Evolving Knowledge of Sex Differences in Brain Structure, Function, and Chemistry

Kelly P. Cosgrove, Carolyn M. Mazure, and Julie K. Staley

Clinical and epidemiologic evidence demonstrates sex differences in the prevalence and course of various psychiatric disorders. Understanding sex-specific brain differences in healthy individuals is a critical first step toward understanding sex-specific expression of psychiatric disorders. Here, we evaluate evidence on sex differences in brain structure, chemistry, and function using imaging methodologies, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single photon emission computed tomography (SPECT), and structural magnetic resonance imaging (MRI) in mentally healthy individuals. MEDLINE searches of English-language literature (1980–November 2006) using the terms sex, gender, PET, SPECT, MRI, fMRI, morphometry, neurochemistry, and neurotransmission were performed to extract relevant sources. The literature suggests that while there are many similarities in brain structure, function, and neurotransmission in healthy men and women, there are important differences that distinguish the male from the female brain. Overall, brain volume is greater in men than women; yet, when controlling for total volume, women have a higher percentage of gray matter and men a higher percentage of white matter. Regional volume differences are less consistent. Global cerebral blood flow is higher in women than in men. Sex-specific differences in dopaminergic, serotonergic, and gamma-aminobutyric acid (GABA)ergic markers indicate that male and female brains are neurochemically distinct. Insight into the etiology of sex differences in the normal living human brain provides an important foundation to delineate the pathophysiological mechanisms underlying sex differences in neuropsychiatric disorders and to guide the development of sex-specific treatments for these devastating brain disorders.

Prior to the 1990s, few studies examined sex differences in symptoms, disease progression, or treatment of psychiatric disorders. Fortunately, in the last decade, research efforts have begun to include the examination of sex differences in studies on brain function and chemistry using animal models and in human studies. In this review, we use the Institute of Medicine definitions of sex and gender. Specifically, "sex" is used to describe distinctions in biology between men and women, whereas "gender is rooted in biology and shaped by environment" and describes one's self-representation as male or female (1).

Sex differences in brain chemistry historically have been evaluated preclinically. For example, they have been examined with autoradiography and histochemistry in animals and postmortem in human brain. A vast preclinical animal literature on sex differences in brain chemistry and structure exists. While these studies provide a necessary foundation for understanding sex differences in brain, it is not yet known how these findings generalize to humans. Postmortem studies also provide useful information but are limited by a variety of methodological factors, such as agonal state at death and postmortem interval. Notably, advances in neuroimaging techniques have afforded the opportunity to evaluate differences in brain structure, function, and chemistry in living men and women throughout the life span. In this review, we evaluate the literature on sex differences in brain structure, chemistry, and function using in vivo imaging methodologies, including single photon emission computed tomography (SPECT), positron emission tomography (PET), and structural and functional magnetic resonance imaging (MRI and fMRI, respec-

tively), as a foundation toward the future review and evaluation of brain sex differences in neuropsychiatric disorders (see 2,3 for additional relevant reviews).

A major biological distinction between women and men is the menstrual cycle, which is associated with variations in female sex steroid hormones over a 28- to 32-day period. Estrogen has been widely studied in the preclinical and clinical literature, especially relating to cognition and neuroprotection (for reviews see 4,5). Estrogen is critically involved in the sexual differentiation of the brain (5) and thus likely contributes to sex differences in brain morphology and neurochemistry. Evaluation of brain structure, function, and chemistry over the course of the menstrual cycle as well as across the life span in women is critical to understanding sex differences in both normal and aberrant behavior. However, in a majority of studies, menstrual cycle stage was not recorded. Given the paucity of information on menstrual cycle effects, this article will review studies that evaluated differences between men and women regardless of whether the menstrual cycle was controlled and will make note of menstrual cycle effects when known. Also, psychosocial factors such as expected gender roles that contribute to differences between men and women may affect sex-specific differences in the brain but are outside the scope of the current review. Finally, in the emerging field of in vivo neuroimaging, there are between-study differences in variables and methodologies that may alter results and interpretations. Here, we review available neuroimaging studies from 1980 to 2006 to evaluate the evidence for the existence of sex differences in the living healthy human brain.

