Comparison of Cognitive Functions between First & Multi-Episode Bipolar Affective Disorder

Thesis Submitted for partial fulfillment of the M.D. degree in Psychiatry

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List of Abbreviations

5-HIAA	**:**	5-hydroxyindolacetic acid.
5-HT	**:**	Serotonin.
BAD	**:**	Bipolar affective disorder.
cAMP	**:**	Cyclic adenosine monophosphate.
Cho/Cr	**:**	Choline to creatine ratio
CNS	**:**	Central nervous system.
CRF	**:**	Corticotrophin-releasing factor.
CSF	**:**	Cerebrospinal fluid.
CSF	**:**	Cerebrospinal fluid.
CT	**:**	Computed tomography.
DA	**:**	Dopamine.
DALYs	**:**	Disability-adjusted life years.
ECT	**:**	Electroconvulsive therapy
FDR	**:**	First degree relative.
fMRI	**:**	Functional magnetic resonance imaging.
GABA	**:**	Gamma amino butyric acid.
GTP	**:**	Guanosine triphosphate.
HDRS	**:**	Hamilton depression rating scale.
HIV	**:**	Human immunodeficiency virus.
HPA	**:**	Hypothalamic–pituitary–adrenal axis.
HVA	**:**	Homovanillic acid.
ICD-10	**:**	International classification of disease – 10
IQ	**:**	Intelligence quotient.
LTM	**:**	Long term memory
MARCKS	**:**	Myristoylated alanine-rich protein kinase C substrate.
MHPG	**:**	3-methoxy-4-hydroxy-phenylglycol.
MRI	**:**	Magnetic resonance imaging.
NE	**:**	Noradrenalin.

P-31 MRS	**:**	Phosphorus-31 magnetic resonance spectroscopy.
PCr	**:**	Phosphocreatine.
PDE	**:**	Phosphodiester.
PET	**:**	Positron emission tomography.
PIP2	**:**	Platelet membrane.
PIQ	**:**	Performance intelligent quotient.
PKC	**:**	Protein kinase C.
PME	**:**	Phosphomonoester.
SD	**:**	Standard deviation.
Trail A	**:**	Trail making test A.
Trail B	**:**	Trail making test B.
UBOs	**:**	Unidentified bright objects.
VIQ	**:**	Verbal intelligent quotient.
WAIS	**:**	Wechsler adult intelligence scale.
WCST 1	**:**	Wisconsin card sorting test perseveration errors.
WCST 2	**:**	Wisconsin card sorting test category completion.
WMS-R	**:**	Wechsler memory scale revised.
YMRS	**:**	Young Mania-Rating Scale.

Subjects and methods

Study design

Cross sectional study

A. Site of research:

The cases were selected from the out patient clinic in the institute of psychiatry (Ain Shams University). The institute is located in Eastern Cairo, and serves a catchments area of about the third of Greater Cairo. It serves both urban and rural areas, including areas around Greater Cairo as well.

The institute provides mental health services to psychiatric patients through the inpatient department and the outpatient clinics. There are three outpatient general psychiatry clinics (A, B, and C), working four days per week.

Subject's selection:

- Two random samples of BPAD patients; group I consists of 50 patients after single manic episode. Group II consists of 50 patients of multiple bipolar episodes. Both groups were studied while in remission as tested by Hamilton and young mania scales.
- A cross matched Control group selected according to our operational criteria, consisted of 50 Egyptian individuals with no apparent physical or neuropsychiatric morbidity. They were matched for age, sex, and other demographic variables as far as possible with the patient group. They have no family history of any psychiatric disorder. The control group was selected randomly from workers and employers working in Ain Shams University Hospitals.

- Written informed consent will be obtained from the subjects and one of their care givers about the nature and the aim of the study.

B. Operational definition:

Single episode BPAD in remission:

Euthymic patients who had single manic episode while in remission.

Multiple episodes BPAD in remission:

Euthymic bipolar patients who had 3 or more episodes of mania, hypomania, depression or mixed.

C. Inclusion criteria for both patient groups (single episode and multiple episode BPAD in remission) random input:

1. Age ranging from 20 – 40 years.
2. With a diagnosis of BPAD -I. and BPAD-II
3. Patients have to be euthymic (Hamilton depression rating scale < 8; young mania rating scale < 6) and stable.
4. Read and write Arabic language.
5. Average IQ.
6. Patient had been euthymic for at least 3 months prior to inclusion.
7. Have not done ECT in the 3-month period prior to inclusion.

D. Exclusion criteria for both patients groups:

1. Gross neurological disorder.
2. Co-morbid psychiatric disorder.
3. Mental retardation.
4. Substance abuse.
5. Organic cause.

E. Control exclusion criteria:

1. Gross neurological disorder.
2. Mental retardation.
3. Substance abuse.
4. Previous history of psychiatric illness.
5. Have a first degree relative with affective disorder.

Control group is going to be cross matched with the patients groups regarding; age, sex and educational level.

Tools:

1. Semi-structured sheet this sheet will be done by the researcher under supervision of the supervisors including Sociodemographic factors, age, sex, marital status, religion, education level, past history, family history, number of episodes, treatment taken in previous episodes.
2. ICD-10 symptoms chick list for both patient groups **(WHO, 1992).**
3. Hamilton depression rating scale for both patient groups **(Fatim, 1994).**
4. Young mania rating scale for both patient groups **(Young et al., 1978)**.
5. General health questioner for the control group (GHQ) (Goldberg and Hillier, 1979) Arabic version of 28 items GHQ **(Okasha et al, 1988).**
6. Wisconsin card sorting test computerized version **(WCST; 1981)**, the trail making test B **(trail B; Reitan, 1958)**: for the executive functions for all groups.
7. Wechsler memory-revised scale for the Memory for all groups **(Wechsler, 1987)**.

8. Trail making test **A (trail A; Reitan, 1958)** for Attention and concentration for all groups.
9. Wechsler IQ test for the Intelligence quotient (IQ) for all groups **to** exclude individuals with mental subnormality **(Wechsler, 1991)**.

- **Procedures:**

A. Pilot study:

Pilot study was done for 2 month earlier in order to determine the exact size of the sample and to determine the size of the sample and the time needed to perform the practical part of the study, also to assess the reliability of clinical diagnosis and assess the reliability and applicability of the used scales.

Results of the pilot study:

1. **Sample size:**

During the period of the pilot study it was found that patients with multiple episodes in remission fulfilling our operational criteria were around 20-30 per month while those of first episodes patients in remission who were fulfilling our operational criteria were around 20-25 per month. So we decided to recruit all patients attending the outpatient clinic fulfilling the inclusion criteria and accepting to participate in the study during a period of about 24 months in order to collect the largest possible number of subjects able to continue the procedure of the study.

2. **Reliability of ICD-10 check list:**

The patients seen during the pilot study period were also seen by the senior supervising colleagues in order to recheck the reliability of the ICD-10 check list.

3. Reliability of the used scales:

The reliability of the scales designed to assess the cognitive functions: the Wechsler adult intelligence Scale (WAIS), Wechsler memory scale the Wisconsin Card Sorting Test (WCST), trail A and Trail B was assured by their use in many previous studies.

The subjects of the study were able to understand the scales administered to them e.g. the general health Questionnaire (GHQ).

B. Study proper

- The study contains 3 groups; group I, fifty patients with single episode BPAD patient in remission. Group II, fifty patients with multiple episodes BPAD patient in remission and fifty control group patients. The first two groups are subjected to the study after remission (euthymic bipolar patients), to avoid the bias which may be caused by the effect of manic or depressive symptoms on the cognitive functions, e.g. attention, concentration, memory.
- Any patient at the outpatient clinic fulfilling the inclusion criteria was referred to be included in the study.
- Both groups I and II underwent the following tests:

a) **Semi-structured sheet** this sheet done by the researcher under supervision of the supervisor including Sociodemographic factors, age, sex, marital status, religion, education level, past history, family history, number of episodes, and psychiatric treatment taken in previous episodes.

b) **ICD 10 check list WHO (1992):**

This is semi structured instrument intended for clinicians' assessment of the psychiatric symptoms and syndromes in the F0-F6 categories of the ICD-10. It consists of a face sheet, screened and modules. Each module consists of a symptom list that may help the user to check the presenting symptom plus considering other possible syndromes and hence the use of other modules in the checklist according to the instructions given. The user should be familiar with the ICD-10 diagnostic criteria.

c) Hamilton depression scale (Fatim, 1994):

Hamilton developed the HDRS during the late50th in response to the need for a standardized measure of the phenomenology of a depressive syndrome. Hamilton finally structured it in 1960. Since then it has become the most commonly used rating scale of depression and has been used as a basis for the construction of other scales. The HDRS was devised only for the use on patients diagnosed as suffering from depression. The doctor for quantifying the results of an interview uses it and has been found to be of great value in assessing results of treatment. The scale contains 17 variables. Some are defined in terms of series

of categories of increasing intensity, while others are defined by a number of equal valued terms.

d) YOUNG mania scale (Young et al., 1978):

The Young Mania Rating Scale (YMRS) is one of the most frequently utilized rating scales to assess manic symptoms. The scale has 11 items and is based on the patient's subjective report of his or her clinical condition over the previous 48 hours. Additional information is based upon clinical observations made during the course of the clinical interview. The items are selected based upon published descriptions of the core symptoms of mania. The YMRS follows the style of the Hamilton Rating Scale for Depression (HAM-D) with each item given a severity rating. There are four items that are graded on a 0 to 8 scale (irritability, speech, thought content, and disruptive/aggressive behavior), while the remaining seven items are graded on a 0 to 4 scale. These four items are given twice the weight of the others to compensate for poor cooperation from severely ill patients. There are well described anchor points for each grade of severity. The authors encourage the use of whole or half point ratings once experience with the scale is acquired. Typical YMRS baseline scores can vary a lot. They depend on the patients' clinical features such as mania (YMRS = 12), depression (YMRS = 3), or euthymia (YMRS = 2). Strengths of the YMRS include its brevity, widely accepted use, and ease of administration. The usefulness of the scale is limited in populations with diagnoses other than mania. The YMRS is a rating scale used to evaluate

manic symptoms at baseline and over time in individuals with mania.

The scale is generally done by a clinician or other trained rater with expertise with manic patients and takes 15–30 minutes to complete.

E) Cognitive Assessment tests including:

The reliability of the scales designed to assess the cognitive functions: the Wechsler adult intelligence scale (WAIS), the Wechsler memory scale (WMS-R), the Wisconsin card sorting test (WCST), was assured by their use in many previous studies, e.g. **(Okasha et al, 1993, EL-Batrawy et al, 2002)**. All the subjects of the study were able to understand the scales administered to them.

A. Wisconsin card sorting test (WCST) (WCST; 1981),.

The Wisconsin card-sorting test (WCST) assesses abstract reasoning ability and the ability to shift cognitive strategies in response to changing environmental contingencies. The test can be considered a measure of executive functions requiring the ability to develop and maintain an appropriate problem solving strategy across changing stimulus conditions in order to achieve a future goal. It requires strategic planning, organized searching, utilizing environmental feedback to shift cognitive tests, directing behavior toward achieving goal scores not only of overall success, but also for specific sources of difficulty on the task e.g. inefficient initial conceptualization, failure to maintain cognitive set, perseveration and inefficient learning across stages of the test.

The WCST consists of four stimulus cards and 128 response cards that depict figures of varying forms (crosses, circles, triangles or stars), colors (red, blue, yellow, or green) and numbers of figures (one, two, three, or four). With the computerized WCST, the one used in our study, the examiner must instruct the subject to make response selections using the keyboard keys. WCST1 describes the total perseveration errors done by the subject during matching the 128 cards. The WCST2 describes the total number of category completed by the subject within the 128 cards matched **(Heaton et al, 1993).**

B. The Wechsler Intelligence Scales (Wechsler, 1991).

The Wechsler intelligence scales were developed by Dr. David Wechsler, a clinical psychologist with Bellevue Hospital. His initial test, the Wechsler-Bellevue Intelligence Scale, was published in 1939 and was designed to measure intellectual performance by adults. Wechsler constructed the WBIS based on his observation that, at the time, existing intelligence tests for adults were merely adaptations of tests for children and had little face validity for older age groups.

Since 1939, three scales have been developed and subsequently revised, to measure intellectual functioning of children and adults. The Wechsler Adult Intelligence Scale-III (WAIS-III) is intended for use with adults. The Wechsler Intelligence Scale for Children-III (WISC-III) is designed for children ages 6 - 16, while the Wechsler Preschool and Primary Scale of Intelligence-R (WPPSI-R) is designed for children age 4 - 6 1/2 years.

C. Wechsler memory scale (WMS-R).

This battery is composed of a variety of subtests measuring free recall or recognition of verbal and visuospatial material. Subtests of the WMS that present good assessment of memory were chosen to the present study **(Wechsler, 1987).**

D. Trail Making Test (TMT) Parts A & B (**Reitan, 1958).**

The trail-making test is a neuropsychological test of visual attention and task switching. The solving of the TMT requires stable focused attention, reasonable eyesight, proficiency in visual scanning and shifting stimuli during search. According **to (Lezak, 1976)** proficiency in shifting tracks is one of the first and most probable ability, which breaks down in a brain damage.

Cutoff scores for impairment are based on normative data instead of earlier recorded scores suggested by Matarazzo because there are other factors which may play a role in an individual's score (ex: age, educational level).

For the control group:

1) **Semi-structured sheet** this sheet will be done by the researcher under supervision of the supervisor including Sociodemographic factors, age, sex, marital status, religion, education level.
2) **General Heath Questionnaire. (GHQ)** (Goldberg and Hiller, 1979) Arabic version of 28 items GHQ **(Okasha et al, 1988)**

Goldberg constructed the general health questionnaire (GHQ) which has been used successfully in community settings and non psychiatric clinical settings in many countries. As brief self report psychiatric symptoms scale, the GHQ has been used as a first stage screening tool in community surveys and epidemiological studies **(Cleary et al., 1982).**

It is a self-administered screening questionnaire for the use in consulting sessions, aimed at detecting those with a diagnosable psychiatric disorder. In its original form, the GHQ consisted of 60 items covering physical symptoms and psychiatric disturbances. It concerns itself with two major classes of phenomena: inability to carry out one's normal healthy functions, and the appearance of new phenomena of a distressing nature.

The GHQ measures the psycho-physiologic symptoms and indicates the minor affective disorders. However, the GHQ also includes items on role functioning, role satisfaction, and outwardly observable behavior, and it contains items that stress on the changing nature of psychological functioning **(Goldberg and Williams, 1988)**

3) Cognitive Assessment tests including:

- **Executive functions** assessed using the Wisconsin card sorting test **(WCST; 1981)**, the trail making test B **(trail B; Reitan, 1958)**
- **Memory** assessed using the Wechsler memory scale **(Wechsler, 1987)**.

- **Attention and concentration** assessed using the trail making test A **(trail A; Reitan, 1958)**
- **Intelligence quotient (IQ)** using the Wechsler test (WAIS) verbal and performance IQ **(Wechsler, 1991)**.

❖ **Data management**

Data were collected, revised, verified, and then edited on P.C.

The data collected were analyzed using the Statistical Package for the Social Sciences (SPSS) version 16.0 **(2007)** by a professional statistician.

The following tests where done:

- Mean
- Standard deviation
- T test for independent samples
- ANOVA= analysis of variance
- Pearson's correlation coefficient (r)
- Chi square test (x2)
- P value :used to indicate level of significance
- P>0.05 =non-significant
- P<0.05 =significant
- P<0,01 =Highly significant
- P< 0,001 =very highly significant.

1. HISTORY

Mental illness is an old as mankind and therapy to mental illness has been known in Egypt as early as three millennia before Christ. I.em.ho.tep, "he who comes in peace", was the physician vizier of pharaoh Zoser, who built the Saqqara pyramid, 2980-2900 BC. He was worshipped at Memphis and a temple was constructed in his honor on the island of Philae. He was also the earliest known physican in history. The temple was a busy center for sleep treatment in what was called the "incubation" or "temple sleep". The course of treatment depended on the manifestations and contents of dreams which were highly affected by the psychoreligious climate of the temple, the confidence in the supernatural powers of the deity and the suggesteive procedures carried out by the divine healers **(Okasha, 1995)**.

The ancient Egyptians were the first to describe mental disorders. The Ebers papyrus at about 1550 BC is among the most important medical papyri of ancient Egypt. Mental disorders including depression are detailed in a chapter of the papyrus called the book of hearts **(Okasha, 1995)**.

The first references to mania and melancholia go back to Araeteus of Capadocia in the second century BC. For centuries, the term “mania” was used to refer to agitation syndromes, whatever their origin **(Pichot, 1995)**.

In the classical area four meanings of "mania" were described: A reaction to an event in the meaning of rage or anger or excitation (like Homer in his Ilias who described "Aias maenomenos", this means "Ajax in rage"). A biologically defined disease (Hippocrates, Aretaeus of Cappadocia and others). A divine state (Socrates, Plato). A kind of temperament, especially in its mild form (Hippocrates). On the other hand "Melancholia" ("melas" = black, and "cholé" = bile) was based on the pre-Hippocratic Greek physicians, who explained psychopathological states of severe sadness and other mental disorders with an interaction of body liquids, especially bile, and the brain **(Marneros and Angst, 2002)**.

He also described the symptoms of melancholia as following:

"The symptoms (of melancholia) are not unclear: (the melancholics) either are quiet or dysphoric, sad or apathetic; additionally they could be angry without reason and suddenly wakening with panic **(Marneros and Angst, 2002)**.

