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Neurological Disorders and Women's Health: Contribution of Molecular Neuroimaging Techniques

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Sex differences in brain physiology and the mechanisms of drug action have been extensively reported. These biological variances, from structure to hormonal and genetic aspects, can profoundly influence healthy functioning and disease mechanisms and might have implications for treatment and drug development. Molecular neuroimaging techniques may help to disclose sex's impact on brain functioning, as well as the neuropathological changes underpinning several diseases. This narrative review summarizes recent lines of evidence based on PET and SPECT imaging, highlighting sex differences in normal conditions and various neurological disorders.
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Introduction

Sex and gender-related differences in terms of behavior and cognition have been previously extensively reported.[1] Defining the primary determinants of these differences is complex and likely involves an interplay between biological and environmental factors.[1] Several lines of evidence also suggest that these differences can be reflected by neuroimaging biomarkers both in healthy subjects and in pathological conditions.[2,3] From a methodological point of view, most studies consider sex as a nuisance variable rather than a significant factor accounting for the different vulnerabilities and trajectories of normal or pathological brain ageing in men and women.[4,5] However, a more systematic investigation of imaging evidence of sex-related differences would be of great interest. As an example, mounting evidence suggests that women are at higher risk of exhibiting

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Alzheimer's Disease (AD) pathophysiology, primarily due to differences in the production and the structure of neurofibrillary tangles between sexes.[6] Similarly, there are documented sex differences between males and females in the neurotransmission system as evaluated using PET tracers.[7,8]

Notably, the main difference in women's brain physiology is related to hormonal cycles or the impact of menopause. These differences in neurotransmission can have implications for understanding the underlying mechanisms of various neurological and psychiatric conditions. Moreover, women have been demonstrated to show more vigorous innate and adaptive immune responses than males.[9,10] These differences in the nature and potency of immune responses result in sex-specific differences in the manifestation and prevalence of malignancies and autoimmune diseases. As neuroinflammation is considered an essential contributor to neuropsychiatric and neurodegenerative disorders, sex differences in neuroinflammation can contribute to variations in the occurrence of such disorders.[11] Contrasting this relative lack of information, on the other hand, the influence of sex on the incidence, distribution, therapy response, and prognosis in patients with brain tumors (irrespective of race, age, and presence of co-morbidities) has been previously evaluated.[12,13] Within all these contexts, molecular neuroimaging techniques may aid in revealing sex's impact on brain functioning, but also the neuropathological changes underpinning several diseases. This narrative review summarizes recent lines of evidence regarding PET and SPECT-based evidence on sex differences in normal conditions and several neurological disorders. The primary lines of evidence are summarized in Table 1.

Influence of Sex on [^{18}F] Fluorodeoxyglucose ([^{18}F]-FDG) PET Imaging

The influence of sex on brain metabolism and thus on [^{18}F]-FDG uptake and distribution in healthy subjects is still controversial. While some studies reported no differences in global and regional resting brain metabolism between males and females in healthy subjects,[14] others have supported the measurable and regional differences.[15]

As a matter of fact, higher brain volume reported in men, greater percentage of white matter,[9] or higher resting cerebral blood flow values observed in women,[16] may theoretically induce sex differences in [^{18}F]-FDG distribution. In a cohort of young adults, Gur et al demonstrated that men showed higher glucose metabolism in temporal-limbic regions and the cerebellum than women.[17] Conversely, in more recent years Yoshizawa et al. analyzed 123 [^{18}F]-FDG-PET scans from healthy adults showed that whole-brain metabolic glucose consumption was higher in females. At a regional level, glucose metabolism in the medial frontal lobe, inferior parietal lobule, and posterior cingulate was higher in females, whereas males had a relatively higher tracer uptake in the inferior temporal lobe in both hemispheres and the cerebellum.[18] Finally, regional heterogeneity in brain glucose consumption was confirmed in a large cohort of 963 healthy subjects.[19] Furthermore, hormones such as estrogen are another potential source of variation in the cerebral metabolism of females.[20,21] In this regard, Allocca et al. evaluated brain FDG PET images of 151 subjects (84 females and 67 males) aged between 20 and 84 years and highlighted a wider negative correlation between age and brain metabolism in females than in males (Fig. 1).

