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CHAPTER

c0025

Sex differences in neuroimaging biomarkers in healthy subjects and dementia

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Abbreviations

dt0010	**AD**	**Alzheimer's** disease
dt0015	**ADD**	Alzheimer's disease dementia
dt0020	**ADNI**	Alzheimer's disease neuroimaging initiative
dt0025	**aMCI**	amnestic mild cognitive impairment
dt0030	**APOE**	apolipoprotein E
dt0035	**BOLD**	blood oxygen level-dependent
dt0040	**CAN**	central autonomic network
dt0045	**CBF**	cerebral blood flow +
dt0050	**CEN**	central executive network
dt0055	**CSF**	cerebrospinal fluid
dt0060	**DAN**	dorsal attention network
dt0065	**DAT**	dopamine transporter
dt0070	**DLB**	dementia with Lewy bodies
dt0075	**DMN**	default mode network
dt0080	**DTI**	diffusion tensor imaging
dt0085	**FA**	fractional anisotropy
dt0090	**FC**	functional connectivity

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dt0095	**FDG-PET**	^{18}F-fluorodeoxyglucose positron emission tomography
dt0100	**fMRI**	functional magnetic resonance imaging
dt0105	**FPN**	frontoparietal network
dt0110	**GM**	gray matter
dt0115	**HE**	Hurst exponent
dt0120	**HPF**	hippocampal parenchymal fraction
dt0125	**^{123}I-β-CIT**	^{123}I 2β-carbomethoxy-3β-(4-iodophenyl) tropane
dt0130	**^{123}I-FP-CIT**	^{123}I-ioflupane
dt0135	**^{123}I-IMP**	*N*-isopropyl p-I-123-iodoamphetamine
dt0140	**MCI**	mild cognitive impairment
dt0145	**MRI**	magnetic resonance imaging
dt0150	**NC**	normal controls
dt0155	**PD**	Parkinson's disease
dt0160	**PET**	positron emission tomography
dt0165	**PiB**	Pittsburgh compound B
dt0170	**pMRI**	perfusion magnetic resonance imaging
dt0175	**QSM**	quantitative susceptibility mapping
dt0180	**rCBF**	regional cerebral blood flow
dt0185	**ROI**	region of interest
dt0190	**RS**	resting state
dt0195	**RS-fMRI**	resting state-functional magnetic resonance imaging
dt0200	**SBR**	specific to nondisplaceable binding ratio
dt0205	**SN**	salience network
dt0210	**SPECT**	single photon emission computed tomography
dt1210	**SUVR**	standardized uptake value ratio
dt0215	**^{99m}Tc-ECD**	^{99m}Tc ethylcysteinate dimer
dt0220	**^{99m}Tc-HMPAO**	^{99m}Tc-hexamethylpropylene amine oxime
dt0225	**TSPO**	translocator protein
dt0230	**VHMC**	voxel-mirrored homotopic connectivity
dt0235	**WM**	white matter

s0010 Introduction

p0240 Sex and gender-related differences in terms of human behavior and cognition have been widely reported over the years and are influenced by an interplay of both biological and environmental factors (Ferretti et al., 2018). Furthermore, several neurological conditions, such as dementias, are sex-predisposed, thus suggesting the importance of sexual dimorphism. However, most studies actually consider sex as a nuisance variable, rather than a major factor accounting for the different vulnerabilities and trajectories of normal or pathological brain aging in men and women.

p0245 Preclinical animal models as well as postmortem studies in humans have provided useful information on the differences in terms of brain structure and neuropathology between females and males (Cosgrove, Mazure, & Staley, 2007). Within this context, the role of neuroimaging techniques has grown in recent years as they provide in vivo information on brain morphology and functioning, but also on the underpinning neuropathological changes, by using specific radiopharmaceuticals to

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t0010 **Table 1** List of imaging techniques discussed in the text.

	Techniques	Tracers
Structural MRI (sMRI)	Volumetric T1-weighted images	
	Quantitative susceptibility mapping (QSM)	
	Diffusion tensor imaging (DTI)	
Functional MRI (fMRI)	Task-related fMRI	
	Resting state (RS)-fMRI	
	Perfusion MRI (pMRI)	
Perfusion SPECT		^{99m}Tc-HMPAO
		^{99m}Tc-ECD
		^{133}Xenon
		^{123}I-IMP
DAT-SPECT	DAT binding	^{123}I-FP-CIT
		^{99m}Tc-TRODAT-1
		^{123}β-CIT
PET	Nigro-striatal assessment	^{18}F-Fluoro-DOPA
	Brain metabolism	^{18}F-FDG
	Amyloid binding	^{11}C-PiB
		^{18}F-AV45 (florbetapir)
	Tau binding	^{18}F AV-1451
	5-HT(1A) receptor binding	^{11}C-WAY-1006
	TSPO binding	^{11}C-PBR28

image the brain through SPECT and PET technologies. Nevertheless, results from different studies are often conflicting due to technical issues and the lack of a systematic approach, and this limits the consideration of sex as a leading factor in experimental and clinical studies.

p0250 Below, we describe the different imaging techniques (Table 1) used to assess sex-related brain differences, both in the healthy and in pathological aging. In addition, we highlight the implications of the findings coming from different studies, and their limitations, which need to be overcome in future neuroimaging studies.

s0015 Structural MRI

p0255 Prior to the 1990s, few studies examined sex differences in the clinical presentation, disease progression, or treatment of psychiatric and neurological disorders and their correlation with brain macro- and microstructure (Cosgrove et al., 2007). Sex-related differences in brain structure have been largely studied in preclinical animal models, and postmortem studies in humans have initially provided useful information, but methodological factors, i.e., agonal state and postmortem interval, may have affected the results. In this scenario, neuroimaging techniques play an important role in evaluating sex-related differences in brain structure in vivo.

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s0020

Structural MRI sex differences in healthy subjects

p0260 Sex differences in regional brain areas of healthy subjects during adulthood and normal aging have been reported in several studies. The different methodologies applied (i.e., image registration and segmentation algorithms) might explain some conflicting findings. The characterization of the spatial-temporal pattern of GM and WM volume changes in normal aging may also allow better understanding of the mechanisms leading to the pathologic changes in neurodegenerative disorders, the risk of which increases with age (Peng et al., 2016).

p0265 Age-related brain volume loss differs between men and women. The volume loss progresses with age in the whole brain, particularly affecting frontal and temporal lobes in men and parietal lobes in women. Moreover, a high degree of heterogeneity was described as for age-related GM volume changes; indeed, some brain regions, including the temporal lobe, hippocampus, and parahippocampal gyrus, are more susceptible to the effect of aging in males (Witelson, Beresh, & Kigar, 2006). In a paper by Peng et al. (2016), a cross-sectional study was conducted of age- and sex-related changes in the GM volume of several brain regions in a population of 124 cognitively normal Chinese adults. In young and middle-aged subjects, female and male subjects showed significant differences in the right middle temporal gyrus, right superior temporal gyrus, left angular gyrus, right middle occipital lobe, left middle cingulate gyrus, and the pars triangularis of the right inferior frontal gyrus, suggesting an interaction between age and sex.

p0270 Király et al. (2016) analyzed T1-weighted images from 53 healthy males and 50 age-matched healthy females by using a surface model-based segmentation approach, and demonstrated a significant age-related decrease in males as compared to females.

p0275 From a pathophysiological point of view, half a century ago, a postmortem study by Hallgren and Sourander (1958) showed that iron accumulates with varying degrees across brain structures, showing a rapid increase until young adulthood, followed by a smaller rise, and then reaching a plateau after midlife. MRI studies focused on brain iron content in healthy adults yielded conflicting results, showing both linear and nonlinear age trends of iron distribution. Nevertheless, in most of these studies, the iron concentration was higher in the subcortical nuclei as compared to the WM and cortex (Bilgic et al., 2012). In addition to age, sex should also be considered a determinant of brain iron levels variability. QSM, an advanced MRI technique, has been used to provide information about tissue magnetic susceptibility. Using this approach, lower susceptibility values in women than men were found in the thalamus and red nucleus by Gong et al. (2015) and in the substantia nigra, after accounting for age, in a study by Persson et al. (2015), in which, in addition, a linear increase with age of pulvinar susceptibility in men was demonstrated. This latter study represents the first in vivo evidence of lower GM subcortical iron levels selectively in women from the postmenopausal stage, suggesting a role of the hormonal axis in neurodegenerative changes.

p0280 As for the WM, aging is a main cause of WM degradation, mostly due to myelin breakdown (Bartzokis et al., 2010). In this context, DTI is a noninvasive in vivo

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method used to provide a quantitative estimation of the microstructural organization of WM by means of the FA, a DTI parameter ranging from 0, when there is an isotropic movement of water molecules (e.g., CSF) to 1, when the movement of water molecules is anisotropic (e.g., fiber bundles). In particular, across the lifespan, the FA progressively increases during the first two decades of life, which relates to myelin maturation, and then decreases, with a faster rate after 60 years, likely reflecting axonal and myelin changes. It is worthy of note that, in the same way as WM microstructure maturation has been demonstrated to be heterogeneous across brain regions, age-related WM changes seem to follow an anteroposterior gradient, with the most evident changes in the anterior part of the corpus callosum with respect to the splenium (Fan et al., 2019).