However, it was not until the nineteenth century that the concepts of mania and depression were linked conceptually and clinically through the first detailed descriptions of the folie circulaire by Falret and the folie à double forme by Baillarger – both the conditions characterized by states of excitation, sadness, and lucid intervals of variable duration **(Pichot, 1995)**.

But the one who truly defined the outlines of the disorder by introducing the longitudinal study as an essential diagnostic tool was Emil Kraepelin whose work Manic–Depressive Insanity

and Paranoia was a watershed in setting out the nosological aspects of bipolar disorders. He drew the boundaries of manic–depressive psychosis with schizophrenia, described the episodic course of the disorder, formulated its inheritability, and characterized its main clinical forms **(Pichot, 1995)**.

Almost as important as the work of Kraepelin were the studies by Leonhard, who postulated a separation between bipolar and unipolar forms of affective disorders from clinical, evolutional, and familial differences **(Pichot, 1995)**.

Although Kraepelin (1921) grouped most major forms of depression under the general rubric of "manic-depressive illness," it was not until Leonhard's (1957) work that patients with both depressive and manic episodes, whom Leonhard termed "bipolar," were distinguished from those exhibiting only recurrent depressions **(Johnson and Kizer, 2002)**.

The 1970s were a turbulent decade for psychiatry. The field's dominant theory (psychoanalysis) and dominant treatment (psychotherapy) were under severe attack both from within and without the medical profession. During the three postwar decades, psychiatry's ruling psychodynamic paradigm viewed mental disorders as conflicts of personality and Intrapsychic conflict. From the end of World War II until the mid-1970s, an environmental and behavioral model of mental disorders (informed by psychoanalytic and sociological thinking) was the organizing model for American psychiatry **(Wilson, 1993)**.

Psychiatric practice in the first part of the twentieth century did not place much stake in particular diagnostic categories. The first official manual of the American Psychiatric Association (APA), the Diagnostic and Statistical Manual of Mental Disorders (DSM-I; 1952), reflected the views of dynamic psychiatrists, especially of Adolf Meyer, the most prominent American psychiatrist of the first half of the twentieth century **(Grob, 1991)**.

The DSM-I and DSM-II made little effort to provide elaborate classification schemes, because overt symptoms did not reveal disease entities but disguised underlying conflicts that could not be expressed directly **(Horwitz, 2002)**.

In 1980, at one stroke, the diagnostically based DSM-III radically transformed the nature of mental illness. In a remarkably short time, psychiatry shed one intellectual paradigm and adopted an entirely new system of classification. The DSM-III imported a diagnostic model from medicine where diagnosis is "the keystone of medical practice and clinical research" **(Goodwin and Guze, 1996)**.

Psychiatry reorganized itself from a discipline where diagnosis played a marginal role to one where it became the basis of the specialty. The DSM-III emphasized categories of illness rather than blurry boundaries between normal and abnormal behavior, dichotomies rather than dimensions, and overt symptoms rather than underlying etiological mechanisms **(Horwitz, 2002)**.

Since 1957, more than 100 studies have examined the family history, natural course, clinical symptoms, personality factors, biology, and pharmacological treatments associated with the bipolar–unipolar distinct Within the bipolar category, a group of disorders appear to form a continuum or spectrum from the milder, subsyndromal form of manic depression, known as "Cyclothymia," to full-blown manic depression, known as Bipolar I Disorder. Indeed, the Diagnostic and Statistical Manual of Mental Disorders (4th ed., DSM-IV; American Psychiatric Association, 1994) identified four types of bipolar disorders: Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder, and Bipolar Disorder Not Otherwise Specified (NOS). According to DSM–IV, Bipolar I Disorder is defined by at least one episode of mania. Symptoms of mania include euphoria and/or

irritability, high energy/activity, rapid speech and increased talkativeness, racing thoughts, high self-confidence/grandiosity, decreased sleep, distractibility, and impulsive, reckless behaviors with a high propensity for negative consequences. Individuals with Bipolar I Disorder may have had prior depressive episodes and most will have subsequent manic or depressive episodes. They may also experience hypomanic episodes and mixed depressive/manic episodes **(Johnson and Kizer, 2002)**.

Bipolar II Disorder differs from Bipolar I in that individuals exhibit one or more hypomanic, instead of full-blown manic, episodes accompanied by the presence of one or more major depressive episodes **(Johnson and Kizer, 2002)**.

Cyclothymiacs Disorder is characterized by recurrent and intermittent mood episodes in which the individual oscillates, or "cycles," between periods of depression and hypomania, with or without normal, euthymic periods in between. However, unlike major depression and mania, both types of mood episodes are of subsyndromal intensity and duration (2-3 days, on average **(Johnson and Kizer, 2002)**.

Rapid cycling is defined as at least four episodes of mood disturbance in the previous 12 months that meet DSM-IV criteria for a major depressive, manic, mixed or hypomanic episode. These distinctions are important because the differential responsiveness to pharmacological interventions is probably due to differences in underlying pathophysiology of these bipolar subtypes **(Kujawa and Nemeroff, 2002)**.

The WHO classification, the International Classification of Disease, 10^{th} edition (ICD-10), is fairly similar but does not include cyclothymia in the definition of bipolar disorders; also, cases of unipolar mania and type II bipolar disorders are classified in a residual category ("other bipolar disorders"). It is also certain, however, that some preliminary criteria were

introduced for incorporating type II bipolar disorders, likely to be in a specific category in the 11th edition of the ICD **(Francesc and Eduard, 2006)**.

Based on epidemiological and family studies and clinical intuition, Akiskal estimated that 4-5% of the general population belongs to a broad bipolar spectrum with predominantly depressive phenomenology and muted bipolar features. These figures contrast the classical figure of 1-1.6% for bipolar disorder. This widening of bipolarity to the detriment of unipolar forms was corroborated by Angst, who demonstrated through epidemiological data that more than 5% of the general population might be affected by bipolar spectrum conditions **(Angst, 1998)**.

Akiskal proposes a number of syndromes as candidates for inclusion in a broadly conceived bipolar spectrum: mania, recurrent depressions with hypomania (irrespective of duration), pharmacologically induced hypomania, as well as depressions in association with cyclothymic and hyperthymic temperaments, and recurrent (pseudo-unipolar) depressions with bipolar family history or cyclic depressions responsive to lithium. He also argues that a substantial proportion of cases categorized as borderline personality disorder and many cases of alcohol abuse belong to the bipolar spectrum **(Cassano et al., 2000)**.

Akiskal's competent and comprehensive appraisal of contemporary classification of mood disorders illustrates very elegantly the evolution of the nosology of bipolar disorder from the antiquity to current days, elucidating how, since before kraepelin, the pendulum in mood disorders classification has moved back and forth between unitary spectrum and discontinuity (unipolar-bipolar) positions. He finally brings support to the spectrum position, even though he concludes that its ultimate range remains undefined. With his distinguished mastery, Akiskal describes various categories of bipolar spectrum, namely mania, hypomania, cyclothymia and hyperthymia. Under the rubric of atypical depression Akiskal

speculates on those conditions which are difficult to be accommodated in DSM or ICD diagnostic criteria, and are liable to be consigned to some wastepaper basket category or even ignored. He argues that the recognition of atypical mood signs/ symptoms and atypical mood syndromes may represent a valuable adjunct to categorical methods of diagnosis and classification of bipolar spectrum **(Cassano et al., 2000)**.

Atypical presentations of depression may characterize special populations of patients, with less predictable clinical course and response to treatment, or peculiar behaviors and lifestyles. In these subjects, bipolar symptoms may remain undetected, masked or misdiagnosed by more visible manifestations. Stated differently, because many bipolar II patients have an underlying cyclothymic temperamental dysregulation, their clinical presentations are varied and inconsistent and often prove confusion in cross section. That is, they could present with cross sectional features of atypical depression, and lifelong history of anxiety states, bulimia, substance abuse, and cluster B personality disorders **(Cassano et al., 2000)**.

Using clinical data and case reports Akiskal states that many major depressions in the DSM-IV schema are, in reality, part of the bipolar spectrum. This approach led to the formulation of a list of prototypes (BP-I, BP-1/2, BP0II, BP-II 1/2, BP-III, BP III1/2, BP-IV along the continuum of mood dysregulation. The major implication of this theory is that the extension of the concept of bipolar spectrum would defend depressed patient unprotected by mood stabilizers from possible negative effects of antidepressants. Second, recognition of some attenuated forms of bipolarity pursuing sub acute or chronic course may prevent from more prognostically unfavorable diagnosis, including borderline or antisocial personality disorder or schizophrenia. Furthermore, this model has shed light on the true prevalence of bipolar **(Cassano et al., 2000).**

2. EPIDEMIOLOGY

The lifelong prevalence rate of bipolar disorder in the United States is 1-1.6%. The 2 types of disorders differ in adult populations, with approximately 0.8% having BPI and 0.5% having BPII. Life long international prevalence rate is 0.3-1.5%. No racial predilection exists. However, a point of historical interest is that clinicians often tend to consider populations of African Americans and Hispanics as more likely to be diagnosed with schizophrenia than with affective disorders and bipolar disorder. BPI occurs equally in both sexes; however, rapid-cycling bipolar disorder (4 or more episodes a year) is more common in women than in men. Incidence of BPII is higher in females than in males. The age of onset of bipolar disorder varies greatly. The age range for both BPI and BPII is from childhood to 50 years, with a mean age of approximately 21 years. Most cases commence when individuals are aged 15-19 years. The second most frequent age range of onset is 20-24 years **(Soreff et al., 2006)**.

Some patients diagnosed with recurrent major depression may indeed have bipolar disorder and go on to develop their first manic episode when older than 50 years. They may have a family history of bipolar disorder. However, for most patients, the onset of mania in people older than 50 years should lead to an investigation for medical or neurological disorders such as cerebrovascular disease **(Soreff et al., 2006)**.

Despite remarkable advances in its detection, treatment, and management bipolar illness remains a highly prevalent disorder of enormous cost society, from an economic and social perspective as well as from the stand point of morbidity and mortality. In 1996, the world heath organization ranked bipolar disorder as one of the 10 leading worldwide causes of both temporary and permanent disability for individuals aged 15-45,

exceeding the number of disability-adjusted life years (DALYs) associated with numerous other serious and chronic medical conditions such as human immunodeficiency virus (HIV) infection, diabetes mellitus, or asthmas **(Murray and Lopez, 1996)**.

By the year 2020, it has been estimated that affective disorders will be second only to ischemic heart disease in DALY rank ordering. Observational studies have found that psychosocial disability often extends far beyond the resolution of affective symptoms among bipolar as well as unipolar patients **(Coryell et al., 1993)**.

As noted in both cross sectional and longitudinal findings from epidemiologic reports, functional disability for patients with severe mood disorders often persists after an index affective episode in ways that appear even more devastating than seen with many chronic medical conditions **(Hays et al., 1995)**.

3. Costs of BPAD

An important factor contributing to high rates of disability is the lag of functional recovery from an affective episode behind symptomatic recovery. Many weeks and months may separate remission of symptoms and recovery of premorbid functional status **(Strakowski et al., 1999)**. In fact, many patients do not reach full functional recovery and recurrent affective episodes may lead to progressive deterioration in functioning between episodes Thus, disability from bipolar disorder is not simply limited to discrete affective episodes **(Solomon et al., 1995)**.

In general, costs, in cost-of-illness studies, have typically been defined as core costs resulting directly from the illness and other related costs, including non-health costs of the illness. Within the core and related cost categories there are direct costs (requiring expenditure of payments) and indirect costs (lost resources). Examples of direct costs include funds spent for hospital and nursing-home stays, physician and other professional services, medicines and equipment. Indirect costs include morbidity (e.g. disability) and mortality costs. Mortality costs include diminished and lost productivity **(Rice, 1994)**.

In the first study to examine the economic cost of bipolar disorder, **Greenberg et al. (1993)** provided estimates of the morbidity costs of the illness. In their analysis, patients with bipolar disorder in treatment were estimated to have lost approximately 152 million cumulative days from work, and untreated patients an additional 137 million days in 1990. Morbidity costs based on diminished productivity from affective symptoms from bipolar disorder or major depression were $6.5 billion for the male workforce and $9.0 billion for the female workforce **(Greenberg et al., 1993)**.

From the studies reviewed above, a number of aspects regarding the economic impact of bipolar disorder are clear.

First, the cost of this illness in disability and human suffering is profound. Second, the economic cost of the illness far outweighs the costs of treatment. Residual and symptoms and persistent social and family and occupational dysfunction are common **(Keck et al., 1998b).**

Good treatments are available and such treatments if properly used should be associated with a substantial reduction in the disease burden associated with bipolar disorder **(Keck et al., 1998b)**.

Thus, decisions regarding the inclusion of medications for patients with bipolar disorder on formularies require consideration of the impact of successful treatment on preventing morbidity and mortality, enhancing productivity and preventing hospitalization **(Keck et al., 1998b)**.

4. Biology and Pathophysiology

Bipolar disorder is a complex, potentially lethal, often chronic psychiatric illness. Bipolar disorder is characterized by the presence of a wide range of affective states including mania or hypomania, depression or mixed states. At any given time these affective states may also have a psychotic component. Transitions between affective states are often abrupt, inconsistent and unpredictable **(Kujawa and Nemeroff, 2002)**.

Many symptoms characteristic of bipolar disorder, such as grandiose and persecutory delusions, impulsivity and irritability, are common to those observed in other psychiatric disorders (American psychiatric association 1994a). Misdiagnosis contributes to the under detection and under treatment of bipolar disorder **(Kujawa and Nemeroff, 2002)**.

The pathophysiology of bipolar disorder remains obscure, despite the fact that clinical symptoms can be effectively treated for many with currently available mood stabilizers **(Tondo et al., 1998)**.

The neurobiological basis of bipolar disorders and the complex interactions of environmental and inherited factors that create vulnerability to abnormal moods remain essentially unknown. However, several lines of research are providing important clues about the type of biological processes underlying moods and their disorders. The established approaches of neurochemistry and pharmacology that gave rise to the present generation of antidepressant and mood-stabilizing drugs have highlighted the importance of neurotransmitters and cell signaling pathways. Advances in neuroimaging techniques have identified several brain regions showing structural or functional changes in subjects with mood disorders, and cognitive deficits found in patients are in keeping with these imaging findings **(Power, 2004)**.

4.1 Genetics:

Bipolar disorder, more so perhaps than any other psychiatric disorders, is strongly influenced by genetic factors **(Cohn, 1997)**.

The genetic components in complex diseases such as bipolar disorder do not follow single-gene inheritance patterns. Although patients may show a common clinical phenotype, the cause of the syndrome probably results from a heterogeneous collection of genetic and/or environmental influences. One remarkably consistent finding has been the considerably higher concordance rate of bipolar disorder in monozygotic twins compared to dizygotic twins, a universally agreed-upon observation **(Escamilla et al., 1999)**.

Twin studies demonstrate a concordance of 33-90% for BPI in identical twins. Adoption studies prove that a common environment is not the only factor that makes bipolar disorder occur in families. Children whose biologic parents have either BPI or a major depressive disorder remain at increased risk of developing an affective disorder, even if they are reared in a home with adopted parents who are not affected. Numerous genetic studies of BPI suggest that multiple different genetic loci, each of small effect, contribute to the affected phenotype **(Majvinberg et al., 2006).**

These effects also appeared to be additive and at least 4 of the genes play a role in biochemical pathways modulated by lithium. Another interesting candidate gene for mania is the CLOCK gene involved in circadian periodicity **(Ewald, 2002)**.

Unfortunately, genetic linkage and association studies have failed to identify the specific gene(s) which carry this risk. However, several groups have provided evidence suggesting that

chromosome 18 carries the genetic risk for bipolar disorder **(Escamilla et al., 1999)**.

Other promising candidate genes and genomic regions of interest include chromosome 21q **(Detera-Wadleigh et al., 1996)**, chromosome Xq **(Pekkarinen et al., 1995)** and chromosome 6pter-p24 **(Ginns et al., 1996)**.

In the 1980s, linkage was reported between bipolar disorder and markers on the X chromosome **(Baron et al., 1987)**.

Most studies pointed to the Xq28 region as the location of the putative X-linked gene, but reports of linkage to factor IX in Xq27. However, **Mendlewicz et al. (1987)** suggested incompatibility in these sets of findings.

When investigators attempted to replicate linkage using highly informative DNA markers, several recombinations between the disease and the markers were noted in these individuals, eliminating most of the support for linkage on the X chromosome **(Baron et al., 1997)**.

4.2 Brain imaging IN BPAD:

The idea that bipolar illness may be related to an alteration in brain structure arose from the astute clinical observation that certain brain lesions produced by brain tumors, stroke or head injury resulted in manic-like behavior **(Strakowski et al., 1994)**.

In general, brain lesions are far more likely to cause depression than mania, but lesions that do induce mania occur more commonly in the orbito-frontal and baso-temporal cortices, the head of the caudate and the Thalamus **(Strakowski et al., 1994)**.

