WOMEN'S HEALTH

Sex differences in age-associated neurological diseases—A roadmap for reliable and high-yield research

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Once taken into consideration, sex differences in neurological diseases emerge in abundance: (i) Stroke severity is significantly higher in females than in males, (ii) Alzheimer's disease (AD) pathology is more pronounced in females, and (iii) conspicuous links with hormonal cycles led to female-specific diagnoses, such as catamenial migraines and epilepsy. While these differences receive increasing attention in isolation, they likely link to similar processes in the brain. Hence, this review aims to present an overview of the influences of sex chromosomes, hormones, and aging on male and female brains across health and disease, with a particular focus on AD and stroke. The focus here on advancements across several fields holds promise to fuel future research and to lead to an enriched understanding of the brain and more effective personalized neurologic care for all.

INTRODUCTION

Personalized medicine aims to appreciate the uniqueness of individual patients and may thereby allow for hand-tailored care (*1*, *2*). There have been impressive advances in diagnostic and therapeutic possibilities (*3*, *4*), computational resources, and medical artificial intelligence (AI) (*5*) in just a handful of recent years. These innovations fuel the implementation of precision medicine (*6*). Despite this very promising progress, it is currently still beyond our capabilities to explicitly embrace the complexity of each individual in practice. Conceivably, however, a great amount of variability between individuals can be captured by considering natural groups, such as older versus younger and male versus female patients. Until true precision medicine is possible, the most effective approach may be to optimize the treatment for these subgroups given the assumption that patients within one subgroup will react more comparably than patients across the entire patient spectrum. In addition, this approach holds promise to enhance our understanding of the underlying biological processes that will eventually be crucial to innovate suitable treatments.

Whether there are any meaningful differences between male and female human brains is a perpetually highly debated topic (*7*). Among others, this discussion has been fueled by a review paper that summarized three decades of neuroimaging literature in healthy human adults (*8*). The review concluded that only 1% in total variance in brain structure and lateralization can be explained by sex after adjusting for brain size (*8*), the sole markedly differing neuroimaging metric (*9*). Independent of neuroimaging, there are also unusually few reports of replicable differences between healthy male and female participants in terms of behavior. Males are consistently found to have better visuospatial skills, while females outperform males in executive speech tasks (*10*, *11*).

However, when studying the diseased brain, there is little doubt that biological sex plays a key role. Considering incidences alone, most neurological diseases confer substantially differing risks for males and females. In this review, we aim to demonstrate how understanding sex differences in neurological disease can be essential to crucially augment our understanding of the healthy human brain in general and its reaction to stressors in the context of disease. While our research focus is on neurological diseases and how they affect the brain, investigating sex differences requires an understanding of the biological system at large.

Therefore, in the first part of this review, we will discuss what is known about the effects of sex-specific genes, hormones, and aging on the brain. In the second part of this review, we will review major breakthroughs of sex-specific research for two of the most common age-associated neurological diseases: Alzheimer's disease (AD) and ischemic stroke. More specifically, we will present sex-specific findings ranging from those relating to disease incidence and prevalence to clinical presentation, pathophysiology, and treatment. The second part will end with a brief overview of sex differences across the entire range of neurological disease (cf. Fig. 1 for an overview of content). In each part, we will highlight pertinent preclinical and clinical research involving cells, animals, and humans. For each instance, we will explicitly state from which setting findings resulted. Where possible, we will correlate respective findings from preclinical and clinical research. Of note, we describe sex differences as relating to biological sex. Hence, we will use the terms males and females. We will focus on those differences originating from sex-specific genetic and hormonal alterations and their effects on anatomy, pathophysiology, disease manifestation, and response to treatment (*12*).

BIOLOGICAL UNDERPINNINGS

Sex-specific genes

Our genes represent our biological foundation. In human mammals, the genetic architecture of males and females differs by an entire chromosome. Data support that about ~300 million years ago, the X and Y chromosomes originated from a regular pair of autosomes (*13*). Autosomes are the paired chromosomes that are not sex chromosomes, i.e., chromosomes 1 to 22 in humans. In total, humans typically have 46 chromosomes (44 autosomes, 2 sex chromosomes,

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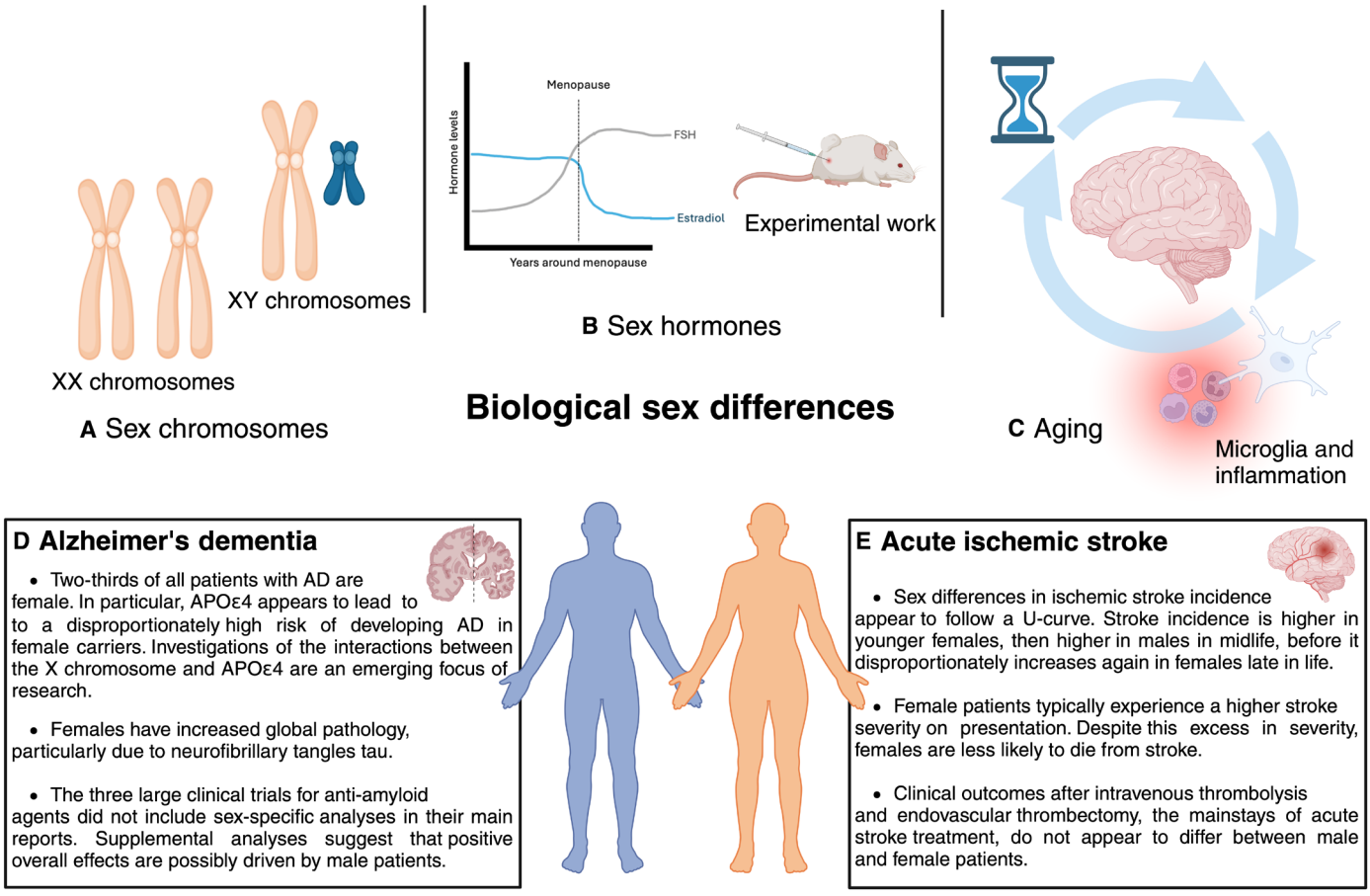

Fig. 1. Biological sex, mediated through sex-specific genetic and hormonal alterations, has vast effects on the human brain, especially in the presence of disease. The first half of this review highlights research relating to effects of (**A**) sex chromosomes, (**B**) sex hormones, and (**C**) sex-specific aging processes on the brain. The second half addresses sex differences uncovered for two of the most burdensome neurological diseases: (**D**) Alzheimer's Disease (AD) and (**E**) Acute Ischemic Stroke (AIS). (A) Sex chromosomes: Recent X chromosome–wide association analyses suggest risk loci on the X chromosome for AD (*185*). There are calls to scrutinize interactions of the X chromosome and APOEε4 (*184*), the gene variant known to have stark effects on AD risk and further neurological diseases (*179*, *405*, *406*). (B) Sex hormones: They have main effects on neuroprotection, neuroplasticity, and memory and may play major roles in the development of AD (*113*, *238*) and outcome of AIS (*319*, *341*). (C) Sex-specific aging and the immune system: Immunosenescence (*155*) and inflammaging (*154*) are main phenomena of an aging immune system. Research into sex differences in AD and further neurological diseases highlights the sex-varying roles of neuroinflammation in general and microglia in particular (*224*, *335*, *336*). In summary, the aim of this review is to inform about the origins of biological sex differences in the brain and foster a greater awareness of each field's progress, encountered obstacles, and solutions. Closer ties between preclinical and clinical work and intensified dialog between researchers investigating the healthy younger and diseased older brain may enrich and accelerate research. Eventually, this approach to cerebral sex differences may augment our understanding of the brain in general. It holds promise to achieve optimal brain health and treatment of brain disease for each individual patient in the actual sense of precision medicine. Figure created with BioRender. A. Bonkhoff (2025); https://BioRender.com/k39p267.

either XX or XY). At the time, the Y chromosome presumably acquired male-specific genes. Centrally among these genes was the so-called SRY-gene (*14*, *15*). This gene initiates the development of male-defining organs via the production of the testis-determining factor. Since then, the X and Y chromosomes have become structurally heteromorphic. Both chromosomes share a limited length of pseudoautosomal regions along which they can still recombine. Other than that, the transmission of the Y chromosome occurs clonally from father to son only (*16*). This mode of transmission has put the Y chromosome at a substantially higher risk of mutations, deletions, and insertions (*17*, *18*). Altogether, it effected the loss of a majority of genes on the Y chromosome (*13*).

Currently, the X chromosome is large and rich in genes (~150 Mb euchromatic size and ~800 genes). The Y chromosome is smaller in comparison and only contains a fraction of the original genes (23 Mb, ~78 genes) (*16*, *19*, *20*). It has even been hypothesized that the Y chromosome could go extinct within the next 10 to 30 million years given the rapid loss of its genes (*17*, *21*). However, the comparison of the Y chromosomes of humans and old world (rhesus) monkeys, whose lineages separated 25 million years ago, have shown that an ongoing gene loss was limited to only certain parts of the chromosome. The majority of the chromosome remained preserved (*22*).

One could reason that subtle sex differences in brain organization despite substantial sex chromosomal differences made sense if genes from sex chromosomes had only local effects in reproductive organs. The expectation of only few sex differences in brain organization could also be reasonable if the differences in genetic makeup were counterbalanced by another mechanism. In the case of two (or more) X chromosomes, "X-inactivation" occurs (*23*). This is a process during which the genes from all but one X chromosome are silenced. This

mechanism essentially counteracts the higher X chromosome gene dosage in females.

However, compensatory processes, such as X-inactivation, are incomplete. At least 15% of X chromosome genes escape this mechanism (*24*). Furthermore, it is indeed the case that sex chromosomes contain a proportionally higher number of sex- and reproduction-related genes as compared to autosomes (*16*, *25*) and the Y chromosome is essential for testes differentiation and spermatogenesis (*16*, *26*). However, our sex chromosomes affect more than just sex organ differentiation (*27*). One example is their unique impact on the immune system (*28*). An effect on the brain is supported by the collection of findings outlined in the following.

First, X-linked genes have been reported to be more highly expressed in brain tissue (*29*). Only recently did large-scale population studies demonstrate significant associations between X-linked genes and brain imaging phenotypes. Examples of these sex-specific associations were spatially specific white matter neurite densities, white-gray matter intensity contrasts, and surface areas (*30*). In rodent studies, the aforementioned SRY-gene has been found to be specifically expressed in the substantia nigra. It here alters the biochemical properties of dopaminergic neurons involved in motor behavior (*31*).

Second, some further evidence for the impact of sex chromosomes specifically on the brain comes from genetic diseases with sex chromosome aberrations, i.e., additions or deletions of the X or Y chromosomes. Examples of these common genetic disorders are Klinefelter syndrome (47, XXY), Turner syndrome (45, X), and XYY syndrome (47, XYY) (*32*, *33*). They are characterized by distinct neuropsychiatric profiles comprising elements such as reduced intellectual ability, motor impairments, and higher frequencies of neurological and psychiatric disorders (*34*). On top of that, these sex chromosome aberrations affect characteristic changes in brain architecture. X chromosome additions have been found to be associated with higher gray matter volumes in parieto-occipital and sensorimotor cortices, and lower volume in insular and temporal regions. The absence of an X chromosome appears to result in the opposite pattern (*34*). Overall, diseases with sex chromosome aberrations hence suggest an effect of sex chromosomes on cerebral organization (*35*). Yet, it is important to consider that chromosomal, hormonal, and other compensatory effects may be compounded in this context. The challenge of chromosomal versus hormonal effects can be circumvented in animal models of "four core genotypes." These models offer the possibility of examining XX males (i.e., with testis) and XY females (i.e., with ovaries) given a relocation of the SRY-gene to an autosome (*36*).

Third, another example for sex chromosome–brain interrelations may be seen in genetic mental retardation. The incidence of mental retardation is sex-specific and features a 30% higher rate in males. Oftentimes, it is linked to genes on the X chromosome (*20*, *37*, *38*). Correspondingly, previous work indicates that the frequency of genes with effects on cognitive abilities is more than threefold higher on the X chromosome than any other chromosome (*37*). This predominance of cognition-relevant genes on the X chromosome resembles the predominance of sex- and reproduction-related genes on the X chromosome (*25*). This circumstance may indicate that certain features, such as gene and protein expressions, are shared between the brain and testis (*39*–*41*).

In addition to these effects directly associated with sex chromosomes, biological sex has also been found to modulate epigenetic mechanisms (*42*). For example, some evaluations suggest that 2.5% of all genes are expressed in a sex- and brain region–specific fashion (*43*). Sex-specific gene expression may hence represent another route through which biological sex can affect differences in the brain.

Sex-specific hormones

By initiating sex organ differentiation, sex chromosomes have indirect, yet ubiquitous effects via sex hormones. The sex hormones most classically studied are the sex-steroid hormones estrogen, more specifically 17β-estradiol (E2), progesterone, and testosterone. Estrogen and progesterone are more dominant in females and testosterone is more dominant in males. All of them have characteristic levels and dynamics in each phase of life (*44*, *45*). Despite this emphasis on estrogen/progesterone versus testosterone in females versus males, it is important to recognize that all three hormones are still present in both sexes. In addition, testosterone's major metabolite via aromatase is estradiol. Naturally, these hormones are commonly regarded as being essential for sexual development (*46*). They are also assumed to have a wide range of physiological functions: Cerebral functions may be some of the most visible ones (*47*).

Some of the first historic evidence for sex hormones influencing brain function, dating back to the 1930s, came from experimental work with guinea pigs. This work showed links between menstrual cycles and reproductive sexual behavior (*48*, *49*). Further observations are animal experiments that indicated lower seizure thresholds during the days of highest estrogen levels (*50*). Another example is the report of two female human patients with dyskinesias that described a noticeable improvement in their symptoms time locked with periods of highest circulating levels of estrogen (*51*). Anatomically, this sex hormone–brain function connection was supported by the detection of receptors for sex hormones in work with rodents. These receptors were first found along the hypothalamic-hypophysial axis and limbic structures. The hypothalamic-hypophysial axis represents the foundation for brain-body communication via the neuroendocrine system (*52*, *53*). Examples of limbic structures are the amygdala and hippocampus (*54*–*56*). Hence, these regions rich in sex hormone receptors are thought to be particularly implicated in the regulation of mood and cognition. Later studies in monkeys and rodents added cortical receptor localizations, such as the prefrontal cortex (*57*). They furthermore suggested characteristic distributions for different receptor subtypes (*58*) and demonstrated broad overlaps for progesterone, estrogen, and testosterone receptors (*56*). Systemic sex steroids can pass the blood-brain barrier (*59*). In addition, they can be to locally synthesized for immediate release (*47*, *60*). Another important, linked theoretical construct is that sex hormones act in two profoundly different ways via organizational and activational mechanisms (*61*, *62*). Organizational effects are assumed to be permanent and occur mainly in early development, while activational effects are thought to be temporary and dynamic, continuing after brain maturation (*63*, *64*).

Neuroprotection, neuroplasticity, and memory

In the previous section, we established that the brain expresses high levels of spatially specific sex hormone receptors that can react to systemic and locally produced sex hormones (*44*, *63*). We will now highlight some of the most salient, interconnected effects of sex hormones that have relevance across diseases: neuroprotection, neuroplasticity, and memory. Experimental work indicates the neuroprotective effects of estrogen, progesterone, and androgens (*60*, *65*, *66*). For example, infarct volumes were smaller in young female rats. This difference disappeared for middle-aged animals in reproductive

senescence (*67*). In support of these findings, infusion of exogenous estrogen within 3 hours of stroke onset led to significant decreases in infarct sizes, even in male animals (*65*, *68*). A comparable effect was observed for progesterone (*69*). Proposed mechanisms are vasodilation and improved cerebral blood flow to the affected brain regions, in addition to potential protection from excitotoxic damage (*65*). Sex hormone–induced changes observed in animals are enhanced myelination and dendritic spine and synapse density in the hippocampus and beyond. They are interpreted as signs of neuroplasticity (*63*, *70*). Functionally, these sex hormone–related structural changes may underlie the augmented learning and memory capacities that have been observed for estradiol in both female and male animals (*47*). Experimental work with animals furthermore suggests that some of the molecular processes resulting in improved memory are sex specific (*47*). For example, sex-varying estradiol receptor subtypes appear to be involved (*71*). Also, hippocampal processes were dependent on protein kinase A exclusively in female animals (*72*). Uniform macroscopic brain organization and downstream behavior may hence be the result of sex-specific molecular processes. This consideration vaguely links to the proposal by some that sex differences in microscopic brain structure and molecular processes may prevent overt sex differences in brain function by compensating for naturally occurring sex differences in physiological environments, e.g., sex hormone levels (*73*).

Female menstrual cycle and hormonal contraception

The female menstrual cycle, which lasts ~28 days in humans, features rhythmic changes in hormonal levels. Estrogen first peaks at the end of the initial follicular half and increases ~8-fold. Progesterone reaches its maximum in the middle of the second luteal half with an ~80-fold increase. In addition, estrogen demonstrates a second, albeit less pronounced peak in the luteal phase (*74*–*76*). The aforementioned estrogen-induced structural changes of hippocampal spine density for example stem from observations of the estrous cycle in female rats (*77*, *78*). It is important to note that rodents experience an estrous cycle with estrogen only rather than a menstrual cycle with estrogen and progesterone (*79*). Even estrogen receptor expression appears to depend on the stage of the estrous cycle (*80*). Chronic coadministration of progesterone decreases estrogen-mediated effects of neuroplasticity (*81*). These findings hint at the complexity of hormonal interactions, the importance of timing, and pulsative nature of hormonal levels. In humans, a correlate of these experimental findings may be the covariation of estrogen levels and hippocampal gray matter volume during the menstrual cycle (*82*). Moreover, a synthesis of multimodal neuroimaging studies accentuated periodic changes of gray matter volumes and activation levels in areas comprising the amygdala, the insula, anterior cingulate, and prefrontal cortex, as well as inferior parietal lobe (*82*). Specifically, functional imaging studies show stronger amygdala activation in combination with enhanced emotion recognition in females during their follicular phase (*83*). In late luteal phases, it has been found that cortical-subcortical functional connectivity and emotion perception is reduced (*84*). More recently, sophisticated studies in humans have leveraged dense sampling to interrogate neuroendocrine effects. Dense sampling refers to longitudinal study designs where one or few participants undergo testing, such as neuroimaging or laboratory workup, at a higher frequency and over a higher number of sessions (*85*, *86*). Pertinent findings were that changes in day-to-day progesterone levels link to volume changes in the medial temporal lobe (MTL) (*87*). Further, sex hormone levels during the menstrual cycle and functional brain connectivity at large, particularly in the default mode and dorsal attention network, were linked (*76*). MTL volume changes disappeared in case of progesterone suppression (*87*, *88*), which reinforces the dependency of brain changes on progesterone variation observed initially. It also emphasizes the need of studying yet another unique situation: hormonal contraception (*89*). In the United States, notably 25% of all females from 15 to 44 years of age use one of the available oral contraceptive pills comprising combined estrogen-progesterone, progesterone-only, and continuous or extended-use versions (*90*). In addition to the just mentioned effects on MTL volume (*87*, *88*), a variety of studies point toward notable effects of contraception use on cognitive performances. The most consistent finding is improved verbal memory with oral contraception use (*91*, *92*).

One important realization at the end of this section is that hormonal levels do not only affect structural cerebral changes, yet they do so rapidly (*63*). Changes can appear on a timescale of hours and days during the menstrual cycle. In addition, these changes are of relevance to behavior and even disease, as we will discuss more in later stages of this review.

Pregnancy

Pregnancy is characterized by marked increases in sex hormone levels that initiate and maintain systemic changes of the maternal body necessary to support fetus growth over the 40-weeks of human gestation. In particular, estrogen levels increase up to 1000-fold, especially in the third semester. With the loss of the placenta, it then almost instantaneously decreases postpartum (*93*). Altogether, this surge during pregnancy results in an estrogen exposure that exceeds the lifetime one of a nonpregnant female (*94*). Studies in rodents suggest the combination of decreased neurogenesis, increased dendritic growth, and myelination (*95*). Moreover, brain immune function is altered during late pregnancy. These changes have been hypothesized to occur to create the "maternal caregiving circuit" (*96*) and facilitate maternal behavior. Key neuroimaging studies in humans across the different stages of pregnancy found widespread reductions in gray matter volume (*94*, *97*). Among others, these reductions were centered on regions along the anterior to posterior midline, bilateral inferior frontal gyri, and temporal cortices (*94*). Concomitantly, increases were noted for white matter integrity, ventricle volume, and cerebrospinal fluid (*98*). These changes correlated with maternal attachment and were still detectable years postpartum (*94*, *99*). Large-scale population studies in turn demonstrated correlations between childbirths and "younger-looking" brains (*100*). Subjectively, many females perceive a worsening of their memory during pregnancy (*101*). Also, there is meta-analytical evidence of memory disturbances during pregnancy and early postpartum (*102*, *103*). These memory disturbances were additionally found to correlate with hormone levels (*104*). In line with these impressions, experimental work in rodents shows decreases in spatial memory performance in late pregnancy and early postpartum. In contrast, spatial memory seems enhanced in late postpartum and middle age (*102*).