p0285 Some investigations have reported a lack of significant interactions between sex and age as regarding WM microstructure (Kanaan et al., 2012). However, it may be argued that WM trajectories also present sex specificity, as age-related myelination changes have been described as being more prominent in males than females in animal models (Yang et al., 2008). One of the possible explanations of the lack of sex-specific DTI findings in aging is the use of conventional DTI-derived measures, which are characterized by low sensitivity to axonal microstructural integrity abnormalities. Advanced multishell diffusion-weighted imaging methods may overcome these issues, due to their capability of separating intra- and extra-axonal diffusion compartments. In this context, a recent paper by Toschi et al. (2020) reported that the so called "restricted signal fraction"—a marker of the combined effect of axonal and myelin integrity—has a greater sensitivity relative to traditional DTI measures in detecting the age at which WM microstructural components start to change. In this study, microstructural changes detected with more advanced techniques were found at a greater extent in women than in men. Indeed, in female subjects, the age-related WM decline was found to begin approximately 14 years later than in males and seemed to preferentially affect the frontal regions.

p0290 In conclusion, according to sMRI findings, sex should be considered as a major determinant in cross-sectional MRI studies focused on the aging brain. This aspect may be of paramount importance when evaluating the changes of GM structures that are consistently related to several neurodegenerative disorders (e.g., AD).

s0025 Structural MRI sex differences in dementia

p0295 Sex-related brain structural differences have been investigated in patients with MCI and ADD, and in cognitively normal subjects carrying AD risk factors (i.e., APOE ε4 allele). A higher risk of developing AD (Gao et al., 1998), greater cognitive impairment (Bai et al., 2009), and functional disability (Dodge et al., 2003) were reported in women, but MRI evidence of a "sexual dimorphism" in AD remains controversial.

p0300 In females with ADD, either smaller hippocampal volumes (Apostolova et al., 2006) or less atrophy (evaluated through CSF volume) in frontal, temporal, and parietal regions (Kidron et al., 1997) were found as compared to males. In a large cohort of

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nearly 400 ADD patients, the whole brain volume was unrelated to sex, and two other studies concluded that the frontal and the medial temporal lobes should be included among the brain regions not differentially associated with sex in ADD. Conversely, temporal lobe degeneration over time has been shown to proceed faster in women with ADD than in men (Skup et al., 2011).

p0305 Taking into account that sex differences have been suggested among patients with AD and those with aMCI across a variety of domains, including cognition and behavior, Skup et al. (2011) obtained longitudinal sMRI data of 197 individuals with probable ADD and 266 with aMCI compared to 224 healthy controls from the ADNI database to assess sex differences in GM atrophy patterns over 2–3 years. In the study, males showed lower volumes over time, compared to females, in bilateral thalamus and right middle temporal gyrus, in both the ADD and aMCI groups, as well as in the left insula in ADD and in the bilateral caudate nucleus in aMCI groups, respectively.

p0310 Conversely, in a 1-year longitudinal MRI study, the 3D profile of progressive atrophy in subjects with probable AD, with amnestic MCI, and healthy controls was mapped, revealing significant age and sex differences in atrophic rates. In particular, brain atrophy rates were about 1%–1.5%/year faster in women than in men (Hua et al., 2010).

p0315 As for the hippocampus, which is one of the regions first affected by AD pathology, no significant volume difference between sexes was disclosed in older adults with subjective memory complaints (Cavedo et al., 2018). These results are in line with a metaanalysis conducted by Tan et al. (2016) on 4000 brains, in which no sex differences in the hippocampal volume were detected. In this setting, Ardekani et al. (2019) measured the HPF on 775 MRI volumetric scans of 198 volunteers from a public database (OASIS1, hiip://oasis-brains.org/), divided into cognitively unimpaired, MCI, or mild/moderate ADD. HPF asymmetry was significantly higher in men after controlling for all the other variables, but there was no sex effect on HPF size. Similar findings were obtained in a recent paper, where no interactive effect of sex on hippocampal volume was detected (Caldwell, Cummings, et al., 2019).

p0320 The APOE e4 genotype has been considered as the strongest genetic risk factor for sporadic AD, and higher risk in females than in males. In addition, female APOE ε4 carriers also showed reduced hippocampal volume with respect to their male counterparts in the MCI and ADD conditions, but results are controversial. One longitudinal study in MCI patients reported no significant association between APOE ε4, sex, and hippocampal atrophy over a 2-year period (Spampinato et al., 2016), whereas female sex and APOE ε4 were associated with a longitudinal reduction of hippocampal volumes in the NC and MCI but not in the ADD groups drawn by the ADNI dataset (Shen et al., 2019). Nevertheless, in a previous study by Holland et al. (2013), women in all cohorts (cognitively preserved, MCI, and ADD) demonstrated higher rates of decline than men. Interestingly, in this study, the magnitude of the sex effect on the decline rates was as large as those of ApoE ε4. The different and relatively short follow-up time in the MCI and ADD cohorts cannot be ruled out as a possible explanation of these conflicting findings.

p0325 Lastly, as for sex-related effects on AD progression, Lee et al. (2018) no differences were found in cortical thickness between males and females in either AD or normal control groups at baseline, after controlling for age, education, disease duration, age at onset (early onset versus late onset), APOE ε4 allele, and intracranial volume. However, women with ADD showed more accelerated cortical thinning than men over a 5-year follow-up.

p0330 Notably, most of the MRI studies tackling sex differences in AD have been longitudinal rather than cross-sectional in nature. Thus, findings likely reflect a faster progression of AD-specific pathology in females in which more severe neurofibrillary degeneration and greater loss of brain parenchyma have been reported and associated with higher cognitive deficit (Filon et al., 2016).

p0335 In addition, some technical issues should be considered. Most of the studies are probably underpowered, and the sample size is not large enough to detect a subtle sex effect on atrophy rates. Furthermore, the different technical approaches used to process MR images over the years may be an important contributor to explain the conflicting results in the literature. For instance, whole brain volume estimation may give different results, depending on whether the correction for the intracranial volume (ICV) has been applied or not. Obviously, this bias becomes increasingly important in MRI studies focused on the effect of sex on brain atrophy. Similarly, several approaches for brain segmentation have been applied in the different investigations, partly due to the advance in technical knowledge of MRI analysis over the years. This is the case, for instance, in the choice to use an intensity-based procedure rather than a model-based approach to segment brain structures. This approach has a particular utility in those regions with low tissue contrast and should be preferred for the segmentation of subcortical GM (Király et al., 2016).

s0030 Conclusions

p0340 An asymmetry of brain volumes and microstructural architecture seems to be present between males and females throughout the lifespan, from adulthood to older age. Furthermore, male and female patients with ADD show different patterns and rate of atrophy progression in crucial sites, although with conflicting results, to which technical issues in MRI analysis and heterogeneity of patients across studies in terms of age, educational level, disease duration, and severity may have contributed.

p0345 Fig. 1 summarizes the main morphological and functional MRI potentialities to apply to sex differences research.

s0035 Functional MRI

p0350 FMRI techniques provide a unique opportunity to elucidate the interplay between sex, brain functions, and behavior. We review evidences of sex-related brain functional differences emerging from distinct fMRI approaches, including task-related fMRI, RS-fMRI, and pMRI.

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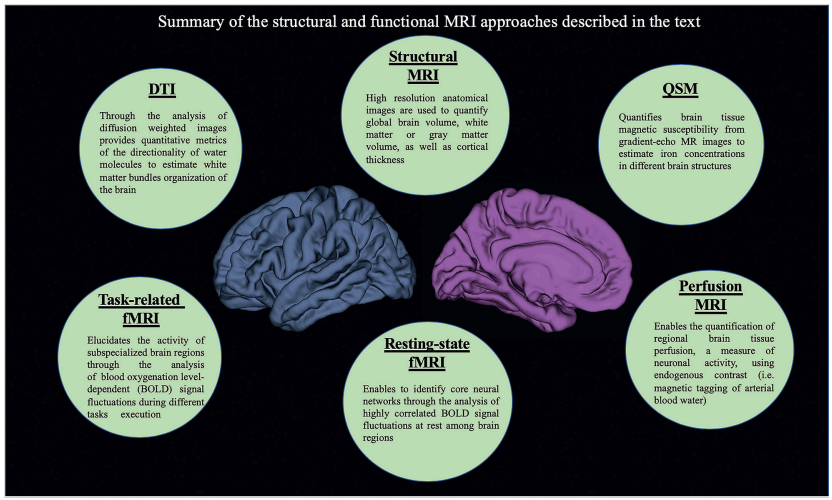

f0010 **FIG. 1**

Summary of the main morphological and functional MRI potentialities to apply to sex differences research, as described in the text.

s0040 ## fMRI sex differences in healthy subjects

p0355 Neuronal activation is supported by a higher oxygen supply provided by an increase in rCBF. This process results in a change in the relative levels of oxyhemoglobin and deoxyhemoglobin detectable by MRI using their differential magnetic susceptibilities. This approach is known as BOLD contrast imaging and is traditionally applied to generate maps reflecting the activity of subspecialized brain regions involved in the execution of different tasks (Lv et al., 2018). Overall, converging evidence suggests that, while some cognitive functions and their cortical substrates are differentially modulated by sex-aging interactions, others are not. Hesselmann et al. (2001) have evaluated signal intensity variations related to aging during a motor stimulation paradigm and found a selective significant decrease of signal intensities with age in males.

p0360 One study investigated the link between age, sex, handedness, and language lateralization index in a large group of healthy participants using both a semantic decision and a verb generation task (Nenert et al., 2017). Notably, the lateralization indices were found to significantly decrease with age only in right-handed men and in temporoparietal cortical areas, suggesting that the evolution of language lateralization in the human brain may follow different trajectories in men and women. Conversely, for other functions, sex-related differences may not be significantly influenced by aging. Ritchey et al. (2011) found enhanced emotion-related activity of the right amygdala and striatum in females relative to males, independently from age, providing evidence that sex effects on the involvement of these structures may be stable across the lifespan. Intriguingly, for some higher order cognitive functions, neither sex nor aging seem to play a significant role.