It was initially felt that lesions in the left frontal lobe tend to result in depression, whereas right fronto-temporal lesions cause mania. These generalizations about laterality are believed by many investigators to be too simplistic, because there are many exceptions to this rule. To understand structural brain alterations in bipolar disorder, more detailed evaluation is required. There have been few anatomical postmortem studies of patients with confirmed bipolar disorder. However, computed tomography (CT) results had suggested that patients with bipolar disorder tended to have larger ventricles than normal volunteers. Ventricular enlargement is typically characteristic of cell loss, but potentially confounding factors such as previous treatment, head injury, and substance use obscured the interpretation of these results. Volumetric brain imaging studies using CT and magnetic resonance imaging (MRI) in patients with mood disorders have suggested atrophy or cell loss in several areas of the brain. Lateral or third ventricle enlargement has been noted by several investigators **(Strakowski et al., 1993)**.

Reduced frontal lobe volumes or areas have also been noted **(Sax et al., 1999)**.

Atrophy or cell loss has also been suggested in the temporal lobe **(Altshuler et al., 1991)**.

Reduced basal ganglia volumes in the putamen complex, caudate and in both caudate and putamen complex have been reported **(Krishnan et al., 1993)**.

Additionally, reduction in amygdala–hippocampus volume or area has been observed **(Swayze et al., 1992)**.

In vivo volumetric magnetic resonance imaging MRI studies have reported subtle structural brain changes in prefrontal, medial temporal and limbic regions in individuals

with bipolar disorder, suggesting disturbances in neuronal survival **(Brambilla et al., 2005)**.

It has been suggested that pathophysiological abnormalities in these neuroanatomical circuits underlie both the affective symptoms and associated attentional dysfunction in bipolar disorder **(Strakowski et al., 1999)**.

Furthermore, findings from gene expression studies of postmortem persons with bipolar disorder versus controls have yielded exciting new insights into the pathophysiology of the disorder. In particular, levels of expression of oligodendrocyte-myelin-related genes appear to be decreased in brain tissue from persons with bipolar disorder **(Davis et al., 2003)**.

Oligodendrocytes produce myelin membranes that wrap around and insulate axons to permit the efficient conduction of nerve impulses in the brain. Therefore, loss of myelin is thought to disrupt communication between neurons, leading to some of the thought disturbances observed in bipolar disorder and related illnesses. Brain imaging studies of persons with bipolar disorder also show abnormal myelination in several brain regions associated with this illness. Interestingly, gene expression and neuroimaging studies of persons with schizophrenia and major depression also demonstrate similar findings, indicating that mood disorders and schizophrenia, may share some biological underpinnings, possibly related to psychosis. These types of data may also lead to the future revision of psychiatric diagnostic manuals based on a new understanding of the etiology of these disorders **(Davis et al., 2003)**.

MRI of patients with bipolar disorder reveals an inordinate number of hyperintense regions. These so-called unidentified bright objects (UBOs) are typically associated with vascular diseases such as hypertension, Binswanger's disease and carotid arteriosclerosis. The percentage of bipolar patients exhibiting

these findings ranges from 5% to 50% compared to approximately 3% for controls. These UBOs (Figure 1) tend to localize in deep white-matter structures that contain fibres that facilitate communication between frontal and temporal regions. The disruption of communicating fibres between fronto-temporal regions may play a major role in the pathophysiology of bipolar disorder. Follow-up postmortem studies of patients with UBOs have demonstrated a number of histological changes in these regions, including small vascular malformations, dilated perivascular spaces, brain cysts, infarcts and necrosis. It is possible that these lesions represent damage from a comorbid disease process unrelated to bipolar disorder; however, recent studies in children and adolescents with mania also reveal an abundance of these UBOs **(Strakowski et al., 1999)**.

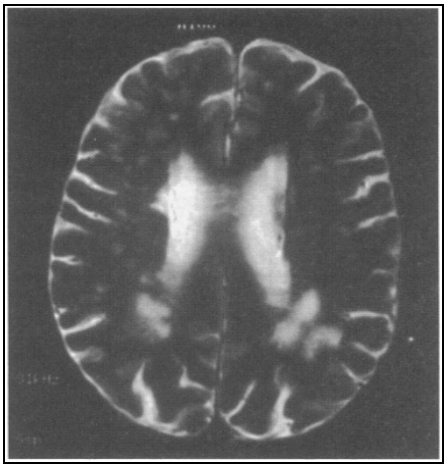

Figure 1: Unidentified bright objects by MRI in BAD (Kujawa and nemeroff, 2002).

Recent advances in functional neuroimaging allow measurement of subtle changes in receptor density, blood flow, and glucose metabolism. Functional neuroimaging takes advantage of the observation that when synaptic activity increases in a brain region, the blood flow to that region transiently increases and an excess of oxygenated blood temporarily bathes the region. Both functional MRI (fMRI) and positron emission tomography (PET) can be used to measure this blood flow increase. PET can also be used to directly measure local glucose metabolism which also increases with increased

neuronal activity. Early studies revealed that bipolar depressed patients had significantly lower cerebrocortical metabolism when compared to either controls or patients with unipolar depression. These changes were state-dependent, i.e. when patients recovered from their depression, these imaging abnormalities resolved **(Marneros and Angst, 2002)**.

In-vivo phosphorus-31 magnetic resonance spectroscopy (P-31 MRS) studies of patients with bipolar disorder have shown lower than normal frontal lobe phosphomonoester (PME) values and pH in the euthymic state, as well as increased PME and pH in depressed and manic states **(Kato et al., 1993)**.

Bipolar patients have also been noted to have significantly lower phosphomonoester (PME) values and significantly higher phosphodiester (PDE) values in both the right and left frontal lobes **(Deicken et al., 1995a)**.

In addition, the right-to-left ratio of frontal phosphocreatine (PCr) was higher in bipolar patients **(Deicken et al., 1995a)**.

Significantly lower PME levels have been noted in both the left and right temporal lobes of patients with bipolar disorder. Data such as these support altered temporal lobe phospholipids metabolism in bipolar disorder **(Deicken et al., 1995b)**.

Localized proton (H-1) magnetic resonance spectroscopy of tissues in vivo has demonstrated several findings in brains of patients with bipolar disorder, including high Cho/Cr ("choline") in basal ganglia **(Stoll et al., 1996)** decreased NA/Cr in the frontal lobe **(Hamakawa et al., 1999)**, and no change detected in temporal cortex **(Silverstone et al., 1999)**.

Magnetic resonance spectroscopy has also been used to examine treatment effects of lithium. No changes in the temporal lobes of normal controls treated with lithium for 1 week were

noted by **(Silverstone et al., 1998)**. However, significant changes in the temporal lobes were noted with amphetamine co-administration **(Silverstone et al., 1999)**.

Increased Cho/Cr in the basal ganglia with lithium treatment has been reported. However, no effect on Cho/Cr in the basal ganglia with lithium treatment was noted in two other studies. Bipolar disorder patients who are lithium responders have been noted to have high baseline basal ganglia Cho/Cr **(Stoll et al., 1996)**.

Functional brain imaging studies using PET and SPECT have shown reduced general blood flow in bipolar disorder patients **(Delvenne et al., 1990)**.

Reduced perfusion of the dorsolateral prefrontal cortex has also been reported in depressed individuals **(Goodwin et al., 1993)**.

Reduced metabolism has been reported in the basal ganglia of patients with bipolar disorder **(Buchsbaum et al., 1986)**.

In the limbic system, increased perfusion of the left amygdala in manic patients and hypo-metabolism of the temporal lobe in bipolar patients have been noted **(Goodwin, 1996).**

Frontal lobe metabolism is reduced in depressed patients with bipolar disorder; this may be state-dependent because frontal lobe metabolism has been observed to be increased in mania **(Goodwin et al., 1996).**

4.3 Neurochemical Changes:

The underlying mechanisms leading to different states and subtypes of bipolar disorder are not well understood. The possibility of markers of underlying biological alterations

specific to subtypes of bipolar disorder such as mixed mania and/or as predictors of treatment response to specific medications would represent an incremental advance in the field. Cortisol is one such candidate biological marker. Studies provide concordant evidence that mixed mania is characterized by hypercortisolism, whereas pure mania is not **(Swann et al., 1986)**. Thus patients with mixed, but not pure mania, exhibit Dexamethasone suppression test (DST) non-suppression at high rates, as well as increases in plasma and cerebrospinal fluid (CSF) cortisol concentrations, and an increase in 24-hour urinary free cortisol concentration. This suggests that patients with mixed mania like those with depression, hyper secrete corticotrophin-releasing factor (CRF) and consequently exhibit hypothalamic–pituitary–adrenal axis (HPA) hyperactivity **(Kujawa and Nemeroff, 2002)**.

Biological studies in bipolar disorder have been hampered by several methodological confounds including diagnostic heterogeneity, trait versus state disturbances, effect of treatment and withdrawal of treatment, and dependence on peripheral models. Despite these limitations, numerous biochemical abnormalities in bipolar disorder have been detected by measuring neurotransmitters and/or their metabolites or hormones in plasma, cerebrospinal fluid and postmortem tissue. The neurochemical receiving most attention in the biology of bipolar disorder are 3-methoxy-4-hydroxy-phenylglycol (MHPG), norepinephrine (NE), serotonin (5-HT), and dopamine (DA). Variable results of plasma MHPG levels do not generally support the concept of a unipolar/bipolar distinction. In general, plasma MHPG levels tend to be lower in bipolar than unipolar depressed patients and, interestingly, are higher in bipolar patients when manic than when depressed. Although depression has often been hypothesized to be at least partially due to a relative deficiency of certain monoamines, including serotonin and norepinephrine, the role of these neurotrasmitters in the pathophysiology of bipolar disorder is less clear. Whether

unipolar depression and bipolar depression represent distinct biological entities remains unresolved **(Kujawa and Nemeroff, 2002)**.

Levels of NE, or its major metabolite, are consistently altered in the CSF of patients with bipolar disorder. The catecholamine hypothesis, simply stated, was that depression resulted from low relative NE levels and mania resulted from high relative NE levels. This has been a difficult hypothesis to evaluate, because of a lack of availability of the necessary tools, but most evidence supports this hypothesis. Interestingly, NE elevations apparently precede the switch into mania **(Kujawa and Nemeroff, 2002)**.

Numerous alterations in the serotonergic and dopaminergic systems have been detected in depression, but little evidence is currently available in bipolar disorders. Alterations in the serotonergic system in depression include decreased CSF 5-hydroxyindolacetic acid (5-HIAA), questionably increased 5-HIAA in psychotic depression, increased postsynaptic 5-HT2 receptors, questionably decreased binding and decreased binding (markers of the 5-HT transporters), blunted prolactin response to fenfluramine, L-tryptophan and clomipramine, and depressive relapse upon tryptophan depletion. Dopamine agonists have been observed to precipitate manic symptoms in susceptible patients. Alterations in the dopaminergic system in depression are supported by the following:

(1) reduced homovanillic acid (HVA), the major DA metabolite, in CSF of depressed patients; **(2)** electroconvulsive therapy (ECT) enhances DA turnover and CSF HVA levels; **(3)** chronic antidepressant therapy possibly enhances DA function; **(4)** depression occurs in up to 40% of Parkinson's disease cases, and **(5)** the requirement for intact relationships of dopamine, serotonin, and norepinephrine for antidepressant response **(Kujawa and Nemeroff, 2002)**.

Mounting evidence of the contribution of glutamate to both bipolar and major depressions, as postmortem study of the frontal lobes with both these disorders revealed that the glutamate levels were increased **(Kujawa and Nemeroff, 2002)**.

Calcium channel blockers have been used to treat mania, which also may result from a disruption of calcium regulation in neurons. The proposed disruption of calcium regulation may be caused by various neurologic insults such as excessive glutaminergic transmission or ischemia. Interestingly, Valproate specifically up-regulates expression of a calcium chaperone protein, GRP 78, which may be one of its chief mechanisms of cellular protection.

Hormonal imbalances and disruptions of the hypothalamic-pituitary-adrenal axis involved in homeostasis and the stress response also may contribute to the clinical picture of bipolar disorder **(Lepping and Menkes, 2007).**

4.4 Molecular and Cellular Alterations in Bipolar Disorder

4.4.1 Protein Kinase C

Protein kinase C (PKC) is a family of phosphorylating enzymes which plays a master role in modulating transmembrane signaling and in regulating many cellular functions. Also, there was increased PKC activity and translocation in brain cortices of patients with bipolar disorder compared to controls, effects which were accompanied by elevated levels of cytosolic and membrane-associated and PKC isozymes. Augmented PKC activation and phorbolester-induced enzyme redistribution have been reported in postmortem frontal cortex of bipolar disorder patients **(Wang and Friedman, 1996)**.

Several studies have implicated persisting enhanced PKC activity as mediators of long-term alterations in neuronal excitability in the CNS following kindling. Heightened PKC-mediated signal transduction has been recently associated with acute mania. This is in contrast to decreased PKC-signal transduction reported in patients with unipolar depression or Schizophrenia. Using blood platelets, these investigators demonstrated higher membrane PKC activity in manic patients compared to unipolar depressed or control subjects. The ratio of membrane to cytosolic PKC activity was significantly higher in mania, when compared to control, depressed or schizophrenic patients **(Wang and Friedman, 1996)**.

Both lithium and valproic acid have been shown to reduce PKC activity, PKC ά, PKC έ, and MARCKS levels. The distinction between lithium and Valproic acid is that lithium is Inositol-responsive, but Valproic acid is not. Treatment of bipolar mania with a PKC inhibitor, Tamoxifen, resulted in a significant decrease in manic symptomatology rated by the Young Mania-Rating Scale (YMRS). These preliminary results suggest that Tamoxifen has Antimanic efficacy, and that PKC inhibitors may be useful agents in the treatment of bipolar disorder, and in further understanding of the biology of this **(Kujawa and Nemeroff, 2002)**.

4.4.2 Cyclic Adenosine Monophosphate in Bipolar Disorder

In recent years numerous studies have reported abnormalities in components of the cyclic adenosine monophosphate (cAMP) signal transduction system, including G proteins, in postmortem brain and peripheral cells of patients with bipolar disorder **(Mitchell et al., 1997)**.

The cAMP-dependent protein kinase (protein kinase A [PKA]) is a central component of the cAMP signaling cascade

because in most situations the intracellular events mediated by cAMP occur through its activation. The PKA holoenzyme is organized as an inactive tetrameric complex composed of a regulatory subunit dimer and two monomeric catalytic subunits. The binding of cAMP to a regulatory subunit dimer results in the release and concomitant activation of the catalytic moieties, which in turn are able to phosphorylate specific substrate proteins, thereby regulating numerous cellular functions **(Spaulding, 1993)**.

The binding of cAMP to PKA regulatory subunits and the activity of PKA are altered by the administration of antidepressants and lithium. Also, alterations in the levels of PKA have been reported after lithium treatment. Moreover, changes in either the phosphorylation state or the levels of other cAMP-dependent phosphoproteins have been reported following treatment with antidepressants and lithium **(Perez, 2000)**.

The cAMP-stimulated phosphorylation of a low-molecular weight platelet protein has been shown to be significantly higher in untreated euthymic patients with bipolar disorder than in controls **(Perez, 2000)**.

This phosphoprotein has been identified as Rap1, a small guanosine triphosphate (GTP)-binding protein. The levels of PKA and Rap1 in platelets from untreated euthymic, depressed, or manic patients with bipolar disorder and healthy controls have been studied. Levels of Rap1 and the catalytic subunit of cAMP-dependent protein kinase were significantly higher in untreated depressed and manic patients with bipolar disorder. Evidence suggests that Rap1 may be involved in several cellular events such as calcium mobilization, cytoskeletal organization, and Phosphoinositide metabolism; most of these measures have also been found to be altered in patients with bipolar disorder **(Wang and Friedman, 1996)**.

Recently, Rap1 was found to be involved in the regulation of signal cascade coupled to neurotrophic factors. This is intriguing, especially in light of recent data suggesting an involvement of neurotrophic factors in mood disorders. It is difficult to envision the molecular mechanisms underlying the alterations in Rap1, PKA and other signaling mechanisms, but findings such as these suggest alterations in the transcriptional, post-transcriptional, translational, or posttranslational processes that are known to regulate proteins that may be involved in the pathobiology of bipolar disorder **(Duman et al., 1997)**.

4.4.3 Phosphoinositide Abnormalities

Several studies have supported abnormalities in the phosphatidyl inositol second-messenger system in bipolar disorder. The relative percentage of platelet membrane PIP2 was found to be significantly higher in manic patients than in comparison subjects **(Brown et al., 1999)**.

Increased sensitivity to agonist stimulation of the Ca^{2+} response in neutrophils of bipolar disorder patients has been observed; these effects were "normalized" by lithium treatment **(Van Calker et al., 1993)**.

Also, numerous studies have reported elevated basal and post-receptor stimulated Ca^{2+} responses in peripheral cells from bipolar disorder patients and increased G alpha q/11 immunoreactivity in postmortem occipital cortex from patients with bipolar disorder **(Van Calker et al., 1993)**.

These elevated levels of G alpha q/11 in bipolar patient brains were accompanied by reduced agonist-induced PI turnover **(Jope et al., 1996)**.

4.4.4 Kindling Mechanism

Many, if not most, patients with bipolar disorder show a pattern of increasing frequency of cycling over time. This

pattern, observed in other disorders such as epilepsy, has suggested that a model of kindling and sensitization might apply to bipolar disorder. Kindling refers to increased responsivity to repeated low-level electrical stimulation. This is seen commonly in seizure disorders, where a seizure focus becomes increasingly sensitive to other electrical events; i.e. the more seizures one has, the more likely the occurrence of additional seizures. The kindling hypothesis also explains the observation that early manic episodes tend to be triggered by external events whereas, after several episodes, manias tend to occur without any precipitants **(Kujawa and Nemeroff, 2002)**.

