Gender differences in human brain

BY

Amani alabdali

Prof. Hanan Ali Prof. Soad shaker

King Abdul-Aziz University

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Abstract:

In this article the difference between the sexes, knowledge of the anatomy and physiology of the brain and then the . comparison between them . The aim of this article, at first know the differences or natural variations in both sexes of women and men. Through the results, we can build the foundation of medical sciences, such as neurology, psychology, anatomy and physiology And the discovery of more effective treatments, especially in the case of diseases that vary in intensity between the sexes. Thus, it was found that there are differences in structure, function and chemistry. With some examples of the disease include or cases differ in the ratio between the sexes. And science progress has been made recently in our understanding of these differences and the implications on the mental diseases such as Alzheimer's, depression, schizophrenia and suicide.

Key words: Mind - Distinction – Sex – Senility - Illness

Introduction:

Everyone knows that the brain is the main engine of the individual, and each engine has structure, function, mechanism.

It's also no secret that male and female are different-very different. The differences between genders, however, extend beyond what the eye can see. Scientists generally study four primary areas of difference in male and female brains: processing, chemistry, structure, and activity. The differences between male

and female brains in these areas show up all over the world, but scientists also have discovered exceptions to every so-called gender rule. **(jantz.,2014)**

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. **(Cahill L.,2006).**

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 lifespan. 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, respectively), as a foundation towards the future review and evaluation of brain sex differences in neuropsychiatric disorders **(Arnold et al.,2004)**

Brain anatomy:

The brain serves many important functions. It gives meaning to things that happen in the world surrounding us. Through the five senses of sight, smell, hearing, touch and taste, the brain receives messages, often many at the same time.

The brain controls thoughts, memory and speech, arm and leg movements, and the function of many organs within the body. It also determines how people respond to stressful situations (i.e.

writing of an exam, loss of a job, birth of a child, illness, etc.) by regulating heart and breathing rates. The brain is an organized structure, divided into many components that serve specific and important functions. The weight of the brain changes from birth through adulthood. At birth, the average brain weighs about one pound, and grows to about two pounds during childhood. The average weight of an adult female brain is about 2.7 pounds, while the brain of an adult male weighs about three pounds. **(www.aans.org)**

The brain is divided into sections. These sections include the cerebrum, the cerebellum, the diencephalon, and the brainstem.

Each of these parts is responsible for certain portions of the brain's overall job. The larger parts are, in turn, divided into smaller areas that handle smaller portions of the work. Different areas often share responsibility for the same task. **(www.healthline.com)**

The Cerebrum: **[figure 1]** The cerebrum or cortex is the largest part of the human brain, associated with higher brain function such as thought and action. The cerebral cortex is divided into four sections, called "lobes": the frontal lobe, parietal lobe, occipital lobe, and temporal lobe. Here is a visual representation of the cortex:

Frontal Lobe- associated with reasoning, planning, parts of speech, movement, emotions, and problem solving Parietal Lobe- associated with movement, orientation, recognition, perception of stimuli Occipital Lobe- associated with visual processing Temporal Lobe- associated with perception and recognition of auditory stimuli, memory, and speech.

Note that the cerebral cortex is highly wrinkled. Essentially this makes the brain more efficient, because it can increase the surface area of the brain and the amount of neurons within it. We will

discuss the relevance of the degree of cortical folding (or gyrencephalization) later.

A deep furrow divides the cerebrum into two halves, known as the left and right hemispheres. The two hemispheres look mostly symmetrical yet it has been shown that each side functions slightly different than the other. Sometimes the right hemisphere is associated with creativity and the left hemispheres is associated with logic abilities. The corpus callosum is a bundle of axons which connects these two hemispheres.

Nerve cells make up the gray surface of the cerebrum which is a little thicker than your thumb. White nerve fibers underneath carry signals between the nerve cells and other parts of the brain and body. **(serendip.brynmawr.edu)**

The cerebellum is (figure 2) located behind the top part of the brain stem (where the spinal cord meets the brain) and is made of two hemispheres (halves).

The cerebellum receives information from the sensory systems, the spinal cord, and other parts of the brain and then regulates motor movements. The cerebellum coordinates voluntary movements such as posture, balance, coordination, and speech, resulting in smooth and balanced muscular activity. It is also important for learning motor behaviors.

It is a relatively small portion of the brain -- about ten percent of the total weight, but it contains roughly half of the brain's neurons, specialized cells that transmit information via electrical signals.

The cerebellum is not unique to humans. Evolutionarily speaking, it is an older portion of the brain. It is present in animals that scientists believe existed before humans. **(www.healthline.com)**

The functions the brain stem governs include respiration, blood pressure, some reflexes, and the changes that happen in the body during what is called the “fight or flight” response. The brain

stem is also divided into several distinct sections: the midbrain, pons, and medulla oblongata.

The diencephalon is inside the cerebrum above the brain stem. Its tasks include sensory function, food intake control, and the body's sleep cycle. As with the other parts of the brain, it is divided into sections. These include the thalamus, hypothalamus, and epithalamus.

The brain is protected from damage by several layers of defenses. Outermost are the bones of the skull. Beneath the skull are the meninges, a series of sturdy membranes that surround the brain and spinal cord. Inside the meninges, the brain is cushioned by fluid. **(www.healthline.com)**

Brain physiology:

Metabolism

Despite weighing only about 3 pounds, the brain consumes as much as 20% of the oxygen and glucose taken in by the body. Nervous tissue in the brain has a very high metabolic rate due to the sheer number of decisions and processes taking place within the brain at any given time. Large volumes of blood must be constantly delivered to the brain in order to maintain proper brain function. Any interruption in the delivery of blood to the brain leads very quickly to dizziness, disorientation, and eventually unconsciousness.