Menopause

The menopause transition occurs at the end of a woman's reproductive life. It is defined by initial irregularity of the menstrual cycle, subsequent intervals of amenorrhea of ≥60 days, and eventually the final menstrual period without any further one for a year (*105*). Once again, estrogen levels undergo pronounced and characteristic changes. They can still be normal or even elevated during earlier stages (*106*). They then start to vary widely, until they are markedly decreased at the end of the transition to reproductive senescence and loss of ovarian

follicles (*107*, *108*). Female rodents and nonhuman primates experience similar changes during their perimenopausal transition (*109*) and offer several frameworks to systematically study related brain changes. One of these frameworks is surgical ovariectomy (*79*). In line with studies of the estrous cycle, ovariectomy and, hence, the removal of circulating sex hormones lead to a stark decrease in dendritic spine density in CA1 pyramidal cells of the hippocampus in rodents (*77*). This process can be reversed with exogenous estrogen and even further augmented with estrogen and progesterone coadministration within the first few hours (*77*, *81*). Natural menopause in rhesus monkeys was found to correlate with a selective loss of a specific kind of synapses in the hippocampus that are known to support enhanced synaptic efficacy (*110*). Moreover, exogenous estrogen in ovariectomized monkeys increased synaptic dendritic spine density and modified spine morphology in the prefrontal cortex (*111*). Further menopause-related changes observed in experimental work with rodents are marked changes of the brain's bioenergetic system with persistent decreases in glucose metabolism (*109*, *112*). In humans, structural and functional neuroimaging studies have shed light on more macroscopic cerebral changes during menopause. In particular, their sex- and menopause status–specific findings underline the value of conducting careful analyses of subgroups to reveal subtle differences (e.g., male and female, and pre-, peri-, and postmenopausal participants) (*113*). Summarizing the effects of eight individual studies, a recent review reported most consistent volume reductions in frontal and parietal brain regions, the insula, basal ganglia, the hippocampus, and amygdala (*114*). Some of these reductions in gray matter volume appeared to recover in the postmenopausal phase (*115*). Functional magnetic resonance imaging studies, particularly focused on memory tasks, suggest increasing bilateral hippocampal connectivity in postmenopausal females (*113*). Moreover, different patterns of memory task evoked activity with stronger recruitment of the left dorsolateral prefrontal cortex and hippocampus were observed in postmenopausal females (*116*). In line with the mentioned experimental work, evaluations of glucose metabolism, amyloid-β deposition, and brain volumes in humans displayed decreases in postmenopausal females compared to males < premenopausal females and < perimenopausal females (*117*). A multitude of studies collectively point to increased glucose metabolism, blood flow, and activation during memory and attentional tasks after estrogen replacement therapy in postmenopausal females, which corroborates these findings further (*118*–*122*). Notably, these changes occur without any correlated notable increases in performance in most cases.

Vasomotor symptoms are one of the hallmarks of menopause. Up to 75% of postmenopausal females regularly experience hot flashes and night sweats (*123*, *124*). These findings may demonstrate once again that sex hormones affect brain function. Hot flashes are thought to be the result of core body temperature elevations in combination with a decreased upper threshold for sweating (*125*). These processes are centrally mediated through the hypothalamic preoptic nucleus, which is the primary thermoregulatory center and particularly densely populated by estrogen receptors (*108*). Similarly, disruptions of sleep, for example, nocturnal awakenings (*126*), also functionally link to a brain region, the hypothalamic suprachiasmatic nucleus, which is rich in estrogen receptors (*108*). Deficits in memory and concentrations are the third well-researched category of menopausal symptoms. They can also be traced back to brain regions rich in estrogen receptors, such as the prefrontal cortex and hippocampus (*108*). Approximately 40% of females in a classic range for menopause note a perceived forgetfulness (*127*). Several meta-analyses on the topic indicate most objective effects on verbal memory performance (*128*–*130*). Less consistent evidence is reported for processing speed, verbal fluency, attention, and working memory (*130*). Of note, longitudinal assessments suggest that change may not happen linearly across perimenopause (*131*). There is also potential for changes to be reversed to premenopausal levels after menopause (*132*). One of the currently unsolved questions is why some postmenopausal females remain unaffected by these cognitive changes (*133*) and for example still exhibit brain activity pattern similar to premenopausal females (*113*). Interactions between all three mentioned symptoms—hot flashes and sleep and cognitive disturbances—are being actively discussed. The "domino hypothesis," which was introduced in the 1980s, postulates that hot flashes are the cause of downstream sleep disruptions and then cognitive disturbances (*134*, *135*). It also appears that menopausal symptoms are more pronounced but similar in nature to those experienced with rhythmicity during the menstrual cycle: changes of the core body temperature (*136*), the quality of sleep (*137*, *138*), and verbal memory enhancements with oral contraception use (*91*, *92*). Menopause, which can be seen as an endocrine senescence and reproductive aging process of the hypothalamus–pituitary gland–ovary axis, has intricate links to general processes of aging. It is even thought to accelerate the aging process (*139*) and menopausal symptoms are, in part, seen to be due to aging itself (*124*).

Before discussing general aspects of aging, we want to pause to acknowledge that the effects of estrogens and aging-related changes in hormone levels on the male brain are less well studied (*140*). In comparison to the more abrupt changes in estrogen and progesterone during the menopause transition, bioavailable testosterone appears to decline more gradually across the life span (in both males and females) (*141*). Moreover, we did not include the effects of sex hormones beyond estrogen, progesterone, and testosterone [e.g., oxytocin, prolactin (*142*), luteinizing hormone (LH), and follicle-stimulating hormone (FSH)] and did not discuss those hormones that are less sex specific but undergo major changes during sex-specific events (e.g., cortisol during pregnancy) (*95*). Last, we did not address interactions between steroid sex hormones and neurotransmitters (*140*, *143*) and did not highlight psychiatric effects (*144*). All of these aspects should be elucidated further in future work.

Sex-specific aging

Age itself is a major risk factor for a multitude of diseases (*145*). It may hence be especially crucial to understand the intricate interactions between biological sex and age and their joint effects on basic pathological mechanisms that are shared across diseases. A seminal publication in 2013 summarized the nine "hallmarks of aging": genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (e.g., inflammation) (*146*). While all of these categories deserve further recognition, we refer to the original publication for in-depth descriptions and will here focus on selected processes that will centrally contribute to our discussion of neurological disease. One general observation for aging-related sex differences is that females have a longer life span than males, reflecting their longer telomeres (*147*). Paradoxically, they, however, experience a greater amount of frailty and physical illness at the end of life (*148*, *149*).

The aging immune system: Immunosenescence, "inflammaging," and related sex differences

Independent of aging, the immune system is highly sex specific: The X chromosome encodes a variety of immune-regulatory genes and all of estrogen, progesterone, and androgen effect a variety of immune processes (*28*). As a result, females in their reproductive years that experience higher cycling estrogen and progesterone levels are more vulnerable to B cell–mediated autoimmunity (e.g., multiple sclerosis (MS), systemic lupus erythematosus, and myasthenia gravis). At the same time, they are less affected by infections or chronic inflammatory diseases (*150*, *151*). Conversely, concentrations of estrogen and progesterone as excessively high as during (late) pregnancy exert an immunosuppressive effect with beneficial effects on autoimmune disease (*152*). This overall pattern changes with age or, rather, menopause and decreasing estrogen and progesterone levels: B cell–mediated autoimmunity decreases, in exchange for an increase in T cell–related autoimmune inflammatory processes (e.g., rheumatoid arthritis) (*150*). Androgens, overall, seem to exert an immunosuppressive effect at physiological levels (*153*).

The aging immune system is particularly affected by immunosenescence and inflammaging (*154*). Immunosenescence comprises processes such as decreasing hematopoietic bone marrow function and thymus involution that contribute to decreasing immune function (*155*). Inflammaging, a term first coined in 2000, describes a chronic, low-grade systemic inflammation observed in older age, with increased levels of serum C-reactive protein and pro-inflammatory cytokines. In particular, the main blood marker interleukin-6 strongly correlates with morbidity and mortality (*154*). Initially, one central driver of this excessive inflammation was seen in persistent viral infections, especially with cytomegalovirus (*156*). More recently, the importance of self-endogenous molecules has been recognized. They result from damaged and dead cells that physiologically increase with age and are less successfully disposed via the proteasome. This recent realization renders inflammaging an autoimmune and autoinflammatory process (*157*). In this context, it has also been recognized that nutrition, obesity (*158*), the gut microbiome, and their age-related changes may play particularly central roles (*159*, *160*). Obesity, for example, has been shown to be linked to a metabolic inflammatory state (*158*). Successful aging, on the other hand, appears to relate to an optimal balance between pro- and anti-inflammatory processes (*161*). Sex differences in immunosenescence and inflammaging need to be elucidated more. So far, current work suggests distinct sex differences in gut microbiome composition and function (*162*, *163*), different metabolic profiles (*164*), and an altogether more accelerated rate of aging-related immune system alterations in males (*151*). These aging processes represent systemic changes, but they are of relevance to the human brain. For example, increasing exposure to self-endogenous molecules is implicated in the development of age-related brain diseases. There is a direct relation in the case of AD and an indirect one through aggravation of cardiovascular diseases (*157*). In addition, an inflammatory environment is thought to contribute to blood-brain barrier changes and breakdown (*165*), peripheral immune cell infiltration, and glial cell activation. These activated glial cells then release further inflammatory cytokines and reactive oxygen species toxic to neurons (*166*).

SEX DIFFERENCES IN NEUROLOGICAL DISEASES

Sex differences in sporadic AD

AD is the most common cause of sporadic dementia and accounts for 60 to 80% of cases. Symptomatically, it is characterized by progressive memory loss and disturbances of further cognitive abilities, such as reasoning, attention, and language. Ultimately, it results in an inability to complete tasks of daily living (*167*). The defining pathophysiologic hallmarks of AD are extracellular amyloid-β plaques and intraneural neurofibrillary tangles tau in combination with neurodegeneration. Amyloid-β accumulation starts decades before tau, marks the preclinical stage of AD, and promotes subsequent neuroinflammation, glial cell activation, synaptic failure, neuronal loss, and eventually the clinical manifestation (*168*–*171*). Vascular disease, including cerebral amyloid angiopathy (CAA), and the extracellular accumulation of phospho-TAR-DNA-binding-protein-43 (pTDP-43) also contribute to the clinical and pathological phenotypes of AD, which enhances the complexity of the picture (*172*, *173*). An abundance of sex differences have been noted that relate to disease prevalence, symptomatic presentation, pathophysiological processes, and therapeutic efficacy (*174*–*177*). We will highlight each of these topics in turn. Similar to previous sections, we display findings from experimental studies with animals and cells in combination with studies involving human participants. We directly state the research scenario for each instance.

Sex differences in AD disease prevalence, risk factors, and clinical presentation

Two-thirds of all patients living with Alzheimer's dementia are female (*167*). The origins of this difference are frequently and controversially discussed. One hypothesis is that it may arise due to a female-specifically enhanced longevity combined with a selective survival of those men with good cardiovascular health and therefore decreased risk of dementia (*174*, *178*). However, in subgroups with specific risk factors, female sex predisposes for a higher AD risk independent of this longevity aspect (*179*). One example of these specific risk factors is Apolipoprotein E ε4 (APOEε4), which is the allelic variant that confers the strongest genetic risk for sporadic AD (*180*). Several large-scale studies suggest that females with an APOE ε3/4 genotype have a higher risk of developing AD, especially at younger ages (*181*, *182*). The origins of this female vulnerability to APOE ε3/4 are an active area of current research and one focus is on potential synergies with the X chromosome itself (*183*, *184*). As mentioned in an initial section, sex chromosome aneuploidies have effects on general intelligence and impairments of, e.g., executive functioning, which suggests a relevance of genes on sex chromosomes to cognitive functions (*34*). More generally, studies indicate distinct roles of X-linked genes in neurodegenerative diseases (*177*). A recent X chromosome–wide association study uncovered a previously unknown risk locus for AD that is thought to regulate processes leading up to amyloid-β accumulation (*185*). With respect to nongenetic risk factors, recent evaluations suggest that up to 45% of AD risk factors (e.g., education, hearing loss, and social isolation) could be modifiable. Sex differences among those modifiable risk factors are relatively underexplored (*186*). Some early studies pointed to faster disease progression in males (*187*, *188*). Nonetheless, more recent studies collectively suggest the opposite: Cognitive decline is observed to be accelerated in females compared to males (*189*–*191*), especially in case of high amyloid-β (*192*) and the presence of the APOEε4 variant (*192*, *193*). Moreover, there is meta-analytical evidence of female patients scoring lower in cognitive tests overall (*194*). Effects may be driven by a higher correlation of cognition and neuropathology in females as we will discuss shortly (*195*). In addition to these sex differences in rates of decline and clinical severity, there are also reports of sex differences in the pattern of accompanying behavioral symptoms, such as agitation and affective symptoms (*176*). Meta-analytical data indicate a

female-specific predominance of depressive and psychotic symptoms. In males, motor behavior and apathy are more pronounced (*196*). Some caution may be warranted when interpreting these results on severity and predominance of symptoms, as some commonly used screening tests may be subject to sex-specific detection bias (*197*).

Sex differences in AD neuropathology

One of the most outstanding neuropathology studies evaluating sex differences in AD demonstrated that there was a substantial divide in the association strength between AD neuropathology load at the time of autopsy and clinical AD diagnosis during lifetime (*198*). AD pathology was measured as a compound score based on the number of neuritic plaques, diffuse plaques, and neurofibrillary tangles in four cortical areas. These four areas comprised the midfrontal, superior temporal, entorhinal, and inferior parietal cortices. For each extra unit of AD pathology, males had a 3-fold increase in odds of AD diagnosis compared to a 20-fold increase for females (*198*). In line with these findings, further studies of preclinical aging and clinical cohorts reported females to be subject to a faster cognitive decline (*192*, *195*) and faster atrophy of the (left) hippocampus for the same amount of AD biomarkers (*195*). In addition, female patients were found to have increased global pathology overall. This difference mostly emerged due to neurofibrillary tangles tau (*198*, *199*). The presence of a higher female-specific tau burden is further supported by cerebrospinal fluid studies resulting in higher tau levels in females (*200*, *201*). Also, similar patterns of female-specific enhanced tau are apparent in positron emission tomography–based neuroimaging studies of preclinical cohorts (*202*, *203*). Experimental work in animals overall supports the assumption of a higher sensitivity to AD pathology in females (*204*), even though results of individual studies have been mixed (*205*).

Sex differences in vascular pathology

The exact underlying mechanisms remain to be fully elucidated, but the substantial contribution of vascular pathology to the development of AD has been brought to light by a wealth of studies (*206*). The most relevant and common forms of vascular pathology affecting the brain are cerebral atherosclerosis, arteriolosclerosis, and CAA (*207*). These have been shown to differentially affect males and females (*208*–*210*). As they have intimate links to ischemic stroke as well, we will discuss sex differences in cerebral atherosclerosis and cerebral small vessel disease (CSVD) in further detail in the stroke section. CAA is a CSVD characterized by amyloid-β plaques within small- to medium-sized cortical and leptomeningeal vessels that progress with age and predispose for lobar intracerebral hemorrhages (*211*, *212*). CAA burden overall has been found to be increased in human male patients compared to females (*210*). Male patients also appear to have disease courses with earlier onset and more frequent hemorrhages (*213*). Of note, some characteristics of CAA, e.g., microbleeds, are increased in females (*214*, *215*) and correspondingly in female rodents (*216*).

Sex differences in neuroinflammation

Microglia are macrophage-like innate immune cells residing in the central nervous system that support brain development and homeostasis of the adult brain. They do so most prominently by clearing debris, such as protein aggregates or apoptotic cells (*217*, *218*). Their potentially crucial role in AD was already discussed by Alois Alzheimer when he described their changes in postmortem brain tissue of patients with AD in 1911 (*219*). Sex differences in their anatomy, gene expression, and function are increasingly being recognized (*218*, *220*, *221*). Studies in rodents have, for example, shown (age- and) male-specific higher density of microglia cells centering on brain regions such as the hippocampus and amygdala (*222*), in addition to a higher antigen-presenting capacity and ability to respond to stimuli (*223*). Specific to AD, human data suggest that microglial activation may sit at the intersection of amyloid-β and tau and may promote tau burden particularly in females (*224*).

Sex differences in the brain's cholinergic system

Another important change thought to contribute to cognitive decline with potential modifications by sex relates to the brain's cholinergic system (*140*, *225*). It broadly influences sensory, attention, and memory functions (*226*) and undergoes degenerative changes during physiological and pathological aging (*227*). Early anatomical studies revealed that the hippocampus and amygdala were regions with particularly high choline acetyltransferase and acetylcholinesterase enzymatic activities (*228*). They receive their cholinergic input from the basal forebrain (*229*, *230*). Several early clinical observations in humans in the 1970s reported reduced cholinergic activity specifically in the brains of patients with AD (*231*). In parallel, anticholinergic drugs were found to reproduce cognitive impairments on the one hand (*232*) and cholinergic drugs to improve cognitive performance on the other hand (*233*). The possibility of a sex-specific regulatory function on the cholinergic system is rendered more likely by studies in rodents showing colocalization of estrogen receptors and cholinergic neurons in their basal forebrain, which allows their interaction in theory (*234*). The coadministration of estrogens and acetylcholinesterase inhibitors appeared to be necessary for enhancing effects on cognition in older animals in one study. Estrogen on its own was ineffective (*235*). Further, human data indicate that treatment with the cholinesterase inhibitor donepezil is more effective in females with certain estrogen receptor genotypes (*236*).

Sex differences in AD treatments

As outlined in a previous section, endocrine aging during menopause and the accompanying drastic changes in sex hormone levels effect vast cerebral changes. These changes are anatomically centered on limbic regions and known to visibly affect memory function. In particular, studies in humans point to worse memory in later life with premature loss of ovarian function (surgically or nonsurgically) (*237*), a higher tau burden with earlier age at menopause (*238*), an increased AD risk with decreased lifetime exposure to estrogens (*188*), and a female-specific higher risk of dementia in the years following menopause (*181*, *239*). Animal studies additionally suggest links between increasing soluble amyloid-β levels with decreasing sex hormones (*240*).

In theory, these insights make estrogen one of the most promising agents as a memory-enhancing and AD-treating drug. In practice, initial meta-analyses of smaller-scale human clinical trials, cohort, and case-control studies in females were consistent with the dementia risk-reducing effects of external estrogen after menopause (*241*–*243*). However, one of the largest randomized, placebo-controlled clinical trials of its kind in the early 2000s concluded that hormone replacement therapy (HRT) with estrogen and progesterone after menopause resulted in a higher risk of dementia compared to placebo (*244*). This Women's Health Initiative Memory Study (WHIMS) (*245*) recruited almost 4900 female participants. At the same time, it was also found that HRT did not significantly reduce the risk of coronary heart disease. Instead, HRT increased risks of stroke, pulmonary embolism, and breast cancer in certain subgroups (*246*). Overall, these findings dampened enthusiasm for HRTs (*246*). Careful (re-)interpretation of data led to the conclusion that estrogen may prevent cognitive decline,

but, importantly, mostly so if initiated within a limited amount of time after loss of ovarian function (*247*). This hypothesis is termed "window of opportunity" (*248*). On the basis of experimental work with animals, it has been hypothesized that this dependency on early timing of estrogen therapy could stem from the necessity of a functioning cholinergic system (*234*), which decays with older age. Alternatively, it could be due to decreasing numbers of estrogen receptors in the hippocampus with long-term depletion of estrogen, rendering late-onset estrogen administration ineffective (*249*). Concurrently, there is the "healthy cell bias of estrogen action" theory that is centered on the assumption that estrogen signaling pathways through mitochondria could have detrimental effects if activated in diseased neurons (*250*). After all, more studies are needed to determine the specific scenarios in which exogenous estrogen may still have a positive impact on brain function. Independent of estrogen as active hormonal agent, there have been promising signs that FSH blockade could improve cognition as well. Work in rodents suggests that FSH accelerates AD pathological burden (*251*).

Last, we want to briefly discuss sex differences in approved AD therapies. A minority of clinical trials that investigated cholinesterase inhibitors and memantine in human participants additionally evaluated sex differences in drug efficacy and safety. A review in 2017 concluded that only 2 out of 48 trials reported sex-specific analyses (*252*). Those two studies did not note any sex differences for donepezil (*253*, *254*). Similarly, neither one of the three main clinical trials for anti-amyloid agents in humans presented sex-specific analyses in their main reports (*255*, *256*). However, supplemental analyses indicate that positive overall effects are possibly driven by male patients (*255*). This finding in particular mandates further scrutinization of sex differences in treatment effects in future studies (*257*).

Sex differences in resilience to AD

A high number of elderly adults technically meet AD diagnosis criteria based on neuropathology at autopsy, yet they did not experience cognitive impairments during their lifetime (*258*). Some work points toward a possible female-specific resilience in humans to developing excessive cognitive decline despite carrying APOEε4, which is observable in case of good cerebrovascular health and less pronounced amyloid-β accumulation (*259*, *260*). In rodents, there is explicit experimental evidence that a second X chromosome can boost resilience to AD (*261*). Last, sex-stratified genome-wide association studies (GWASs) indicate that the genetic basis for resilience to develop AD may be sex specific. It may primarily link to immune-related pathways in females and cardiovascular-related pathways in males (*262*). These results suggest that sex-informed approaches will be of relevance to disease prevention and mitigation.

Sex differences in acute ischemic stroke

Ischemic stroke is the most frequently occurring kind of stroke and happens when the brain is subjected to insufficient blood supply due to an obstructed vessel (*263*). If it is deprived of adequate perfusion for a crucial amount of time, the brain tissue in the vessel's supply territory undergoes cell death and stops functioning normally. This stroke-related abnormal function results in typical combinations of neurological symptoms. One in four adults experiences a stroke in their lifetime (*264*) and a substantial number of patients remains considerably disabled (*265*). Therefore, stroke creates a substantial socioeconomic and personal burden of disease, that, like for AD, will only increase in future years in view of an aging society (*266*, *267*). Also similar to AD, research has revealed a great variety of sex differences affecting stroke incidence, symptoms of presentation, risk factor profiles and stroke etiology, outcome, therapeutic approaches, and efficacies. The initial passages of this section predominantly state findings from research involving human participants. Later passages then also feature research findings originating from experimental work with animals.

Sex differences in stroke incidence and clinical presentation

Sex differences in ischemic stroke incidence differ throughout the life span and appear to follow a U-curve. Stroke incidence is higher in younger females, which is likely due to their unique risk profile. In particular, oral contraceptive use and pregnancy-associated complications, such as preeclampsia, increase the stroke risk severalfold (*268*–*270*). Stroke incidence is then higher in males in midlife (*271*), before it increases again in females late in life (*272*, *273*). Classically, it has been assumed that female patients more frequently present with atypical stroke symptoms, which may explain their higher rate of (mis)diagnoses as stroke mimics (*274*, *275*). Females do have a higher rate of migraine leading to true stroke mimics (*276*). Meta-analytical data also suggest that they present with nonfocal symptoms, such as headaches, generalized weakness, confusion, and mental status changes, more often (*277*, *278*). Nonetheless, it does not come at the expense of focal symptoms: Generally, similar percentages of motor and speech deficits are observed for male and female patients (*277*, *278*). The five most frequent symptoms of stroke have been found to be similar across males and females (*279*).

Sex differences in risk factor profiles

Cardiovascular risk factors are well known to substantially influence the occurrence of stroke. They factor into common categorizations of stroke etiology, have therapeutic relevance, and affect outcomes. All these realizations make the study of their sex-specific characteristics particularly essential. Conceivably, males and females can experience a specific risk factor at varying rates, and/or the risk factor can affect their risk of stroke in sex-specific ways. The efficacy of their treatment is yet another dimension. One of the greatest nonmodifiable stroke risk factors is simply age. Female patients are typically several years older at stroke onset than male patients are (*280*, *281*). This difference in age correlates with their generally higher burden of comorbidities and pre-stroke disability (*282*). The metabolic syndrome describes a collection of risk factors that frequently cluster: insulin resistance, abdominal adiposity, dyslipidemia, and hypertension. Its presence is an important risk factor for stroke across both males and females, with a stronger effect in females (*283*, *284*). However, males, on average, experience symptoms of the metabolic syndrome earlier in life (*285*). Of note, patients with Turner syndrome, i.e., X chromosome monosomy (45, X), oftentimes experience a wide range of these conditions, namely, diabetes mellitus, hypertension, obesity, and dyslipidemia (*286*, *287*). Likely as a result, they have a higher prevalence of stroke that has marked effects on their life span (*287*, *288*). The high frequency of cardiac malformations and the higher risk of aortic dissections in this syndrome are also implicated in increased stroke risk (*289*, *290*). In terms of frequency, males are more likely to smoke and drink more alcohol. Both aspects represent further stroke risk factors (*280*, *282*). In case of smoking, meta-analytical data speak of smoking being a risk factor of equal strength in both males and females (*291*). Only in subgroups did it appear that smoking was more harmful in females in Western regions, yet not in Asian ones (*291*). Of note, quitting to smoke confers a risk reduction of similar strength in both males and females (*291*). Atrial fibrillation is another stroke risk factor of particular importance

as atrial fibrillation–related cardioembolic strokes tend to be particularly severe (*292*). Broadly, male sex is linked to a higher risk of atrial fibrillation, but absolute numbers for males and female patients are comparable (*293*). These comparable absolute numbers are explained by the fact that age is a main risk factor for atrial fibrillation and females are older on average (*293*). Furthermore, female patients with atrial fibrillation and additional cardiovascular risk factors more often present with stroke. The CHA2DS2-VASc score, which evaluates the necessity of oral anticoagulation in case of atrial fibrillation, acknowledges this sex-specific risk by adding an extra point for female sex (*294*). Study data indicate that female patients with atrial fibrillation may have a higher residual risk of stroke even when treated with warfarin (*295*). Sex differences in stroke risk factors are mirrored by differences relating to stroke etiology: Large vessel occlusion stroke is consistently more often observed in males, while the opposite is true for cardioembolic strokes (*296*, *297*). Overall, males are affected by more severe atherosclerosis earlier in life (*298*, *299*). This increased severity is indicated by a higher vulnerability of their plaques, which is true for both cerebral arteries (*298*, *299*) and coronary ones (*300*). In addition, males appear to have a higher burden of lacunar stroke (*296*, *297*) and tend to experience CSVD more often (*209*). This is a sex difference we already alluded to in the previous section on AD. CSVD is radiographically characterized by white matter hyperintensities (WMHs) (*301*). WMHs are also increased in small vessel stroke subtypes (*302*). They have been found to evolve with sex- and menopause-specific time courses: Females, compared to males of similar age, appear to have a higher WMH burden and accelerated worsening evident only after menopause (*303*).