Methods and Materials

MEDLINE searches were conducted of English-language literature (1980–November 2006) using the terms sex, gender, PET, SPECT, MRI, fMRI, morphometry, neurochemistry, and neurotransmission. Bibliographies of articles were reviewed to extract additional relevant sources. Studies that examined or reported analyses on sex differences, regardless of the direction of the finding, were selected. The emphasis was on studies seeking to directly examine a priori the effect of sex on brain structure, function, or chemistry.

From the Division of Psychiatry SPECT Imaging (KPC, JKS), Yale University School of Medicine and the Veterans Affairs Connecticut Healthcare System, and Women's Health Research at Yale (CMM), Yale University School of Medicine, New Haven, Connecticut.

Address reprint requests to Kelly P. Cosgrove, Ph.D., Yale University School of Medicine and the VACHS, 950 Campbell Avenue/116A6, West Haven, CT 06516; E-mail: kelly.cosgrove@yale.edu.

Data Synthesis

Imaging Techniques

Brain structure (also referred to as morphology) has been historically studied using computed tomography (CT). Computed tomography is an imaging technique that combines x-ray images into two-dimensional cross-sectional images of the brain. In CT, small amounts of x-ray radiation are passed through the body, and different tissues in the body absorb the radiation to different extents. Images are obtained in thin slices by x-ray tubes and detectors that circle the body. While CT is frequently used in clinical settings, brain structure is increasingly being examined using magnetic resonance imaging both in clinical and research settings. Magnetic resonance imaging is a noninvasive technique for visualizing brain structures and for differentiating between gray and white matter and cerebrospinal fluid (CSF). Magnetic resonance imaging is superior to CT in that it provides significantly improved resolution for delineating different brain regions compared with CT. Magnetic resonance imaging uses tuned radiofrequency coils to detect radio signals given off by the excited nuclei in the brain as they are returning to equilibrium. The amount of contrast between tissues may be changed by varying the image acquisition sequence depending on the question being asked (see 6 for further technical details on MRI).

Brain function is commonly evaluated by measuring changes in regional brain activity that occur in response to a change in a cognitive or physical task or drug challenge. Regional brain activity is studied by measuring changes in the oxygenation of hemoglobin in blood (blood oxygenation level-dependent [BOLD] signal) using fMRI and also is measured using radiolabeled markers of blood flow and PET or SPECT cameras to detect the photons released during the radioactive decay of the compounds (7). For PET, brain regional activity is measured by monitoring glucose metabolism with [^{18}F]fluorodeoxyglucose (FDG) uptake or by measuring changes in the rates of blood flow using [^{15}O]H$_2$O. For SPECT, blood flow is measured using ^{133}Xe, which is an inert gas that when inhaled is taken up in the blood and distributed throughout the cerebral cortex. Technetium-99m hexamethylpropylene amine oxime ([^{99m}Tc]HMPAO) SPECT provides a measure of both blood flow and metabolism, as it is a highly lipophilic compound with prolonged retention in brain ($t_{1/2} > 6$ hours) that is converted into a hydrophilic compound in brain and hence is effectively trapped with little washout and redistribution over several hours after injection. Technetium-99m ethyl cysteinate dimer (^{99m}Tc-ECD) distributes similarly to HMPAO in the brain with shorter brain retention and greater stability.

Brain chemicals, including receptors and transporters present in low concentrations (nm to pm range) in brain, are measured using "trace" doses of highly specific radioactive drugs (called radiotracers) and imaged using a PET or SPECT camera. Currently, there are only a few sites for which specific radiotracers exist, including the serotonin (5-HT) transporter, 5-HT$_{1A}$ receptor, and 5-HT$_{2A}$ receptor; dopamine (DA) D$_1$ receptors, D$_2$ receptors, and the DA transporter; gamma-aminobutyric acid (GABA)$_A$-benzodiazepine receptors; β$_2$-containing nicotinic acetylcholine receptors; and mu opioid receptors. Tracers are currently under development for other chemical sites in brain including, but not limited to, amyloid, metabotropic glutamate receptors 1 to 5, *N*-methyl-D-aspartate (NMDA) receptors, muscarinic receptors, 5-HT$_{1B}$ receptors, 5-HT$_6$ and 5-HT$_7$ receptors, and cannabinoid receptors that will be available soon to explore sex differences in brain neurochemistry. While a variety of radiotracers and methods exist to examine brain chemistry, relatively few have been used to examine sex differences. The majority of studies reporting sex differences in brain chemistry have focused on serotonin and dopamine systems and emerging evidence also suggests differences in GABA systems. Ideally, a radiotracer for use in vivo in living humans that targets the estrogen receptors will be developed, which will greatly advance our knowledge in the area of sex differences and hormonal influences in psychiatry.