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p0365 Another study has investigated the lateralization of brain hemodynamic activity related to attention processes using an event-related fMRI auditory oddball task (Stevens, Calhoun, & Kiehl, 2005). The authors found greater right hemisphere activity for target detection and novelty processing, but the asymmetry effects did not differ with respect to the age or sex of the participants.

p0370 Unlike task-related fMRI, RS-fMRI is acquired in the absence of a stimulus or a task, and the analysis is therefore focused on spontaneous BOLD signal alterations (Lv et al., 2018). With this approach, some studies were able to identify core brain networks sustaining distinct cognitive functions, including: (a) the DMN, which comprises the precuneus/posterior cingulate, lateral parietal, and mesial prefrontal cortex—this network is primarily activated under resting conditions, but it also facilitates or monitors active tasks (working memory, in particular); (b) the DAN, which comprises middle temporal visual areas, superior parietal lobule, the cortical regions near the intraparietal sulcus and ventral premotor cortex, and is mainly engaged during externally directed attentional tasks; (c) the SN, which is primarily composed of the anterior insula and dorsal anterior cingulate cortex and is primarily involved in detecting and filtering salient stimuli, as well as in recruiting CEN and DMN structures; and (d) the FPN, primarily composed of the dorsolateral prefrontal cortex and posterior parietal cortex, particularly engaged during attention and cognitive control process.

p0375 Notably, RS fMRI also enables the investigation of connectivity alterations within and between these networks, and evaluation of how different factors, including sex, may differentially mediate these associations. Jamadar et al. (2018) showed greater connectivity in the SN for males compared to females, while the opposite pattern was observed in the DMN.

p0380 Other studies focused on the asymmetry of spontaneous cerebral activity in relation to sex. A previous study investigated the relationship between multiple intelligence measures and the degree of coherent functional activity between corresponding cortical areas using VHMC (Santarnecchi et al., 2015), finding a trend towards increased correlation between mirrored connectivity and intelligence quotient scores in the prefrontal cortex and precuneus/cuneus regions in females. Another study has evaluated the lateralization of RS networks (Agcaoglu et al., 2015) finding a higher right lateralization of the lingual gyrus within the visual network and more left lateralization of the inferior frontal gyrus within the frontal network in males. However, it is noteworthy that sex-related connectivity changes are not fixed, as they interact with aging.

p0385 Sie et al. (2019) investigated sex-related differences between multiple networks and the CAN, a network primarily involved in the control of visceromotor, neuroendocrine, pain, and behavioral responses. With aging, females demonstrated reduced negative connectivity in the posterior midcingulate gyrus with dorsal precuneus/posterior cingulate cortex and left angular gyrus, possibly suggesting a decay in the suppression of the sympathoexcitation associated with decrease in estrogen levels. Conversely, males showed an increased positive connectivity in posterior midcingulate gyrus with right supramarginal gyrus, and in ventromedial prefrontal cortex

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with ventral precuneus, suggesting greater parasympathetic regulation with advancing age. Scheinost et al. (2015) showed common and divergent trajectories of age-related connectivity changes across the main RS networks in males and females. In the DMN, males and females both showed age-related decreases in connectivity, while in the FPN, males and females manifested opposing aging trajectories, with an overall negative correlation with age remaining significant only in females. Furthermore, the networks responsible for the basic senses showed differential aging patterns for males and females, with an inverse correlation between connectivity and aging in the visual network selectively observed in females. Overall, these sex differences in aging trajectories may play a role in age-related changes in normal cognition, as well as in the susceptibility to neurological and psychiatric diseases. A subsequent study looking at sex-related effects of aging on DMN, DAN, and SN connectivity, however, found significant global reductions in older males compared to younger males, while for females, age did not modulate intra-network connectivity (Goldstone et al., 2016).

p0390 Sex-related differences in VMHC have also been evaluated in relation to aging. A pivotal study from Zuo et al. (2010) demonstrated age-related increases in VMHC of the dorsolateral prefrontal cortex and decreases in VMHC of the amygdala in males, while the opposite pattern was observed in females. Another study, exploring fractal complexity of the RS-fMRI signal across the adult lifespan using HE analysis (Dong et al., 2018), showed that, overall, global mean HE increases with age, indicating a progressive reduction of BOLD activity complexity. However, females exhibited higher HE values in the parietal lobe independently of age, while the interaction between age and sex showed a significant effect in the right parahippocampal gyrus, suggesting that the aging effect on BOLD complexity is different between sexes in this region.

p0395 PMRI is an innovative MRI approach that enables the noninvasive quantification of regional brain tissue perfusion using labeled inflowing arterial protons as an endogenous tracer. One study combining pMRI and transcranial Doppler explored sex-related differences in cerebral hemodynamics and their relation to central hemodynamics (Tarumi et al., 2014). Global CBF and wave reflection were higher, while diastolic CBF velocity was lower, in women compared to men, suggesting that female sex may increase central pulse pressure, which in turn may reduce diastolic but raise pulsatile CBF. Another study looked at the effects of physical activity and sex on CBF in older adults, finding greater cortical perfusion in women compared to men, and particularly in women who engaged in strength training compared to women who did not. This effect was absent in men, suggesting that cerebrovascular function may be moderated not only by sex, but also by strength training (Xu et al., 2014). PMRI research is now also focusing on the interaction between sex and aging. A first study comparing CBF between healthy elderly and young subjects showed larger age-related CBF decline in men compared to females (Asllani et al., 2009). However, divergent findings come from a study showing higher CBF in young premenopausal women compared to both young men and older postmenopausal women (Liu, Lou, & Ma, 2016). As outlined by the authors, these findings (replicating older

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studies with molecular imaging techniques, Krejza, 2001; Ohkura, 1994; Rodriguez, 1988) might be explained by sex hormones differences between women and men. Another study examined the influence of cardiac function on CBF in aged subjects (Henriksen et al., 2014), finding that CBF was higher in females compared to males, and that CBF decrease related to aging tended to be restricted to females.

fMRI sex differences in dementia

Sex-related fMRI differences have also been investigated in patients with ADD, with MCI, and cognitively normal subjects carrying AD risk factors (i.e., APOE ε4 allele). A previous study investigated FC alterations and their behavioral correlates in older females with and without MCI relative to their male counterparts (Huang et al., 2015). The authors found that brain function of subcortical-cortical loops was disrupted in older females with MCI, and that regional RS function of the left precuneus was significantly associated with altered episodic memory in these cases, suggesting a link between network dysregulation and susceptibility to cognitive dysfunction. Converging evidence for a significant involvement of the precuneus in females at risk of AD comes from studies evaluating the interaction between sex, brain functional alterations, and AD risk factors. A pivotal study by Damoiseaux et al. (2012) demonstrated that female APOE ε4 carriers showed significantly reduced DMN connectivity, which was most pronounced in the precuneus, compared with either female APOE ε3 homozygotes or male APOE ε4 carriers, whereas male ε4 carriers differed minimally from male APOE ε3 homozygotes. Furthermore, subsequent studies have suggested that not only the precuneus, but also its functional connections with the hippocampus might be altered in cognitively normal female APOE ε4 carriers and prone to significant age-related decrease (Heise et al., 2014). Taken together, these preliminary observations suggest that greater vulnerability of these connections might be one reason contributing to the increased AD risk in female APOE ε4 carriers.

However, divergent findings come from other studies. Caldwell, Zhuang, et al. (2019) found greater anterior DMN/posterior DMN connectivity related to better verbal learning in cognitively normal women with an APOE ε4 allele and amyloid PET positivity compared to their ε4 negative counterparts, while no similar significant results were observed in men. Another study, looking at the effects of sex on RS FC in cognitively normal individuals with subjective memory complaints has shown a significant reduction of the DMN FC in men compared to women, but the authors did not find any significant effects when looking at the interaction between sex, APOE, and amyloid status in specific hubs (Cavedo et al., 2018).

Conclusions

In healthy aged populations, task-related fMRI studies suggest a complex interaction between sex and neural correlates of common brain processes. For some functions, the involvement of specific brain regions seems to be influenced by both aging and sex, for other functions only by sex, and for other functions by neither of these

factors. RS-fMRI studies have evidenced a differential vulnerability of core brain networks in males and females, and an overall trend towards greater lateralization in males and greater homotopic connectivity in females. Notably, both sexes seem to manifest age-related decreases in RS FC, but females have been shown to be more vulnerable to network-specific decline. On the other hand, pMRI studies have been more consistent in reporting higher CBF, as well as more pronounced CBF decline, in females compared to men.

p0415 Less evidence is available for sex-related fMRI differences in dementia. The available studies have mainly focused on RS FC alterations in prodromal and symptomatic stages of AD, mainly reporting DMN hubs FC reductions and altered connectivity of these regions with other brain structures in female APOE ε4 carriers, partially explaining the increased vulnerability to AD in these subjects.

p0420 In conclusion, while the emerging evidence suggests sex to be a key factor modulating brain functioning, some limitations of the current lines of research need to be highlighted. Overall, there is a considerable paucity of fMRI studies looking at sexual dimorphisms in the human brain compared to sMRI studies. Moreover, while few fMRI studies have specifically investigated sex-related changes in aged populations, exploring this aspect would be pivotal to better understanding how age-related diseases, such as AD, differentially impact on the main correlates of brain functions in males and females. Finally, it is noteworthy that fMRI studies looking at sex differences in dementia have mainly looked at RS FC alterations, while in task-related and pMRI studies sex is often considered as a variable to correct for instead of a modulatory element to investigate on its own. Future studies are therefore warranted to broaden our knowledge on the complex interactions between brain functions, sex, aging, and pathology. See Fig. 1 for a summary of the main fMRI potentialities.