Certain anticonvulsants such as carbamazepine and valproate and, perhaps, lamotrigine, topiramate and gabapentin, are effective treatments for certain patients with bipolar disorder, lending further support for the kindling hypothesis. However, not all anticonvulsants are effective in the treatment of bipolar disorder (e.g. phenytoin and phenobarbital) **(Kujawa and Nemeroff, 2002)**.

5. Cognitive Functions

5.1 Dimensions of Cognition:

Cognition can be defined as the mental process of knowing and includes aspects such as awareness, perception, reasoning, and judgment. The field of neuropsychology focuses primarily on assessing aspects of cognition via a variety of computerized and pencil and paper tests to assay brain function. Cognitive dimensions include the following:

Sensation: sensation is the initial sensory stimulation that results in the physiological arousal necessary to register information entering the cognitive processing system **(Goldberg & Burdick, 2008)**.

Perception: perception is the process of using the senses to acquire information about the surrounding environment or situation, which involves an active processing of a nearly constant stream of incoming data **(Goldberg & Burdick, 2008)**.

Attention: attention is believed by many to be the most basic cognitive construct to reflect conscious processing of information. It involves alertness, mental focus, serious consideration, and concentration. Attention can be broken into three systems: arousal (vigilance), orienting and detection **(Goldberg & Burdick, 2008)**.

Arousal is believed to be an autonomic process involving the ability to achieve and maintain an alert state **(Goldberg & Burdick, 2008)**.

Orienting is also known as attentional shifting, orienting is an automatic process involved in target detection that allows the subject to localize a target for analysis **(Goldberg & Burdick, 2008)**.

Detection is a complex attentional construct involving multiple overlapping concepts. Detection involves conscious processing by cortical areas, often refers to as selective attention, and includes such skills as inhibition of automated responses, filtering of irrelevant competing information (conflict) and dividing attention to process more than one stimulus at a time **(Goldberg & Burdick, 2008)**.

Working memory: it includes any mental process that entails temporary storage and manipulation of information **(Goldberg & Burdick, 2008)**.

Memory, memory is the ability of the mind to retain learned information and knowledge of past events and experiences to retrieve them. There are three stages of memory: encoding, storage and retrieval.

Encoding (registration), it is the stage in which an organism takes in and combines information for storage.

Storage: storage is the stage in which a permanent record of the perceived information is formed.

Retrieval is the recall of information that was encoded and stored typically in response to some cue or query.

Executive function: this domain encompasses an array of capacities that are generally believed to engage and control the other cognitive processes of attention, working memory, learning and memory.

Intelligence: cognition was once believed to be a unitary construct that most closely resembled the notion of intelligence, or intellectual capacity. However, normal intellectual function as defined by an average intelligence quotient does not necessarily imply normal neuropsychological function **(Goldberg & Burdick, 2008)**.

5.2 Cognitive Dysfunction in Bipolar Affective Disorder

According to Kraepelin 1991 bipolar disorder has been associated with an episodic rather than chronic course. However, research over the last 30 years has consistently revealed diminished occupational, educational, psychosocial, and residential functioning that persists long past symptomatic recovery in a significant proportion of bipolar patients **(Tohen et al., 2000)**.

A review of studies on psychosocial outcome in patients with bipolar disorder revealed that 30-60% of individuals failed to regain full functioning in occupational and social domains **(MacQueen et al., 2001)**.

Research has provided some idea of the time course of functional impairment in bipolar disorder. Illness onset appears to be associated with a decline in functioning. For some patients, this reduced functioning persists. In a 2 year follow up study, a clear decline from premorbid levels was found in occupational functioning in 36% of bipolar patients **(Harrow et al., 1990)** and About 75% of patients remain below premorbid levels of functioning at 1-year follow up **(Conus et al., 2006)**.

Likewise, patients at 5 years follow up were more likely than healthy relatives to report declines in job status and income, and less likely to report improvement **(Coryell et al., 1993)**.

Tsuangs et al. (1979) finding of poor outcome 30 years after illness onset suggests that a subgroup of patients never recovers premorbid levels of functioning.

Thus, although medication improves symptoms, such treatment is more limited in affecting functional outcome. In addition, reduced functioning is consistent across bipolar bipolar II and I disorders **(Kebede et al., 2006)**.

Life time duration of bipolar disorder has been associated with cognitive dysfunction and a negative impact on memory and executive functions has been found **(Van Gorp et al., 1998)**.

5.2.1 Euthymia

Despite substantial evidence of cognitive deficits during acute affective episodes, much of the early research in the cognitive function of bipolar disorder assumed that when patients recovered, they returned to normal functioning in all domains and regained intact cognitive abilities. However, more recent studies have cast doubt on this assumption, suggesting that during euthymia, deficits may persist in sustained attention, verbal memory, verbal fluency, and executive functioning **(Martinez-Aran et al., 2004b)**.

5.2.2 Depression

Cognitive deficits associated with depression vary with the patient's age, severity of depression, and co morbidity; however, even mild depression in unmedicated patients is associated with significant impairment. Memory and concentration problems are among the core symptoms of depression and are reflected in the cognitive profile of depressive disorders. Deficits have been found in performance on 8measures of memory and of sustained attention or concentration **(Smith et al., 2006)**.

5.2.3 Mania

The investigation of cognition in mania is inherently difficult because of associated psychotic features, distractibility, and impulsivity, which have significantly hindered but not totally prevented research of this phase of bipolar illness. Predictably, manic patients have been found to have difficulty in concentrating or attending and to be more impulsive when making decisions **(Clark and Goodwin, 2004)**.

However, mania has also been linked with information processing and executive functioning deficits that include, in particular difficulties with problem solving, attentional set shifting, and controlling inhibition **(Clark et al., 2001)**.

5.2.4 Psychotic Features

Selva et al. (2007) have reported that a history of psychotic symptomatology does indeed impact specific cognitive function in patients with bipolar I disorder, and importantly, also influences health related quality of life and functioning. Specifically during periods of euthymia, bipolar patients with a history of psychotic symptoms demonstrate significant impairment relative to bipolar patients without psychosis on specific aspects of frontal executive function and spatial working memory **(Glahn et al., 2007)**.

In contrast bipolar patients with or without psychosis performed comparably on measure of attention, fluency, memory and psychomotor speed **(Daban et al., 2006)**.

Rocca et al. (2008) reported that a history of psychosis also has been associated with impaired verbal fluency in his studies. Furthermore, patients, with bipolar disorder who have a positive family history of any psychotic disorder in a first degree relative have been shown to perform significantly worse than patients with no such family history **(Tabares-Seisdedos et al., 2003)**.

Taken together, these data support the notion that a history of psychosis in patients with bipolar disorder, or in their first degree relatives, worsens the cognitive course of the illness with regard to specific Neurocognitive impairments. This notion is compatible with the existence of some common genetic factors along the psychosis continuum including psychotic affective disorders and major psychotic illnesses such as schizophrenia **(Rocca et al., 2008)**.

Nevertheless the direction of causality is unclear, mood episodes may adversely affect neuropsychological performance, or impaired cognitive function may contribute to the development and exacerbation of mood symptoms. Similarly, cognitive dysfunction may be an expression of the disease phenotype and not necessarily bear any direct relation to mood symptoms **(Selva et al., 2007)**.

5.3 The Endophenotype Concept

The national institute of mental health convened a work group to develop a strategic plan for genetic mood disorders research. To use an endophenotype approach to facilitate identification of susceptibility genes, They argues that to be an endophenotype it should be highly heritable, associated with the illness, be independent of clinical state and indicate that impairment cosegregates with the illness within a family, with non affected family members showing impairment relative to the general population. Fitting with the above criteria is the neuropsychological and neuroimaging measures for bipolar disorder **(Lenox et al., 2002)**.

Neuropsychological of bipolar patients may be confounded by several factors such as the use of medication, the presence of subsyndromal symptoms and the possibility that patients have suffered lasting neuroanatomical changes due to prior episodes **(Glahn et al., 2004)**.

Investigating cognitive function in healthy individuals at high risk of developing bipolar disorder avoids many of these confounds and sheds light on whether this aspect of the disease phenotype is shared by those at genetic risk for the disorder. First degree relatives of bipolar patients are therefore, able to address whether cognitive impairment is a trait like feature of the disorder independent of symptoms **(Chang et al., 2003)**.

Furthermore, family studies of bipolar disorders reveals that individuals with genetic predisposition for the illness do not necessarily manifest the illness, when in fact they do carry genetic risk (genotype) variants linked with the disorder. Similarly, clinical diagnosis may include subjects whose outward symptoms may resemble those of bipolar disorder (known as phenocopies) but who in fact lack the true bipolar genotype. Such misclassification ultimately results into diagnostic confusion **(Risch and Merikangas, 1996)**.

Evidence from the first-degree relative (FDR) studies documented subtle signs of impairment in those at high genetic risk for bipolar disorder in several components of executive function and verbal memory. One possible interpretation of these findings is that patients with greater cognitive impairment are less able to manage their illness and suffer a poorer illness course as a result. However, the presence of subtle deficits in FDRs provides an indication that cognitive impairment may represent a trait vulnerability factor in the development of bipolar disorder which is present before illness onset but worsens as the illness progresses **(Chang et al., 2003)**.

Twin studies of bipolar disorder have shown dramatically different concordance rates, depending on which diagnostic criteria were utilized, how the samples were ascertained, and how assessments were conducted. Difference across studies also reflects changing diagnostic criteria over time. For example, the early twin study by **Bertelsen et al. (1977)**, one of the most highly cited studies demonstrating the high heritability of bipolar disorder, utilized non-structured clinical interviews and diagnosed affectedness according to principles established by Emil Kraepelin in the early twentieth century. More recent twin studies **(Kieseppa et al., 2005)** have relied on semi structured interviews and have utilized modern diagnostic criteria e.g. DSM-IV-TR which require a specific number and duration of symptoms in order to pass the threshold for a diagnosis of the

disorder. These studies have identified substantially lower concordance rates, for both monozygotic and dizygotic twins, than did bertelsen et al 1977 **(Goldberg and Burdick, 2008)**.

A more sophisticated approach would be to use other traits that correlate with the illness status but might be more sensitive than psychiatric illness. These traits are often conceptualized as risk factors for an illness and are termed allied phenotypes. In the late 1960s, Gottesman and Shields coined the term endophenotype to describe these hidden (endo) traits for psychiatric genetic research. An endophenotype is conceptualized as an indicator of biological processes mediating between genotype and phenotype. Using endophenotype markers may be adventitious because they are generally less complex than their associated phenotype and thus may be more readily linked to specific genetic loci **(Gottesman and Gould, 2003)**.

Strakowski et al. (2005) noted that abnormalities in some neuroanatomical regions (e.g. subengual prefrontal cortex, striatum, and amygdala) exist early in the course of illness and may predate illness onset. Other anatomical regions (e.g., cerebellar vermis, lateral ventricles, inferior prefrontal regions) appear to degenerate with repeated affective episodes. These regions may represent the effects of illness progression. Based on these observations and converging data from functional and physiological imaging Strakowski et al have proposed a model of bipolar disorder that involves dysfunction within striatal-thalamic-prefrontal networks and the associated limbic modulating regions (amygdale, midline cerebellum), suggesting that diminished prefrontal modulation of subcortical and medial temporal structures within the anterior limbic network (amygdala, anterior striatum, thalamus results in the dysregulation of mood found in bipolar disorder.

There is little empirical data from which to determine how common it is for cognitive deficits to arise in individuals before

the onset of bipolar disorder because very few studies have been carried out with high risk populations. One notable observation, has been that premorbid intellectual and reading comprehension skills among adolescents who were later hospitalized for non psychotic bipolar mania appear indistinguishable from those who remained psychiatrically healthy **(Reichenberg et al., 2002)**.

By contrast, adolescents who subsequently developed schizophrenia showed marked impairment across multiple intellectual and comprehension measures. Similarly, in the Maudsley family study, premorbid intelligence quotient was found to be lower among individuals who later developed schizophrenia, but not bipolar disorder, as compared with healthy controls **(Toulopoulou et al., 2006)**.

Precisely what characteristics best define the prodromal phase of bipolar disorder remain at issue, and the extent to which cognitive manifestations of illness may be evident before, or alongside, the first emergence of affective signs in high risk individuals is largely unknown **(Correll et al., 2007)**.

Although it is unclear at this time how common cognitive impairments are among individuals diagnosed with bipolar disorder, a significant portion of patients with bipolar disorder complain of cognitive difficulties **(Burdick et al., 2005)**.

Findings with respect to the impact of longer duration of illness on cognitive impairment are contradictory. Proton magnetic resonance spectroscopy studies have reported an association between illness duration and hippocampal neuronal loss (as measured by N-acetylaspartate levels) **(Deicken et al., 2003)**.

Regarding the age of onset, several studies did not find a significant relationship between age at onset and cognitive performance **(El Badri et al., 2001)**.

However, the risk of developing dementia seems to increase with the number of episodes in unipolar depressive and bipolar affective disorders. On average, the rate of dementia tended to increase 13% with every episode leading to hospital admission for unipolar patients and 6% with every episode leading to admission for bipolar patients **(Kessing and Andersen, 2004)**.

Furthermore, formal neuropsychological deficits have also been documented in asymptomatic patients who do not complain of cognitive difficulties, indicating that neuropsychological impairments may be more widespread than clinical experience. Indeed, there is now significant evidence that cognitive dysfunction occurs across several domains among patients with bipolar disorder and that these impairments seem to be somewhat independent of mood state and psychotropic usage.

A recent review concluded that the most consistent trait in bipolar disorder appear to be verbal learning and memory, sustained attention, and executive functioning **(Quraishi and Frangou, 2002)**.

Thus far, measures of these cognitive domains appear to be the most likely candidate Neurocognitive endophenotype for bipolar disorder **(Glahn et al., 2004)**.

5.4 Trait Markers in Bipolar Affective Disorder

5.4.1 Sustained attention:

Attention is a complex Neurocognitive domain with several subcomponents and represents an important area of focus, because intact attentional capacity is essential to all higher cognitive skills. Sustained attention, or vigilance, is impaired in patients with bipolar disorder regardless of whether they are studied during periods of mania or depression and the observed impairment do not remit completely during euthymia, in addition selective attention deficits during acute episodes do not normalize during euthymia **(Clark et al., 2005)**.

These broad patterns of attentional deficits were not causally related to residual symptomatology, supporting their trait like characteristics **(Thompson et al., 2005)**.

5.4.2 Memory:

Given that acute mania is associated with dysregulation of a multitude of brain systems, it is perhaps not surprising that memory is also impaired. Although the general assumption in the past was that memory recovered with resolution of the acute phase of illness, evidence suggests that functional recovery of all memory systems is not complete. The impact of bipolar disorder on certain aspects of memory is substantial, detectable even in the euthymic or asymptomatic phase of the disease, and perhaps a function of total illness burden. Despite recognition that memory deficits may persist into the euthymic phase of illness, there is an unfortunate paucity of data examining the extent of which this deficit contribute to the ongoing functional impairment that is apparent in some people with bipolar disorder **(Ferrier et al., 2004)**.

The term memory encompasses several relatively discrete neural system see figure 2.

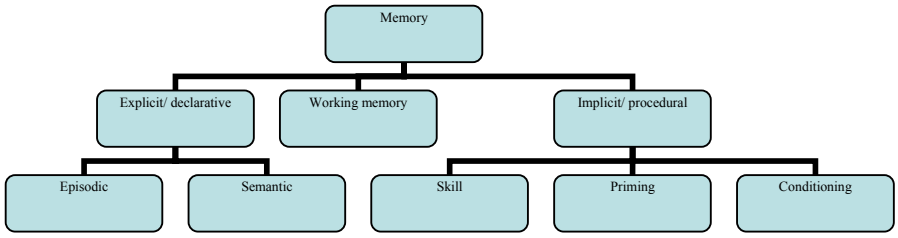

Figure 2: Memory subtypes (cognitive dysfunction in bipolar disorder Goldberg and Burdick 2008)

Explicit memory, which can also be called declarative memory, requires conscious and intentional recollection of information that can be assessed directly by measures of recall and recognition. Explicit memory includes both semantic and

episodic forms: semantic memory is related to factual knowledge and language acquisition and is generally resistant to decline until extensive neural damage occurs, such as in dementia. There is no reliable evidence that semantic memory is impaired in mood disorder. Episodic memory, which is the memory for past events, is more vulnerable, however, and is impaired in several psychiatric disorders, including bipolar disorder **(Elgamal et al., 2008)**.

Several studies have evaluated verbal memory function in bipolar patient across a range of mood states, and generally have reported that patients with bipolar disorder are impaired on tests of recall even in the euthymic state, whereas recognition is generally affected only in the symptomatic phase of illness **(Martinez-Aron et al., 2004 a)**.

Verbal memory is the cognitive domain that has been most consistently associated with duration of illness. In their systemic review, **Robinson & Ferrier, (2006)** showed that five of eleven studies reported at least a significant relationship between chronicity of bipolar disorder and a cognitive measure and the length of illness negatively correlated with cognitive tests.

Patients with bipolar disorder overall appear to use a similar semantic clustering i.e. organizational strategy to that used by healthy controls but show impaired encoding of verbal information **(Bearden et al., 2006)**.

In general, most studies report that recall memory, is subtype of explicit declarative memory, remains impaired in patients with euthymic bipolar disorder **(Depp et al., 2007)**.