Sex Differences in Brain Structure

It has been long known that women have smaller brain volumes than men, which is explained in part by their smaller stature. Average brain volumes (excluding cerebral spinal fluid, meninges, and other nonbrain tissue) of 1130 cc for women and 1260 cc for men were reported based on normal subjects of European ancestry from a convergence of studies (8–10). Allen *et al.* (8) reported that the whole brain and most major subdivisions (e.g., hemispheres, frontal and temporal lobes, left parietal lobe, insula, and cerebellum) were significantly larger in men compared with women, but the proportional sizes of individual regions in relation to total hemisphere volume were similar. While men have greater brain volume (11), greater CSF volume or lateral ventricles (11–14), and greater sulcal volume (15) compared with women, ventricular volumes (12,16) and intracranial areas corrected for differences in cranial size do not vary between sexes (13).

Gray and white matter volumes also vary by sex (17,18). When covaried for intracranial volume, height, and weight, women have a higher percentage of gray matter, whereas men have a higher percentage of white matter and CSF (15). The gray/white matter ratio was consistently higher in frontal, temporal, parietal, and occipital lobes; cingulate gyrus; and insula in women versus men (9,15,17,19,20). Thicker gray matter in the parietal cortex in women versus men has been consistently shown (17,21,22) and is evident across the life span (23). While the evidence for sex differences in brain morphometry is convincing, there are some studies that contradict these findings. For example, no sex difference was reported when controlling for brain size in total gray matter volume (10,24) and one study reported greater gray matter volume as a percentage of total intracranial volume in men versus women (25).

Sex differences in the human brain are of increasing interest, mostly due to widely held beliefs about sex differences in cognitive abilities, namely better verbal skills in women and better spatial abilities in men. In men, intelligence quotient (IQ) correlates with gray matter volume in the frontal and parietal lobes, whereas in women, IQ correlates with gray matter volume in the frontal lobe and Broca's area, which is involved in language (20), suggesting that men and women use different brain areas to achieve a similar IQ. Thus, while differences in total brain size are less meaningful, size differences in smaller brain structures (19,26,27) are important for normal behaviors and diseases and may reflect the prevalence or course of disease in men and women (Table 1). Importantly, there is high variability between individuals in these studies that likely results from genetic and environmental influences, which are important considerations when evaluating sex differences.

Age-related brain volume loss differs between men and women (see 28 for review). Understanding of sex differences in the developing human brain is rapidly increasing (23,29,30). Young girls have larger hippocampal volume (26,31), whereas the amygdala is larger in boys (14,30). Interestingly, enzymes for

Table 1. Sex Differences in Whole Brain and Selected Brain Regions from in vivo MRI Studies

Sex Difference	Brain Area	Sample Size (M/F)	Age Range	Reference
Men > Women	Total Volume	23/23	22–49	(8)
		10/10	17–37	(26)
		34/35	18–80	(11)
		69/48	19–41	(9)
		79/37	1–80	(10)
	White Matter	40/40	18–45	(15)
		10/10	17–37	(26)
		13/30	24–82	(103)
	CSF	40/40	18–45	(15)
		25/39	18–64	(12)
	Total Corpus Callosum	23/23	22–49	(8)
	Cerebellum	77/113	18–81	(104)
		48/49	15–69	(22)
	Pons	77/113	18–81	(104)
	Caudate	17/12	18–78	(105)
	Amygdala	27/21	25–52	(19)
	Hypothalamus	27/21	25–52	(19)
	Frontomedial Cortex	27/21	25–52	(19)
Women > Men	Gray Matter	40/40	18–45	(15)
		43/17	22–43	(106)
	Caudate	10/10	17–37	(26)
	Hippocampus	10/10	17–37	(26)
	Frontoorbital Cortex	27/21	25–52	(19)
		57/59	18–49	(107)
	Superior Frontal and Lingual Gyri	27/21	25–52	(19)
Men = Women	Pons	51/49	20–85	(108)
	Hippocampus	39/41	18–42	(109)
		57/59	18–49	(107)
	Thalamus	32/25	21–82	(27)
		51/49	20–85	(108)
	Amygdala	57/59	18–49	(107)