Sex differences in stroke severity and stroke sequelae

Female patients typically experience a higher stroke severity on initial presentation and more severe long-term stroke sequelae. In many cases, these differences survive the correction for confounding factors, such as the female-specific higher age and prestroke disability (*265*, *297*, *304*–*307*). Despite this disproportionally high severity, females are less likely to die from stroke (*266*, *305*, *308*). Cognitive impairment and dementia are frequently noted symptoms poststroke (*309*). Large population studies suggest a 50-fold increase of dementia risk compared to the general population (*310*). With respect to sex differences, study data suggest that females may experience an acceleration of cognitive decline poststroke (*311*). More specifically, female patients may have a higher risk of disturbances of language, attention, and executive functioning, which is contrasted by a higher risk of verbal memory disturbances in males (*312*). The sensitivity of the Mini Mental State Examination was found to be more sensitive but less specific in detecting relevant cognitive deficits in females compared to males (*312*). This finding once again underscores the importance of ensuring validity of common measurement instruments in distinct subgroups. Poststroke depression affects one-third of patients with stroke (*313*, *314*) and correlates with an increased burden of disability and higher rate or mortality (*313*, *315*). As is the case for major depression, poststroke depression occurs more frequently in female patients (*45*, *316*, *317*).

Possible origins of sex differences based on experimental work

Why do these sex differences in stroke severity and further symptoms arise? Experimental work with rodents may grant some further mechanistic insights and motivate hypotheses for future work. As already briefly mentioned in our section on sex hormones, early work with rodents indicated that lesion size after experimental stroke was larger in young male rats than in female ones (*318*). After ovariectomy and a decrease in endogenous estrogen levels, lesion sizes in female rats resembled those in males (*318*). These observations put estrogen and its potential neuroprotective and additionally noted vasculoprotective effects at center stage. A rich collection of subsequent experiments disentangled effects further (*319*): In female rodents, lesion size was found to depend on the stage of the estrous cycle (*320*, *321*). Larger lesions were noticed in metestrus characterized by low estrogen levels (*320*, *321*). Estrogen replacement in both male (*65*) and ovariectomized female animals (*69*, *322*) decreased lesion sizes overall. This finding is consistent with reports from studies on myocardial infarction (*300*). Nevertheless, these studies also demonstrated the importance of appreciating the subtleties of experimental setups. Results slightly differed depending on timing, route, and dose of estrogen replacement: e.g., long-term versus short-term application, time after vessel occlusion, and physiological doses versus supraphysiological ones. Despite a main study focus on estrogen, there is also evidence of positive effects of progesterone on ischemic injury and functional recovery when administered in the postischemic phase (*69*, *323*, *324*). Sporadic reports indicate dose- and time-dependent positive effects of testosterone (*325*, *326*).

On a cellular level, male-derived hippocampal neurons and astrocytes experience greater ischemic injury than female-derived ones (*327*–*330*). More generally, cell death pathways are assumed to be influenced by biological sex (*331*, *332*). For example, male neurons were shown to be more vulnerable to excitotoxic cell death and female ones were shown to be more prone to experience apoptotic (programmed) cell death (*333*). Neuronal injury triggers neuroinflammatory processes and, similar to AD, microglia may have central roles. They support phagocytosis, reduce neuroinflammation, and facilitate neuronal repair (*334*). These anti-inflammatory functions appear to be more enhanced in female microglia (*335*). Accordingly, transplanting female microglia into male mice was found to be neuroprotective (*218*, *336*). In rodent models, the APOE genotype seems to modify the responsiveness of microglia to estrogen: Anti-inflammation seems to be reduced in the case of APOEε4 (*337*, *338*). Last, emerging research suggests that the microbiome-gut-brain axis contributes to a sex-specific inflammatory response to stroke. Exemplarily, a higher gut permeability and the associated higher systemic inflammatory response could be linked to worse stroke outcomes and a higher risk of hemorrhagic transformation in male rodents (*332*, *339*, *340*). Taking everything into account, current results of experimental work in rodents are illustrative, but do not explain why outcomes in patients with stroke are typically worse in females.

Possible origins of sex differences based on human studies

Unlike in AD, preclinical and clinical studies in stroke are less closely matched and have varying focuses. With respect to lesion volume, there are only a few human neuroimaging studies that separately evaluated lesion volume in male and female patients: They did not detect any sex differences (*304*, *341*, *342*). However, there are no studies specifically investigating associations between the level of sex hormones and lesion sizes in humans. Hence, it is a possibility that lesion volume did not differ between male and female patients, as most female patients experienced stroke after their menopause. There are several conceivable origins of sex differences in the presentation and severity of stroke. They could be (i) due to sex variations in neuroanatomy, (ii) due to differences in how brain structure relates to brain function, and (iii) variations in mechanism-related lesion distributions and frequencies. Regarding neuroanatomy,

there are several defined variants of the circle of Willis that represents the backbone of cerebral blood supply by connecting anterior and posterior circulations (*343*). Some of these variants even have described associations to sex (*344*). However, these sex-specific variations do not relate to the middle cerebral artery, which is the most relevant vessel with respect to ischemic stroke (*345*). Vessel diameter (*346*–*348*), cerebral blood flow (*349*–*351*), and collateral status (*352*, *353*) have also been found to be influenced by sex. In the context of stroke, missing collaterals are linked to more unfavorable outcomes across male and female patients. Good collateral status, however, is specifically linked to better outcomes in male patients, as compared to female patients (*353*). With respect to stroke mechanisms and lesion distributions, cerebral atherosclerosis may manifest in a sex-specific fashion. Early data suggested a male predominance for intracranial atherosclerotic lesions (*354*). More recent data rather point toward more extracranial atherosclerosis in males (*208*). For intracranial atherosclerosis, there are no consistent report of differences (*208*, *299*). At least one recent large-scale study that recruited ~6500 patients with acute ischemic stroke noted more frequent symptomatic stenoses of the middle cerebral artery in female patients that went along with more frequent striatocapsular stroke injury (*342*). This constellation was contrasted with more frequent extracranial internal carotid and vertebral artery stenoses, as well as more frequent cerebrocortical and cerebellar strokes in males (*342*). The authors of this study hypothesized that these differences in lesion distribution could explain the sex differences seen in stroke severity to a substantial amount. Overall, this study represents one of the few that explicitly tested for sex differences in lesion anatomy and its findings contrast those of other studies that did not find any (*341*, *355*, *356*). Future research is warranted to resolve this discrepancy.

Independent of differences in structural lesion distributions, it is possible that similarly configurated lesions cause different patterns of stroke symptoms depending on whether they occur in a female or male brain. Lesion-symptom studies have traditionally been very valuable to infer functions of individual brain regions (*357*, *358*). Despite their century long history, only a few studies have evaluated the impact of biological sex. Some of the earliest sex-specific reports stem from studies of patients with lesion in the 1960s and 1970s. They were particularly centered on elucidating sex-specific lesion effects on intelligence (*10*, *359*) and sex differences in hemispheric asymmetry (*360*, *361*). Sex-specific lesion-symptom associations with respect to stroke severity and more classic stroke outcomes have been reported only recently. It was found that left-hemispheric stroke lesions in the vicinity of the posterior circulation were linked to a higher stroke severity (*341*, *342*) and worse functional outcomes (*355*) specifically in females.

Sex differences in stroke treatments

Intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) are the mainstays of stroke treatment in the acute time window (*362*). Several meta-analyses indicate that female patients were underrepresented in stroke trials, e.g., due to their older age and poorer prestroke functional status (*363*, *364*). This circumstance will require some changes in recruitment strategies in future years (*365*). On the basis of existing human data, the following conclusions are possible: IVT was introduced in 1995 (*366*) and subsequent meta-analytical evaluations indicated a lower rate of utilization in female patients (*367*). Data from more recent years suggest that this divergence has since decreased (*368*), if not resolved (*297*, *369*). Of note, independent of utilization rates, clinical outcomes after IVT do not appear to differ between male and female patients (*370*). On the whole, EVT appears to be equally used in female and male patients (*371*). Possibly, there are some regional patterns and a higher frequency of EVT in female patients in Europe (*297*, *369*). Similar to IVT, main outcomes after EVT do not seem to differ between females and males. This has been shown by post hoc evaluations of trial data (*372*), registry data (*373*, *374*), and especially also those analyses that carefully accounted for sex differences in further sociodemographic and clinical characteristics (*375*). Perhaps, though, there is some excess gain in disability-adjusted life years in female patients after EVT (*376*).

The clinical approval of medications targeting a reduction in poststroke neuroinflammation is still pending. Minocycline, a tetracycline, has been shown to reduce neuroinflammation in rodent studies (*377*) and to improve clinical outcome in humans in small clinical trials (*378*). Effects were observed to be greater in male patients (*379*). Despite the promising preclinical findings of estrogen poststroke emphasized in earlier sections, there has not been a translation to actual clinical management of acute stroke to date (*331*). Ambitions to perform human studies on the effects of hormone therapy largely subsided after the humbling findings of increased stroke risk in the Women's Health Initiative mentioned earlier (*246*, *380*). On top of that, smaller trials with human participants indicated increased stroke severity with hormone therapy (*381*). It should be noted, however, that the nature of these human studies was disease prevention, rather than acute treatment. Moreover, hormone therapy in humans included a combination of estrogen and progesterone, which is different from the common paradigms in experimental work featuring only one sex hormone. Altogether, more work will be needed in future years that appreciates the subtleties in, e.g., route, dosage, and timing of hormonal therapy. It will also have to consider the potential systemic effects of estrogen, going beyond the brain.

Further neurological diseases

In this review, we have focused on two of the most prevalent and disabling neurological diseases that are more frequently observed in advanced age. We do want to remark that distinctive sex differences are also clearly apparent for neurological diseases that can manifest at any younger and premenopausal age as well. Simply considering prevalences, most neurological diseases have a predilection for a specific sex. In case of MS, females are more susceptible to the disease than males are (*382*, *383*). This may be an expected difference based on general evaluations of sex differences in autoimmune diseases (*384*). Nonetheless, males diagnosed with MS experience worse disease progression (*385*). A decreased relapse probability during (late) pregnancy, followed by an increase in the first few months postpartum may hint at sex hormone influences on disease activity (*386*). Migraine, which is one of the most prevalent headache disorders, has an incidence ratio of 2:1 to 3:1 for females compared to males (*387*). Females additionally report more severe characteristics, such as longer headache duration, more frequent recurrence, and greater disability (*387*). The link between hormonal variations during regular menstrual cycles appears to be particularly strong, which created the diagnostic entity of menstrual migraines (*388*). In contrast, males are, in general, more likely to suffer from brain tumors, which aligns with general trends for malignancies (*389*). Effects are most pronounced for ependymoma and certain subtypes of high-grade glioma (*390*). Similarly, the incidence of epilepsy is

overall higher in males (*391*). Some variations are apparent for specific forms of epilepsy. For example, catamenial epilepsy describes seizures in females that are more frequent in specific stages of the menstrual cycle (*392*). Parkinson disease (PD) is both more prevalent and more severe in males (*393*). It was found that genes implicated in the pathogenesis of PD, if mutated, are up-regulated in males, but not in females (*394*). Also, the dopaminergic system is central to the pathophysiology of PD. Dysfunction of the dopaminergic system is associated with cognitive decline, and experimental work suggests a neuroprotective effect of estrogen (*140*, *395*). In addition, estrogen appears to increase dopamine efficacy (*140*, *395*).

Last, we did not elaborate on stark sex differences in comorbidities of neurological disease, such as accompanying depression (*317*, *396*). We also did not comment on sex differences arising for the pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics of a multitude of implicated drugs (*397*, *398*). Those differences can, for example, lead to a more severe side effect profile in females with an, on average, smaller body habitus. To name a specific example, female patients with PD experience a greater severity of levodopa-induced dyskinesias (*399*).

FURTHER REMARKS AND OUTLOOK

Biological sex, through genetics, epigenetics, and sex hormones, has vast effects on the human brain. In health and homeostasis, many of these differences between male and female brains may be concealed and inapparent, as sex differences in microscopic brain structure compensate for effects of sex hormones with innately varying levels in males and females (*73*, *400*). Brain disease, which disrupts this homeostasis, may hence be one of the lenses through which to effectively examine cerebral sex differences. Studying sex differences in the diseased brain may help us gain greater understanding of underlying anatomy, mechanical processes, ensuing presentations, and therapy efficacies.

While each neurological disease entity has its own specific pathophysiology and defining clinical syndrome, many of the main themes relating to sex-specific mechanisms and the research thereof generalize from one disease to the next. The role of sex hormones in neuroprotection, neuroplasticity, and memory and their potential therapeutic usage, sex-specific involvements of the immune system, microglia in particular, and interactions of sex and aging and effects of central genetic variants, such as APOEε4, are, for example, studied within each disease category.

Therefore, a greater awareness of each field's progress, encountered obstacles, and their solutions has the potential to substantially enhance and accelerate research into sex differences. Intensified dialog may even prompt innovative ideas to start out with (*401*). To name some concrete examples resulting from our review: It could be fruitful to alternate a disease-focused approach with a mechanism- or symptom-focused one. For example, one could compare results of estrogen treatment effects across health and various diseases in experimental and clinical setups. Naturally, intensified cross-talk between preclinical and clinical research teams has the potential to close gaps and contribute to explain why so many findings between preclinical and clinical work differ. It may help to fully appreciate systematic differences in study properties, such as the exact experimental model, age of animals or humans, and recorded metrics. It may motivate their careful comparison and eventually inspire each other's next immediate steps.

Moreover, some fields may classically be more advanced with respect to certain topics and represent a source of insight and inspiration. One example is the concept of brain and cognitive reserve that has been intensely studied in AD (*402*) but has only begun to draw attention in the stroke field (*403*). In contrast, cardiovascular risk factors and potential modification by sex have been deeply studied in stroke. These results may be of immediate relevance to other diseases. Moreover, many neurological diseases coincide and are complicated by the same comorbidities. One of the most well-known brain pathology studies, for example, noted that, at death, a substantial number of community-dwelling older persons had evidence of both AD and cerebral infarction (*404*). Further, the APOEε4 variant is known to have (sex-specific) effects on multiple neurological diseases (*179*, *405*, *406*), and depression complicates most neurological diseases (*317*, *396*). Thus, it is even more relevant to understand how sex differences may affect multiple diseases and the healthy brain at the same time.

Last, the review of sex differences across neurological diseases and their origins is, first and foremost, an impressive demonstration of the brain's complexity due to the multilayered interplay of

Box 1. Directions for future sex-informed research of neurological diseases.

Historically, there has been a predominance of males in both experimental and clinical work, with ambitions for adjustment and rectification in the last decade. On the other hand, most studies on the effect of estrogen have been conducted in females and the nature of effects is less known in males. Furthermore, many studies involving human participants do not explicitly differentiate between sex and gender (*281*, *409*). It is rare that human participants are asked about their sex at birth, and it is usually assumed by the rater or data collector. It may be the case that reported sex and sex at birth are aligned in most cases. However, it is currently difficult to disentangle related effects. Overall, sex, gender, and social identities in their entirety (*408*) should become naturally and automatically reported and evaluated variables. More sex- and gender-informed studies that go beyond a binary delineation and aim for sufficiently large subgroups are also needed. Specifically, those studies should evaluate relevance for sex- and gender-specific approaches to preventative and therapeutic regimen.

Future work should focus on building large and comprehensive datasets that capture data in greater granularity. For example, in female patients, more variables with respect to reproductive history should be recorded. Sex hormones, i.e., estrogen, progesterone, and testosterone, in addition to, e.g., oxytocin, prolactin, LH, FSH, and cortisol, could be measured on a more regular basis and investigated in greater detail. Another improvement could be the routine measurement of patient-reported outcomes (*410*). Data that are gathered in clinical routine should be made more readily available for analysis by collaborative research teams. At best, individual centers in various countries and continents will harmonize their approaches.

Past studies in AD and stroke indicate that some testing instruments, such as the Mini Mental State Examination (*312*), may have sex-specific sensitivities. Therefore, it will be paramount to ensure that tools are similarly sensitive in subgroups to prevent missed diagnoses and capture meaningful outcomes to all patients.

Future work in both animals and humans should embrace the complexity of multiway interactions, such as structure-function-behavior or sex-age, and more regularly consider multisystem effects, such as the gut-brain axis or immune system–brain effects. Sex chromosomes should be included more regularly in GWASs, as incentivized by promising recent findings (*185*).

structure and function underlying behavior. Understanding sex differences necessitates understanding subtle processes from micro- to macroscale (*44*). It requires taking into account dynamic changes of sex hormones and neurotransmitters, particularities of specific brain regions, explicit timings, and the overall age and constitution of participants. In practical terms, these requirements imply, at best, an understanding of research that ranges from experimental work with cells, rodents, monkeys, and humans, to epidemiology and clinical trials. It requires understanding techniques and their results from areas such as genetics, biochemistry, pathology, and neuroimaging. It benefits from the ability of handling large datasets and complex statistical modeling beyond linear relationships. While historically exceeding realistic capabilities of a single researcher, AI may help to allow for groundbreaking advancements to address outstanding questions (*407*).

We would like to point out that considering biological female and male sex as done in this review represents a simplified version of investigating the effects of sex. We did not explore the effects of gender or sexual orientation and associated psychosocial and cultural factors on brain organization and function (*408*). These psychosocial and cultural factors, for example, comprise lifestyle, help-seeking behavior, economic power, and access to health care. Gender-related behaviors are assumed to affect epigenetic changes with resulting modifications of sex-related effects (*12*). Another limitation may be seen in the fact that we evaluated sex differences in only a binary fashion. Therefore, despite the richness of displayed studies, a lot more work is needed to eventually generate the most effective therapeutic regimen for each individual patient (Box 1). In the end, we hope to have conveyed some examples of how the study of sex differences in neurological disease in preclinical and clinical work informs our understanding of the brain in general and holds promise to augment brain health and treatment of brain disease for each individual patient in the actual sense of precision medicine.

