks of AD [82,83]. Considerable data suggest that both transmitter and modulator effects of estrogen on plasticity and cognitive performance are related to, or rely upon, interactions with cholinergic transmission. The latter seem to be mediated via ER $\alpha$ , but not ER $\beta$  [84,85]. Pongrac and colleagues showed that estradiol increases high-affinity choline uptake via MAPK [86] which leads to increase in cholinergic drive. Estradiol has been reported to stimulate CREB signaling in basal forebrain cholinergic neurons in adult mice, an effect that was blocked by inhibition of MEK1/2 [87]. These findings show that estradiol can act via ER $\alpha$  to activate MAPK signaling, leading to CREB phosphorylation, with effects on a range of processes governed by cholinergic activity [7].

Neuroactive effects of estrogen have been also shown by studies of dendritic spine dynamics and neuronal morphology [88-90]. Changes in neuronal morphology are likely to impact the dynamics of neural circuits as well as synaptic integration. Induced by estrogen increase in dendritic spine numbers and synaptic contacts in the hippocampus, hypothalamic nuclei and amygdala have been implicated in amelioration of cognition in primates [91]. Overall, these findings show that estrogens via modulation of synaptic transmission and promotion of adult neurogenesis and dendritic spine plasticity could regulate higher brain function and protect against cognitive decline with memory loss of AD.

Concerning more specifically the neurobiology of AD and estrogens, the protective effect of female hormones is partly associated with the reduction of A $\beta$  toxicity [92]. The latter is mediated via promoting A $\beta$  clearance by activation of microglial phagocytosis and enhancement of A $\beta$  degradation, in addition to regulation of the levels of major proteases responsible for A $\beta$  breakdown and non-amyloidogenic processing of APP protein [14]. The regulation of APP processing by estrogens involves activation of MARK/ERK, lowering the level of BACE1, which is the rate-limiting enzyme for A $\beta$  production, also implicated in the pathobiology of AD and schizophrenia [14,93]. The protective effects of estrogen are also mediated via its anti-apoptotic action, seemingly using stimulation of the expression of anti-apoptotic Bcl-xL and Bcl-w and inhibition of pro-apoptotic Bim, and by this, protecting neurons from A $\beta$  neurotoxicity [94]. Importantly, estrogens have been also reported to lower the toxicity of hyperphosphorylated tau, known as a key component of neurofibrillary tangles. The latter involves modulation of the activity of phosphatases or kinases, including most importantly, PKA, Wnt, and GSK-3 $\beta$  [95]. In light of these complex regulatory processes, it is conceivable that a menopause-related decrease in ovarian estrogen might contribute to the onset of AD in women with their higher susceptibility.

The notion that brain-estrogen deficiency might elevate the risk of AD received further support from preclinical studies demonstrating that genetic inhibition of aromatase in female AD transgenic mice leads to acceleration of the pathology, as compared to controls [96,97]. These findings are in line with the results of studies of brain aromatase expression and polymorphisms in women, as well as with changes in estrogen activity in the brain of AD patients [12,97,98]. Accordingly, analysis of estrogen level changes in postmortem brain showed considerably lower levels in AD women as compared to age-matched healthy controls [10,99], confirming the potential role of the estrogen decline in the pathobiology of the disease. At the same time, markers for estrogen biosynthesis in AD brain, as well as serum levels of estrogens, remained unchanged, inferring a decline of brain estrogen only. The latter has been confirmed by indirect evidence, with aromatase mRNA levels found elevated in the astrocyte of AD patients [12,98]. Of note, during physiological aging, the aromatase levels in the brain are significantly increased. In agreement with the overall reduction of brain estrogen and downregulation of its functions in women with AD, the general decline

in activity of sex steroids has been reported as a common trend. Indeed, numerous reports have shown an age-related sex-independent increase in aromatase expression in brain regions with above-average susceptibility to AD, and their significant downregulation in AD [11,100]. In light of the above mentioned, the differences in brain estrogen levels in women affected with AD as compared to healthy can qualify only as suggestive of higher risks of AD in a fraction (13–15%) of aged women.