These are findings from hypothesis-driven studies on sex differences in brain morphology with MRI selected from over 75 studies. All references controlled for total brain volume.

CSF, cerebrospinal fluid; F, female; M, male; MRI, magnetic resonance imaging.

estrogen synthesis (32) and estrogen receptor messenger RNA (mRNA) have been localized to the hippocampus (33,34), whereas androgen receptors are more prevalent in the amygdala (35) (see 36 for further discussion on estrogen receptor distribution and the relationship to psychiatry). In adult men, volume loss in whole brain, frontal, and temporal lobes increases with age, whereas in women, volume loss in hippocampus and parietal lobes increases with age (37). In adult men and women, global gray matter decreases linearly with age with a steeper decline in men (24,38), a finding that has been confirmed postmortem (39). The reasons for these differences are not clear but may be related to the female sex steroids. There have been no studies evaluating the female sex steroids estrogen and progesterone and their receptor systems in the living human brain because the tools are currently unavailable. These questions will be addressed when PET or SPECT radioligands with specificity for estrogen, progesterone, and androgen receptors are developed. Until the role of these important steroid hormones are understood in the living human brain, it is important that control subjects are well matched to the patient population by sex and by age. Since many brain disorders are associated with volume differences in regional brain structures, understanding the influences of sex along with age-specific developmental changes in sex steroid hormones, such as during puberty and menopause, are important. The relationship between regional brain volumes and the underlying neurochemical milieu in the healthy brain provides the crucial basis for understanding the pathophysiological mechanisms of neuropsychiatric disorders.

Sex Differences in Brain Function

A majority of studies have demonstrated that women consistently have higher global cerebral blood flow (CBF) compared with men during rest (40,41) and cognitive activity (41–45) regardless of the brain imaging modality (Table 2). Consistent with the findings of sex differences in cerebral blood flow, cerebral metabolic rate of glucose utilization (CMRglu) tends to be higher in women versus men (46), particularly in the orbital frontal area (47), although not consistently (48–50). However, global CMRglu may be inversely correlated with brain size such that individuals with smaller brains have higher CMRglu (48,51), effectively negating sex differences in metabolism. Regional CMRglu varied significantly with menstrual cycle phase, suggesting that there are acute hormonal effects on brain glucose metabolism (52). These findings cast doubt on the interpretations of studies that did not control for menstrual cycle phase or hormone levels and highlight the importance for future studies to control biological parameters known to affect cerebral blood flow, such as the menstrual cycle.

The direct implications of sex differences in global cerebral blood flow on psychiatric disorders are unclear; however, increased blood flow in the brains of women may lead to a better distribution of psychotropic drugs in the brain. There is some

Table 2. Data on Sex Differences in Brain Perfusion Studies in Healthy Men and Women