REFERENCES AND NOTES

1. F. S. Collins, H. Varmus, A new initiative on precision medicine. *N. Engl. J. Med.* **372**, 793–795 (2015).
2. I. S. Kohane, Ten things we have to do to achieve precision medicine. *Science* **349**, 37–38 (2015).
3. D. R. Corey, Nusinersen, an antisense oligonucleotide drug for spinal muscular atrophy. *Nat. Neurosci.* **20**, 497–499 (2017).
4. D. Dubey, S. J. Pittock, C. R. Kelly, A. McKeon, A. S. Lopez-Chiriboga, V. A. Lennon, A. Gadoth, C. Y. Smith, S. C. Bryant, C. J. Klein, A. J. Aksamit, M. Toledano, B. F. Boeve, J.-M. Tillema, E. P. Flanagan, Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. *Ann. Neurol.* **83**, 166–177 (2018).
5. M. Moor, O. Banerjee, Z. S. H. Abad, H. M. Krumholz, J. Leskovec, E. J. Topol, P. Rajpurkar, Foundation models for generalist medical artificial intelligence. *Nature* **616**, 259–265 (2023).
6. J. W. Ayers, A. Poliak, M. Dredze, E. C. Leas, Z. Zhu, J. B. Kelley, D. J. Faix, A. M. Goodman, C. A. Longhurst, M. Hogarth, D. M. Smith, Comparing physician and artificial intelligence chatbot responses to patient questions posted to a public social media forum. *JAMA Intern. Med.* **183**, 589–596 (2023).
7. L. Eliot, The trouble with sex differences. *Neuron* **72**, 895–898 (2011).
8. L. Eliot, A. Ahmed, H. Khan, J. Patel, Dump the "dimorphism": Comprehensive synthesis of human brain studies reveals few male-female differences beyond size. *Neurosci. Biobehav. Rev.* **125**, 667–697 (2021).
9. A. N. Ruigrok, G. Salimi-Khorshidi, M.-C. Lai, S. Baron-Cohen, M. V. Lombardo, R. J. Tait, J. Suckling, A meta-analysis of sex differences in human brain structure. *Neurosci. Biobehav. Rev.* **39**, 34–50 (2014).
10. J. McGlone, Sex differences in human brain asymmetry: A critical survey. *Behav. Brain Sci.* **3**, 215–227 (1980).
11. K. R. Laws, K. Irvine, T. M. Gale, Sex differences in cognitive impairment in Alzheimer's disease. *World J. Psychiatry* **6**, 54–65 (2016).
12. F. Mauvais-Jarvis, N. Bairey Merz, P. J. Barnes, R. D. Brinton, J.-J. Carrero, D. L. DeMeo, G. J. De Vries, C. N. Epperson, R. Govindan, S. L. Klein, A. Lonardo, P. M. Maki, L. D. McCullough, V. Regitz-Zagrosek, J. G. Regensteiner, J. B. Rubin, K. Sandberg, A. Suzuki, Sex and gender: Modifiers of health, disease, and medicine. *Lancet* **396**, 565–582 (2020).
13. B. Charlesworth, The evolution of sex chromosomes. *Science* **251**, 1030–1033 (1991).
14. A. H. Sinclair, P. Berta, M. S. Palmer, J. R. Hawkins, B. L. Griffiths, M. J. Smith, J. W. Foster, A.-M. Frischauf, R. Lovell-Badge, P. N. Goodfellow, A gene from the human sex-determining region encodes a protein with homology to a conserved DNA-binding motif. *Nature* **346**, 240–244 (1990).
15. D. Bachtrog, Y-chromosome evolution: Emerging insights into processes of Y-chromosome degeneration. *Nat. Rev. Genet.* **14**, 113–124 (2013).
16. J. F. Hughes, S. Rozen, Genomics and genetics of human and primate y chromosomes. *Annu. Rev. Genomics Hum. Genet.* **13**, 83–108 (2012).
17. J. A. M. Graves, Sex chromosome specialization and degeneration in mammals. *Cell* **124**, 901–914 (2006).
18. K. Lindblad-Toh, C. M. Wade, T. S. Mikkelsen, E. K. Karlsson, D. B. Jaffe, M. Kamal, M. Clamp, J. L. Chang, E. J. Kulbokas III, M. C. Zody, E. Mauceli, X. Xie, M. Breen, R. K. Wayne, E. A. Ostrander, C. P. Ponting, F. Galibert, D. R. Smith, P. J. DeJong, E. Kirkness, P. Alvarez, T. Biagi, W. Brockman, J. Butler, C.-W. Chin, A. Cook, J. Cuff, M. J. Daly, D. DeCaprio, S. Gnerre, M. Grabherr, M. Kellis, M. Kleber, C. Bardeleben, L. Goodstadt, A. Heger, C. Hitte, L. Kim, K.-P. Koepfli, H. G. Parker, J. P. Pollinger, S. M. J. Searle, N. B. Sutter, R. Thomas, C. Webber, J. Baldwin, A. Abebe, A. Abouelleil, L. Aftuck, M. Ait-Zahra, T. Aldredge, N. Allen, P. An, S. Anderson, C. Antoine, H. Arachchi, A. Aslam, L. Ayotte, P. Bachantsang, A. Barry, T. Bayul, M. Benamara, A. Berlin, D. Bessette, B. Blitshteyn, T. Bloom, J. Blye, L. Boguslavskiy, C. Bonnet, B. Boukhgalter, A. Brown, P. Cahill, N. Calixte, J. Camarata, Y. Cheshatsang, J. Chu, M. Citroen, A. Collymore, P. Cooke, T. Dawoe, R. Daza, K. Decktor, S. DeGray, N. Dhargay, K. Dooley, K. Dooley, P. Dorje, K. Dorjee, L. Dorris, N. Duffey, A. Dupes, O. Egbiremolen, R. Elong, J. Falk, A. Farina, S. Faro, D. Ferguson, P. Ferreira, S. Fisher, M. F. Gerald, K. Foley, C. Foley, A. Franke, D. Friedrich, D. Gage, M. Garber, G. Gearin, G. Giannoukos, T. Goode, A. Goyette, J. Graham, E. Grandbois, K. Gyaltsen, N. Hafez, D. Hagopian, B. Hagos, J. Hall, C. Healy, R. Hegarty, T. Honan, A. Horn, N. Houde, L. Hughes, L. Hunnicutt, M. Husby, B. Jester, C. Jones, A. Kamat, B. Kanga, C. Kells, D. Khazanovich, A. C. Kieu, P. Kisner, M. Kumar, K. Lance, T. Landers, M. Lara, W. Lee, J.-P. Leger, N. Lennon, L. Leuper, S. L. Vine, J. Liu, X. Liu, Y. Lokyitsang, T. Lokyitsang, A. Lui, J. Macdonald, J. Major, R. Marabella, K. Maru, C. Matthews, S. M. Donough, T. Mehta, J. Meldrim, A. Melnikov, L. Meneus, A. Mihalev, T. Mihova, K. Miller, R. Mittelman, V. Mlenga, L. Mulrain, G. Munson, A. Navidi, J. Naylor, T. Nguyen, N. Nguyen, C. Nguyen, T. Nguyen, R. Nicol, N. Norbu, C. Norbu, N. Novod, T. Nyima, P. Olandt, B. O'Neill, K. O'Neill, S. Osman, L. Oyono, C. Patti, D. Perrin, P. Phunkhang, F. Pierre, M. Priest, A. Rachupka, S. Raghuraman, R. Rameau, V. Ray, C. Raymond, F. Rege, C. Rise, J. Rogers, P. Rogov, J. Sahalie, S. Settipalli, T. Sharpe, T. Shea, M. Sheehan, N. Sherpa, J. Shi, D. Shih, J. Sloan, C. Smith, T. Sparrow, J. Stalker, N. Stange-Thomann, S. Stavropoulos, C. Stone, S. Stone, S. Sykes, P. Tchuinga, P. Tenzing, S. Tesfaye, D. Thoulutsang, Y. Thoulutsang, K. Topham, I. Topping, T. Tsamla, H. Vassiliev, V. Venkataraman, A. Vo, T. Wangchuk, T. Wangdi, M. Weiand, J. Wilkinson, A. Wilson, S. Yadav, S. Yang, X. Yang, G. Young, Q. Yu, J. Zainoun, L. Zembek, A. Zimmer, E. S. Lande, Genome sequence, comparative analysis and haplotype structure of the domestic dog. *Nature* **438**, 803–819 (2005).
19. H. Skaletsky, T. Kuroda-Kawaguchi, P. J. Minx, H. S. Cordum, L. D. Hillier, L. G. Brown, S. Repping, T. Pyntikova, J. Ali, T. Bieri, A. Chinwalla, A. Delehaunty, K. Delehaunty, H. Du, G. Fewell, L. Fulton, R. Fulton, T. Graves, S.-F. Hou, P. Latrielle, S. Leonard, E. Mardis, R. Maupin, J. M. Pherson, T. Miner, W. Nash, C. Nguyen, P. Ozersky, K. Pepin, S. Rock, T. Rohlfing, K. Scott, B. Schultz, C. Strong, A. Tin-Wollam, S.-P. Yang, R. H. Waterston, R. K. Wilson, S. Rozen, D. C. Page, The male-specific region of the human Y chromosome is a mosaic of discrete sequence classes. *Nature* **423**, 825–837 (2003).
20. M. T. Ross, D. V. Grafham, A. J. Coffey, S. Scherer, K. McLay, D. Muzny, M. Platzer, G. R. Howell, C. Burrows, C. P. Bird, A. Frankish, F. L. Lovell, K. L. Howe, J. L. Ashurst, R. S. Fulton, R. Sudbrak, G. Wen, M. C. Jones, M. E. Hurles, T. D. Andrews, C. E. Scott, S. Searle, J. Ramser, A. Whittaker, R. Deadman, N. P. Carter, S. E. Hunt, R. Chen, A. Cree, P. Gunaratne, P. Havlak, A. Hodgson, M. L. Metzker, S. Richards, G. Scott, D. Steffen, E. Sodergren, D. A. Wheeler, K. C. Worley, R. Ainscough, K. D. Ambrose, M. A. Ansari-Lari, S. Aradhya, R. I. S. Ashwell, A. K. Babbage, C. L. Bagguley, A. Ballabio, R. Banerjee, G. E. Barker, K. F. Barlow, I. P. Barrett, K. N. Bates, D. M. Beare, H. Beasley, O. Beasley, A. Beck, G. Bethel, K. Blechschmidt, N. Brady, S. Bray-Allen, A. M. Bridgeman, A. J. Brown, M. J. Brown, D. Bonnin, E. A. Bruford, C. Buhay, P. Burch, D. Burford, J. Burgess, W. Burrill, J. Burton, J. M. Bye, C. Carder, L. Carrel, J. Chako, J. C. Chapman, D. Chavez, E. Chen, G. Chen, Y. Chen, Z. Chen, C. Chinault, A. Ciccodicola, S. Y. Clark, G. Clarke, C. M. Clee, S. Clegg, K. Clerc-Blankenburg, K. Clifford, V. Cobley, C. G. Cole, J. S. Conquer, N. Corby, R. E. Connor, R. David, J. Davies, C. Davis, J. Davis, O. Delgado, D. DeShazo, P. Dhami, Y. Ding, H. Dinh, S. Dodsworth, H. Draper, S. Dugan-Rocha, A. Dunham, M. Dunn, K. J. Durbin, I. Dutta, T. Eades, M. Ellwood, A. Emery-Cohen, H. Errington, K. L. Evans, L. Faulkner, F. Francis, J. Frankland, A. E. Fraser, P. Galgoczy, J. Gilbert, R. Gill, G. Glöckner,

S. G. Gregory, S. Gribble, C. Griffiths, R. Grocock, Y. Gu, R. Gwilliam, C. Hamilton, E. A. Hart, A. Hawes, P. D. Heath, K. Heitmann, S. Hennig, J. Hernandez, B. Hinzmann, S. Ho, M. Hoffs, P. J. Howden, E. J. Huckle, J. Hume, P. J. Hunt, A. R. Hunt, J. Isherwood, L. Jacob, D. Johnson, S. Jones, P. J. de Jong, S. S. Joseph, S. Keenan, S. Kelly, J. K. Kershaw, Z. Khan, P. Kioschis, S. Klages, A. J. Knights, A. Kosiura, C. Kovar-Smith, G. K. Laird, C. Langford, S. Lawlor, M. Leversha, L. Lewis, W. Liu, C. Lloyd, D. M. Lloyd, H. Loulseged, J. E. Loveland, J. D. Lovell, R. Lozado, J. Lu, R. Lyne, J. Ma, M. Maheshwari, L. H. Matthews, J. McDowall, S. McLaren, A. McMurray, P. Meidl, T. Meitinger, S. Milne, G. Miner, S. L. Mistry, M. Morgan, S. Morris, I. Müller, J. C. Mullikin, N. Nguyen, G. Nordsiek, G. Nyakatura, C. N. O'Dell, G. Okwuonu, S. Palmer, R. Pandian, D. Parker, J. Parrish, S. Pasternak, D. Patel, A. V. Pearce, D. M. Pearson, S. E. Pelan, L. Perez, K. M. Porter, Y. Ramsey, K. Reichwald, S. Rhodes, K. A. Ridler, D. Schlessinger, M. G. Schueler, H. K. Sehra, C. Shaw-Smith, H. Shen, E. M. Sheridan, R. Shownkeen, C. D. Skuce, M. L. Smith, E. C. Sotheran, H. E. Steingruber, C. A. Steward, R. Storey, R. M. Swann, D. Swarbreck, P. E. Tabor, S. Taudien, T. Taylor, B. Teague, K. Thomas, A. Thorpe, K. Timms, A. Tracey, S. Trevanion, A. C. Tromans, M. d'Urso, D. Verduzco, D. Villasana, L. Waldron, M. Wall, Q. Wang, J. Warren, G. L. Warry, X. Wei, A. West, S. L. Whitehead, M. N. Whiteley, J. E. Wilkinson, D. L. Willey, G. Williams, L. Williams, A. Williamson, H. Williamson, L. Wilming, R. L. Woodmansey, P. W. Wray, J. Yen, J. Zhang, J. Zhou, H. Zoghbi, S. Zorilla, D. Buck, R. Reinhardt, A. Poustka, A. Rosenthal, H. Lehrach, A. Meindl, P. J. Minx, L. W. Hillier, H. F. Willard, R. K. Wilson, R. H. Waterston, C. M. Rice, M. Vaudin, A. Coulson, D. L. Nelson, G. Weinstock, J. E. Sulston, R. Durbin, T. Hubbard, R. A. Gibbs, S. Beck, J. Rogers, D. R. Bentley, The DNA sequence of the human X chromosome. *Nature* **434**, 325–337 (2005).

21. R. J. Aitken, J. A. M. Graves, Human spermatozoa: The future of sex. *Nature* **415**, 963–963 (2002).
22. J. F. Hughes, H. Skaletsky, L. G. Brown, T. Pyntikova, T. Graves, R. S. Fulton, S. Dugan, Y. Ding, C. J. Buhay, C. Kremitzki, Q. Wang, H. Shen, M. Holder, D. Villasana, L. V. Nazareth, A. Cree, L. Courtney, J. Veizer, H. Kotkiewicz, T.-J. Cho, N. Koutseva, S. Rozen, D. M. Muzny, W. C. Warren, R. A. Gibbs, R. K. Wilson, D. C. Page, Strict evolutionary conservation followed rapid gene loss on human and rhesus Y chromosomes. *Nature* **483**, 82–86 (2012).
23. M. F. Lyon, Gene action in the X-chromosome of the mouse (*Mus musculus* L.). *Nature* **190**, 372–373 (1961).
24. L. Carrel, H. F. Willard, X-inactivation profile reveals extensive variability in X-linked gene expression in females. *Nature* **434**, 400–404 (2005).
25. G. M. Saifl, H. S. Chandra, An apparent excess of sex- and reproduction-related genes on the human X chromosome. *Proc. R. Soc. Lond. B. Biol. Sci.* **266**, 203–209 (1999).
26. B. Capel, Vertebrate sex determination: Evolutionary plasticity of a fundamental switch. *Nat. Rev. Genet.* **18**, 675–689 (2017).
27. A. P. Arnold, Sexual differentiation of brain and other tissues: Five questions for the next 50 years. *Horm. Behav.* **120**, 104691 (2020).
28. C. Libert, L. Dejager, I. Pinheiro, The X chromosome in immune functions: When a chromosome makes the difference. *Nat. Rev. Immunol.* **10**, 594–604 (2010).
29. D. K. Nguyen, C. M. Disteche, Dosage compensation of the active X chromosome in mammals. *Nat. Genet.* **38**, 47–53 (2006).
30. S. M. Smith, G. Douaud, W. Chen, T. Hanayik, F. Alfaro-Almagro, K. Sharp, L. T. Elliott, An expanded set of genome-wide association studies of brain imaging phenotypes in UK Biobank. *Nat. Neurosci.* **24**, 737–745 (2021).
31. P. Dewing, C. W. K. Chiang, K. Sinchak, H. Sim, P.-O. Fernagut, S. Kelly, M.-F. Chesselet, P. E. Micevych, K. H. Albrecht, V. R. Harley, E. Vilain, Direct regulation of adult brain function by the male-specific factor SRY. *Curr. Biol.* **16**, 415–420 (2006).
32. J. Nielsen, M. Wohlert, Chromosome abnormalities found among 34,910 newborn children: Results from a 13-year incidence study in Arhus, Denmark. *Hum. Genet.* **87**, 81–83 (1991).
33. L. Abramsky, J. Chapple, 47,XXY (Klinefelter syndrome) and 47,XYY: Estimated rates of and indication for postnatal diagnosis with implications for prenatal counselling. *Prenat. Diagn.* **17**, 363–368 (1997).
34. D. S. Hong, A. L. Reiss, Cognitive and neurological aspects of sex chromosome aneuploidies. *Lancet Neurol.* **13**, 306–318 (2014).
35. A. Raznahan, N. R. Lee, D. Greenstein, G. L. Wallace, J. D. Blumenthal, L. S. Clasen, J. N. Giedd, Globally divergent but locally convergent X- and Y-chromosome influences on cortical development. *Cereb. Cortex* **26**, 70–79 (2016).
36. A. P. Arnold, X. Chen, What does the "four core genotypes" mouse model tell us about sex differences in the brain and other tissues? *Front. Neuroendocrinol.* **30**, 1–9 (2009).
37. U. Zechner, M. Wilda, H. Kehrer-Sawatzki, W. Vogel, R. Fundele, H. Hameister, A high density of X-linked genes for general cognitive ability: A run-away process shaping human evolution? *Trends Genet.* **17**, 697–701 (2001).
38. H.-H. Ropers, B. C. J. Hamel, X-linked mental retardation. *Nat. Rev. Genet.* **6**, 46–57 (2005).
39. B. Matos, S. J. Publicover, L. F. C. Castro, P. J. Esteves, M. Fardilha, Brain and testis: More alike than previously thought? *Open Biol.* **11**, 200322 (2021).
40. J. Guo, P. Zhu, C. Wu, L. Yu, S. Zhao, X. Gu, In silico analysis indicates a similar gene expression pattern between human brain and testis. *Cytogenet. Genome Res.* **103**, 58–62 (2004).
41. J. H. Guo, Q. Huang, D. J. Studholme, C. Q. Wu, Z. Zhao, Transcriptomic analyses support the similarity of gene expression between brain and testis in human as well as mouse. *Cytogenet. Genome Res.* **111**, 107–109 (2005).
42. B. Gegenhuber, M. V. Wu, R. Bronstein, J. Tollkuhn, Gene regulation by gonadal hormone receptors underlies brain sex differences. *Nature* **606**, 153–159 (2022).
43. D. Trabzuni, A. Ramasamy, S. Imran, R. Walker, C. Smith, M. E. Weale, J. Hardy, M. Ryten, North American Brain Expression Consortium, Widespread sex differences in gene expression and splicing in the adult human brain. *Nat. Commun.* **4**, 2771 (2013).
44. B. S. McEwen, T. A. Milner, Understanding the broad influence of sex hormones and sex differences in the brain. *J. Neurosci. Res.* **95**, 24–39 (2017).
45. L. E. Salminen, M. A. Tubi, J. Bright, S. I. Thomopoulos, A. Wieand, P. M. Thompson, Sex is a defining feature of neuroimaging phenotypes in major brain disorders. *Hum. Brain Mapp.* **43**, 500–542 (2022).
46. J. D. Wilson, F. W. George, J. E. Griffin, The hormonal control of sexual development. *Science* **211**, 1278–1284 (1981).
47. L. R. Taxier, K. S. Gross, K. M. Frick, Oestradiol as a neuromodulator of learning and memory. *Nat. Rev. Neurosci.* **21**, 535–550 (2020).
48. W. C. Young, E. W. Dempsey, H. I. Myers, Cyclic reproductive behavior in the female guinea pig. *J. Comp. Psychol.* **19**, 313–335 (1935).
49. W. C. Young, R. W. Goy, C. H. Phoenix, Hormones and sexual behavior. *Science* **143**, 212–218 (1964).
50. E. Terasawa, P. S. Timiras, Electrical activity during the estrous cycle of the rat: Cyclic changes in limbic structures. *Endocrinology* **83**, 207–216 (1968).
51. P. Bedard, P. Langelier, A. Villeneuve, Œstrogens and extrapyramidal system. *Lancet* **310**, 1367–1368 (1977).
52. R. Cajal, Cajal, R., y 1894 An. Soc. esp. Hist. nat, 2, p. 214 (1894).
53. G. W. Harris, The induction of ovulation in the rabbit, by electrical stimulation of the hypothalamo-hypophysial mechanism. *Proc. R. Soc. Lond.B Biol. Sci.* **122**, 374–394 (1997).
54. D. Pfaff, M. Keiner, Atlas of estradiol-concentrating cells in the central nervous system of the female rat. *J Comp Neurol* **151**, 121–157 (1973).
55. W. E. Stumpf, Estradiol-concentrating neurons: Topography in the hypothalamus by dry-mount autoradiography. *Science* **162**, 1001–1003 (1968).
56. W. E. Stumpf, M. Sar, Steroid hormone target sites in the brain: The differential distribution of estrogen, progestin, androgen and glucocorticosteroid. *J. Steroid Biochem.* **7**, 1163–1170 (1976).
57. A. C. J. Wang, Y. Hara, W. G. M. Janssen, P. R. Rapp, J. H. Morrison, Synaptic estrogen receptor-α levels in prefrontal cortex in female rhesus monkeys and their correlation with cognitive performance. *J. Neurosci.* **30**, 12770–12776 (2010).
58. S. W. Mitra, E. Hoskin, J. Yudkovitz, L. Pear, H. A. Wilkinson, S. Hayashi, D. W. Pfaff, S. Ogawa, S. P. Rohrer, J. M. Schaeffer, B. S. McEwen, S. E. Alves, Immunolocalization of estrogen receptor β in the mouse brain: Comparison with estrogen receptor α. *Endocrinology* **144**, 2055–2067 (2003).
59. W. M. Pardridge, L. J. Mietus, Transport of steroid hormones through the rat blood-brain barrier: Primary role of albumin-bound hormone. *J. Clin. Invest.* **64**, 145–154 (1979).
60. P. S. Herson, I. P. Koerner, P. D. Hurn, Sex, sex steroids, and brain injury. *Semin. Reprod. Med.* **27**, 229–239 (2009).
61. C. H. Phoenix, R. W. Goy, A. A. Gerall, W. C. Young, Organizing action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. *Endocrinology* **65**, 369–382 (1959).
62. A. Arnold, R. Gorski, Gonadal steroid induction of structural sex differences in the central nervous system. *Annu. Rev. Neurosci.* **7**, 413–442 (1984).
63. E. Catenaccio, W. Mu, M. L. Lipton, Estrogen- and progesterone-mediated structural neuroplasticity in women: Evidence from neuroimaging. *Brain Struct. Funct.* **221**, 3845–3867 (2016).
64. M. M. Herting, E. R. Sowell, Puberty and structural brain development in humans. *Front. Neuroendocrinol.* **44**, 122–137 (2017).
65. L. D. McCullough, N. J. Alkayed, R. J. Traystman, M. J. Williams, P. D. Hurn, Postischemic estrogen reduces hypoperfusion and secondary ischemia after experimental stroke. *Stroke* **32**, 796–802 (2001).
66. C. J. Pike, T.-V. V. Nguyen, M. Ramsden, M. Yao, M. P. Murphy, E. R. Rosario, Androgen cell signaling pathways involved in neuroprotective actions. *Horm. Behav.* **53**, 693–705 (2008).
67. N. J. Alkayed, S. J. Murphy, R. J. Traystman, P. D. Hurn, Neuroprotective effects of female gonadal steroids in reproductively senescent female rats. *Stroke* **31**, 161–168 (2000).
68. S.-H. Yang, J. Shi, A. L. Day, J. W. Simpkins, Estradiol exerts neuroprotective effects when administered after ischemic insult. *Stroke* **31**, 745–750 (2000).
69. C. L. Gibson, S. P. Murphy, Progesterone enhances functional recovery after middle cerebral artery occlusion in male mice. *J. Cereb. Blood Flow Metab.* **24**, 805–813 (2004).
70. C. Barth, A. Villringer, J. Sacher, Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. *Front. Neurosci.* **9**, 37 (2015).
71. J. G. Oberlander, C. S. Woolley, 17β-Estradiol acutely potentiates glutamatergic synaptic transmission in the hippocampus through distinct mechanisms in males and females. *J. Neurosci.* **36**, 2677–2690 (2016).