#### 4.3. Estrogen as a neuroprotective agent in AD

In concordance with the neuroprotective role of estrogen, studies in APP transgenic mice with low levels of brain estrogen developed early-onset neuropathological changes, with more severe AD-like pathology reported in ovariectomized APP females [101,102]. Experimental induction of brain estrogen deficiency caused intensified neuropathological phenotype in female mice, as compared to the ovariectomized APP line [97]. Together with discussed above clinical evidence from humans, these and numerous other studies infer the neuroprotective role of estrogen, with the menopausal reduction in its activity contributing to the higher number of AD women with the more severe manifestation of the pathology. This view is in agreement with the reported effects of surgical menopause on the development of cognitive decline and AD. Clinical studies of the association between age at surgical menopause with cognitive decline and AD pathology showed that early age at surgical menopause was significantly associated with cognitive decline and AD neuropathology [103]. ERT for at least 10 years, when administered 5-year premenopausal window had protective effects, with overall better cognitive performance. The same study showed no association of cognitive decline with natural menopause.

The notion of the protective role of estrogen is also supported by more recent clinical evidence, with emerging areas for therapeutic interventions. Accordingly, aromatase inhibitors (AIs) such as letrozole, anastrozole, and exemestane, which have been approved for the treatment of breast cancer, display neuroprotective effects against AD [104,105]. Indeed, anastrozole treatment has been reported to restore the impaired processing speed and verbal memory in postmenopausal women with breast cancer, as compared to drug-free healthy women [100,105]. Similar findings were reported by earlier studies with the use of anastrozole, with the drug-treated group, showing no impairment in cognitive performance [106,107]. Nevertheless, evidence from tamoxifen (estrogen receptor modulator) studies suggests that its administration may involve a risk for cognitive impairments, particularly in advanced-aged women [108,109]. As tamoxifen and other inhibitors of estrogen receptors interfere with estrogen receptor signaling, it was proposed that changes in brain estrogen levels and activity might be involved in cognitive impairments of AD. The results of systematic clinical trials of estrogen-containing hormone therapy in AD patients remain inconclusive, with little systematic evidence available supporting improvements of cognitive symptoms [110,111].

#### 5. Conclusion and future directions

Deficient estrogen activity in the brain seems to be a common denominator of schizophrenia and AD, two major mental disorders characterized by cognitive deficit and psychotic episodes. Both conditions show estrogen-related complex manifestations in their onset and clinical advancement. Estrogens seem to play a protective role in the brain, via various mechanisms, either acting at a slow rate, through nuclear receptors ER $\alpha$  and ER $\beta$ , or rapidly, through activation of membrane ER and MAPK signaling pathways (MAPK pathway can also deliver its effects via slow genomic signaling).

Regarding schizophrenia, there is a pressing need for medication that would target not only positive but also negative symptoms. Based on the distribution of ERs throughout the brain, which overlaps with structures involved in the pathogenesis of schizophrenia, and due to

ERs involvement in the pharmacological effect of antipsychotic medication and premorbid abnormalities, ER signaling has been implicated in the etiology of the disease, and thus, might be targeted in order to counteract, normalize and cure the disease symptoms. At this stage, however, failure to replicate findings of numerous reports (listed in [112]), render estrogen therapy as an experimental add-on treatment option.

Regarding AD, hormonal changes associated with menopausal transition and in the post-menopause period demonstrated estrogen's potential of influencing processes associated with disease manifestation and pathogenesis. There is also ample evidence that estrogens reduce A $\beta$  levels and toxicity, and optimize functions of both, neurons and glia. In animal studies, estrogen deficiency has been linked to the elevated risk of AD-like neuropathology and behavioral phenotype. Despite promising indications, randomized clinical trials failed to show that hormone therapy improves cognitive symptoms in women with AD. Unfortunately, no conclusive clinical trial data is also available to validate the critical window hypothesis, which suggests that hormone therapy initiated at a younger age, before the onset of menopause, may reduce the risk of AD.

In conclusion, estrogen therapy of both schizophrenia and AD remains experimental. Well-designed preclinical studies with convergent evidence from laboratory models, and long-term clinical trials using surrogate biomarkers of brain function and neural pathology, are needed to provide relevant answers to the conflicting findings reported in many basic and translational studies.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors of this study report no financial interests.

#### Author's contribution

R.A., J.G.P., and S.V.O. conceived the study; all three authors prepared the manuscript, reviewed, commented, and approved the final submission version.

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