s0055 Perfusion SPECT

p0425 SPECT aims to measure the nonquantitative brain distribution of lipophilic radiopharmaceuticals, such as ^{99m}Tc-HMPAO, ^{99m}Tc-ECD, and ^{123}I-IMP. The distribution of these tracers to brain tissue is a function of rCBF and differs one for each as a consequence of the retention mechanism within the brain. Hence, they do not allow quantitative measures and are only roughly correlated with rCBF as measured by quantitative tools, such as $H_2^{15}O$ PET or ^{133}Xenon SPECT, which is an abandoned SPECT (or planar) technique because of the poor spatial resolution. The most appropriate term for SPECT findings is, therefore, "brain perfusion (distribution)," while the term "rCBF," often used to report SPECT findings, should be discouraged.

s0060 Perfusion SPECT sex differences in healthy subjects

p0430 Early studies with quantitative tools repeatedly showed that females have higher CBF than males in all regions and at all ages, with differences declining in the post-menopausal period (Rodriguez et al., 1988). An effect of estrogens and of a lower

oxygen carrying capacity (i.e., a lower hemoglobin concentration) are some among the suggested mechanisms. As for the relative regional distribution of perfusion values, available studies obtained controversial results: the lack of sex differences found by Callen et al. (2004) was inconsistent with the ^{99m}Tc-ECD SPECT study by Van Laere et al. (2001), who found a higher perfusion in men in the bilateral cerebellum and in the left anterior temporal and orbitofrontal cortices, and a significantly higher perfusion in women's right inferior parietal cortex. This was in line with other ^{133}Xenon SPECT studies in which females disclosed either increased absolute global CBF (Devous et al., 1986) or rCBF values in temporoparietal areas in comparison to males (Slosman et al., 2001).

p0435 Sex differences in brain perfusion have been reported in older healthy volunteers by means of ^{99m}Tc-ECD SPECT, and also after partial-volume effect correction (Li et al., 2004). Women showed higher regional perfusion in the left inferior frontal gyrus, bilateral middle temporal, and left superior temporal gyri. Such sex differences were consistent with the better performance in women in verbal tasks, which are related to the activity of the left inferior frontal gyrus; whereas, men had higher regional perfusion in the left superior frontal gyrus and in several areas of the right hemisphere, i.e., the cerebellum, middle frontal, fusiform and postcentral gyri, parietal lobule, and precuneus. This is in keeping with the greater ability of men in visuospatial tasks, which involve the right parietal and occipitotemporal regions.

p0440 By far the largest study was performed by means of ^{99m}Tc-HMPAO-SPECT in 119 young healthy subjects and in a psychiatric population of 26,683 patients (Amen et al., 2017). Women displayed relatively higher perfusion in prefrontal regions, in the limbic lobe, and in the areas involved in the DMN, namely the posterior cingulate cortex/precuneus, temporo-parietal regions, and medial temporal lobes.

p0445 The increased perfusion in limbic areas has been associated with the highest rate of mood disorders in women, as amygdala and limbic lobe are involved in emotional processing. On the other hand, the relative hyperperfusion in the DMN structures, which was described in young females by some authors (Amen et al., 2017; Jones et al., 1998; Slosman et al., 2001), is difficult to interpret. DMN is a pivotal network in memory functioning, especially in episodic memory retrieval, and is typically affected in AD. Indeed, DMN typically displays hypoperfusion even at MCI stage of AD, in keeping with the FDG PET hypometabolic pattern (Morbelli et al., 2015; Fig. 2). In this setting, it was speculated that the increased estrogen-related perfusion (Krejza et al., 2001) might exert a protective role on DMN in young females.

s0065 Perfusion SPECT sex differences in dementia

p0450 Perfusion SPECT is a useful surrogate marker of neuronal activity and thus it is regarded as a neurodegeneration biomarker. Indeed, patterns of perfusion and brain metabolism closely overlap in conditions of normal brain autoregulation, with more similarities with FDG-PET for ^{99m}Tc-ECD than ^{99m}Tc-HMPAO. However, PET technology allows higher spatial resolution and has thus replaced SPECT, at least in high-income countries.

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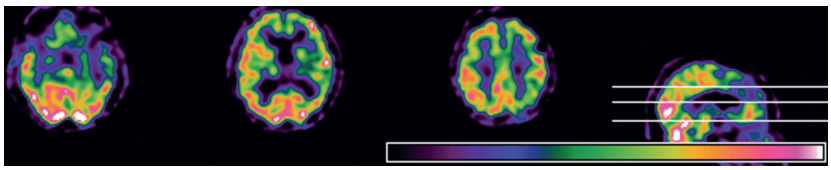

f0015 **FIG. 2**

Perfusion SPECT (^{99m}Tc-HMPAO) shown in three transaxial sections in a 79-year-old woman (5 years of education) with aMCI (mini mental state examination score 23/30, no impairment in autonomy in everyday life activities). The scan shows reduced tracer uptake in the right medial temporal lobe (on *left*), left lateral temporal cortex *(middle)*, and left parietal and posterior cingulate cortex *(right)*.

p0455 Studies specifically focusing on sex-related differences of brain perfusion in AD patients are lacking. In a study of 300 ADD patients, females exhibited greater perfusion heterogeneity and asymmetry, as the left hemisphere was more affected (Ott et al., 2000). On the other hand, a greater hypoperfusion in males with AD was described in the parietal and posterior cingulate (Hanyu et al., 2004; Nitrini et al., 2000) and in anterior and middle cingulate cortices (Callen et al., 2004). In the study by Callen et al. (2004), both ^{99m}Tc-HMPAO SPECT and co-registered MRI were used to map the limbic system in 20 men and 20 women with probable ADD compared to 40 age-, sex-, and education-matched normal controls. In the ADD group, men displayed more regions of hypoperfusion, paralleling brain atrophy, in anterior and middle cingulate regions, whereas in women, hypoperfusion was only evident in the anterior thalamus.

p0460 In a study with (^{123}I-IMP) SPECT in 30 men and 30 women with AD, Hanyu et al. (2004) reported the typical posterior pattern of hypoperfusion in both sexes. Male patients, however, had a more severe hypoperfusion in the parietal lobe and posterior cingulate, consistent with Nitrini et al. (2000); whereas, females displayed reduced perfusion in additional areas, including the medial frontal lobe and medial temporal regions (Fig. 3).

p0465 Men have a more severe decrease of rCBF in the parietooccipital and medial parietal lobes, whereas women have a more severe decrease of rCBF in the lateral, medial, and orbital frontal lobes, and medial and inferior temporal regions. The color of the outer contour corresponds to a Z score of 7.

p0470 Notably, the sex differences in brain perfusion found in healthy adults show similarities with those in AD patients, mostly regarding the lower perfusion in parietal and limbic lobes in men (Amen et al., 2017; Jones et al., 1998; Van Laere et al., 2001). The more severe and widespread relative perfusion changes found in men compared to women, despite the similar cognitive status, might suggest that deeper AD-related brain changes are needed for clinical signs to become apparent in men, a concept reminiscent of the cognitive reserve theory. Moreover, it may indicate that the sensitivity of SPECT for the diagnosis of AD may be somehow flattened in female patients in the earliest stages. Such results also support the hypothesis that AD pathology may express differently in men and women, although the underlying biological mechanisms remain mostly unexplained.

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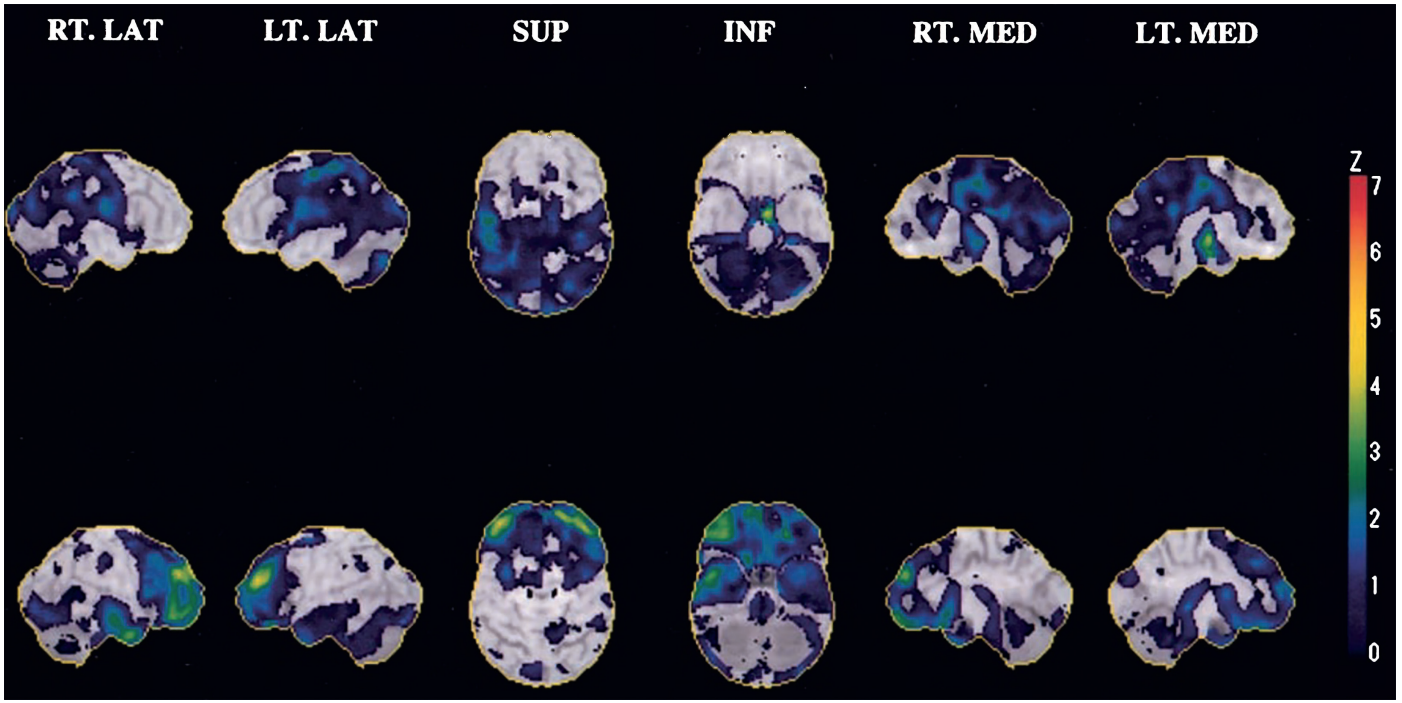

FIG. 3

Statistical maps showing the relative decrease of rCBF in men with AD compared with that in women with AD (top) and in women with AD compared with that in men with AD (bottom).