72. A. Jain, G. Z. Huang, C. S. Woolley, Latent sex differences in molecular signaling that underlies excitatory synaptic potentiation in the hippocampus. *J. Neurosci.* **39**, 1552–1565 (2019).
73. G. J. De Vries, Minireview: Sex differences in adult and developing brains: Compensation, compensation, compensation. *Endocrinology* **145**, 1063–1068 (2004).
74. G. E. Abraham, W. D. Odell, R. S. Swerdloff, K. Hopper, Simultaneous radioimmunoassay of plasma FSH, LH, progesterone, 17-hydroxyprogesterone, and estradiol-17β during the menstrual cycle. *J. Clin. Endocrinol. Metabol.* **34**, 312–318 (1972).
75. R. Stricker, R. Eberhart, M.-C. Chevailler, F. A. Quinn, P. Bischof, R. Stricker, Establishment of detailed reference values for luteinizing hormone, follicle stimulating hormone, estradiol, and progesterone during different phases of the menstrual cycle on the Abbott ARCHITECT® analyzer. *Clinical Chemistry and Laboratory Medicine (CCLM)* **44**, 883–887 (2006).
76. L. Pritschet, T. Santander, C. M. Taylor, E. Layher, S. Yu, M. B. Miller, S. T. Grafton, E. G. Jacobs, Functional reorganization of brain networks across the human menstrual cycle. *Neuroimage* **220**, 117091 (2020).
77. E. Gould, C. S. Woolley, M. Frankfurt, B. S. McEwen, Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. *J. Neurosci.* **10**, 1286–1291 (1990).
78. C. S. Woolley, B. S. McEwen, Estradiol mediates fluctuation in hippocampal synapse density during the estrous cycle in the adult rat. *J. Neurosci.* **12**, 2549–2554 (1992).
79. S. V. Koebele, H. A. Bimonte-Nelson, Modeling menopause: The utility of rodents in translational behavioral endocrinology research. *Maturitas* **87**, 5–17 (2016).
80. L. Mendoza-garcés, C. A. Mendoza-rodríguez, F. Jiménez-trejo, O. Picazo, M. C. Rodríguez, M. Cerbón, Differential expression of estrogen receptors in two hippocampal regions during the estrous cycle of the rat. *Anat. Rec.* **294**, 1913–1919 (2011).
81. C. S. Woolley, B. S. McEwen, Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle in the rat. *J Comp Neurol* **336**, 293–306 (1993).
82. M. Dubol, C. N. Epperson, J. Sacher, B. Pletzer, B. Derntl, R. Lanzenberger, I. Sundström-Poromaa, E. Comasco, Neuroimaging the menstrual cycle: A multimodal systematic review. *Front. Neuroendocrinol.* **60**, 100878 (2021).
83. B. Derntl, C. Windischberger, S. Robinson, E. Lamplmayr, I. Kryspin-Exner, R. C. Gur, E. Moser, U. Habel, Facial emotion recognition and amygdala activation are associated with menstrual cycle phase. *Psychoneuroendocrinology* **33**, 1031–1040 (2008).
84. R. Dan, L. Canetti, T. Keadan, R. Segman, M. Weinstock, O. Bonne, I. Reuveni, G. Goelman, Sex differences during emotion processing are dependent on the menstrual cycle phase. *Psychoneuroendocrinology* **100**, 85–95 (2019).
85. R. A. Poldrack, T. O. Laumann, O. Koyejo, B. Gregory, A. Hover, M.-Y. Chen, K. J. Gorgolewski, J. Luci, S. J. Joo, R. L. Boyd, S. Hunicke-Smith, Z. B. Simpson, T. Caven, V. Sochat, J. M. Shine, E. Gordon, A. Z. Snyder, B. Adeyemo, S. E. Petersen, D. C. Glahn, D. Reese Mckay, J. E. Curran, H. H. H. Göring, M. A. Carless, J. Blangero, R. Dougherty, A. Leemans, D. A. Handwerker, L. Frick, E. M. Marcotte, J. A. Mumford, Long-term neural and physiological phenotyping of a single human. *Nat. Commun.* **6**, 8885 (2015).
86. L. Pritschet, C. M. Taylor, T. Santander, E. G. Jacobs, Applying dense-sampling methods to reveal dynamic endocrine modulation of the nervous system. *Curr. Opin. Behav. Sci.* **40**, 72–78 (2021).
87. C. M. Taylor, L. Pritschet, R. K. Olsen, E. Layher, T. Santander, S. T. Grafton, E. G. Jacobs, Progesterone shapes medial temporal lobe volume across the human menstrual cycle. *Neuroimage* **220**, 117125 (2020).
88. N. Lisofsky, M. Riediger, J. Gallinat, U. Lindenberger, S. Kühn, Hormonal contraceptive use is associated with neural and affective changes in healthy young women. *Neuroimage* **134**, 597–606 (2016).
89. N. Petersen, A. M. Beltz, K. V. Casto, C. M. Taylor, E. G. Jacobs, I. Sundström-Poromaa, B. Pletzer, Towards a more comprehensive neuroscience of hormonal contraceptives. *Nat. Neurosci.* **26**, 529–531 (2023).
90. D. B. Cooper, P. Patel, Oral contraceptive pills, in *StatPearls* (StatPearls Publishing, 2024); http://ncbi.nlm.nih.gov/books/NBK430882/.
91. A. M. Warren, C. Gurvich, R. Worsley, J. Kulkarni, A systematic review of the impact of oral contraceptives on cognition. *Contraception* **90**, 111–116 (2014).
92. K. L. Mordecai, L. H. Rubin, P. M. Maki, Effects of menstrual cycle phase and oral contraceptive use on verbal memory. *Horm. Behav.* **54**, 286–293 (2008).
93. L. A. M. Galea, J. K. Wide, A. M. Barr, Estradiol alleviates depressive-like symptoms in a novel animal model of post-partum depression. *Behav. Brain Res.* **122**, 1–9 (2001).
94. E. Hoekzema, E. Barba-Müller, C. Pozzobon, M. Picado, F. Lucco, D. García-García, J. C. Soliva, A. Tobeña, M. Desco, E. A. Crone, A. Ballesteros, S. Carmona, O. Vilarroya, Pregnancy leads to long-lasting changes in human brain structure. *Nat. Neurosci.* **20**, 287–296 (2017).
95. C. Servin-Barthet, M. Martínez-García, C. Pretus, M. Paternina-Pie, A. Soler, O. Khymenets, Ó. J. Pozo, B. Leuner, O. Vilarroya, S. Carmona, The transition to motherhood: Linking hormones, brain and behaviour. *Nat. Rev. Neurosci.* **24**, 605–619 (2023).
96. K. G. Lambert, C. H. Kinsley, Brain and behavioral modifications that accompany the onset of motherhood. *Parenting* **12**, 74–88 (2012).
97. M. Paternina-Die, M. Martínez-García, D. Martín de Blas, I. Noguero, C. Servin-Barthet, C. Pretus, A. Soler, G. López-Montoya, M. Desco, S. Carmona, Women's neuroplasticity during gestation, childbirth and postpartum. *Nat. Neurosci.* **27**, 319–327 (2024).
98. L. Pritschet, C. M. Taylor, D. Cossio, J. Faskowitz, T. Santander, D. A. Handwerker, H. Grotzinger, E. Layher, E. R. Chrastil, E. G. Jacobs, Neuroanatomical changes observed over the course of a human pregnancy. *Nat. Neurosci.* **27**, 2253–2260 (2024).
99. M. Martínez-García, M. Paternina-Die, E. Barba-Müller, D. Martín de Blas, L. Beumala, R. Cortizo, C. Pozzobon, L. Marcos-Vidal, A. Fernández-Pena, M. Picado, E. Belmonte-Padilla, A. Massó-Rodriguez, A. Ballesteros, M. Desco, Ó. Vilarroya, E. Hoekzema, S. Carmona, Do pregnancy-induced brain changes reverse? The brain of a mother six years after parturition. *Brain Sci.* **11**, 168 (2021).
100. A.-M. G. de Lange, T. Kaufmann, D. van der Meer, L. A. Maglanoc, D. Alnæs, T. Moberget, G. Douaud, O. A. Andreassen, L. T. Westlye, Population-based neuroimaging reveals traces of childbirth in the maternal brain. *Proc. Natl. Acad. Sci. U.S.A.* **116**, 22341–22346 (2019).
101. P. M. Brindle, M. W. Brown, J. Brown, H. B. Griffith, G. M. Turner, Objective and subjective memory impairment in pregnancy. *Psychol. Med.* **21**, 647–653 (1991).
102. P. Duarte-Guterman, B. Leuner, L. A. M. Galea, The long and short term effects of motherhood on the brain. *Front. Neuroendocrinol.* **53**, 100740 (2019).
103. S. J. Davies, J. A. Lum, H. Skouteris, L. K. Byrne, M. J. Hayden, Cognitive impairment during pregnancy: A meta-analysis. *M. J. Aust.* **208**, 35–40 (2018).
104. J. F. Henry, B. B. Sherwin, Hormones and cognitive functioning during late pregnancy and postpartum: A longitudinal study. *Behav. Neurosci.* **126**, 73–85 (2012).
105. S. D. Harlow, M. Gass, J. E. Hall, R. Lobo, P. Maki, R. W. Rebar, S. Sherman, P. M. Sluss, T. J. de Villiers, STRAW + 10 Collaborative Group, Executive summary of the stages of reproductive aging workshop + 10: Addressing the unfinished agenda of staging reproductive aging. *J. Clin. Endocrinol. Metabol.* **97**, 1159–1168 (2012).
106. N. Santoro, The menopausal transition. *Am. J. Med.* **118**, 8–13 (2005).
107. H. G. Burger, E. C. Dudley, D. M. Robertson, L. Dennerstein, Hormonal changes in the menopause transition. *Recent Prog. Horm. Res.* **57**, 257–275 (2002).
108. R. D. Brinton, J. Yao, F. Yin, W. J. Mack, E. Cadenas, Perimenopause as a neurological transition state. *Nat. Rev. Endocrinol.* **11**, 393–405 (2015).
109. F. Yin, J. Yao, H. Sancheti, T. Feng, R. C. Melcangi, T. E. Morgan, C. E. Finch, C. J. Pike, W. J. Mack, E. Cadenas, R. D. Brinton, The perimenopausal aging transition in the female rat brain: Decline in bioenergetic systems and synaptic plasticity. *Neurobiol. Aging* **36**, 2282–2295 (2015).
110. Y. Hara, C. S. Park, W. G. M. Janssen, M. T. Roberts, J. H. Morrison, P. R. Rapp, Synaptic correlates of memory and menopause in the hippocampal dentate gyrus in rhesus monkeys. *Neurobiol. Aging* **33**, 421.e17–421.e28 (2012).
111. J. Hao, P. R. Rapp, A. E. Leffler, S. R. Leffler, W. G. M. Janssen, W. Lou, H. McKay, J. A. Roberts, S. L. Wearne, P. R. Hof, J. H. Morrison, Estrogen alters spine number and morphology in prefrontal cortex of aged female rhesus monkeys. *J. Neurosci.* **26**, 2571–2578 (2006).
112. J. Yao, R. Irwin, S. Chen, R. Hamilton, E. Cadenas, R. D. Brinton, Ovarian hormone loss induces bioenergetic deficits and mitochondrial β-amyloid. *Neurobiol. Aging* **33**, 1507–1521 (2012).
113. E. G. Jacobs, B. K. Weiss, N. Makris, S. Whitfield-Gabrieli, S. L. Buka, A. Klibanski, J. M. Goldstein, Impact of sex and menopausal status on episodic memory circuitry in early midlife. *J. Neurosci.* **36**, 10163–10173 (2016).
114. N. Z. Ramli, M. F. Yahaya, N. A. Mohd Fahami, H. Abdul Manan, M. Singh, H. A. Damanhuri, Brain volumetric changes in menopausal women and its association with cognitive function: A structured review. *Front. Aging Neurosci.* **15**, 1158001 (2023).
115. L. Mosconi, V. Berti, J. Dyke, E. Schelbaum, S. Jett, L. Loughlin, G. Jang, A. Rahman, H. Hristov, S. Pahlajani, R. Andrews, D. Matthews, O. Etingin, C. Ganzer, M. de Leon, R. Isaacson, R. D. Brinton, Menopause impacts human brain structure, connectivity, energy metabolism, and amyloid-beta deposition. *Sci. Rep.* **11**, 10867 (2021).
116. E. G. Jacobs, B. Weiss, N. Makris, S. Whitfield-Gabrieli, S. L. Buka, A. Klibanski, J. M. Goldstein, Reorganization of functional networks in verbal working memory circuitry in early midlife: The impact of sex and menopausal status. *Cereb. Cortex* **27**, 2857–2870 (2017).
117. A. Rahman, E. Schelbaum, K. Hoffman, I. Diaz, H. Hristov, R. Andrews, S. Jett, H. Jackson, A. Lee, H. Sarva, S. Pahlajani, D. Matthews, J. Dyke, M. J. de Leon, R. S. Isaacson, R. D. Brinton, L. Mosconi, Sex-driven modifiers of Alzheimer risk: A multimodality brain imaging study. *Neurology* **95**, e166–e178 (2020).
118. S. E. Shaywitz, B. A. Shaywitz, K. R. Pugh, R. K. Fulbright, P. Skudlarski, W. E. Mencl, R. T. Constable, F. Naftolin, S. F. Palter, K. E. Marchione, L. Katz, D. P. Shankweiler, J. M. Fletcher, C. Lacadie, M. Keltz, J. C. Gore, Effect of estrogen on brain activation patterns in postmenopausal women during working memory tasks. *JAMA* **281**, 1197–1202 (1999).
119. P. M. Maki, S. M. Resnick, Longitudinal effects of estrogen replacement therapy on PET cerebral blood flow and cognition. *Neurobiol. Aging* **21**, 373–383 (2000).
120. J. L. Eberling, B. R. Reed, J. E. Coleman, W. J. Jagust, Effect of estrogen on cerebral glucose metabolism in postmenopausal women. *Neurology* **55**, 875–877 (2000).

121. M. C. Stevens, V. P. Clark, K. M. Prestwood, Low-dose estradiol alters brain activity. *Psychiatry Res. Neuroimaging* **139**, 199–217 (2005).
122. J. A. Dumas, A. M. Kutz, M. R. Naylor, J. V. Johnson, P. A. Newhouse, Increased memory load-related frontal activation after estradiol treatment in postmenopausal women. *Horm. Behav.* **58**, 929–935 (2010).
123. N. F. Woods, E. S. Mitchell, Symptoms during the perimenopause: Prevalence, severity, trajectory, and significance in women's lives. *Am. J. Med.* **118**, 14–24 (2005).
124. P. Monteleone, G. Mascagni, A. Giannini, A. R. Genazzani, T. Simoncini, Symptoms of menopause—Global prevalence, physiology and implications. *Nat. Rev. Endocrinol.* **14**, 199–215 (2018).
125. R. R. Freedman, Menopausal hot flashes: Mechanisms, endocrinology, treatment. *J. Steroid Biochem. Mol. Biol.* **142**, 115–120 (2014).
126. L. Dennerstein, E. C. Dudley, J. L. Hopper, J. R. Guthrie, H. G. Burger, A prospective population-based study of menopausal symptoms. *Obstet. Gynecol.* **96**, 351–358 (2000).
127. E. B. Gold, B. Sternfeld, J. L. Kelsey, C. Brown, C. Mouton, N. Reame, L. Salamone, R. Stellato, Relation of demographic and lifestyle factors to symptoms in a multi-racial/ethnic population of women 40–55 years of age. *Am. J. Epidemiol.* **152**, 463–473 (2000).
128. M. T. Weber, P. M. Maki, M. P. McDermott, Cognition and mood in perimenopause: A systematic review and meta-analysis. *J. Steroid Biochem. Mol. Biol.* **142**, 90–98 (2014).
129. R. Reuben, L. Karkaby, C. McNamee, N. A. Phillips, G. Einstein, Menopause and cognitive complaints: Are ovarian hormones linked with subjective cognitive decline? *Climacteric* **24**, 321–332 (2021).
130. E. Hogervorst, J. Craig, E. O'Donnell, Cognition and mental health in menopause: A review. *Best Pract. Res. Clin. Obstet. Gynaecol.* **81**, 69–84 (2022).
131. M. T. Weber, L. H. Rubin, P. M. Maki, Cognition in perimenopause: The effect of transition stage. *Menopause* **20**, 511–517 (2013).
132. G. A. Greendale, M.-H. Huang, R. G. Wight, T. Seeman, C. Luetters, N. E. Avis, J. Johnston, A. S. Karlamangla, Effects of the menopause transition and hormone use on cognitive performance in midlife women. *Neurology* **72**, 1850–1857 (2009).
133. D. M. Rentz, B. K. Weiss, E. G. Jacobs, S. Cherkerzian, A. Klibanski, A. Remington, H. Aizley, J. M. Goldstein, Sex differences in episodic memory in early midlife: Impact of reproductive aging. *Menopause* **24**, 400–408 (2017).
134. S. Campbell, M. Whitehead, Oestrogen therapy and the menopausal syndrome. *Clin. Obstet. Gynaecol.* **4**, 31–47 (1977).
135. E. Bonanni, A. Schirru, M. C. Di Perri, U. Bonuccelli, M. Maestri, Insomnia and hot flashes. *Maturitas* **126**, 51–54 (2019).
136. F. C. Baker, F. Siboza, A. Fuller, Temperature regulation in women: Effects of the menstrual cycle. *Temperature* **7**, 226–262 (2020).
137. R. Manber, R. R. Bootzin, Sleep and the menstrual cycle. *Health Psychol.* **16**, 209–214 (1997).
138. F. C. Baker, K. A. Lee, Menstrual cycle effects on sleep. *Sleep Med. Clin.* **17**, 283–294 (2022).
139. M. E. Levine, A. T. Lu, B. H. Chen, D. G. Hernandez, A. B. Singleton, L. Ferrucci, S. Bandinelli, E. Salfati, J. E. Manson, A. Quach, C. D. J. Kusters, D. Kuh, A. Wong, A. E. Teschendorff, M. Widschwendter, B. R. Ritz, D. Absher, T. L. Assimes, S. Horvath, Menopause accelerates biological aging. *Proc. Natl. Acad. Sci. U.S.A.* **113**, 9327–9332 (2016).
140. J. K. Russell, C. K. Jones, P. A. Newhouse, The role of estrogen in brain and cognitive aging. *Neurotherapeutics* **16**, 649–665 (2019).
141. E. Fabbri, Y. An, M. Gonzalez-Freire, M. Zoli, M. Maggio, S. A. Studenski, J. M. Egan, C. W. Chia, L. Ferrucci, Bioavailable testosterone linearly declines over a wide age spectrum in men and women from the baltimore longitudinal study of aging. *J. Gerontol. A Biol. Sci. Med. Sci.* **71**, 1202–1209 (2016).
142. E. H. van den Burg, I. D. Neumann, Bridging the gap between GPCR activation and behaviour: Oxytocin and prolactin signalling in the hypothalamus. *J. Mol. Neurosci.* **43**, 200–208 (2011).
143. D. R. Rubinow, P. J. Schmidt, C. A. Roca, Estrogen–serotonin interactions: Implications for affective regulation. *Biol. Psychiatry* **44**, 839–850 (1998).
144. D. Deecher, T. H. Andree, D. Sloan, L. E. Schechter, From menarche to menopause: Exploring the underlying biology of depression in women experiencing hormonal changes. *Psychoneuroendocrinology* **33**, 3–17 (2008).
145. C. Franceschi, P. Garagnani, C. Morsiani, M. Conte, A. Santoro, A. Grignolio, D. Monti, M. Capri, S. Salvioli, The continuum of aging and age-related diseases: Common mechanisms but different rates. *Front. Med.* **5**, 10.3389/fmed.2018.00061 (2018).
146. C. López-Otín, M. A. Blasco, L. Partridge, M. Serrano, G. Kroemer, The hallmarks of aging. *Cell* **153**, 1194–1217 (2013).
147. M. Gardner, D. Bann, L. Wiley, R. Cooper, R. Hardy, D. Nitsch, C. Martin-Ruiz, P. Shiels, A. A. Sayer, M. Barbieri, S. Bekaert, C. Bischoff, A. Brooks-Wilson, W. Chen, C. Cooper, K. Christensen, T. De Meyer, I. Deary, G. Der, A. D. Roux, A. Fitzpatrick, A. Hajat, J. Halaschek-Wiener, S. Harris, S. C. Hunt, C. Jagger, H.-S. Jeon, R. Kaplan, M. Kimura, P. Lansdorp, C. Li, T. Maeda, M. Mangino, T. S. Nawrot, P. Nilsson, K. Nordfjall, G. Paolisso, F. Ren, K. Riabowol, T. Robertson, G. Roos, J. A. Staessen, T. Spector, N. Tang, B. Unryn, P. van der Harst, J. Woo, C. Xing, M. E. Yadegarfar, J. Y. Park, N. Young, D. Kuh, T. von Zglinicki, Y. Ben-Shlomo, Halcyon study team, Gender and telomere length: Systematic review and meta-analysis. *Exp. Gerontol.* **51**, 15–27 (2014).
148. S. N. Austad, Why women live longer than men: Sex differences in longevity. *Gend. Med.* **3**, 79–92 (2006).
149. S. Hägg, J. Jylhävä, Sex differences in biological aging with a focus on human studies. *eLife* **10**, e63425 (2021).
150. R. H. Straub, The complex role of estrogens in Inflammation. *Endocr. Rev.* **28**, 521–574 (2007).
151. M. R. Gubbels Bupp, Sex, the aging immune system, and chronic disease. *Cell. Immunol.* **294**, 102–110 (2015).
152. S. M. Gold, R. R. Voskuhl, Estrogen and testosterone therapies in multiple sclerosis, in *Progress in Brain Research*, J. Verhaagen, E. M. Hol, I. Huitenga, J. Wijnholds, A. B. Bergen, G. J. Boer, D. F. Swaab, Eds. (Elsevier, 2009), vol. 175 of *Neurotherapy: Progress in Restorative Neuroscience and Neurology*, pp. 239–251; https://sciencedirect.com/science/article/pii/S0079612309175167.
153. M. R. Gubbels Bupp, T. N. Jorgensen, Androgen-induced immunosuppression. *Front. Immunol.* **9**, 794 (2018).
154. C. Franceschi, M. Bonafè, S. Valensin, F. Olivieri, M. De Luca, E. Ottaviani, G. De Benedictis, Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann. N. Y. Acad. Sci.* **908**, 244–254 (2000).
155. A. Gruver, L. Hudson, G. Sempowski, Immunosenescence of ageing. *J. Pathol.* **211**, 144–156 (2007).
156. A. M. Simanek, J. B. Dowd, G. Pawelec, D. Melzer, A. Dutta, A. E. Aiello, Seropositivity to cytomegalovirus, inflammation, all-cause and cardiovascular disease-related mortality in the United States. *PLOS ONE* **6**, e16103 (2011).
157. C. Franceschi, P. Garagnani, G. Vitale, M. Capri, S. Salvioli, Inflammaging and 'Garb-aging'. *Trends in Endocrinol. Metab.* **28**, 199–212 (2017).
158. M. F. Gregor, G. S. Hotamisligil, Inflammatory mechanisms in obesity. *Annu. Rev. Immunol.* **29**, 415–445 (2011).
159. E. Biagi, L. Nylund, M. Candela, R. Ostan, L. Bucci, E. Pini, J. Nikkïla, D. Monti, R. Satokari, C. Franceschi, P. Brigidi, W. D. Vos, Through ageing, and beyond: Gut microbiota and inflammatory status in seniors and centenarians. *PLOS ONE* **5**, e10667 (2010).
160. M. G. Rooks, W. S. Garrett, Gut microbiota, metabolites and host immunity. *Nat. Rev. Immunol.* **16**, 341–352 (2016).
161. A. Santoro, E. Bientinesi, D. Monti, Immunosenescence and inflammaging in the aging process: Age-related diseases or longevity? *Ageing Res. Rev.* **71**, 101422 (2021).
162. J. G. M. Markle, D. N. Frank, S. Mortin-Toth, C. E. Robertson, L. M. Feazel, U. Rolle-Kampczyk, M. von Bergen, K. D. McCoy, A. J. Macpherson, J. S. Danska, Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. *Science* **339**, 1084–1088 (2013).
163. E. Jašarević, K. E. Morrison, T. L. Bale, Sex differences in the gut microbiome–brain axis across the lifespan. *Philos. Trans. R. Soc. Lond. B: Biol. Sci.* **371**, 20150122 (2016).
164. F. Mauvais-Jarvis, Sex differences in metabolic homeostasis, diabetes, and obesity. *Biol. Sex Differ.* **6**, 14 (2015).
165. A. Varatharaj, I. Galea, The blood-brain barrier in systemic inflammation. *Brain Behav. Immun.* **60**, 1–12 (2017).
166. J. A. Prenderville, P. J. Kennedy, T. G. Dinan, J. F. Cryan, Adding fuel to the fire: The impact of stress on the ageing brain. *Trends Neurosci.* **38**, 13–25 (2015).
167. Alzheimer's Association (2024); https://alz.org/getmedia/76e51bb6-c003-4d84-8019-e0779d8c4e8d/alzheimers-facts-and-figures.pdf.
168. C. R. Jack Jr., D. A. Bennett, K. Blennow, M. C. Carrillo, B. Dunn, S. B. Haeberlein, D. M. Holtzman, W. Jagust, F. Jessen, J. Karlawish, E. Liu, J. L. Molinuevo, T. Montine, C. Phelps, K. P. Rankin, C. C. Rowe, P. Scheltens, E. Siemers, H. M. Snyder, R. Sperling, C. Elliott, E. Masliah, L. Ryan, N. Silverberg, NIA-AA research framework: Toward a biological definition of Alzheimer's disease. *Alzheimers Dement.* **14**, 535–562 (2018).
169. H. Hampel, J. Hardy, K. Blennow, C. Chen, G. Perry, S. H. Kim, V. L. Villemagne, P. Aisen, M. Vendruscolo, T. Iwatsubo, C. L. Masters, M. Cho, L. Lannfelt, J. L. Cummings, A. Vergallo, The amyloid-β pathway in Alzheimer's disease. *Mol. Psychiatry* **26**, 5481–5503 (2021).
170. A. Pichet Binette, N. Franzmeier, N. Spotorno, M. Ewers, M. Brendel, D. Biel, Alzheimer's Disease Neuroimaging Initiative, O. Strandberg, S. Janelidze, S. Palmqvist, N. Mattsson-Carlgren, R. Smith, E. Stomrud, R. Ossenkoppele, O. Hansson, Amyloid-associated increases in soluble tau relate to tau aggregation rates and cognitive decline in early Alzheimer's disease. *Nat. Commun.* **13**, 6635 (2022).
171. M. A. Busche, B. T. Hyman, Synergy between amyloid-β and tau in Alzheimer's disease. *Nat. Neurosci.* **23**, 1183–1193 (2020).
172. C. R. Jack Jr., J. S. Andrews, T. G. Beach, T. Buracchio, B. Dunn, A. Graf, O. Hansson, C. Ho, W. Jagust, E. McDade, J. L. Molinuevo, O. C. Okonkwo, L. Pani, M. S. Rafii, P. Scheltens, E. Siemers, H. M. Snyder, R. Sperling, C. E. Teunissen, M. C. Carrillo, Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's association workgroup. *Alzheimers Dement.* **20**, 5143–5169 (2024).
173. S. M. Greenberg, B. J. Bacskai, M. Hernandez-Guillamon, J. Pruzin, R. Sperling, S. J. van Veluw, Cerebral amyloid angiopathy and Alzheimer disease—One peptide, two pathways. *Nat. Rev. Neurol.* **16**, 30–42 (2020).
174. M. M. Mielke, P. Vemuri, W. A. Rocca, Clinical epidemiology of Alzheimer's disease: Assessing sex and gender differences. *Clin. Epidemiol.* **6**, 37–48 (2014).

