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REVIEW ARTICLE

Sex differences in neuromodulatory subcortical systems and their implications for Alzheimer's disease

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Abstract

Neuromodulatory subcortical systems (NSSs) are uniquely susceptible to dementia-related pathology, leading to frequent molecular and behavioral impairments associated with altered function of these nuclei. Some of these systems display clear sex-specific cytoarchitecture and signaling leading to distinct physiology and behavioral outputs in males and females, while other regions display nominal sex differences. However, the relevance of sex differences in modulating dysfunction of NSSs in Alzheimer's disease (AD) and related dementias is not well understood. This review is a joint effort by the Neuromodulatory Subcortical Systems and Sex and Gender Differences in Alzheimer's Disease Professional Interest Areas of the Alzheimer's Association. We review sex differences in NSSs, both in non-disease states and in AD models and patients. We highlight the possible role of NSSs in driving sex-specific AD susceptibility and potential footholds for sex-based interventions targeting these systems. We conclude by outlining immediate and long-term actions to address the intersection of NSSs, sex, and AD.

KEYWORDS
acetylcholine, brainstem, corticotropin releasing hormone, dopamine, histamine, hypothalamus, neuromodulatory subcortical systems, norepinephrine, orexin/hypocretin, oxytocin, selective vulnerability, serotonin, sex differences, vasopressin

Highlights

- Neuromodulatory subcortical systems are uniquely vulnerable in Alzheimer's disease.
- Biological sex is an important factor that modulates dementia risk and progression.
- Neuromodulatory subcortical systems show sex differences in structure and function.
- Sex-dependent neuromodulatory nuclei dysfunction in dementia is understudied.

1 | INTRODUCTION

Dementias are widely recognized as disorders of severe memory decline, with the most prevalent form being Alzheimer's disease (AD). However, neuropsychiatric symptoms including anxiety, depression, social dysfunction, apathy, and sleep disturbances are highly prevalent, often emerging prior to cognitive deficits, and persist throughout the disease course.[1–3] These early symptoms point to dysfunction in neural systems beyond those canonically used for diagnosis, specifically the involvement of neuromodulatory subcortical systems (NSSs) located in the brainstem and hypothalamus. The neuromodulators produced by these nuclei are critical for regulating molecular processes and behaviors that go awry in AD.[4] Moreover, AD symptoms associated with dysfunction of NSSs appear coincident with accumulation of disease-specific pathological hallmarks in these regions.[1,4–13]

We have previously proposed that understanding the mechanisms underlying selective vulnerability of NSSs is critical for improving outcomes and treatment options targeting these systems.[4] However, biological sex is one factor that has received little attention in its potential to modulate the susceptibility of NSSs in AD. There are well described sex differences in AD, which occur more frequently in women than men and often follow a more severe clinical trajectory in women.[14–22] While women's increased longevity is frequently cited as a key contributing factor, this explanation remains controversial. For example, while animal models consistently show sex differences in neuromodulator signaling, behavioral outcomes, and vulnerability to amyloid beta (Aβ) and tau, human studies remain limited and inconsistent. This could be due to a failure to adequately account for sex-specific variables such as hormonal contraceptive use, menstrual cycle phase, or menopausal status. Such factors can significantly alter neuromodulator synthesis, turnover, and receptor expression, ultimately affecting function and dysfunction of neural circuits. Importantly, NSSs exhibit inherent sex differences in their organization, structure, signaling, and biochemical properties even under non-disease contexts. Therefore,

understanding the ways in which sex shapes NSSs form and function may be key to explaining selective vulnerability and divergent clinical outcomes in men and women, as well as to guiding the design of more precise diagnostic and therapeutic strategies.

This joint effort by the Neuromodulatory Subcortical Systems and Sex and Gender Differences in Alzheimer's Disease Professional Interest Areas of the Alzheimer's Association reviews sex differences in NSSs (Table 1). Moving forward, we will use the term "preclinical" to describe studies using cell lines, rodents, non-human primates, and other non-human subjects. Similarly, in cases in which preclinical models are discussed, we will use the terms "male/female" to refer to subjects whereas human studies will refer to participants as men/women. Finally, when discussing menopause in women, unless otherwise stated these women were spontaneously menopausal, as opposed to those that had been subject to early ovarian removal. We focus on nine key neuromodulators: acetylcholine, dopamine (DA), norepinephrine (NE), serotonin (5-HT), corticotropin releasing hormone (CRH), oxytocin (OXT), arginine vasopressin (AVP), histamine (HA), and orexin (OX)/hypocretin. These systems arise from distinct subcortical nuclei but are similar in their widespread projections to cortical and limbic regions. Their broad connectivity and susceptibility to early pathology position these regions as central influencers of molecular and behavioral symptoms of AD, in addition to disease progression. While some of these nuclei have been heavily implicated in the pathophysiology of AD (e.g., acetylcholine, DA, NE), others currently lack mechanistic depth (e.g., AVP, OXT, HA), particularly in the context of sex differences. We have therefore provided a broad overview of notable sex differences under baseline conditions and/or in AD for each NSS, along with outstanding questions to be addressed by future research (Figure 1). By further discussing these outcomes, especially in the context of sex, we may be able to better delineate mechanisms and symptoms that result in precision treatments for dementia.

2 | ACETYLCHOLINE

Acetylcholine is a neurotransmitter involved in higher order cortical processes including memory and attention.[23,24] The cholinergic system is located in two main subcortical nuclei, the basal forebrain cholinergic system (BFCS), which includes the nucleus basalis of Meynert (NBM), and the brainstem cholinergic nuclei composed of the pedunculo-pontine and lateral dorsal tegmental nuclei. Both systems possess long-range projections that innervate the majority of the cortical and subcortical regions.[25] Multiple studies reported volume loss of the BFCS with AD.[26–31] BFCS loss is particularly associated with accumulation of tau pathology, which has been hypothesized to be the initiating factor in the decline of cholinergic neurons.[8,9] Cell loss occurs relatively early in disease progression, with changes in BFCS volume predictive of future deterioration of other subcortical structures, particularly the entorhinal and perirhinal cortices.[28] Using the radiotracer [^{18}F]-FEOBV, studies have shown that cholinergic terminals throughout the cortex also decline with advancing disease stage.[32] Deterioration of cognitive abilities follows this structural loss, with deficits in ability to exert top-down control on attentional processes.[33–35] While there is less evidence for brainstem cholinergic decline than for the BCFS, *post mortem* studies of AD patients and [^{18}F]-FEOBV imaging of patients with Lewy body dementia have both shown degeneration of the brainstem cholinergic nuclei with increasing pathological burden.[36,37]

2.1 | Baseline sex differences in cholinergic system structure and function

The cholinergic system is especially relevant to the topic of sex differences in AD, as acetylcholine is modulated by estrogenic signaling, particularly via estradiol in the cortex.[38] Estradiol modulates BFCS function mainly through the estrogen receptor ERα and is responsible for increasing levels of choline acetyltransferase,[39] an enzyme crucial for the synthesis of acetylcholine. Compared to the gradual decrease of sex hormones in men, estradiol levels in women are greatly diminished after menopause, and it is believed that this loss of estradiol directly affects cholinergic integrity, which may increase the risk of developing AD for some women.[38,40]

The BFCS also shows distinctive sex differences with AD progression both in structure and function particularly early in the disease process. Structurally, BFCS atrophy differs across the sexes, both in terms of loss of neuronal density as well as in the reduction of receptor activity. Animal studies tend to focus on changes in cholinergic structure and function after ovariectomy, as it has been shown that cholinergic volumes do not differ between male and intact female animals.[41,42] In female rats, ovariectomy results in a reduction of cholinergic neurons of the NBM compared to intact female rats or those treated with unopposed estradiol.[43] Reduction of cholinergic neurons in the BFCS also leads to a reduction of cortical projections, with ovariectomized female rats displaying reductions in cholinergic innervation of the entorhinal cortex.[44] In humans, BFCS volume changes occur earlier in women compared to men.[45] Specifically, NBM volume is reduced in women compared to men that are cognitively unimpaired or have mild cognitive impairment (MCI). Notably, there was a greater reduction in NBM volume in healthy older women > 36 years of age relative to men. Furthermore, a *post mortem* study of AD patients showed that androgen receptors are lower in women compared to men, both in the vertical limb of the diagonal band of Broca, and the NBM.[46] Comparatively, there is less evidence for sex differences in the decline of the brainstem cholinergic system, beyond functional connectivity between brainstem and precuneus being preserved in men but not women with MCI.[47] However, given the nature of the early involvement of cholinergic dysfunction in the development of AD, and the impact of the hormonal shift at menopause on the cholinergic system, studies have been focused on the ability of exogenous hormones to address this imbalance.

TABLE 1 Summary of studies on sex differences in NSSs.

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Gibbs, 1998[41,$]	Sprague–Dawley rats	Male and female	No differences were seen in medial septum or NBM cholinergic neurons between sexes at any of the ages. Ovariectomized rats had lower choline acetyltransferase and trkA activity in the medial septum and NBM; estradiol partially restored choline acetyltransferase activity.
Veng et al., 2003[42,$]	F344 rats	Male and female	Young male rats had larger BFCS neurons and better spatial memory, whereas aged rats showed no differences between sexes on spatial memory or cholinergic neuron density.
Yamamoto et al., 2007[43,*]	Wistar rats	Female	Rats receiving estradiol or J 861 had higher levels of choline acetyltransferase positive neurons than ovariectomized rats.
Batallán Burrowes et al., 2022[44,*]	Long Evans rats	Female	Rats receiving estradiol had similar M_1 receptor proteins and vesicular acetylcholine transporter as intact rats, and greater protein levels compared to ovariectomized rats.
Gibbs et al., 1994[49,*]	Sprague-Dawley rats	Female	Estradiol increased levels of choline acetyltransferase in the medial septum and NBM, and reduced nerve growth factor and trkA in the hippocampus, medial septum, and NBM.
Gibbs et al., 1998[64,*]	Sprague-Dawley rats	Female	Rats given estradiol performed better than sham under scopolamine or lorazepam challenge on passive avoidance task.
Rapp et al., 2003[68,*]	Rhesus macaques	Female	Monkeys given estradiol performed better on spatial and working memory tasks than monkeys given vehicle.
Gibbs, 2000[48,*]	Sprague-Dawley rats	Female	Rats given estradiol or estradiol and progesterone performed better than vehicle on a spatial memory task. Early initiation of estradiol and progesterone resulted in better performance than later initiation.
Vongher & Frye, 1999[85,*]	Long Evans rats	Female	Rats given estradiol and progesterone performed better on water maze compared to rats given vehicle. Estradiol and progesterone improved choline acetyltransferase significantly compared to estradiol alone or vehicle.
Ishunina et al., 2002[46,$]	Human *post mortem*	Men and women	In women with AD, androgen receptors were significantly reduced in the NBM and vertical limb of the diagonal band of Broca compared to men with AD.
Shi et al., 2024[45,$]	Human	Men and women	Significant early changes in basal forebrain volume were observed between MCI and healthy controls for women only. Longitudinal reduction in volumes were seen only in healthy control women.
Smith et al., 2011[53,*]	Human	Women	The group receiving estradiol and progesterone showed increased cholinergic uptake in hippocampus and posterior cingulate versus estradiol alone or placebo.
Norbury et al., 2007[54,*]	Human	Women	Compared to premenopausal women, postmenopausal women had lower muscarinic acetylcholine receptor density. Estradiol users had higher muscarinic acetylcholine receptor density compared to non-users.
Dumas et al., 2006[65,*]	Human	Women	Estradiol pretreatment attenuated cognitive impairment under anticholinergic challenge more than placebo.
Dumas et al., 2012[66,*]	Human	Women	There was increased cortical activation during working memory task under anticholinergic challenge. Estradiol treatment reduced cortical activation compared to placebo.

(Continues)

TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Dumas et al., 2008[67,*]	Human	Women	Estradiol pretreatment attenuated cognitive impairment under anticholinergic challenge in younger but not older women.
Conley et al., 2022[78,*]	Human	Women	Higher endorsement of cognitive complaints was associated with worse performance under anticholinergic blockade.
Espeland et al., 2004[81,*]	Human	Women	Women who received conjugated equine estrogen performed worse on the Modified Mini-Mental State Examination.
Shumaker et al., 2004[82,*]	Human	Women	Treatment with conjugated equine estrogen with or without medroxyprogesterone caused higher dementia risk compared to placebo.
Sherwin & Grigorova, 2011[86,*]	Human	Women	Combined treatment with conjugated equine estrogen and micronized progesterone resulted in better working memory performance versus other treatments.
Conley et al., 2024[88,*]	Human	Women	Micronized progesterone interferes with the ability of estradiol to mitigate anticholinergic blockade
Dopamine			
Andén et al., 1964[89,*]	Albino and hooded rats	Unspecified	Dopaminergic neurons originating in the substantia nigra terminate in the striatum.
Swanson, 1982[90,*]	Albino rats	Male	Independent populations of aminergic and non-aminergic neurons in the VTA project to nuclei in the telencephalon, diencephalon, and brainstem.
Kritzer & Creutz, 2008[105,$]	Sprague–Dawley rats	Male and female	Expression of androgen and ERs in mesocortical projection neurons varied by region, cell, and sex. 30% of mesocortical projection neurons were dopaminergic in males; in females the proportion was 54%.
Walker et al., 2000[106,$]	Sprague–Dawley rats	Male and female	Electrical stimulation of medial forebrain bundle in vivo and ex vivo elicited significantly more DA release in the caudate nucleus of females than males. DA reuptake was also faster in females, while DA receptor affinity was no different between males and females.
Xiao & Becker, 1994[109,$]	Holtzman rats	Male and female	Female rats had significantly higher extracellular striatal DA concentrations in proestrus and estrus than in diestrus or after gonadectomy. Orchidectomy had no effect on extracellular striatal DA concentrations in male rats.
Locklear et al., 2017[111,†]	Sprague–Dawley rats	Male and female	Orchidectomy led to higher rates of burst firing in VTA neurons of male rats in a testosterone-sensitive, estrogen-insensitive manner. Orchidectomy also increased burst firing in PFC neurons that project to the VTA in a testosterone-sensitive manner. Gonadally intact males and females exhibited no differences in burst firing dynamics of VTA neurons.
Kokras et al., 2018[112,$]	Wistar rats	Male and female	Sex differences in the open field test and forced swim test were eliminated by gonadectomy but not aromatase inhibition. Aromatase inhibition did, however, decrease NE and DA turnover rates in the hippocampus and PFC of male and female rats. Aromatase inhibition also enhanced serotonergic turnover rates in the hippocampus of males and females, irrespective of gonadectomy.

(Continues)

TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Aubele & Kritzer, 2011[113,*]	Sprague–Dawley rats	Male	PFC extracellular DA levels were significantly lower in male rats 4 days after gonadectomy, but supplementation of both estradiol and testosterone to gonadectomized males maintained PFC DA at control levels. PFC extracellular DA levels were significantly higher in male rats 28 days after gonadectomy compared to intact controls. Testosterone, but not estradiol, supplementation maintained PFC DA concentrations at control levels for long-term gonadectomized rats. Neither short- nor long-term gonadectomy affected motor cortex DA concentrations.
Aubele & Kritzer, 2012[114,*]	Sprague–Dawley rats	Male	Findings showed that VTA neurons that project to the PFC express androgen receptors in male rats. PFC infusion of an AMPA receptor antagonist led to lower levels of PFC DA in intact males and gonadectomized males treated with testosterone propionate, but not in gonadectomized males that received either estradiol or vehicle. PFC infusion of NMDA receptor antagonists led to higher levels of PFC DA in intact males and gonadectomized males treated with testosterone propionate, but decreased PFC DA levels in gonadectomized male rats that received either estradiol or vehicle.
Nobili et al., 2017[122,*]	Tg2576 mice	Male	Tg2576 mice exhibited an age-dependent loss of dopaminergic VTA (but not SNpc) neurons at pre-plaque stages. VTA neuron loss was associated with lower DA release in the hippocampus and nucleus accumbens shell and impairment in CA1 synaptic plasticity, memory performance, and food reward processing.
Nam et al., 2018[124,*]	CD11b-expressing cells from C57Bl/6 mice	Unspecified	DA was able to modulate metal ions, metal-free Aβ, metal-bound Aβ, and reactive oxygen species through its own oxidative transformations. Moreover, DA combatted oxidative stress by reducing induction of inflammatory mediators and upregulating expression of the antioxidant-producing enzyme heme oxygenase-1.
Lansdell et al., 2023[126,$]	5xFAD mice	Male and female	Female 5xFAD mice had a higher striatal plaque density and exhibited more hyperactivity than males. Hyperactivity was correlated with higher striatal plaque burden and changes in DA signaling in the dorsal striatum.
Habibi et al., 2024[130,*]	Wistar rats	Female	Ovariectomy and AD-like phenotype caused cognitive impairment, altered protein expression, and decreased antioxidant marker levels compared to controls. Estrogen therapy and/or treatment with young plasma therapy restored these outcomes to control levels in ovariectomized rats.
Pacelli et al., 2015[131,*]	Neurons from TH-GFP mice cultured in vitro	Unspecified	Compared to VTA or olfactory bulb dopaminergic neurons, those of the SNpc had a higher basal rate of mitochondrial oxidative phosphorylation, a smaller reserve capacity, and an elevated level of oxidative stress, in part due to the complexity of their axonal arborizations.
Pissadaki & Bolam, 2013[132,*]	Digitally simulated neurons modeled after rat dopaminergic neurons	Male	Energy cost of axon potential propagation and recovery of the membrane potential increased with the size and complexity of the axonal arbor. This suggests that the complex arborizations of SNpc neurons heighten energy requirements. Electrophysiological properties of the model were based on findings from adult male rats.

(Continues)

TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Manza et al., 2022[102,$]	Human	Men and women	Women have higher DA release in ventral striatum relative to men. No sex differences in dorsal caudate DA release or in D2/3 receptor density in either ventral striatum or dorsal caudate.
Kaasinen et al., 2001[99,$]	Human	Men and women	Women have higher D2 receptor density in frontal cortex compared to men.
Pohjalainen et al., 1998[95,$]	Human	Men and women	Women have lower striatal D2 receptor affinity compared to men. There was no sex difference in D2 receptor density.
Laakso et al., 2002[100,$]	Human	Men and women	Women had higher DA synthesis capacity in caudate, trending in putamen, compared to men.
Munro et al., 2006[104,$]	Human	Men and women	Men had higher DA release compared to women in ventral striatum, caudate, and putamen. No sex differences in baseline D2/3 receptor density. Men also rated the positive effects of amphetamine higher than women.
Jacobs & D'Esposito, 2011[107,*]	Human	Women	Effects of estradiol on an N-back working memory task depend on baseline DA, measured with a catechol-O-methyltransferase polymorphism as a proxy for prefrontal DA function.
Pirskanen et al., 2005[127,$]	Human	Men and women	Several genotypes at the ERβ gene locus were more frequent in women with AD relative to healthy women controls, while genotype frequency did not differ for men AD patients compared to men controls.
Oveisgharan et al., 2023[128,$]	Human *post mortem*	Men and women	ER DNA methylation and RNA expression in dorsolateral PFC related to cognitive decline and AD pathology. Results were most pronounced in women, less robust in men.
Brown et al., 2012[97,$]	Human	Men and women	Men smokers had lower striatal D2 receptor availability compared to both women smokers and men non-smokers, while women smokers and women non-smokers did not differ in receptor availability.
Iwaki et al., 2021[98,$]	Human	Men and women	Across several cross-sectional and longitudinal cohorts, female Parkinson's disease patients were more likely to develop dyskinesia, whereas men were more likely to have more difficulties in daily living over time and more cognitive impairment.
Lavalaye et al., 2000[101,$]	Human	Men and women	Women had higher striatal DA transporter density compared to men.
Mozley et al., 2001[103,$]	Human	Men and women	Women had higher DA transporter availability in caudate, which related to better verbal learning performance.
Taylor et al., 2023[108,†]	Human	Men and women	Women who use hormonal contraceptives had higher DA synthesis capacity compared to participants who did not use hormonal contraceptives. Higher DA synthesis capacity was related to greater cognitive flexibility across both groups.
Kemppainen et al., 2003[115,*]	Human	Men and women	In AD patients, hippocampal D2/3 receptor density was lower compared to controls. Higher receptor density was associated with better memory performance in both groups.
Nagaraja & Jayashree, 2001[116,*]	Human	Men and women	The DA agonist piribedil improved cognition in older individuals with MCI.

(Continues)

TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Ciampa et al., 2024[118,†]	Human	Men and women	A genetic polymorphism in the DA transporter gene and a polymorphism in the BDNF gene interacted to predict greater cross-sectional and longitudinal PET measures of Aβ and tau pathology and hippocampal atrophy.
Roussotte et al., 2015[119,*]	Human	Men and women	AD patients were significantly more likely than patients with MCI or healthy controls to carry a DA transporter gene polymorphism associated with greater expression in vitro. This allele was associated with poorer cognitive performance and faster ventricular expansion.
Beach et al., 2012[120,*]	Human *post mortem*	Men and women	A higher striatal plaque density score was highly correlated with a Braak neurofibrillary tangle stage of V or VI and presence of dementia.
Stratmann et al., 2016[121,*]	Human *post mortem*	Men and women	Tau pathology was present in subcortical dopaminergic nuclei in Braak stage 0 and I AD patients.
Norepinephrine			
Evans et al., 2024[168,$]	5xFAD mice	Male and female	LC chemogenetic silencing and chronic beta-blocker treatment increased central nervous system inflammation and impaired memory. Microglia adrb2 knockdown attenuated inflammation in females only.
Braun & Feinstein, 2019[173,*]	5xFAD mice	Male	Vindeburnol treatment in male 5xFAD mice reduced amyloid burden, normalized exploratory and anxiety-like behavior, and likely restored LC–NA function through cAMP-dependent BDNF signaling.
Kelly et al., 2019[169,*]	Tg344-AD rats	Male and female	LC fiber loss in Tg344-AD rats led to spatial and working memory deficits, blood–brain barrier disruption, increased Aβ, and vascular remodeling.
Ross et al., 2019[189,$]	CRH overexpressing mice	Male and female	CRH overexpression increased $A\beta_{1\text{-}42}$ accumulation in LC somatodendrites and PFC terminals. In the PFC, Aβ in NE axon terminals was increased in female CRH overexpressing mice. Additionally, swollen microvessels with lipid-laden vacuoles were detected in female CRH overexpressing mice, a sign of blood–brain barrier dysfunction.
Kummer et al., 2014[170,*]	APP/PS1 crossed with Ear2 KO mice	Male and female	Genetic LC neuron loss in APP/PS1 mice caused NE depletion, synaptic plasticity deficits, and spatial memory impairments independent of Aβ pathology. NE supplementation partially reversed deficits.
Hammerschmidt et al., 2013[171,*]	APP/PS1 crossed with DBH KO mice	Male and female	Genetic NE depletion in APP/PS1 mice exacerbated spatial memory deficits and long-term potentiation impairment without increasing Aβ or causing LC neurons loss.
Kalinin et al., 2007[172,*]	V717F-APP mice	Male	LC lesions in male V717F-APP mice increased Aβ plaque load, glial activation, and amyloid precursor protein C-terminal fragments. NE deficiency reduced neprilysin activity and microglial Aβ clearance.
O'Neil et al., 2007[161,*]	APP/PS1 mice	Female	Aged female APP/PS1 mice showed a 24% loss of LC neurons and fiber loss in cortex and hippocampus, which was absent in younger mice.
Heneka et al., 2006[160,*]	APP23 mice	Female	LC degeneration in female APP23 mice elevated glial activation, Aβ plaque load, neuronal death, and cognitive deficits.