In this regard, disturbances in metabolic and hormonal factors during mid-life have been hypothesized to contribute to higher AD prevalence among women. Perimenopausal and postmenopausal women have been shown to exhibit neuronal volume loss (including hippocampal volume), relative hypometabolism, and slightly but measurable higher rates of AD-endophenotype biomarkers-based progression compared to premenopausal women.[22,23]

If conflicting data are available in the healthy control group, the relationship between sex and brain metabolism is even more complex in neurodegenerative diseases. Some of this preliminary evidence might provide a link with the different levels of brain reserve in males and females. Perneczky et al.[24] suggested a different protective effect of education between men and women. Malpetti et al.[25] investigated gender differences in brain metabolic activity and resting-state metabolic network connectivity by considering the effects of education and occupation in a large dataset of healthy subjects and AD patients. Of note, in AD patients, the impact of education and occupation on brain metabolism was different according to sex. The correlation between reserve proxies and brain metabolism was observed in the posterior temporoparietal cortex in males and the frontal and limbic cortex in females. Furthermore, metabolic connectivity showed greater efficiency in the posterior default-mode network in males and the anterior frontal executive network in females.[26] In a similar framework, there is accumulating evidence that the association of apolipoprotein E4 (APOE4) with the risk of developing AD is modified by sex.[27]

Jiang and colleagues found a significant APOE4/sex interaction for cerebral glucose metabolism but not verbal memory, hippocampal volumes or cortical amyloid burden. Specifically, female APOE4 carriers showed significantly higher cerebral glucose metabolism than female APOE4 non-carriers, whereas male APOE4 carriers had lower cerebral glucose metabolism than male APOE4-noncarriers. Accordingly, the effect of APOE4 on cerebral glucose metabolism seems to be altered by sex in individuals with memory impairment.[28]

Hormonal influence on brain metabolism has also demonstrated effects in the presence of epileptic seizures. Various metabolic patterns between sexes with the same diagnosis have been highlighted and explained by the estrogen and progesterone level changes in the menstrual cycle, as also shown by PET imaging.[29] Noe et al. mentioned that epilepsy patterns are different in women than in men related to hormone changes.[30] These studies provide a basis for discussing diagnosis and treatment options in epileptic patients with more focus on gender differences.

Table 1 Differences in PET and SPECT Tracers Binding Between Male and Female: Summary of Main Available Evidence

Tracers	Healthy Subjects	Neurological Disorders	References
[18F] FDG	Controversial results. A significant age-by-sex effect was detected only related to a worse age-related metabolic reduction in the posterior cingulate cortex bilaterally in women > 50 yrs.	1. higher rates of metabolic AD-endophenotype biomarkers-based progression compared to premenopausal women; 2. the effect of APOE4 on cerebral glucose metabolism seems to be altered by sex in individuals with memory impairment	20-23
Amyloid PET	Despite equal levels of global cognition and after controlling for age, education, and clinical comorbidities, men showed higher amyloid load, neurodegeneration, and lower functional connectivity (FC) in the Default-mode Network compared with women (possible link with higher brain resilience in men)	A meta-analysis of PET studies revealed no sex differences in amyloid positivity among individuals with subjective cognitive impairment, aMCI, or non-amnestic MCI	31,32,38,39
TAU PET	The amyloid burden seems more strongly associated with regional atrophy in women than men. This association seems to be mediated by a higher tau burden in women	Longitudinal data demonstrated that the tau accumulation rate is more significant in females since earlier stages of AD	41,44
Tracers for neuroinflammation	1. A higher volume of distribution for tracers targeting TSPO was highlighted in females. 2. TSPO radioligands showed a higher uptake with increased pro-inflammatory mediator transcript levels in response to lipopolysaccharide in aged females compared to adult females and aged males	-	48-52
Tracers for neurotransmission	Dopaminergic Imaging: the mean striatal 123I-FP-CIT SBR value is higher in women than in men −> this difference seems to be more evident for those of younger age	Dopaminergic imaging: 1. 123I-FP-CIT SBR is higher in women than in men in PD at motor symptoms onset, without any differences between the rate of decline of the tracer binding over time; 2. 123I-FP-CIT SBR is higher in prodromal DLB patients with different patterns of connectivity in females compared to males, mostly involving extrastriatal regions	57,60
Amino acid PET	Higher uptake in the normal tissue in females	Brain tumors in female patients have the same [18F]FET uptake as male tumors −> as lesion-to-brain ratio in female patients could be systematically lower than in male patients, simply because they have a higher uptake in the normal tissue (further investigation is needed given the potential impact of this evidence)	71

Abbreviations: DLB, dementia with Lewy Bodies; MCI, mild cognitive impairment; PD, Parkinson's disease; PET, positron emission tomography; SPECT, single photon emission computed tomography.