Reproduced with permission from Hanyu, H., et al. (2004). Differences in regional cerebral blood flow patterns in male versus female patients with Alzheimer disease. American Journal of Neuroradiology, 25(7), 1199–1204.

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p0475 Estrogens may exert a protective role by reducing the cerebrovascular resistance with the consequent increase in brain perfusion (Krejza et al., 2001; Ohkura et al., 1994) and by promoting the synaptogenesis in the entorhinal cortex via an apolipoprotein E-dependent mechanism (Stone et al., 1998; Chapter 2). Hence, the postmenopausal drop of estrogen might explain the higher vulnerability for AD in females (Mosconi, Berti, Guyara-Quinn, et al., 2017; see also Chapter 9).

p0480 Some evidence has suggested a sex effect on brain perfusion due to the APOE ε4 genotype (Lehtovirta et al., 1998). However, according to other authors, neither a correlation between APOE genotype and perfusion patterns (Swartz, Black, & St George-Hyslop, 1999) nor an overall higher female risk of developing AD due to APOE ε4 (Neu et al., 2017) were found. Thus, the genetic role in the sex differences of brain perfusion in AD needs to be further investigated.

p0485 Finally, low education has a similarly harmful effect in both sexes, but has been historically more common in women (see Chapter 12). Hence, the studies that evaluated sex differences in brain perfusion could have been biased by cultural effects, as older women might show significant cognitive deficits even with less severe AD pathology.

s0070 Conclusions

p0490 Sex-related differences in either global or regional brain perfusion have been described in healthy subjects and in AD patients. While higher absolute CBF in women is well established, results are more controversial and heterogeneous regarding regional perfusion distribution. Methodological differences may account for discrepancies, for example, in terms of data analysis (visual versus statistical analysis), as well as others technical issues, such as the considered regions of interest or the tracers, i.e., ^{99m}Tc-HMPAO and ^{99m}Tc-ECD (Nitrini et al., 2000) or ^{123}I-IMP (Hanyu et al., 2004), or whether partial volume-correction was performed (Li et al., 2004).

p0495 Several authors have tried to explain such sex differences, but the underlying biological mechanisms are only partially understood. Hormonal balance, education, and genetics have been proposed as factors influencing brain perfusion and might exert either a protective or an enhancing role in neurodegenerative diseases as well. Investigations concerning sex disparities in terms of brain perfusion are meaningful in understanding the different AD vulnerability and the trajectories of normal or pathological brain aging in men and women. In addition, setting up normal databases for statistical image analysis and interpreting the pathological findings according to sex differences might be paramount in clinical practice and in pharmacological trial design.

s0075 DAT SPECT

p0500 DAT SPECT imaging is a tool for the study of the nigrostriatal dopaminergic system, and is used to confirm nigrostriatal impairment in patients with suspected neurodegenerative parkinsonism and, in the dementia field, for differential diagnosis between AD and DLB. In the current DLB diagnostic criteria, low DAT SBR in basal ganglia is as an indicative biomarker, allowing a diagnosis of probable DLB in the

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presence of one on more core clinical features (McKeith et al., 2017). ^{123}I-FP-CIT SPECT is currently the most studied and available presynaptic radiopharmaceutical for DAT SPECT imaging.

DAT SPECT sex differences in healthy subjects

p0505 In animal models, DAT mRNA measured by in situ hybridization was found to be higher in female compared to male rats. Moreover, early neuroendocrinology studies found a significant positive correlation between estradiol levels and DAT expression, suggesting that sex differences may also be found in humans (Morissette, Biron, & Di Paolo, 1990). Several studies have focused on sex differences in DAT imaging in healthy subjects. A study by Kuikka et al. (1997) investigating 39 healthy subjects with ^{123}I-β-CIT SPECT described higher heterogeneity in women in both the left and right striatum, but no significant differences in average levels between males and females.

p0510 Further studies failed to find significant sex differences in overall striatal DAT availability using ^{123}I-β-CIT-SPECT (Best et al., 2005; Ryding et al., 2004; van Dyck et al., 1995). Moreover, in a small sample of 10 women, no significant ^{123}I-β-CIT-SPECT differences were disclosed between the follicular and the luteal phases of the menstrual cycle (Best et al., 2005). However, other studies showed significant sex differences in basal ganglia DAT SBR using ^{123}I-FP-CIT SPECT or ^{99m}Tc-TRODAT-1 SPECT. In detail, women showed from 2.8% to 16.3% higher striatal DAT binding compared with men (Chen et al., 2013; Eusebio et al., 2012; Lavalaye et al., 2000; Mozley et al., 2001; Staley et al., 2001). One possible explanation of such conflicting results is that these studies were all based on ROI analysis, which could have led to an underestimation of a "sex effect." Indeed, MRI studies have shown that basal ganglia in women have a smaller volume than in men (Gunning-Dixon et al., 1998), thus, possibly leading to an relative increase of DAT density in women compared with men. Therefore, Eusebio et al. (2012) conducted a whole-brain, voxel-based analysis of ^{123}I-FP-CIT-SPECT images (thus without predefined ROI) of 51 healthy subjects, and showed a significantly higher tracer SBR in bilateral caudate, putamen, and opercular cortices in women compared with men. This was the first investigation that also focused on the extra-striatal regions and was followed by another study that again described a higher mean ^{123}I-FP-CIT SBR in the thalamus of healthy women compared with men. Furthermore, mean tracer SBR in the pons were slightly higher in men than in women, but this difference did not reach statistical significance (Koch et al., 2014). However, it should be noted that the ^{123}I-FP-CIT is not selective for DAT, but it has an affinity to the serotonin transporter (Arnaldi et al., 2015), thus the extra-striatal regions uptake likely reflects the serotonergic system activity rather than the dopaminergic one in specific regions.

p0515 In 2013, a study promoted by the European Association of Nuclear Medicine investigated SBR in the basal ganglia using the software BasGan v2 in 122 healthy controls (67 men) from 13 centers across Europe (ENC-DAT). The mean striatal SBR value was higher in women than in men. Moreover, this difference seems to be more evident for those of younger age (Nobili et al., 2013; Fig. 4). Based on the data

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of this study, the following formulas can be used to estimate SBR in a single subject, as functions of age and sex:

$$\text{Caudate SBR}\left(\text{Men}\right) = 6.800 - 0.273 * \text{age} \pm 1.88$$
$$\text{Putamen SBR}\left(\text{Men}\right) = 6.702 - 0.339 * \text{age} \pm 1.77$$
$$\text{Caudate SBR}\left(\text{Women}\right) = 7.232 - 0.273 * \text{age} \pm 1.88$$
$$\text{Putamen SBR}\left(\text{Women}\right) = 7.116 - 0.339 * \text{age} \pm 1.77$$

p0520 The result of the ENC-DAT study has been confirmed in the Japanese population, which is known to have a higher prevalence of a significant polymorphism involving a variable number of tandem repeats in the 3′ untranslated region of SLC6A3 gene coding for the DAT. These carriers have a reduced expression of DAT mRNA and protein. Specifically, in a study conducted in 30 healthy controls, the average SBR in males was lower compared with females in each decade (Yamamoto et al., 2017). The importance of a "sex and age correction" in the evaluation of DAT diagnostic exams was also underlined by Nichols et al. (2018) in 132 patients. In the study, DAT-SPECT data, when adjusted by sex and age, could better distinguish patients with PD and DLB from those with essential tremor compared with unadjusted data.

p0525 ^{18}F-Fluoro-DOPA PET imaging is not a marker of DAT availability, but it is able to investigate presynaptic dopaminergic function by studying the amino acid decarboxylase activity. Studies with ^{18}F-Fluoro-DOPA PET confirmed the results of DAT SPECT studies, by showing that women had significantly higher striatal ^{18}F-Fluoro-DOPA uptake (Ki values) than men, with a more marked difference at caudate level (Laakso et al., 2002).

p0530 Overall, despite some conflicting results, it seems that there is a significant effect of sex on brain DAT availability, with women having higher striatal DAT levels compared with men. However, the physiological basis of this finding remains unknown. As this difference usually mitigates in postmenopausal decades, an effect of estrogen levels on DAT production/availability might be suggested, as demonstrated in animal models, but this hypothesis requires confirmation.

s0085 DAT SPECT sex differences in dementia

p0535 The role of sex in the nigrostriatal dopaminergic system in dementia patients remains poorly understood, and the few studies that investigated sex differences in DAT SPECT in neurodegenerative disorders mainly focus on Parkinson's disease (PD).

p0540 In PD patients a 16% higher ^{123}I-FP-CIT SBR was found in women compared with men at motor symptoms onset, without any differences between the rate of decline of the tracer binding over time (Haaxma et al., 2007). Such difference in striatal DAT SBR seems physiological rather than specifically PD-related and also could explain the known delay of PD motor symptoms onset in women compared to men (Twelves, Perkins, & Counsell, 2003). This is consistent with another ^{123}I-FP-CIT SPECT study in a large PD cohort, which showed no significant sex-diagnosis interaction, thus confirming that the sex difference is not strictly related to PD (Kaasinen et al., 2015).

p0545 Table 2 summarizes the main papers and results of presynaptic dopaminergic imaging dealing with sex differences.