(Continues)

TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Flynn et al., 2025[179,$]	LC-htauE14 in TH-Cre rats	Male and female	Probiotic supplementation improved spatial learning, reduced inflammation in htauE14 rats, and inhibited GSK-3β activity in female rats. Female htauE14 rats had greater GFAP expression. Microbiome analyses were conducted in females only.
Omoluabi et al., 2025[181,$]	LC-htauE14 in TH-Cre rats	Male and female	LC htauE14 caused mitochondrial and memory deficits, rescued by L-type calcium channel blockade. snRNA-seq revealed alterations linked to synaptic and ion channel function in males and changes in metabolism and development in females. DBH was upregulated in the male LC.
Kelberman et al., 2023[177,*]	TgF344-AD rats	Male and female	LC neurons showed early hyperactivity in foot-shock induced firing, followed by hypoactivity with age.
Omoluabi et al., 2021[182,*]	LC-htauE14 in TH-Cre rats	Male and female	Phasic LC activation prevented tau-induced behavioral deficits and LC axonal degeneration. Stress-like tonic patterns worsened LC neuronal health and was associated with depressive behavior.
Ghosh et al., 2019[180,*]	LC-htauE14 in TH-Cre rats	Male and female	LC hyperphosphorylated tau model mimicking human pretangle origin. LC htau expression caused age-dependent olfactory learning deficits, axonal loss, and tau spread.
Ahnaou et al., 2019[175,*]	P301L mice with LC K18 fibrils	Male	LC tau seeding induced early, progressive disruption of hippocampal CA1 network activity without detectable tau spread.
Rorabaugh et al., 2017[176,*]	TgF344-AD rats	Male and female	LC pretangle tau accumulation occurred before hippocampal or cortical tau pathology, accompanied by axonal loss and NE deficits without frank neuron loss. Chemogenetic LC activation restored reversal learning.
Iba et al., 2015[174,*]	PS19 mice with LC tau fibrils	Male and female	LC tau seeding led to early ipsilateral tau pathology and neuron loss by 6–12 months, with contralateral LC showing tau clearance. Tau spread followed LC connectivity but spared hippocampus and entorhinal cortex.
Iversen et al., 1983[190,*]	Human *post mortem*	Men and women	Patients with AD dementia displayed ≈ 60% reduction in LC cells compared to controls.
Pearson et al., 1983[191,*]	Human *post mortem*	Unspecified	Localization of catecholaminergic neurons in the human brainstem by using tyrosine hydroxylase immunocytochemistry.
Kemper et al., 1987[192,*]	Human *post mortem*	Unspecified	Localization of adrenergic and noradrenergic neurons in the human brainstem by using DBH immunocytochemistry.
German et al., 1988[193,*]	Human *post mortem*	Unspecified	Computer-assisted estimation of the number of LC cells and their spatial distribution in the human brainstem.
Chan-Palay & Asan, 1989[194,*]	Human *post mortem*	Men and women	Patients with AD displayed a rostro-caudal gradient of LC neuronal loss, while patients with Parkinson's disease displayed uniform and more severe loss of LC neurons.
Chan-Palay & Asan, 1989[195,*]	Human *post mortem*	Men and women	Computer-assisted quantification of the morphology and distribution of LC neurons, with a description of four classes of LC neurons (large multipolar, large elliptical bipolar, small multipolar, and small ovoid bipolar).
Baker et al., 1989[196,*]	Human *post mortem*	Unspecified	Computer-assisted estimation of the number of LC and subcoeruleus cells in the human brainstem.
Chan-Palay, 1991[197,*]	Human *post mortem*	Men and women	Patients with Parkinson's disease displayed severe loss of LC neurons compared to controls.

(Continues)

TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
German et al., 1992[198,*]	Human *post mortem*	Men and women	Patients with AD and Down syndrome displayed a rostro-caudal gradient of LC neuronal loss, while patients with Parkinson's disease displayed uniform loss of LC neurons.
Kubis et al., 2000[199,*]	Human *post mortem*	Men and women	Scarce LC neuronal loss is observed across normal aging.
Busch et al., 1997[200,*]	Human *post mortem*	Women	LC neurons showed early susceptibility to neurofibrillary tangle formation, but significant neuronal loss appeared at least 25 years later.
Vijayashankar & Brody, 1979[201,*]	Human *post mortem*	Men	After age 63, LC neuronal population decreased by 40%.
Mouton et al., 1994[202,*]	Human *post mortem*	Men	Older age was not associated with the total number of pigmented LC neurons or their size.
Ohm et al., 1997[203,*]	Human *post mortem*	Men	Total number of LC cells was not associated with older age or early neurofibrillary changes. There were no hemisphere differences in the number of LC neurons.
Mann & Yates, 1979[204,†]	Human *post mortem*	Men and women	Older age was associated with a 5%–10% decrease in LC nucleolar volume and a decrease in melanin content. No sex differences were observed in LC nucleolar volume or melanin content.
Wree et al., 1980[205,$,†]	Human *post mortem*	Men and women	Older age was associated with a loss of LC neurons. The left side of the LC contained more neurons than the right. No sex differences were observed in total number of LC neurons, but loss of LC cells begins earlier in men than women.
Tomlinson et al., 1981[206,$]	Human *post mortem*	Men and women	Controls displayed a gradual loss of LC neurons from middle to old age. Patients with AD displayed more severe LC neuronal loss, particularly when Aβ was present in the neocortex. There were slightly higher numbers of LC neurons in control women than control men.
Braak & Del Tredici, 2011[138,*]	Human *post mortem*	Men and women	38 out of the 42 cases aged < 30 displayed pretangle tau material in the LC; 19 of those cases displayed pretangle tau material in the LC in the absence of pretangle tau material in the transentorhinal region.
Braak et al., 2011[5,*]	Human *post mortem*	Men and women	By age 40, pretangle tau material was present in the LC in all 2332 cases examined.
Buchman et al., 2012[207,*]	Human *post mortem*	Men and women	LC neuronal density was associated with the severity of global parkinsonism proximate to death.
Dugger et al., 2012[208,*]	Human *post mortem*	Men and women	LC neuronal loss was more pronounced in Lewy body dementia patients than in AD or controls. LC neurons were more vulnerable to α-synuclein in Lewy body dementia and to tau pathology in AD.
Keren et al., 2015[209,*]	Human *post mortem*	Men and women	Cross-validation of a 7T LC-sensitive MRI sequence with histological localization of LC neuromelanin cells.
Eser et al., 2018[210,*]	Human *post mortem*	Men and women	Progressive supranuclear palsy and corticobasal degeneration patients showed more tau inclusions in LC neurons than AD patients, but AD patients displayed more extreme LC neuronal loss.
Theofilas et al., 2018[211,*]	Human *post mortem*	Men and women	Intraneuronal caspase activation and macroautophagy markers in the LC emerge in early Braak stages and increase with stage progression.
Ehrenberg et al., 2018[1,*]	Human *post mortem*	Men and women	Neuropsychiatric symptoms of agitation, anxiety, appetite changes, depression, and sleep disturbances emerged as early as in Braak I–II stages and correlated with tau but not Aβ pathology.

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TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Oh et al., 2019[212,*]	Human *post mortem*	Men and women	AD patients displayed substantial loss of LC neurons, which was not observed in progressive supranuclear palsy and corticobasal degeneration patients.
Zahola et al., 2019[213,*]	Human *post mortem*	Men and women	A reduction in secretagogin expression in the LC was observed starting from Braak stages III–IV and paralleled the loss of tyrosine hydroxylase.
Tong & Chen, 2021[214,*]	Human *post mortem*	Men and women	LC neuronal loss was associated with the occurrence of dyskinesia in advanced Parkinson's disease patients.
Oh et al., 2022[10,*]	Human *post mortem*	Men and women	AD patients showed greater loss of LC neurons compared to progressive supranuclear palsy. Higher number of LC neurons was associated with shorter total sleep time and greater REM latency.
Murray et al., 2022[215,*]	Human *post mortem*	Men and women	Lower LC neuronal density was associated with higher plasma p-tau$_{181}$ and higher plasma p-tau$_{217}$.
Gilvesy et al., 2022[6,*]	Human *post mortem*	Men and women	Dendritic atrophy was the first sign of degeneration of LC tau-positive neurons. Tau pathology was more pronounced in the dorsal LC.
Torso et al., 2023[216,*]	Human *post mortem*	Men and women	LC hypopigmentation was associated with worse cortical diffusivity metrics.
Beardmore et al., 2024[217,*]	Human *post mortem*	Men and women	Increasing Braak stage was associated with LC neuronal loss, increased microglial markers, and reduction in neuromelanin.
Bueichekú et al., 2024[137,*]	Human *post mortem*	Men and women	LC tangle density was related to tangles in medial temporal lobe structures and in the inferior temporal cortex.
Fructuoso et al., 2025[218,*]	Human *post mortem*	Men and women	LC neuronal loss was most pronounced in AD and Parkinson's disease patients. AD patients further displayed endosomal alterations, while Parkinson's disease and Down syndrome patients exhibited lysosomal changes. Down syndrome patients showed elevated levels of a kinase involved in neurodegenerative processes.
Hary et al., 2025[219,*]	Human *post mortem*	Men and women	LC tau accumulation was present from Braak stages I and II. Tau pathology was most severe in the middle portion of the LC.
Theofilas et al., 2017[165,†]	Human *post mortem*	Men and women	LC volume decreased by 8.4% for each increase in Braak stages. LC neuronal population started to decrease from Braak stages III to VI. These effects were more pronounced in the middle and rostral LC. No age-related changes were observed in Braak stages 0–I. No sex differences were observed in LC volume or in number of LC neurons.
Wilson et al., 2013[162,†]	Human *post mortem*	Men and women	Higher LC neuronal density was associated with slower rate of cognitive decline, while higher LC tangle density was associated with faster cognitive decline. LC neuronal density further moderated the association between Lewy bodies and cognitive decline. No sex differences were observed in number of LC neurons or in number of hyperphosphorylated tau-positive LC neurons.
Wilson et al., 2013[220,†]	Human *post mortem*	Men and women	Higher density of Lewy bodies in the LC was associated with more depressive symptoms, while neither LC tangle density nor the number of LC tyrosine hydroxylase-immunoreactive neurons were associated with depressive symptoms. No sex differences were observed in number of LC neurons or in number of hyperphosphorylated tau-positive LC neurons.

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TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Kelly et al., 2017[163,†]	Human *post mortem*	Men and women	MCI and AD patients displayed reductions in genes regulating mitochondrial function and neuritic/structural plasticity compared to controls. No sex differences were observed in number of LC neurons.
Kelly et al., 2021[221,†]	Human *post mortem*	Men and women	LC neuronal oxidative stress and pontine arteriolosclerosis differentiated healthy controls with high pathology from MCI patients. No sex differences were observed in number of LC neurons.
Jacobs et al., 2021[222,†]	Human *post mortem*	Men and women	MCI and AD patients exhibited greater LC tangle density compared to controls, but no overall group difference was observed for LC neuronal density. LC tangle density was associated with increased cortical Aβ density and Thal phase. No sex differences were observed in number of LC neurons or in LC tangle density. Low LC intensity was related to elevated tau and Aβ burden as well as AD-related memory decline. No sex differences were observed in LC intensity.
Beckers et al., 2024[223,†]	Human *post mortem*	Men and women	Tangle density in the left versus right LC was equivalent across individuals with or without AD pathology, but neuronal density was higher in the left caudal LC among individuals with AD pathology. No sex differences were observed in number of LC neurons or in LC tangle density.
Ehrenberg et al., 2017[11,†]	Human *post mortem*	Men and women	Approximately 8% of LC neurons displayed hyperphosphorylated tau intraneuronal cytoplasmic inclusions in Braak stage 0. The proportion of tau-positive LC neurons was higher in late Braak stages compared to early Braak stages. No sex differences were observed in number of hyperphosphorylated tau-positive LC neurons.
Freeze et al., 2023[224,$]	Human *post mortem*	Men and women	LC hypopigmentation was associated with higher odds of cerebral amyloid angiopathy and arteriolosclerosis, independent of cortical AD pathology. Men had a higher probability of displaying LC hypopigmentation compared to women.
Van Egroo et al., 2024[225,$]	Human *post mortem*	Men and women	*Ante mortem* 24-hour rest–activity rhythm fragmentation was associated with increased odds of LC hypopigmentation, particularly in individuals with cortical AD pathology and independently of comorbid pathologies. Men showed higher probability of LC hypopigmentation compared to women.
Trujillo et al., 2019[227,†]	Human	Men and women	Low macromolecular content in the LC contributed to contrast derived from 2D-T1-weighted turbo-spin-echo sequence with magnetization transfer contrast. No sex differences were observed in LC intensity.
Betts et al., 2017[226,†]	Human	Men and women	Description of a novel T1-weighted fast low angle shot MR sequence at 3T to investigate the LC along its rostrocaudal axis. Older adults showed regional increase in maximum (but not median) LC intensity confined to the rostral third of the LC. No sex differences were observed in LC intensity.
Berger et al., 2023[237,†]	Human	Men and women	LC intensity was higher in older than younger adults, whereas LC activity during an oddball task showed no age-related differences. No sex differences were observed in LC intensity.
Takahashi et al., 2015[238,†]	Human	Men and women	LC intensity was reduced in patients with MCI and AD compared to cognitively normal individuals. No sex differences were observed in LC intensity.

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TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Calarco et al., 2022[239,†]	Human	Men and women	LC intensity showed no significant association with age and was not different between older adults with and without late-life depression. LC intensity was correlated with cognitive performance. No sex differences were observed in LC intensity across any group.
Liu et al., 2019[240,†]	Human	Men and women	A quadratic relationship between LC intensity and age was described, with a peak occurring at ≈ 60 years. Age-related decline in LC intensity was restricted to the rostral part of the LC. No sex differences were observed in LC intensity.
Shibata et al., 2006[241,†]	Human	Men and women	A quadratic relationship between LC intensity and age was described, with a peak occurring at ≈ 59 years. No sex differences were observed in LC intensity.
Jacobs et al., 2023[166,†]	Human	Men and women	LC intensity started to decrease 12 years before clinical onset in presenilin-1 E280A carriers. High LC intensity was associated with low cortical tau and high memory performance in carriers compared to non-carriers. No sex differences were observed in LC intensity across any group.
Riley et al., 2025[242,$]	Human	Men and women	A quadratic relationship between LC intensity and age was described, with a peak occurring at ≈ 60 years. Greater rostral LC intensity was associated with greater fluid cognition in participants above the 50th percentile for age. Rostral LC intensity was higher in women compared to men and in Black participants.
Bachman et al., 2023[243,$]	Human	Men and women	Five weeks of heart rate variability biofeedback training decreased LC intensity in young adults, which was further associated with reduced sympathetic nervous system activity. Higher LC intensity was observed in young women compared to young men.
Bachman et al., 2021[244,$]	Human	Men and women	In older adults, lower LC intensity was related to greater cortical thickness in parietal, frontal, and occipital regions. Higher LC intensity was observed in women compared to men.
Galgani et al., 2025[245,$]	Human	Men and women	Women showed higher LC intensity than men in cognitively normal and MCI participants. Men exhibited a positive association between LC intensity and volume in frontotemporal area compared to women.
Galgani et al., 2023[246,$]	Human	Men and women	Rostral LC intensity was reduced in AD and MCI who converted to dementia during follow-up. Higher LC intensity was observed in women compared to men in cognitively normal and MCI participants who later converted to dementia.
Clewett et al., 2016[247,$]	Human	Men and women	Higher verbal intelligence and higher cognitive reserve were associated with higher LC intensity in older adults. LC intensity was higher in older adults compared to younger adults and lower in women compared to men.
Beckers et al., 2024[248,†]	Human	Men and women	At high levels of astrocyte reactivity, lower arborization complexity in LC neurites was associated with lower arborization complexity in frontotemporal cortical and subcortical regions. No sex differences were observed.
Wearn et al., 2024[249,†]	Human	Men and women	High isodendritic core microstructural integrity derived from a multiparametric mapping protocol was associated with higher white matter neurite density and arborization complexity in limbic tracts. No sex differences were observed in LC microstructure.

(Continues)

TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Bennett et al., 2024[250,†]	Human	Men and women	Maximum LC intensity was more sensitive to age than mean LC intensity and LC microstructural integrity. Higher LC microstructural integrity was associated with more consistent memory performance. Females showed lower LC microstructural integrity compared to males but no sex differences in LC intensity were observed. Age-related changes in LC intensity and microstructure were larger in men than women.
Zhang et al., 2016[251,$]	Human	Men and women	The LC and VTA/SNpc showed both shared and distinct functional connectivity patterns, with the LC enhancing attentional orienting and sensorimotor responses to salient stimuli. Lower LC functional connectivity was observed with the hippocampus, parahippocampus, and middle temporal gyrus in women compared to men.
Um et al., 2023[252,$]	Human	Men and women	At elevated frontal Aβ burden, higher LC functional connectivity was observed with the right postcentral gyrus and right supramarginal gyrus in women compared to men.
Filkowski et al., 2017[253,$]	Human	Men and women	Women showed higher functional task activation in the bilateral amygdala, hippocampus, and regions of the dorsal midbrain including the periaqueductal gray/superior colliculus and LC compared to men.
Ludwig et al., 2024[254,†]	Human	Men and women	Older adults showed increased LC responses during emotional and task-related salient events compared to younger adults. No sex differences were observed in LC functional activation in response to emotional salience, task-related salience, or memory performance.
Kilpatrick et al., 2025[†]	Human	Men and women	Higher left LC functional connectivity with the executive control network was observed in women compared to men, and was mostly driven by differences between men and premenopausal women.
Koops et al., 2025[256,†]	Human	Men and women	Higher LC metabolism was observed during preclinical stages, as defined by the presence of elevated Aβ burden, but was lower when elevated tau and cognitive impairment are present. This increase in metabolism was associated with attenuated memory decline, particularly in participants with high Aβ burden. LC metabolism decreased with age and was higher in women compared to men.
Serotonin			
Rosecrans, 1970[285,$]	CD rats and Swiss albino mice	Male and female	Females from each species have both a more functional 5-HT system and a higher rate of rearing.
Biegon & McEwen, 1982[306,*]	Sprague–Dawley rats	Female	Estradiol may have a direct effect on modifying 5-HTR availability, while exerting a slow effect on the same receptors through an interaction with intracellular estrogen receptors.
Uphouse et al., 1986[308,*]	F344 rats	Female	Differential binding of 5-HT to cortical membranes during the estrous cycle is most likely the result of 5-HT$_1$Rrather than 5-HT$_2$R. Changes in 5-HT binding in a brain area nearly devoid of sex steroid receptors suggest that the hormonal fluctuations accompanying the female estrous cycle influence brain areas other than those classically thought to regulate neuroendocrine function.
Carlsson & Carlsson, 1988[284,$]	Sprague–Dawley rats	Male and female	5-HT levels were significantly higher in females than males in the brainstem and limbic forebrain and tended to be so in the cortex. 5-HIAA levels were significantly higher in females in all five brain regions.

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TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Haleem et al., 1990[283,$]	Sprague–Dawley rats	Male and female	5-HT and/or 5-HIAA concentrations tended to be higher in female rats than in males with only substantial differences in the hippocampus where female values were 34% and 36% higher, respectively. This is consistent with 5-HT synthesis being 53% greater in female than male hippocampus.
Sumner & Fink, 1993[309,*]	Wistar rats	Female	Results showed a 290% increase in 5-HT_2R mRNA in the DRN and a 25% decrease in the medial preoptic area in response to a single injection of estradiol, implying a mechanism for estrogen's positive feedback on luteinizing hormone and prolactin release.
Sumner & Fink, 1995[305,*]	Wistar rats	Female	Estradiol significantly increases density of 5-HT_{2A}R in the cerebral cortex and nucleus accumbens of female rats.
Borisova et al., 1996[299,$]	Wistar rats	Male and female	Female rats showed higher 5-HT content and uptake in the anterior and middle hypothalamus compared to males. Neonatal castration of males eliminated this difference by increasing 5-HT levels to those seen in females.
Fink et al., 1996[304,*]	Wistar rats	Female	Estrogen stimulates an increase in D2 receptors in the striatum and density of 5-HT_{2A}R binding sites in areas of the brain concerned with the control of mood, mental state, and behavior. This may explain the efficacy of estrogen therapy or 5-HT reuptake blockers in the treating of depressive symptoms of the premenstrual syndrome and indicates sex differences in schizophrenia may be due to estrogen by way of 5-HT_{2A}R.
McQueen et al., 1997[311,*]	Wistar rats	Female	Insertion of estradiol benzoate in ovariectomized rats increases the number of cells that expressed *Slc6a4* mRNA in the DRN and increased SERT-binding sites in lateral septum, basolateral amygdala, ventral nucleus of thalamus, and ventromedial hypothalamic nucleus. SERT-binding sites in these rats were 15% lower in central periaqueductal gray.
Holschneider et al., 1998[296,*]	Sprague–Dawley rats	Female	High-dose estrogen replacement in ovariectomized rats reduced monoamine oxidase activity, an enzyme responsible for 5-HT degradation, in a tissue-specific manner, decreasing monoamine oxidase-B in peripheral organs and monoamine oxidase-A in the hypothalamus and amygdala.
Zhang et al., 1999[301,$]	Sprague–Dawley rats	Male and female	Male rats showed higher *Htr1a* mRNA in the hypothalamus and amygdala but lower levels in the hippocampus compared to females. *Htr2a* mRNA was mostly similar across sexes, except for lower expression in the female ventromedial hypothalamus, while receptor binding was higher in females' hippocampus. Gonadectomy in males increased H*tr1a* and decreased *Htr2a* mRNA, effects reversed by testosterone. These findings suggest that testosterone regulates 5-HTR expression and may contribute to sex differences in mood and stress responses.
Lu et al., 2001[290,*]	Sprague–Dawley rats	Female	DRN 5-HT neurons projecting to the medial preoptic area in female rats express ERβ, but not ERα. Number of ERβ-expressing neurons do not differ between ovariectomized and estradiol-treated groups.
Gundlah et al., 2001[291,*]	Rhesus macaques	Female	Most 5-HT (SERT positive) neurons in DRN and median raphe nucleus express ERβ mRNA and protein. ERβ expression remained stable regardless of the ovarian hormone status.

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TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Klink et al., 2002[286,$]	Sprague–Dawley rats	Male and female	The DRN 5-HT systems differ significantly between sexes and undergo changes during pregnancy and the postpartum period.
Sheng et al., 2004[298,$]	Wistar rats and C57Bl/6 mice	Male and female	Sex steroids may modulate the affective regulation of the serotonergic system through ERα and/or ERβ in 5-HT neurons of the mouse rostral DRN, but not through androgen receptors. Such effects may differ by sex and species, as suggested by the prominent sex differences in androgen receptor expression and prominent species differences in ERα and ERβ expression.
Imwalle et al., 2005[294,*]	ERβ KO mice	Female	Female mice lacking ERβ showed higher anxiety-like behavior and reduced 5-HT levels in the bed nucleus of the stria terminalis, preoptic area, and hippocampus compared to wild-type females.
Bertrand et al., 2005[310,*]	Aromatase KO mice	Female	Low estrogen conditions, induced by ovariectomy or aromatase KO, enhanced SERT function in the hippocampus despite reduced SERT density, leading to heightened sensitivity to fluoxetine.
Donner & Handa, 2009[292,*]	Sprague–Dawley rats	Female	Activation of ERβ in DRN increased *Tph2* mRNA expression, enhancing 5-HT synthesis in female rats. Systemic ERβ agonist treatment led to anxiolytic effects while direct DRN infusion promoted active stress-coping without changing anxiety levels.
Bethea et al., 2011[316,*]	Japanese macaques	Female	Three years after ovariectomy, female macaques showed reductions in 5-HT neurons, as well as *Fev*, *Tph2*, *SERT*, and *5-HT$_{1A}$* mRNA expression.
Hiroi & Handa, 2013[293,*]	RN46A-B14 cell line derived from embryonic rat medullary raphe cells and mouse-derived hippocampal cell line HT-22	Unspecified	Estradiol and ERβ agonism increased DRN *Tph2* expression through an estrogen response element within its promoter.
Philippe et al., 2022[303,†]	Sprague–Dawley rats	Male and female	Based on the hypothermal and corticosteroid responses to 8-OH-DPAT, the data suggest that stress habituation is met by an increase in the sensitivity of presynaptic 5-HT$_{1A}$R in males, and by an increase in the sensitivity of a population of postsynaptic receptors in both sexes.
Goel et al., 2014[302,$]	Sprague–Dawley rats	Male and female	Females show a greater hypothalamic-pituitary-adrenal axis response compared to males. The 5-HT$_{1A}$R agonist, WAY, reduced the corticosterone response in males but not females. WAY administration increased total Fos activation in the DRN, but only in males. There was a negative correlation between estrogen and Fos responses within tryptophan hydroxylase-positive cells in the DRN of WAY-administered females and a positive correlation found between estrogen and *Htr1a* mRNA expression localized to the region of the zona incerta in close proximity to the paraventricular nucleus of the hypothalamus.
Castañé et al., 2015[329,*]	5-HT$_{2A}$R KO and "wild-type" mice of unstated lineage	Male	Fluoxetine reduced immobility in the tail suspension test in both wild-type and 5-HT$_{2A}$R KO mice, but impaired memory in the novel object recognition test only in wild-type mice. Both genotypes showed similar increases in extracellular 5-HT, but fluoxetine enhanced pyramidal neuron activity in 5-HT$_{2A}$R KO mice only. 5-HT$_{2A}$R may contribute to fluoxetine-induced memory deficits by disrupting the excitatory-inhibitory balance in the PFC.