Sex Difference in Amyloid PET Data

Sex-related differences in amyloid PET studies are often mentioned in the literature, primarily as marginal analyses. Only a small number of studies using in vivo PET analyses in AD subjects have specifically focused on the sex-dependent relationship with amyloid burden.

The similar prevalence of amyloid positivity in male and female normal elderly individuals was actually highlighted in the vast majority of studies.[31,32] Only a few cross-sectional studies studies suggested a modest but measurable sex differences in the global Aβ burden in clinically normal older adults.[33,34] Other results are controversial. For instance, the slightly higher uptake of the amyloid PET tracer [^{11}C]-PIB in men compared to women in the temporal and occipital lobes, as described by Scheinin et al.[35], was not confirmed by other reports, which have indicated higher [^{11}C]-PIB uptake in women than in men.[36,37]

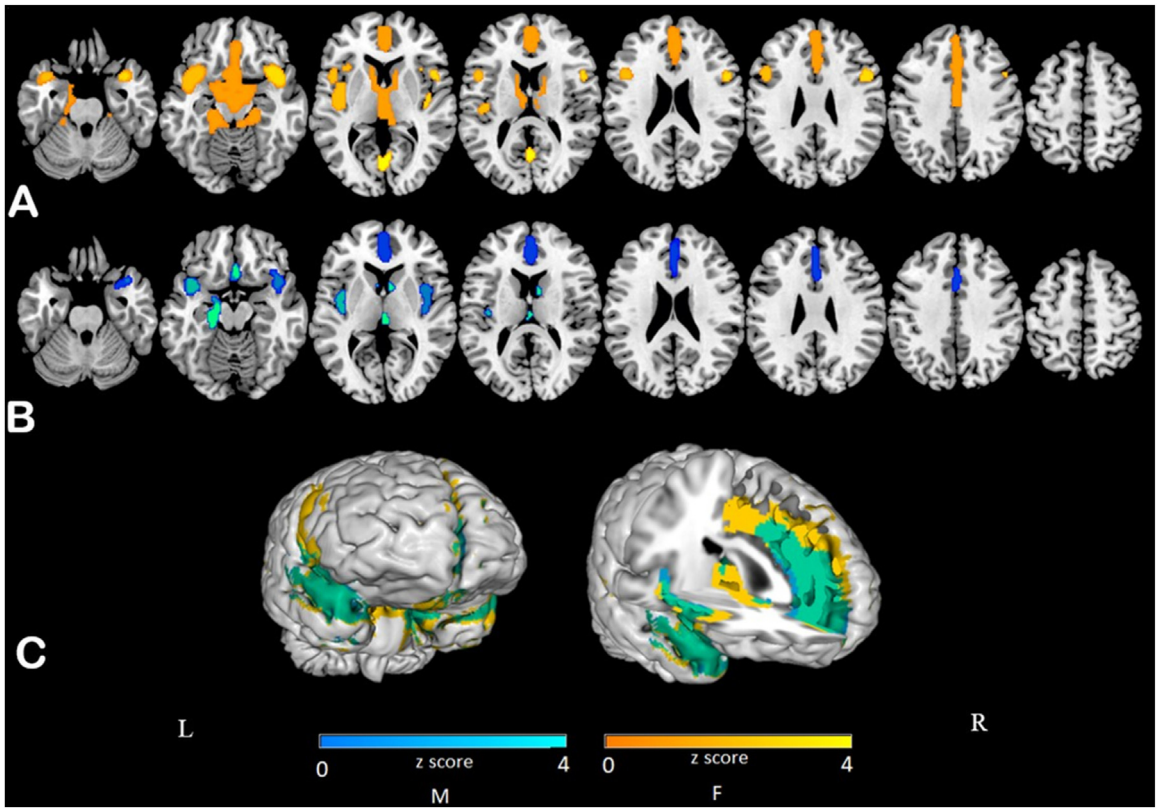

Figure 1 Correlation between aging and brain metabolism. Using P as a reference, statistical parametric maps (SPMs) showed a wider negative correlation between age and 18F-FDG uptake value in female (**A**) than in the male group (**B**). SPMs are represented on a color-coded scale and displayed on a standard MRI. In the surface representation (**C**) of SPMs, green represents common areas between females (F) and males (M) analyses. Reproduced with permission from reference 21.