Implicit memory, which is also identified as non declarative or procedural memory, includes the acquisition of skills, priming, and conditioning. In contrast to explicit memory, implicit memory does not require intentional and conscious recollection of learned material; examples include driving a car,

playing a musical instrument, or correctly speaking one's native language. Retention and retrieval are exhibited without the awareness of remembering the event **(Elgamal et al., 2008)**.

Although explicit memory function in patient with bipolar disorder has been studied in some detail, only a few studies have evaluated implicit memory in these patients.

Kwapil et al. (1990) found performance of patients with bipolar disorder on recognition of semantic priming was similar to that of healthy controls and better than that of patients with schizophrenia **(Altshuler et al., 2004)**.

This is not surprising, given that implicit memory is not impaired in patients with korsakoff syndrome **(Kopelman & Corn, 1988)**.

Working memory is a multicomponent system that requires the ability to temporarily store and simultaneously manipulate information. Working memory involves a central executive system that modulates two main subsystems; the phonological and visuospatial. Tasks may access different aspects of working memory or be dependent on other cognitive functions, such as attention, and in fact, there is no agreed-on border that delineates an attention task from a working memory task **(Baddeley, 2001)**.

The results of studies examining working memory in symptomatic bipolar disorder patients favor the existence of a working memory deficit, but this deficit may be a state marker of psychosis **(McGrath et al., 2001)**.

In another study, both symptomatic and euthymic patients performed equivelantly to healthy controls on a delayed response task as a measure of spatial delayed working memory **Thompson et al. (2005)**. Another study of working memory indicated that

independent of psychosis, non depressed, first-episode bipolar patients performed equivalently to healthy controls **(Albus et al., 1996)**.

In contrast to studies of symptomatic patients, majority of studies evaluating euthymic patients do not report problems with working memory. Euthymic patients were significantly impaired compared with controls on a visual memory span backward task, but the difference was not apparent when age, premorbid intelligence, and depressive symptoms were controlled; the deficit on a digit backward test remained significant even after controlling for such variables **(Ferrier et al., 1999)**.

These studies suggest that working memory problems may be apparent on specific aspects of certain tasks although the nature of the underlying deficit that would result in the specific patterns observed is unknown **(Safa Elgamal et al., 2008)**.

Several aspects of memory are reportedly impaired in euthymic bipolar disorder patients. Performance on verbal measures of immediate and delayed recall is impaired in remitted bipolar disorder patients who have low levels of affective symptoms and in patients with strictly defined euthymic bipolar disorder **(Martinez- Aron et al., 2004a)**.

Visual memory performance has received little attention in euthymic bipolar disorder patients; however, deficits on measure of visuospatial recognition in a group of euthymic patients compared with healthy controls had been noticed by **(Rubinsztein et al., 2000)**.

It is important to reiterate that memory is hierarchically subserved by multiple cognitive processes that occur earlier in processing, including attention. Hence, memory may not be reliably assessable in patients with attentional problems unless formal Neurocognitive testing is undertaken. Patients themselves may also report memory difficulties when in fact they may more

accurately have deficits in other domains of information processing e.g. impaired attention or executive function **(Martinez -Aron et al., 2004a)**.

5.4.3 Executive functions:

Recent studies indicate that impaired executive function is the most consistently reported Neurocognitive deficit in euthymic bipolar disorder patients. After controlling variables such as age, estimated intellectual function, and subsyndromal affective symptoms, several studies have demonstrated deficits in components of executive function, including planning, set shifting, cognitive control and verbal fluency **(Goldberg and Burdick, 2008).**

Dixon et al. (2004) assessed the relationship between cognitive function and symptomatology in bipolar disorder by comparing patients during mania, depression, and remission and the results supported the prevalence of executive deficits, including cognitive control (response initiation, strategic thinking, and inhibitory control) across mood states, which persists during euthymia.

5.5 Factors Associated with Poor Cognitive Functioning

The association between psychopathological symptoms and functional disability may be less robust than generally thought, but by contrast, persistent cognitive deficits may be more closely linked to social and occupational functioning as seen in other severe psychiatric disorders such as schizophrenia **(Carpenter and Strauss, 1991)**. The association between affective symptoms and impaired functioning is overestimated by most clinicians, when cognitive deficits more likely consititute better predictors of poor outcome **(Jaeger el al., 2007)**.

5.5.1 Premorbid Deficits:

Precisely what characteristics best define the prodromal phase of bipolar disorder remain at issue, and the extent to which cognitive manifestations of illness may be evident before, or alongside, the first emergence of affective signs in high risk individuals is largely unknown **(Correll et al., 2007)**.

5.5.2 Genetic Contribution:

Support to genetic contribution to cognitive dysfunction in bipolar disorder is found in a study by **Decina et al. (1983)** in which children of bipolar proband had significantly higher verbal IQ (VIQ) than performance IQ (PIQ) scores as measured by the Wechsler Intelligence scale for children- revised.

Cornblatt et al. (1992) studied children with an affectively ill parent and observed some degree of attentional impairment using a continuous performance test. Nevertheless, consistent with the findings in affected adult, the deficits in affective risk children were of lesser magnitude than those of schizophrenia risk children, not stable over time, and not directly related to later behavioral disturbance.

Winters et al. (1981) found that the high risk children showed increased reaction time on visual search task but did not demonstrate dysfunctions in other cognitive domains. Finally, **McDonough et al. (2002)** reported a significantly higher incidence of PIQ-VIQ discrepancy in subjects at high risk for bipolar disorder than in healthy controls. Moreover, the high risk group performed worse than healthy controls on measures of reading, spelling and arithmetic.

5.5.3 Psychotic Symptoms:

The presence of psychotic symptoms, or specifically the previous history of psychotic symptoms, appears to be associated with poor cognitive functioning in patients with bipolar disorder **Rocca et al. (2008)**, although not all studies agree **(Selva et al., 2007)**.

Albus et al. (1996) studied first-episode patients with and without paychotic symptoms. Those patients with psychotic symptoms showed poorer performance on cognitive measures, independent of diagnosis (unipolar disorder, bipolar disorder, schizophrenia). Consistent with these findings, **Martinez -Aran et al. (2008)** observed that bipolar patients with a prior history of psychotic symptoms were more impaired on verbal memory functioning than patients without such a history. In contrast, current evidence indicates that in schizophrenia, cognitive dysfunction is a more stable trait and is associated with negative and disorganized syndromes rather than with positive symptoms.

5.5.4 Bipolar Subtypes

Harkavy et al. (2006) found that both bipolar I and bipolar II patients performed significantly worse than healthy controls on a wide range of Neurocognitive measures. Moreover, although performance on most measures was comparable between bipolar I and bipolar II subjects, it was significantly poorer for bipolar II than bipolar I subjects on a psychomotor task and on a measure of selective attention inhibition.

Torrent et al. (2006) in contrast, reported that although bipolar II patients were impaired on an executive function task, bipolar I subjects were generally more impaired than patients with bipolar II disorder, perhaps related to a history of psychotic symptoms which by definition is absent in bipolar II disorder, which is still a matter of debate. However, cognitive problems may be more inclusive of the bipolar spectrum.

Tavares et al. (2007) studies a group of unipolar depressed unmedicated patients, and found pervasive executive dysfunction, suggesting that these cognitive deficits are not specific to the bipolar spectrum.

5.5.5 Subclinical Symptomatology

There is evidence that many patients with bipolar disorder are symptomatic most of the time, despite adequate treatment. However, in many studies, patients are simply described as euthymic, or recovered. The presence of subsyndromal or persistent residual depressive symptoms has been shown to be associated with more difficulties in social and occupational functioning. However, the direction of causality is not clear because it is feasible that patients with significant psychosocial problems are more likely to develop depressive symptoms **(Altshuler et al., 2002)**.

5.5.6 Hormonal Factors

Hypercortisolemia can occur in depressed and manic phases of bipolar disorder. Some studies have suggested that high levels of cortisol may produce damage to the hippocampus, even after the acute episode has resolved. The hippocampus provides negative feedback to the hypothalamic pituitary adrenal axis and has an important role in declarative memory, emotional processing and vulnerability to stress in patients with mood disorders **(Brown et al., 1999)**.

Nevertheless, a study on the Neurocognitive performance of euthymic bipolar patients did not find any association between cognitive measures and Hypercortisolemia **(Thompson et al., 2005)**.

Abnormal elevation of Homocysteine, the homologue of cysteine and metabolite of methionine, has been implicated as a correlate of several cardiovascular, metabolic, and central nervous system disorders. Elevated levels of Homocysteine have been associated with cognitive impairment in other wise healthy older adults, and at least one recent report suggests that the presence of elevated Homocysteine levels in euthymic bipolar disorder patients may, independent of age, be associated with overall cognitive deficits and, in particular, impairment in

attention, language, and immediate recall **(Dittmann et al., 2007)**.

There is also a growing interest in the role of Homocysteine and folate metabolism in depression; it remains unknown whether l methylfolate supplementation could exert a beneficial effect on cognitive problems associated with depression **(Dittmann et al., 2007)**.

5.5.7 Duration of illness

Life time duration of bipolar disorder has been associated with cognitive dysfunction **(Johnstone, 1985)**, and negative impact on memory and executive functions has been found. **Van Gorp et al. (1998)** findings with respect to the impact of longer duration of illness on cognitive impairment are contradictory. The length of illness negatively correlated with scores on tests of executivce function **(Thompson et al., 2005)** psychomotor speed **(Martinez -Aran et al., 2004a)**, and verbal memory **(Canvangh et al., 2002)**. Proton magnetic resonance spectroscopy studies also have reported an association between illness duration and hippocampal neuronal loss as measured by N-acetylaspartate levels **(Deicken et al., 2003)**.

Verbal memory is the cognitive domain that has been most consistently associated with duration of illness. In this regard a higher number of past manic episodes were also associated with poorer performance on verbal memory **(Thompson et al., 2005)**.

5.5.8 Length of Euthymia

Duration of euthymia is the length of time an individual is in clinical remission before neuropsychological testing. None of the studies have reported any significant associations between duration of euthymia and performance on cognitive tests **(Thompson et al., 2005)**.

5.5.9 Number of Episodes

Cognitive deficits in euthymic patients seem to be related to the frequency of episodes in both bipolar and unipolar patients, with manic episodes impacting neuropsychological impairment most extensively **(Martinez-Aran et al., 2004b)**.

Moreover, the risk of the eventual development of dementia in patients with either unipolar depression or bipolar disorder increases as a function of episode number. Rapid cycling and severity of the episodes may also contribute to Neurocognitive impairment **(Martinez-Aran et al., 2004b)**.

Number of episodes of either polarity has been associated with diminished verbal fluency in euthymic bipolar patients as compared with healthy controls **(Rocca et al., 2008)**.

Rapid cycling and severity of episodes may also contribute to Neurocognitive impairment **(Johnson and Magaro, 1987)**. Convincing correlations between cognitive impairment and number of episodes make a strong argument for improved long term management.

5.5.10 Number of Hospitalizations

Most studies have reported that bipolar patients with a higher number of hospitalizations demonstrate poorer performance on cognitive measures.

Rubinsztein et al. (2000) described a relationship between visual memory measures and the number of admissions, whereas **Martinez-Aran et al. (2004b)** observed that the number of hospitalizations correlated with verbal memory performance. **Thompson et al. (2005)** reported relationships between number of hospitalizations and several neuropsychological domains, including verbal fluency, spatial memory, psychomotor speed, and executive function.

Zubieta et al. (2001) described a specific pattern of relationship between executive functioning measures and admissions for mania.

Clark et al. (2002), in contrast, reported a relation ship between cognitive performance on several tasks and admissions for depressive episodes. It is likely that the number of hospital admissions constitutes an indirect measure of the severity of individual episodes as well as of the course of illness.

5.5.11 Effect of Psychotropics

Studies that report iatrogenic effects of psychotropic agents are limited by variations in assessment measures and drug doses, frequent combination drug regimens, diverse clinical groups with disorders other than bipolar disorder e.g. epilepsy, migraine and neuropathic pain. In addition, inferences about the Neurocognitive effects of psychotropic agent in psychiatric disorders other than bipolar illness e.g. schizophrenia further complicate interpretation about disease-versus drug-specific effects. Furthermore, clinical parameters such as chronicity or the number of recurrent affective episodes may impinge on Neurocognitive dimensions such as verbal fluency and early information processing. However with several specific exceptions, most psychotropic agents cause only relatively mild cognitive problems in patients with bipolar disorder. Most notably, these include diminished associative fluency, verbal memory, and motor performance associated with lithium, subtle deficits related to learning, memory and reaction time associated with Divalproex or Carbamazepine, motor slowing, memory impairment, and word finding difficulty with Topiramate, overall cognitive dulling with anticholinergic agents and disinhibition as well as impaired attention and memory with benzodiazepines. Moreover, cognitive complaints that may be related to medications are often transient or dose dependent, and monitoring for several weeks may be advisable to determine

whether they subside, before assuming the need to discontinue a treatment **(Goldberg and Burdick, 2008)**.

6. Comorbidity on BPAD Cognitive Functions

Regarding comorbidity, There were no differences in comorbidity between bipolar I and bipolar II. Both lifetime and current Axis I comorbidity were associated with an earlier age of onset. Current Axis I comorbidity was associated with history of both cycle acceleration and more severe episodes over time **(Brieger, 2000)**.

Large epidemiological studies have found that a high proportion (more than 50%) of bipolar subjects in North America have a lifetime history of alcohol abuse/dependency **(Fogarty et al., 1994)**. Bipolar subjects with a history of alcohol dependence had additional decrements in executive (i.e., frontal lobe) functions when compared with controls **(Van Gorp et al., 1998).**

The prevalence of drug abuse is difficult to estimate, as drug users often have an interest – for example for legal reasons – in not confirming their problem. Therefore the quality of diagnostic information gathered from persons with a drug problem is often low, resulting in unclear reliability of such "dual diagnoses" **(Bryant et al., 1992)**.

Lifetime diagnoses of anxiety disorders are very common in bipolar patients. Panic disorders are particularly frequent amongst subjects with bipolar disorders. Epidemiological studies found an 18–33% frequency. A connection has also been postulated between bipolar disorder and obsessive–compulsive disorder (OCD) **(McElroy et al., 1996)**.

Anxiety symptoms or full syndromes are common in patients with bipolar disorder, appearing in half or more of

individuals surveyed in community based samples **(Grant et al., 2005)**.

Anxiety also has been shown to be associated with psychopathology in mood spectrum disorders with psychotic features. In bipolar disorder, anxiety is related to poor functional outcome and suicidality. Specifically, generalized and social anxiety disorders appear associated with current suicidal ideation and behaviors in outpatients with bipolar disorder. The association of anxiety with bipolar disorder is important both theoretically and clinically. Anxiety is known to impact negatively and significantly on the cognitive interpretation of feared stimuli, and it is likely that this, in combination with the cognitive deficits that commonly occur in bipolar disorders, contributes to the poorer prognosis that patients with comorbid anxiety manifest **(Simon et al., 2007b)**.

Most studies agree that in bipolar patients cluster B personality disorders (antisocial, borderline, narcissistic, histrionic) are more common than cluster A or cluster C personality disorder This is not very surprising, as there is a certain overlap between diagnostic criteria for cluster B personality disorders and bipolar disorders **(Zarate and Tohen, 1999b)**. Bipolar patients with personality disorders differed from bipolar patients without personality disorders in the severity of their residual mood symptoms, even during remission **(George et al., 2003).**

There are several other disorders in which affected subjects have been reported to exhibit bipolar affective disorder Symptomatology more frequently than expected. These include body dysmorphic disorder, somatization disorder, and bulimia. Nevertheless, for these disorders the available data do not permit any more than hypothetical conclusions **(Perugi et al., 1997)**.

Migraine is significantly more frequent in bipolar patients than in controls **(Breslau et al., 1994)**.

Secondary manias can probably occur in almost any general medical condition that affects the central nervous system **(Sax & Strakowski, (1999).** The most frequent precipitants of mania were corticosteroids, human immunodeficiency virus (HIV) infection, and Temperolimbic epilepsy. The most frequent precipitants of depression were stroke, Parkinson's disease, and HIV infection (**Rundell & Wise 1989).**

RESULTS

Sample characteristics:

A- Demographic characteristics:

Regarding the demographic data the sample of our study consisted of 150 subjects. Fifty diagnosed as multiple episode BAD in remission. (Thirty were males=60% 20 females=40%). fifty diagnosed as having first episode BAD in remission (33 males=66%, 17 females=34%) and 50 cross matched healthy control subjects 29 males=58%, 21 females=42%). The mean age of the multiple episode group was 36.1+/- 7.8, for the single episode was 26.4+/- 4.7 and for the control group was 31.3+/- 8.07.

There were no statistical significance difference between the group of patients and the control subjects regarding the age, gender, religion, marital status, education, occupational level, and this is described in Table 1 which represents the mean values and standard deviations of demographic characteristics of patients and the control group.