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TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Cao et al., 2014[297,*]	Tph2-CreER mice crossed with Esr(fl/fl) mice	Female	Estrogen replacement suppressed binge-like eating in ovariectomized females by activating DRN 5-HT neurons through ERα and inhibition of small conductance calcium-activated potassium channel currents.
Breitinger et al., 2001[327,*]	NIE-115 mouse neuroblastoma cells	Unspecified	The mechanism of the channel-opening process, receptor desensitization, and receptor inhibition by nicotine, cocaine, and fluoxetine were investigated. Two different forms of the 5-HT_3R, each with a different desensitization rate, were observed.
He et al., 2023[295,$]	Esr2(fl/fl) mice	Male and female	DRN specific ERβ deletion increased anxiety-like behavior only in females but reduced passive coping in males.
Khan et al., 2023[178,†]	htau mice	Male and female	Depressive-like symptoms were observed at 4 months in both sexes, and hyperlocomotion observed in males. These changes coincided with lower density of 5-HT neurons, downregulation of 5-HT markers, reduced excitability of 5-HT neurons, and hyperphosphorylated tau in the DRN. Inflammatory markers were upregulated in the DRN, which may promote tau phosphorylation and aggregation. Loss of 5-HT innervation to the entorhinal cortex and dentate gyrus of the hippocampus was observed, and may have contributed to depressive-like behaviors.
Tian et al., 2023[334,*]	5xFAD mice	Male and female	In 5xFAD mice, hippocampal 5-HT release was markedly reduced despite only modest decreases in serotonergic fiber density or 5-HT content. Oligomeric Aβ impaired 5-HT release by inducing mitochondrial dysfunction in 5-HT neurons.
Wang et al., 2023[340,*]	hAPP-J20 mice crossed with ePet-Cre mice	Male and female	5-HT signaling is disrupted in the hippocampus of hAPP-J20 mice, contributing to early hyperactivity of CA1 neurons. Activation of median raphe nucleus 5-HT neurons reduced CA1 hyperexcitability and improved memory through 5-HT_{1A}R- and 5-HT_{3A}R-dependent mechanisms.
Torres et al., 2024[129,$]	Esr1-Cre, Esr2-Cre, Tph2-iCreER, Rosa26-LSL-tdTomato, ER-EGFP, and ER-ZsGreen mice	Male and female	In females, estrogen promotes higher baseline activity of DRN 5-HT neurons, and suppresses their firing to alcohol, contributing to binge-like drinking. In males, exogenous estrogen blunts alcohol-induced activation of DRN 5-HT neurons and alters expression of estrogen and 5-HT-related genes in DRN. Activation of ERα- or Erβ-expressing DRN neurons reduces binge drinking in both sexes.
Murakawa et al., 2024[289,*]	Erβ-iCre mice	Female	Excitation of DRN–ERβ neurons is necessary for the decline of lordosis after estrous. Fiber photometry showed DRN–ERβ neuronal activation in response to male intromission was significantly more prolonged on day 2 compared to day 1 of estrus. DRN–ERβ neuronal excitation serves as an inhibitory modulator and is responsible for the decline in receptivity during non-estrous phases.
Khan et al., 2024[338,$]	DRN P301L Tau in ePet-Cre mice	Male and female	Human P301L tau expression in DRN 5-HT neurons led to anxiety-like behavior in both sexes but females showed greater vulnerability exhibiting additional social disinhibition, MCI, and more severe disruption of 5-HT neuron excitability.

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TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Chen et al., 2024[339,*]	5xFAD, CaMKII-Cre, and GAD2-Cre mice	Male	In 5XFAD mice, DRN 5-HT neuron excitability and projections to CA1 hippocampal neurons were reduced. Activating the DRN 5HT-CA1 pathway and 5-HT_{1B}R or 5-HT_4R alleviated depressive-like and cognitive symptoms by restoring synaptic plasticity.
Young et al., 1980[282,$]	Human	Men and women	Cerebrospinal fluid concentrations of 5-HT metabolite 5-HIAA and tryptophan were higher in women than men, suggesting greater 5-HT metabolism in women.
Tejani-Butt et al., 1995[314,*]	Human *post mortem*	Unspecified	SERT sites are decreased in the DRN (especially lateral wings), hippocampal CA2, and entorhinal cortex.
Biver et al., 1996[300,$]	Human	Men and women	Men had higher 5-HT_2R binding capacity than women, particularly in frontal and cingulate cortices.
Nishizawa et al., 1997[280,$]	Humans	Men and women	5-HT synthesis was ≈ 52% higher in men compared to women.
Kugaya et al., 2003[307,*]	Human	Women	Estrogen replacement therapy enhanced 5-HT_{2A}R binding in right PFC and anterior cingulate regions of postmenopausal women. Receptor upregulation in the inferior frontal gyrus correlated with estradiol levels.
Thomas et al., 2006[313,*]	Human *post mortem*	Unspecified	SERT density is reduced in the PFC of AD patients compared to healthy elderly and depressed subjects. SERT levels are similar between AD patients with and without major depression or between control and depressed groups.
Ouchi et al., 2009[315,*]	Humans	Men and women	In AD patients, SERT binding in the striatum and other projection areas is reduced compared to healthy controls, regardless of depression status. Depressed AD patients showed greater SERT loss and lower SERT binding correlated with higher depression scores but not cognitive impairment. SERT binding potential levels were correlated with reduced glucose metabolism in the right dorsolateral PFC in AD patients.
Cirrito et al., 2011[318,*]	APP/PS1 hemizygous mice; humans	Female; men and women	In mice, SSRIs lowered interstitial fluid Aβ by 25% and chronic citalopram treatment halved plaque burden via an ERK-dependent mechanism. In humans, prior antidepressant use correlated with lower cortical amyloid load.
Sheline et al., 2020[319,*]	Human	Men and women	Short-term escitalopram treatment reduced cerebrospinal fluid Aβ levels by 9.4% compared to placebo in cognitively normal older adults, with greater effects in participants without preexisting amyloid accumulation.
Smith et al., 2017[312,*]	Human	Men	Individuals with MCI showed reduction in SERT availability across cortical, limbic, striatal, thalamic, and sensorimotor regions compared to matched controls. This decrease was more prominent than gray matter loss or blood flow reductions and correlated with poorer auditory verbal and visuospatial memory performance.
Pierson et al., 2025[337,$]	DRN P301L Tau in C57Bl/6 mice; human *post mortem*	Male and female; men and women	Tau pathology was detected in the DRN of controls (47.37%) and AD patients (90%). In mice, targeted DRN expression of human P301L tau induced depressive-like behavior, neuronal hyperexcitability, and astrocyte activation in the DRN. Males showed broader affective disruption (reduced social interaction, reduced sucrose preference, hyperlocomotion). Females showed a selective social interaction deficit only.

(Continues)

TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Terstege et al., 2025[324,†]	Human	Men and women	The DRN of AD patients showed reduced metabolic activity. SSRI treatment is associated with lower plasma phosphorylated tau levels and improved DRN metabolism.
Mo et al., 2025[325,$]	Human	Men and women	SSRI use was associated with faster cognitive decline. Higher doses were associated with greater risk of dementia and mortality. Men displayed greater cognitive decline than women in multiple dementia variants.
Corticotropin releasing hormone			
Bangasser et al., 2017[188,$]	Tg2576 mice crossed with CRH overexpressing mice and CaMKII-tTA mice, CRH overexpressing mice, and Tg2576 mice	Male and Female	Female triple transgenic mice have significantly increased levels of phosphorylated β-secretase relative to male triple transgenic mice. Female CRH overexpressing mice exhibited significantly higher levels of phosphorylated tau in both soluble and insoluble fractions compared to female wild-type mice and all male groups. No sex difference in phosphorylated β-secretase was observed in the Tg2576 mice lacking CRH overexpression. Female triple transgenic mice had a greater number of Aβ plaques and worse short-term memory compared
Campbell et al., 2015[375,*]	PSAPP mice crossed with CRH_1 KO or heterozygous mice	Female	Partial and complete ablation of CRH_1 reduced Aβ burden in the hippocampus, insular, rhinal, and retrosplenial cortices via decreased levels of Aβ peptides and Aβ C-terminal fragments.
Dong et al., 2012[368,*]	Tg2576 mice crossed with CRH overexpressing mice and CaMKII-tTA mice, CRH overexpressing mice crossed with CaMKII-tTA, and Tg2576 mice	Unspecified	At 3–4 months, mice with hypothalamic-pituitary-adrenal axis overactivation developed a Cushingoid phenotype with elevated brain CRH and CRH_1 levels. By 6 months, triple transgenic mice exhibited higher $A\beta_{1\text{-}42}$ and plaque burden, the most severe dendritic loss, and severe working and contextual memory deficits compared to Tg2576 mice. Doxycycline treatment, which suppresses CRH transgene expression, prevented the increased Aβ deposition and improved working memory in triple transgenic mice and reversed increased anxiety-like behaviors in double transgenic mice.
Dong et al., 2014[369,*]	Tg2576 mice	Male and female	Administration of the CRH_1 antagonist antalarmin for 1 week significantly reduced $A\beta_{1\text{-}42}$ levels in isolated stressed mice. Administration of antalarmin for 6 months significantly decreased plasma corticosterone levels, $A\beta_{1\text{-}42}$ levels and Aβ plaque deposition in the cortex and hippocampus, and blocked the effects of isolation stress on anxiety and memory.
Kang et al., 2007[370,*]	Tg2576 Mice	Male and female	Acute restraint stress increased interstitial fluid Aβ levels by 32% and led to significantly higher hippocampal CRH levels immediately after stress. Corticosterone administration did not alter Aβ levels, but exogenous CRH increased Aβ levels in a dose-dependent manner. A CRH_1 antagonist blocked the acute stress-induced increase in Aβ.
Hebda-Bauer et al., 2013[411,$]	3xTg-AD mice	Male and female	During early-stage pathology, 3xTg-AD males showed lower CRH mRNA in the paraventricular nucleus of the hypothalamus compared to wild-type males, with no difference detected between females. Female 3xTg-AD mice exhibited significantly higher Aβ immunoreactivity in hippocampus and the basolateral amygdala compared to male 3xTg-AD mice.

(Continues)

TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Hoorgan et al., 2007*	Tg2576 mice	Male	CRH levels in Tg2576 mice were increased in the cingulate, frontal, perirhinal, and entorhinal cortices. In contrast, hippocampal CRH levels were decreased in Tg2576 mice at 18 months, and were lower in the hypothalamus at 18 and 24 months.
Lv et al., 2020[403,*]	ICR mice with intracerebroventricular injection of $A\beta_{1\text{-}42}$	Male	Serum corticosterone levels, glucocorticoid receptor, and in the frontal cortex and hippocampus increased in $A\beta_{1\text{-}42}$-treated mice. Phosphorylation of cAMP response element binding decreased during the same period. These effects returned to normal by 8 months. $A\beta_{1\text{-}42}$ mice showed deficits in the Morris water task. Adrenal gland to body weight ratio also increased at 1 month, peaked at 4 months, and normalized by 8 months.
Zhang et al., 2016[371,$]	PSAPP	Male and female	CRH antagonist R121919 reduced $A\beta$ plaques and amyloid precursor protein C-terminal fragments in both male and female AD mice. β-secretase activity was decreased in treated females but not in males. In females, the treatment rescued dendritic and synaptic marker loss in the cortex and hippocampus. In males, treatment prevented only a minor loss of a synaptic marker in the cortex. CRH_1 antagonist treatment also prevented spatial memory deficits only in female AD mice, resulting in performance comparable to control females. Treatment had no effect on cognitive performance of male AD mice, which did not show memory impairment at this age.
Campbell et al., 2015[375,*]	CRH overexpressing mice	Female	Overexpression of CRH was associated with increased tau phosphorylation in the hippocampus, which was rescued by the CRH_1 antagonist R121919. R121919 treatment significantly reduced c-Jun N-terminal kinase phosphorylation in CRH overexpressing mice, despite no significant changes observed with activated and inactivated GSK-3β levels.
Carroll et al., 2011[374,*]	Tg2576, PS19, and CRH overexpressing mice	Male	Chronic stress promoted subregion-specific hippocampal tau hyperphosphorylation, soluble and insoluble tau aggregation, and neurodegeneration. These effects were correlated with impaired learning and memory in a fear conditioning paradigm. Chronic corticosterone administration did not mimic these stress-induced effects, but these effects were prevented with CRH_1 antagonist pretreatment.
Rissman et al., 2007[373,*]	CHR_1 and CHR_2 KO mice	Male	Acute restraint stress increased hippocampal phosphorylated tau. This effect was not prevented by blocking the stress-induced rise in glucocorticoids but was blocked by genetic or pharmacologic antagonism of CRH_1.
Rissman et al., 2012[372,*]	CHR_1 CHR_2 KO mice	Male	Repeated, but not acute, restraint stress increased hippocampal phosphorylated tau in wild-type and CRH_2 KO mice. In contrast, CRH_1 and CRH double KO mice, or wild-type mice pretreated with a CRH_1 antagonist, failed to show stress-induced alterations in phosphorylated tau. stress produced an overlap between hippocampal CRH_1 expression and cells positive for phosphorylated tau.
De Souza et al., 1986[359,*]	Human *post mortem*	Men and women	CRH levels decreased while CRH receptor levels increased in the temporal, frontal, and occipital cortices of AD patients. These changes were correlated with decreased choline acetyltransferase activity.

(Continues)

TABLE 1 (Continued)

Citation	Species/model	Sex	Summary
Acetylcholine			
Whitehouse et al., 1987[360,*]	Human *post mortem*	Unspecified	CRH immunoreactivity was decreased in the frontal, temporal, and occipital cortices in AD, Parkinson's disease, and progressive supranuclear palsy patients. Reductions in immunoreactivity were correlated with reduced choline acetyltransferase activity.
Pomara et al., 1989[361,*]	Human	Men and women	CRH immunoreactivity in cerebrospinal fluid of AD patients was unchanged compared to controls. However, in AD patients, cognitive deficits were worse in patients with lower CRH immunoreactivity in cerebrospinal fluid.
Frederiksen et al., 1991[378,$]	Human *post mortem*	Men and women	CRH concentration positively correlated with age in controls. There were no differences in CRH concentration in patients with schizophrenia. Mean CRH concentration was higher in the hypothalamus of women.
Stroud et al., 2011[391,$]	Human	Men and women	Girls over puberty displayed increasing cortisol levels after CRH challenge whereas boys showed no change. The effect in girls was due to prolonged time to reach peak cortisol and delayed return to baseline.
Gallucci et al., 1993[394,$]	Human	Men and women	In response to ovine CRH administration, plasma adrenocorticotropin hormone response was greater and more prolonged in women.
Oxytocin			
Jackson et al., 2013[467,*]	B6.Cg-Tg(APPswe, PSEN1dE9)85Dbo mice	Female	The OXT gene is downregulated in a mouse model of AD.
El-Ganainy et al., 2022[487,*]	Aluminum chloride-induced AD in Sprague–Dawley rats	Female	Intranasal OXT treatment improved cognition in the Morris water maze and reduced acetylcholinesterase activity, Aβ deposition, ERK1/2, GSK-3β kinase, caspase-3, and tau levels.
Ye et al., 2022[484,*]	APP/PS1 mice	Female	Nanogel delivery of OXT prevented cognitive decline and hippocampal atrophy, inhibited inflammatory signaling, and delayed both Aβ deposition and neuronal apoptosis.
Takahashi et al., 2022[486,*]	Intracerebroventricular injection of Aβ_{25-35} in ddY mice	Male	Intranasal OXT treatment improved working and spatial memory.
Cheng et al., 2023[483,*]	APP/PS1 mice	Female	An engineered macrophage-biomimetic versatile nanoantidote loaded with OXT improved working and spatial memory.
Selles et al., 2023[465,*]	Aβ infusion and APP/PS1 mice	Male	Various AD models displayed reduced OXT levels. Intranasal OXT treatment attenuated microglial activation; altered amyloid plaque morphology; and reversed social, object recognition, and spatial memory deficits.
Koulousakis et al., 2023[485,*]	APP/PS1 mice	Female	Intranasal OXT treatment improved spatial and working memory, decreased sociability, and reduced diffuse/dense core plaque ratio.
Usmani et al., 2024[466,*]	5xFAD mice	Male	5xFAD mice show reduced OXT expression levels. Intranasal OXT treatment improved performance in cognitive tests and reduced Aβ deposition only when combined with gonadotropin-releasing hormone.
Ye et al., 2024[488,*]	APP/PS1 mice	Male	Intranasal OXT treatment improved cerebral hemodynamics and glymphatic drainage, enhanced intracranial lymphatic clearance of Aβ, ameliorated cognitive impairment, and restored dysregulated meningeal transcriptional profiles.

(Continues)

TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Zhang et al., 2024[480,*]	APP/PS1 mice	Male	APP/PS1 mice showed reduced hippocampal OXT levels.
Sarahian et al., 2025[489,*]	$A\beta_{25-35}$ hippocampal injection in Wistar rats	Male	Intranasal OXT treatment improved working and spatial memory and increased the expression of synaptic plasticity-related genes.
Li et al., 2025[468,*]	APP/PS1 mice	Male	APP/PS1 mice displayed no difference in number of OXT neurons but had reduced serum OXT levels. Intranasal OXR treatment during social isolation increased sociability while having no effect on social novelty or memory. Treatment further reduced Aβ deposition and microglia number, and attenuated anxiety- and depression-like behaviors.
Rodeck et al., 1960[549,*]	Albino rats (Dusseldorf strain)	Male and female	OXT expression in the hypothalamus was slightly lower in aged rats.
Kania et al., 2020[558,$]	Sprague–Dawley rats	Male and female	AVP neurons are more numerous than OXT neurons in the paraventricular nucleus. More OXT neurons were observed in males than females. OXT cells exhibited broader action potential shapes and slower hyperpolarizing after-potential kinetics. Male OXT neurons displayed higher membrane resistance and slower hyperpolarizing after-potential kinetics than females.
Kelberman et al., 2024[543,*]	Prairie voles	Male and female	Number of OXT neurons in the paraventricular nucleus increase with age.
Fliers et al., 1985[429,*]	Brown-Norway rats	Male	OXT fiber density was similar in young and old rats.
Freda et al., 2022[504,$]	C57Bl/6 Mice	Male and female	Tracing of OXT and AVP neurons revealed largely conserved inputs between the two neuronal populations. Outputs of each neuromodulator differed, and sex differences were more pronounced in the AVP system.
Fliers et al., 1985[429,†]	Human *post mortem*	Men and women	Mean profile area and size of OXT cells in the paraventricular nucleus and supraoptic nucleus did not change with aging or in patients with senile dementia of the AD type. No sex differences were observed.
Wierda et al., 1991[430,†]	Human *post mortem*	Men and women	The number of OXT neurons was unchanged in aging and AD. No sex differences were observed.
Ishunina & Swaab, 1999[431,†]	Human *post mortem*	Men and women	No differences were found in any morphometric measure of OXT neurons in the paraventricular nucleus over the course of aging. No sex differences were observed.
Raskind et al., 1986[469,*]	Human	Men	Cerebrospinal fluid levels of OXT did not differ between young, elderly, or AD participants.
Mazurek et al., 1987[470,*]	Human *post mortem*	Men and women	OXT levels in the hippocampus and temporal cortex of AD patients were significantly higher than controls.
Petekkaya et al., 2021[471,*]	Human	Men and women	Patients with mild AD displayed decreased OXT signal and increased OXT concentration that were associated with increased right parahippocampal gyrus volume. OXT signal was lower in controls compared to those with mild AD, but OXT concentration was higher in those with mild AD.
Zou et al., 2022[472,*]	Human	Men and women	Changes in OXT signaling pathway genes were common in MCI and cerebral small vessel disease patients that transition to AD.

(Continues)

TABLE 1 (Continued)

Citation	Species/model	Sex	Summary
Acetylcholine			
Santiago et al., 2022[473,$]	Human *post mortem*	Men and women	OXT signaling pathway genes were identified as switch genes (key genes in the progression of AD) only in male AD patients.
Vasopressin			
Hernández et al., 2016[501,*]	Wistar rats	Male	AVP neurons from the hypothalamic neurosecretory pathway connect to GABAergic neurons in the central amygdala. AVP infusion to the amygdala mimicked effects of water-deprivation stress (increase anxiety-like behavior). Maternal separation increased the density of AVP innervation to the amygdala.
Mieda et al., 2015[515,*]	AVP-Bmal1 KO mice	Male and female	*Bmal1* deletion in AVP-producing neurons increased activity time, reduced suprachiasmatic nucleus genes associated with intracellular communication, and disrupted normal oscillatory patterns of cells.
Woodson & Bergan, 2023[503,†]	AVP-ires-CRE and R26-LSL-tdTomato mice	Male and female	Major inputs to AVP-expressing neurons in the paraventricular nucleus originate from the hypothalamus and thalamus and come from mostly non-peptidergic cells. Inputs were similar in males and females.
Rodeck et al., 1960[549,*]	Albino rats (Dusseldorf strain)	Male and female	AVP expression in the hypothalamus did not change with age.
Kania et al., 2020[558,$]	Sprague–Dawley rats	Male and female	AVP neurons are more numerous than OXT neurons in the paraventricular nucleus. More AVP neurons were observed in males than females. AVP cells exhibited narrower action potential shapes and faster hyperpolarizing after-potential kinetics. Male and female AVP electrophysiological properties were largely similar.
Kelberman et al., 2024[543,*]	Prairie voles	Male and female	Number of AVP neurons in the paraventricular nucleus did not change with age.
Wang et al., 1994[510,*]	Prairie voles	Male	Injection of AVP to the septum increased paternal behavior in male prairie voles, while antagonism of the AVP 1a receptor reduced paternal behavior.
Dobie et al., 1991[511,*]	F344 rats	Male	Fewer AVP labelled cells were observed in the bed nucleus of the stria terminalis in aged animals. The cells of aged animals were also less intensely labelled. Testosterone, which helps synthesize AVP in this brain region, was also lower in old animals.
Rigney et al., 2023[512,$]	AVP-iCre mice	Male and female	Inputs to the AVP neurons in the bed nucleus of the stria terminalis and amygdala mainly originated from the hypothalamus and olfactory bulbs, respectively. Both AVP neuronal populations project mainly to subcortical structures. Output density generally skewed male, while input density was mixed based on location.
Fliers et al., 1985[429,*]	Brown-Norway rats	Male	AVP fiber density across multiple brain regions decreased with age, but was spared in the paraventricular thalamus and solitary tract.
Van Zwieten et al., 1993[514,*]	Brown-Norway rats	Male	AVP immunoreactive cell bodies decreased in the medial amygdala and LC in aged animals. Testosterone levels were reduced beginning at middle age, which correlated with the number of AVP-immunoreactive cell bodies in both brain regions.