A meta-analysis of PET studies revealed no sex differences in amyloid positivity among individuals with subjective cognitive impairment, aMCI, or non-amnestic MCI consistent with postmortem studies of AD subjects.[38,39]

Directly tackling the sex differences in AD using in vivo imaging biomarkers, Cavedo et al. found a significantly higher load of brain amyloid in the anterior cingulate cortex in men than in women.[40] Despite equal levels of global cognition and after controlling for age, education, and clinical comorbidities, men showed higher amyloid load, neurodegeneration, and lower functional connectivity (FC) in the Default-mode Network compared with women. These findings suggest that men may have higher brain resilience to the pathophysiological AD processes.

Sex Differences Highlighted by TAU PET Studies

The limited sex differences in Aβ deposition in older adults support the notion that sex differences are more likely to appear downstream after the onset of Aβ accumulation. Hence, it is meaningful to investigate the influence of sex on the interplay between amyloid and tau deposition in vivo.

Bachmann and colleagues tested models for sex differences, revealing that amyloid burden was more strongly associated with regional atrophy in women than in men. These associations were likely mediated by higher tau burden in women, indicating that influences of pathological pathways on cognition and sex-specific vulnerabilities are dissociable already in the early stages of neuropathology and cognitive impairment.[41] Moreover, in elevated cerebrospinal fluid (CSF) tau levels have been reported in women compared with men as a function of APOE ε4 status and Aβ. Recently, the availability of TAU PET tracers has allowed to deepen this finding in terms of quantity, timing, and regional deposition of tau with respect to amyloid.[6] Similarly, a study with Flortaucipir PET assessed the association between the patterns of brain tau accumulation and other well-established AD factors in a cohort composed of both healthy elderly subjects and early AD patients.[42] Highly associated patterns of greater [^{18}F]-AV-1451 binding and increased annualized change in cortical amyloid β plaques measured with PET were also explored. In the study, TAU PET tracer retention was associated with age and cross-sectional amyloid PET tracer retention but not with education, sex, or APOE genotype. However, in the analysis uncorrected for confounding effects, females disclosed greater [^{18}F]-AV-1451 binding in diffuse cortical regions, namely lateral temporal, parietal, and frontal regions.[42,43] Finally, a longitudinal PET study comprising four cohorts, demonstrated that the tau accumulation rate is more significant in females and younger amyloid-b-

positive individuals, while amyloid-b accumulation is more significant in APOE e4 carriers and older individuals.[44] Taken altogether, these findings provide important elements for the design of clinical trials and might improve our understanding of factors associated with faster tau aggregation and spread.

Sex Influence From PET Imaging of Neuroinflammation

Activated glial cells are considered a proxy for neuroinflammation. Differences in microglial function and number between the different sexes have been observed. The sex differences in microglial number and morphology were brain region dependent, with an increase in males early in development and in females later in life.[45] Similarly, the number of astrocytes, differentiation and function is highly sex-specific. Astrocytes in females have a higher mitochondrial metabolism compared to males and a higher resistance to oxidative stress, while male astrocytes have a higher recovery rate.[46]

The 18kDa translocator protein (TSPO) is the most widely used target for neuroinflammation tracers. TSPO radioligands are influenced by the rs6971 polymorphisms, which divide the population into a high, medium and low-affinity binder group. Recently, Peyronneau showed that human CYP3A4 is involved in the metabolism of [^{18}F]-DPA714, a second-generation TSPO radioligand. Cytochrome P450 are mainly responsible for the variability in drug pharmacokinetics and, therefore, the response to drugs.[47]