Ligand	Sample Size (M/F)	Age Range	Main Finding	Reference
[^{99m}Tc]ECD	43/46	20–81	M > F cerebellum, L anterior temporal and orbitofrontal cortex F > M parietal cortex	(103)
[^{99m}Tc]ECD	24/15	45–59	F > M in R cerebellum	(104)
[^{99m}Tc]HMPAO	20/25	46–60	F > M in R cerebellum	(104)
[^{99m}Tc]HMPAO	67/85	50–92	F > M global perfusion, corpus callosum, inferior temporal and inferior parietal areas	(42)
^{133}Xe	30/32	18–26	F > M CBF	(41)
^{133}Xe			F > M CBF	(43)
^{133}Xe	56/41	20–59	F > M CBF	(40)
^{123}I	7/7	20–30	F > M CBF	(45)
[^{18}F]FDG	22/22	47–80	M > F R insula, middle temporal gyrus, medial frontal lobe F > M hypothalamus, cerebellum M = F global metabolism	(105)
[^{18}F]FDG	15/13	36–52	F > M cerebellum	(106)
[^{18}F]FDG	15/13	36–52	M = F global metabolism	(106)
[^{15}O]H$_2$O	8/6	20–35	F > M CBF	(44)
[^{18}F]FDG	37/24	20–34	M = F global metabolism M > F cerebellum, temporal and cingulate regions	(107)
[^{18}F]FDG	21/18	19–35	F > M CMRglu F > M orbital frontal area	(47)
[^{18}F]FDG	18/15	21–38	M = F global metabolism	(49)
[^{18}F]FDG	29/29	21–81	M = F global metabolism	(51)
[^{18}F]FDG	7/7	25–39	F > M CMRglu	(46)
[^{18}F]Deoxyglucose	47/33	18–67	M = F global metabolism	(48)
[^{18}F]FDG	17/23	18–78	M = F global metabolism	(50)

Studies using ^{99m}Tc, ^{133}Xe, and ^{123}I are SPECT, whereas the ligands ^{18}F and ^{15}O are for PET.

CBF, cerebral blood flow; CMRglu, cerebral metabolic rate of glucose utilization; F, female; [^{18}F]FDG, 18F-fluorode-oxyglucose; ^{123}I, iodine-123; M, male; [^{15}O]H$_2$O, oxygen-15 labeled water; PET, positron emission tomography; ROI, region of interest; SPECT, single photon emission computed tomography; SPM, statistical parametric mapping; SVD, singular value decomposition; [^{99m}Tc]ECD, technetium-99m ethyl cysteinate dimer; [^{99m}Tc]HMPAO, technetium-99m hexamethylpropylene amine oxime; ^{133}Xe, xenon-133.

evidence in postmenopausal women that estrogen increases regional cerebral blood flow (53,54); thus, estrogen may account for some of the variability in blood flow and metabolism between men and women. These differences may explain why some drugs are more effective for treating neuropsychiatric disorders in women versus men (55).

Hormones may modulate arousal circuitry in women. Circulating estrogen has been shown to reduce arousal in women via the hypothalamic-pituitary-adrenal axis (56). However, postmenopausal women had decreased arousal compared with premenopausal women in response to erotic videos, which was reversed with the administration of estradiol (57). Men outperformed women (in the early follicular phase of the menstrual cycle when estrogen and progesterone levels are relatively low) at a task requiring response inhibition to obvious versus less obvious stimuli; however, no sex differences in neural activation were associated with different performance levels (58). A similar study determined that sex differences in performance on verbal and spatial cognitive tasks were not significantly related to endogenous hormone levels in men or in women during the early follicular phase of the menstrual cycle (59). This suggests that individual performance level may have a greater impact on brain activation patterns than sex and that, in some studies, high individual variability in performance on cognitive tasks may preclude meaningful findings of sex differences. However, even when men and women are equally successful at a performance task, sex differences have been noted (60,61).

