ABSTRACT

The clinical manifestations of MDD are not limited to mood symptoms, but also include a range of cognitive and motor symptoms. Thus, MDD is considered a multifactorial disorder which varies in terms of symptom severity, psychiatric co-morbidity, and clinical course, including recurrence and response to treatment.

In the last years, cognitive impairment in depression has been widely reported. It is clear that cognitive symptoms persist after remission of psychopathological symptoms but little is known about the pathophysiological events linking depression and cognitive impairment. Novel biological, structural and functional neuroimaging techniques have allowed a better definition of this relation. Depression and cognitive dysfunction share a common neuropathological platform in cortical and sub-cortical brain areas implicated in emotional and cognitive processing which may be under the control of genetic and environmental factors.

Cognitive gender differences are still reported, typically with a life-long advantage for men in tasks assessing visuospatial and mathematical abilities, whereas women are often found to outperform men in tasks assessing episodic memory and reading literacy. In other cognitive tasks, such as category fluency and vocabulary, gender differences are typically not observed. Although biologically based explanations for these differences have been proposed, there are also studies indicating that societal factors influence cognitive gender differences.

Keyword:

- Gender
- Differences
- Cognitive
- Dysfunction
- Depressive

INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent and disabling disorder. Several studies showed the high prevalence of the disorder among the population. Community surveys in 14 countries have estimated that the lifetime prevalence of MDD is 12 percent ***(Kessler et al., 2011)***, and the World Health Organization ranks MDD as the 11th greatest cause of disability and mortality in the world. In the United States, MDD ranks second among all diseases and injuries as a cause of disability ***(Murray et al., 2012)***. The disease has also shown high prevalence in certain Arabic-speaking countries ***(Desouky et al., 2015)***.

The relation between MDD and cognitive functions decline has been addressed in previous studies. Only a subset of individuals with MDD (30-40%) reach symptomatic remission after adequate treatment with a first-line antidepressant, and many patients do not reach premorbid levels of psychological functioning ***(Bortolato et al., 2016)***. Major depression was found to have a clinically significant impact on psychomotor speed, declarative memory, working memory, executive functions and attention ***(Papakostas et al., 2014)***. These deficits were found to be significant in both first and recurrent episodes of MDD ***(Lee et al., 2012)***. In one study of 274 subjects with major depression, 71% ranked difficulty concentrating among the top most troubling symptoms ***(Pandina et al., 2009)***.

Another study has linked cognitive dysfunction to the treatment outcome of MDD ***(McLennan & Mathias, 2010)***.

The DSM-5 clearly defines subtypes in major depression such as melancholic and atypical subtypes of MDD. Comparing different cognitive functions across MDD subtypes may help in the identification of neurocognitive patterns according to the specificity of MDD markers. Additionally, few studies aimed at delineating between trait- and state- like cognitive alterations, *i.e*., the deficits occurring exclusively during depressed episodes and those occurring prior, between and after MDD episodes ***(Gonda et al., 2015)***.

On the other hand, the relation between gender difference and severity of cognitive dysfunction in MDD has been addressed in several studies. One study by Sarosi *et al* studied the relationship between gender differences and the severity of cognitive dysfunction in MDD and they found that depressed women showed worse results ***(Sarosi et al., 2008)***. Another study by Cole *et al* found similar results in depressed girls ***(Cole et al., 2009)***. To our knowledge, no studies have addressed the gender difference in cognitive dysfunction among Egyptian patients diagnosed with major depressive disorder. This study aims at identifying the gender difference in cognitive dysfunction in a sample of Egyptian patients with MDD.

Rationale of the Study:

Major depressive disorder is a serious disorder with many health and morbidity-related outcomes. Cognitive impairment related to major depression is a well-known phenomenon. Gender difference in the degree of how depression affects cognition is still controversial. Identifying the effect of gender on the degree of cognitive performance related to major depressive disorder would allow better understanding of the needs of the patients and help in improving the expected outcomes.

Hypothesis:

The alternate hypothesis (H1) states that there is a gender difference in cognitive performance among patients with major depression disorder.

The null hypothesis (H0) states that there is no gender difference in cognitive performance among patients with major depression disorder.

AIM OF THE STUDY

The aim of this study is:

1. To identify the gender differences in cognitive performance among patients with major depressive disorder.
2. To describe the clinical factors associated with cognitive impairment in patients with major depressive disorder.

Chapter 1
BACKGROUND AND GENDER DIFFERENCES IN PROFILE OF SYMPTOMS OF MAJOR DEPRESSIVE DISORDER

Epidemiology and Burden of Disease

Major depressive disorder (MDD) is a common, often severe disorder associated with high rates of non-recovery, recurrence, and comorbidity. Convergent evidence indicates that MDD is the leading cause of disability among patients in both developed and emerging economies ***(McIntyre et al., 2015)***. MDD is an increasingly prevalent public health concern, affecting an estimated 350 million people globally. The 2011 World Mental Health survey of 17 countries found that approximately one in 20 people has experienced a depressive episode. Depressive symptoms have a considerable impact on mortality risk for suicide and cardiovascular and other diseases as well as impaired cognitive and social functioning. In this respect, the burden of disease and the associated economic costs stemming from depression are great ***(Noh et al., 2016)***.