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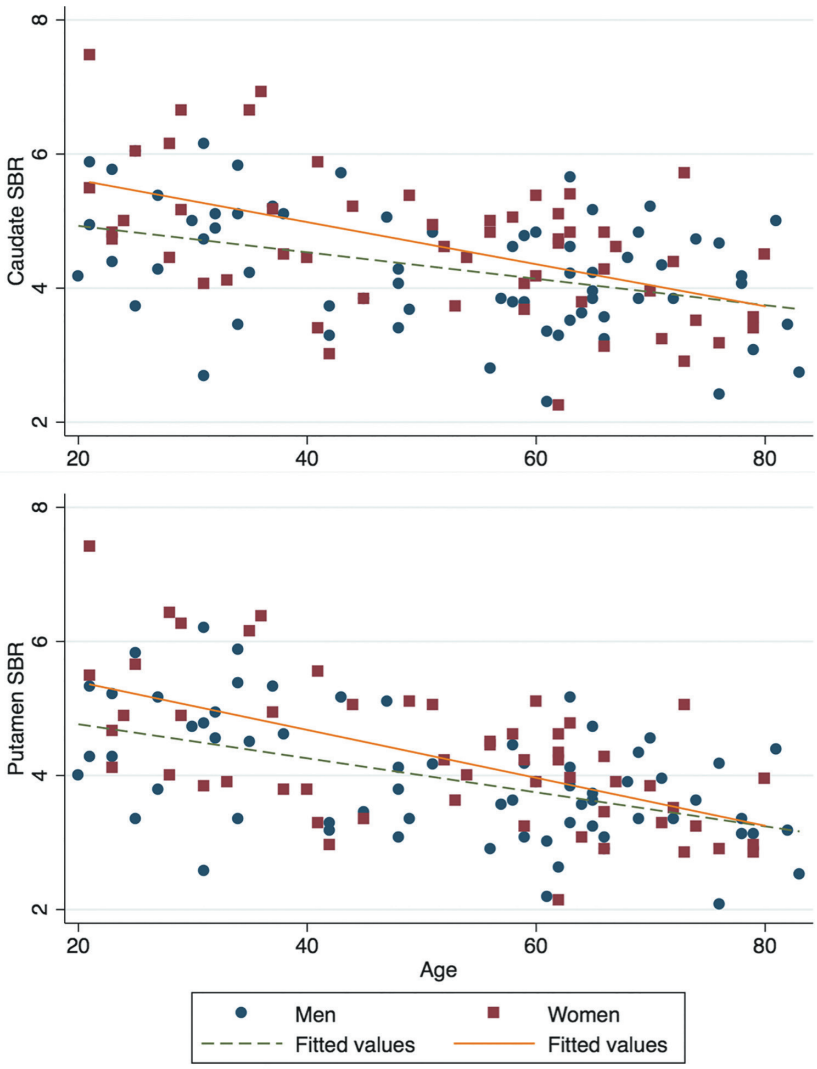

f0025 **FIG. 4**

Bilateral average of Caudate and Putamen SBR in men and women, as a function of age. *Blue circles* represent men and *red squares* represent women. *Green dotted lines* represent fitted values for men and *orange solid lines* represent fitted values for women.

Data from ENC-DAT study Nobili, F., et al. (2013). Automatic semi-quantification of [123I]FP-CIT SPECT scans in healthy volunteers using BasGan version 2: Results from the ENC-DAT database. European Journal of Nuclear Medicine and Molecular Imaging, 40(4), 565–573. doi: 10.1007/s00259-012-2304-8.

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t0015

Table 2 PET and SPECT studies in healthy subjects reporting sex effect on striatal DAT binding.

Difference	*n*	Tracer	Notes	No-difference	*n*	Tracer	Notes
Lavalaye et al. (2000)	45	[123I]FP-CIT		Van Dyck et al. (1995)	28	[123I]β-CIT	
Mozley et al. (2001)	66	[99mTc]TRODAT-1		Kuikka et al. (1997)	39	[123I]β-CIT	Higher heterogeneity in women
Staley et al. (2001)	42	[123I]β-CIT		Ryding et al. (2004)	23	[123I]β-CIT	
Laakso et al. (2002)	35	[18F]FDOPA	Population of premenopausal women	Weng et al. (2004)	40	[99mTc] TRODAT-1	No differences also in 78 PD
Wong, Müller, Kuwabara, Studenski, and Bohnen (2012)	85	[123I]β-CIT	Differences only before 60years	Best et al. (2005)	122	[123I]β-CIT	
Eusebio et al. (2012)	51	[123I]FP-CIT		van Dyck et al. (2005)	96	[123I]β-CIT	
Nobili et al. (2013)	122	[123I]FP-CIT		Jakobson Mo et al. (2013)	51	[123I]FP-CIT	But decline age-related only in women
Chen et al. (2013)	112	[99mTc]TRODAT-1					
Koch et al. (2014)	103	[123I]FP-CIT	Extra-striatal regions				
Kaasinen et al. (2015)	230	[123I]FP-CIT	Confirmed on 231 PD				
Yamamoto et al. (2017)	30	[123I]FP-CIT	Japanese population				

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s0090

FDG-PET

p0550 Several FDG-PET studies have focused on the effect of sex on brain metabolism to highlight possible metabolic differences and corresponding behavioral discrepancies between men and women. The higher brain volume reported in men, together with the greater percentage of white matter (Cosgrove et al., 2007), or the higher resting rCBF values observed in women (Ragland et al., 2000), may theoretically induce inter-sex differences in FDG distribution. Furthermore, hormones such as estrogen are another potential source of variation in the cerebral metabolism of females (Reiman et al., 1996).

s0095

FDG-PET sex differences in healthy subjects

p0555 The impact of sex on brain FDG uptake and its distribution in healthy subjects is highly controversial. Some studies reported no differences in global and regional resting cerebral FDG uptake between males and females in the healthy human brain metabolism (Kim, Kim, & Kim, 2009; Miura et al., 1990). However, they also found that the equivalence in brain FDG consumption between sexes was partially contradicted by the analysis of specific age-related metabolic changes. Indeed, higher degrees of insula hypometabolism was observed in aged men, while a sex-specific, age-related hypometabolism involving the caudate nucleus was reported in females. Therefore, the authors indicated the occurrence of sex-specific cerebral metabolic changes associated with aging documented by FDG uptake distribution.

p0560 On the other hand, several studies have highlighted the occurrence of sex-specific differences in normal brain FDG distribution in resting conditions regardless of aging. In a pivotal study conducted on a cohort of young adults (mean age of 28 years), men showed higher glucose metabolism in temporal-limbic regions and the cerebellum compared to women (Gur et al., 1995). Some years later, Yoshizawa et al. (2014) analyzed 123 FDG-PET scans from healthy adults by means of a statistical parametric mapping (SPM) approach, showing that the overall cerebral glucose metabolism in females was higher than in males. At regional level, glucose metabolism in the medial frontal lobe, inferior parietal lobule, and posterior cingulate was higher in females, while males had a relatively higher tracer uptake in the cerebellum and in the bilateral inferior temporal lobes. As observed by the authors, this difference in tracer uptake was consistent with sexual differentiation in the neuropsychological profile of enrolled patients. Indeed, females outperformed males on verbal learning tests, while males performed better on visuospatial memory tests. These data are also consistent with older neuropsychological studies showing that healthy females are superior to males in language and verbal learning tasks, while males outperform in spatial and motor assignments (Maccoby & Jacklin, 1974). The results of Yoshizawa and colleagues were only partially confirmed by Hu et al. (2013), who also observed higher levels of brain metabolism restricted to the posterior cortex (including posterior-parietal lobes, occipital lobes, bilateral thalami, and hypothalamus) in females compared to males. The authors also noted significant sex differences

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within and between brain glucose metabolic networks. Finally, the existence of a regional heterogeneity in brain glucose consumption was confirmed in a large cohort of 963 healthy subjects (Kakimoto et al., 2016). In particular, the study demonstrated sex-specific hypometabolism in the parietal cortex in males and in the ventrolateral frontal cortex in females. As observed by the authors, this sex-related divergence seems to match the well-known popular saying: "men don't listen, and women can't read maps." Interestingly, these differences decline with advancing age, thus restricting the inter-sex differences to young adulthood.

p0565 Several factors might account for these conflicting results: on the one hand, the difficulty in recruiting a homogenous sample of patients by age, education, and neuropsychological profile; on the other hand, the technical inconsistencies across studies in terms of image analysis and correction (or no correction) procedures, or the difference in brain size and skull thickness between gender groups. These issues might be confounding factors, ultimately affecting the validity of the results (Miura et al., 1990). Finally, some of the inconsistencies might result from neglecting the possible interaction between different covariates, e.g., the sex-by-APOE interaction. Indeed, while several studies have included sex as a covariate in the analyses, they often did not explicitly test either the presence of APOE genotype in recruited patients or the occurrence of a specific APOE-sex interaction. The finding that the APOE effect on AD risk is stronger in women than in men was extensively reported (Farrer et al., 1997; Payami et al., 1996; Poirier et al., 1993). However, only a few studies have assessed the APOE-by-sex interaction on AD biomarkers. For instance, Sampedro et al. (2015) enrolled a cohort of healthy subjects from the ADNI database with available CSF and/or 3T-MRI and/or FDG-PET. As expected, APOE ε4 carriers had lower CSF Aβ1–42 and higher CSF p-tau181p values than noncarriers, but the APOE-by-sex interaction was significant only for brain metabolism. Sex stratification showed that female APOE ε4 carriers presented widespread brain hypometabolism (and cortical thinning) compared to female noncarriers, whereas, male APOE ε4 carriers showed only a small cluster of hypometabolism and regions of cortical thinning compared to male noncarriers (Fig. 5). In other words, women were metabolically more susceptible to the APOE ε4 genotype. Altogether, these findings suggest that sex can markedly modify the interplay between APOE ε4 genotype and brain metabolism.