(Continues)

TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Rood et al., 2013[529,$]	C57Bl/6 Mice	Male and female	Gonadectomy and electrolytic lesions were used to eliminate AVP expression in the bed nucleus of the stria terminalis and amygdala, and the suprachiasmatic nucleus, respectively. AVP neurons emanating from the bed nucleus of the stria terminalis and amygdala innervate modulatory nuclei whereas those originating in the suprachiasmatic nucleus project to regions important for hormone regulation. Generally, but not always, males had higher AVP fiber density than females.
Ishunina & Swaab, 1999[431,$]	Human *post mortem*	Men and women	AVP cell size was larger in elderly than young women and correlated with age in the paraventricular nucleus. AVP cell size was larger in young men than young women. Sex differences were more pronounced in the left hemisphere paraventricular nucleus.
Raskind et al., 1986[469,*]	Human	Men	Cerebrospinal fluid levels of AVP was lower in AD patients compared to young or old participants. Plasma AVP levels did not differ between the three groups but the AD group lacked high values present in young and old participants.
Petekkaya et al., 2021[471,*]	Human	Men and women	Patients with mild AD displayed increased AVP concentration associated with increased right parahippocampal gyrus volume. There were no significant differences in AVP signal or concentration between those with mild AD and controls.
Son et al., 2024[59,*]	Human *post mortem*	Men and women	AVP neurons in the suprachiasmatic nucleus were selectively vulnerable to developing neurofibrillary tangles and tau fibrils. The paraventricular nucleus and supraoptic nucleus only showed mild tau pathology in late Braak stages. The suprachiasmatic nucleus also showed early immune dysregulation, but was largely spared from amyloid pathology. Number of AVP neurons in the suprachiasmatic nucleus decreased with increasing disease stage.
Goudsmit et al., 1990[547,†]	Human *post mortem*	Men and women	There was no loss in total cell number or volume in the supraoptic nucleus or paraventricular nucleus during aging or in AD. There was a decrease in both volume and total cell count in the supraoptic nucleus during both aging and AD. No sex differences were found.
Fliers et al., 1985[429,†]	Human *post mortem*	Men and women	Mean profile area of AVP cells in the paraventricular nucleus and supraoptic nucleus decreased up to the sixth decade of life and then gradually increased. Size of AVP cells did not change with aging. There were no deviations from aging found in patients with senile dementia of the AD type and no sex differences were observed.
Lucassen et al., 1997[548,*]	Human *post mortem*	Men and women	AVP mRNA in the paraventricular nucleus and supraoptic nucleus were unchanged during aging and in AD. There were negative correlations between the volume of AVP mRNA and age in the supraoptic nucleus of AD patients. There was a positive correlation between paraventricular nucleus AVP mRNA and cerebrospinal fluid pH.
Histamine			
Zou et al., 2025[613,*]	5xFAD mice	Male and female	The H3R antagonist/inverse agonist pitolisant improved memory and cognitive flexibility, restored cortical slow-wave coherence and normalized frequency, reduced soluble and insoluble Aβ levels and plaque burden, decreased dystrophic neurite area and density, and increased cathepsin B/D levels and enzyme activity. Beneficial effects were blocked by cathepsin inhibitor treatment. Beneficial effects were similar between sexes but not statistically assessed.

(Continues)

TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Zhang et al., 2023[618,*]	3xTg-AD mice	Female	Depression-like behavior and L-histidine levels were increased in hippocampus of aged female 3xTg-AD mice. There were no changes in HA levels.
Wang et al., 2022[612,*]	APP/PS1 mice	Male	The H3R antagonist/inverse agonist thioperamide reduced neuroinflammation and cognitive deficits via gliosis inhibition and astrocyte phenotype switching through CREB signaling.
Wang et al., 2019[614,*]	APP/PS1 mice	Male and female	The H3R antagonist LC1405 improved learning and memory in APP/PS1 mice and upregulated both acetylcholine and HA.
Mani et al., 2017[611,*]	B6.129-Tg(APPSw)40Btla/J mice	Male	The H3R antagonist ciproxifan improved learning and memory, increased acetylcholine levels and decreased acetylcholinesterase activity, reduced oxidative stress and neuroinflammation markers in the absence of reductions in brain Aβ levels.
Delay-Goyet et al., 2016[610,*]	THY-Tau22 mice	Male	The H3R antagonist/inverse agonist SAR110894 reduced tau hyperphosphorylation, neurofibrillary tangles, and prevented cognitive deficits after 6 months of treatment.
Sundvik et al., 2013[616,*]	Presenilin1 KO zebrafish	Male and female	Presenilin knockout embryos displayed decreased HA neurons at 7-days postfertilization compared to wild-type. This phenotype normalized by 2 months.
Bardgett et al., 2011[608,*]	Tg2576 mice	Male and female	The H3R antagonist ciproxifan improved cognitive deficits and reduced hyperactivity in Tg2576 mice.
Bitner et al., 2011[609,*]	Tg2576 & TAPP mice	Male and female	The histamine H3R inverse agonist ABT-239 normalized the reduced CREB and GSK-3β phosphorylation Tg2576 mice. The H3R inverse agonist ABT-239 reversed tau hyperphosphorylation in spinal cord and hippocampus of TAPP mice.
Van Meer et al., 2007[615,*]	ApoE KO mice	Male	The H3R antagonist/inverse agonist thioperamide was associated with reduced histamine release in the amygdala of ApoE knockout mice.
Mazurkiewicz-Kwilecki & Prell, 1986[619,*]	Sprague–Dawley rats	Male	12-month-old rats displayed higher hypothalamic, midbrain and cortical HA concentrations than 3-month-old rats.
Mazurkiewicz-Kwilecki & Prell, 1984[620,*]	Sprague–Dawley rats	Male	12-month-old rats displayed higher hypothalamic HA after stress, midbrain and cortical HA concentrations than 3-month-old rats.
Medhurst et al., 2009[617,*]	TASTPM mice; Human *post mortem*	Unspecified; men and women	There were no differences in H3R expression in TASTPM mice. AD patients displayed normal levels of H3R expression throughout the brain.
Oh et al., 2022[10,*]	Human *post mortem*	Men and women	Results showed increased tau burden in TMN HA neurons and demonstrated correlation with total sleep time.
Oh et al., 2019[212,*]	Human *post mortem*	Men and women	Unbiased stereological analysis demonstrated 62% decline in histaminergic neurons in the late stage of AD, which was associated with AD-specific tau toxicity.
Shan et al., 2012[580,$]	Human *post mortem*	Men and women	There was significant global and regional HA neuronal loss in the TMN in AD patients. In contrast, L-histidine decarboxylase mRNA expression levels in TMN did not show any changes. However, medial TMN showed a significant decline in AD. H3R mRNA expression in PFC increased only in females in Braak V–VI over Braak 0–II, while histamine methyltransferase mRNA expression was upregulated in Braak III–IV, and V–VI over Braak 0–II.

(Continues)

TABLE 1 (Continued)

Citation	Species/model	Sex	Summary
Acetylcholine			
Motawaj et al., 2010[585,$]	Human	Men and women	Cerebrospinal fluid tele-methylhistamine levels declined significantly in AD patients. In contrast, cerebrospinal fluid tele-methylhistamine levels showed an age-associated increase during normal aging. There was a significant decline in cerebrospinal fluid tele-methylhistamine levels in male and female AD patients. The extent of decline was greater in females.
Panula et al., 1997[584,*]	Human *post mortem*	Men and women	HA concentration significantly declined in hypothalamus, hippocampus, and temporal lobes of AD patients.
Prell et al., 1990[607,$]	Human	Men and women	A increase in HA metabolites cerebrospinal fluid levels were seen in normal aging individuals, with females showing higher levels than males.
Cacabelos et al., 1989[583,*]	Human *post mortem*	Unspecified	HA levels in patients with senile dementia of the AD type were higher across various brain regions.
Mazurkiewicz-Kwilecki & Nsonwah, 1989[582,*]	Human *post mortem*	Men and women	There was a decline in HA and histidine levels across cortical areas and in the caudate nucleus of AD patients.
Orexin			
Keenan et al., 2024[698,$]	rTg4510 mice	Male and female	Chronic OX-B receptor antagonism improved sleep/wake patterns and cognitive function in a manner dependent on tau pathology and sex.
Keenan et al., 2022[697,$]	rTg4510 mice	Male and female	GABAergic and OX-targeting hypnotics enhance sleep during the active phase in tau-transgenic rTg4510 mice. Sex-dependent differences are observed in rTg4510 mice in response to OX-B receptor-selective antagonists.
Taheri et al., 1999[652,$]	Wistar rats	Male and female	Female rats showed higher levels of OX-A and prepro-OX mRNA in the lateral and posterior hypothalamus.
Jöhren et al., 2002[653,$]	Wistar rats	Male and female	Female rats showed higher levels of OX-A and prepro-OX mRNA in the lateral and posterior hypothalamus
Jöhren et al., 2001[654,$]	Wistar rats	Male and female	There was sex-dependent expression of OX-A and OX-B receptors in the hypothalamus, pituitary, and adrenal glands.
Silveyra et al., 2007[656,$]	Sprague–Dawley rats	Male and female	There were cyclical changes in prepro-OX and receptor expression in adult females, particularly during proestrus.
Lu et al., 2017[670,$]	Human *post mortem*	Men and women	OX-A immunoreactivity increased only in women with major depressive disorder. Loss of normal diurnal OX variation in patient tissue supported women-specific OX involvement in major depressive disorder-related sleep and mood disruption.
Fronczek et al., 2012[683,$]	Human *post mortem*	Men and women	Marked loss of hypothalamic OX neurons and reduced cerebrospinal fluid OX-A levels in AD compared to controls. Cerebrospinal fluid levels of OX-A were higher in female compared to male controls, which was not present in the AD group.
Schmidt et al., 2013[171,$]	Human	Men and women	Cerebrospinal fluid OX-A levels were higher in women than men across diagnostic groups. This was interpreted as sex-dependent physiological regulation rather than a result of disease.

(Continues)

TABLE 1 (Continued)

Acetylcholine			
Citation	**Species/model**	**Sex**	**Summary**
Wennström et al., 2012[685,$]	Human	Men and women	Women AD patients showed highest cerebrospinal fluid OX-A levels. Women Lewy body dementia patients had the lowest cerebrospinal fluid OX-A levels. Women controls had intermediate cerebrospinal fluid OX-A levels. There were no significant differences among males.
Dauvilliers et al., 2014[686,†]	Human	Men and women	Cerebrospinal fluid OX-A levels were high in AD dementia and MCI groups compared to controls, but no sex differences were observed within or across diagnostic categories.
Liguori et al., 2014[687,†]	Human	Men and women	Higher cerebrospinal fluid OX-A levels were observed in moderate-to-severe AD compared to controls with no differences between mild AD and controls. There were no sex differences detected in any group.
Liguori et al., 2016[688,*]	Human	Men and women	There was higher cerebrospinal fluid OX-A levels in MCI patients compared to controls.
Lozano-Tovar et al., 2025[689,$]	Human	Men and women	Cerebrospinal fluid OX-A levels were higher in moderate AD, non-fluent primary aphasia, and idiopathic normal pressure hydrocephalus than controls. Within clinical groups there were no sex differences, but men in the control group displayed higher OX-A levels than women.

Notes: Sex differences in the OXT and AVP systems have been extensively reviewed elsewhere.[417–420] Therefore, we highlight newer results and those which are pertinent to AD in the above table. Citations with similar authors from the same year are differentiated with superscripts associated with their reference number.

Abbreviations: 5-HT, serotonin; 5-HIAA, 5-Hydroxyindoleacetic acid; Aβ, amyloid beta; AD, Alzheimer's disease; AVP, arginine vasopressin; BACE-1, beta secretase 1; BDNF, brain-derived neurotrophic factor; BFCS, basal forebrain cholinergic system; cAMP, cyclic adenosine monophosphate; CRH, corticotropin releasing hormone; DA, dopamine; DBH, dopamine beta-hydroxylase; DRN, dorsal raphe nucleus; ER, estrogen receptor; ERK, extracellular regulated kinase; GFAP, glial fibrillary acidic protein; GSK-3β, glycogen synthase kinase 3 beta; HA, histamine; htau, human tau; KO, knock-out; LC, locus coeruleus; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NBM, nucleus basalis of Meynert; NE, norepinephrine; NMDA, *N*-methyl-D-aspartic acid; NSSs, neuromodulatory subcortical systems; OX, orexin, OXT, oxytocin; PET, positron emission tomography; PFC, prefrontal cortex; p-tau, phosphorylated tau; REM, rapid eye movement; SERT, serotonin transporter; SNpc, substantia nigra pars compacta; snRNA-seq, single nuclei RNA sequencing; SSRI, selective serotonin reuptake inhibitor; TMN, tuberomammillary nucleus; trkA, tropomyosin receptor kinase A; VTA, ventral tegmental area.

*Indicates sex differences were not tested.

$Indicates the presence of sex differences.

†Indicates sex differences were tested for, but no differences were found.

2.2 | Hormone replacement therapy as a critical modifier of cholinergic function

Hormone therapy through the use of exogenous estrogens and progestins has been proposed as a potential neuroprotective strategy, largely due to its influence on cholinergic tone.[38,48] Exogenous estradiol modulates cholinergic activity in both animal models[48–51] and humans.[43,52–54] Epidemiological studies also link hormone therapy with a reduced risk of developing AD,[55,56] even in women with early life ovarian removal.[57] However, findings from studies assessing the impact of hormone therapy on cognitive performance have been mixed.[58,59] Several factors can affect the ability of hormone therapy to boost cholinergic tone. These factors include the timing of the initiation of hormone therapy relative to the menopause transition, the duration of use, route of administration, and the specific combination of hormonal compounds.

When evaluating the beneficial effects of exogenous estrogens in cognitively unimpaired postmenopausal women, studies often use a stressor or pharmacological challenge to identify underlying cholinergic dysfunction. Cholinergic antagonists, such as mecamylamine (nicotinic receptors) or scopolamine (muscarinic receptors) are often used for this purpose.[60–63] A single dose of estradiol attenuates scopolamine-induced memory impairments in ovariectomized rats.[64] Similarly, postmenopausal women who receive oral estradiol for 3 months perform better on working memory and attention tasks under an anticholinergic challenge compared to those on placebo.[65,66] Interestingly, these beneficial effects appear to be age dependent. Estradiol mitigates the anticholinergic challenge only in younger postmenopausal women, while older women showed worsened performance while on estradiol.[67] This pattern aligns with preclinical data demonstrating that cognitive benefits of exogenous estradiol treatment are greatest when treatment occurs closer to ovariectomy.[68,69] These studies highlight the importance of the timing of hormone therapy initiation relative to menopause, a fundamental concept of the critical window hypothesis.[67,70,71] Most studies report improved cognitive outcomes when hormone therapy begins within the first few

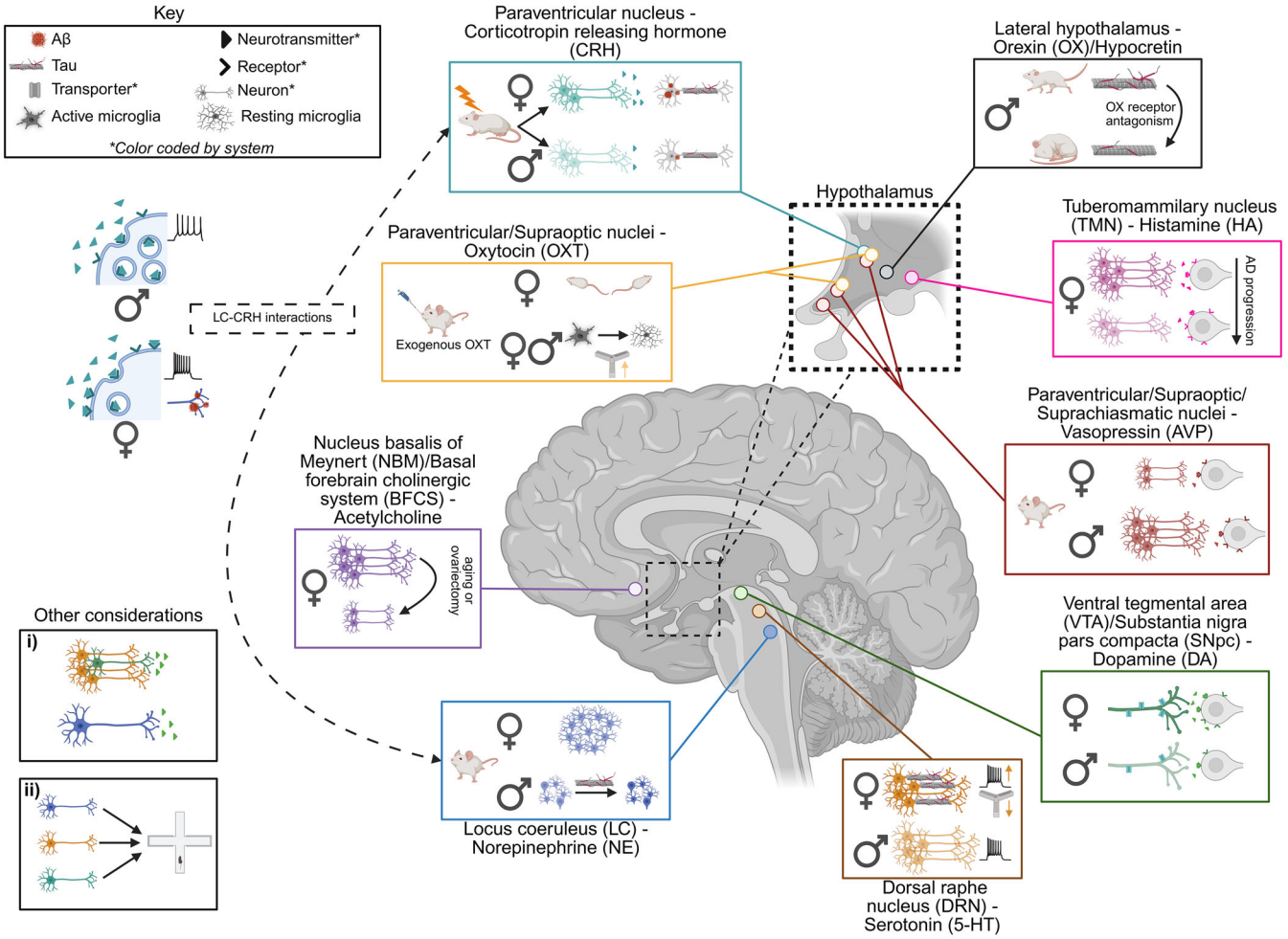

FIGURE 1 Overview of sex differences in neuromodulatory subcortical systems (NSSs) under baseline conditions and in Alzheimer's disease (AD). Nucleus basalis of Meynert (NBM)/basal forebrain cholinergic system (BFCS) – acetylcholine: Cholinergic decline (lower volume, neuron number, innervation, receptor activity) is observed after ovariectomy and in aging women. Outstanding question(s): What factors influence the efficacy of hormone replacement therapy for alleviating cholinergic decline (age at initiation, treatment duration, hormone formulation)? Ventral tegmental area (VTA)/substantia nigra pars compacta (SNpc) – dopamine (DA): At baseline, females/women display greater DA receptor and transporter density, release, and synthesis capacity (darker shading = greater synthesis capacity). Preclinical AD models show more severe DA-related behavioral phenotypes and DA plaque burden along with reduced transporter density and synthesis capacity in females. Outstanding question(s): Can we leverage large, publicly available datasets to confirm preclinical sex differences in human populations? Locus coeruleus (LC) – norepinephrine (NE): At baseline, the female LC is larger in volume, has more neurons, and more elaborate dendritic fields. LC tau expression induces upregulation of NE synthesis genes in males only. Outstanding question(s): How do these robust sex differences in animal models translate to the human condition, including vulnerability of and treatment strategies targeting the LC–NE system? Dorsal raphe nucleus (DRN) – serotonin (5-HT): Most studies report higher 5-HT synthesis, metabolism, and turnover in females/women, while males display higher neuronal firing at baseline. Tau expression in DRN 5-HT neurons causes spatial working memory deficits and impairs neuronal excitability that is specific to females. Outstanding question(s): To what extent is AD vulnerability shaped by DRN 5-HT dysfunction, particularly during periods of hormonal transition? Paraventricular nucleus – corticotropin releasing hormone (CRH): CRH levels are higher in women/females, especially in response to stress. Stress increases AD pathology and inflammation to a greater extent in women/females. Outstanding question(s): Sex differences in CRH levels and CRH_1 receptor distribution appear to be age dependent, but how do these development differences impact susceptibility to and progression of AD? LC–CRH interactions: Female LC neurons have a higher discharge rate in response to CRH and lower CRH receptor internalization relative to male LC neurons. Only females show colocalization of amyloid beta (Aβ) in LC axons in response to forebrain CRH overexpression. Outstanding question(s): What is the extent of crosstalk between other systems, their dependence on sex, and the implications for AD? Paraventricular/supraoptic nuclei – oxytocin (OXT): Sex differences in OXT structure and function are highly species specific and sometimes contradictory. Preclinical studies show that exogenous OXT (e.g., intranasal OXT) rescues behavioral and molecular AD-related phenotypes in both sexes, including protection against working and spatial memory decline and a reduction in neuroinflammation. One study demonstrates that OXT can induce social deficits in female AD mice. Outstanding question(s): How do these preclinical findings translate to humans; specifically, how does AD impact OXT-producing neurons and downstream signaling, and how might these changes affect AD-related symptoms in a sex-dependent manner? Paraventricular/supraoptic/suprachiasmatic nuclei – vasopressin (AVP): At baseline, males have more and larger AVP neurons, and greater innervation density and receptor expression. Whether these differences translate to humans is unknown. Diffuse expression and differing susceptibility of AVP nuclei suggest contributions to distinct facets of AD. Outstanding question(s): What is the extent of AVP dysfunction along AD progression and how is this modified by sex? Tuberomammillary nucleus (TMN) – histamine (HA): Androgens methylate HA, reducing baseline

years of menopause, whereas initiation ≥ 5 years later reduces beneficial effects.[70,72–74] The hypothesis suggests that estradiol's beneficial effects on the cholinergic system are most pronounced while the nuclei are still structurally intact.