Risk Factors Implicated in MDD

Depression likely represents a group of heterogenous disorders that interact with each others. Thus, it can be considered as the final common pathway of different disease

processes that occur across a biopsychosocial continuum. With putting the biopsychosocial paradigm in context, several factors can contribute to the development of depression symptoms ***(Kendler et al., 2006)***. Those risk factors were found to affect the prevalence of depression in certain population:

1. Gender

The prevalence of depression is approximately two times greater in females compared to males. A cross-national survey was conducted on adult samples of both males and females in different developing (Colombia, Lebanon, Mexico, South Africa and Ukraine) and developed (Belgium, France, Germany, Israel, Italy, Japan, the Netherlands, New Zealand, Spain and the United Stated) countries revealed higher the lifetime prevalence of major depressive disorder in females in comparison to males with Odds Ratio of 1.9 ***(Seedat et al., 2009)***. Several theoretical explanations have been proposed for gender differences in rates of MDD, most of which postulate that women possess biological and psychological vulnerabilities that both increase rates of stressful life events and increase women's likelihood of developing MDD in the face of stressful life events ***(Harkness et al., 2010)***.

2. Race

A survey of United States adults in the community found the lifetime prevalence of major depression for whites was 18

percent, Caribbean blacks was 13 percent, and African Americans was 10 percent. However, major depression was more chronic and associated with greater functional impairment in both African Americans and Caribbean blacks, compared with whites ***(Williams et al., 2007)***.

3. Age

One of the most important reasons for a shift in the presentation of MDD across the life span may be the different underlying biological and psychosocial mechanisms causing depression. Early depression onset has often been shown to be associated with personality (especially neuroticism). In older age, the likelihood for a somatic pathway to depression might increase. Neurobiological factors, such as cerebrovascular disease, neurodegeneration, and inflammation, may impact the response of the brain towards stress, and therefore might increase the susceptibility to depression ***(Schaakxs et al., 2017)***.

4. Social relationships

Perceived marital dissatisfaction and negative marital quality at baseline are risk factors for an incident major depressive episode ***(Overbeek et al., 2006)***. On an empirical level, social isolation and negative social interactions are associated with depression and suicide ***(Holma et al., 2010)***. Meta-analyses have shown that interventions addressing social relationships, including couples therapy and peer support may

be effective in reducing depressive symptoms ***(Pfeiffer et al., 2011)*** based on a conclusion that social relationships may influence mental health outcomes through multiple mechanisms including influence on health-related behaviours, engagement in social activities, transfer and exchange of social support, and access to material resources ***(Teo et al., 2013)***.

5- Familial functioning and childhood adversity

Familial function and childhood adversity are linked to altered Hypothalamic- Pituitary- Adrenal (HPA) Stress responses in humans, which are associated with an increased risk for multiple forms of psychopathology ***(Heim et al., 2001)***. There is evidence for decreased hippocampal glucocorticoid receptor expression in several psychopathological conditions associated with suicide, including schizophrenia and mood disorders ***(Webster et al., 2002)***. Suicide is also strongly associated with a history of childhood abuse and neglect, and this effect is independent of that associated with psychopathology. Thus, environmental events that associate with decreased hippocampal glucocorticoid receptor expression and increased HPA activity enhance the risk of depression and suicide ***(McGowan et al., 2009)***.

6- Parent- Child attachment

Mothers who feel depressed and anxious are, not surprisingly, less positive towards their babies. High levels of

maternal stress are associated with less-sensitive childcare. The children of highly stressed primary caregivers tend to develop more insecure parental attachment which predicts behavioural inhibition in childhood and an increased risk for depression ***(Fish et al., 2004)***.

7- Childhood adversities

Twelve dichotomous childhood adversities (CAs) occurring before age 18 years were identified to have significant association to adult mental disorders including MDD based on previous studies ***(Comijs et al., 2007)***. These CAs include 3 types of interpersonal loss (parental death, parental divorce, and other separation from parents or caregivers), 4 types of parental maladjustment (mental illness, substance abuse, criminality, and violence), 3 types of maltreatment (physical abuse, sexual abuse, and neglect) and 2 other CAs (life-threatening childhood physical illness in the respondent and extreme childhood family economic adversity) ***(Green et al., 2010)***.

Diagnosis of Major Depressive Disorder

According to DSM-5, major depressive disorder is characterized by a history of one or more major depressive episodes and no history of mania or hypomania.

A major depressive episode manifests with five or more of the following symptoms for at least two consecutive weeks,

at least one symptom, must be either depressed mood or loss of interest or pleasure.