Sensory

The brain receives information about the body's condition and surroundings from all of the sensory receptors in the body. All of this information is fed into sensory areas of the brain, which put this information together to create a perception of the body's internal and external conditions. Some of this sensory information is autonomic sensory information that tells the brain subconsciously about the condition of the body. Body temperature, heart rate, and blood pressure are all autonomic senses that the body receives. Other information is somatic sensory information

that the brain is consciously aware of. Touch, sight, sound, and hearing are all examples of somatic senses.

Motor Control

Our brain directly controls almost all movement in the body. A region of the cerebral cortex known as the motor area sends signals to the skeletal muscles to produce all voluntary movements. The basal nuclei of the cerebrum and gray matter in the brainstem help to control these movements subconsciously and prevent extraneous motions that are undesired. The cerebellum helps with the timing and coordination of these movements during complex motions. Finally, smooth muscle tissue, cardiac muscle tissue, and glands are stimulated by motor outputs of the autonomic regions of the brain.

Processing

Once sensory information has entered the brain the association areas of the brain go to work processing and analyzing this information. Sensory information is combined, evaluated, and compared to prior experiences, providing the brain with an accurate picture of its conditions. The association areas also work to develop plans of action that are sent to the brain's motor regions in order to produce a change in the body through muscles or glands. Association areas also work to create our thoughts, plans, and personality.

Learning and Memory

The brain needs to store many different types of information that it receives from the senses and that it develops through thinking in the association areas. Information in the brain is stored in a few different ways depending on its source and how long it is needed. Our brain maintains short-term memory to keep track of the tasks in which the brain is currently engaged. Short-term memory is believed to consist of a group of neurons that stimulate each other in a loop to keep data in the brain's memory. New information replaces the old information in short-term memory

within a few seconds or minutes, unless the information gets moved to long-term memory.

Long-term memory is stored in the brain by the hippocampus. The hippocampus transfers information from short-term memory to memory-storage regions of the brain, particularly in the cerebral cortex of the temporal lobes. Memory related to motor skills (known as procedural memory) is stored by the cerebellum and basal nuclei.

Homeostasis

The brain acts as the body's control center by maintaining the homeostasis of many diverse functions such as breathing, heart rate, body temperature, and hunger. The brainstem and the hypothalamus are the brain structures most concerned with homeostasis.

In the brainstem, the medulla oblongata contains the cardiovascular center that monitors the levels of dissolved carbon dioxide and oxygen in the blood, along with blood pressure. The cardiovascular center adjusts the heart rate and blood vessel dilation to maintain healthy levels of dissolved gases in the blood and to maintain a healthy blood pressure. The medullary rhythmicity center of the medulla monitors oxygen and carbon dioxide levels in the blood and adjusts the rate of breathing to keep these levels in balance.

The hypothalamus controls the homeostasis of body temperature, blood pressure, sleep, thirst, and hunger. Many autonomic sensory receptors for temperature, pressure, and chemicals feed into the hypothalamus. The hypothalamus processes the sensory information that it receives and sends the output to autonomic effectors in the body such as sweat glands, the heart, and the kidneys.

Sleep

While sleep may seem to be a time of rest for the brain, this organ is extremely active during sleep. The hypothalamus

maintains the body's 24-hour biological clock, known as the circadian clock. When the circadian clock indicates that the time for sleep has arrived, it sends signals to the reticular activating system of the brainstem to reduce its stimulation of the cerebral cortex. Reduction in the stimulation of the cerebral cortex leads to a sense of sleepiness and eventually leads to sleep.

In a state of sleep, the brain stops maintaining consciousness, reduces some of its sensitivity to sensory input, relaxes skeletal muscles, and completes many administrative functions. These administrative functions include the consolidation and storage of memory, dreaming, and development of nervous tissue.

There are two main stages of sleep: rapid eye movement (REM) and non-rapid eye movement (NREM). During REM sleep, the body becomes paralyzed while the eyes move back and forth quickly. Dreaming is common during REM sleep and it is believed that some memories are stored during this phase. NREM sleep is a period of slow eye movement or no eye movement, culminating in a deep sleep of low brain electrical activity. Dreaming during NREM sleep is rare, but memories are still processed and stored during this time.

Reflexes

A reflex is a fast, involuntary reaction to a form of internal or external stimulus. Many reflexes in the body are integrated in the brain, including the pupillary light reflex, coughing, and sneezing. Many reflexes protect the body from harm. For instance, coughing and sneezing clear the airways of the lungs. Other reflexes help the body respond to stimuli, such as adjusting the pupils to bright or dim light. All reflexes happen quickly by bypassing the control centers of the cerebral cortex and integrating in the lower regions of the brain such as the midbrain or limbic system.

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 (CSF), meninges, and other non-brain tissue) of 1,130 cc for females and 1,260 cc for males were reported based on normal subjects of European ancestry from a convergence of studies **(Allen et al.,2002)**

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 to women, but the proportional sizes of individual regions in relation to total hemisphere volume were similar. While men have greater brain volume **(Gur et al,.1991)** greater CSF volume or lateral ventricles **(Giedd et al,.1996),** greater sulcal volume **(Neurosci et al,.1999),** and intracranial areas corrected for differences in cranial size do not vary between sexes **(Agartz et al,.1992).**

Gray and white matter volumes also vary by sex **(Allen et al,.2003).** 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 **(Gur et al,.1991).** The gray/white matter ratio was consistently higher in frontal, temporal, parietal, and occipital lobes, cingulate gyrus, and insula in women versus men, Thicker gray matter in the parietal cortex in women versus men has been consistently shown **(Allen et al,.2003).** and is evident across the life span **(Sowell et al,.2007).**

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 **(Egaas et al,.2000)** and one study reported greater gray matter volume as a percentage of total intracranial volume in men versus women **(Johnsrude et al,.2001).** 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, 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 **(Haier et al,.2005)** 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 **(Filipek et al,.1994)**