s0100 ## FDG-PET sex differences in dementia

p0570 If conflicting data are available in the healthy control group, the relationship between sex and brain metabolism is even more complicated in neurodegenerative diseases. Indeed, different protective effects on the brain between males and females might occur, further complicating the interconnection between sex and brain metabolism in pathological conditions. A few available studies have assessed this issue, mainly focusing on the cognitive reserve. Perneczky et al. (2007) suggested a different protective effect of education between men and women. Malpetti et al. (2017) investigated gender differences in brain metabolic activity and resting-state network connectivity

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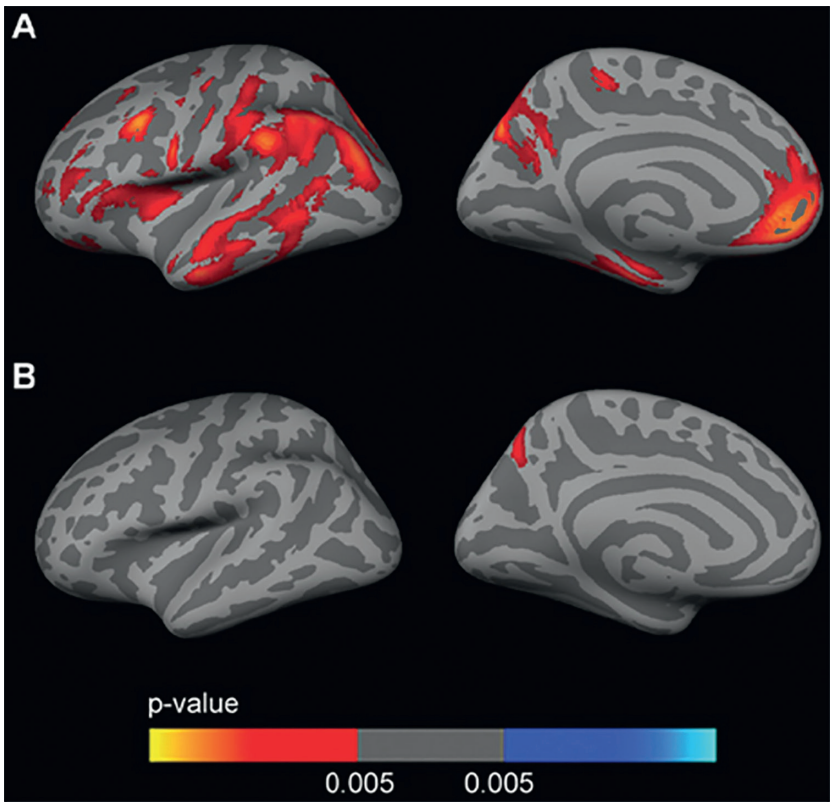

f0030 **FIG. 5**

Sex-stratified FDG analyses in APOE4 carriers and APOE4 noncarriers. Comparison between apolipoprotein E ε4 allele (APOE4) carriers and APOE4 noncarriers ($P < .005$ uncorrected) in females (Panel A) and males (Panel B), co-varied for age and years of education across the lateral and medial views of the cerebral cortex. As shown, women were metabolically more susceptible to APOE4 genotype.

Reproduced from Sampedro, F., et al. (2015). APOE-by-sex interactions on brain structure and metabolism in healthy elderly controls. Oncotarget 6(29), 26663–26674. doi:10.18632/oncotarget.5185.

measured by FDG-PET by also considering the effects of education and occupation in a large dataset of healthy controls 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. Similarly, metabolic connectivity showed greater efficiency in the posterior DMN in males, and in the anterior frontal executive network in females. Based on these data, the authors hypothesized that sex differences in the correlation of education and occupation with brain metabolism in AD might reflect a difference

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strategy in coping with neurodegeneration, which recruits frontal executive neural resources in females. To interpret this divergence between sexes, it is crucial to take into account the socioeconomic factors that characterized the past century, where women had fewer opportunities for higher education and occupational attainment and, instead, were more engaged in familial and social activities. These historical aspects with socially determined gender roles, behaviors, businesses, and attributes are somehow mirrored in the AD samples of these studies. The sex differences might, therefore, be explained by gender-related aspects, including different levels and types of education and occupation and by other sociodemographic factors that might contribute to cognitive strategies and, consequentially, to brain function and networks.

s0105

Amyloid PET

p0575

Sex differences in Aβ burden findings are controversial, and too few imaging studies are available to allow a comprehensive overview of the relationship between sex and amyloid load (Ferretti et al., 2018). Sex-related differences are often found in literature as marginal analyses and only a few studies using in vivo PET analyses in AD subjects have focused on the sex-dependent relationship with amyloid burden as a specific factor.

s0110

Amyloid PET sex differences in healthy subjects

p0580

The similar prevalence of amyloid positivity in male and female normal elderly individuals is a converging piece of evidence from most of the studies (Jack et al., 2015, 2017). Minimal, if any, sex differences have been found in cross-sectional study of the global Aβ burden in clinically normal older adults (Altmann et al., 2014; Buckley et al., 2018; Mielke et al., 2012; Mosconi, Berti, Quinn, et al., 2017). Other results are controversial; for instance, the slightly higher uptake of PiB found in men compared to women in the temporal and occipital lobes by Scheinin et al. (2014) was not confirmed by other reports, which have indicated higher PiB uptake in women than men (Mosconi et al., 2018; Rahman et al., 2020; Vemuri et al., 2017).

s0115

Amyloid PET sex differences in dementia

p0585

A metaanalysis of PET studies revealed no sex differences in amyloid positivity among individuals with subjective cognitive impairment, aMCI, or nonamnestic MCI (Jansen et al., 2015). A similar metaanalysis focused on patients with AD is currently lacking. However, postmortem studies of AD subjects suggest that there is no sex difference in the occurrence or distribution of Aβ plaques (Barnes et al., 2005). Similarly, sex seems to have no impact on CSF Aβ value in patients with AD dementia and prodromal AD or in cognitively normal individuals (Holland et al., 2013; Mattsson et al., 2017). Some authors suggested that sex differences are more likely to follow the onset of Aβ accumulation (Hohman et al., 2018; Vest & Pike,

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2013). This hypothesis has found some traction in a study comparing age, sex, and APOE ε4 effects on memory, brain structure, and amyloid PET (PiB) in cognitively normal individuals aged 30 to 95 years old (Jack et al., 2015).

p0590 One of the few studies directly tackling the sex differences in AD using in vivo imaging biomarkers found a significantly higher load of brain amyloid in the anterior cingulate cortex in men than in women (Cavedo et al., 2018). In this study, despite equal levels of global cognition and after controlling for age, education, and clinical comorbidities, men showed higher amyloid load and neurodegeneration and lower FC in the DMN compared with women. These findings suggest that men may have higher brain resilience to the pathophysiological AD processes. On the same line, Pike et al. (2011) observed that women have more evident cognitive impairment than men even with a smaller amyloid burden, suggesting that they might be more susceptible to AD pathology. This also implies that factors other than the brain amyloid load could contribute to clinical outcome at the individual level, such as the menopausal stage (Mosconi et al., 2018; Mosconi, Berti, Quinn, et al., 2017; Rahman et al., 2020), and family history (Villeneuve et al., 2018). Conversely, in one of the few studies focused on the relative contribution and interaction of several factors in the accumulation of cortical amyloid, the effect of sex was marginally significant ($P = .03$) since women showed higher standardized uptake value ratios (SUVRs) than men (Murphy et al., 2013). On the same line, other findings suggested that, although the sex differences in amyloid PET were not significant, elderly women with AD tended towards a greater β-amyloid load (Buckley et al., 2019; Jack et al., 2015; Oveisgharan et al., 2018).

p0595 Despite the lack of clear significant sex differences in PET at any age—both for amyloid-negative and amyloid-positive subjects—one study found a trend for a sex × amyloid burden interaction ($P = .062$) with episodic memory, and a significant sex × amyloid burden interaction with visuospatial functions (Pike et al., 2011). Interestingly, no association was evident between sex and APOE genotype, as confirmed by different studies (Cavedo et al., 2018; Jack et al., 2015; Jansen et al., 2015). Another study observed amyloid-moderated sex differences in tau signal was largely restricted to the temporal lobe, suggesting AD-specific female vulnerability to temporal lobe tauopathy in the presence of β-amyloid (Buckley et al., 2020) (for a discussion on sex and gender-differences in CSF measures of amyloid pathology, see Chapter 4).

s0120 Conclusions

p0600 Strong evidence of sex difference in concentrations of Aβ is still lacking, and this might be due to a low number of studies specifically investigating this topic. Indeed, in most studies about biomarkers the results are adjusted for age and sex, thereby hindering examination of sex differences. Moreover, methodological issues, namely differences in study design, sample size, and the age of recruited subjects, might account for the discrepancies between studies. Even if controversial, overall, such results might suggest that sex does not mediate the effect of amyloid on the volumetric, metabolic, and functional imaging markers of AD, and thus that the effect of sex seems independent from the amyloid status.