Table (1): Sociodemographic sample characteristics

Variable	single		Multiple		Control				
Age	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**f**	**P**	**Sig**
	26.48	4.75	36.16	7.835	38.6	7.84	1.755	0.018	NS
Sex	**freq**	**%**	**freq**	**%**	**Freq**	**%**	**Chi sq**	P	**sig**
Male	33	66	30	60	29	58	0.731	0.694	NS
female	17	34	20	40	21	42			
Religion									
Muslim	48	96	47	94	49	98	1.042	0.594	NS
Christian	2	4	3	6	1	2			
Marital status									
Married	27	27.8	30	30.9	30	60	12.098	0.147	NS
Single	23	51.1	15	33.3	17	34			
Divorced			4	100	2	50			
Widow			2	50	0	50			
total									
Education									
Primary	0	0	2	4	1	2	14.54	0.24	NS
Preparatory	0	0	5	10	1	2			
Secondary	23	46	17	34	12	24			
University	27	54	26	52	36	72			
Post graduate	0	0	0	0	0				
Occupation									
Manual	17	34	16	32	15	30	9.129	0.166	NS
Employer	13	26	13	26	24	48			
Manager	8	16	8	16	6	12			
House wife	12	24	13	26	5	10			

B- Description of clinical characteristics of the patients:

Clinical characteristics of the patient group including duration of illness, age of onset, number of admissions, number of episodes, duration of longest episode, number of manic episodes, and depressive, and number of ECT sessions. All are described in table 2.

Table (2): Description of the main clinical characteristics of group II patients

	Mean	+/- SD
Duration of illness(years)	12.4	7.0
Age of onset	24.2	4.06
Number of admission	4.4	1.5
No of episodes	5.800	2.02
Longest duration episode (weeks)	7.2	3.02
Manic episodes	4.54	2.02
Depressive episodes	1.26	1.32
ECT number	36.4	12.5

All the patients were diagnosed as bipolar affective disorder. Group I were presented in remission after their single manic episode. Another 50 patients, group II classified according to our operational diagnosis as having multiple episode bipolar affective disorder. They were presented in remission; 36 (72%) had a recent episode of mania and 14 (28%) had a recent episode of depression before remission. All of the patients had psychotic features along the course of their illness. As regards family history; 33 (22%) patients had positive family history While 67 (44%) patients had negative family history of psychiatric illness.

Table (3): Description of Hamilton and young mania scale among group I and II

	Mean	+/- SD
HDRS	5.15	2.64
YMRS	3.21	1.59

Results show that patients showed no residual affective symptoms during the study.

COMPARISON BETWEEN ALL GROUPS

Comparison between all variances using ANOVA test showed high significant difference between all groups in all tests except there was no statistical difference in between IQ. Results showed in table 4, 5, 6.

Table (4): Comparison between group II, group I and control group using ANOVA test regarding trail A making test and Trail B making test and WCST

	Multiple N=50		Single N=50		Control N=50		f	p
	Mean	**SD**	**mean**	**SD**	**Mean**	**SD**		
Trail A	152.0	45.46	94.4000	7.71957	83.7047	4.21423	94.605	.000
Trail B	369.4	286.35	264.50E2	40.19201	232.562	23.23804	9.135	.000
WCST1	28.620	12.233	26.1400	6.91939	10.5200	3.72657	68.313	.000
WCST 2	2.020	1.846	4.4000	1.44279	5.8400	.42185	98.505	.000

Trail A= trail A making test, Trail B= Trail B making test, WCST 1= Wisconsin card sorting test perseveration error, WCST2= Wisconsin card sorting test category completion.

The table shows that multiple episode performed significantly worse than first and control in all tests of trail A, trail B, and WCST and first episode group performed worse than healthy control in all tests.

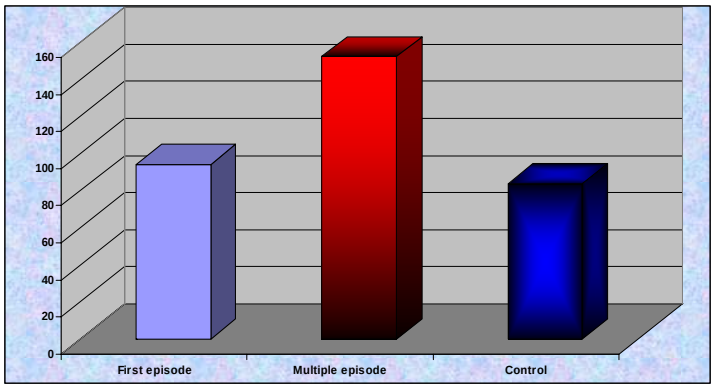

Figure (3): Bar chart showing comparison between the three studied groups as regard trail A.

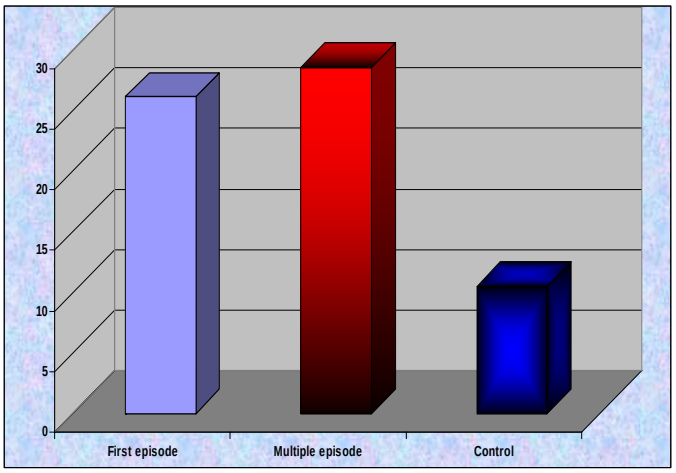

Figure (4): Bar chart showing comparison between the three studied groups as regard WCST.

Table (5): Comparison between group II, group I and control group using ANOVA regarding Wechsler IQ (WAIS)

	Multiple N=50		Single N=50		Control N=50		F	P
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Comprehension	11.90	3.30	11.300	1.7641	10.44	2.97	3.530	0.032
Arithmetic	7.90	2.51	7.100	1.2817	8.18	2.96	2.80	0.064
Digit span	8.32	1.62	6.820	1.0240	8.82	1.64	25.38	0.000
Similarity	11.06	2.67	9.180	0.8253	11.68	2.07	20.933	0.000
Vocabulary	11.88	2.17	9.580	0.6727	9.84	1.74	28.995	0.000
Picture arrangement	11.28	1.64	7.620	2.009	9.76	2.68	36.384	0.000
Picture combination	10.98	1.34	9.300	1.1293	10.38	1.49	20.391	0.000
Block design	8.70	1.50	6.520	0.735	9.76	2.53	44.366	0.000
Object assembly	9.54	2.10	7.000	0.606	10.94	2.12	64.407	0.000
Digit symbol	8.92	1.27	7.360	0.525	11.02	2.48	62.580	0.000
Verbal IQ	95.20	11.34	90.220	6.024	100.58	9.71	15.531	0.000
Perform IQ	104.8	8.78	84.860	4.798	104.06	9.83	97.371	0.000
Total IQ	94.94	20.45	86.580	4.616	100.8	8.87	14.926	0.000

WAIS= Wechsler intelligent quotient.

The table shows that there was a statistical significant difference between the groups regarding all WAIS subscales

Table (6): Comparison between group II, group I and control group using ANOVA test regarding memory as tested by the WMS-R

	Multiple N=50		Single N=50		Control N=50		f	p
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Information	5.560	0.704	5.320	.47121	5.9800	.14142	22.672	.000
Mental control	4.540	1.417	4.780	1.2743	5.7800	.76372	15.389	.000
Logic memory	9.910	3.333	11.910	1.1939	13.9300	1.71729	39.140	.000
Digital sp forward	5.020	1.039	4.140	0.3505	6.4400	.54060	135.011	.000
Digit sp back	4.400	1.370	3.660	0.4785	5.3000	.78895	37.076	.000
Associative learn	20.710	7.334	17.300	2.0652	21.8240	1.49892	13.819	.000
Total memory	65.120	11.231	62.930	3.3012	74.5100	4.08018	36.934	.000

WMS-R= Wechsler memory revised.

The table shows that there was a statistical difference between all groups, and total memory was much affected in single episode than in multiple episodes. The logic memory was less affected in single episode than on multiple episodes.

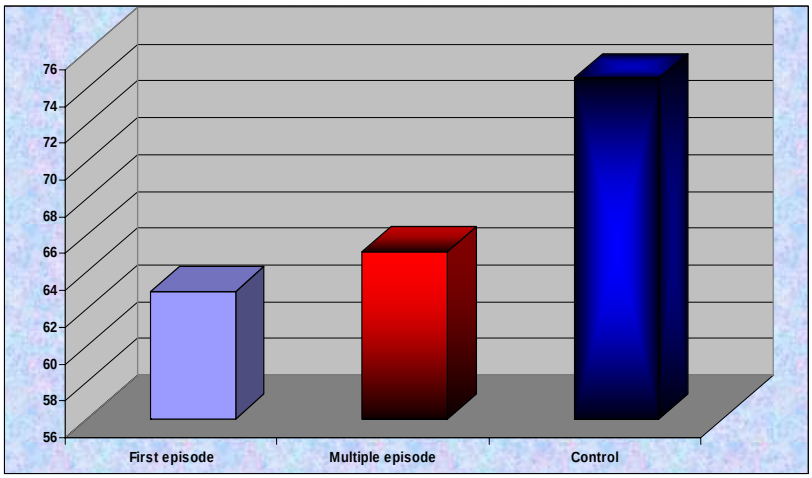

Figure (5): Bar chart showing comparison between the three studied groups as regard memory.

Difference between males and female BAD patients regarding Attention, Executive Functions, IQ and Memory.

Table (7): Comparison between male and female patients regarding Attention, Executive Functions, IQ and Memory

Variable	Male N= 63		Female N= 37		t	p	Sig
	Mean	+/- SD	Mean	+/- SD			
Trail A	112.9	46.9	105.5	25.7	1.101	0.273	NS
Trail B	293.6	218.6	281.2	70.4	0.417	0.678	NS
WCST 1	22.3	11.3	20.9	12.1	0.695	0.488	NS
WCST 2	3.9	2.2	4.3	1.9	-0.88	0.380	NS
Total IQ	99.7	21.4	103	14.1	-1.065	0.289	NS
Logic memory	11.4	3.2	12.7	1.6	-2.653	0.009	VHS
Visual reproduction	10.7	1.7	10.7	1.01	0.269	0.788	NS
Total memory	66.750	9.745	68.741	6.664	01.367	0.174	NS

Trail A=trail A making test, Trail B=trail B making test. WCST1=Wisconsin card sorting test perseveration errors, WCST2=Wisconsin card sorting test category competitions

The table shows that there was no statistical difference between both male and female patients regarding Trail A, trail B, WCST, WAIS and total WMS-R. However, there is a statistical significant difference among the verbal memory test (logic memory) in favor of female bipolar patients.

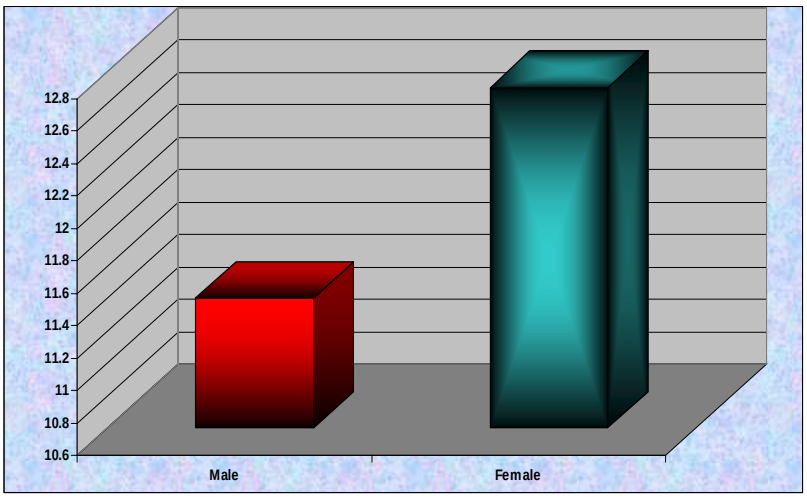

Figure (6): Bar chart showing comparison between males and females as regard logic memory.

Difference between group I patients and healthy control group regarding Executive Function and Attention.

Table (8): Comparison between single episode patients (group I) and control group regarding trail A, trail B, and WCST

Variable	single N=50		Control N=50		t	p	Sig
	Mean	+/- SD	Mean	+/- SD			
Trail A	94.00	7.719	83.704	4.214	8.599	0.000	VHS
Trail B	264.5	40.192	232.5	23.238	4.865	0.000	VHS
WCST 1	26.14	6.919	10.520	3.726	14.054	0.000	VHS
WCST 2	4.400	1.442	5.840	0.421	-6.774	0.000	VHS

The table shows that single episode patients performed worse than control group on Trail A, Trail B, WCST, and the results were highly statistically significant.

Table (9): Comparison between group I and control group regarding WMS-R

	Single N=50		Control N=50		t	P	Sig
	Mean	**+/- SD**	**Mean**	**+/- SD**			
Information	5.320	0.471	5.980	0.141	-9.468	0.000	VHS
Mental Control	4.780	1.274	5.780	0.763	-4.759	0.000	VHS
Logic memory	11.910	1.193	13.930	1.717	-6.829	0.000	VHS
Digit span forward	4.140	0.350	6.440	0.540	-25.243	0.000	VHS
Digit span backward	3.660	0.478	5.300	0.7889	-12.518	0.000	VHS
Visual reproduction	10.800	1.010	10.660	0.960	0.710	0.479	NS
Total memory	62.930	3.301	74.51	4.080	-15.601	0.000	VHS

WMS-R = Wechsler memory revised.

The table shows that first episode patients performed worse than healthy control group and the results were highly statistically significant except for the visual reproduction subscale of WMS-R which showed no statistical significance.

Multiple episode patients (group II) and healthy control group:

Table (10): Comparison between multiple episodes patients and control group regarding trail A, trail B, and WCST

	Multiple (n=50)		Control (n=50)		t	P	Sig
	Mean	**+/- SD**	**Mean**	**+/- SD**			
Trail A	152.1	45.4	83.7	42.1	10.588	0.000	VHS
Trail B	369.4	289.35	232.5	23.238	3.368	0.001	VHS
WCST 1	28.620	12.23	10.520	3.726	10.008	0.000	VHS
WCST 2	2.02	1.84	5.84	0.421	-14.265	0.000	VHS

Trail A=trail A making test, Trail B=trail B making test. WCST1=Wisconsin card sorting test perseveration errors, WCST2=Wisconsin card sorting test category competitions.

The table shows that multiple episode patients performed worse than healthy control group regarding trail A, trail B, and WCST. And the results showed a statistical significance.

Table (11): Comparison between group II patients and control group regarding WMS-R and its subtests

	Multiple (n=50)		Control (n=50)		t	P	Sig
	Mean	**+/- SD**	**Mean**	**+/- SD**			
Information	5.65	0.70	5.98	0.141	-4.133	0.000	VHS
Mental Control	4.54	1.41	5.78	0.76	-5.44	0.000	VHS
Logic memory	9.91	3.33	13.9	1.71	-7.581	0.000	VHS
Digit span forward	5.02	1.03	6.4	0.54	-8.568	0.000	VHS
Digit span backward	4.40	1.37	5.3	0.78	-4.025	0.000	VHS
Visual reproduction	10.68	2.15	10.66	0.96	-0.60	0.952	NS
Total memory	65.12	11.23	74.51	4.08	-5.556	0.000	VHS

WMS-R= Wechsler memory revised.

The table shows that group II patients performed worse than healthy control group regarding total memory score as tested by WMS-R. However, the visual reproduction subtest did not show a statistical significance difference.

Difference between group II patients and group I patients regarding Attention and Executive Functions

Table (12): Comparison between group II patients and group I patients as tested by Trail A, Trail B, and WCST

Variable	Multiple N=50		single N=50		t	p	Sig
	Mean	+/- SD	Mean	+/- SD			
Trail A	152.	45.46	94.4000	7.719	8.843	0.000	VHS
Trail B	369.	286.35	264.5	40.192	2.565	0.012	HS
WCST 1	28.62	12.23	26.140	6.919	1.248	0.215	NS
WCST 2	2.02	1.84	4.4000	1.442	-7.183	0.000	VHS

The table shows that multiple episode patients performed worse than first episode patient however the results showed a statistical significant difference in trail A, Trail B and WCST 2 (category completion) but multiple episodes did not show statistical difference in perseveration errors as tested by WCST1.

Table (13): Comparison between group II and group I regarding WAIS and WMS-R

	Multiple N=50		single N=50		t	p	Sig
	Mean	**+/- SD**	**Mean**	**+/- SD**			
Verbal IQ	97.140	10.23	90.220	6.024	4.119	0.000	VHS
Perform IQ	105.9	9.50	84.860	4.798	13.997	0.000	VHS
Total IQ	96.66	20.788	86.580	4.616	3.347	0.001	VHS
Logic memory	9.91	3.333	11.910	1.193	-3.994	0.000	VHS
Visual reproduction	10.68	2.158	10.800	1.010	-0.356	0.723	NS
Total memory	65.12	11.231	62.930	3.301	1.323	0.189	NS

WAIS= Wechsler intelligent quotient, WMS-R= Wechsler memory revised. Logic memory measures = verbal memory, visual reproduction = non verbal memory.

The table shows that multiple episode patients performed better than first episode patient regarding WAIS (Wechsler intelligent quotient- revised), regarding WMS-R (Wechsler memory scale). The table shows that there was no statistical significant difference between the two groups regarding the total memory score, the visual reproduction. However, the logic memory subtest was better favoring the first episode group with a very high statistical difference in between them.