Understanding of sex differences in the developing human brain is rapidly increasing **(Sowell et al,.2007).** Young girls have larger hippocampal volume **(Filipek et al ,.1994)** whereas the amygdala is larger in boys **(Giedd et al,.1996),** Interestingly, enzymes for estrogen synthesis and estrogen receptor mRNA have been localized to the hippocampus **(Gundlah et al,.2000)** whereas androgen receptors are more prevalent in the amygdala **(Clark et al,.1988)**

In adult men, volume loss in whole brain, frontal and temporal lobes increase with age, whereas in women, volume loss in hippocampus and parietal lobes increases with age **(Murphy et al,.1996).** In adult men and women, global grey matter decreases linearly with age with a steeper decline in men **(Johnsrude et al,.2001).** a finding that has been confirmed postmortem **(Witelson et al,.2006).**

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 controls 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 **(Kelly et al,.2009)**

Sex Differences in Brain Chemistry

Serotonin

There is a wealth of preclinical and clinical evidence supporting sex differences in serotonin (5-HT) neurotransmission **(Fink et al,.1998).** Whole blood 5-HT levels are higher in women compared to men **(Ortiz et al,.1988)** which appears to be genetically determined **(Weiss et al,.2005),** and men synthesize serotonin significantly faster than women **(Nishizawa et al,.1997)** 5-HT 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 **(Kessler et al,.1993**) and may impact pharmacological treatments that target 5-HT neurotransmission. Healthy women have higher 5-HT transporter availability in the diencephalon and brainstem compared to men **(Staley et al,.2001)** and 5-HT transporters are selectively decreased in an age-specific manner in depressed women but not in depressed men. 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 mood in young women**(Staley et al,.2006) (see Figure 3).** It has been suggested that young women may be more responsive to selective

serotonin reuptake inhibitors versus tricyclic antidepressants compared to older women and men **(Kornstein et al,.2001)**
Indeed, in a placebo-controlled study, women receiving estrogen (vs. placebo) had an accelerated response to sertraline **treatment (Rasgon et al,.2007)** Women have higher 5-HT1A receptor numbers than men in certain brain regions **(Parsey et al,.2002)**, a finding that has been both confirmed **(Arango et al,.1995).**
While a sex difference in 5-HT2A receptors has been reported **(Biver et al,.1996)**, there is substantial evidence supporting no difference in receptor levels **(Adams et al,.2004)**
but a difference in radiotracer metabolism that may give the appearance of higher 5-HT2receptor number **(Adams et al., 2004).**
Interestingly, studies on the effects of exogenous sex steroids in postmenopausal women have demonstrated higher 5HT2A binding throughout the cerebral cortex in women treated with estradiol plus progesterone replacement **(Moses et al,.2000)** and higher 5HT2A receptors in the right prefrontal cortex of postmenopausal women receiving estrogen therapy **(Kugaya et al,.2003)**
Additional clinical studies in premenopausal women, which 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. DA 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 to men **(Riccardi et al,.2006).**

The DA transporter, which functions to regulate synaptic DA availability, is higher in women compared to men **(Staley et al,.2001)**. The lack of difference between sexes in one study may be due to the large age range and inclusion of postmenopausal women **(van Dyck et al,.1995).**

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.

Moreover, the length of hormone therapy in post-menopausal 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 **(Smith et al,.2001).**

Women also express higher numbers of cortical muscarinic acetylcholine receptors **(Yoshida et al,.2000)** Women have higher cortical GABA levels than men as measured with magnetic resonance spectroscopy (MRS) **(Sanacora et al,.1999).**

GABA levels in healthy and unmedicated women with premenstrual dysphoric disorder (PMDD) vary across the menstrual cycle **(Epperson et al,.2002) 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 **(Zubieta et al,.1999).** 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 [11C] carfentanil, such that higher estradiol levels were associated with a lower mu-opioid receptor density **(Smith et al,.1998).**

Sex Differences in Brain Function

Most studies have demonstrated that women consistently have higher global cerebral blood flow (CBF) compared to men during rest and cognitive activity **(Gur et al,.1982)** regardless of the brain imaging modality. 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 **(Baxter et al,.1987)**

particularly in the orbital frontal area **(Andreason et al,.1994)** although not consistently However, global CMRglu may be inversely correlated with brain size such that individuals with smaller brains have higher CMRglu **(Hatazawa et al,.1987),** 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 **(Reiman et al,.1996)**

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 evidence in postmenopausal women that estrogen increases regional cerebral blood flow **(Maki and Resnick,.2000)**

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 **(Staley et al,.2006)**

Hormones may modulate arousal circuitry in women. Circulating estrogen has been shown to reduce arousal in women via the hypothalamic-pituitary-adrenal axis **(Goldstein et al,.2005)** However, postmenopausal women had decreased arousal compared to premenopausal women in response to erotic videos which was reversed with the administration of estradiol **(Archer et al,.2006).**

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 **(Halari and Kumari,.2005).**

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 **(Halari et al,.2005).** 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 **(Frings et al,.2006)**

Aging

Male and female brains are known to develop differently, and even to age differently at the neuroanatomical level. Distinct differences in the male and female brains were noted in the developing fetus between 16-36 weeks of pregnancy. The corpus callosum showed a thicker measurement in female fetuses than in male fetuses suggesting sex dimorphism of human corpus callosum and raise the possibility that prenatal sex hormones may play a role in determining callosal development **(Achiron et al,.2001)**

The brains of men and women are indeed different from birth. Yet the differences are subtle. They might be found only among the synapses in brain structures responsible for specific cognitive abilities **(Witelson et al,.1995)**

(see figure 4) Although the brain and its regions become well differentiated during fetal development, much of the maturational process occurs after birth. MRI analysis of a sample of children with the age range of 7-11 years and compared to adults, suggests earlier maturation of females **(Caviness et al,.1996)** Adolescent brain development appears to be different in males and females. Males age 6-17 years have been shown to display more prominent age-related decreases in gray matter (the part of the brain that allows us to think) and increases in white matter (which transfers information between distant regions) than females.