175. C. M. Mazure, J. Swendsen, Sex differences in Alzheimer's disease and other dementias. *Lancet Neurol.* **15**, 451–452 (2016).
176. M. T. Ferretti, M. F. Iulita, E. Cavedo, P. A. Chiesa, A. S. Dimech, A. S. Chadha, F. Baracchi, H. Girouard, S. Misoch, E. Giacobini, Women's Brain Project and the Alzheimer Precision Medicine Initiative, Sex differences in Alzheimer disease—The gateway to precision medicine. *Nat. Rev. Neurol.* **14**, 457–469 (2018).
177. C. Lopez-Lee, E. R. S. Torres, G. Carling, L. Gan, Mechanisms of sex differences in Alzheimer's disease. *Neuron* **112**, 1208–1221 (2024).
178. G. Chêne, A. Beiser, R. Au, S. R. Preis, P. A. Wolf, C. Dufouil, S. Seshadri, Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimers Dement.* **11**, 310–320 (2015).
179. A. Altmann, L. Tian, V. W. Henderson, M. D. Greicius, Alzheimer's Disease Neuroimaging Initiative Investigators, Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann. Neurol.* **75**, 563–573 (2014).
180. E. H. Corder, A. M. Saunders, W. J. Strittmatter, D. E. Schmechel, P. C. Gaskell, G. W. Small, A. D. Roses, J. L. Haines, M. A. Pericak-Vance, Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**, 921–923 (1993).
181. S. C. Neu, J. Pa, W. Kukull, D. Beekly, A. Kuzma, P. Gangadharan, L.-S. Wang, K. Romero, S. P. Arneric, A. Redolfi, D. Orlandi, G. B. Frisoni, R. Au, S. Devine, S. Auerbach, A. Espinosa, M. Boada, A. Ruiz, S. C. Johnson, R. Koscik, J.-J. Wang, W.-C. Hsu, Y.-L. Chen, A. W. Toga, Apolipoprotein E genotype and sex risk factors for Alzheimer disease: A meta-analysis. *JAMA Neurol.* **74**, 1178–1189 (2017).
182. M. E. Belloy, S. J. Andrews, Y. Le Guen, M. Cuccaro, L. A. Farrer, V. Napolioni, M. D. Greicius, APOE genotype and Alzheimer disease risk across age, sex, and population ancestry. *JAMA Neurol.* **80**, 1284–1294 (2023).
183. D. B. Dubal, C. Rogine, Apolipoprotein E ε4 and risk factors for Alzheimer disease—Let's talk about sex. *JAMA Neurol.* **74**, 1167–1168 (2017).
184. R. F. Buckley, M. Seto, How is the X chromosome involved in Alzheimer disease? *JAMA Neurol.* **81**, 1028–1029 (2024).
185. M. E. Belloy, Y. Le Guen, I. Stewart, K. Williams, J. Herz, R. Sherva, R. Zhang, V. Merritt, M. S. Panizzon, R. L. Hauger, J. M. Gaziano, M. Logue, V. Napolioni, M. D. Greicius, Role of the X chromosome in Alzheimer disease genetics. *JAMA Neurol.* **81**, 1032–1042 (2024).
186. G. Livingston, J. Huntley, K. Y. Liu, S. G. Costafreda, G. Selbæk, S. Alladi, D. Ames, S. Banerjee, A. Burns, C. Brayne, N. C. Fox, C. P. Ferri, L. N. Gitlin, R. Howard, H. C. Kales, M. Kivimäki, E. B. Larson, N. Nakasujja, K. Rockwood, Q. Samus, K. Shirai, A. Singh-Manoux, L. S. Schneider, S. Walsh, Y. Yao, A. Sommerlad, N. Mukadam, Dementia prevention, intervention, and care: 2024 report of the lancet standing commission. *Lancet* **404**, 572–628 (2024).
187. K. L. Lapane, G. Gambassi, F. Landi, A. Sgadari, V. Mor, R. Bernabei, Gender differences in predictors of mortality in nursing home residents with AD. *Neurology* **56**, 650–654 (2001).
188. C. J. Pike, Sex and the development of Alzheimer's disease. *J. Neurosci. Res.* **95**, 671–680 (2017).
189. J. T. Tschanz, C. D. Corcoran, S. Schwartz, K. Treiber, R. C. Green, M. C. Norton, M. M. Mielke, K. Piercy, M. Steinberg, P. V. Rabins, J.-M. Leoutsakos, K. A. Welsh-Bohmer, J. C. S. Breitner, C. G. Lyketsos, Progression of cognitive, functional, and neuropsychiatric symptom domains in a population cohort with Alzheimer dementia: The cache county dementia progression study. *Am. J. Geriatr. Psychiatry* **19**, 532–542 (2011).
190. K. Tifratene, P. Robert, A. Metelkina, C. Pradier, J. F. Dartigues, Progression of mild cognitive impairment to dementia due to AD in clinical settings. *Neurology* **85**, 331–338 (2015).
191. K. A. Lin, K. R. Choudhury, B. G. Rathakrishnan, D. M. Marks, J. R. Petrella, P. M. Doraiswamy, Alzheimer's Disease Neuroimaging Initiative, Marked gender differences in progression of mild cognitive impairment over 8 years. *Alzheimers Demen. (N Y)* **1**, 103–110 (2015).
192. R. F. Buckley, E. C. Mormino, R. E. Amariglio, M. J. Properzi, J. S. Rabin, Y. Y. Lim, K. V. Papp, H. I. L. Jacobs, S. Burnham, B. J. Hanseeuw, V. Doré, A. Dobson, C. L. Masters, M. Waller, C. C. Rowe, P. Maruff, M. C. Donohue, D. M. Rentz, D. Kirn, T. Hedden, J. Chhatwal, A. P. Schultz, K. A. Johnson, V. L. Villemagne, R. A. Sperling, Alzheimer's Disease Neuroimaging Initiative, Australian Imaging, Biomarker and Lifestyle study of ageing, Harvard Aging Brain Study, Sex, amyloid, and APOE ε4 and risk of cognitive decline in preclinical Alzheimer's disease: Findings from three well-characterized cohorts. *Alzheimers Dement.* **14**, 1193–1203 (2018).
193. A. J. Polsinelli, P. E. Logan, K. A. Lane, M. K. Manchella, S. Nemes, A. B. Sanjay, S. Gao, L. G. Apostolova, APOE ε4 carrier status and sex differentiate rates of cognitive decline in early- and late-onset Alzheimer's disease. *Alzheimers Dement.* **19**, 1983–1993 (2023).
194. K. Irvine, K. R. Laws, T. M. Gale, T. K. Kondel, Greater cognitive deterioration in women than men with Alzheimer's disease: A meta analysis. *J. Clin. Exp. Neuropsychol.* **34**, 989–998 (2012).
195. M. E. I. Koran, M. Wagener, T. J. Hohman, Alzheimer's Neuroimaging Initiative, Sex differences in the association between AD biomarkers and cognitive decline. *Brain Imaging Behav.* **11**, 205–213 (2017).
196. W. S. Eikelboom, M. Pan, R. Ossenkoppele, M. Coesmans, J. R. Gatchel, Z. Ismail, K. L. Lanctôt, C. E. Fischer, M. E. Mortby, E. van den Berg, J. M. Papma, Sex differences in neuropsychiatric symptoms in Alzheimer's disease dementia: A meta-analysis. *Alzheimers Res. Ther.* **14**, 48 (2022).
197. K. A. Lin, P. M. Doraiswamy, When Mars versus Venus is not a cliché: Gender differences in the neurobiology of Alzheimer's disease. *Front. Neurol.* **5**, 288 (2015).
198. L. L. Barnes, R. S. Wilson, J. L. Bienias, J. A. Schneider, D. A. Evans, D. A. Bennett, Sex differences in the clinical manifestations of Alzheimer disease pathology. *Arch. Gen. Psychiatry* **62**, 685–691 (2005).
199. S. Oveisgharan, Z. Arvanitakis, L. Yu, J. Farfel, J. A. Schneider, D. A. Bennett, Sex differences in Alzheimer's disease and common neuropathologies of aging. *Acta Neuropathol.* **136**, 887–900 (2018).
200. R. Babapour Mofrad, B. M. Tijms, P. Scheltens, F. Barkhof, W. M. van der Flier, S. A. M. Sikkes, C. E. Teunissen, Sex differences in CSF biomarkers vary by Alzheimer disease stage and APOE ε4 genotype. *Neurology* **95**, e2378–e2388 (2020).
201. T. J. Hohman, L. Dumitrescu, L. L. Barnes, M. Thambisetty, G. Beecham, B. Kunkle, K. A. Gifford, W. S. Bush, L. B. Chibnik, S. Mukherjee, P. L. De Jager, W. Kukull, P. K. Crane, S. M. Resnick, C. D. Keene, T. J. Montine, G. D. Schellenberg, J. L. Haines, H. Zetterberg, K. Blennow, E. B. Larson, S. C. Johnson, M. Albert, D. A. Bennett, J. A. Schneider, A. L. Jefferson, Alzheimer's Disease Genetics Consortium and the Alzheimer's Disease Neuroimaging Initiative, Sex-specific association of apolipoprotein E with cerebrospinal fluid levels of tau. *JAMA Neurol.* **75**, 989–998 (2018).
202. R. F. Buckley, E. C. Mormino, J. S. Rabin, T. J. Hohman, S. Landau, B. J. Hanseeuw, H. I. L. Jacobs, K. V. Papp, R. E. Amariglio, M. J. Properzi, A. P. Schultz, D. Kirn, M. R. Scott, T. Hedden, M. Farrell, J. Price, J. Chhatwal, D. M. Rentz, V. L. Villemagne, K. A. Johnson, R. A. Sperling, Sex differences in the association of global amyloid and regional tau deposition measured by positron emission tomography in clinically normal older adults. *JAMA Neurol.* **76**, 542–551 (2019).
203. R. F. Buckley, A. O'Donnell, E. R. McGrath, H. I. L. Jacobs, C. Lois, C. L. Satizabal, S. Ghosh, Z. B. Rubinstein, J. M. Murabito, R. A. Sperling, K. A. Johnson, S. Seshadri, A. S. Beiser, Menopause status moderates sex differences in tau burden: A Framingham PET study. *Ann. Neurol.* **92**, 11–22 (2022).
204. T. Melnikova, D. Park, L. Becker, D. Lee, E. Cho, N. Sayyida, J. Tian, K. Bandeen-Roche, D. R. Borchelt, A. V. Savonenko, Sex-related dimorphism in dentate gyrus atrophy and behavioral phenotypes in an inducible tTa:APPsi transgenic model of Alzheimer's disease. *Neurobiol. Dis.* **96**, 171–185 (2016).
205. D. B. Dubal, L. Broestl, K. Worden, Sex and gonadal hormones in mouse models of Alzheimer's disease: What is relevant to the human condition? *Biol. Sex Differ.* **3**, 24 (2012).
206. Y. Iturria-Medina, R. C. Sotero, P. J. Toussaint, J. M. Mateos-Pérez, A. C. Evans, The Alzheimer's Disease Neuroimaging Initiative, Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nat. Commun.* **7**, 11934 (2016).
207. L. T. Grinberg, D. R. Thal, Vascular pathology in the aged human brain. *Acta Neuropathol.* **119**, 277–290 (2010).
208. S. Voigt, H. van Os, M. van Walderveen, I. C. van der Schaaf, L. J. Kappelle, A. Broersen, B. K. Velthuis, P. de Jong, R. Kockelkoren, N. Kruyt, A. Algra, M. Wermer, DUST study group, Sex differences in intracranial and extracranial atherosclerosis in patients with acute ischemic stroke. *Int. J. Stroke* **16**, 385–391 (2021).
209. L. Jiménez-Sánchez, O. K. L. Hamilton, U. Clancy, E. V. Backhouse, C. R. Stewart, M. S. Stringer, F. N. Doubal, J. M. Wardlaw, Sex differences in cerebral small vessel disease: A systematic review and meta-analysis. *Front. Neurol.* **12**, 756887 (2021).
210. M. Shinohara, M. E. Murray, R. D. Frank, M. Shinohara, M. DeTure, Y. Yamazaki, M. Tachibana, Y. Atagi, M. D. Davis, C.-C. Liu, N. Zhao, M. M. Painter, R. C. Petersen, J. D. Fryer, J. E. Crook, D. W. Dickson, G. Bu, T. Kanekiyo, Impact of sex and APOE4 on cerebral amyloid angiopathy in Alzheimer's disease. *Acta Neuropathol.* **132**, 225–234 (2016).
211. A. Charidimou, G. Boulouis, M. P. Frosch, J.-C. Baron, M. Pasi, J. F. Albucher, G. Banerjee, C. Barbato, F. Bonneville, S. Brandner, L. Calviere, F. Caparros, B. Casolla, C. Cordonnier, M.-B. Delisle, V. Deramecourt, M. Dichgans, E. Gokcal, J. Herms, M. Hernandez-Guillamon, H. R. Jäger, Z. Jaunmuktane, J. Linn, S. Martinez-Ramirez, E. Martínez-Sáez, C. Mawrin, J. Montaner, S. Moulin, J.-M. Olivot, F. Piazza, L. Puy, N. Raposo, M. A. Rodrigues, S. Roeber, J. R. Romero, N. Samarasekera, J. A. Schneider, S. Schreiber, F. Schreiber, C. Schwall, C. Smith, L. Szalardy, P. Varlet, A. Viguier, J. M. Wardlaw, A. Warren, F. A. Wollenweber, M. Zedde, M. A. van Buchem, M. E. Gurol, A. Viswanathan, R. A.-S. Salman, E. E. Smith, D. J. Werring, S. M. Greenberg, The Boston criteria version 2.0 for cerebral amyloid angiopathy: A multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *The Lancet Neurology* **21**, 714–725 (2022).
212. A. Viswanathan, S. M. Greenberg, Cerebral amyloid angiopathy in the elderly. *Ann. Neurol.* **70**, 871–880 (2011).
213. E. A. Koemans, J. P. Castello, I. Rasing, J. R. Abramson, S. Voigt, V. Perosa, T. W. van Harten, E. W. van Zwet, G. M. Terwindt, M. E. Gurol, J. Rosand, S. M. Greenberg,

M. A. A. van Walderveen, A. Biffi, A. Viswanathan, M. J. H. Wermer, Sex differences in onset and progression of cerebral amyloid angiopathy. *Stroke* **54**, 306–314 (2023).
214. C. W. Yoon, J.-H. Rha, H.-K. Park, S.-H. Park, S. Kwon, B. C. Kim, Y. C. Youn, J. H. Jeong, H. J. Han, S. H. Choi, Sex differences in the progression of cerebral microbleeds in patients with concomitant cerebral small vessel disease. *Front. Neurol.* **13**, 1054624 (2022).
215. E. A. Koemans, V. Perosa, W. M. Freeze, H. Lee, M. G. Kozberg, G. T. Coughlan, R. F. Buckley, M. J. Wermer, S. M. Greenberg, S. J. van Veluw, Sex differences in histopathological markers of cerebral amyloid angiopathy and related hemorrhage. *Int. J. Stroke* **19**, 947–956 (2024).
216. M. E. Maniskas, A. F. Mack, D. Morales-Scheihing, C. Finger, L. Zhu, R. Paulter, A. Urayama, L. D. McCullough, B. Manwani, Sex differences in a murine model of cerebral amyloid angiopathy. *Brain Behavior Immun. Health* **14**, 100260 (2021).
217. M. Prinz, S. Jung, J. Priller, Microglia biology: One century of evolving concepts. *Cell* **179**, 292–311 (2019).
218. L. Kodama, L. Gan, Do microglial sex differences contribute to sex differences in neurodegenerative diseases? *Trends Mol. Med.* **25**, 741–749 (2019).
219. H. J. Möller, M. B. Graeber, The case described by Alois Alzheimer in 1911. Historical and conceptual perspectives based on the clinical record and neurohistological sections. *Eur. Arch. Psychiatry Clin. Neurosci.* **248**, 111–122 (1998).
220. E. G. Reed, P. R. Keller-Norrell, Minding the gap: Exploring neuroinflammatory and microglial sex differences in Alzheimer's disease. *Int. J. Mol. Sci.* **24**, 17377 (2023).
221. D. Zhu, A. Montagne, Z. Zhao, Alzheimer's pathogenic mechanisms and underlying sex difference. *Cell. Mol. Life Sci.* **78**, 4907–4920 (2021).
222. J. M. Schwarz, P. W. Sholar, S. D. Bilbo, Sex differences in microglial colonization of the developing rat brain. *J. Neurochem.* **120**, 948–963 (2012).
223. D. Guneykaya, A. Ivanov, D. P. Hernandez, V. Haage, B. Wojtas, N. Meyer, M. Maricos, P. Jordan, A. Buonfiglioli, B. Gielniewski, N. Ochocka, C. Cömert, C. Friedrich, L. S. Artiles, B. Kaminska, P. Mertins, D. Beule, H. Kettenmann, S. A. Wolf, Transcriptional and translational differences of microglia from male and female brains. *Cell Rep.* **24**, 2773–2783.e6 (2018).
224. K. B. Casaletto, E. Nichols, V. Aslanyan, S. M. Simone, J. S. Rabin, R. La Joie, A. M. Brickman, K. Dams-O'Connor, P. Palta, R. G. Kumar, K. M. George, C. L. Satizabal, J. Schneider, J. Pa, Sex-specific effects of microglial activation on Alzheimer's disease proteinopathy in older adults. *Brain* **145**, 3536–3545 (2022).
225. R. T. Bartus, R. L. Dean III, B. Beer, A. S. Lippa, The cholinergic hypothesis of geriatric memory dysfunction. *Science* **217**, 408–414 (1982).
226. P. Bentley, J. Driver, R. J. Dolan, Cholinergic modulation of cognition: Insights from human pharmacological functional neuroimaging. *Prog. Neurobiol.* **94**, 360–388 (2011).
227. M. G. Baxter, A. A. Chiba, Cognitive functions of the basal forebrain. *Curr. Opin. Neurobiol.* **9**, 178–183 (1999).
228. M.-M. Mesulam, L. Volicer, J. K. Marquis, E. J. Mufson, R. C. Green, Systematic regional differences in the cholinergic innervation of the primate cerebral cortex: Distribution of enzyme activities and some behavioral implications. *Ann. Neurol.* **19**, 144–151 (1986).
229. M. McKinney, J. T. Coyle, J. C. Hedreen, Topographic analysis of the innervation of the rat neocortex and hippocampus by the basal forebrain cholinergic system. *J Comp Neurol* **217**, 103–121 (1983).
230. E. C. Ballinger, M. Ananth, D. A. Talmage, L. W. Role, Basal forebrain cholinergic circuits and signaling in cognition and cognitive decline. *Neuron* **91**, 1199–1218 (2016).
231. M. D. Kopelman, The cholinergic neurotransmitter system in human memory and dementia: A review. *Q. J. Exp. Psychol. A* **38**, 535–573 (1986).
232. D. A. Drachman, J. Leavitt, Human memory and the cholinergic system. A relationship to aging? *Arch. Neurol.* **30**, 113–121 (1974).
233. D. A. Drachman, Memory and cognitive function in man: Does the cholinergic system have a specific role? *Neurology* **27**, 783–790 (1977).
234. R. Hammond, R. B. Gibbs, GPR30 is positioned to mediate estrogen effects on basal forebrain cholinergic neurons and cognitive performance. *Brain Res.* **1379**, 53–60 (2011).
235. R. B. Gibbs, R. Mauk, D. Nelson, D. A. Johnson, Donepezil treatment restores the ability of estradiol to enhance cognitive performance in aged rats: Evidence for the cholinergic basis of the critical period hypothesis. *Horm. Behav.* **56**, 73–83 (2009).
236. R. Scacchi, G. Gambina, E. Broggio, R. M. Corbo, Sex and ESR1 genotype may influence the response to treatment with donepezil and rivastigmine in patients with Alzheimer's disease. *Int. J. Geriatr. Psychiatry* **29**, 610–615 (2014).
237. J. Ryan, J. Scali, I. Carrière, H. Amieva, O. Rouaud, C. Berr, K. Ritchie, M.-L. Ancelin, Impact of a premature menopause on cognitive function in later life. *BJOG* **121**, 1729–1739 (2014).
238. G. T. Coughlan, T. J. Betthauser, R. Boyle, R. L. Koscik, H. M. Klinger, L. B. Chibnik, E. M. Jonaitis, W.-Y. W. Yau, A. Wenzel, B. T. Christian, C. E. Gleason, U. G. Saelzler, M. J. Properzi, A. P. Schultz, B. J. Hanseeuw, J. E. Manson, D. M. Rentz, K. A. Johnson, R. Sperling, S. C. Johnson, R. F. Buckley, Association of age at menopause and hormone therapy use with tau and β-amyloid positron emission tomography. *JAMA Neurol.* **80**, 462–473 (2023).
239. S. Pertesi, G. Coughlan, V. Puthusseryppady, E. Morris, M. Hornberger, Menopause, cognition and dementia–A review. *Post Reprod. Health* **25**, 200–206 (2019).
240. A. Jayaraman, J. C. Carroll, T. E. Morgan, S. Lin, L. Zhao, J. M. Arimoto, M. P. Murphy, T. L. Beckett, C. E. Finch, R. D. Brinton, C. J. Pike, 17β-Estradiol and progesterone regulate expression of β-amyloid clearance factors in primary neuron cultures and female rat brain. *Endocrinology* **153**, 5467–5479 (2012).
241. K. Yaffe, G. Sawaya, I. Lieberburg, D. Grady, Estrogen therapy in postmenopausal women: Effects on cognitive function and dementia. *JAMA* **279**, 688–695 (1998).
242. E. S. LeBlanc, J. Janowsky, B. K. S. Chan, H. D. Nelson, Hormone replacement therapy and cognition: Systematic review and meta-analysis. *JAMA* **285**, 1489–1499 (2001).
243. H. D. Nelson, L. L. Humphrey, P. Nygren, S. M. Teutsch, J. D. Allan, Postmenopausal hormone replacement therapy: Scientific review. *JAMA* **288**, 872–881 (2002).
244. S. A. Shumaker, C. Legault, S. R. Rapp, L. Thal, R. B. Wallace, J. K. Ockene, S. L. Hendrix, B. N. Jones III, A. R. Assaf, R. D. Jackson, J. Morley Kotchen, S. Wassertheil-Smoller, J. Wactawski-Wende, WHIMS Investigators, Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: The Women's health initiative memory study: A randomized controlled trial. *JAMA* **289**, 2651–2662 (2003).
245. S. A. Shumaker, B. A. Reboussin, M. A. Espeland, S. R. Rapp, W. L. McBee, M. Dailey, D. Bowen, T. Terrell, B. N. Jones, The Women's Health Initiative Memory Study (WHIMS): A trial of the effect of estrogen therapy in preventing and slowing the progression of dementia. *Control. Clin. Trials* **19**, 604–621 (1998).
246. J. E. Rossouw, G. L. Anderson, R. L. Prentice, A. Z. LaCroix, C. Kooperberg, M. L. Stefanick, R. D. Jackson, S. A. A. Beresford, B. V. Howard, K. C. Johnson, J. M. Kotchen, J. Ockene, Writing Group for the Women's Health Initiative Investigators, Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* **288**, 321–333 (2002).
247. R. B. Gibbs, R. Gabor, Estrogen and cognition: Applying preclinical findings to clinical perspectives. *J. Neurosci. Res.* **74**, 637–643 (2003).
248. D. A. Davey, Alzheimer's disease, dementia, mild cognitive impairment and the menopause: A 'window of opportunity'? *Womens Health (Lond. Engl.)* **9**, 279–290 (2013).
249. Q.-Q. Zhang, D. Han, R.-m. Wang, Y. Dong, F. Yang, R. K. Vadlamudi, D. W. Brann, C terminus of Hsc70-interacting protein (CHIP)-mediated degradation of hippocampal estrogen receptor-α and the critical period hypothesis of estrogen neuroprotection. *Proc. Natl. Acad. Sci. U.S.A.* **108**, E617–E624 (2011).
250. R. D. Brinton, The healthy cell bias of estrogen action: Mitochondrial bioenergetics and neurological implications. *Trends Neurosci.* **31**, 529–537 (2008).
251. J. Xiong, S. S. Kang, Z. Wang, X. Liu, T.-C. Kuo, F. Korkmaz, A. Padilla, S. Miyashita, P. Chan, Z. Zhang, P. Katsel, J. Burgess, A. Gumerova, K. Ievleva, D. Sant, S.-P. Yu, V. Muradova, T. Frolinger, D. Lizneva, J. Iqbal, K. A. Goosens, S. Gera, C. J. Rosen, V. Haroutunian, V. Ryu, T. Yuen, M. Zaidi, K. Ye, FSH blockade improves cognition in mice with Alzheimer's disease. *Nature* **603**, 470–476 (2022).
252. M. Canevelli, F. Quarata, F. Remiddi, F. Lucchini, E. Lacorte, N. Vanacore, G. Bruno, M. Cesari, Sex and gender differences in the treatment of Alzheimer's disease: A systematic review of randomized controlled trials. *Pharmacol. Res.* **115**, 218–223 (2017).
253. S. M. Greenberg, M. K. Tennis, L. B. Brown, T. Gomez-Isla, D. L. Hayden, D. A. Schoenfeld, K. L. Walsh, C. Corwin, K. R. Daffner, P. Friedman, M. E. Meadows, R. A. Sperling, J. H. Growdon, Donepezil therapy in clinical practice: A randomized crossover study. *Arch. Neurol.* **57**, 94–99 (2000).
254. B. Winblad, K. Engedal, H. Soininen, F. Verhey, G. Waldemar, A. Wimo, A.-L. Wetterholm, R. Zhang, A. Haglund, P. Subbiah, Donepezil Nordic Study Group, A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* **57**, 489–495 (2001).
255. C. H. van Dyck, C. J. Swanson, P. Aisen, R. J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L. D. Kramer, T. Iwatsubo, Lecanemab in early Alzheimer's disease. *N. Engl. J. Med.* **388**, 9–21 (2023).
256. S. Budd Haeberlein, P. S. Aisen, F. Barkhof, S. Chalkias, T. Chen, S. Cohen, G. Dent, O. Hansson, K. Harrison, C. von Hehn, T. Iwatsubo, C. Mallinckrodt, C. J. Mummery, K. K. Muralidharan, I. Nestorov, L. Nisenbaum, R. Rajagovindan, L. Skordos, Y. Tian, C. H. van Dyck, B. Vellas, S. Wu, Y. Zhu, A. Sandrock, Two randomized phase 3 studies of aducanumab in early Alzheimer's disease. *J. Prev Alzheimers Dis.* **9**, 197–210 (2022).
257. R. F. Buckley, J. Gong, M. Woodward, A call to action to address sex differences in Alzheimer disease clinical trials. *JAMA Neurol.* **80**, 769–770 (2023).
258. I. Driscoll, J. Troncoso, Asymptomatic Alzheimer's disease: A prodrome or a state of resilience? *Curr. Alzheimer Res.* **8**, 330–335 (2011).
259. J. A. Palmer, C. S. Kaufman, E. D. Vidoni, R. A. Honea, J. M. Burns, S. A. Billinger, Sex differences in resilience and resistance to brain pathology and dysfunction moderated by cerebrovascular response to exercise and genetic risk for Alzheimer's disease. *J. Alzheimers Dis.* **90**, 535–542 (2022).
260. J. A. Palmer, C. S. Kaufman, E. D. Vidoni, R. A. Honea, J. M. Burns, S. A. Billinger, Cerebrovascular response to exercise interacts with individual genotype and