The importance of identifying optimal treatment windows is also exemplified by studies examining individuals with subjective cognitive complaints,[75,76] a transition stage associated with greater risk of progressing to MCI or AD. In these individuals, estradiol appears less effective in counteracting cholinergic disruption. In a study of cortical activation of working memory, postmenopausal women with greater self-reported cognitive complaints exhibited greater overall cortical activation compared to participants who reported fewer complaints. Such activation suggests increased neuronal effort is required to successfully complete tasks.[77] Under an anticholinergic challenge, these postmenopausal women performed worse, regardless of whether they received 3 months of estradiol or placebo.[78]

Finally, composition of the hormone therapy regimen also determines its effects on cognition and cholinergic system integrity. Hormone therapy typically combines estrogen and progesterone replacement, with the former compensating for reduced circulating estradiol and the latter preventing endometrial hypoplasia.[79,80] Both estrogen and progestin types influence cognitive and cholinergic performance. For example, conjugated equine estrogens increased incidence of dementia and MCI in women in the Women's Health Initiative.[81,82] This effect was most pronounced in older women who were long past menopause,[83] consistent with the critical window hypothesis. Progestins themselves can have differential effects on cholinergic function and cognitive performance, both alone and in combination with estrogens.[84] Beneficial effects of progesterone have been seen in ovariectomized mice, in which progesterone in conjunction with estradiol improved choline acetyltransferase activity compared to estradiol or progesterone alone.[85] A beneficial effect of combined hormone therapy was also seen in postmenopausal women who initiated treatment earlier after menopause. Compared to estrogen therapy alone, women taking estrogens and progestins had greater cholinergic uptake of the radiotracer N-[^{11}C]methylpiperidin-4-yl propionate in the hippocampus and posterior cingulate.[53] However, like estrogens, the type of progestins seem to influence their ability to modulate cholinergic tone. For example, medroxyprogesterone acetate, the most commonly used progestin, impairs cognitive performance in both in animal models and human studies.[86,87] In contrast, micronized progesterone tends to be less harmful and may even improve some cognitive measures.[86] However, in the presence of an anticholinergic agent, micronized progesterone interferes with estradiol's ability to improve cognitive performance.[88] Overall, while preclinical research generally supports the neuroprotective role of hormone therapy through enhanced cholinergic function, evidence from studies in postmenopausal women are mixed. This variability likely reflects differences in age at initiation, treatment duration, hormone formulation, and underlying cholinergic system integrity.

2.3 | Future directions

Cholinergic system decline is synonymous with AD progression and has been proposed as a factor in the sex disparity of AD, due to its relationship with estrogens and the consequences of the menopause transition.[38,39] Both animal and human studies show that loss of estradiol increases the vulnerability to cholinergic decline, driven in part by increased tau propagation. Due to the relationship between the cholinergic system and estrogens, a particular focus of past research has been on whether the use of exogenous hormones can mitigate the loss of estradiol after menopause. The benefits of hormone therapy on cholinergic function and cognitive performance are inconclusive, owing to a complex interaction of factors, including the timing of replacement therapy, that impact the ability of hormone therapy to improve performance. Moreover, not all women develop AD, and a better understanding of the underlying vulnerability of some women for cholinergic dysfunction and AD progression should be a focus of future research. Measurements of cholinergic integrity, like cholinergic radiotracers, in conjunction with new fluid biomarkers, may offer a more accurate way of probing the relationships among the cholinergic system, hormone therapy, and AD pathological burden.

3 | DOPAMINE

Dopaminergic circuits originate from the substantia nigra pars compacta (SNpc) and the ventral tegmental area (VTA).[89,90] Dopaminergic neurons in the SNpc project to the dorsal striatum, forming the nigrostriatal pathway, which is critical for movement and action selection.[91] In contrast, dopaminergic neurons in the VTA project to the ventral striatum and nucleus accumbens, forming the mesolimbic pathway, and to the prefrontal cortex (PFC), forming the mesocortical pathway. The former is implicated in reward processing and motivated behavior, while the latter is important for cognition.[92,93] Additionally,

circulating levels in males compared to females. Women show greater loss of TMN neurons and HA synthesis enzymes but have greater HA receptor expression in AD. Outstanding question(s): Given HA signals immune responses in the periphery, what are the sex-dependent effects of peripheral HA signaling on AD progression? Lateral hypothalamus – orexin (OX)/hypocretin: Males appear more responsive to pharmacological OX interventions (reduced hyperphosphorylated tau, normalization of sleep patterns), though responses in females are underexplored. While human evidence for sex differences in OX signaling remains inconsistent, dual OX receptor antagonists improve sleep in AD patients regardless of sex. Outstanding question(s): Does hormonal status and/or other sex-related factors influence the efficacy of OX-based therapeutics for sleep, AD, and their interaction? Other considerations: (1) What is the role of non-primary neurotransmitters released by NSSs in AD (e.g., DA release from the LC or DRN subpopulations)? (2) What are the relative contributions of different NSSs to the same symptoms (e.g., contributions of NE vs. 5-HT vs. CRH in anxiety-like behaviors)? How are these phenotypes modified by sex? Figure generated in bioRender.

dopaminergic neurons in both the SNpc and VTA project to the hippocampus, where DA release supports synaptic plasticity and memory formation.[94]

3.1 | Baseline sex differences in dopaminergic circuits and regulation by sex hormones

Sex differences in dopaminergic circuits are evident across the lifespan[95] and impact trajectories for many DA-related disorders, such as Parkinson's disease, schizophrenia, and substance use disorder.[96–98] For example, human neuroimaging studies reported higher D2/3 receptor density, transporter density, striatal DA release, and DA synthesis in women than men.[99–103] However, other studies, although fewer, reported either opposite results, such as higher DA release in men than women,[104] or null effects (e.g., D2/3 receptor density[102]). Findings from preclinical studies also generally confirm the existence of sex differences in dopaminergic circuits. For instance, there are robust sex differences in the degree of connectivity between the VTA/SNpc and its targets. In female rats, 50% of the projections from the VTA to the PFC are dopaminergic, while in male rats this proportion is only 30%.[105] Similarly, DA release in the dorsal striatum is greater in females relative to males, suggesting that, like the PFC, the dorsal striatum of females receives denser dopaminergic input than that of males.[106]

Not only does the dopaminergic system vary by sex, but it is also regulated by gonadal hormones. Women with greater baseline DA in the PFC display a negative association between PFC-dependent cognitive function and levels of estradiol.[107] An investigation of the neural and cognitive effects of contraceptive use found that hormonal contraceptive users had greater DA synthesis capacity in the dorsal striatum and better cognitive flexibility relative to non-users.[108] Importantly, across groups, higher DA synthesis capacity was associated with greater cognitive flexibility. Considered together, these clinical studies provide clear evidence that sex hormones potently influence DA function that is relevant for optimal cognitive function, particularly in women.

Similarly, in preclinical studies, striatal DA release is positively correlated with estradiol levels in intact female rats and the administration of estradiol and progesterone to ovariectomized female rats increases striatal DA release.[109] In contrast, androgens have no effect on striatal DA properties, but instead appear to regulate cortical DA function in males.[109–111] Androgens tonically suppress DA release in the PFC,[111] and testosterone inhibits burst firing in PFC-projecting VTA neurons.[112–114] Consequently, androgen regulation contributes to lower basal PFC DA levels in males, increasing their susceptibility to cortical hypodopaminergia.[110,112]

3.2 | The dopaminergic system in AD and the moderating influence of sex

Even without considering sex as a modifying factor, there is evidence of DA dysfunction in AD.[115–117] Studies using genetic polymorphisms to infer individual differences in DA function have demonstrated links between the rs6347 DA transporter polymorphism, Aβ, and tau pathology,[118] as well as an increased risk for developing AD and greater cortical shrinkage with expansion of the ventricles.[119] In addition, Aβ plaque burden in the striatum is predictive of AD severity,[120] and dopaminergic midbrain nuclei accumulate tau pathology before it spreads to cortical regions,[121] suggesting these midbrain areas may be vulnerable in early stages of AD. Similarly, in the Tg576 mouse model of AD, selective neuronal loss in the VTA (but not in the SNpc) was observed prior to Aβ plaque formation.[122] This dysregulation of DA circuitry not only affects midbrain DA nuclei but also impacts the targets of their projections. In AD patients, hippocampal D2 receptor density is lower than in healthy controls.[115] Given that higher D2 receptor density is correlated with better memory performance, the reduction in hippocampal D2 receptors in AD patients could account for memory impairments characteristic of AD. Consistent with these clinical findings, VTA neuron loss in Tg576 mice is correlated with lower hippocampal DA levels, lower CA1 synaptic plasticity, worse memory performance, and impaired reward learning.[122] Based on these findings, degeneration of the VTA in AD may lead to deficits in DA-dependent hippocampal function and contribute to memory impairments typically associated with AD.

Although it is unclear how DA dysfunction might be mechanistically related to AD, it is possible that AD pathology and aging-related dysregulated DA may exacerbate each other, leading to worse clinical outcomes. For example, oxidative stress and Aβ aggregation in AD are linked to mitochondrial DNA damage, mitochondrial dysfunction, inflammation, and cytotoxicity.[123] The administration of DA and its derivatives, however, can combat the effects of oxidative stress and Aβ aggregation.[124] Hence, AD-associated hypodopaminergia may weaken the usual protective effects exerted by DA and, as a consequence, make neurons more vulnerable to oxidative damage. Interestingly, a DA receptor agonist improves cognition in individuals with MCI,[116] thus providing additional support for the supposition that increased DA levels may protect against cognitive decline.

Few studies have considered sex as a moderating factor in the bidirectional interplay between AD and the DA system, despite well-established sex differences in AD presentation.[125] For example, women with AD often present with greater severity of depressive symptoms, aberrant motor behavior, and psychotic symptoms, all of which are associated with DA dysfunction. Such sex-dependent presentation of AD suggests sex-specific AD-related changes to this system. This notion is supported by work using the 5xFAD mouse model, in which females exhibited greater striatal Aβ plaque burden, hyperlocomotion, and reduced stereotypies compared to males.[126] Additionally, female, but not male, 5xFAD mice exhibited reduced DA transporter and tyrosine hydroxylase expression.[126] Beyond this recent work, however, very little is known about the DA-linked mechanisms underlying the greater susceptibility and sensitivity of females to AD pathology, underscoring the need for more research in this area.

Although the mechanisms that contribute to sex differences are not well understood, gonadal hormones appear to be involved. Estrogen receptor polymorphisms are associated with increased AD risk in

women.[127] DNA methylation and RNA expression of estrogen receptor genes, particularly *GPER1*, in the PFC is associated with greater cognitive decline and higher *post mortem* indices of AD pathology, with more pronounced effects in women.[128] Although there is no direct link between hormonal modulation of DA and AD development, it is conceivable that hormone-related changes in the DA system during menopause, a period when estradiol levels decline, may place women at a higher risk for developing AD. Estradiol protects against Aβ and tau pathology, oxidative stress, and mitochondrial damage while loss of estradiol after menopause reduces antioxidant capacity.[129] These findings are consistent with evidence from a rodent A$\beta_{1\text{-}42}$ infusion model of AD. While ovariectomy induced hippocampal oxidative stress in aged female rats, estradiol administration ameliorated detrimental effects.[130] Greater oxidative stress likely impacts cellular function throughout the brain, but dopaminergic neurons may be particularly affected as they have high energy requirements.[131,132] Hence, the typical age-related reduction in circulating hormones may increase female risk for AD due to changes in the metabolic function and capacity of DA neurons.

Intriguingly, although men have a lower AD risk than women overall, men, especially of healthy older populations, can present with quicker and more severe cognitive decline.[133] This sex difference may be attributed to baseline differences in dopaminergic projections from the VTA to the PFC and the influence of androgens on DA release in the PFC from neurons originating in the VTA.[113,114] Hence, both gonadal hormones and other factors associated with biological sex could be considered risk factors predisposing males to developing cortical hypodopaminergia and AD-associated cognitive deficits. However, more work is needed to test this hypothesis and examine how AD-related changes in the DA system may account for sex differences in metrics of disease severity, especially given evidence that women with AD show more pronounced cognitive decline than men.[14–22,133]

3.3 | Future directions

The evidence for sex differences in the dopaminergic system support a link between its sex-specific dysfunction and AD. Like other NSSs, hormonal regulation of the dopaminergic system may be a critical mediator of sex differences in AD. Relative to other neuromodulators, however, far less is known about how sex-dependent alterations in the dopaminergic system contribute to the pathophysiology of AD. One limitation of existing clinical studies is that they lack the statistical power necessary to effectively analyze sex differences. Hence, an important future direction in this field is to leverage large, publicly available datasets (e.g., the Alzheimer's Disease Neuroimaging Initiative) to study how both dopaminergic and hormone-related genetic polymorphisms relate to neural measures of AD pathology and cognitive trajectories. Another critical avenue of research is to identify how interactions between DA and other neurotransmitters, such as 5-HT and NE, impact AD pathology. Although preclinical studies have demonstrated an association between DA and 5-HT in AD,[134] no clinical studies exist that explore such a relationship. Similarly, the locus coeruleus (LC), although known for being the brain's primary source of NE,[135] also synthesizes DA[94,136] and is especially vulnerable to tau pathology.[11] For these reasons, this nucleus is of primary interest for future research on how interactions between DA and NE may influence sex-dependent vulnerability to AD.

4 | NOREPINEPHRINE

Extensive evidence implicates the LC, the brain's primary, but not exclusive, source of NE, as a central node in the early stages of AD pathogenesis.[5,137–139] The LC–NE system is a key component of the brain's arousal and stress network, supporting alertness, attention, and cognition.[140–147] Notably, hyperphosphorylated tau in its pretangle form accumulates in LC neurons decades before clinical symptoms, suggesting a brainstem origin of AD pathology.[5,148] This observation has spurred increasing interest in the LC's role in shaping AD vulnerability.[149,150] Given that AD is more prevalent in women than men, LC degeneration, an early AD hallmark, has been hypothesized to be more pronounced in women, partially due to estradiol decline during and after perimenopause. Such hormonal changes may exacerbate NE depletion, thereby accelerating tau propagation and cognitive decline.[149]

4.1 | Intrinsic vulnerability of the LC–NE system in female rodents

Rodent models have shown that the LC exhibits marked sex differences, with females displaying larger LC volume, greater neuronal counts, and more elaborate dendritic arborization compared to males.[151–155] While these features may enhance arousal regulation and neuromodulatory capacity, they also increase metabolic demand and sensitivity to oxidative stress, potentially rendering the female LC more vulnerable to degeneration during aging or chronic stress exposure. Recent transcriptomic and proteomic analyses have also shed light on sex-dependent LC vulnerability. For instance, the female LC in mice expresses elevated levels of stress-responsive genes such as *Ptger3*, which modulates LC excitability and anxiety-like behaviors.[156] Estradiol also enhances NE biosynthesis by upregulating tyrosine hydroxylase, the rate-limiting enzyme in NE production.[157,158] On the other hand, proteomic signatures suggest reduced regulation of protein turnover and stress pathways, including eukaryotic initiation factor 2 signaling and glucocorticoid response, in the female rodent LC.[159] These molecular differences may compromise resilience to neurodegenerative processes, contributing to the greater AD susceptibility observed in women.

Increasingly, animal models of amyloidosis have been used to examine LC degeneration, but few incorporate sex-stratified analyses. In studies of female APP mice, N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine-induced LC lesions resulted in increased plaque burden, glial activation, and cognitive deficits.[160] Aged female

APP/PS1 mice exhibited selective LC neuron loss despite preserved dopaminergic systems,[161] aligning with human evidence of early LC degeneration in AD.[162–167] One study found that LC chemogenetic silencing or adrenoceptor blockade exacerbated central nervous system inflammation,[168] with Adrb1 knockdown in microglia intensifying inflammatory responses exclusively in females, indicating sex-specific differences in adrenergic signaling.

Studies using TgF344-AD rats and APP transgenic mice with LC lesions reported increased Aβ deposition, synaptic deficits, and cognitive impairment but did not analyze sex differences.[169–171] Other investigations in males show that in V717F-APP, LC noradrenergic depletion increased Aβ plaque burden and reduced neprilysin, a key Aβ-degrading enzyme, highlighting NE's role in Aβ clearance.[172] Similarly, in male 5xFAD mice, vindeburnol confers neuroprotection by upregulating tyrosine hydroxylase, reducing Aβ plaque load, and improving behavior via cyclic adenosine monophosphate-mediated brain-derived neurotrophic factor upregulation.[173] While informative for males, these studies underscore the need for comparable data in females to elucidate sex-specific mechanisms of LC degeneration and AD progression.

Animal models of tau pathology within the LC have provided critical insight into early-stage AD but, like most amyloid models, often lacked sex-stratified analyses. Transgenic models carrying the human *MAPT* P301S or P301L mutation linked to frontotemporal dementia[174,175] are widely used to study tauopathy. In PS19 mice (P301S), tau fibril injection into the LC induced rapid tau aggregation and neuronal loss on the ipsilateral side compared to the contralateral LC, which exhibited tau clearance and minimal cell loss, likely reflecting lateralization of pathological burden and more effective degradation.[174] In P301L mice, similar injections disrupted hippocampal network activity without overt tau propagation.[175] Although both sexes were included in the previous two studies, outcomes were not analyzed separately by sex. Similarly, TgF344-AD rats show early LC tau accumulation accompanied by axonal degeneration and cognitive decline that precedes entorhinal and hippocampal pathology.[176] A follow-up study identified age- and stage-dependent dysregulation of LC firing,[177] though sex differences were not assessed.

Emerging findings suggest that sex significantly modulates tau-related LC vulnerability. In human tau (htau) overexpressing mice,[178] males displayed greater hyperactivity and anxiety, whereas both sexes exhibited depressive-like behaviors and LC pathology. These results indicate shared neuropathology but divergent behavioral outcomes. LC-targeted models using pseudophosphorylated htauE14 have substantiated foundational studies that pretangle tau pathology originates in the LC and contributes to AD progression.[5,179–182] htauE14 induces LC degeneration and tau spread, impairing olfactory learning.[180] These effects were reversed by driving LC–NE activity in a way that mimics its natural response to novelty.[182] A more recent report shows that LC htauE14 triggers peripheral and central nervous system inflammation and blood–brain barrier disruption.[179] Comparing transcriptional signatures of the LC in females and males to htauE14, males showed broad downregulation of synaptic and ion channel genes, while females showed targeted alterations in metabolic and developmental pathways.[181] Notably, only males displayed an upregulation of NE synthesis genes, suggesting that males, but not females, may mount a compensatory response. On the other hand, probiotic treatment rescued learning and reduced inflammation, with hippocampal glycogen synthase kinase 3 beta suppression observed only in females.[179] These molecular distinctions likely underlie observed sex-specific behavioral and neuropathological outcomes in response to tau pathology in the LC.

4.2 | LC–NE interactions with CRH

The LC–NE system has intricate reciprocal connections with other neuromodulatory systems that, unlike other systems, have been functionally characterized. One such neuromodulator is the stress-related neuropeptide CRH, which regulates the LC in a sex-dependent manner. Compared to males, LC neurons in adult female rats are more sensitive to local CRH infusions (causing increased neuronal discharge rate) as indicated by a left shift in the CRH dose–response curve.[151] Further, after local CRH administration, females show increased cyclic adenosine monophosphate-mediated cellular signaling as well as reduced swim stress–induced internalization of CRH_1 compared to males.[183]

While more sensitive to CRH, female LC neurons are less adaptable to high levels of CRH, which can occur during chronic stress. This is due to reduced CRH_1 receptor internalization compared to males.[184] Additionally, female LC CRH_1 receptors are more highly coupled to the Gs-protein, which can lead to prolonged NE release and heightened arousal during stress.[183,185,186] These types of baseline LC–CRH sex differences may enhance female risk for stress-induced cognitive impairments and anxiety by altering signaling in LC terminal regions. Indeed, CRH infusions into the LC produce theta oscillations in the medial PFC selectively in female rats but decrease low-frequency activity in the medial PFC in males.[187] These infusions increase and decrease medial PFC–orbitofrontal cortex coherence in females and males, respectively, but only alter orbitofrontal cortex activity in males, resulting in a delayed decrease in delta frequency power.[187] These sex-specific effects of CRH signaling in the LC are important to consider when assessing sex differences in the behavioral response to stress. In the cortex, CRH_1-Gs signaling is also enhanced in females, and this effect is linked to greater activation of AD pathways (Aβ and tau processing) and more cortical Aβ accumulation in CRH-overexpressing female mice compared to CRH-overexpressing male mice.[188] Last, conditionally overexpressing forebrain CRH in adult male and female mice redistributes Aβ peptides in somatodendritic processes in the LC. However, only females exhibit increased colocalization of Aβ42 in LC axon terminals in the PFC and display more pronounced blood–brain barrier disruption.[189] Thus, while the sex differences in LC–CRH interactions may lead to adaptations that support resilience in acute stress contexts, chronic CRH overactivation could predispose the female LC to metabolic overload, degeneration, Aβ accumulation, and tau pathology.

4.3 | Mixed human evidence of sex differences in LC–NE structure and function

While animal models provide crucial mechanistic insights into sex-specific LC vulnerability, human *post mortem* and neuroimaging studies offer the opportunity to validate and translate these preclinical findings across the lifespan and disease stages. However, compared to preclinical investigations, human work on the LC–NE system rarely explores sex differences because of the limited number of cases examined[190–199] or the exclusive use of women[200] or men.[201–203] The findings from those that do explore sex differences do not always align with results reported in rodents. Some studies report no sex differences in LC neuronal number, nucleolar volume, or melanin content across the lifespan,[204,205] while others observed more LC neurons and delayed cell loss in women.[205,206] Recent large-scale autopsy studies in aging, AD, and other neurodegenerative disorders have also rarely examined sex differences in LC integrity.[1,5,6,10,137,138,207–219] Among those that considered the effect of sex, findings varied: while some found no differences in LC volume,[165] neuronal number,[162,163,165,220–223] or hyperphosphorylated tau–positive LC neurons,[11,162,220,222,223] others have found greater LC hypopigmentation, a proxy for neurodegeneration, in men.[224,225]

Technical advances in imaging the LC with magnetic resonance imaging (MRI) have improved our ability to visualize the LC in vivo in humans, enabling reliable visualization and segmentation of this brainstem nucleus with high precision.[222,226–231] These methodological breakthroughs have facilitated a growing body of research demonstrating the central role of LC structure and function in pathological manifestations of AD in humans, including early tau burden, cognitive decline, and clinical progression.[232–236] Consequently, MRI-derived LC integrity has emerged as a critical early biomarker for AD-related neurodegenerative processes, showing promise for detecting at-risk individuals.

Most in vivo MRI studies investigating sex differences in LC macrostructural integrity report no differences between men and women. These studies have used a combination of young and old adults,[226,237] older adults only,[238,239] cognitively normal individuals assessed across the lifespan,[227,240,241] cognitively impaired older adults,[222] and individuals with autosomal dominant AD.[166] However, in an ethnically and socioeconomically diverse lifespan sample, some studies reported higher LC MRI signal intensity in women compared to men[242] in both healthy young and old individuals,[243–246] and MCI patients[245] who progressed to AD.[246] There was one exception reporting lower LC intensity in women compared to men.[247] Finally, three studies reported mixed findings on sex differences in LC microstructural integrity derived from diffusion-weighted imaging and quantitative multiparametric mapping, showing either no differences in lifespan and older cohorts[248,249] or preserved LC microstructural integrity in men compared to women across young and older adults.[250]

Regarding LC function in humans, limited evidence suggests that healthy young and middle-aged women exhibit lower functional connectivity between the LC and the hippocampus, parahippocampus, and middle temporal gyrus.[251] One study reported older women with elevated levels of frontal Aβ burden show higher functional connectivity with somatosensory regions, suggesting women mount compensatory mechanisms to maintain optimal salience detection despite increased pathology.[252] A well-known role of the LC is in emotional processing[142] and a meta-analysis of 56 functional MRI studies using various emotional stimuli revealed higher activations in several brain regions in women, including the amygdala and hippocampus, and most notably in the LC.[253] However, when specifically examining LC function during an emotional memory task, one recent study found no sex differences in LC activation in response to emotional salience, task-related salience, and memory performance[254]; we interpret this with caution because the emotional stimuli used might not have been sufficiently intense to elicit sex differences in LC response. In addition, functional connectivity at rest between the left LC and the executive control network was higher in women than men, primarily driven by premenopausal women.[255] Moreover, LC fluorodeoxyglucose positron emission tomography (PET) signals were higher in women compared to men for both cognitively healthy and impaired individuals,[256] which suggests that greater LC metabolism may provide increased resilience against the effect of AD-related processes.[257]

4.4 | Future directions

Although animal models have established robust sex differences in LC structure and function, evidence for sex-specific vulnerability to AD pathology remains incomplete, and inconsistent with human studies. Systematic investigation of these differences in both animals and humans remains crucial to advance the field.