These changes in brain composition appear to be linked to developmental processes in which nerve cell connections are “pruned” in gray matter and made more efficient (myelinated) in white matter. The more dramatic changes seen in males may be related to the different effects of estrogen and testosterone on the brain **(De Bellis et al,.2001)**

Adolescents’ brains undergo a substantial “pruning” or reduction in gray matter volume during adolescence, which happens about two years earlier in girls, compared to boys. Girls

also reach puberty two years earlier than boys. It is well-established that prefrontal cortex, a part of the brain that relates to planning ahead and knowing the consequences of one's actions, develops earlier in girls compared to boys. Areas of the brain involved in language and fine motor skills (such as handwriting) mature about six years earlier in girls than in boys. It has been concluded that when it comes to mathematics, the brain of a 12-year-old girl resembles that of an 8-year-old boy. Brain volume decreased with age among men, but hardly at all among women. Moreover, those anatomical changes appeared to be closely tied to a gradual decline in mental performance in men. "There is something going on in the male brain that is not going on in the female brain" **(Witelson et al,.1995)**

Age-related reductions in brain volume are sexually dimorphic, lateralized, and region specific. Greater decrements in brain volume occur with age in the frontal lobe than in the temporal lobe and in both regions, it is greater in men than in women **(Cowell et al,.1994)**

Total number of neurons in human neocortex was reduced by 10% over the life span in both sexes, and sex and age were the main determinants of the total number of neurons in neocortex that was determined using a modern stereological method **(Pakkenberg B and Gundersen HJ,.1997)**

Some brain regions, all frontal and temporal cortical regions and some basal ganglia structures show age-associated volume decline and men undergo more accelerated cerebral aging than women. The associations of age with reduced grey matter is generally less prominent in subcortical regions. These are stronger for men than women in the dorsolateral prefrontal cortex **(Haug H,.1987)**

Age-related loss of neurons (18-20%), which was mirrored in volume losses, was found to occur in the primary visual cortex in both sexes in all layers except IV. Males, but not females, also

lost neurons (15%) from layer V/VI of the ventral medial prefrontal cortex and showed an overall decrease in volume of this region. In contrast, dorsal medial prefrontal cortex showed no age-related changes. **(Yates et al,.2008)**

Women are less vulnerable to age related changes in mental abilities, whereas men are particularly susceptible to aging effects on left hemispheric functions **(Gur et al,.1991)**

GENDER AND HEALTH-SEEKING BEHAVIOR

To reduce gender disparities in health, the provision of medical services alone is clearly inadequate. **(Ahmed et al,.2000)** Viewing health through a gender lens necessitates steps to improve women's access, affordability and appropriateness to the health services. Health services for women tend to focus on their reproductive functions, neglecting the needs of women outside the reproductive ages. A lack of female medical personnel is sometimes a barrier for women to utilise healthcare services**.(Paolisso M and Leslie J,.1995**) Poor women fi nd themselves without access to healthcare more often than men from the same social group, even in rich countries like the United States**.(Krieger N and Zierler S,.1995)** In many developing countries, women complain about lack of privacy, confi dentiality and information about options and services available.**(Vlassoff C,.1994)** Another barrier is that medical doctors either attribute different meanings to identical symptoms for presenting male and female patients, **(Malterud K and Okkes I,.1998)** or attribute women's illnesses to psychiatric disorders and prescribe inappropriate medication.

Women's higher mental and physical morbidity have also been hypothesised as being caused by their gender sensitivity to physical cues and to the social acceptability of sick roles for women.**(Sen,.2002)** On the other hand, emotional and cognitive capacities of women themselves may limit their access to healthcare**.(Papanek H,.1998**)

GENDER DIFFERENCES IN MENTAL HEALTH DISORDERS

gender differences in mental disorders extend beyond differences in the rates of various disorders or their differential time of onset or course and include a number of factors that can affect risk or susceptibility، diagnosis, treatment and adjustment to mental disorder **.(Astbury J,.2006)** Gender differences in prevalence of mental disorders vary across age groups. Conduct disorder is the commonest psychiatric disorder in childhood, with three times as many boys as girls being affected**. (Scott S,.1998)** During adolescence، girls have a higher prevalence of depression and eating disorders, and engage more in suicidal ideation and suicide attempts than boys, who are more prone to engage in high risk behaviours and commit suicide more frequently.

(Hawton et al,.2002) In adulthood, women had a higher prevalence of most affective disorders and non-affective psychosis, and men had higher rates of substance use disorders and antisocial personality disorder**. (Linzer et al,.1996)** Men may develop alternative disorders in response to stress, such as antisocial behaviour and alcohol abuse. They may be more likely to have been socialised to express anger or other forms of acting out, whereas women may be more likely to have been socialised to express dysphoria in response to stress. In support of this, studies have shown that expected gender differences in depressive disorders were balanced out by higher male rates of alcohol abuse and drug dependency. **(Kessler et al,.1994)**

Alzheimer's disease (AD)