Comparison between bipolar patients with negative family history and patients with positive family history:

Table (14): Comparison between patients with negative family history and patients with positive family history regarding Attention, Executive Functions, Intelligence, and Total Memory as measured by Trail A, Trail B, WCST1 and 2, WAIS and WMS-R

Variable	Negative FH N=67		Positive FH N=33		t	p	Sig
	Mean	+/- SD	Mean	+/- SD			
Trail a	119.1	34.66	131.6	57.17	-1.360	0.177	NS
Trail b	299.7	65.88	351.9	354.6	-1.171	0.245	NS
WCST 1	28.059	11.246	26.000	6.595	0.971	0.334	NS
WCST 2	3.25	2.054	3.121	2.027	0.305	0.761	NS
Total IQ	91.76	18.425	91.33	8.56	0.127	0.900	NS
Total memory	64.41	8.135	63.227	8.724	0.672	0.503	NS

Trail A= trail A making test, Trail B= Trail B making test, WCST1=Wisconsin card sorting test perseveration error, WCST2=Wisconsin card sorting test category completion.

The table shows that there was no statistical significance between the two groups regarding trail A, trail B, WCST 1 and 2, WAIS and WMS-R.

Correlation between number of ECT and executive functions, attention, and total memory score:

Table (15): Correlation between number of ECT and trail A, Trail B, WCST and Total Memory Score

NO of ECT	Pearson	P	Sig
Trail A	-0.666***	0.000	VHS
Trail B	-0.251**	0.012	HS
WCST 1	-0.125	0.215	NS
WCST 2	0.587**	0.000	VHS
Total IQ	-0.320**	0.001	VHS
Logic memory	-0.204*	0.042	S
Total memory	-0.132	0.189	NS

The table shows that increase in the ECT is inversely proportionate with trail A test and trail B test with a significant statistical difference. The WCST1 showed no statistical significance. ECT was directly proportionate with WCST2, and inversely proportionate with the total IQ with a high statistical significance. Number of ECT was inversely proportionate to the logic memory subtest of Wechsler memory scale. But there was no statistical correlation with total memory score.

Correlation between the Duration of illness and cognitive functions:

Correlation between duration of illness and the cognitive functions. Results are shown in table 16.

Table (16): Correlation between duration of illness and Attention, Executive Functions, and Memory as tested by trail A, trail B, WCST 1 and 2, and WMS-R

Duration of illness	Pearson test	Sig 2 tail	Sig
Trail A	0.294***	0.003	VHS
Trail B	0.072	0.477	NS
WCST1	0.288***	0.004	VHS
WCST2	-0.317***	0.001	VHS
Logic memory	0.033	0.744	NS
Visual reproduction	0.237*	0.017	HS
Total memory score	0.231*	0.021	HS

The table shows that duration of illness is directly proportion to trail A test, and directly proportionate to WCST1 and inversely proportionate to WCST2 with a high statistical correlation. The duration of illness was not statistically correlated with the logical memory subtest of Wechsler but was positively correlated with the total WMS-R.

Correlation between number of episodes and cognitive affection

Table (17): Correlation between number of episodes and bipolar disorder regarding attention, executive function, and memory as tested by trail A, trail B, WCST1 and 2, WAIS and WMS-R

No of episodes	Pearson test	Sig 2 tail	Sig
Trail A	**-0.217**	**0.131**	**NS**
Trail B	**-0.029**	**0.840**	**NS**
WCST1	**0.422****	**0.002**	**VHS**
WCST2	**-0.130**	**0.367**	**NS**
Logic memory	**0.010**	**0.945**	**NS**
Visual reproduction	**-0.007**	**0.959**	**NS**
Total memory score	**-0.069**	**0.632**	**NS**

The table shows that number of episodes is positively correlated with the score of WCST 1,

Correlation between Age of onset of illness and attention, executive functions, intelligence and memory as tested by trail A, trail B, WCST 1 and 2, WAIS and WMS-R.

Table (18): Correlation between age of onset and trail A, trail B, WCST 1 and 2, WAIS and WMS-R.

Age of onset	Pearson test	Sig 2 tail	Sig
Trail a	**0.385*** **	**0.000**	**VHS**
Trail b	**0.262*** **	**0.009**	**VHS**
WCST 1	**0.009**	**0.930**	**NS**
WCST 2	**-0.193**	**0.055**	**NS**
Total IQ	**-0.027**	**0.792**	**NS**
Logic memory	**-0.467*** **	**0.000**	**VHS**
Visual reproduction	**-0.198***	**0.048**	**S**
Total memory	**-0.168**	**0.094**	**NS**

The table shows that the age of onset showed positive statistical correlation with the Trail A test, Trail B test but there was no statistical correlation with WCST 1 and 2. Regarding logic memory there was negative statistical correlation with age of onset and negative statistical correlation with visual reproduction (non verbal memory) with no statistical correlation with the total memory score.

DISCUSSION

Bipolar disorder is characterized by intermittent and recurrent episodes of mania and depression. These pathological mood states have a clear impact on cognitive functions Neuropsychological testing aims to determine the pattern of cognitive dysfunction in a disorder via the use of standardized quantitative assessment **(Goldberg and Burdick, 2008).**

Several domains of cognitive function are disrupted in BAD including attention, executive function and memory **(Quraishi and Frangou (2002)**. Bipolar disorder also appears to be characterized by both transient (state related) and enduring (trait-related) changes in cognition. Trait markers may be genetic in origin and may represent potential endophenotype for bipolar disorder. Alternatively, the trait marker may be acquired during the illness course and hence reflect the length of the illness and the number of previous episodes **(Cavanagh et al., 2002).**

The information gained through neuropsychological assessment can be applied at the level of individual patient to guide psychological intervention and monitor treatment **(Stuss and Levine 2002).**

Our aim was to assess objectively the presence of cognitive deficits in bipolar patients in remission, to identify if these deficits represent a reliable trait marker, and to correlate these deficits with the recurrence of the disease.

Cognitive dysfunction

The cognitive functions studied in this thesis were chosen on the basis of the results of multiple studies which showed that the commonly affected cognitive functions in case of bipolar disorder were the memory, executive functions and attention **(Ferrier et al., 2004)**.

Comparison between all groups using ANOVA test regarding attention and executive functions, intelligent quotient and memory as tested by trail A, Trail B and WCST, WAIS and WMS-R as shown in table 4, 5, 6 respectively, revealed that there was significant statistical difference between all groups.

Comparing attention, executive functions, IQ and memory between males and females patients as measured by trail A, trail B, WCST, WAIS and WMS-R as shown in table 7.

Results showed no significant difference regarding attention, and executive function. However, females performed better in the verbal memory as tested by the logic memory subtest of WMS-R. This could be explained by studies of cognition in normal subjects which have reported that, on average, women perform better than men on tasks of verbal fluency and verbal memory. Such normal cognitive differences may be associated with sex differences in brain structures **Collaer & Hines (1995)**. Preliminary magnetic resonance imaging studies of small groups of normal subjects have reported that with adjustment for total brain volume, women had a larger hippocampus, dorsolateral prefrontal cortex and superior temporal gyrus than men **(Filipek et al., 1994)**. These results were consistent with **Rabie et al. (2002)** who found that female bipolar patients performed better than male patients in the test of verbal paired associate which is a test of verbal memory.

In contrast with our study **Kolur et al. (2006)** did not fi nd a significant difference among male and females regarding cognitive functions. And inconsistent with **Ferrier et al. (2004)**

who found no gender differences between patients with bipolar disorder in similar studies.

In our study group I patients performed worse than healthy control group regarding executive functions and attention as tested by trail A, trail B and WCST as shown in table 8.

Executive function is a broad term that refers to a collection of higher level cognitive processes, including planning, working memory, strategy deployment, inhibitory control and cognitive flexibility **(Stuss & Levine, 2002)**. Executive function is considered to be intrinsically related to the integrity of the prefrontal cortex (PFC). Damage to the ventral aspects of the PFC is associated with a distinct profile in which patients' behavior becomes socially inappropriate, impulsive and emotionally labile. With tendency to make risky decisions associated with long term negative repercussions **(Bechara et al., 1994)**.

The presence of cognitive impairment as early as the first episode in bipolar patients might point to the hypothesis that cognitive deficit is a trait marker in bipolar disorder. Recent structural neuroimaging, histopathological, and neuropsychological studies suggest the presence of trait abnormalities in frontal cortices of individuals with bipolar disorder. Decreases in gray matter volume, glial cell density and nonpyramidal cell density in layer II in frontal cortices were also present.

Strakowski et al. (2005) noted that abnormalities in some neuroanatomical regions (e.g. subgenual prefrontal cortex, striatum, and amygdala) exist early in the course of illness and may predate illness onset. Therefore, executive functions and attention being a function of frontal lobe may explain their impairment in first episode bipolar patients.

Moreover, regarding attention; from literature it is apparent that there is an overlap between attention and executive function; as part of executive function (cognitive flexibility) is measured by the ability to shift attention from one task to the other. This could be also explained by the neruoanatomy of brain structures which are affected in bipolar disorder as above mentioned. In consistence with our study, **Najt et al. (2005)** found sustained attention impairment in bipolar patients regardless of whether they are studied during periods of mania or depression and the observed impairment do not remit completely during euthymia **(Zalla et al., 2004; Clark et al., 2005)**. Also, **Thompson et al. (2005)** reported a broad pattern of attentional impairment in a group of euthymic bipolar disorder patients compared with healthy group.

Evidence from other sources suggests that cognitive deficits are evident at an early stage of the illness **(Albus et al., 1996)** and in unaffected first degree relatives of bipolar patients who may share genetic vulnerability to the disorder **(Gourvitch et al., 1999; Ferrier et al., 2004; Zalla et al., 2004; Kieseppa et al., 2005)**. This lends weight to the possibility that cognitive impairment is a trait marker of bipolar patients. Finally monozygotic twins to bipolar patients showed significant impairment on selective attention, sustained attention, executive function, language processing and working declarative memory and these results also prove the hypothesis that discrete cognitive impairment is present before the onset of affective disorder and are genetically transmitted. Thus, cognitive function may be a candidate endophenotype for affective disorders **(Glahn et al., 2004)**.

Regarding memory functions group I showed impaired memory when compared to healthy control as tested by the WMS-R scale shown in table (9).

Given that acute mania is associated with the dysregualtion of a multitude of brain systems, it is perhaps not surprising that memory is also impaired. Although the general assumption in the past was that memory recovered with resolution of the acute phase of illness, evidence suggests that functional recovery of all memory systems is not complete **(Ferrier et al., 2004**). The impact of bipolar disorder on certain aspects of memory is substantial, detectable, even in the euthymic or asymptomatic phase of the disease **(Thompson et al., 2005)**.

Dorsolateral regions of frontal cortex have been implicated in memory functions. Frontal regions, especially prefrontal areas, are also considered important for keeping memory information online to be used in giving a response, also known as working memory. Working memory is the memory that has a limited capacity (7 ± 2 items) and that can be retained without rehearsal for only a short period of time (e.g. 10 seconds) Moreover, temporal regions of the brain most notably the hippocampus are also associated with the formation of new long-term memories. **(Banish et al., 2002)**. Structural changes in these areas in bipolar disorder may account for the memory impairment found early in the disorder. However, non verbal memory did not show a significant difference in our study which is in consistence with **(Van Gorp et al., 1998; Martinez et al., 2004b; Altshuler et al., 2004)** who found no impairment in visual (non verbal) memory in a group of euthymic bipolar patients.

In consistence with our study **Jill et al. (2005)** found that euthymic patients perform poorer than healthy control ones on Rey auditory verbal learning test (RAVLT), a test for verbal memory.

In summary, results of euthymic patients regarding verbal recall favor that the impairment extends into the euthymic phase, which favors considering verbal memory as a trait marker

whereas studies of visual memory in euthymic patients have produced inconsistent findings.

Comparison between group II and healthy control group regarding executive functions and attention as tested by trail A, trail B and WCST shown in table (10)

Our results show that multiple episode patients performed worse than healthy control group. Presence of this impairment among multiple episodes bipolar patients can be explained by the same explanation carried on for single episode bipolar however, the question is whether these impairments progress with the progression of the illness should be put into consideration when comparing both groups together.

Impairment in executive functions among remitted bipolar patients in our study is consistent with the above mentioned correlation between neurocognitive functions and structure brain changes in bipolar disorders. Our results are also in consistence with recent studies which indicates that impaired executive function is the most consistently reported neurocognitive deficit in euthymic bipolar disorder patients **(Krabbendam et al., 2000; Thompson et al., 2005)**.

In contrast with our study **(Cavanagh et al., 2002; Clark et al., 2002)** failed to find impaired executive functions in people with bipolar disorder. However, the discrepancy of the results could be explained by the broad definition of executive functions and its broad range of components that are not all influenced by the bipolar disorder.

Comparison between group II and healthy control group regarding memory as tested by WMS-R scale shown in table (11) our study shows that multiple episodes performed worse than healthy control group in all aspects of the Wechsler memory scale. Results show that verbal memory is impaired and this is consistent with **Jill et al. (2005)**, while the results are also

consistent with **(Van Gorp et al., 1998; Martinez et al., 2004b; Altshuler et al., 2004)** who found no impairment in visual (non verbal) memory in a group of euthymic bipolar patients.

As above mentioned memory impairment is present in first episode patients and persists in the euthymic stage. And this memory impairment belongs to structural changes in the frontal and temporal cortex. And the question is whether this impairment is progressive and shows more impairment with the progression with the illness or not.

Comparison between group II and group I patients regarding executive functions and attention as tested by trail A, trail B, WCST shown in table (12) show that multi episode patients performed worse than first episode patients and this could be explained by the effect of progression of the illness.

On the contrary WCST 1 test was not statistically significant which could be explained by the fact that executive functions is divided into many domains, which could not be all affected equally at the same time by the illness.

It is still unclear when cognitive deficits develop in relation to the natural history of illness. Studies in euthymic bipolar patients have reported correlations between neuropsychological deficits and a greater number of illness episodes and more severe course of illness this association has been interpreted as indicative of a progressive disease process. It has been proposed that stress induced hyperchortisolaemia during an affective episode may result in hippocampal cell toxicity, decreased glucocorticoid receptors and eventual cell and tissue death **(Altshuler, 1993)**. The prefrontal cortex may also be susceptible to stress induced neurotoxicity because it too has glucocorticoid receptors and strong reciprocal connections with the Hippocampus **(Rajkowska, 2000)**. This ongoing destructive process may be responsible for cognitive impairments in bipolar disorder. Although this is a plausible biological mechanism, the direction of causality cannot be determined from the above studies. Associations between illness characteristics and neuropsychological deficits may be an indication that patients with cognitive impairments are more vulnerable to developing severe bipolar disorder. Longitudinal studies within subject are

required to determine whether deficits worsen with time. This study is consistent with several studies that reported that patients with a more severe course of prior illness and greater number of episodes, frequent hospitalizations, suffer greater neurocognitive decline **(Kessing, 1998; Van Gorp et al., 1998; Denicoff et al., 1999).**

One of the confounding factors during neurocognitive testing in bipolar patients is the effect of the medication. However, in their review **Bearden et al. (2007)** suggested that the cognitive impairments in bipolar illness are unlikely to be a primary effect of medication. Furthermore, in a comparison study of euthymic patients with bipolar disorder and controls, neurocognitive impairment was observed not only in patients receiving mood stabilizers monotherapy but also in those who were drug free **Goswami et al. (2002)**. Nonetheless, many patients within this study were taking several psychotropic medications at varying doses, and was unknown what were the effects of combined therapy might be, particularly over time.

Comparison between group II and group I patients regarding memory as tested by WAIS and WMS-R as shown in table 13.

This study shows that verbal memory was more impaired in multiple episode patients as tested by the logic memory subtest of WMS-R. Verbal memory is an episodic explicit memory which is known to be vulnerable to be affected in many psychiatric illnesses including bipolar disorder in contrast to semantic explicit memory which is affected only late after neural loss as in dementia **(Elgamal et al., 2008)**. This is in consistent with **Seidman et al. (2002)** who found that patients with bipolar disorder performed poorly compared with controls on logical memory subtest of WMS-R as a measure of verbal memory. IN general, most studies reported that recall memory – a subtype of explicit declarative memory remains impaired in patients with euthymic bipolar disorder **(Martinez-Aran et al., 2000;**

Goswami et al., 2006; Depp et al., 2007) .In contrast, some investigators have found that the degree of verbal learning impairment diminishes when key variables are controlled, for example **Clark et al. (2002)** observed that after they controlled for mood symptoms, the detected impairment on the California verbal memory test has dissipated**.**

Comparison between bipolar disorders patients with positive family history and bipolar patients with negative family history regarding cognitive functions as tested by the trail a, trail b, WCST, WAIS, and WMS-R scale as shown in table (14) results show that there was not significant difference between the two groups regarding the mentioned cognitive functions.

These results are in consistent with **Kolur et al. (2006)** who found no significant difference in cognitive functions based on presence or absence of family history. This is also consistent with **Goswami et al. (2006)** who reported that genetic influence as reflected in family history of affective disorder, was absent from his study findings, although 59.5% of the group with bipolar disorder had a family history of mood disorder.

Correlations between bipolar patient's cognitive functions (executive functions and attention and memory) and number of ECT sessions received as tested by the Trail A, Trail B, WCST, WAIS, and WMS-R scale shown in table (15)

Surprisingly the results showed that increase in the number of ECT has a negative correlation with the trail A and Trail B test indicating an improvement in the performance of the tests. Results also showed that the number of ECT was inversely proportionate to the IQ score. It was also inversely proportionate to the logic memory score. But the total memory score was not affected.