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s0125

Emerging PET modalities

p0605 The ductility of PET technology allows investigation in vivo not only of neurodegeneration, but also of brain chemistry, neuroinflammation, and protein deposition. Hence, in recent years efforts have been dedicated to developing specific tracers able to assess the deposition of pathological proteins other than amyloid (Cosgrove et al., 2007; Schain & Kreisl, 2017).

s0130

Tau PET sex differences in healthy subjects and dementia

p0610 Specific tracers to track tau pathology, such as THK5317, THK5351, AV-1451, and PBB3, have been used in the research setting, both in healthy subjects and in patients with different tauopathies, including AD (Saint-Aubert et al., 2017). Pathological tau is a hallmark of several neurodegenerative diseases. However, various tau isoforms are observed in different neurodegenerative diseases (Spillantini & Goedert, 1998). Normal tau promotes the stability of microtubules in the nervous system, but its pathological hyperphosphorylation leads to the formation of neurofibrillary tangles, which are among the earliest pathophysiological changes in AD, spreading from the entorhinal cortex and hippocampus to the neocortex during the course of the disease (Ziontz et al., 2019). Mounting evidence suggests that women are at higher risk of exhibiting AD pathophysiology, mostly due to differences in the production and the structure of neurofibrillary tangles between sexes (Buckley et al., 2019; Cáceres & González, 2020; Hohman et al., 2018). However, the sex-specific risk of the clinical progression in early AD remains to be fully elucidated.

p0615 Sex differences in Aβ deposition alone have not been reported in older adults, supporting 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 gender on the interplay between amyloid and tau deposition in vivo. Elevated CSF tau levels have been reported in women compared with men as a function of APOE ε4 status and Aβ, and recently, the availability of TAU PET tracers has allowed us to deepen this finding in terms of quantity, timing, and regional deposition of tau with respect to amyloid (Buckley et al., 2019; see also Chapter 4). In the Mayo Clinic Study of Aging, Jack et al. (2017) aimed to evaluate the clinical characteristics and prevalence of each ATN (i.e., amyloidosis/tauopathy/neurodegeneration) profile in cognitively unimpaired individuals. Participants were thus classified according to normal (A−) or abnormal (A+) amyloid by means of amyloid PET, normal (T−), or abnormal (T+) tau using tau PET, and normal (N−), or abnormal (N+) neurodegeneration, or neuronal injury according to cortical thickness by MR imaging. In both men and women, A−T−N− was the most prevalent until age late 70s, but the prevalence of A+T+N+ and A−T+N+ progressively increased from the age of 50 years and was the most prevalent after 80 years. Of note, by the age of 85 years, more than 90% of men and women had at least one abnormal biomarker. As for the sex differences, only a slight prevalence of A−T−N+ was found in men from age 65 to 75 years. Hence, the prevalence of each ATN group and biomarker

abnormality is mostly influenced by age even in individuals who remain cognitively unimpaired over time (Jack et al., 2017).

p0620 Similarly, a study with 18F-AV-1451 TAU 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 (Tosun et al., 2017). Highly associated patterns of greater 18F-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 18F-AV-1451 binding in diffuse cortical regions, namely lateral temporal, parietal, and frontal regions. Conversely, in 54 cognitively normal subjects, higher 18F-AV-1451 retention, and thus tau pathology, was related to older age, male sex, black race, and amyloid positivity, especially in the frontal and parietal white matter and thalamus (Ziontz et al., 2019).

p0625 Finally, the study by Buckley et al. (2019) assessed the association between sex and regional Aβ and tau deposition as measured with 11C-PIB and 18F-AV-1451 PET, respectively, in a large dataset of clinically normal individuals (193 belonging to the Harvard Aging Brain Study and 103 from the ADNI database). In both cohorts, no clear association of sex with regional tau was found, but among those individuals with higher Aβ burden, the females disclosed higher entorhinal cortical tau than the males. In other words, clinically normal older women with higher levels of global Aβ exhibit higher levels of tau burden than men, specifically involving the entorhinal cortex. More recently, the same group examined sex differences in tau-PET signal across the brain, both as a main effect and interaction with global Aβ and APOEε4 carriage in a cohort of 343 clinically normal individuals and 55 MCI individuals (Buckley et al., 2020). The authors observed that women showed higher SUVRs than men, not only in the temporal but also in many extratemporal regions, such as the parietal, middle frontal, lateral occipital, fusiform, supramarginal, cuneus, banks of the superior temporal sulcus, and frontal/temporal pole regions. Of note, many of these regions remained significantly different between the sexes even after adjusting for Aβ status. Higher tau-PET signals in these regions translated to accelerated cognitive decline in women as compared to men.

p0630 Taken together, these findings support a biological substrate underpinning sex-related differences in tau deposition in AD, but further studies in large samples are needed.

s0135 Neurotransmission PET sex differences in healthy subjects and dementia

p0635 The ductility of PET technology and the development of tracers targeting different neurotransmission pathways has allowed us to investigate sex-specific differences in dopaminergic, serotonergic, and GABAergic systems in healthy subjects (Cosgrove et al., 2007). Even though sex differences in AD patients have been poorly

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investigated, some authors have focused on the serotoninergic system, as serotonin (5-HT) is involved in cognition and plays an important role in AD. In particular the study by Parsey et al. (2002) aimed to determine the effects of age, sex, and severity of lifetime aggressive behavior on 5-HT(1A) receptor binding potential in vivo by means of PET with [carbonyl-C-11]WAY-100635, which is a high affinity 5-HT(1A) antagonist. Significantly higher binding potential was evident in females compared with males in the dorsal raphe, amygdala, anterior cingulate, cingulate body, and medial and orbital prefrontal cortex. This is consistent with previous pharmacological studies, in which lower 5-HT(1A) binding was found in males and in more aggressive individuals. As 5-HT receptors, namely 5-HT(2A), were found to play a role in AD, such evidence might have implications for both the etiological basis and therapeutic management of AD patients. For instance, gender-oriented studies in AD patients might suggest the opportunity to selectively manipulate the hormonal system to influence the clinical and neurocognitive course of symptoms related to the serotoninergic system (Versijpt et al., 2003).

s0140

Neuroinflammation PET sex differences in healthy subjects and dementia

p0640 In the last 20 years, PET imaging has also focused on different targets to investigate in vivo neuroinflammation (Schain & Kreisl, 2017). In particular, most radioligands are specific for the 18 kDa TSPO, which is considered a useful marker of neuroinflammation as is it highly expressed in activated microglia and reactive astrocytes in the events of brain injury and inflammation. However, it remains unknown whether age and sex have an effect on neuroinflammation, mostly due to the small sample size of the few studies and the high technical challenges associated with production and analysis of PET TSPO radioligands.

p0645 In a study on 48 healthy subjects by means of TSPO-specific ^{11}C-PBR28 PET, the total tracer distribution volume was found to increase significantly with age in nearly all regions but it was not affected by sex or body mass index (Paul et al., 2019). In a larger database of 140 healthy subjects studied with the same PET tracer, a significant sex difference was revealed in all brain regions, as females showed a higher volume of distribution of the tracer. Moreover, a subgroup analysis revealed a positive correlation between volume distribution and age in all regions in male subjects, whereas age had no effect on TSPO levels in female subjects (Tuisku et al., 2019). Accordingly, although gender-related data obtained with tracers for neuroinflammation in AD patients are still not available, available studies suggest that age and sex can be confounding factors and should be taken into account in future studies (sex differences in the immune system and microglial function are described in Chapter 3).

s0145

Conclusions

p0650 Investigations concerning sex disparities are pivotal to understanding the different vulnerability and the trajectories of normal or pathological brain aging in men and

women, and neuroimaging techniques play an important role in evaluating in vivo those sex-related differences in brain structure and function. A physiological asymmetry of brain volumes and microstructural architecture throughout the lifespan between sexes, but also differences in the patterns and rate of atrophy progression, have been described. Indeed, a higher susceptibility to AD pathology seems to be present in women, mostly due to divergences in the production and the structure of neurofibrillary tangles, as has emerged from tau-specific PET studies. On the other hand, conflicting results have emerged from functional studies in which a complex interaction between sex and neural correlates of brain processes, regional blood flow, and metabolism seem to be underpinned by factors such as hormonal balance, education, and genetics. However, the weight of methodological differences and technical issues is still not negligible. Indeed, differences in the choice of cohorts, study design, equipment, tracers, data analysis, considered region of interest, brain segmentation, and partial volume correction might explain most of the conflicting results.

p0655 In conclusion, there is an urgent need for a more systematic appraisal of sex differences in neuroimaging studies. To set up normal databases for image analysis and to interpret the pathological findings according to the sex differences, rather than considering sex as nuisance factor in biomarker studies, might be of paramount importance in clinical practice and in pharmacological trial design.

s0150 Chapter highlights

u0010 • Conflicting evidence of sex-related differences in brain structure and functioning have been presented, both in normal and pathological brain aging from neuroimaging studies.

u0015 • Methodological and technical issues, as well as differences in biology and environment are crucial factors to be considered.

u0020 • A more systematic approach to sex differences in neuroimaging studies may have a substantial impact on clinical practice and in drug trial design.

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Non-Print Items

Abstract

Several studies have investigated sex differences in morphological and functional neuroimaging in healthy conditions, but few data are available on the specific effect of sex on neuroimaging in dementia and related disorders. Sex is more often considered as a confounding variable than as a variable of interest. Furthermore, especially in the dementia field, the data are drawn from studies designed for other specific aims, and discrepant results are often found due to different equipment, studied cohorts, and analytical methods. Notably, investigating this aspect would be pivotal to better understand how age-related diseases, such as dementia, differentially impact on the main correlates of brain functions in males and females. We review some of the main findings of the literature, highlighting the need for a more systematic appraisal of sex and even gender differences in future neuroimaging studies.

Keywords: Sex, Aging, Dementia, MRI, Brain structure, Brain function, Brain connectivity, SPECT, PET, Brain metabolism

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