Alzheimer's disease (AD) is the most prevalent type of dementia, comprising about 60%–70% of all dementia cases. **(Reitz et al,.2011)** Beta-amyloid plaques, neurofibrillary tangles, and neurodegeneration are the hallmark pathologic characteristics of AD. Clinically, AD is a progressive disorder characterized by loss of memory and overall cognitive functioning and by

behavioral symptoms such as apathy, depression, and anxiety; vocabulary and crystallized abilities are preserved. The burden of AD is high, with more than 5 million people currently affected in the US alone. Presently, one in nine people aged 65 and older has AD and more than one in three people aged 85 and older are affected**.(Thies W and Bleiler L. 2013)(see figure 5)** With the increasing age of the population, it is estimated that 14–16 million Americans will be diagnosed with the disease by 2050 unless new treatments to prevent or delay the onset of AD are identified**.(Hebert et al,.2013)**Women are disproportionally affected by AD; they are more likely to become caregivers to AD patients, and are also more likely to develop AD. **(Thies W and Bleiler L. 2013)** In contrast, some studies suggest that men are at greater risk of developing mild cognitive impairment (MCI), a state between the normal cognitive changes associated with aging and early dementia.**(Petersen RC,.2011)** Sex-related differences in the rate of progression after a diagnosis of AD and in the response to treatments have also been reported. In the present review, we will first summarize sex differences in cognitive aging, in the prevalence and incidence of MCI and AD, and in the rate of progression after an AD diagnosis. We will then discuss sex-specific differences in the neuroimaging measures used to study AD. Lastly, we will review potential reasons for the described differences between men and women considering factors both related to biology (sex) and to society and culture (gender)**(Vest RS and Pike CJ,.2013)**

AD The prevalence of AD is significantly higher in women compared to men. Recent estimates suggest that almost two-thirds of the individuals diagnosed with AD are women. **(Hebert et al,.2013).** A reason for the higher prevalence among women may be that they live longer, on average, than men.**(Plassman et al,.2007)** By contrast, incidence studies examining sex differences in AD are equivocal.

The majority of studies conducted in the US have not observed sex differences in the rates of developing AD.**(Rocca et al 1998)** In contrast to these studies, the Cache County Study (Cache County, UT, USA), did report a higher incidence of AD in men than women until age 78, after which women had a higher incidence than men.**(Miech et al,.2005)** Similarly, the Mayo Clinic Study of Aging recently reported that the rate of progression from MCI to AD was similar in men and women aged 70–79, but higher in women than men after age 80.**(Roberts et al,.2013)**Consistent with these last two studies, most studies from European and Asian**(Fratiglioni et al,.2013)** populations have also observed a higher incidence in women after the age of 80–85 years. The reasons for these disparities across studies and geographic regions are not clear. Discrepancies could be due to the use of different diagnostic criteria for AD versus other forms of dementia, such as vascular dementia or Lewy body dementia. The differences may also be due to small sample sizes at the upper range of the age distribution, resulting in unstable estimates. Finally, some differences across Europe, Asia, and North America may be due to social, cultural, and historical events. For example, the impact of World War II and the following Cold War era have been very different across continents. Some of these historical events may have affected men and women differently. Notably, a metaanalysis of 13 studies of populations in the US, Europe, and Asia did show that women were at a significantly greater risk of developing AD, but not other dementias. **(Gao et al,.1998)** Interestingly, women also have a faster rate of cognitive and functional decline after a diagnosis of AD. **(Agüero et al,.1998)**

Depression

At present, the definitions of depressive disorders remain arbitrary because of the absence of clear markers or ‘natural’ thresholds in symptom distribution. The tendency of females to report more depressive symptoms than males might be responsible

for their greater likelihood of meeting criteria for a depressive disorder, even though males and females with depressed mood report similar levels of subjective, social and occupational impairment **(Angst & Dobler-Mikola, 1984).**

Several studies have shown that a female preponderance in rates of depression occurs at low symptom thresholds and becomes more pronounced as the number of symptoms increases. Moreover, similar relationships between levels of depression and occupational impairment have been reported in males and females **(Kessler et al, 1993); (Fennig et al, 1994).**

Measurement procedures

Clinical manifestations of depression differ by gender, with females more often reporting disturbances of appetite and sleep, fatigue, somatic anxiety and hypochondriasis **(Frank et al, 1988); (Young et al, 1990); (Silverstein, 1999).** Thus, the inclusion of gender-dimorphic items in rating scales and diagnostic algorithms may influence depression rates. In fact, gender differences in symptom profile tend to be limited in type and severity, and gender-specific response patterns on rating scales for depression do not seem fully to account for gender differences in levels of depression **(Steer et al, 1989) (Stommel et al, 1993).**

Effect of recall

The issue of temporal stability in reporting mental disorders has received direct attention in several studies, suggesting that passage of time greatly affects accuracy of recall **(Bromet et al, 1986) (Dohrenwend, 1989).** No consistent gender-specific recall patterns have been reported, which might result in an artefactual female preponderance in depression rates. Indeed, females outnumber males even when depressive episodes are assessed over short time periods preceding examination in order to limit the recall bias. Also, there are no significant gender differences in the temporal distribution of depressive episodes, no gender-by-time interaction in the likelihood of reporting depressive symptoms or,

even, a better recall of past episodes in males **(Coryell et al, 1992; Fennig et al, 1994).** A sophisticated approach based on longitudinal design and corroborative witness reports, allowing for partial correction of the tendency of males to forget or minimise previous episodes, found a trend for higher lifetime rates of depression in females at the time of the emergence of gender differences in social roles **(Wilhelm & Parker, 1994); (Wilhelm et al, 1997).**

Course of illness

Gender differences during depression, rather than in its occurrence, might be responsible for the higher prevalence rates among females. Findings are controversial: some studies report higher rates of first-onset depression in females rather than a greater number, or longer duration, of episodes **(Kessler et al, 1993) ;(Wilhelm et al, 1997);** others show a female preponderance in recurrent and chronic depression **(Stefànsson et al, 1994) (Bracke, 1998)**. In any case, the course of illness loses its relevance in computing lifetime prevalence rates, which are consistently higher in females than in males.