amyloid-beta deposition to influence response inhibition with aging. *Neurobiol. Aging* **114**, 15–26 (2022).
261. E. J. Davis, L. Broestl, S. Abdulai-Saiku, K. Worden, L. W. Bonham, E. Miñones-Moyano, A. J. Moreno, D. Wang, K. Chang, G. Williams, B. I. Garay, I. Lobach, N. Devidze, D. Kim, C. Anderson-Bergman, G.-Q. Yu, C. C. White, J. A. Harris, B. L. Miller, D. A. Bennett, A. P. Arnold, P. L. De Jager, J. J. Palop, B. Panning, J. S. Yokoyama, L. Mucke, D. B. Dubal, A second X chromosome contributes to resilience in a mouse model of Alzheimer's disease. *Sci. Transl. Med.* **12**, eaaz5677 (2020).
262. J. M. Eissman, L. Dumitrescu, E. R. Mahoney, A. N. Smith, S. Mukherjee, M. L. Lee, P. Scollard, S. E. Choi, W. S. Bush, C. D. Engelman, Q. Lu, D. W. Fardo, E. H. Trittschuh, J. Mez, C. C. Kaczorowski, H. Hernandez Saucedo, K. F. Widaman, R. F. Buckley, M. J. Properzi, E. C. Mormino, H. S. Yang, T. M. Harrison, T. Hedden, K. Nho, S. J. Andrews, D. Tommet, N. Hadad, R. E. Sanders, D. M. Ruderfer, K. A. Gifford, X. Zhong, N. S. Raghavan, B. N. Vardarajan, The Alzheimer's Disease Neuroimaging Initiative (ADNI), Alzheimer's Disease Genetics Consortium (ADGC), A4 Study Team, M. A. Pericak-Vance, L. A. Farrer, L. S. Wang, C. Cruchaga, G. D. Schellenberg, N. J. Cox, J. L. Haines, C. D. Keene, A. J. Saykin, E. B. Larson, R. A. Sperling, R. Mayeux, M. L. Cuccaro, D. A. Bennett, J. A. Schneider, P. K. Crane, A. L. Jefferson, T. J. Hohman, Sex differences in the genetic architecture of cognitive resilience to Alzheimer's disease. *Brain* **145**, 2541–2554 (2022).
263. Stroke.org; https://stroke.org/en/about-stroke/types-of-stroke/ischemic-stroke-clots.
264. G. 2016 Lifetime Risk of Stroke Collaborators, Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016. *N. Engl. J. Med.* **379**, 2429–2437 (2018).
265. M. Kelly-Hayes, A. Beiser, C. S. Kase, A. Scaramucci, R. B. D'Agostino, P. A. Wolf, The influence of gender and age on disability following ischemic stroke: The Framingham Study. *J. Stroke Cerebrovasc. Dis.* **12**, 119–126 (2003).
266. P. B. Gorelick, The global burden of stroke: Persistent and disabling. *Lancet Neurol.* **18**, 417–418 (2019).
267. H. A. Wafa, C. D. A. Wolfe, E. Emmett, G. A. Roth, C. O. Johnson, Y. Wang, Burden of stroke in Europe. *Stroke* **51**, 2418–2427 (2020).
268. L. A. Gillum, S. K. Mamidipudi, S. C. Johnston, Ischemic stroke risk with oral contraceptives: A meta-analysis. *JAMA* **284**, 72–78 (2000).
269. T. Johansson, P. Fowler, W. E. Ek, A. Skalkidou, T. Karlsson, Å. Johansson, Oral contraceptives, hormone replacement therapy, and stroke risk. *Stroke* **53**, 3107–3115 (2022).
270. E. C. Miller, H. J. Gatollari, G. Too, A. K. Boehme, L. Leffert, R. S. Marshall, M. S. V. Elkind, J. Z. Willey, Risk factors for pregnancy-associated stroke in women with preeclampsia. *Stroke* **48**, 1752–1759 (2017).
271. S. A. E. Peters, C. Carcel, E. R. C. Millett, M. Woodward, Sex differences in the association between major risk factors and the risk of stroke in the UK Biobank cohort study. *Neurology* **95**, e2715–e2726 (2020).
272. M. V. Vyas, F. L. Silver, P. C. Austin, A. Y. X. Yu, P. Pequeno, J. Fang, A. Laupacis, M. K. Kapral, Stroke incidence by sex across the lifespan. *Stroke* **52**, 447–451 (2021).
273. V. J. Howard, T. E. Madsen, D. O. Kleindorfer, S. E. Judd, J. D. Rhodes, E. Z. Soliman, B. M. Kissela, M. M. Safford, C. S. Moy, L. A. McClure, Sex and race differences in the association of incident ischemic stroke with risk factors. *JAMA Neurol.* **76**, 179–186 (2019).
274. J. G. Merino, M. Luby, R. T. Benson, L. A. Davis, A. W. Hsia, L. L. Latour, J. K. Lynch, S. Warach, Predictors of acute stroke mimics in 8187 patients referred to a stroke service. *J. Stroke Cerebrovasc. Dis.* **22**, e397–e403 (2013).
275. A. Y. X. Yu, A. M. Penn, M. L. Lesperance, N. S. Croteau, R. F. Balshaw, K. Votova, M. B. Bibok, M. Penn, V. Saly, J. Hegedus, C. Zerna, E. Klourfeld, L. Bilston, Z. M. Hong, S. B. Coutts, SpecTRA Study Group, Sex differences in presentation and outcome after an acute transient or minor neurologic event. *JAMA Neurol.* **76**, 962–968 (2019).
276. A. Y. X. Yu, M. D. Hill, N. Asdaghi, J.-M. Boulanger, M.-C. Camden, B. C. V. Campbell, A. M. Demchuk, T. S. Field, M. Goyal, M. Krause, J. Mandzia, B. K. Menon, R. Mikulik, F. Moreau, A. M. Penn, R. H. Swartz, S. B. Coutts, Diagnosis of Uncertain-Origin Benign Transient Neurological Symptoms (DOUBT) Study Group, Sex differences in diagnosis and diagnostic revision of suspected minor cerebral ischemic events. *Neurology* **96**, e732–e739 (2021).
277. M. Ali, H. J. A. van Os, N. van der Weerd, J. W. Schoones, M. W. Heymans, N. D. Kruyt, M. C. Visser, M. J. H. Wermer, Sex differences in presentation of stroke: A systematic review and meta-analysis. *Stroke* **53**, 345–354 (2022).
278. S. Shajahan, L. Sun, K. Harris, X. Wang, E. C. Sandset, A. Y. Yu, M. Woodward, S. A. Peters, C. Carcel, Sex differences in the symptom presentation of stroke: A systematic review and meta-analysis. *Int. J. Stroke* **18**, 144–153 (2023).
279. S. L. Gall, G. Donnan, H. M. Dewey, R. Macdonell, J. Sturm, A. Gilligan, V. Srikanth, A. G. Thrift, Sex differences in presentation, severity, and management of stroke in a population-based study. *Neurology* **74**, 975–981 (2010).
280. M. J. Reeves, C. D. Bushnell, G. Howard, J. W. Gargano, P. W. Duncan, G. Lynch, A. Khatiwoda, L. Lisabeth, Sex differences in stroke: Epidemiology, clinical presentation, medical care, and outcomes. *Lancet Neurol.* **7**, 915–926 (2008).
281. K. M. Rexrode, T. E. Madsen, A. Y. X. Yu, C. Carcel, J. H. Lichtman, E. C. Miller, The impact of sex and gender on stroke. *Circ. Res.* **130**, 512–528 (2022).
282. J. Ospel, N. Singh, A. Ganesh, M. Goyal, Sex and gender differences in stroke and their practical implications in acute care. *J. Stroke* **25**, 16–25 (2023).
283. B. Boden-Albala, R. L. Sacco, H.-S. Lee, C. Grahame-Clarke, T. Rundek, M. V. Elkind, C. Wright, E.-G. V. Giardina, M. R. DiTullio, S. Homma, M. C. Paik, Metabolic syndrome and ischemic stroke risk. *Stroke* **39**, 30–35 (2008).
284. X. Li, X. Li, H. Lin, X. Fu, W. Lin, M. Li, X. Zeng, Q. Gao, Metabolic syndrome and stroke: A meta-analysis of prospective cohort studies. *J. Clin. Neurosci.* **40**, 34–38 (2017).
285. A. D. Pradhan, Sex differences in the metabolic syndrome: Implications for cardiovascular health in women. *Clin. Chem.* **60**, 44–52 (2014).
286. C. H. Gravholt, S. Juul, R. W. Naeraa, J. Hansen, Morbidity in turner syndrome. *J. Clin. Epidemiol.* **51**, 147–158 (1998).
287. M. Silberbach, J. W. Roos-Hesselink, N. H. Andersen, A. C. Braverman, N. Brown, R. T. Collins, J. De Backer, K. A. Eagle, L. F. Hiratzka, W. H. Johnson Jr., D. Kadian-Dodov, L. Lopez, K. H. Mortensen, S. K. Prakash, E. V. Ratchford, A. Saidi, I. van Hagen, L. T. Young, American Heart Association Council on Cardiovascular Disease in the Young; Council on Genomic and Precision Medicine; and Council on Peripheral Vascular Disease, Cardiovascular health in turner syndrome: A scientific statement from the American Heart Association. *Circ. Genom. Precis. Med.* **11** , e000048 (2018).
288. C. H. Gravholt, M. H. Viuff, S. Brun, K. Stochholm, N. H. Andersen, Turner syndrome: Mechanisms and management. *Nat. Rev. Endocrinol.* **15**, 601–614 (2019).
289. L. A. Matura, V. B. Ho, D. R. Rosing, C. A. Bondy, Aortic dilatation and dissection in Turner syndrome. *Circulation* **116**, 1663–1670 (2007).
290. S. Thunström, E. Krantz, E. Thunström, C. Hanson, I. Bryman, K. Landin-Wilhelmsen, Incidence of aortic dissection in Turner syndrome. *Circulation* **139**, 2802–2804 (2019).
291. S. A. E. Peters, R. R. Huxley, M. Woodward, Smoking as a risk factor for stroke in women compared with men. *Stroke* **44**, 2821–2828 (2013).
292. C. Lang, L. Seyfang, J. Ferrari, T. Gattringer, S. Greisenegger, K. Willeit, T. Toell, S. Krebs, M. Brainin, S. Kiechl, J. Willeit, W. Lang, M. Knoflach, Austrian Stroke Registry Collaborators, Do women with atrial fibrillation experience more severe strokes? Results from the Austrian stroke unit registry. *Stroke* **48**, 778–780 (2017).
293. J. G. Andrade, M. W. Deyell, A. Y. K. Lee, L. Macle, Sex differences in atrial fibrillation. *Can. J. Cardiol.* **34**, 429–436 (2018).
294. R. A. Joundi, L. E. Cipriano, L. A. Sposato, G. Saposnik, Stroke Outcomes Research Working Group, Ischemic stroke risk in patients with atrial fibrillation and CHA2DS2-VASc score of 1: Systematic review and meta-analysis. *Stroke* **47**, 1364–1367 (2016).
295. S. B. Pancholy, P. S. Sharma, D. S. Pancholy, T. M. Patel, D. J. Callans, F. E. Marchlinski, Meta-analysis of gender differences in residual stroke risk and major bleeding in patients with nonvalvular atrial fibrillation treated with oral anticoagulants. *Am. J. Cardiol.* **113**, 485–490 (2014).
296. A. Förster, A. Gass, R. Kern, M. E. Wolf, C. Ottomeyer, K. Zohsel, M. Hennerici, K. Szabo, Gender differences in acute ischemic stroke: Etiology, stroke patterns and response to thrombolysis. *Stroke* **40**, 2428–2432 (2009).
297. A. K. Bonkhoff, A. Karch, R. Weber, J. Wellmann, K. Berger, Female stroke: Sex differences in acute treatment and early outcomes of acute ischemic stroke. *Stroke* **52**, 406–415 (2021).
298. D. H. K. van Dam-Nolen, N. C. M. van Egmond, P. J. Koudstaal, A. van der Lugt, D. Bos, Sex differences in carotid atherosclerosis: A systematic review and meta-analysis. *Stroke* **54**, 315–326 (2023).
299. X. Yan, M. Tang, J. Gao, L. Wang, L. Li, N. Ma, X. Shi, X. Lei, X. Zhang, Sex differences in intracranial atherosclerotic plaques among patients with ischemic stroke. *Front. Cardiovasc. Med.* **9**, 860675 (2022).
300. V. Regitz-Zagrosek, G. Kararigas, Mechanistic pathways of sex differences in cardiovascular disease. *Physiol. Rev.* **97**, 1–37 (2017).
301. M. O'Sullivan, Leukoaraiosis. *Pract. Neurol.* **8**, 26–38 (2008).
302. N. S. Rost, R. M. Rahman, A. Biffi, E. E. Smith, A. Kanakis, K. Fitzpatrick, F. Lima, B. B. Worrall, J. F. Meschia, R. D. Brown Jr., T. G. Brott, A. G. Sorensen, S. M. Greenberg, K. L. Furie, J. Rosand, White matter hyperintensity volume is increased in small vessel stroke subtypes. *Neurology* **75**, 1670–1677 (2010).
303. V. Lohner, G. Pehlivan, G. Sanroma, A. Miloschewski, M. D. Schirmer, T. Stöcker, M. Reuter, M. M. B. Breteler, Relation between sex, menopause, and white matter hyperintensities: The Rhineland Study. *Neurology* **99**, e935–e943 (2022).
304. G. S. Silva, F. O. Lima, E. C. S. Camargo, W. S. Smith, M. H. Lev, G. J. Harris, E. F. Halpern, W. Koroshetz, K. L. Furie, Gender differences in outcomes after ischemic stroke: Role of ischemic lesion volume and intracranial large-artery occlusion. *Cerebrovasc. Dis.* **30**, 470–475 (2010).
305. C. Dehlendorff, K. K. Andersen, T. S. Olsen, Sex disparities in stroke: Women have more severe strokes but better survival than men. *J. Am. Heart Assoc.* **4**, e001967 (2015).
306. C. Renoux, J. Coulombe, L. Li, A. Ganesh, L. Silver, P. M. Rothwell, Oxford Vascular Study, Confounding by pre-morbid functional status in studies of apparent sex differences in severity and outcome of stroke. *Stroke* **48**, 2731–2738 (2017).
307. B. Manwani, L. D. McCullough, On the basis of sex: Outcomes after ischemic stroke. *Stroke* **50**, 2285–2287 (2019).