Animal studies have shown that sex can modulate LC vulnerability in AD through several mechanisms. Specifically, females exhibit higher inflammatory responses after loss of adrenergic signaling, enhanced CRH_1-Gs protein coupling that leads to prolonged stress responses, and greater blood–brain barrier disruption, all of which could influence tau pathology initiation and clearance.[149,179,188,189] Regarding Aβ pathology, lesion and chemogenetic silencing studies have indicated that LC impairment can exacerbate Aβ deposition and associated neuroinflammation,[160,168] but the underlying mechanisms and whether they vary between sexes remain unclear and require targeted experimental investigation.

A major limitation across clinical as well as animal model studies is the lack of information about sex hormone–related factors in female participants (e.g., hormone levels, menstrual/estrous cycle phases, contraceptive use, menopausal/reproductive senescence status, history of gynecological surgery, or hormone replacement therapy), despite evidence that sex hormones (especially estradiol) modulate LC structure and function.[149,226,258] In addition, most human studies have examined specific age ranges or have pooled diverse age groups without isolating the critical menopausal transition at which the risk of health problems rise in women[259] including higher tau deposition.[260] Finally, several studies have pooled cognitively normal and impaired partici-

pants together, limiting our understanding of sex-specific patterns of LC changes across disease stages.

The vulnerability of the LC to declining estradiol combined with early tau accumulation might represent a key pathway explaining the well-documented higher risk for women to develop AD, especially during menopausal transition and early life ovarian removal.[57,261–268] However, critical gaps remain in our understanding of sex-specific molecular and cellular mechanisms underlying such LC vulnerability to tau and Aβ pathogenesis, including sex differences in neuroimmune, neuroendocrine, and neurovascular regulation. Understanding how hormonal changes influence LC vulnerability during the lifespan, and how this association is modified by AD pathology, genetic risk factors and other environmental factors such as stress, especially during prodromal phases of the disease, could inform sex-specific prevention strategies and optimal windows for intervention.

5 | SEROTONIN

A common feature of early-stage AD is the loss of 5-HT neurons and the development of tau pathology in the dorsal raphe nucleus (DRN), suggesting a relative susceptibility of these neurons to the detrimental effects of protein aggregation.[12,13] The DRN is the largest of the 5-HT–producing nuclei, but also contains GABAergic, glutamatergic, dopaminergic, and other peptidergic subtypes.[269] Dysfunction of 5-HT circuitry results in disruptions to sleep architecture and mood, particularly manifesting as depression.[270,271] Given that both depression and AD are more prevalent in women than in men,[272–274] and that depression is both a risk factor for and a symptom of AD,[275–278] 5-HT dysfunction may contribute to sex-dependent vulnerabilities underlying AD pathology and progression.

5.1 | Baseline sex differences in 5-HT dynamics and function

5-HT, one of the brain's most abundant monoamine neurotransmitters, is released in nearly all brain regions.[279] In humans, PET imaging has shown higher 5-HT synthesis rates in men[280] and women,[281] while cerebrospinal fluid studies indicate greater 5-HT metabolism in women.[282] Meanwhile, female rodents tend to exhibit faster rates of 5-HT synthesis and turnover,[283] particularly after 5-HT depletion challenge.[284,285] These differences may partially be explained by female rodents' higher expression of tryptophan hydroxylase, the primary rate-limiting enzyme for 5-HT production.[284] Interestingly, in contrast to 5-HT synthesis and metabolism, the rate of 5-HT neuronal firing is ≈ 41% higher in male than female rats, possibly reflecting a compensatory biological adaptation.[286]

Sex hormones exert strong regulatory effects on 5-HT signaling in the DRN. Both ERα and ERβ are expressed in DRN cells,[287,288] with ≈ 70% to 80% of receptor-expressing cells being serotonergic.[288] ERβ in DRN cells contributes to the regulation of estrous in rodents,[289] and is expressed in a subset of DRN 5-HT neurons projecting to the medial optic area in rodents, as well as in serotonin transporter (SERT)-expressing DRN neurons in non-human primates.[290,291] Within these neurons, ERβ directly regulates transcription of the tryptophan hydroxylase gene via an estrogen response element present in the gene's promoter region.[292,293] In female mice containing the ERβ null mutation, 5-HT levels are significantly lower in postsynaptic brain regions compared to wild types.[294] Genetic ablation of ERβ specifically in the DRN induces anxiety-like behaviors in female mice, but not in males.[295] Estrogens also modulate the expression of the enzymes responsible for 5-HT degradation, including monoamine oxidase A in the brain and monoamine oxidase B in the periphery, in female rats.[296] In addition to these effects, estrogen signaling suppresses binge-like eating through ERα-dependent activation of 5-HT neurons in female mice,[297] and modulates binge-like alcohol drinking through ERα and ERβ-dependent mechanisms in both sexes.[288] Androgen receptors, in contrast, are mainly expressed in the male DRN, and are primarily observed in non-serotonergic neurons.[298] Moreover, neonatal gonadectomy in males increases 5-HT release and reuptake in the hypothalamus,[299] suggesting that early-life masculinization contributes to sex-dependent differences in 5-HT signaling.

5.2 | Sex differences in 5-HT receptor expression and hormonal regulation

Sex differences in 5-HT receptor (5-HTR) expression vary across brain regions and physiological state. PET imaging showed reduced 5-HT_{2A}R binding in the frontal, parietal, temporal, and cingulate cortices of women compared to men.[300] In rodents, females also have region-specific differences in 5-HT_{2A}R mRNA levels compared to males; however, these transcriptional changes do not correspond to differences in 5-HT_{2A}R binding in these areas.[301] 5-HT_{1A}R expression is greater in the hypothalamus and amygdala of male and in the hippocampus of female rodents; yet no sex difference in 5-HT_{1A}R binding has been detected in these areas.[301] These findings are supported by the differential responses of male and female rodents to repeated restraint stress, with increased expression of 5-HT_{1A}R in the DRN of males and in the hippocampus of females.[302,303]

Sex differences in 5-HT function, via 5-HTRs and SERT, appear to be strongly influenced by sex hormones. Although estrogens have not yet been shown to interact with every 5-HTR subtype, experimental manipulations of estradiol levels in rodents affect 5-HT_{2A}R[304,305] and 5-HT_1R.[306] Estradiol administration increases 5-HT_{2A}R density in the cerebral cortex and nucleus accumbens of female rats,[305] and in the PFC of postmenopausal women.[307] However, the effect of estradiol on postsynaptic 5-HTRs appear to be cyclical, with reduced 5-HT_1R and 5-HT_2R expression during proestrus when estradiol levels are high, and increased expression during periods of low circulating estradiol.[306] In parallel, 5-HT binding to brain tissue is lower during proestrus and higher during estrous, again implying a cyclical nature to the expression of 5-HTRs.[308] On the other hand, ovariectomy of rodents decreases overall expression of 5-HT_1Rs,[306] 5-HT_{2A}Rs,[305,309] and causes SERT dysfunction[310] which can be rescued by supplemen-

tation with exogenous estradiol.[311] Together, these findings indicate that sex hormones profoundly influence serotonergic function by modulating 5-HT synthesis, degradation, and release; 5-HTR expression patterns; and developmental dynamics in neurotransmission, thereby contributing to sex-dependent differences in 5-HT signaling.

5.3 | Selective serotonin reuptake inhibitors and hormonal modulation in AD

The most widely used antidepressants, selective serotonin reuptake inhibitors (SSRIs), bind to SERT leading to reduced 5-HT reuptake and increased 5-HT concentration in the presynaptic terminals of 5-HT neurons. The role of SSRIs in AD treatment has long been debated due to the relation among SERT, depression, and AD. Expression of SERT in cortical and limbic areas is reduced in patients with MCI[312] and AD,[313,314] and this loss is more pronounced in AD patients with depression.[315] Importantly, SERT itself is subject to hormonal regulation, where estradiol can interact with SERT to modulate 5-HT signaling. For example, ovariectomy in female rodents[310,311] and macaques[316] reduces SERT expression. These findings point to a close interaction between serotonergic regulation and sex hormones, which may help explain the observations that women are more likely than men to develop depression during early- and mid-life,[272,273] and are twice as likely to develop AD.[274] On the other hand, depression serves as a risk factor for AD.[317] Moreover, mid- and late-life depression may be secondary to early AD pathology, as AD-associated depression correlates with tau and Aβ biomarkers,[276,277] and individuals with high genetic AD risk experience more depression in mid-life.[278] Therefore, enhancing 5-HT transmission with SSRIs may represent a potential therapeutic approach in AD.

Experimental evidence shows SSRI treatment can reduce Aβ levels in rodents[318] and in healthy older adults.[319] SSRIs additionally reduced AD-like pathology and improved cognitive function in AD mouse models (for review, see Mdawar et al.[320]). With respect to cognition, SSRI use has been linked to both positive and negative cognitive outcomes in AD patients.[321–324] Escitalopram, a common SSRI, is associated with a higher risk of developing dementia,[322] and faster cognitive decline in individuals with dementia.[325] Conversely, fluoxetine has been reported to enhance cognitive performance in AD patients.[326] Both escitalopram and fluoxetine show high selectivity for SERT over other reuptake transporters, and both induce long-term downregulation of pre-synaptic 5-HT_{1A}Rs. However, fluoxetine additionally inhibits 5-HT_{2C}R and 5-HT_3Rs,[327,328] and exerts uncharacterized effects on 5-HT_{2A}R,[329] suggesting that differential mechanisms could contribute to the efficacy of these medications. While more studies are needed to determine whether sex influences SSRI efficacy in AD, evidence that SSRIs are less effective in postmenopausal women and that estrogen therapy enhances SSRI response suggests that hormonal status may be a critical determinant of treatment efficacy.

The decline in estradiol after menopause accelerates AD progression in women,[330] providing further evidence that female sex increases vulnerability to AD in advanced age. During normal aging, ER density increases in women and is negatively associated with mood and cognitive performance.[331] In women with AD, loss of ERβ in the frontal cortex is more severe than in age-matched controls, with much of this reduction localized to mitochondria.[332] Reduced ERβ in the DRN has been linked to decreased 5-HT synthesis,[293] and ERβ loss impairs mitochondrial polarization,[332] which is essential for both 5-HT homeostasis and because 5-HT itself supports mitochondrial function.[333,334] Therefore, exacerbated reductions in ERβ may be particularly detrimental, depleting 5-HT as well as promoting neurodegeneration. Neuroimaging evidence further supports these associations: PET and MRI studies show that estrogen loss correlates with white matter degradation across several brain regions and a 30% greater burden of Aβ plaques compared to age-matched men.[335] Notably, exogenous administration of estradiol restores ERβ expression in the hippocampus of aging rodents,[336] suggesting that estradiol therapy may help preserve serotonergic integrity and mitigate cognitive and affective decline in AD.

5.4 | Sex differences in serotonergic systems in mouse models of AD pathology

Although the DRN has received comparatively less attention in AD research, growing evidence highlights its vulnerability to early tau pathology. Mouse models have additionally provided critical insight into how DRN dysfunction contributes to AD-like prodromal symptoms. In mice expressing wild-type htau, hyperphosphorylated tau appears in the DRN as early as 4 months of age, accompanied by reduced 5-HT neuron density, decreased neuronal excitability, increased inflammation, and diminished serotonergic innervation of the entorhinal cortex and hippocampus.[178] These changes coincide with the emergence of depressive-like behaviors, preceding cognitive decline and underscoring the link between early 5-HT dysfunction and prodromal symptoms in AD.[178] In DRN-targeted hyperphosphorylation-prone htau expressing mice,[337] social interaction deficits were observed in both sexes, while reward-related behaviors were disrupted only in males, again at early time points and in the absence of cognitive impairment. A more selective DRN 5-HT neuron-targeted hyperphosphorylation-prone htau mouse model revealed anxiety-like behaviors and altered stress coping in both sexes, while social disinhibition and spatial working memory deficits were restricted to females.[338] Notably, only females exhibited impairments in 5-HT neuron excitability at an early stage of pathology. Together, these findings demonstrate that DRN tau pathology contributes to the early emergence of AD-like behavioral symptoms and suggest that women may be particularly vulnerable to 5-HT dysfunction during prodromal stages.

In several widely used AD mouse models, DRN 5-HT neuron projections in postsynaptic regions were reported to be disrupted at relatively early ages. In 2-month-old 5xFAD mice, DRN 5-HT positive projections were significantly reduced in the dorsal CA1 of the hippocampus, medial septum and lateral hypothalamus, accompanied by decreased Tph2 expression and lower 5-HT levels compared to

wild-type mice.[339] Remarkably, optogenetic activation of DRN 5-HT projections in the dorsal CA1 was sufficient to reverse depressive-like behaviors and cognitive impairments. Similarly, in hAPP-J20 mice overexpressing human amyloid precursor protein with familial AD mutations, 5-HT fiber density and 5-HT_{1A}R and 5-HT_{3A}R expression were diminished in the CA1 region.[340] In this model, chemogenetic activation of median raphe 5-HT neurons, which densely project to the CA1, restored circuit excitability and improved cognitive function independently of Aβ pathology. While these studies provide compelling evidence that 5-HT dysfunction contributes to early behavioral and cognitive phenotypes through CA1 projections, they did not consider sex as a biological variable, highlighting an important direction for future studies.

5.5 | Future directions

Despite substantial evidence linking serotonergic dysfunction to AD progression and sex-specific risk, the underlying mechanisms remain unclear. Recent studies using DRN-targeted mouse pathology models have started to reveal early vulnerability and sex-specific effects,[178,337,338] establishing a valuable platform to investigate how 5-HT dysfunction contributes to AD progression. Hormone manipulations and sex chromosome analyses will be crucial for identifying the biological substrates of sex-specific susceptibility to AD in both mouse models and humans. A critical direction is to establish whether hormonal windows of vulnerability act though serotonergic pathways to influence risk factors such as depression and to what extent this accelerates AD progression. Given the early implication of 5-HT in AD, and the substantial basal sex differences in the serotonergic system, future work should use both preclinical and clinical approaches to define the sex-dependent therapeutic potential of SSRIs. Clinical trials should stratify participants by sex, menopausal status, and genotype to determine whether any type of estrogen supplementation modifies SSRI effects on serotonergic signaling and cognition during peri and postmenopausal periods. Clarifying the interaction among sex steroids, 5-HT function, and AD risk will be essential for developing treatment strategies, especially for women who face disproportionately higher AD risk.[341]

6 | CORTICOTROPIN RELEASING HORMONE

One common biological mechanism conferring susceptibility to neuropsychiatric symptoms, which puts individuals at a higher risk of developing AD, is stress.[342–344] CRH is one of many neuropeptides that mediate the autonomic, behavioral, endocrine, and immune responses to stress via binding at two G protein-coupled receptors, CRH_1 and CRH_2.[345–348] CRH_1 regulates cortisol (corticosterone in rodents) output from the hypothalamic-pituitary-adrenal axis, which is pronounced in anxiety, depressive disorders,[349–352] and AD.[353–355] Specifically, AD patients exhibit several stress system abnormalities including elevated levels of cortisol,[356–358] reduced CRH-positive cells, and upregulated CRH_1 expression in the cortex.[359–361] These increases in cortisol often occur at the MCI stage before AD pathophysiology becomes severe[353,358,362,363] and are associated with faster rates of cognitive decline.[353,362] Like humans, evidence from transgenic models suggests that increased corticosterone levels often precede Aβ plaque formation.[364–366] Later stages of AD, characterized by worsening memory and cognitive impairments, involve CRH_1-dependent Aβ-[366–371] and hyperphosphorylated tau-induced[372–374] hippocampal dysfunction. For instance, chronic stress or intra-hippocampal CRH infusions increase levels of hippocampal Aβ and hyperphosphorylated tau, effects that are blocked by CRH_1 antagonists.[370,373,374] AD mice heterozygous or null for CRH_1 have reduced hippocampal Aβ levels,[375] while mice overexpressing CRH have elevated hyperphosphorylated tau[188,376] and Aβ plaques.[188,369] Furthermore, AD mice exhibit higher levels of CRH within stress circuitry and an anxiogenic phenotype, which are eliminated in AD mice heterozygous for CRH_1.[364] Collectively, these data highlight a critical role for CRH_1 in modulating both early- and late-stage AD clinical pathology and underscore the need for future research examining sex differences in the role of central CRH_1 systems in driving AD pathology across various stages of the disease.[377]

6.1 | Sex differences in CRH levels and interactions with stress

Human[378] and rodent[379–382] adult females generally exhibit higher baseline hypothalamic CRH levels compared to males, which is associated with elevated levels of corticosterone and heightened anxiety in female rodents.[383–388] These sex differences in hypothalamic CRH expression appear to be age dependent. For example, at 6 months, male mice have elevated hypothalamic CRH levels compared to females, whereas at 18 months females exhibit a trend toward higher levels.[389] Additionally, in female mice, a significant increase in hypothalamic CRH levels occurs during aging, which is absent in males.[389] Although studies examining sex differences in baseline cortisol levels in humans are mixed,[390] there are reports of baseline cortisol levels increasing as women transition through puberty, while at the same time, levels decrease in men.[391] Interestingly, one study reported no differences in baseline cortisol levels in younger adults (22–36 years), but in older adults (67–88 years), women exhibited higher cortisol levels. This finding suggests that increased hypothalamic-pituitary-adrenal axis output during aging could be one mechanism underlying the heightened risk for AD in women.[392]

In response to stress, female rats exhibit higher levels of CRH in the paraventricular nucleus of the hypothalamus compared to males,[380,393] although this sex effect is stressor[393] and age[389] dependent. Compared to men, intravenous CRH administration increases adrenocorticotropic hormone and cortisol levels in both adult and adolescent women, respectively.[391,394] Last, a meta-analysis examining challenge-induced cortisol release in humans found that older subjects (69 ± 6 years) exhibited a larger cortisol response than younger subjects (28 ± 5 years), an effect that was significantly larger in women

than men.[395] To clarify the discrepancies in baseline sex differences for cortisol in humans, future studies need to control for the role of sex hormones in regulating hypothalamic-pituitary-adrenal axis output, the age of the participants, and the potential influence of circadian patterns on cortisol release.[390,396]

6.2 | Sex differences in CRH receptors and signaling

Studies examining baseline sex differences in CRH_1 expression indicate unique distribution patterns in hypothalamic nuclei between males and females. There is a trend for sex differences in total hypothalamic CRH_1 expression across the lifespan in mice, with females showing an increase compared to males when collapsed across age.[389] Interestingly, 18-month-old males and females exhibit increased hypothalamic CRH_1 levels compared to 1-month-old animals of the same sex, suggesting increases in hypothalamic CRH_1 may be associated with increased probability of AD progression during aging regardless of sex. Intriguingly, in a series of studies using a CRH_1 reporter mouse line,[397] two discrete hypothalamic nuclei displayed sex-specific patterns of CRH_1-expressing cell clusters; in females, higher baseline CRH_1 levels were found within the anteroventral periventricular nucleus and in males higher CRH_1 levels were found in the paraventricular nucleus of the hypothalamus.[398,399] These CRH_1 cell groups showed sex differences in cellular activation after acute restraint stress, with an increase in CRH_1 activity in the anteroventral periventricular nucleus in females and an increase in CRH_1 activity in the paraventricular nucleus of the hypothalamus in males. These effects also occur after 9 days of chronic variable stress.[400] Interestingly, postpartum female mice have elevated CRH_1 levels in the anteroventral periventricular nucleus compared to nulliparous females, as well as an increase in restraint stress-activated anteroventral periventricular nucleus CRH_1 neurons.[401] It would be interesting to know if these sex differences in CRH_1 expression change across the lifespan, as previous reports examining the entire hypothalamus indicate age-dependent effects with females exhibiting higher CRH_1 levels compared to males at 12, but not 1, 6, or 18 months of age.[389] In summary, these data suggest that differences in hypothalamic subnuclei CRH_1 distribution may contribute to sex differences in various stress-related disease states including AD.

6.3 | Sex as a mediator of CRH dysfunction in AD

Although many studies report an impact of corticosterone on pathology and behavioral outcomes in AD in males and females,[402–404] recent research indicates that sex differences also play an important role. Specifically, rodent AD models show that females demonstrate greater sensitivity to stress manipulations, including heightened anxiety,[405] whereas results from memory tests are mixed.[405–407] In addition to behavioral outcomes, studies report sex-dependent changes in AD pathology after stress, with female mice exhibiting greater Aβ, tau, and inflammation.[405,408] Cortical phosphoproteomic responses to chronic stress are also largely sex specific.[405] However, in humans, men with amnestic MCI were more likely to show deficits in episodic memory after acute psychosocial stress and express higher cortisol levels compared to normal aging men and women.[409] In sum, these findings are supportive of a role for sex in determining behavioral and neurobiological outcomes after stress. However, studies are yet to identify specific neural systems mediating these outcomes.

In AD, stress also has a sex-specific impact on CRH systems. Several studies in AD models report that females exhibit a significantly greater corticosterone response to stress, which may ultimately influence the expression of AD-related pathology.[405,407,410] Additionally, elevated corticosterone levels are observed in female but not male AD mice in the absence of an explicit stressor.[411] This may occur due to lower basal CRH levels in the paraventricular nucleus of the hypothalamus in males.[402,411] In human subjects, elevated cortisol during midlife is associated with the highest Aβ burden in cortical regions 15 years later.[412] Critically, this association was significant only in women, particularly those who were postmenopausal. Recently, several studies identified sex differences in CRH_1 receptor pathways that may mediate the increased vulnerability in females to AD pathology after stress.[183,188] Administering a CRH_1 antagonist prior to stress blocked the subsequent increase in expression of hippocampal Aβ only in female AD mice.[408] Administration of inhibitors of protein kinase A or extracellular regulated kinase, which are activated by CRH_1, also block the expression of Aβ in the hippocampus, suggesting that a CRH_1/protein kinase A/extracellular regulated kinase signaling pathway may mediate female-specific effects of stress on AD pathology.[408] In males, the expression of β-arrestin is thought to reduce CRH_1 signaling and thereby offer protection from the effects of stress on AD pathology.[183] Consistent with this hypothesis, β-arrestin knockout male mice showed elevated Aβ expression in response to stress.[408] Taken together, these studies provide important insight into components of CRH signaling pathways that mediate sex-specific effects of stress on AD pathology.

6.4 | Future directions

CRH systems are implicated in neuropsychiatric symptoms that increase AD risk as well as AD pathology. To further elucidate the role of hypothalamic CRH in AD progression, levels of corticosterone, CRH, and CRH_1 expression should be examined in rodent AD models at timepoints prior to disease onset and during the earliest stages of disease. Ideally, these studies will help clarify discrepancies in CRH expression reported between rodent AD models[402] and *post mortem* human brains.[359] Additionally, while numerous studies have examined the causal role of hippocampal CRH in regulating AD pathophysiology, a mechanistic understanding of sex differences in CRH_1 signaling pathways, neural circuits implicated, and the downstream consequences of such sex differences are understudied and thus, poorly understood. Studies manipulating the hypothalamic CRH systems in AD models are needed to further define the role of CRH in AD progression. Sex differences in hypothalamic nuclei CRH_1 distribution likely contribute to sex differences in stress-related disease states, but studies are needed to determine whether this effect extends to AD models and how this

may affect AD progression. Last, future research examining sex differences in CRH–LC signaling in AD models is needed, particularly across the lifespan and reproductive stages, to determine whether this stress system represents causal mechanism of heightened AD risk in women.