Differential mortality in males and females with depression has been also considered but can hardly account for gender differences in depression, since these appear at puberty through adult life and decrease in older cohorts, when the differential effect of mortality is expected to be more pronounced.

Help-seeking and illness behavior

Females are more likely to report physical and psychological symptoms and to seek medical help, although few gender differences have been detected in illness behavior, sick role or defence style **(Spinhoven & Kooiman, 1997); (Gijsbers van Wijk et al, 1999).** Females do not appear to report milder symptoms than males on mental health scales **(Tousignant et al, 1987)** and gender does not seem to predict under-reporting of

psychological symptoms **(Lyness et al, 1995); (Cantwell et al, 1997).**

Depression spectrum

Developmental pathways towards depression may differ by gender, with females suffering from pre-existing anxiety disorders and males experiencing more externalizing disorders, such as alcoholism, antisocial personality and drug misuse. In this regard, the concept of 'depression spectrum disease' has been suggested to identify a specific gene-environment interaction leading to depression in females and alcoholism in males. At present, the evidence suggests that the above-mentioned disorders may share genetic and environmental factors with depression but cannot be considered simply as indirect manifestations of depression **(Cadoret et al, 1996;Kendler et al, 1997; Stallings et al, 1997; Dawson & Grant, 1998).**

Prior depression and anxiety disorders

Females are at greater risk of depression and anxiety disorders at earlier ages than males, and this may partly account for their preponderance in rates of adult depression. Among possible reasons accounting for the greater risk to females and at earlier ages, psychological attributes such as neuroticism may be key determinants, acting as vulnerability factors in response to life events **(Wilhelm et al, 1997).**

Depressive episodes in childhood and adolescence, rather than those at older ages, predict more episodes and longer duration of depression in adult life and provide a strong link between adverse experiences in childhood and adult depression **(Kendler et al, 1993; Parker et al, 1997; Bifulco et al, 1998).** Considerable attention has been devoted to the role of anxiety. Using discrete-time survival models, **(Kessler et al,.1996)** showed that the associations between major depression and first onsets of other mental disorders in the same year as depression were generally strong and persistent over many years, and especially so for

generalised anxiety. More recently, **(Parker et al,.1997)** assessed risk factors differentiating early-onset (that is, at an age younger than 26 years) from late-onset depression and found that anxiety disorders were more likely to precede early-onset than late-onset depression. Finally, **(Breslau et al,.1995**) showed that controlling for prior anxiety disorders reduced by more than 50% the size of the estimated association between gender and depression.

Neurotransmitter systems

Gender differences have been reported in two neurotransmitter systems traditionally implicated in the pathophysiology of depression (namely noradrenalin and serotonin), but their role is still unclear.

The changing rate of plasma levels of 3-methoxy-4-hydroxyphenylglycol with age may differ in males and females with depression. Whereas most females with depression are below or above the reference range according to age, most males with depression lie within reference ranges. By inference, an age-related gender difference in vulnerability to dysregulation of the noradrenalin system has been suggested **(Halbreich & Lumley, 1993).** Similarly, the ageing process of some serotonin systems might be more apparent in females than males, as measured by diurnal variations in imipramine binding and serotonin uptake in platelets. The likelihood of a relationship between food intake, weight gain and depressed mood in females, with brain serotonin being involved in these disturbances of mood and appetite, is intriguing **(Wurtman, 1993).**

Gender difference in suicide

BEHAVIOR

Rates of suicide in most countries, including Denmark, are higher in males than in females. China is one important exception, with very high rates in females, especially young women in rural areas **(Cheng & Lee, 2000).** In recent years, several countries have experienced an increase in suicide rates in males, particularly in the

younger age groups **(Cantor, 2000).** In contrast, suicide rates of females have declined, especially in older women, or remained fairly stable, particularly in the young. This pattern is especially marked in the UK **(Hawton, 1992),** with an overall rise in male rates and a decrease in female rates **(Kelly & Bunting, 1998)**. It suggests that causal factors and, possibly, protective factors have changed in different directions in the two genders. Social factors, especially linked to changes in gender roles, seem the most likely explanation **(Hawton, 1998).**

In contrast to suicides, rates of deliberate self-harm (DSH) are usually higher in females than males. The World Health Organization/EURO Multicentre Study of Suicidal Behavior has demonstrated this pattern throughout countries in Europe, with findings from Helsinki indicating that Finland may be one exception **(Schmidtke et al, 1996).** There has, however, been an increase in rates of DSH in males in some countries. In the UK, this trend has been particularly marked in young males **(Hawton et al, 1997).**

THE NATURE OF SUICIDAL ACTS

The excess rate of DSH in females, plus the stronger association between DSH and suicide in males **(Hawton & Fagg, 1988; Hawton et al, 1998),** suggest that acts of DSH by females are more often based on non-suicidal motivation. In females, the appeal function of DSH, whereby DSH is used to communicate distress or to modify the behavior and reactions of other people, seems more common. In males, DSH is more often associated with greater suicidal intent. It is interesting that in community samples, suicidal ideation is reported far more often by females than males **(Paykel et al, 1974).**

It is well recognized that males tend to use violent means of both suicide and DSH more often than do females. Greater suicidal intent, aggression, knowledge regarding violent means and less

concern about bodily disfigurement, are all likely explanations for the excess of violent suicide in males.