Sex Differences in Brain Chemistry

Serotonin. There is a wealth of preclinical and clinical evidence supporting sex differences in serotonin neurotransmission (62). Whole blood 5-HT levels are higher in women compared with men (63), which appears to be genetically determined (64), and men synthesize serotonin significantly faster than women (65). Serotonin functions to coordinate complex sensory and motor patterns during a variety of behavioral states and is implicated in the pathology of mood disorders, sleep and eating disorders, and schizophrenia. Sex differences in 5-HT function may underlie the known gender difference (women > men) in the prevalence of depression (66) and may impact pharmacological treatments that target 5-HT neurotransmission. Healthy women have higher 5-HT transporter availability in the diencephalon and brainstem compared with men (67) and 5-HT transporters are selectively decreased in an age-specific manner in depressed women but not in depressed men (55). Since the 5-HT transporter functions to regulate 5-HT neurotransmission, these findings suggest that baseline 5-HT function may be higher in women versus men and that dysregulation of this function in young depressed women may explain in part a unique, sex-specific pathophysiological mechanism underlying depressed
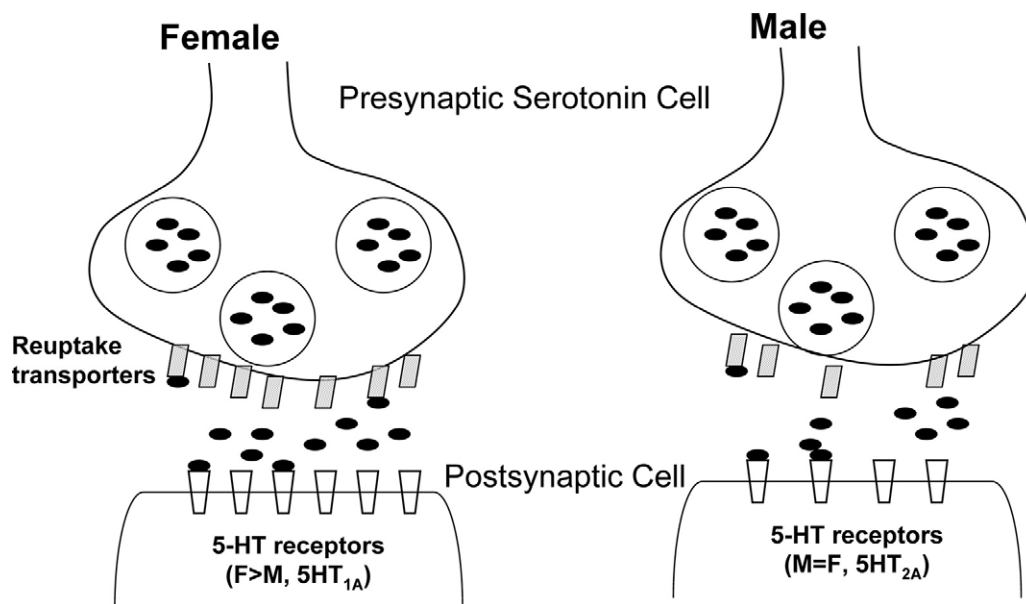
Figure 1. Proposed sex differences in a 5-HT synapse, with higher 5-HT reuptake transporters, neurotransmission, and $5HT_{1A}$ receptors in women versus men. 5-HT, serotonin.

mood in young women (55) (Figure 1). It has been suggested that young women may be more responsive to selective serotonin reuptake inhibitors (SSRIs) versus tricyclic antidepressants compared with older women and men (68). Indeed, in a placebo-controlled study, women receiving estrogen (vs. placebo) had an accelerated response to sertraline treatment (69). This is especially important as many antidepressants have a delayed onset of action (up to several weeks) that is not well understood.

Women have higher $5\text{-}HT_{1A}$ receptor numbers than men in certain brain regions (70), a finding that has been both confirmed (71) and unsubstantiated (72) in previous postmortem studies. While a sex difference in $5\text{-}HT_{2A}$ receptors has been reported (73), there is substantial evidence supporting no difference in receptor levels (74,75) but a difference in radiotracer metabolism that may give the appearance of higher $5\text{-}HT_2$ receptor number (74). Interestingly, studies on the effects of exogenous sex steroids in postmenopausal women have demonstrated higher $5HT_{2A}$ binding throughout the cerebral cortex in women treated with estradiol plus progesterone replacement (76) and higher $5HT_{2A}$ receptors in the right prefrontal cortex of postmenopausal women receiving estrogen therapy (77). Additional clinical studies in premenopausal women that take into account fluctuating hormones and radiotracer metabolism are needed to determine the mechanism by which hormones regulate the receptor and to determine implications (e.g., the effect of hormones on psychotropic medication such as SSRIs) for psychiatric disorders.

Dopamine. Dopaminergic function is also enhanced in women compared to men. Dopamine is important for reward processes including the reinforcing effects of most drugs of abuse and has been implicated in a variety of neuropsychiatric disorders including Parkinson's disease, which is more prevalent in men than women, and schizophrenia, for which sex differences exist in the onset and course of the disorder. Amphetamine-induced DA release in the right globus pallidus and right inferior frontal gyrus was higher in women compared with men (78). The DA transporter, which functions to regulate synaptic DA availability, is higher in women compared with men

(67,79,80). The lack of difference between sexes in one study may be due to the large age range and inclusion of postmenopausal women (81). Dopamine transporter availability does not appear to differ by menstrual cycle phase and fluctuating gonadal hormones (82).