Within the different affinity binder groups, the TSPO signal is very heterogeneous, which might be attributed to exogenous factors such as sex known to influence CYP3A4. The latter was recently confirmed with faster metabolism in females than males (55.03 ± 9.36% versus 59.35 ± 7.41%), while $SUV_{70\text{-}90}$ was not influenced by sex. Similar findings in a multicenter study using [^{11}C]-PBR28 in which a higher Vt (volume of distribution) value in females was observed.[48,49] In line with these findings, [18F]-VC701 by means of another TSPO radioligand, showed a higher uptake with increased pro-inflammatory mediator transcript levels in response to lipopolysaccharide in aged females compared to adult females and aged males.[50] The administration of 17beta-estradiol seems to protect neural function and promote recovery through immune regulation. Possibly, estrogens in females limit neuroinflammation, explaining why an increased neuroinflammatory response is seen in aged females as estrogen levels significantly decrease after menopause.[51]

Cannabinoid receptor type 2 (CB2R) is another target for neuroinflammation. Sex differences in the cannabinoid system have been described, although most studies highlight a sex difference in CB1R.[52] Nevertheless, both CB1R and CB2R are critical to masculinize or femininize playing with agonism of both receptors, leading to an increase in female play, and antagonism, resulting in an increase in male play.[53] The latter also suggests a sex difference in the CB2R tracers; however, to our knowledge, no studies have investigated the sex difference's effect on the Vt values.

Colony stimulation receptor type 1 (CSF1R) radioligands can also be used as a proxy for neuroinflammation. Although no clinical studies have investigated sex differences, PLX5622-CSF1R inhibitor seems to influence microglial elimination in female rats, while no effect was observed in male rats.[54] Although clinical studies have been performed with [^{11}C]-CPPC, a gender effect has not been studied yet to our knowledge.[55]

Moreover, sex differences in B-cell gene expression have been described, which may influence CD19 and CD20, two other targets for neuroinflammation. No clinical studies to investigate this effect have been performed.[56] Again, this illustrates the important contribution of sex to the different neuroinflammation targets, that must be closely investigated in tracers for neuroinflammation.

Sex-Specific Features on SPECT and PET Tracers for Neurotransmission

Functional imaging of neurotransmission can provide valuable insight into unravelling the pathophysiology of many neurological/psychiatric diseases. It may shed light on the varying prevalence and symptom profiles of certain conditions, such as attention deficit hyperactivity disorder and addiction, between females and males. Ultimately, this approach could open up possibilities for more personalized, sex-specific therapies for these diseases.

However, the influence of sex on tracers for neurotransmission is complex and influenced by multiple other factors besides sex hormones, including genetics and individual variability. Moreover, as sex hormone levels vary based on the menstrual cycle and during life (pre- and post-menopausal), it is essential to recognize that these differences could be dynamic. Ongoing research is crucial in elucidating these differences and their clinical relevance further.

Dopaminergic System

Differences in the dopaminergic system may contribute to sex-based variations in reward processing, motivation, and susceptibility to addiction. Dopamine plays a crucial role in neuropsychiatric disorders, including Parkinson's Disease (where females are less affected) and schizophrenia (where females are affected at a later age and with a more protracted disease course). Studies have shown that men and women may exhibit differences in dopamine receptor density and binding affinity. The availability of the dopamine transporter (located presynaptically), which regulates synaptic dopamine availability, is higher in women than men. Lavalaye et al. found significantly higher [^{123}I]-FP-CIT binding ratios in healthy females compared to males, which was in line with preclinical studies and replicated in other clinical studies.[57] Pohjalainen et al. found that females have a lower affinity for the dopamine postsynaptic D2 receptor affinity in a study using [^{11}C]-raclopride, suggesting an increased endogenous striatal dopamine concentration in women.[58] In pathological conditions, sex differences in dopaminergic

neurotransmission and related connectivity have been observed with molecular imaging techniques both in Parkinson's disease and in Dementia with Lewy bodies (DLB).[59-61] Boccalini et al. highlighted sex-specific differences in [^{123}I]-FP-CIT binding in prodromal DLB (pDLB) patients. Specifically, a trend for lower [^{123}I]-FP-CIT binding was evident in pDLB females. pDLB females also exhibited different patterns of connectivity compared to males, mostly involving extrastriatal regions (Fig. 2). The results might suggest the presence of a sex-related regional vulnerability to alpha-synuclein pathology.[60]

Serotonergic System

Serotonin plays a central role in brain development, stress reactivity, mood and several psychiatric disorders. Alterations in the serotonergic system are associated with various psychiatric disorders, including depression and anxiety. These disorders often exhibit sex differences in prevalence and symptomatology.