ETIOLOGICAL FACTORS

As the findings of Qin et al indicate, mental illness is the predominant factor found in suicides of both genders. Their data suggest that this is an even greater risk in females. As the authors point out, however, their results are based solely on history of inpatient admission and therefore would have greatly underestimated the full contribution of psychiatric disorders. Their results do not inform us about the nature of the psychiatric illnesses from which their suicides suffered. Psychological autopsy studies clearly demonstrate that affective disorders predominate in suicides of both genders, with comorbidity of personality disorders in 40-50% and other comorbid psychiatric disorders in even more cases **(Henriksson et al, 1993; Foster et al, 1997).**

Substance misuse disorders are, however, generally more common in male suicides **(Murphy, 2000),** and individuals with schizophrenia who kill themselves are also predominantly male **(De Hert & Peuskens, 2000).** Eating disorders, especially anorexia nervosa, carry a high risk of suicide **(Harris & Barraclough, 1997)** and most sufferers are female.

TREATMENT AND PREVENTION

More females than males seek help from general practitioners for mental health problems. This probably explains why the apparent benefits of the educational programmer in detection and treatment of depression for general practitioners on the Swedish island of Gotland were confined to females, more of whom were treated for depression and fewer of whom committed suicide **(Rutz et al, 1999).** While improved detection and management of psychiatric disorder is undoubtedly a key factor in the prevention of suicidal behavior in males as well as females, there is increasing evidence, with the results of Qin et al adding to

this, that alterations in socio-economic conditions are also very relevant to suicide prevention in males.

Suicide prevention strategies understandably include ensuring that clinicians and others likely to encounter people at risk have adequate risk-assessment skills. Although the predictive power of schedules to assist risk assessment is unlikely ever to be substantial **(Goldney, 2000),** the findings of the Danish study raise the question of whether different, if overlapping, risk-assessment schedules are required for the two genders.

Little research attention has been paid to possible gender differences in response to treatment in people at risk of suicidal acts. Clinical impression suggests that compliance of male patients is poorer than that of females. There is also some indication from treatment studies that fewer male than female DSH patients benefit from treatments that they are offered **(Hawton, 1997).** While this may reflect differences in overall attitudes to help, it could also result from the style of therapy that is available. Gender differences in verbal abilities and the reluctance of many males to share emotional problems may make some of the usual talking therapies less attractive to some males, at least initially. Treatment programmes that have more of a practical emphasis, perhaps focused on problem-solving, could prove more successful in engaging males at risk.

Sex differences in the incidence and prevalence of schizophrenia

Disease incidence provides a measure of how many new cases are expected to occur in a given population over a given period of observation. This may be particularly important in disorders such as schizophrenia which are effectively groups of symptoms making up syndromes where up to a third of new cases do not develop into chronic illness **(Jablensky et al,.2000**)

Gradients in the incidence of a disorder across time and place can provide powerful clues to help unravel aetiology. However,

variations in incidence are also well described within or between various populations. This implies that aetiological or risk factors are not uniformly distributed. Sex differences in the incidence, or prevalence, presentation and outcome of illnesses represents an important boundary between risk groups **(Jablensky et al,.2003)**

Most psychiatrists believe that women have a later onset of schizophrenia and a better course of illness than men and that these two phenomena are related to one another, i.e. a worse illness subtype occurs earlier and therefore accounts for the worse prognosis in men; or, later illness onset in women represents a less aggressive illness and allows for better outcome. To a great extent the epidemiological literature encourages such views. Incidence rate ratios tell of rates of disease within specified time frames. They do not reflect the interactions seen in some studies between disease age of onset and gender. Whilst the rate ratio curve for incidence is normally distributed, the curves for age at onset are not. Men show a modal incidence in their early twenties and perhaps a second peak around middle age. Women also show modal onset in their early twenties, but this is a lower frequency, somewhat broader mode and is followed by a more pronounced peak in middle age than men **(Drake et al,.1993)**

Sex and age at onset differences in the clinical presentation and course of non-affective psychosis are key biomarkers and may provide important clues to the aetiology of the disorder. However, conclusions from this literature have been unclear because of small sample sizes, lack of follow up or the bias inherent in non-incident samples **(Castle et al.,1993)**

aged 10–65 was examined for differences in presentation and course of disorder over a 12–18 month follow up period **(Drake et al.,1993).** Admixture analysis suggested underlying distributions with modes in the early 20s and mid 40s for each sex. Men predominated under 43 years and women over 43 **(Figure 1).**

Sex differences in presentation and course of illness

Sex differences in symptom expression have important implications for a number of reasons. For example, symptom presentation and course likely play an important role in determining treatment regimens and understanding sex differences in treatment response. Gender differences in clinical presentation and course have been reported as broadly consistent in different countries and cultures **(Goldstein et al,.1997)**

Recently, Drake et al. (in submission) addressed the relationship between sex, age at onset and symptom presentation and course in a large first episode sample. Consistent with previous studies, early onset cases (women and men) showed worse overall Positive and Negative Symptom Scale (PANSS) score, negative and cognitive symptoms and worse depression-anxiety scores in women. Overall, independent of age at onset, men presented with more negative symptoms and women with more mood symptoms. The association of older age at onset with fewer negative and cognitive symptoms at presentation among women was also consistent with other findings **(Grossman et al,.2008)**

In many studies, women have a better prognosis than men over 2–10 years for many measures **(Angermayer et al,.1990)**

The evidence about how age and gender interact to predict risk of onset and course of illness is less consistent. There are some suggestions of minimal sex differences in age at onset in familial cases **(Leung & Chue,.2000)**

To summarize, at onset older age and affective symptoms predict better course and are associated with female sex in most studies. Young onset, negative and disorganized symptoms predict worse short and medium term outcomes and are in the main associated with male sex. There is no strong evidence that sex or age predict course independently of precisely assessed symptom profile at presentation. On the other hand, often in clinical practice symptoms are not measured precisely, so at presentation sex and

age still have a role as reliable and obvious indicators of likely course. Illness course over the first two years also appears to mediate the effect of sex on long-term outcomes **(Harrison et a2001)**

Sex-specific effects on brain development and sex differences in schizophrenia brain