Premenopausal women have higher striatal presynaptic DA synthesis than age-matched men (83). However, sex differences in D_2 receptors are inconsistent (84,85) (Table 3). The D_2 receptor availability may vary with fluctuations in sex steroid hormones across the menstrual cycle (86), although the finding has not been confirmed (87). Larger sample sizes and repeated measures over the menstrual cycle are necessary to address this question in healthy living human subjects. Fluctuations in hormones in healthy premenopausal women may lead to larger variability in outcome measures compared with men and to postmenopausal women and, consequently, may preclude findings of sex differences. Together, these studies suggest that healthy women may have higher presynaptic dopaminergic tone in striatum and higher extrastriatal DA receptor density and availability compared with men. These results have implications for the many disease states in psychiatry, such as schizophrenia, that are associated with disturbances in DA neurotransmission and show differences by sex in rate and course. Specifically, higher dopaminergic tone in women may protect against the development of schizophrenia, alcoholism, and other diseases with established disturbances in DA function. In adults, alcoholism affects twice as many men as women and many studies have documented sex differences in the prevalence of and symptoms of schizophrenia (88–90). Notably, estrogen may possess neuroprotective qualities in its interaction with the DA system, especially with regard to schizophrenia (91). A second increase in the incidence of schizophrenia in women between the ages of 45 and 54 may be attributed to menopause and decreasing sex steroid hormone levels (92). If women have higher dopaminergic tone, antidopaminergic treatment drugs may be more effective in women versus men (see 93,94 for reviews). In early Parkinson's disease, a robust sex difference in prefrontal monoaminergic activity (95) may be associated with observed clinical sex differ-

Table 3. Summary of Findings on Sex Differences in Brain Chemistry in Healthy Male and Female Subjects

Topic	Ligand	Sample Size (M/F)	Age Range	Brain Region	Main Finding	References
Serotonin Neurotransmission						
5-HT Transporter	[^{123}I]β-CIT	9/12	29–51	Brainstem	F > M	(67)
5-HT$_{1A}$ Receptor	[^{11}C]WAY-100635	13/12	23–57	Amygdala, hippocampus, cingulate, medial and orbital prefrontal cortex	F > M	(70)
5-HT$_{2A}$ Receptor	[^{18}F]altanserin	11/11	23–64	Frontal, cingulate cortex	F > M	(73)
	[^{18}F]altanserin	30/22	21–79	Cortical areas	F = M	(74)
	[^{18}F]setoperone	11/15	19–43	Cortical areas	F = M	(75)
Dopamine Neurotransmission						
DA Transporter	[^{123}I]β-CIT	9/12	29–51	Striatum	F > M	(67)
	[^{123}I]FP-CIT	23/22	18–83	Striatum	F > M	(79)
	TRODAT-1	30/36	18–75	Caudate nucleus	F > M	(80)
	[^{123}I]β-CIT	70/52	18–88	Striatum	F = M	(82)
DA Synthesis	[^{18}F]fluorodopa	23/12	20–60	Caudate, putamen	F > M	(83)
D$_2$ Receptor	[^{11}C]raclopride	33/21	19–82	Striatum	F < M affinity	(84)
	[^{11}C]FLB 457	12/12	33–74	Frontal cortex	F > M binding potential	(85)
GABA Neurotransmission	MRS	11/7	28–49	Occipital cortex	F > M cortical GABA	(99)

[^{123}I]β-CIT, [^{123}I]2beta-carbomethoxy-3beta-(4-iodophenyl)tropane; DA, dopamine; F, female; [^{11}C]FLB 457, [*O*-methyl-^{11}C]-(S)-(-)-5-bromo-*N*-((1-ethyl-2-pyrrolidinyl)methyl)-2,3-dimethoxybenzamide; [^{123}I]FP-CIT, [^{123}I]-2beta- carbometoxy-3beta- (4-iodophenyl)-N- (3-fluoropropyl)nortropane; GABA, gamma-aminobutyric acid; 5-HT, serotonin; M, male; MRS, magnetic resonance spectroscopy; TRODAT-1, 2β-((N,N'-bis(2-mercaptoethyl)ethylene diamino)methyl), 3β-(4-chlorophenyl)tropane; [^{11}C]WAY-100635, [^{11}C](3)H-(N-(2-(1-(4-(2-methoxyphenyl)-1-piperazinyl)ethyl)-N-(2-pyridyl) cyclohexane-carboxamide.

ences, such that men have more severe parkinsonian motor problems than women (96), which DA likely underlies.