Serotonin receptors (5-HTR) are part of a complex pathway in the brain and can be divided into different subtypes, and PET tracers are available for several subtypes. For instance, [^{11}C]-WAY100635 can be used to measure the

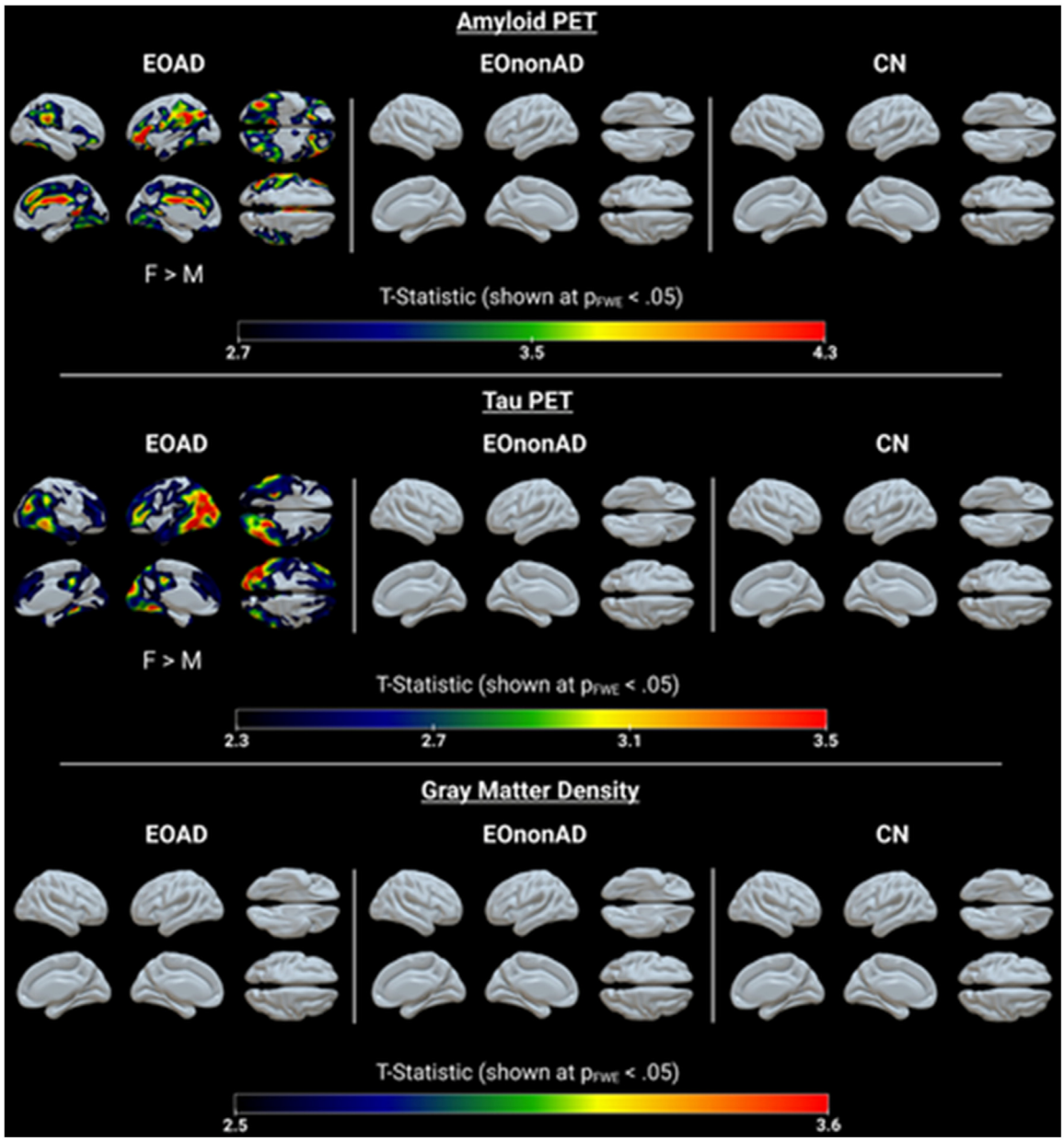

Figure 2 Dopaminergic connectivity results in males and female DLB patients. The matrices represent the significant differences obtained when comparing partial correlation coefficients between DLB < controls, DLB males < controls males and DLB females <controls females, in the dopaminergic networks. The color bar displays the Z scores' values to compare partial correlation coefficients' strengths. Altered connections are presented: in red, the increased and in blue, the decreased connections compared with Controls. DLB, Dementia with Lewy Bodies. Reproduced with permission from reference 60.