308. C. Carcel, X. Wang, E. C. Sandset, C. Delcourt, H. Arima, R. Lindley, M. L. Hackett, P. Lavados, T. G. Robinson, P. Muñoz Venturelli, V. V. Olavarría, A. Brunser, E. Berge, J. Chalmers, M. Woodward, C. S. Anderson, Sex differences in treatment and outcome after stroke: Pooled analysis including 19,000 participants. *Neurology* **93**, e2170–e2180 (2019).
309. N. S. Rost, J. F. Meschia, R. Gottesman, L. Wruck, K. Helmer, S. M. Greenberg, DISCOVERY Investigators, Cognitive impairment and dementia after stroke: Design and rationale for the DISCOVERY study. *Stroke* **52**, e499–e516 (2021).
310. S. T. Pendlebury, P. M. Rothwell, Oxford Vascular Study, Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: Analysis of the population-based Oxford Vascular Study. *Lancet Neurol.* **18**, 248–258 (2019).
311. A. T. Bako, T. Potter, J. Tannous, A. P. Pan, C. Johnson, E. Baig, B. Downer, F. S. Vahidy, Sex differences in post-stroke cognitive decline: A population-based longitudinal study of nationally representative data. *PLOS ONE* **17**, e0268249 (2022).
312. L. G. Exalto, N. A. Weaver, H. J. Kuijf, H. P. Aben, H.-J. Bae, J. G. Best, R. Bordet, C. P. L. H. Chen, R. S. van der Giessen, O. Godefroy, B. Gyanwali, O. K. L. Hamilton, S. Hilal, I. M. C. Huenges Wajer, J. Kim, L. J. Kappelle, B. J. Kim, S. Köhler, P. L. M. de Kort, P. J. Koudstaal, J.-S. Lim, S. D. J. Makin, V. C. T. Mok, R. J. van Oostenbrugge, M. Roussel, J. Staals, M. D. C. Valdés-Hernández, N. Venketasubramanian, F. R. J. Verhey, J. M. Wardlaw, D. J. Werring, X. Xu, M. J. E. van Zandvoort, J. M. Biesbroek, F. M. Chappell, G. J. Biessels, Sex differences in poststroke cognitive impairment: A multicenter study in 2343 patients with acute ischemic stroke. *Stroke* **54**, 2296–2303 (2023).
313. G. C. Medeiros, D. Roy, N. Kontos, S. R. Beach, Post-stroke depression: A 2020 updated review. *Gen. Hosp. Psychiatry* **66**, 70–80 (2020).
314. M. L. Hackett, K. Pickles, Part I: Frequency of depression after stroke: An updated systematic review and meta-analysis of observational studies. *Int. J. Stroke* **9**, 1017–1025 (2014).
315. R. G. Robinson, R. E. Jorge, Post-stroke depression: A review. *A. J. Psychiatry.* **173**, 221–231 (2016).
316. GBD 2019 Mental Disorders Collaborators, Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry* **9**, 137–150 (2022).
317. C. W. Yoon, C. D. Bushnell, Stroke in women: A review focused on epidemiology, risk factors, and outcomes. *J. Stroke* **25**, 2–15 (2023).
318. N. J. Alkayed, I. Harukuni, A. S. Kimes, E. D. London, R. J. Traystman, P. D. Hurn, Gender-linked brain injury in experimental stroke. *Stroke* **29**, 159–65; discussion 166 (1998).
319. L. D. McCullough, P. D. Hurn, Estrogen and ischemic neuroprotection: An integrated view. *Trends Endocrinol. Metab.* **14**, 228–235 (2003).
320. H. V. O. Carswell, N. H. Anderson, J. S. Clark, D. Graham, B. Jeffs, A. F. Dominiczak, I. M. Macrae, Genetic and gender influences on sensitivity to focal cerebral ischemia in the stroke-prone spontaneously hypertensive rat. *Hypertension* **33**, 681–685 (1999).
321. H. V. O. Carswell, A. F. Dominiczak, I. M. Macrae, Estrogen status affects sensitivity to focal cerebral ischemia in stroke-prone spontaneously hypertensive rats. *Am. J. Physiol. Heart Circ. Physiol.* **278**, H290–H294 (2000).
322. R. Rusa, N. J. Alkayed, B. J. Crain, R. J. Traystman, A. S. Kimes, E. D. London, J. A. Klaus, P. D. Hurn, 17β-Estradiol reduces stroke injury in estrogen-deficient female animals. *Stroke* **30**, 1665–1670 (1999).
323. S. J. Murphy, M. T. Littleton-Kearney, P. D. Hurn, Progesterone administration during reperfusion, but not preischemia alone, reduces injury in ovariectomized rats. *J. Cereb. Blood Flow Metab.* **22**, 1181–1188 (2002).
324. M. Liu, S. Dziennis, P. D. Hurn, N. J. Alkayed, Mechanisms of gender-linked ischemic brain injury. *Restor. Neurol. Neurosci.* **27**, 163–179 (2009).
325. M. Uchida, J. M. Palmateer, P. S. Herson, A. C. DeVries, J. Cheng, P. D. Hurn, Dose-dependent effects of androgens on outcome after focal cerebral ischemia in adult male mice. *J. Cereb. Blood Flow Metab.* **29**, 1454–1462 (2009).
326. N. Quillinan, G. Deng, H. Grewal, P. S. Herson, Androgens and stroke: Good, bad or indifferent? *Exp. Neurol.* **259**, 10–15 (2014).
327. A. Heyer, M. Hasselblatt, N. von Ahsen, H. Häfner, A.-L. Sirén, H. Ehrenreich, In vitro gender differences in neuronal survival on hypoxia and in 17β-estradiol-mediated neuroprotection. *J. Cereb. Blood Flow Metab.* **25**, 427–430 (2005).
328. H. Li, S. Pin, Z. Zeng, M. M. Wang, K. A. Andreasson, L. D. McCullough, Sex differences in cell death. *Ann. Neurol.* **58**, 317–321 (2005).
329. M. Liu, P. D. Hurn, C. E. Roselli, N. J. Alkayed, Role of P450 aromatase in sex-specific astrocytic cell death. *J. Cereb. Blood Flow Metab.* **27**, 135–141 (2007).
330. M. Liu, E. A. Oyarzabal, R. Yang, S. J. Murphy, P. D. Hurn, A novel method for assessing sex-specific and genotype-specific response to injury in astrocyte culture. *J. Neurosci. Methods* **171**, 214–217 (2008).
331. C. L. Gibson, Cerebral ischemic stroke: Is gender important? *J. Cereb. Blood Flow Metab.* **33**, 1355–1361 (2013).
332. M. B. Tariq, J. Lee, L. D. McCullough, Sex differences in the inflammatory response to stroke. *Semin. Immunopathol.* **45**, 295–313 (2023).
333. L. Du, H. Bayir, Y. Lai, X. Zhang, P. M. Kochanek, S. C. Watkins, S. H. Graham, R. S. B. Clark, Innate gender-based proclivity in response to cytotoxicity and programmed cell death pathway. *J. Biol. Chem.* **279**, 38563–38570 (2004).
334. H. Neumann, M. R. Kotter, R. J. M. Franklin, Debris clearance by microglia: An essential link between degeneration and regeneration. *Brain* **132**, 288–295 (2009).
335. H. A. Seifert, G. Benedek, J. Liang, H. Nguyen, G. Kent, A. A. Vandenbark, J. A. Saugstad, H. Offner, Sex differences in regulatory cells in experimental stroke. *Cell. Immunol.* **318**, 49–54 (2017).
336. A. Villa, P. Gelosa, L. Castiglioni, M. Cimino, N. Rizzi, G. Pepe, F. Lolli, E. Marcello, L. Sironi, E. Vegeto, A. Maggi, Sex-specific features of microglia from adult mice. *Cell Rep.* **23**, 3501–3511 (2018).
337. C. D. Bushnell, P. Hurn, C. Colton, V. M. Miller, G. del Zoppo, M. S. V. Elkind, B. Stern, D. Herrington, G. Ford-Lynch, P. Gorelick, A. James, C. M. Brown, E. Choi, P. Bray, L. K. Newby, L. B. Goldstein, J. Simpkins, Advancing the study of stroke in women. *Stroke* **37**, 2387–2399 (2006).
338. C. M. Brown, E. Choi, Q. Xu, M. P. Vitek, C. A. Colton, The *APOE4* genotype alters the response of microglia and macrophages to 17β-estradiol. *Neurobiol. Aging* **29**, 1783–1794 (2008).
339. Y. El-Hakim, K. K. Mani, A. Eldouh, S. Pandey, M. T. Grimaldo, A. Dabney, R. Pilla, F. Sohrabji, Sex differences in stroke outcome correspond to rapid and severe changes in gut permeability in adult Sprague-Dawley rats. *Biol. Sex Differ.* **12**, 14 (2021).
340. H. Ahnstedt, A. Patrizz, A. Chauhan, M. Roy-O'Reilly, J. W. Furr, M. S. Spychala, J. D'Aigle, F. W. Blixt, L. Zhu, J. Bravo Alegria, L. D. McCullough, Sex differences in T cell immune responses, gut permeability and outcome after ischemic stroke in aged mice. *Brain Behav. Immun.* **87**, 556–567 (2020).
341. A. K. Bonkhoff, M. D. Schirmer, M. Bretzner, S. Hong, R. W. Regenhardt, M. Brudfors, K. L. Donahue, M. J. Nardin, A. V. Dalca, A.-K. Giese, M. R. Etherton, B. L. Hancock, S. J. T. Mocking, E. C. McIntosh, J. Attia, O. R. Benavente, S. Bevan, J. W. Cole, A. Donatti, C. J. Griessenauer, L. Heitsch, L. Holmegaard, K. Jood, J. Jimenez-Conde, S. J. Kittner, R. Lemmens, C. R. Levi, C. W. McDonough, J. F. Meschia, C.-L. Phuah, A. Rolfs, S. Ropele, J. Rosand, J. Roquer, T. Rundek, R. L. Sacco, R. Schmidt, P. Sharma, A. Slowik, M. Söderholm, A. Sousa, T. M. Stanne, D. Strbian, T. Tatlisumak, V. Thijs, A. Vagal, J. Wasselius, D. Woo, R. Zand, P. F. McArdle, B. B. Worrall, C. Jern, A. G. Lindgren, J. Maguire, D. Bzdok, O. Wu, MRI-GENIE and GISCOME Investigators and the International Stroke Genetics Consortium, N. S. Rost, Outcome after acute ischemic stroke is linked to sex-specific lesion patterns. *Nat Commun* **12**, 3289 (2021).
342. W.-S. Ryu, J. Chung, D. Schellingerhout, S.-W. Jeong, H.-R. Kim, J. E. Park, B. J. Kim, J.-T. Kim, K.-S. Hong, K. B. Lee, T. H. Park, S.-S. Park, J.-M. Park, K. Kang, Y.-J. Cho, H.-K. Park, B.-C. Lee, K.-H. Yu, M. S. Oh, S. J. Lee, J. G. Kim, J.-K. Cha, D.-H. Kim, J. Lee, M.-K. Han, M. S. Park, K.-H. Choi, J. Lee, H.-J. Bae, D.-E. Kim, Biological mechanism of sex difference in stroke manifestation and outcomes. *Neurology* **100**, e2490–e2503 (2023).
343. B. J. Alpers, Anatomical studies of the circle of Willis in normal brain. *AMA Arch. NeurPsych.* **81**, 409–418 (1959).
344. M. E. H. Ophelders, M. J. A. van Eldik, I. N. Vos, Y. S. Beentjes, B. K. Velthuis, Y. M. Ruigrok, Anatomical differences of intracranial arteries according to sex: A systematic review and meta-analysis. *J. Neuroradiol.* **51**, 10–15 (2024).
345. M. Corbetta, L. Ramsey, A. Callejas, A. Baldassarre, C. D. Hacker, J. S. Siegel, S. V. Astafiev, J. Rengachary, K. Zinn, C. E. Lang, L. T. Connor, R. Fucetola, M. Strube, A. R. Carter, G. L. Shulman, Common behavioral clusters and subcortical anatomy in stroke. *Neuron* **85**, 927–941 (2015).
346. H. M. Lindekleiv, K. Valen-Sendstad, M. K. Morgan, K.-A. Mardal, K. Faulder, J. H. Magnus, K. Waterloo, B. Romner, T. Ingebrigtsen, Sex differences in intracranial arterial bifurcations. *Gend. Med.* **7**, 149–155 (2010).
347. J. Krejza, M. Arkuszewski, S. E. Kasner, J. Weigele, A. Ustymowicz, R. W. Hurst, B. L. Cucchiara, S. R. Messe, Carotid artery diameter in men and women and the relation to body and neck Size. *Stroke* **37**, 1103–1105 (2006).
348. H. R. Müller, C. Brunhölzl, E. W. Radü, M. Buser, Sex and side differences of cerebral arterial caliber. *Neuroradiology* **33**, 212–216 (1991).
349. W. Liu, X. Lou, L. Ma, Use of 3D pseudo-continuous arterial spin labeling to characterize sex and age differences in cerebral blood flow. *Neuroradiology* **58**, 943–948 (2016).
350. J. S. R. Alisch, N. Khattar, R. W. Kim, L. E. Cortina, A. C. Rejimon, W. Qian, L. Ferrucci, S. M. Resnick, R. G. Spencer, M. Bouhrara, Sex and age-related differences in cerebral blood flow investigated using pseudo-continuous arterial spin labeling magnetic resonance imaging. *Aging* **13**, 4911–4925 (2021).
351. N. L. Damestani, J. Jacoby, S. M. Yadav, A. E. Lovely, A. Michael, M. Terpstra, M. Eshghi, B. Rashid, C. Cruchaga, D. H. Salat, M. R. Juttukonda, Associations between age, sex, APOE genotype, and regional vascular physiology in typically aging adults. *Neuroimage* **275**, 120167 (2023).
352. E. J. A. Wiegers, M. J. H. L. Mulder, I. G. H. Jansen, E. Venema, K. C. J. Compagne, O. A. Berkhemer, B. J. Emmer, H. A. Marquering, A. C. G. M. van Es, M. E. Sprengers, W. H. van Zwam, R. J. van Oostenbrugge, Y. B. W. E. M. Roos, C. B. L. M. Majoie, B. Roozenbeek, H. F. Lingsma, D. W. J. Dippel, A. van der Lugt, MR CLEAN Trial and MR

CLEAN Registry Investigators, Clinical and imaging determinants of collateral status in patients with acute ischemic stroke in MR CLEAN trial and registry. *Stroke* **51**, 1493–1502 (2020).
353. C. Lagebrant, B. Ramgren, A. Hassani Espili, A. Marañon, C. Kremer, Sex differences in collateral circulation and outcome after mechanical thrombectomy in acute ischemic stroke. *Front. Neurol.* **13**, 878759 (2022).
354. R. J. Wityk, D. Lehman, M. Klag, J. Coresh, H. Ahn, B. Litt, Race and sex differences in the distribution of cerebral atherosclerosis. *Stroke* **27**, 1974–1980 (1996).
355. A. K. Bonkhoff, M. Bretzner, S. Hong, M. D. Schirmer, A. Cohen, R. W. Regenhardt, K. L. Donahue, M. J. Nardin, A. V. Dalca, A.-K. Giese, M. R. Etherton, B. L. Hancock, S. J. T. Mocking, E. C. McIntosh, J. Attia, O. R. Benavente, S. Bevan, J. W. Cole, A. Donatti, C. J. Griessenauer, L. Heitsch, L. Holmegaard, K. Jood, J. Jimenez-Conde, S. J. Kittner, R. Lemmens, C. R. Levi, C. W. McDonough, J. F. Meschia, C.-L. Phuah, A. Rolfs, S. Ropele, J. Rosand, J. Roquer, T. Rundek, R. L. Sacco, R. Schmidt, P. Sharma, A. Slowik, M. Söderholm, A. Sousa, T. M. Stanne, D. Strbian, T. Tatlisumak, V. Thijs, A. Vagal, J. Wasselius, D. Woo, R. Zand, P. F. McArdle, B. B. Worrall, C. Jern, A. G. Lindgren, J. Maguire, M. D. Fox, D. Bzdok, O. Wu, N. S. Rost, MRI-GENIE and GISCOME Investigators and the International Stroke Genetics Consortium, Sex-specific lesion pattern of functional outcomes after stroke. *Brain Commun.* **4**, fcac020 (2022).
356. S. Ceylan, S. Aeschbacher, A. Altermatt, T. Sinnecker, N. Rodondi, M. Blum, M. Coslovsky, S. Evers-Dörpfeld, S. Niederberger, D. Conen, S. Osswald, M. Kühne, M. Düring, J. Wuerfel, L. Bonati, SWISS-AF Investigators, Sex differences of vascular brain lesions in patients with atrial fibrillation. *Open Heart* **9**, e002033 (2022).
357. A. K. Bonkhoff, N. S. Rost, M. D. Schirmer, Networks with lesions, in *Connectome Analysis* (Elsevier, 2023), pp. 391–408.
358. A. R. Vaidya, M. S. Pujara, M. Petrides, E. A. Murray, L. K. Fellows, Lesion studies in contemporary neuroscience. *Trends Cogn. Sci.* **23**, 653–671 (2019).
359. J. Inglis, J. S. Lawson, A meta-analysis of sex differences in the effects of unilateral brain damage on intelligence test results. *Can. J. Psychol.* **36**, 670–683 (1982).
360. M. Hausmann, Why sex hormones matter for neuroscience: A very short review on sex, sex hormones, and functional brain asymmetries. *J. Neurosci. Res.* **95**, 40–49 (2017).
361. M. Hirnstein, K. Hugdahl, M. Hausmann, Cognitive sex differences and hemispheric asymmetry: A critical review of 40 years of research. *Laterality: Asymm. Body Brain Cognit.* **24**, 204–252 (2019).
362. W. J. Powers, Acute ischemic stroke. *N. Engl. J. Med.* **383**, 252–260 (2020).
363. C. Carcel, M. Woodward, G. Balicki, G. L. Koroneos, D. A. de Sousa, C. Cordonnier, C. Lukaszyk, K. Thompson, X. Wang, L. Davies, M. Bassi, C. S. Anderson, S. A. Peters, E. C. Sandset, Trends in recruitment of women and reporting of sex differences in large-scale published randomized controlled trials in stroke. *Int. J. Stroke* **14**, 931–938 (2019).
364. B. Strong, J. Pudar, A. G. Thrift, V. J. Howard, M. Hussain, C. Carcel, G. De Los Campos, M. J. Reeves, Sex disparities in enrollment in recent randomized clinical trials of acute stroke: A meta-analysis. *JAMA Neurol.* **78**, 666–677 (2021).
365. C. Carcel, M. Reeves, Under-enrollment of women in stroke clinical trials: What are the causes and what should be done about it? *Stroke* **52**, 452–457 (2021).
366. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, Tissue plasminogen activator for acute ischemic stroke. *N. Engl. J. Med.* **333**, 1581–1587 (1995).
367. M. Reeves, A. Bhatt, P. Jajou, M. Brown, L. Lisabeth, Sex differences in the use of intravenous rt-PA thrombolysis treatment for acute ischemic stroke: A meta-analysis. *Stroke* **40**, 1743–1749 (2009).
368. B. Strong, L. D. Lisabeth, M. Reeves, Sex differences in IV thrombolysis treatment for acute ischemic stroke: A systematic review and meta-analysis. *Neurology* **95**, e11–e22 (2020).
369. R. Weber, C. Krogias, J. Eyding, D. Bartig, S. H. Meves, A. H. Katsanos, V. Caso, W. Hacke, Age and sex differences in ischemic stroke treatment in a nationwide analysis of 1.11 million hospitalized Cases. *Stroke* **50**, 3494–3502 (2019).
370. C. Bushnell, V. J. Howard, L. Lisabeth, V. Caso, S. Gall, D. Kleindorfer, S. Chaturvedi, T. E. Madsen, S. L. Demel, S.-J. Lee, M. Reeves, Sex differences in the evaluation and treatment of acute ischaemic stroke. *Lancet Neurol.* **17**, 641–650 (2018).
371. M. Ouyang, S. Shajahan, X. Liu, L. Sun, C. Carcel, K. Harris, C. S. Anderson, M. Woodward, X. Wang, Sex differences in the utilization and outcomes of endovascular treatment after acute ischemic stroke: A systematic review and meta-analysis. *Front. Glob. Womens Health* **3**, 1032592 (2023).
372. V. Chalos, I. R. de Ridder, H. F. Lingsma, S. Brown, R. J. van Oostenbrugge, M. Goyal, B. C. V. Campbell, K. W. Muir, F. Guillemin, S. Bracard, P. White, A. Dávalos, T. G. Jovin, M. D. Hill, P. J. Mitchell, A. M. Demchuk, J. L. Saver, W. H. van Zwam, D. W. J. Dippel, HERMES Collaborators, Does sex modify the effect of endovascular treatment for ischemic Stroke?: A subgroup analysis of 7 randomized trials. *Stroke* **50**, 2413–2419 (2019).
373. M. Deb-Chatterji, A. Konnopka, F. Flottmann, H. Leischner, J. Fiehler, C. Gerloff, G. Thomalla, Patient-reported health-related quality of life after stroke thrombectomy in clinical practice. *Neurology* **95**, e1724–e1732 (2020).
374. R. W. Regenhardt, A. C. Turner, J. A. Hirsch, M. J. Young, N. M. Alotaibi, C. J. Stapleton, A. B. Patel, T. M. Leslie-Mazwi, N. S. Rost, M. R. Etherton, Sex-specific differences in presentations and determinants of outcomes after endovascular thrombectomy for large vessel occlusion stroke. *J. Neurol.* **269**, 307–315 (2022).
375. M. Romoli, S. Banerjee, F. Cordici, K. Lobotesis, M. Longoni, E. Lafe, I. Casetta, A. Katsanos, L. Palaiodimou, A. Zini, M. Ruggiero, T. N. Nguyen, G. Tsivgoulis, L. D'Anna, Impact of sex on thrombectomy outcomes in ischemic stroke: A propensity score-matched study, systematic review, and meta-analysis. *Stroke Vasc. Interv. N.* **4**, 10.1161/SVIN.123.001196 (2024).
376. S. A. Sheth, S. Lee, S. J. Warach, J. Gralla, R. Jahan, M. Goyal, R. G. Nogueira, O. O. Zaidat, V. M. Pereira, A. Siddiqui, H. Lutsep, D. S. Liebeskind, L. D. McCullough, J. L. Saver, Sex differences in outcome after endovascular stroke therapy for acute ischemic stroke. *Stroke* **50**, 2420–2427 (2019).
377. I. F. Ugidos, C. Pistono, P. Korhonen, M. Gómez-Budia, V. Sitnikova, P. Klecki, I. Stanová, J. Jolkkonen, T. Malm, Sex differences in poststroke inflammation: A focus on microglia across the lifespan. *Stroke* **53**, 1500–1509 (2022).
378. K. Malhotra, J. J. Chang, A. Khunger, D. Blacker, J. A. Switzer, N. Goyal, A. V. Hernandez, V. Pasupuleti, A. V. Alexandrov, G. Tsivgoulis, Minocycline for acute stroke treatment: A systematic review and meta-analysis of randomized clinical trials. *J. Neurol.* **265**, 1871–1879 (2018).
379. M. R. Amiri-Nikpour, S. Nazarbaghi, M. Hamdi-Holasou, Y. Rezaei, An open-label evaluator-blinded clinical study of minocycline neuroprotection in ischemic stroke: Gender-dependent effect. *Acta Neurol. Scand.* **131**, 45–50 (2015).
380. S. Wassertheil-Smoller, S. Hendrix, M. Limacher, G. Heiss, C. Kooperberg, A. Baird, T. Kotchen, J. D. Curb, H. Black, J. E. Rossouw, A. Aragaki, M. Safford, E. Stein, S. Laowattana, W. J. Mysiw, WHI Investigators, Effect of estrogen plus progestin on stroke in postmenopausal women: The women's health initiative: A randomized trial. *JAMA* **289**, 2673–2684 (2003).
381. C. M. Viscoli, L. M. Brass, W. N. Kernan, P. M. Sarrel, S. Suissa, R. I. Horwitz, A clinical trial of estrogen-replacement therapy after ischemic stroke. *N. Engl. J. Med.* **345**, 1243–1249 (2001).
382. R. R. Voskuhl, The effect of sex on multiple sclerosis risk and disease progression. *Mult. Scler.* **26**, 554–560 (2020).
383. L. C. Golden, R. Voskuhl, The importance of studying sex differences in disease: The example of multiple sclerosis. *J. Neurosci. Res.* **95**, 633–643 (2017).
384. C. C. Whitacre, Sex differences in autoimmune disease. *Nat. Immunol.* **2**, 777–780 (2001).
385. K. A. Ribbons, P. M. Elduff, C. Boz, M. Trojano, G. Izquierdo, P. Duquette, M. Girard, F. Grand'Maison, R. Hupperts, P. Grammond, C. Oreja-Guevara, T. Petersen, R. Bergamaschi, G. Giuliani, M. Barnett, V. van Pesch, M.-P. Amato, G. Iuliano, M. Fiol, M. Slee, F. Verheul, E. Cristiano, R. Fernandez-Bolanos, M.-L. Saladino, M. E. Rio, J. Cabrera-Gomez, H. Butzkueven, E. van Munster, L. Den Braber-Moerland, D. L. Spitaleri, A. Lugaresi, V. Shaygannejad, O. Gray, N. Deri, R. Alroughani, J. Lechner-Scott, Male sex is independently associated with faster disability accumulation in relapse-onset MS but not in primary progressive MS. *PLOS ONE* **10**, e0122686 (2015).
386. S. Vukusic, R. Marignier, Multiple sclerosis and pregnancy in the 'treatment era'. *Nat. Rev. Neurol.* **11**, 280–289 (2015).
387. K. G. Vetvik, E. A. MacGregor, Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurol.* **16**, 76–87 (2017).
388. B. Raffaelli, T. P. Do, B. A. Chaudhry, M. Ashina, F. M. Amin, H. Ashina, Menstrual migraine is caused by estrogen withdrawal: Revisiting the evidence. *J. Headache Pain* **24**, 131 (2023).
389. M. B. Cook, K. A. McGlynn, S. S. Devesa, N. D. Freedman, W. F. Anderson, Sex disparities in cancer mortality and survival. *Cancer Epidemiol. Biomarkers Prev.* **20**, 1629–1637 (2011).
390. T. Sun, A. Plutynski, S. Ward, J. B. Rubin, An integrative view on sex differences in brain tumors. *Cell. Mol. Life Sci.* **72**, 3323–3342 (2015).
391. D. S. Reddy, The neuroendocrine basis of sex differences in epilepsy. *Pharmacol. Biochem. Behav.* **152**, 97–104 (2017).
392. B. S. Koppel, C. L. Harden, Gender issues in the neurobiology of epilepsy: A clinical perspective. *Neurobiol. Dis.* **72**, 193–197 (2014).
393. S. Meoni, A. Macerollo, E. Moro, Sex differences in movement disorders. *Nat. Rev. Neurol.* **16**, 84–96 (2020).
394. G. E. Gillies, I. S. Pienaar, S. Vohra, Z. Qamhawi, Sex differences in Parkinson's disease. *Front. Neuroendocrinol.* **35**, 370–384 (2014).
395. E. Jacobs, M. D'Esposito, Estrogen shapes dopamine-dependent cognitive processes: Implications for women's health. *J. Neurosci.* **31**, 5286–5293 (2011).
396. R. A. Marrie, S. B. Patten, H. Tremlett, C. Wolfson, S. Warren, L. W. Svenson, N. Jette, J. Fisk, CIHR Team in the Epidemiology and Impact of Comorbidity on Multiple Sclerosis, Sex differences in comorbidity at diagnosis of multiple sclerosis: A population-based study. *Neurology* **86**, 1279–1286 (2016).
397. M. Gandhi, F. Aweeka, R. M. Greenblatt, T. F. Blaschke, Sex differences in pharmacokinetics and pharmacodynamics. *Annu. Rev. Pharmacol. Toxicol.* **44**, 499–523 (2004).
398. J. Tamargo, G. Rosano, T. Walther, J. Duarte, A. Niessner, J. Kaski, C. Ceconi, H. Drexel, K. Kjeldsen, G. Savarese, C. Torp-Pedersen, D. Atar, B. Lewis, S. Agewall, Gender differences in the effects of cardiovascular drugs. *Eur. Heart J. Cardiovasc. Pharmacother.* **3**, 163–182 (2017).

399. N. Golfrè Andreasi, L. M. Romito, R. Telese, R. Cilia, A. E. Elia, A. Novelli, G. Tringali, G. Messina, V. Levi, G. Devigili, S. Rinaldo, A. A. Franzini, R. Eleopra, Short- and long-term motor outcome of STN-DBS in Parkinson's disease: Focus on sex differences. *Neurol. Sci.* **43**, 1769–1781 (2022).
400. M. M. McCarthy, A. P. Arnold, Reframing sexual differentiation of the brain. *Nat. Neurosci.* **14**, 677–683 (2011).
401. I. Yanai, M. J. Lercher, It takes two to think. *Nat. Biotechnol.* **42**, 18–19 (2024).
402. M. J. Valenzuela, P. Sachdev, Brain reserve and dementia: A systematic review. *Psychol. Med.* **36**, 441–454 (2006).
403. M. D. Schirmer, M. R. Etherton, A. V. Dalca, A.-K. Giese, L. Cloonan, O. Wu, P. Golland, N. S. Rost, Effective reserve: A latent variable to improve outcome prediction in stroke. *J. Stroke Cerebrovasc. Dis.* **28**, 63–69 (2019).
404. J. A. Schneider, Z. Arvanitakis, W. Bang, D. A. Bennett, Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology* **69**, 2197–2204 (2007).
405. S. T. Pendlebury, D. Poole, A. Burgess, J. Duerden, P. M. Rothwell, APOE-ε4 genotype and dementia before and after TIA and stroke: Population-based cohort study. *Stroke* **51**, 751–758 (2020).
406. S. Pang, J. Li, Y. Zhang, J. Chen, Meta-analysis of the relationship between the APOE gene and the onset of Parkinson's disease dementia. *Parkinsons Dis.* **2018**, 9497147 (2018).
407. S. Gao, A. Fang, Y. Huang, V. Giunchiglia, A. Noori, J. R. Schwarz, Y. Ektefaie, J. Kondic, M. Zitnik, Empowering biomedical discovery with AI agents. *Cell* **187**, 6125–6151 (2024).
408. E. Dhamala, J. A. Ricard, L. Q. Uddin, L. A. M. Galea, E. G. Jacobs, S. W. Yip, B. T. T. Yeo, M. M. Chakravarty, A. J. Holmes, Considering the interconnected nature of social identities in neuroimaging research. *Nat. Neurosci.* **28**, 222–223 (2025).
409. T. M. Burton, T. E. Madsen, R. Karb, K. L. Furie, Importance of sex and gender differences in enrollment and interpretation of stroke clinical trials. *J. Stroke Cerebrovasc. Dis.* **33**, 107735 (2024).
410. L. C. Oliveira, A. Ponciano, C. Tuozzo, A. Viswanathan, N. S. Rost, M. R. Etherton, Poststroke disability: Association between sex and patient-reported outcomes. *Stroke* **54**, 345–353 (2023).

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