Other Receptor Systems. Although not as well studied, differences between men and women have been reported for other receptor systems. These include the cholinergic system, which is involved in memory and cognition; the GABAergic system, the major inhibitory neurotransmitter system involved in mood and memory; and the opioid system, which is involved in pain and reward processes. Imaging the vesicular acetylcholine transporter, a marker of cholinergic synaptic density, demonstrated that women with an early onset of menopause have higher concentrations of cholinergic synaptic terminals (97). Moreover, the length of hormone therapy in postmenopausal women was positively correlated with the concentrations of cholinergic synaptic terminals in cortical areas and the posterior cingulate, suggesting that hormone therapy may positively influence the survival of cholinergic cells in postmenopausal women (97). Women also express higher numbers of cortical muscarinic acetylcholine receptors (98).

Women have higher cortical GABA levels than men as measured with magnetic resonance spectroscopy (MRS) (99). Gamma-aminobutyric acid levels in healthy and unmedicated women with premenstrual dysphoric disorder (PMDD) vary across the menstrual cycle (100) such that cortical GABA levels declined between the follicular and luteal phase in healthy women and increased between the follicular and luteal phase in women with PMDD. This indicates that GABA neurotransmission in tightly regulated by the menstrual cycle.

Higher mu-opioid binding in women versus men has been reported throughout cortical and subcortical regions (101). Additionally, women in the follicular phase of their menstrual cycle appear to have a negative correlation between fluctuating estradiol and mu-opioid receptor availability in the amygdala and hypothalamus as measured with [^{11}C]carfentanil, such that higher estradiol levels were associated with a lower mu-opioid receptor density (102).

More studies on the effects of menstrual cycle and sex in other major neurochemical systems are seriously needed to establish a foundation of brain neurochemistry necessary for delineating the neurochemical differences between men and women in neuropsychiatric disorders.

Conclusions

The development of MRI, PET, SPECT, fMRI, and MRS has afforded the opportunity to evaluate sex differences in brain morphology and chemistry in the living human brain. A review of the studies using these modalities over the last 26 years suggests that while brain structure, function, and neurochemistry of healthy men and women are similar in many ways, there are important differences. While men have greater overall brain volume than women, relative to total volume, sex-specific regional differences exist. Men have a larger amygdala and hypothalamus, while women have a larger caudate and hippocampus. These regional differences may be related to the distribution of estrogen and androgen receptors. Global cerebral blood flow is consistently higher in women than in men, while global cerebral metabolism is equivalent. Differences in regional blood flow and metabolism are less well understood. Sex differences in the serotonin (5-HT transporter, 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors), dopamine (DA transporter), and GABA (neurotransmitter levels) systems have been documented, with tendencies toward higher numbers in women compared with men. Importantly, these sex differences in brain morphology, function, and neurochemistry likely impact normal and abnormal behavior and may increase vulnerability to certain types of neuropsychiatric disorders.

These sex-specific differences in the healthy brain highlight the need to evaluate sex differences in neuropsychiatric disorders, especially those that differ in prevalence and symptoms between men and women. Unfortunately, many of the studies reported here were incidental findings and were not hypothesis driven and thus often lacked critical variables, such as menstrual cycle phase, menstrual status (e.g., perimenopausal, menopausal), and hormonal contraceptive use, necessary to evaluate differences in brain between men and women in a scientifically meaningful manner.

It is our hope that this review encourages researchers not only to develop more hypothesis-driven research studies to evaluate sex differences in the living human brain but also to collect the necessary information about menstrual cycle status and phase in women to allow a thorough evaluation of the effects of sex on brain function in normal behavior and psychiatric disorders. Improving our knowledge about sex differences in the living human brain will enhance our ability to develop sex-specific treatments for neuropsychiatric brain disorders.

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