expression of the 5-HTR1A subtype. In a [^{11}C]-WAY100635 PET study, women had higher 5-HT1A receptor expression than men in several brain regions, including the dorsal raphe, amygdala, anterior cingulate, cingulate body, medial- and orbital prefrontal cortex.[62,63] Moreover, women are thought to have higher 5-HT transporter availability in the diencephalon and brainstem than men as measured using [^{123}I]-beta-CIT SPECT.[62] Studies exploring sex differences in other receptors, like 5-HT2A receptors, have not yielded entirely conclusive results.

Other Receptor Systems

The cholinergic system is involved in memory and cognition. Various PET/ SPECT ligands are available to imaging cholinergic neurotransmission, for instance, neurodegenerative diseases.[64] The gamma-aminobutyric acid (GABA) system is the primary inhibitory neurotransmitter that regulates various functions, including anxiety, mood, and motor control. The opioid system is involved in pain and reward processes. To date, there is less research on sex differences in other receptor systems. Research into opioid receptors has shown some sex-specific relations, but the findings vary depending on the specific opioid receptor subtype and the brain region being studied. For instance, higher mu-opioid receptor (MOR) binding in women versus men has been reported throughout cortical and subcortical regions.[65] MOR is the primary target for most opioid analgesics. These differences may contribute to variations in opioid responses and analgesic efficacy between sexes.

Sex-Specific Features on Amino Acid PET for Brain Tumor Imaging

Amino acid PET is increasingly used in clinical routine to depict vital tumor tissue.[66] Radiolabeled amino acids such as the radiotracer O-(2-[^{18}F]-fluoroethyl)-L-tyrosine ([^{18}F]-FET) or L-[S-methyl-^{11}C] ([^{11}C]-MET)-PET is taken up by tumor cells through amino acid transporters, which are upregulated in actively proliferating tumor cells.[67] The increased uptake of amino acid tracers in tumor tissue compared to normal brain tissue allows the visualization of metabolic active tumors on PET images with high tumor-to-brain contrast. They have been shown to be helpful in various clinical settings for brain tumor patients enabling differentiation between tumor tissue and peritumoral healthy brain, as well as facilitating the detection of tumor recurrence and assessing treatment-related changes and response.[68] The cut-off for distinguishing tumoral tissue from healthy brain tissue and for tumor segmentation and volumetric measurements is typically based on a lesion-to-brain ratio.[69] In this context, the uptake intensity of the healthy brain, which serves as "background," is essential and significantly influences diagnostic accuracy. However, physiological amino acid uptake reflecting the amino-acid metabolism of the brain appears to differ between men and women.

In this context, Verger and colleagues conducted a study investigating the factors influencing the [^{18}F]-FET uptake in the brain[70] examining negative PET scans of 107 subjects through comprehensive analysis techniques, including Statistical Parametric Mapping (SPM) for whole-brain quantitative analysis and volumes of interest (VOIs) analysis. The study identified sex and body mass index (BMI) as significant factors associated with increased uptake of in the brain. Overall, women showed a higher [^{18}F]-FET uptake of normal brain tissue than men and a weak positive correlation existed between body mass index (BMI) and uptake. These factors consistently influenced uptake across different brain areas.[70]

This information is crucial since the lesion-to-brain ratio is used to plan surgical resections or radiation treatment in patients with aggressive gliomas. Provided that brain tumors in female patients have the same [^{18}F]-FET uptake as male tumors, which is currently unknown, the lesion-to-brain ratio in female patients would be systematically lower than in male patients, simply because they have a higher uptake in normal tissue. One potential confounder that needs to be considered is the differences in body composition between men and women. Women have a lower percentage of lean body weight and, consequently, metabolically active body mass.[71] The calculation of SUV is usually performed by radioactivity injected per body weight, body surface area or lean body mass.[69] Therefore, differences in body composition might influence results between male and female patients.