1. Loss of interest or pleasure in most or all activities, nearly every day.
2. Insomnia or hypersomnia nearly every day.
3. Significant weight loss or weight gain (eg, 5 percent within a month) or decrease or increase in appetite nearly every day.
4. Psychomotor retardation or agitation nearly every day that is observable by others.
5. Fatigue or low energy, nearly every day.
6. Decreased ability to concentrate, think, or make decisions, n early every day.
7. Thoughts of worthlessness or excessive or inappropriate guilt, nearly every day.
8. Recurrent thoughts of death or suicidal ideation, or a suicide attempt.

In addition, the symptoms cause significant distress or psychological impairment, and are not the direct result of substance or general medical condition. Bereavement does not exclude the diagnosis of a major depressive episode ***(American Psychiatric Association, 2013)***.

MDD Secondary to Medical Diseases

Depression is sometimes caused by another medical illness which is defined in DSM-5 under the title 'Depressive disorder due to another medical condition'. Findings form the history, physical examination and laboratory investigations indicate that the disturbance is caused by a specific medical condition (e.g. adrenal disorders, Huntington disease, hypercortisolism, hypothyroidism, infectious mononucleosis, multiple sclerosis, obstructive sleep apnea, Parkinson disease, systemic lupus erythematosus, traumatic brain injury, vit B12 deficiency and others) ***(American Psychiatric Association, 2013)***.

Diagnosis of MDD due to medical conditions

The following alarming signs should raise the suspicion to a possible medical etiology explaining the depressive symptoms:

1- Severe new onset depression.

2- New onset depression in elderly or in a younger adult with a significant medical condition, acute or chronic.

3- New onset or recurrent depression that cannot be explained by the patient's psychological stressors and circumstances.

4- Treatment resistant depression.

5- Depression with significant coexisting neurocognitive impairment or anxiety ***(American Psychiatric Association, 2013)***.

Pathogenesis and Neurobiology of MDD

On neural circuit level:

The cerebral cortex is a high-level centre of emotional processing and behavioural regulation. Most structural studies have reported abnormal grey matter in MDD patients. The most commonly reported volume reductions are in regions such as the orbitofrontal cortex, anterior cingulate cortex, prefrontal cortex and inferior parietal cortex. Grey matter volume is comprised of cortical thickness and cortical surface area, with surface area having the most influence. Cortical thickness reflects the size, density and arrangement of neurons. The mechanism of cortical thinning is still unclear ***(Zhao et al., 2016)***.

Anhedonia, which is a core symptom of depression, is likely to be explained by neural aberrations which lead to different responses of the functional neurons to rewards ***(Phillips et al., 2015)***. MDD is characterized by decreased responsiveness of fronto-striatal brain regions to rewarding stimuli, including decreased anticipation of forthcoming rewards, reduced pleasure derived from reward presentation, and impaired reward-based learning. The current efforts to

understand the pathophysiology of MDD and treatment response in MDD have recently shifted from focus on brain activation patterns to identifying distributed synchronous brain networks implicated in core symptom dimensions of MDD ***(Kaiser et al., 2015)***.

On cellular metabolism level:

Mechanistic target of rapamycin (mTor) is a protein kinase which functions to regulate cell growth, proliferation, survival, motility, protein synthesis, autophagy and transcription. mTor functions by integrating the input from certain pathways, including branched chain amino acids (BCAAs) (particularly leucine), insulin, and growth factors. A BCAA-induced chronic activation of mTor induces insulin resistance and early beta cell dysfunction. Furthermore, mTor is found to be dysregulated during depressive episodes, and ketamine-induced activation of mTor is associated with a short-term decrease of depressive symptoms in patients suffering from major depression ***(Hay et al., 2004)***.

On genetics level:

Depression is due to multiple small genetic effects as well as environmental influences specific to each individual, with altered gene expression occurring during brain development and in response to stress. Genes probably contribute to vulnerability towards depression that requires

additional non-genetic factors to produce the disorder as the following ***(Sullivan et al., 2000)***.

Epigenetics

Epigenetics refers to changes in chromosomes that do not alter the nucleotide base sequence, but nevertheless change gene expression and thus possibly contribute to episodes of depression. Epigenetic phenomena may involve environmental factors (e.g., early life experiences or chronic stress), which induce changes such as histone acetylation and methylation of deoxyribonucleic acid ***(Dalton et al., 2014)***. As global levels of histone acetylation increase, this adaptation promotes a resilient outcome because histone deacetylase enzyme inhibition in certain brain regions induces antidepressant like responses. Whereas, inhibition of the histone methy-ltranseferase enzyme promotes susceptibility towards depression, and its activation promotes resilience ***(Wilkinson et al., 2009)***. Thus, under chronic social stress, susceptible individuals manifest depression, while resilient ones avoid most of these deleterious symptoms despite being subjected to the same level of stress ***(Vialou et al., 2013)***.

Pharmacogenetics

Genetic factors in patients with major depressive disorder may influence response to antidepressants. Evidence shows that polymorphisms related to expression of certain