Animal and human studies clearly demonstrate that normal development of the brain differs in females and males, in large part this is mediated by the regulatory effects of sex steroid hormones and genes on normal sexual differentiation **(Allen & Gorski,.1986)**

The consequences of early insults to, or genetically determined disruption of, brain development are likely to be influenced by such sex-specific developmental effects **(Goldstein et al,.2006)**

In addition to understanding the influence of differences in the healthy female and male brain in the face of disease, an understanding of sex-specific brain abnormalities in schizophrenia may also provide important aetiological clues **(Goldstein et al.,2002)**

Sex differences in the brain in schizophrenia

(see figures 6-7-8) It is increasingly recognized that normal sex differentiated brain development has important implications for understanding sex differences in neurodevelopmental and psychiatric disorder. Schizophrenia is a neurodevelopmental disorder with fetal and early postnatal origins and therefore it is likely that sex differences in brain abnormalities in schizophrenia are initiated at the time of the early sexual differentiation of the brain, that is, during fetal and early postnatal development **(Goldstein & Walder,.2006)**

This premise has support from animal studies demonstrating differential brain abnormalities and behavioral consequences, depending on the timing of the insult during fetal and early

postnatal brain development, for female compared with male animals **(Goldman et al,.1974)**

In men with schizophrenia, MRI and postmortem studies reported larger lateral and third ventricles, and anterior temporal horn; smaller medial temporal volumes, e.g. hippocampus and amygdala, Herschel's gyrus, superior temporal gyrus, and overall smaller frontal and temporal lobe volumes, although findings were not wholly consistent **(Flaum et al.,1995)**

Other abnormalities more likely to be found in men than women with schizophrenia included greater sulcal volume and smaller thalamic size which together suggested somewhat more pervasive brain damage in men than women **(Nopoulos et al.,1997)**

Recently, work has reported region-specific structural brain abnormalities in women dependent on the region assessed. Some have reported smaller volumes of heteromodal association areas among women with schizophrenia than men (e.g. dorsolateral prefrontal cortex and superior temporal gyrus (STG) and orbital prefrontal cortex. Others found smaller volumes of STG in men, and similar abnormalities in women and men in dorsolateral prefrontal cortex **(Gur et al,.2000)**

Studies have demonstrated different differences between women and men with schizophrenia compared with their healthy controls, depending on the prefrontal region assessed **(Goldstein et al.,2002)**

Overall, findings suggest that factors contributing to the normal sexual dimorphisms of developing and adult brain (i.e. early developmental effects of hormones and genes on sexual differentiation) are the same factors that result in sex-specific brain abnormalities in schizophrenia **(Goldstein et al.,2002)**

This is consistent with the timing of premorbid developmental effects implicated in schizophrenia and is supported by some preliminary evidence. **(Szeszko et al,.2002)**

also provide evidence for differential sex effects in brain abnormalities during the premorbid period using MRI and neuropsychological stimuli in first episode patients. This study reported an association between anterior hippocampal volume and executive and motor functioning in male patients, which was not present in women. Moreover, anterior hippocampal volume was more strongly associated with motor functioning among male than female patients. First episode studies are important to allow accurate adjustment for differing age at onset in women and men with schizophrenia (Drake et al., in submission) and to minimize the effect of sex differences in treatment.

Sex differences in treatment

Brain sexual dimorphism and function are associated with sex differentiated distribution of gonadal hormones and their receptors **(McEwen et al,.1983)**
and these include brain regions implicated in the metabolic pathways of psychotropic drugs **(Goldstein et al.,2001)**

However, factors more difficult to measure are also likely to have an important effect on sex differentiated treatment outcomes in schizophrenia. For example, worse outcomes in men may be related to substance abuse, which is more common in men in general, and in men with schizophrenia in particular. The Australian Low Prevalence Study **(Jablensky et al.,2000)**

reported that 36% of men with a psychotic disorder had a history of illicit substance abuse or dependence compared to 16% of women. Comparison rates for the general population were 3% and 1% for men and women, respectively, and these rates are likely underestimated. It is well known that substance abuse has a profound negative effect on illness course; affecting relapse rates and hospitalizations, and being associated with poor social outcomes including housing, criminality and vulnerability to physical diseases such as hepatitis C and HIV. However, the worst outcomes for men have been recorded in the literature antedating

the widespread use of illicit substances in the community. It is unlikely, therefore, that substance abuse is the sole explanation of gender difference in outcomes. Poorer premorbid and social functioning in men with schizophrenia **(Goldstein & Link, 1988)** may exacerbate illness course by making engagement with treatments and services more difficult and by worsening social isolation, which in itself promotes poor functioning.

Sex differences in response to antipsychotic medications may also reflect differential effects of treatment on particular kinds of symptoms and cognitive dysfunctions. For example, recent studies reported superior cognitive improvement in women than men treated with olanzapine, risperidone and clozapine **(Howard et al.,2001)**

Alternatively, some atypical antipsychotics, such as clozapine may work better than typical agents on negative symptoms, which are more likely found in men, or on affective symptoms, which are more likely found in women **(Goldstein & Link, 1988).** Examining sex differences in treatment response to particular symptoms and particular cognitive functions may be more informative than assessing overall change in symptom severity.

Conclusion

The male and the female brains show anatomical, functional and biochemical differences in all stages of life. These differences begin early during development due to a combination of genetic and hormonal events and continue throughout the lifespan of an individual, and are involved in many functions in heath as well as in diseases. Mental and emotional health is extremely important to healthy aging. Sex differences need to be considered in studying brain structure and function. It may raise the possibility of early diagnosis and precise treatment and management for neurological diseases, and may help physicians and scientists to discover new diagnostic tools to explore the brain

differences. Understanding the development of normal brain and differences between the sexes is important for the interpretation of clinical imaging studies.

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