Apart from treatment planning, dynamic [^{18}F]-FET PET imaging contributes to the prognosis and survival outcomes of gadolinium-negative gliomas. This imaging technique allows for the characterization of distinct patterns in Gd-negative tumors, including homogeneously increasing, homogeneously decreasing time activity curves (TACs), and mixed patterns within the same tumor. Studies have shown that these different TAC patterns are associated with different clinical courses and prognoses. For example, tumors with a homogeneously increasing TAC pattern have a higher 5-year survival rate compared to tumors with a mixed or homogeneously decreasing TAC pattern. Additionally, quantitative measurements such as minimal time-to-peak (TTP min) have been found to be highly correlated with qualitative TAC measurements and can further contribute to predictive models.[72]

By providing information about the biological subgroups and clinical courses of Gd-negative gliomas, dynamic [^{18}F]-FET PET imaging serves as a powerful imaging biomarker that can aid in patient counselling and treatment planning and guide the decision-making process for personalized treatment strategies.[72] However, the impact of sex on dynamic [^{18}F]-FET PET imaging and thus treatment planning has not yet been investigated.

Further research is needed to fully understand the impact of sex on amino acid (AA) PET for brain tumor imaging firstly focusing on the tracer uptake behavior. There is evidence suggesting that the imaging pattern of [^{11}C]-MET of astrocytic gliomas differs between male and female patients, potentially affecting the predictability of IDH mutation

status.[73] For other AA brain tumor imaging probes, such as [18F]-Fluoro-DOPA, no studies regarding sex differences and brain tumor uptake behavior have been published. Additionally, it is necessary to understand whether the different uptake of normal brain tissue and, thus, the potential differences in lesion-to-brain ratio affect treatment decisions and target delineations. The impact of sex needs to be further investigated not only in the initial treatment planning but also in response assessment by amino-acid PET.

Conclusion

Investigations concerning sex differences are pivotal for understanding the different vulnerabilities and the trajectories of normal or pathological brain ageing in both men and women. Neuroimaging techniques play an important role in evaluating sex-related characteristics in brain structure and function *in vivo*. Some conflicting results have emerged from functional studies on whether differences between biological sexes exist. There is a complex relationship between sex and neural interactions of brain processes, regional brain blood flow, metabolism and neuropathological protein depositions underpinned by factors such as hormonal balance, genetics and education. Differences in the choice of cohorts, study design, equipment, tracers, data analysis, considered region of interest, brain segmentation, and partial volume correction might explain the majority of conflicting results indeed, albeit limited, PET and SPECT-based evidence on sex differences in normal conditions and several neurological disorders.

In conclusion, there is an urgent need for a more systematic appraisal of sex differences in neuroimaging studies, which may have a substantial impact on clinical practice and the design of drug trials.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Valentina Garibotto reports a relationship with Swiss National Science Foundation, by the Velux foundation, by the Schmidheiny foundation, the Boninchi foundation and by the Aetas foundation that includes: funding grants. Nathalie L Albert reports a relationship with Novartis Advanced Accelerator Applications, Telix Pharmaceuticals, Servier, Novocure that includes: consulting or advisory and funding grants. Silvia Morbelli reports a relationship with Italian Ministry of University and Research that includes: funding grants. Kathrin Heinrich reports a relationship with Roche, Taiho, BMS, Merck, Servier, MSD (Institutional), Merck, Janssen, Amgen, Merck, Servier that includes: funding grants and travel reimbursement. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Ozgul Ekmekcioglu: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Nathalie L. Albert:** Methodology, Supervision, Writing – original draft, Writing – review & editing. **Kathrin Heinrich:** Writing – original draft. **Nelleke Tolboom:** Writing – original draft, Writing – review & editing. **Donatienne Van Weehaeghe:** Writing – original draft, Writing – review & editing. **Tatiana Traub-Weidinger:** Writing – original draft, Writing – review & editing. **Lutfiye Ozlem Atay:** Writing – original draft. **Valentina Garibotto:** Supervision, Writing – original draft, Conceptualization, Writing – review & editing. **Silvia Morbelli:** Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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