7 | OXYTOCIN

OXT is a small neuropeptide produced in the paraventricular, supraoptic, and accessory nuclei of the mammalian hypothalamus.[413] OXT is stored in large dense-core vesicles located in the soma, dendrites, and along the axon. OXT was initially believed to be released as a hormonal factor from the somatic and dendritic regions and largely had effects in the central nervous system via volume transmission to reach presynaptic neurons at a distance. More recently, axon fibers projecting throughout the brain have been identified which, upon stimulation, can release OXT in target regions.[414] Upon release, OXT binds to the G-protein coupled OXT receptor, which canonically stimulates the Gq pathway. However, it has also been shown to lead to Gi and Go activation.[415] OXT neurons project to brain areas implicated in AD pathogenesis, including the hippocampus, cerebral cortex, and amygdala, all of which express OXT receptors to varying degrees.[413,416] While OXT is well known for its peripheral physiological effects (e.g., milk let-down response and fetal ejection), there is strong evidence highlighting its central effects.[413] OXT's role in modulating social behavior is particularly relevant in the context of AD.[413] Social withdrawal is an early symptom of AD,[3] and social isolation increases the risk and progression of dementia.[417]

7.1 | Baseline sex differences in the OXT system

Sex differences in the OXT system across species have been recently reviewed elsewhere.[418–421] A host of studies indicate a lack of sex differences in the number of OXT neurons and innervation density.[422–433] When sex differences are present, females tend to show greater numbers of OXT neurons and innervation than males.[424–426,434] Meanwhile, OXT receptor expression shows largely the opposite pattern, with males displaying higher levels of OXT receptors than females.[433,435–439] Thus, there is a potential sex distinction in the structure of the OXT system at the level of the cell bodies versus target regions. However, such sex differences, or lack thereof, are highly brain region and species specific.[418,419,422–433,436,438,440–444] OXT receptor expression is further modulated by gonadal hormones, likely through ERα. Testosterone administration to neonatal female rats leads to higher OXT receptor densities whereas gonadectomy of adult male and female rats decreases OXT receptor density.[438,444] OXT receptor expression is also higher in estrous compared to non-estrous females, but still significantly lower than males.[433] Of note, sex differences are most commonly reported in rodent species whereas a vast majority of human and non-human primate studies indicate no sex differences in characteristics of the OXT system.[418] Such species differences are important to keep in mind when considering sex as a variable in AD-related OXT dysfunction, in addition to the translational value of any preclinical findings.

However, OXT itself promotes sex-specific behaviors, including promoting sexual behavior in males and parturition and post-partum behavior in females.[421,445–447] However, a major focus of OXT research in AD should be on the potential impact it has on social behavior,[448] especially given its sex-specific effects. OXT has been most well studied in its facilitatory role in forming partner preferences in monogamous species. This includes prairie voles and humans, with effects typically being stronger in females.[449,450] However, such effects are not exclusive to females, as antagonism of OXT receptors in the lateral septum blocks pair bonding and brain-wide knockout of the OXT receptor reduces consolation behavior in male prairie voles.[451,452] In non-monogamous species, such as rats, OXT administration can improve social recognition and reverse social avoidance in males, but not females.[453–456] Interestingly, early-life manipulations of the OXT system can have effects well into adulthood. For example, neonatally applied OXT induces aggressive mate-guarding behavior in adult female prairie voles.[457] Neonatal antagonism of OXT receptors also decreases alloparental care in male prairie voles and social approach behavior in female CD-1 mice.[458,459] Comparing sex differences in the effects of OXT across species indicates the presence of some species-specific behavioral effects that are seemingly in opposition (e.g., greater behavioral effects in female prairie voles and male rats, but relatively similar effects in both sexes in humans).[418,419] Together, these results again underscore the need to consider species in the sex-specific effects of OXT. In humans, OXT can also induce sex-specific behavioral effects.[418–420,460–463] Underlying sex differences in the neurobiological effects of OXT may lead to these behavioral differences but, in some situations, may also culminate in similar behavioral output in males and females.[418]

Effects of early-life OXT manipulation on late-life phenotypes and in the pathophysiology of AD are interesting to consider but have yet to be explored. Given the high prevalence of social deficits in AD,[3] understanding the contributing role of OXT dysfunction is of great importance. Further delineating the moderating influence of sex is also critical given the sex differences in AD symptomology. While women typically suffer greater incidence of neuropsychiatric symptoms,[19,125,464] men exhibit more severe symptoms in the social domain such as aggression, apathy, and agitation.[125] Neural underpinnings of such differences have yet to be identified, but they might be partially due to single nucleotide polymorphisms in the OXT receptor gene which have sex-specific effects on social behavior.[418] OXT is also known to reduce anxiety in both sexes, and appears to influence memory, with clear relevance to AD, but more work needs to be done to solidify its precise effects and any dependence on sex.[421]

7.2 | OXT dysfunction in AD patients and models

Preclinical studies of OXT dysregulation in AD rodent models reveal downregulation of OXT levels in both male and female APP/PS1[465,466] and female B6.APBTg mice[467] and reduced serum OXT levels in male

APP/PS1 mice.[468] However, these studies did not compare results between females and males and therefore do not account for any potential impact of sex in these AD models.

Human studies on the impact of AD on the OXT system present conflicting evidence. One of the first studies of OXT neurons in tissue from human AD patients used cell number and size as proxies for peptide production, and no significant differences were observed for OXT neurons compared to normal aging.[429] In this study, men and women were pooled due to a lack of significant morphological differences between sexes. These results were replicated in later studies analyzing normally aging populations and AD patients.[430,431] There were similarly no sex differences in morphological parameters of OXT neurons in the supraoptic or paraventricular nucleus,[431] though sample sizes were low. Another study in male patients showed no significant difference in cerebrospinal fluid OXT levels.[469] In another study including samples from men and women,[470] AD patients displayed increased levels of OXT in the hippocampus and temporal cortex. In contrast, recent work that included men and women reported lower serum OXT levels in AD patients.[471] Two other recent studies show OXT signaling pathway dysregulation in the blood and entorhinal cortex of AD patients.[472,473] In the case of the entorhinal cortex, this phenotype was only observed in men. These studies highlight how a failure to evaluate sex-specific changes in the OXT system can lead to conflicting findings and hinder our understanding of AD-related dysfunction. If there are sex differences in the effects of AD on the OXT system, future work could focus on evaluating the use of OXT-based therapeutics. Moreover, human studies investigating OXT system dysfunction in AD patients are limited and variable, likely due to the complexity of the system, the heterogeneity of the populations studied, the lack of sex-stratified analyses, and the limitations of the available methods. Furthermore, circuit-specific defects that emerge in a disease stage–specific manner may not be captured by the approaches described above. Given these limitations, the involvement of the system as a pathological hallmark in human patients remains to be fully determined.

7.3 | OXT as a potential treatment for AD

While OXT is well tolerated and improves social symptoms in the context of frontotemporal dementia,[474–476] there is only one study with a small number of AD participants revealing limited but positive outcomes on social cognition after intranasal OXT treatment.[477] However, low sample sizes have precluded analyzing the potential modifying effect of sex on patient outcomes. Meanwhile, the number of preclinical studies evaluating OXT as a therapeutic approach in AD has increased in the last few years. Such studies demonstrate the protective effects of exogenous OXT treatment at the molecular, cellular, network and behavioral levels. In vitro, the use of primary cultures or cell lines allow for the study of the effect of OXT after exposure to Aβ or other factors related to AD pathology.[465,478] Work on network- and synaptic-level responses has been performed in brain slices [465,479] and organoids.[480,481] These studies suggest that the protective effects of OXT in AD models are mediated by changes in synaptic plasticity,[479] inflammation,[465,480] and cell death.[478] OXT protects against Aβ-induced toxicity through the extracellular regulated kinase pathway, both in the PC12 cell line[478] and in hippocampal slices.[479] OXT is also anti-inflammatory[482] and can reduce microglial activation in AD models[465,483,484] through inhibition of Toll-like receptor 4–mediated pro-inflammatory signaling[483] and extracellular regulated kinase/p38 mitogen-activated protein kinase and cyclooxygenase-2 /inducible nitric oxide synthase nuclear factor kappa beta signaling pathways.[484] Using human induced pluripotent stem cell–derived cerebral organoids revealed that OXT further enables Aβ clearance by upregulating triggering receptor expressed on myeloid cells 2, a key modulator of microglial phagocytosis.[481] Together, evidence collected in vitro supports OXT as a therapeutic approach to target AD-associated pathways.

In preclinical AD models, multiple groups have shown that exogenous OXT can rescue behavioral and molecular AD-related phenotypes.[465,468,483–489] The protective effects of OXT observed in mouse models have been proposed to be mediated by reducing cell death[484,487] or inflammation,[468,484,487] and by increasing Aβ clearance.[466,468,484,485,487,488] At the behavioral level, cognitive benefits of OXT have been the primary focus in AD models.[465,484–487] Comparatively, there are few studies looking at the effects of OXT on social behaviors in these models. Intranasal OXT rescued the reduced sociability in APP/PS1 male mice.[465] Other work has assessed the consequences of OXT treatment on social memory using the 5-trial social task and found that OXT protects against social memory loss in APP/PS1 male mice.[465] In contrast, other studies have not observed altered sociability in APP/PS1 females, but rather showed reduced sociability in this model *after* OXT treatment.[485] Whether these differences in OXT effects are due to sex-specific mechanisms or variations in experimental protocols is unknown, and should be investigated in future studies.[490]

7.4 | Future directions

Research into sex differences in dysfunction of the OXT system in AD and the potential therapeutic benefits of exogenous OXT is in its infancy. More studies are needed to understand whether and to what extent the OXT system is impacted in AD, and the moderating effects of sex. However, one of the main limitations in probing this system is the lack of reliable methods to measure brain levels of OXT. OXT is usually measured using enzyme-linked immunosorbent assay and these measurements are mostly done in blood or saliva. Unfortunately, there is some evidence showing that such samples are not direct readouts of OXT levels in the brain.[491] Alternatively, *post mortem* histological analysis of human brain tissue using validated and reliable OXT antibodies could reveal changes in cell number, innervation, receptor distribution, and levels throughout the brain.

Exogenous OXT has been proposed as a treatment for AD, due in part to the early constellation of social dysfunction that persists throughout disease course. Yet, much of this work is based on relatively limited preclinical evidence showing benefits of OXT in AD models,

both at the neuropathological and behavioral levels. Given the stark species differences in the OXT system, more work needs to be done, and caution should be taken when interpreting and translating findings from preclinical models to humans. Considering these factors highlights the need for more work at the human and *post mortem* levels. Human studies can be further expanded to include robust clinical trials testing the therapeutic effects of OXT in AD patients. When designing such trials, dose and administration protocols need to be carefully defined, including route of administration, treatment duration, and the inclusion of behavioral therapy as part of the treatment. Such considerations are due to the fact that OXT has been shown to increase the salience of social behaviors,[413,492,493] opening the possibility of achieving greater therapeutic benefits in positive social contexts. Although human and non-human primate research shows few sex differences in the OXT system, controlling and analyzing results by sex will help clarify any potential modifying effects of sex on the therapeutic benefits of OXT treatment.

8 | ARGININE VASOPRESSIN

AVP is a hormone with wide-ranging effects on physiology and behavior. AVP-expressing neurons are primarily located in the hypothalamus, with projections extending to the basal forebrain, midbrain, and brainstem nuclei. Research across species has extensively characterized the AVP neuronal system, highlighting its conserved biological roles across species to regulate neurosecretion, sleep/wake cycles, circadian rhythms, social behaviors, and the stress responses.[494,495] There are also extra-hypothalamic AVP neuronal populations that display intrinsic differences based on sex.[496] Given that disturbances in homeostatic regulation are common in AD, studying the AVP system function/dysfunction and its associated dependence on sex may provide insights into disease mechanisms.

8.1 | Dispersed organization of the AVP system and underlying sex differences

In the hypothalamus, AVP neurons are divided into three major nuclei, each with distinct organization and specialized functions. AVP neurons in the supraoptic nucleus are magnocellular and regulate water balance and blood pressure.[494,497,498] Suprachiasmatic nucleus AVP neurons are parvocellular and orchestrate circadian rhythms.[499,500] The paraventricular nucleus includes both magnocellular and parvocellular AVP neurons that regulate social and emotional behaviors, modulate autonomic activity, and stimulate the release of adrenocorticotropic hormone, which is essential for stress responses.[494,497,501,502] Collectively, these hypothalamic AVP neurons are both neuroendocrine and neuromodulatory, with axonal projections to extra-hypothalamic regions such as the basal forebrain, midbrain, and brainstem. They are conserved in form and function across species.[418,421,496] AVP axonal projections emanating from hypothalamic areas are typically denser in males than females.[503,504]

Immunohistochemistry, RNAscope, and retrograde tracing studies have also revealed AVP-expressing neurons in extra-hypothalamic areas such as basal forebrain and amygdala. AVP neurons in these regions modulate social, emotional, and anxiety-related behaviors. The bed nucleus of the stria terminalis in the basal forebrain coordinates acute stress responses by inhibiting CRH secretion and influencing paraventricular AVP activity.[505] The amygdala plays a central role in fear and anxiety regulation.[506] Within the amygdala, the central nucleus serves as the primary output region orchestrating behavioral and physiological fear responses,[501] while the basal, lateral, and medial subdivisions process and integrate incoming information. AVP signaling reduces innate fear responses through local GABAergic neurons and provides feedback to the hypothalamic–pituitary–adrenal axis, thereby linking emotional regulation with neuroendocrine responses.[501,507–509] AVP neurons in these regions contribute directly to sex differences in behavior. In prairie voles, AVP injected into the lateral septum increased paternal responsiveness.[510] Similarly, the number of AVP neurons in the amygdala is greater in male mice in response to testosterone.[507] Structural investigations corroborate these findings; quantification of AVP immunoreactivity revealed that AVP neurons and fibers are more abundant in males than females in the septal nucleus, bed nucleus of the stria terminalis, and amygdala.[511–514]

AVP neurons are also present in other hypothalamic regions, such as the zona incerta and median eminence. Although these nuclei do not contain large populations of AVP-synthesizing neurons, AVP immunoreactivity is detected in synaptic terminals projecting from the hypothalamus. While sex differences in these areas have not been thoroughly studied, both the zona incerta and median eminence play important roles in regulating the hypothalamic–pituitary–adrenal axis in response to stress,[495,503,515] which is a sex-dependent process (see section 6).

AVP release exerts its effects via binding to two G-protein coupled receptor subtypes, AVPR1A and AVPR1B.[516] AVPR1A receptors are widely expressed across multiple brain regions, whereas AVPR2B receptors exhibit more restricted distribution within the hippocampus, amygdala, olfactory bulb, and hypothalamic–pituitary–adrenal axis.[418,517–519] AVP receptors expressed in subcortical regions exhibit marked sex differences with direct implications for behavior. Autoradiographic quantification reveals higher densities of AVP binding in the ventromedial hypothalamus and premammillary nuclei of male hamsters compared to female hamsters.[520] In addition, AVPR1A binding densities are also higher in male Wistar rats, showing distinctive subregional differences in the hypothalamus and basal forebrain such as the medial posterior bed nucleus of the stria terminalis, anteroventral thalamus, tuberal lateral hypothalamus, and stigmoid hypothalamus.[418] Behaviorally, blocking AVPR1A receptors in the DRN and lateral habenula reduces social behaviors, particularly urine marking, ultrasonic vocalization, and territorial aggression in male mice, but has no effect in females.[521] More recently, a study reported sex-specific distributions of AVPR1A receptors across mouse subcortical regions, reinforcing the previous findings that AVP receptor localization shapes AVP neuronal function. These findings provide targets for investigating the mechanisms underlying sex differences in AVP function.[517]

Overall, most studies[418,421] indicate that, compared to females, the male AVP system comprises larger neurons, greater amounts of AVP mRNA, and higher fiber density, receptor binding, and levels in plasma and urine.[423,425,428,431,432,436,520,522–542] There are some reports of the opposite or null effects, but species differences are much less pronounced compared to the OXT system.[543–545]

8.2 | AVP neurons show differing susceptibility in AD patients

The cytoarchitecture of AVP neuronal hubs demonstrate region-dependent susceptibility in healthy aging and AD, with some modulating influence of sex. In the two major AVP magnocellular hubs, the paraventricular and supraoptic nuclei, human studies across normal aging and in AD found no significant sex differences in total cell number or volume.[546–548] However, in old rodents (> 24 months) and humans (> 80 years) cellular hypertrophy is observed in the paraventricular and supraoptic nuclei that is absent during midlife.[429,549] Several human studies further suggest that AVP neurons remain activated in old age, displaying enlarged individual cell size in both normal aging and AD without neuronal loss.[550,551] This finding is rather atypical compared to other subcortical nuclei, which usually display severe loss of cell bodies and subsequent neurotransmission. However, these conclusions are limited by the small number of human studies and pooled analyses, underscoring the need for larger scale stereological studies that would be able to clearly identify any sex differences. In fact, evidence from quantitative stereology in rhesus monkeys suggests possible sex differences. There was a significant increase in neuron and glia counts in the male paraventricular nucleus with age, particularly > 20 years (roughly equivalent to > 60 years in humans).[552] Cellular hypertrophy also correlated with age, though the effect did not reach significance.

Suprachiasmatic nucleus AVP neurons play a critical role in regulating circadian rhythms and are selectively vulnerable to AD-associated pathology. Suprachiasmatic nucleus neuron number declines in individuals > 80 years, in contrast to the stable, or even increased number, in animal models.[547,553] In AD, suprachiasmatic nucleus AVP neurons are also significantly reduced.[547,553,554] However, evidence for sex differences in suprachiasmatic nucleus degeneration is limited. Although some data suggest a possible male-biased decline, this was not statistically significant.[547,553] Recent analyses combining quantitative histology and proteomics in AD brains reported neither sex-specific neuronal loss nor tau accumulation in suprachiasmatic nucleus AVP neurons.[554] This study also found no significant age-related changes, though data from individuals > 80 years remain sparse. Although circadian rhythms themselves differ between sexes[555,556] and circadian disruption in AD often presents with sex-specific features,[557] the neuronal influences, including that of AVP, underlying these sex differences in both baseline circadian rhythms and disease-related changes in AD remain unresolved. Addressing this gap will require studies that integrate clinical phenotypes with neuropathological findings, while accounting for AD heterogeneity, demographic variables, and intrinsic biological factors, including well controlled cohort studies that include sex as a variable.

Age-related AVP neuronal loss outside these brain regions has been documented.[511–514] However, studies directly quantifying AVP neuronal loss in AD, and whether this differs between sexes, remain limited. For regions like the basal forebrain nuclei, which regulate social behaviors, fear, and anxiety, understanding sex-specific AVP phenotypes in AD is of particular importance.

8.3 | Future directions

The AVP system, composed of multiple dispersed brain regions, is a critical modulator of physiology and behavior often disrupted in AD. The function of AVP neurons in the brain depends on their receptors and the target brain regions receiving efferent projections. Such effects are further modulated by sex differences, with healthy males across species typically displaying greater AVP function and sensitivity to AVP interventions. The diffuse nature and distinct functional outputs of each AVP region raises the interesting possibility that different AVP-expressing regions contribute to specific facets of AD. Yet, the overall extent and nature of these changes remain poorly characterized, highlighting the need for comprehensive preclinical and clinical studies that include sex as a factor. Furthermore, AVP-synthesizing regions appear to be separable into either selectively vulnerable or resistant to AD, but the mechanism for these differences is not well understood. Because hypothalamic AVP-synthesizing neurons act as central regulators of extra-hypothalamic AVP circuits, investigating sex differences within this system is of high importance. Future research should move beyond localized characterization and toward a more integrated, intra-network understanding. This includes interactions with other subcortical neuromodulatory systems, such as CRH and OXT, the latter of which frequently colocalizes with AVP circuits and also exhibits some sex differences.[457,458,558,559]

9 | HISTAMINE

HA, also known as 1H-imidazole-4-ethanamine or ergamine, is a low molecular weight endogenous alkylamino compound that plays a critical role in wakefulness, cognition, and immune regulation.[560,561] In the brain, the sole histaminergic hub is the posterior hypothalamic tuberomammillary nucleus (TMN). The histaminergic neurons of TMN synthesize HA through oxidative decarboxylation of L-histidine by a rate-limiting enzyme, L-histidine decarboxylase, in the presence of co-factor pyridoxal-5′-phosphate.[562] In the human brain, the TMN constitutes a diffusely organized population of large HA neurons (diameter 25–40 microns), located at the intersection of the caudal tuberal and rostral mammillary regions. These multipolar neurons have three to six primary dendrites and contain darkly stained peripheral endoplasmic reticulum, with typical irregularities in the cell membrane. These cells

are also characterized by substantial lipofuscin aggregation.[563,564] The number of HA neurons in humans varies between 64,000 and 150,000 neurons.[212,563,565,566] Although the TMN forms the core of the medial hypothalamic zone, it extends substantially into the lateral hypothalamic zone.[567] In addition to TMN HA neurons, mast and endothelial cells also produce traces of HA in the brain.[568]

As a part of the monoaminergic extra-thalamic pathways, TMN HA neurons maintain reciprocal connections with the OX/hypocretin neurons of the lateral hypothalamus and LC–NE neurons to promote wakefulness.[569,570] Besides these reciprocal connections, the unmyelinated axons of the TMN HA neurons send widespread dense innervations to hypothalamic sleep-promoting nuclei and the basal forebrain, as well as diffuse innervations to the neocortex.[567,571] HA neurons exert their neuromodulatory function through the four G-protein-coupled metabotropic histamine receptors. The postsynaptic excitatory H1Rs are primarily localized in cortical astrocytes, hippocampal, hypothalamic, and striatal neurons, whereas H2Rs are widely distributed in the basal ganglia, hippocampus, and amygdala. The presynaptic H3Rs are predominantly distributed in the cerebral cortex and subcortex, where they can function either as inhibitory auto-receptors or heteroreceptors. The immune regulatory H4Rs are expressed in the spinal cord, hippocampus, and cerebral cortex in humans and rats.[572,573] These receptor subtypes differ markedly in their ligand binding affinity, with H3R and H4R displaying stronger binding than H1R and H2R.[574] Based on the HA availability, microenvironment, and activation state, HA receptors can mediate inflammatory signals, hippocampal neurogenesis, and modulate anxiety-related behavior, fear, and recognition memory.[575–578]

Post mortem human studies and rodent models have shown loss of cortical and hypothalamic HA regulation in AD.[10,579–582] There is profound loss of TMN HA neurons associated with AD-specific phosphorylated tau aggregation.[579] Subsequent analysis revealed a significant negative correlation between TMN neuron counts and clinical sleep measures, including sleep maintenance and proportion of time spent in N2 and rapid eye movement sleep stages, while a positive correlation was noted with wake after sleep onset.[10] There is also a region-specific loss of HA neurons in the TMN, with the most severe loss in the rostral TMN and the least in the caudal TMN. This region-specific neuronal loss was accompanied by a significant downregulation of L-histidine decarboxylase mRNA only in the medial TMN.[580] Although TMN HA neurons declined significantly in AD, there is also a substantial increase in HA levels in the posterior hypothalamus in AD patients,[583] in spite of overall cortical HA levels declining significantly.[584] These region-specific alterations within the HA system suggest a compensatory response to the substantial loss of TMN HA neurons. Furthermore, reduction in HA metabolic products in cerebrospinal fluid[585] indicates altered HA levels and metabolism, which can potentially affect the brain's immune environment through microglial activation.[586] Together, these studies demonstrate that the HA system is severely affected in AD, but the pattern, precise mechanism, and any sex differences of neuronal loss in AD are unknown.

9.1 | Sex differences in the histaminergic system and interactions with sex hormones

The histaminergic system exhibits sex differences in tone, receptor expression patterns, and function, with compelling evidence that gonadal hormones play a key role in this relationship. TMN neurons express estrogen receptors ERα and ERβ in both sexes,[587,588] and a large percentage of HA-synthesizing neurons in the TMN express nuclear ERα.[589] Female rats have higher levels of HA in the brain.[590] This is partially a result of the influence of androgens on HA methylation, which reduces HA levels in males.[591] Female rats also display higher levels of cortical H1Rs and H2Rs than males.[592,593] Further, HA receptors are colocalized with estrogen receptors in the ventromedial nucleus of the hypothalamus.[594] HA binding sites in rat cortex are denser in adult female rats compared to males and prepubertal animals of both sexes.[595]

Considerable evidence highlights the critical role of ovarian and androgenic steroids in sex-specific expression of HA receptors and histaminergic function. HA levels and functional interactions with other neurotransmitter systems vary across the estrous cycle.[596,597] Prepubertal ovariectomized females show reduced HA binding sites at levels comparable to males, which is reversed by estradiol replacement.[595] Ovariectomy also reduces H1R binding and expression of H1R mRNA in the hypothalamus,[594,598] both of which are reversed by estradiol. The effects of ovariectomy and estradiol appear to be mediated primarily by ERα.[594] Evidence of the expression of progesterone and androgen receptors on TMN neurons is limited. However, adjacent hypothalamic regions, including the posterior hypothalamic nucleus, dorsomedial nucleus, ventromedial nucleus, infundibular nucleus, and bed nucleus of the stria terminalis, do express ERβs and influence histaminergic tone and function.[599,600] Progesterone specifically reduces the increased expression of H1Rs caused by estradiol, possibly through direct or indirect modulation of TMN neurons.[594]

Several recent studies have linked sex differences in the histaminergic system to sex differences in brain function and behavioral/cognitive functions. In female mice, exogenous HA increases striatal DA release via H3Rs in animals with high estrogen levels, whereas in males, HA reduces striatal dopamine release mediated by H2Rs.[597] After neuroinflammatory responses or exposure to drugs that alter H3R function, female mice display greater regulation of HA release compared to males, which may be hormonally mediated and confer a neuroprotective advantage.[601] Female mice also display greater sensitivity to the arousing effects of H1R antagonism.[602] Longer retention of object memory has been observed in female rats, potentially linked to greater H1R and H2R expression in females.[592] Similar dose-dependent improvements in memory performance in both sexes were seen after acute administration of the H3R antagonist thioperamide.[592] Acute chemogenetic activation of TMN HA neurons improved object recognition memory in female but not male mice.[603] H1R and corticosterone bioperiodicity are tightly linked, with females showing lower H1R bioperiodicity and greater food consumption than males during dietary restriction.[593,604] Collectively, these observations

illustrate a clear influence of sex on histaminergic function that could contribute to sex differences in how this neurotransmitter affects AD symptoms, pathology, and progression.

9.2 | Sex differences in histaminergic systems in human and animal models of AD

Changes observed in AD and models of AD include receptor binding, expression, and composition of functional domains, all of which are highly predictive of cognitive deficits as observed in AD patients.[605] Such findings support the potential for histaminergic drugs as effective AD treatments. However, while there are compelling sex differences in the HA system there is a paucity of data on how the alterations in histaminergic function in AD vary with sex, mainly owing to the inclusion of only one sex or the absence of rigorous assessments of sex differences in available studies.

A wealth of data has identified alterations in the histaminergic system in AD which are linked to cognitive decline and blood–brain barrier disruption.[606] A few *post mortem* human studies have examined HA neuronal changes in AD patients, but the effect of sex in the progression of AD remains unknown. A substantial (57%) loss of TMN neurons occurs in AD patients.[580] There are sex-dependent changes in TMN neurons in AD, which, although not statistically significant, were substantially more pronounced in women (67%) than in men (34%) relative to controls. TMN L-histidine decarboxylase mRNA expression levels showed non-significant decreases in AD patients compared to controls. This decline parallels the changes in TMN neuron number, with women showing a steeper decline than men, specifically in AD patients relative to controls. Finally, sex-dependent changes in HA projections across AD stages were assessed in the PFC. Both H3R and histamine-N-methyltransferase mRNA expression in the PFC was significantly increased in women at Braak stage V to VI compared to 0 to II. Additionally, in women, HA metabolism increased starting at Braak stage III to IV.[580]

To characterize the biological profiles of AD, various neurotransmitter metabolites have been studied in cerebrospinal fluid. Comparing tele-methylhistamine levels in the aging brain to that of AD patients revealed a contrasting trend in HA metabolism. Whereas HA metabolism tends to increase in normal aging, it declines in AD patients. This reduction in cerebrospinal fluid levels of tele-methylhistamine was sex dependent, with a greater decline in women AD patients than men AD patients.[585] The age-associated increase in tele-methylhistamine also depends on sex, with women having higher tele-methylhistamine levels than men.[585,607] In addition, tele-methylimidazoleacetic acid levels increased ≈ 30% in the cerebrospinal fluid during aging, and middle-aged women also displayed higher levels than men.[607] This contrast in cerebrospinal fluid levels of HA metabolites in normal aging and AD indicates a reduction in HA function, potentially due to TMN neuronal degeneration. Based on this work, modulating H3Rs with an inverse agonist may be able to normalize HA tone and improve sleep/wake dysfunction and cognition in AD patients.

To this end, rodent AD models have been leveraged to study the effects of pharmacological manipulation of the HA system. Improvements in cognitive and learning/memory deficits have been consistently observed after treatment with H3R antagonists or H3R inverse agonists in several transgenic models, including 5xFAD, APP_{Tg2576}, B6.129-Tg(APPSw)40Btla/J, THY-Tau22, and BL/6-Tg APP/PS1 mice.[608–614] H3R antagonists and inverse agonists reduced pathological protein accumulation, normalized cellular signaling pathways, reduced neuroinflammation and gliosis, decreased oxidative stress markers, increased acetylcholine levels, enhanced protein clearance mechanisms, reduced dystrophic neurite pathology, and restored cortical slow-wave coherence and frequency patterns. One study found that HA release was reduced in the amygdala of ApoE(−/−) mice.[615] Just over half of these studies with pharmacological interventions were conducted exclusively in males, with only one study using females alone to examine the effects of ABT-239 in TAPP mice for tau pathology.[609] Three studies included both sexes but pooled or segregated the data for analysis without a statistical assessment of sex differences.[608,613,614] However, beneficial effects appeared similar between males and females.[613] Animal studies without pharmacological intervention that pooled sexes for analysis report either transient decreases in HA neuron number early in embryonic development that normalizes in adulthood or no difference in H3Rs expression in TASTPM mice, similar to observations in humans.[616,617] One study including sex differences observed that 3xTg-AD mice displayed decreased L-histidine expression in females and not males, without commensurate changes in HA levels.[618]

Male Sprague–Dawley rats display increased hypothalamic, midbrain, and cortical HA levels over the course of aging, which is increased under conditions of stress.[619,620] HA receptor preservation in transgenic models and advanced aging suggest that providing HA or an agonist may be a promising treatment strategy. H3R inverse agonists, such as ABT-239 and SAR152954, have been effective in improving brain plasticity, learning, and memory in rodent models of fetal alcohol spectrum disorders, even into adulthood and well after the neurodevelopmental insult.[621–624] Future work should aim to conduct rigorous evaluations of sex differences in responses to histaminergic interventions to better understand underlying mechanisms of AD pathology and potential variation in response to treatment with histaminergic drugs.

9.3 | Peripheral HA and AD pathology as mediated by sex

Sex differences in peripheral histaminergic function, particularly related to immune responses, potentially contribute to divergent AD susceptibility and response to histaminergic treatments. In female rats, mast cells display greater susceptibility to sex steroid modulation of HA release and perinatal androgens contribute to organizing lifelong sex differences in mast cell function, with males exhibiting reduced HA content and attenuated degranulation responses.[625–627] Castration reduces peritoneal HA concentrations in males,[628] and testosterone

exerts selective anti-inflammatory effects on mast cells sourced from women donors, but not men.[629]

H4Rs are predominantly expressed on immune cells and orchestrate mast cell recruitment and activation,[630,631] potentially underlying the relationship between peripheral sex differences and central neuroinflammatory responses. Emerging evidence suggests that peripheral histaminergic dysfunction influences AD pathogenesis through multiple mechanisms that could be sex dependent. Aβ peptides trigger mast cell degranulation through pannexin1-dependent mechanisms,[632] while mast cell proteases can generate Aβ N-termini,[633] creating positive feedback loops between AD pathology and neuroinflammation caused by the peripheral immune response.[634] HA promotes astrocyte neuroprotection and microglial neurotoxicity,[635–637] while simultaneously disrupting blood–brain barrier integrity and altering neurotransmitter function.[637–639] Notably, females display greater vulnerability to HA-mediated disruption of blood–brain barrier integrity.[606,640,641] Mast cell deficiency improved cognition in an AD mouse model;[642] however, the vast majority of studies have either excluded females or failed to assess sex differences statistically.[643,644] This represents a critical knowledge gap in understanding how the mechanisms discussed here may contribute to the increased prevalence of AD in females.

9.4 | Future directions

Substantial sex differences in the HA system are well documented across neurobiological and behavioral domains that hold considerable relevance for understanding sex differences in AD. Higher HA receptor expression, enhancements in histaminergic modulation, decline in HA metabolism, and distinct patterns of HA–neurotransmitter interactions are evident in healthy women. Such differences have been linked to sex differences in cognition, learning and memory, and arousal in which the histaminergic system plays a key role. Despite robust evidence of sex differences in histaminergic function and general alterations to this system in AD, there is limited research examining the role of sex on histaminergic function in the context of AD.

There are several other important future steps that should be performed to appropriately understand sex as a modifier of histaminergic dysregulation in AD. For example, histaminergic anatomical organization and connectivity have not been characterized in AD. Although H3R antagonists and inverse agonists have shown considerable therapeutic promise in preclinical models of AD, the efficacy and potential synergy with other AD treatments have not been rigorously investigated or examined across sexes. Potential alterations in the peripheral histaminergic system, particularly mast cell dysfunction and disruptions in blood–brain barrier integrity, represent another understudied domain in which sex differences could contribute to AD pathogenesis. Finally, whether and how the histaminergic system compensates at different stages of AD progression and how such effects vary with sex need to be examined.

10 | OREXIN/HYPOCRETIN

Neuropeptides OX-A and -B (OX-A/B, also known as hypocretin 1 and 2) are released by a specific group of neurons localized to a limited area in the tuberal region of the hypothalamus behind the paraventricular nucleus. The OX system plays a key role in regulating the transition between wakefulness and sleep, orchestrates thermoregulation and blood pressure, participates in motivation/reward and feeding, and interacts with the neuroendocrine system.[645]

Disruption or degeneration of the OX system leads to symptoms of narcolepsy in both humans and animal models.[646] OX circuitry exhibits distinct synaptic architecture, characterized by excitatory glutamatergic input and a specialized glutamatergic receptor profile. This synaptic architecture supports the system's rapid activation in response to salient stimuli and underlies its role in regulating arousal, motivation, and survival-relevant behaviors. Thus, the role of OX in regulating the sleep–wake cycle has been largely documented in narcolepsy type 1 (or in OX knock-out animal models), which has expanded our understanding of the relevant role of this neurotransmitter in other brain functions and disease states.[646–648]

10.1 | OX system and sex hormone interactions

After the discovery of two OX types, OX-A and -B, and their receptors, OX1R and OX2R,[649,650] a separate report demonstrated that OX modulates luteinizing hormone secretion in an estrogen-dependent manner.[651] In particular, the effects of OX-A and -B on luteinizing hormone secretion were investigated in ovariectomized rats with or without supplementation of ovarian hormones. Intracerebroventricular administration of OX-A and -B rapidly stimulated luteinizing hormone secretion in a dose- and time-dependent manner in ovariectomized rats pretreated with estradiol and progesterone. Ten minutes after injection, peak plasma luteinizing hormone levels were significantly higher in OX-A-treated rats compared to those treated with OX-B. Conversely, in ovariectomized rats without steroid priming, both OX-A and -B suppressed luteinizing hormone secretion. Thus, OXs are part of a group of hypothalamic signaling molecules that neurochemically link reproductive function with energy homeostasis.[651]

10.2 | OX expression and function depend on sex hormones

In rodents, sex differences have been reported in OX peptide expression, function, and receptor distribution across the hypothalamus, pituitary, adrenal glands, and gonads. Female rats show higher levels of OX-A and prepro-OX mRNA in the lateral and posterior hypothalamus,[652,653] and greater OX1R expression in the hypothalamus compared to males. In contrast, males exhibit higher OX1R expression in the pituitary and OX2R in the adrenal glands compared to females.[654] These expression patterns are hormonally regulated:

gonadectomy increases pituitary OX1R in male rats (reversed by testosterone) and estradiol replacement in ovariectomized female rats produces a similar but stronger effect.[655] Despite these dynamic effects, long-term hormonal manipulations do not appear to significantly alter hypothalamic OX expression.[653,655] In contrast, rapid, cyclical changes in prepro-OX and receptor expression have been observed in adult females, particularly during proestrus.[656]

OX terminals innervate gonadotropin-releasing hormone neurons, which express OX1R and respond directly to OX by increasing gonadotropin-releasing hormone release.[657–660] This supports a dual mechanism of luteinizing hormone regulation: indirectly via hypothalamic gonadotropin-releasing hormone release and directly at the pituitary level,[660] particularly in females. Estradiol modulates these interactions: OXs suppress luteinizing hormone in ovariectomized rats while enhancing luteinizing hormone release in estradiol-treated animals.[651,661,662] Estradiol has also been reported to suppress OX-A activity directly,[663] although most OX neurons do not co-express estrogen receptor ERα or androgen receptor, suggesting that hormonal control may occur via afferent inputs.[664]

These sex-specific expression patterns are developmentally programmed as proestrus-associated upregulation of OX genes is abolished in neonatally androgenized females.[665] Moreover, combined estradiol and progesterone treatment in perinatally demasculinized males mimicked the female-like pattern, indicating that perinatal testosterone imprints the sex-specific regulation of both OX and gonadotropin-releasing hormone/luteinizing hormone systems, possibly through epigenetic mechanisms.

Beyond reproductive control, OXs are involved in other sex-specific behaviors and pathologies, such as male sexual motivation,[664,666] sex-specific obesity patterns,[667,668] and differential stress responses, depression susceptibility, and related disorders.[669,670] Nonetheless, much of what is known about OX function is based on male data, leaving the female phenotype underexplored.

10.3 | Clinical evidence of sex differences in orexinergic systems

Understanding the complex interplay among female sex hormones, orexinergic signaling, sleep disruption, and tau pathology may yield novel insights into the sex-specific progression of AD and support the development of tailored therapeutic strategies. However, clinical data on sex differences in human OX expression remain limited, with a notable lack of mechanistic studies across the lifespan. Most available evidence derives from research on sleep disorders (with narcolepsy being a prototypical model of OX deficiency[671]), including neuropsychiatric and neurodegenerative conditions.[672]

Such sleep and mental health disorders show marked sex differences in prevalence.[673–675] Specifically, the higher incidence of insomnia, circadian sleep–wake rhythm disorders, internalizing mental health conditions, and AD in women, particularly during hormonal transitions such as puberty and menopause,[676,677] aligns with preclinical findings of enhanced OX expression and reactivity in females. Along with growing evidence suggesting a possible link to hyperactivation of the OX system,[678,679] insomnia is consistently more prevalent in women,[680] whereas narcolepsy appears to be more common in men.[681]

Studies directly measuring OX-A levels in humans, whether via *post mortem* brain analysis or cerebrospinal fluid sampling, have yielded inconsistent findings. Complicating matters, plasma OX-A levels, despite being easier to access, do not correspond to the cerebrospinal fluid OX-A concentrations.[682] One *post mortem* study of patients with major depressive disorder found increased hypothalamic and cortical OX-A immunoreactivity in women, but not in men, as well as an absence of diurnal OX-A regulation in cerebrospinal fluid samples collected from patients,[670] suggesting sex-specific involvement of OX-A in major depressive disorder-related sleep and mood disruptions.

Another *post mortem* study revealed a loss of hypothalamic OX neurons and reduced cerebrospinal fluid OX-A levels in late-stage AD, with no significant sex effects reported.[683] On the other hand, when AD patients were compared to cognitively normal controls, higher cerebrospinal fluid OX-A levels were observed in women compared to men, regardless of diagnosis.[684] A similar trend was reported across AD, dementia with Lewy bodies, and healthy controls, where differences in cerebrospinal fluid OX-A levels were primarily driven by sex. Specifically, women exhibit higher and lower OX-A cerebrospinal fluid levels in AD and in dementia with Lewy bodies, respectively.[685] Notably, this study suggests that sex-specific dysfunction of the OX system may be disease dependent. Still, these interpretations should be considered with the fact that anti-dementia treatments prescribed to patients may have affected sleep and OX neurotransmission. Conversely, some have found no sex differences in cerebrospinal fluid OX-A levels across diagnostic groups, although OX-A cerebrospinal fluid levels were higher in AD groups.[686] Likewise, higher cerebrospinal fluid OX-A concentrations have been reported in patients with moderate-to-severe AD versus controls, but not in patients with mild AD, and no sex-related differences were found.[687] However, a subsequent investigation revealed higher cerebrospinal fluid levels of OX-A in patients with MCI compared to controls, again with no reported sex differences.[688]

A more recent multicenter study involving patients with a range of neurocognitive disorders (including mild to severe AD, behavioral variant frontotemporal dementia, non-fluent primary aphasia, and idiopathic normal pressure hydrocephalus) and elderly controls, reported higher cerebrospinal fluid OX-A levels across most disorder groups compared to controls.[689] While no sex differences were detected, men in the control group exhibited higher cerebrospinal fluid OX-A levels than women. This finding diverges from preclinical models but may reflect age-related hormonal shifts that were not accounted for, given the mean age of > 60 years in the human control group which may diminish estradiol-mediated modulation of OX-A signaling.

10.4 | Considering sex in the therapeutic potential of OXs in AD

Interest in OX as a therapeutic target for neurodegenerative diseases, especially AD, is growing.[673] Enhanced OX activation in females—linked to greater stress vulnerability—may contribute to sex-specific susceptibility to AD.[669] Moreover, estrogen receptors have been localized in neurons containing neurofibrillary tangles,[690,691] although hormone therapies have shown limited benefit in clinical trials.[692] Given the role of estradiol in sleep regulation[693–696] and the central importance of OX in the sleep–wake cycle, the intersection among estrogens, sleep, and OX signaling in AD pathophysiology, particularly in women, deserves greater attention.

Two recent studies using rTg4510 tauopathy mice highlight key sex differences in OX responses to pharmacological intervention.[697,698] Acute OX2R antagonism improves non–rapid eye movement sleep and reduces hyperarousal in male mice, but these effects are transient or absent in females despite equivalent drug exposure. Chronic treatment in males also reduces hyperphosphorylated tau levels and improves glymphatic clearance, effects that were similarly absent in females. In animal model studies, suvorexant, a dual OX receptor antagonist, increases rapid eye movement sleep in both sexes but fails to resolve hyperarousal, whereas zolpidem, a positive allosteric modulator of the $GABA_A$ receptor, shows limited impact.[697,698] Parallel evidence in humans shows that degeneration of subcortical wake-promoting neurons correlates strongly with disrupted sleep phenotypes in AD and progressive supranuclear palsy patients, suggesting a mechanistic substrate for arousal dysregulation in tauopathies.[10] These results suggest that females may have intrinsic resistance to OX2R-targeted therapies, potentially due to altered receptor function or divergent tau-related circuitry. In agreement with this possibility, chronic administration of lemborexant, another dual OX receptor antagonist, improves sleep–wake cycle, reduces reactive microgliosis, and mitigates brain atrophy in male tauopathy mice.[699] This further underscores the therapeutic relevance of modulating OX signaling in AD models and its potential sex-dependent effects.

Finally, with increasing clinical interest in dual OX receptor antagonists for insomnia disorder[700] and their potential utility in AD,[701] preliminary findings suggest good tolerability in both sexes. In a large trial, suvorexant showed comparable efficacy in women and men with insomnia disorder, though adverse events were more frequently reported in women.[702] In a separate placebo-controlled study in patients with mild-to-moderate AD and comorbid insomnia disorder, suvorexant significantly improved objective sleep measures without sex-related differences in efficacy.[703] However, neither trial accounted for hormonal status or menopause/menopausal transition. Furthermore, dual OX receptor antagonists, by targeting both OX1R and OX2R, may obscure potential sex differences in receptor-specific OX regulation and pharmacodynamics.[682]

Overall, human evidence remains inconclusive. Existing studies are predominantly cross-sectional, often with small sample sizes that do not incorporate hormonal profiling or stratified analyses. Longitudinal research is required to clarify whether sex modulates OX signaling across aging and neurodegeneration, and whether OX-targeting therapies warrant sex-specific dosing or timing.

10.5 | Future directions

OX plays a major role in sleep–wake cycles, disruption of which is one of the most common occurrences throughout the course of AD. Although human studies have shown inconsistent results, it is clear that the OX system is sensitive to sex hormones and pharmacological effects of OX interventions are sex dependent. Thus, future research should establish longitudinal cohorts with serial cerebrospinal fluid OX level assessments, alongside core biomarkers of neurodegeneration (Aβ/tau), objective sleep–wake metrics (e.g., actigraphy, polysomnography), and cognitive evaluations, with adequate power for sex and hormonal subgroup analyses. Therapeutic investigations should conduct sex-balanced randomized controlled trials of dual OX receptor antagonists, especially in older adults with cognitive complaints or early-stage AD, including pharmacokinetic/pharmacodynamic profiling and biomarker or imaging endpoints. Measuring the potential differences in OX neurotransmission during the various physiological phases of men's and women's lives, in light of the continuous modifications of sex hormone levels, is also warranted. Finally, further emphasis should be placed on exploring the marked sex differences in the effectiveness of OX2R antagonism, specifically focusing on the sex-dependent interactions between tau pathology and the OX system. These insights may inform the development of hypnotic treatments for tauopathy-related neurodegenerative diseases. Notably, enhancing sleep and reducing hyperarousal after disease onset has been shown to restore cognitive function in male tau transgenic mice, even without reducing phosphorylated tau levels.[39] Although the mechanisms remain unclear, these findings reinforce the therapeutic potential of sleep modulation against neurodegeneration via the OX system.

11 | DISCUSSION

NSSs are increasingly being recognized as key players in the early stages of AD, and their dysfunction persists throughout disease progression. These systems are responsible for regulating mood, stress, social behaviors, sleep, and cognition, accumulating early, disease-specific pathology that ultimately leads to neuronal degeneration. NSSs display varying degrees of sex differences in structure, function, and response to sex hormones. Such sex-specific differences are generally less well explored in humans and AD but could contribute to the well-documented sex disparities in incidence, symptom progression, and neuropathology.

In this review, we summarize evidence of sex differences across nine NSSs. Variability in reported sex differences across human and model systems stems, in part, from methodological gaps, including the lack of sex-disaggregated data, underpowered samples, and failure to account for hormonal status across the lifespan. This has resulted in mixed findings, with some failing to examine sex altogether. Without consistent,

sex-informed experimental designs, the field risks overlooking critical mechanisms that shape AD vulnerability, particularly at the earliest stages of disease when mitigation strategies would be most effective. Moving forward, research on NSSs, and dementias more broadly, must systematically include sex as a biological variable, incorporate hormonal context, and report findings by sex in both human studies and animal models to resolve discrepancies in the literature. Doing so will strengthen and clarify our understanding of NSSs involvement in dementia, supporting the development of more targeted and effective interventions for both women and men. Some considerations for future studies are to determine the extent to which each one of these NSSs contribute to overlapping symptoms (e.g., AVP and OXT in social deficits, LC–NE and DRN 5-HT in depression), the amount of cross-talk occurring between each system (e.g., LC–NE and CRH), and the extent to which non-primary neurotransmitters (e.g., DA release from DRN subpopulations, galanin release from the LC) play a role in disease processes.

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