The impairment in logic memory among patients with more ECT sessions could be explained by the fact that these

patients had more episodes, more hospital admissions, and more duration of illness which could explain their deterioration. However, there was no deterioration in the executive functions and attention in this group of patients.

Since ECT affects both temporal and frontal lobes, it is logical that its effect would not be limited to amnesia, but would involve both memory and non-memory neuropsychological functions **(Calev et al., 1995).**

Sackeim (2000) hypothesizes that the traditional view that amnesia results from damage to medial temporal lobe structures alone may be wrong, since it is known both that frontal lobe damage can result in amnesia as extensive as that seen after ECT and that ECT exerts its most profound effects on the prefrontal cortex.

If this hypothesis holds, then frontal functions must be affected as well as memory.

Three trials, two controlled and one small and uncontrolled, support the theory of frontal lobe involvement in functional impairment, although assessments were carried out only during or immediately after ECT **(Neylan et al., 2001; Rami-Gonzalez et al., 2003; Schulze-Rauschenbach et al., 2005)**.

Regarding IQ, patients with more ECT sessions performed worse than those with fewer sessions. However, the direction of causality is not known whether those patients with less IQ are more vulnerable to severity of affective disorder or the affective disorders cause deterioration of cognitive functions. Thus, when the total number of ECT given are higher is an indication of severity of the illness as a result of the lower IQ or, is it the severity of the illness that lead to the deterioration of the IQ in those patients. Regarding total memory, it had no statistical

correlation with the total number of ECT. Finally, the results of our study could not be interpreted as a direct effect of ECT on our sample since our inclusion criteria excluded any patient who had an ECT 3 months prior to our study and these data could be useful for examining the permanent effect of ECT rather than the immediate ones.

Correlation between duration of illness and bipolar disorder patients regarding cognitive functions as tested by Trail A, Trail B, WCST, WAIS and WMS-R as shown in table (16)

Results show that duration of illness is inversely proportionate with the executive functions and attention. Proton magnetic resonance spectroscopy studies have reported an association between illness duration and hippocampal neuronal loss (as measured by N-Acetyl Aspartate levels) **Deicken et al. (2003)**. In consistent with our study, life time duration of bipolar disorder has been associated with cognitive dysfunction **Johnstone et al. (1985)** and negative impact on executive functions has been found by **Van Gorp et al. (1998)**. Also the length of illness was negatively correlated with scores on tests of executive function (**Clark et al., 2002; Thompson et al., 2005)**.

Regarding memory the results showed no correlation between the verbal memory score and duration of illness. In contrast with our study verbal memory was negatively affected by the duration of illness **(Cavanagh et al., 2002; Deckersbach et al., 2004b**).

Measuring cognitive functions in patients with a long duration of bipolarity could be hindered by several confounds including those which could have a positive impact on the outcome like cognitive behavioral therapy, neuroprotective effect of medications on compliant patients', and perhaps the avoidance of neurotoxic effect of some psychotropic medications in non compliant ones.

Researches show that some medications have a neuroprotective effect especially the mood stabilizing effects of some anticonvulsants particularly those capable of inhibiting excitatory amino acids such as glutamate and other psychotropic medications **(Li et al., 2002)**.

In consistence with our results, **Yucel et al. (2008)** found bilateral increases in volume of the hippocampus over time. And found also some evidence of improvement in verbal memory performance over a 4-year measurement period as assessed by the California Verbal test which is Consistent with preclinical literature supporting the neuroprotective effects of lithium.

It remains largely speculative whether neuroprotection at the cellular level confers clinical benefit for either affective symptoms or neurocognitive functioning. Nevertheless, structural magnetic resonance imaging studies suggest that even brief exposure to lithium (< 4-8 weeks) in patients with bipolar disorder may lead to increases in overall gray matter by 3%-4% **(Moore et al., 2000; Bearden et al., 2007)** and in hippocampal volume **(Bearden et al., 2007; Yucel et al., 2008)**. Moreover, prolonged lithium treatment can normalize the altered striatal shape and decreased anterior cingulated volume present in drug naive patients **(Sassi et al., 2004; Hwang et al., 2006)**.

Additionally, magnetic resonance spectroscopy studies have demonstrated increases in gray matter myoinositil levels, accompanied by decreases in glutamate, glutamine, and gamma amino butyric acid (GABA) concentrations in bipolar disorder patients treated with lithium **Friedman et al. (2004)**. Such increase in gray matter volume is presumed to reflect increased dendritic arborization. However, the clinical significance of such neurotropically associated volumetric increase remains unknown.

It is worth mentioning that none of the following studies have reported any significant associations between duration of euthymia and performance on cognitive tests **(El Badri et al.,**

2001; MacQueen et al., 2001; Clark et al., 2002; Thompson et al., 2005). Since the duration of euthymia did not impact cognition in bipolar patients while the duration of illness had that impact then the effect could be probably due to the number of episode as the effect happens only when the patient was symptomatic not euthymic.

Correlation between number of episodes and executive functions, attention, IQ and memory as tested by trail A, trail B, WCST, WAIS and WMS-R shown in table: (17) the study results show that the number of episodes were inversely correlated with the executive functions which reflects the effect of the progression of the illness and its negative impact on cognitive functions. This is consistent with **Kissing et al. (1998)** who related more cognitive impairment to the more frequency of the episodes, with manic episode effect more extensively as mentioned by **(Van Gorp et al., 1998; Martinez Aran et al., 2004b)**. Regarding attention our study did not show significant correlation with the number of episodes. In consistent with our study **Kolur et al. (2006)** did not find a correlation between the numbers of episodes on subgroup analysis of a group of patients with bipolar disorder.

Regarding verbal memory our results showed non significant correlation with the number of episodes. This is inconsistent with **Rocca et al. (2008)** who found that the number of episode of either polarity has been associated with diminished verbal fluency in euthymic bipolar patients. Furthermore, other studies show that measures that were most strongly correlated with manic episodes were those involving verbal memory **(Cavanagh et al., 2002; Clark et al., 2002; Deckersbach et al., 2004b; Martinez-Aran et al., 2004a)**. Moreover, the risk of eventual development of dementia in patients with either unipolar depression or bipolar disorder increases as a function of episode number **(Rocaa et al., 2008)**. Verbal memory impairment also showed a strong correlation with the number of

previous manic episodes **(Cavanagh et al., 2002; Clark et al., 2002; Deckersbach et al., 2004b; Martinez-Aran et al., 2004a)**.

Correlation between age of onset and executive functions, attention, memory and IQ as tested by trail A, trail B, WCST, WAIS –R and WMS-R as shown in table (18) results of our study showed that the age of onset did not correlate significantly with total memory score, but showed a negative correlation with verbal memory and non verbal memory.

Our study also showed that later Age of onset was inversely correlated with the attention and executive function and this is in consistence with **Martinez-Aran et al. (2004a)** who reported a relationship between later age of onset of bipolar disorder and poorer performance on measures of psychomotor speed and executive functions. In contrast other studies did not find a significant correlation between age of onset and cognitive performance **(El-Badri et al., 2001; Zubieta et al., 2001; Deckersbach et al., 2004b)**.

Limitations

Limitations:

Although this study came out with significant findings yet it is not without limitations:

1. A larger study would preferably target a community sample; this would have needed a large team of researchers, which is beyond the scope of MD thesis. However, the sample of patients included in this study was quite representative for the epidemiological and clinical characteristics of bipolar disorder.
2. Our study was cross sectional one. A more comprehensive study was to perform a longitudinal study to assess cognitive functions in each individual prior to the onset of illness and along the course of the illness. However, this needs larger and more adherent group.
3. A more comprehensive study would correlate the cognitive dysfunction to functional imaging, e.g. PET study. This would have needed a specialized center with guaranteed accuracy and much more resources.
4. Interpretation of the results is sometimes difficult from the neuropsychological point of view because of overlap between the cognitive functions assessed by each test.
5. A more detailed study would consider the effect of medications on cognitive functions, as there is still some debate in literature about its long term effect on cognitive functions.
6. In our study it was difficult to illustrate the effect of each drug separately on the cognitive functions due to absence of patients on monotherapy. Furthermore, the most methodologically effective technique is to examine drug free patients. However, in contemporary clinical practice it is extremely rare to find patients with established bipolar disorder who are medication free.

Recommendations

Recommendation:

- ***Clinical recommendations:***
  1. This study tends to consider executive functions, attention and verbal memory as a trait marker in bipolar affective disorder.
  2. This trait markers would be of value in predicting the prognosis of patients presented with acute polymorphic psychosis, and the future expectations about their diagnosis whether schizophrenia or bipolar disorder.
  3. Impairment in learning and memory might affect the patient's ability to remember directions for medications. This needs psychoeducation to the patient and family.
  4. The presence of cognitive impairments in between attacks may help to explain the difficulties in psychological and occupational functioning in patients with bipolar disorder during remission.
  5. Individuals who are of high risk for bipolar disorder requires close monitoring for early signs of bipolar illness in order to do early intervention followed by psycho-education for the patient and family very early in the course of illness which may help to indirectly slow the progression of cognitive deficits by effectively preventing relapse.
  6. Rehabilitation programs should be adapted to improve cognitive impairment in bipolar disorder.

- ***Future research:***
  1. High risk group studies are a valuable adjunct to investigation into temporal evolution of cognitive dysfunction in bipolar disorder. Additional benefit of such studies is that they are unlikely to be confounded by medication or effects of illness chronicity.

2. More psychometric researches are needed to find more batteries that would cover all cognitive functions and to be more specific to each cognitive domain.
3. Stabilizing the psychometric tests in all research in order of better and more reliable comparison between results.
4. More research is needed to investigate the effect of pharmacotherapy and start to correlate between the neuroprotective effects of some drugs and clinical improvement in cognitive functions of patients.
5. More research into the effects of ECT on cognitive functions.
6. More research into families of patients with Bipolar disorder in order to find out an organic marker for the illness.

Summary and Conclusions

There is a growing consensus that persistent cognitive deficits are common in patients with bipolar disorders even when they are euthymic. Apart from certain exceptions, studies of remitted patients have generally reported deficits in several cognitive domains. However, many of these studies have not controlled for residual affective symptoms, which would have a substantial bearing on their results. When this has been done enduring deficits have been observed in either memory or executive functions, or a combination of these areas. Precisely what characteristics best define the prodromal phase of bipolar disorder remain at issue, and the extent to which cognitive manifestations of illness may be evident before, or alongside, the first emergence of affective signs in high risk individuals is largely unknown. Furthermore, the direction of causality is unclear, mood episodes may adversely affect neuropsychological performance, or impaired cognitive function may contribute to the development and exacerbation of mood symptoms.

Some of the evidence suggests that recurring episodes of bipolar disorder are associated with greater cognitive disturbance. It has been proposed that successive episodes cause subtle damage to key brain areas leading to the neurological and cognitive impairment observed in bipolar disorder. However, the evidence linking cognitive deficits with indicators of severity, progression of the illness is not always consistent. The most direct approach to determine the course of cognitive abnormalities in bipolar disorder would be a longitudinal follow up of first episode subjects with repeated assessment of their cognitive functioning. This is usually difficult and expensive. Alternatively, cognitive functions of patients in their first episodes could be compared with patients who have already experienced multiple episodes. Such strategy has been successfully used in schizophrenia. Unlike other areas of

medicine, psychiatry at present has no biochemical markers or laboratory tests on which to base its diagnosis. Instead subjective assessments form the basis of both clinical and research psychiatric diagnosis. Furthermore, family studies of bipolar disorders reveals that individuals with genetic predisposition for the illness do not necessarily manifest the illness, when in fact they do carry genetic risk (genotype) variants linked with the disorder. Similarly, a clinical diagnosis may include subjects whose outward symptoms may resemble those of bipolar disorder (known as phenocopies) but who in fact lack the true bipolar genotype. Such misclassification resulted into diagnostic confusion and lead to a new approach which is the use of an endophenotype which describes the hidden traits of the illness. It is an indicator of biological processes mediating between genotype and phenotype. Using endophenotype markers may be adventitious because they are generally less complex than their associated phenotype. Two endophenotype considered for bipolar disorder are the neuropsychological assessment, the main concern of our study, and the neuroimaging of bipolar disorder.

Cognitive impairment can have several adverse consequences for patients of BAD in terms of disability, quality of life, and outcome. Individuals with bipolar disorder are at risk for an addiction, they are also at risk of committing suicide or homicide when acting on their delusions. Therefore, this must be a priority area for future research.

So we assessed cognitive functions of a group of euthymic and stable bipolar patients after a single episode. Compared and contrast cognitive profiles of those patients with those who had experienced multiple episodes, both while in remission. The results were compared with a cross matched control group.

The cases were selected from the out patient clinic in the institute of psychological medicine (Ain Shams University). The institute is located in Eastern Cairo, and serves a catchments area

of about the third of Greater Cairo. It serves both urban and rural areas, including areas around Greater Cairo as well, which represents a true random sample of the Egyptian population. There are three outpatient general psychiatry clinics (A, B, and C), working four days per weak.

Two random samples of bipolar disorder patients were chosen one after the first manic episode and the other after multiple episodes. Each group consisted of 50 patients. A cross matched Control group selected consisted of 50 Egyptian individuals with no apparent physical or neuropsychiatric morbidity. They were matched for age, sex, and other demographic variables as far as possible with the patient group. They have no family history of any psychiatric disorder. The control group was selected randomly from workers and employers working in Ain Shams University Hospitals. A semi structured sheet was done for the entire sample including sociodemographic factors to ensure that sample was matched. ICD-10 symptoms check list to diagnose bipolarity, Hamilton and Young mania scale was given to ensure absence of residual affective symptoms followed by neurocognitive assessment including the following trail A (attention and concentration), trail B, WCST-CV (executive functions), WAIS to exclude any patient who are mentally subnormal, and WMS-R (memory assessment) to the patient groups. Regarding the control group a general health questionnaire was given to ensure that they are free from any illness which was followed by the same battery done for the patient group.

The main findings in the study were

There was no statistical significant difference among the three groups regarding the occupational level and socioeconomic status, which ensures that the three groups were matched.

Regarding the demographic data the sample of our study consisted of 150 subjects. Fifty diagnosed as multiple episode BAD in remission. (Thirty were males=60% 20 females=40%). fifty diagnosed as having first episode BAD in remission (33

males=66%, 17 females=34%) and 50 cross matched healthy control subjects 29 males=58%, 21 females=42%).

The mean age of the multiple episode bipolar groups was 36.1+/-7.8, for the first episode bipolar patients was 26.4 +/- 4.7 and the control group was 38.6+/-7.8.

By the end of our study we came up with the following conclusions:

Results show that there was no difference between male and female bipolar patients regarding attention, executive functions and total memory score. Yet, there was statistical difference in verbal memory favoring female patients.

Patients with ***single manic episode*** showed impairment in attention, executive function and total memory score compared to healthy control. The presence of such impairment in bipolar patients as early as the first episode and their continuous presence even in remission indicate that these cognitive deficits are trait markers and could be used as an endophenotype for the illness. However, regarding the temporal evolution, it is still not clear whether they occurred prior to the illness or accompanying the illness.

Patients with bipolar disorder with ***multiple episodes*** in remission performed worse than those with single episode patients' in attention, executive function which indicates that there is progressive nature of the illness.

Results show that bipolar patients with positive ***family history*** of psychiatric illness did not differ in the cognitive impairments compared to those with negative family history.

Results show that the earlier age of onset is associated with more declines in executive functions and attention.

Results show that ***duration of illness*** is inversely proportionate to attention and executive functions.

Results show that number of episodes is inversely related to executive functions.

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الملخص العربى

هناك اتفاق على وجود قصور فى القدرات المعرفيه عند مرضي الاضطراب الوجدانى ثنائى القطب حتى بعد الشفاء من الأعراض الوجدانية. وبخلاف بعض الاستثناءات اجمعت الدراسات على ذلك على الرغم من ان العديد من هذه الدراسات لم تراعى تأثير الاعراض الوجدانيه على نتائج القدرات المعرفية التى تؤدى الى نتائج غير دقيقة.

تحديدا متى يظهر القصور فى القدرات المعرفية فهو أمر غير مؤكد. فقد تبدأ قبل ظهور الاعراض الوجدانية او تصاحبها او تكون نتيجة لها غير معروف تحديدا. وهل المرضى ذوى القدرات المعرفية الضعيفة يصابون باعراض وجدانية اشد ام أن الأعراض الوجدانية تؤثر سلبيا على القدرات المعرفية ، هذا غير محدد.

ولا تزال نتائج الدراسات حول قصور القدرات المعرفية او تدهورها الناتج عن مده المرض ، عدد نوبات الاصابة وعوامل اخرى غير محددة وتظهر الدراسات نتائج غير متفقة.

الطريقة المثلى لدراسة المرض هى عن طريق الدراسة الطولية لمتابعه نفس المريض منذ الاصابة الاولى ومتابعة القدرات المعرفية مع كل تكرار للاصابة ولكن هذه الطريقة مكلفة وتستلزم فترة زمنيه اطول للبحث مع وجود احتمالية لعدم استمرار المريض بالبحث. البديل لهذه النوعية من الدراسات هى مقارنه القدرات المعرفية بين مجموعة من المرضى من ذوى الاصابة الواحده بمجموعه اخرى من ذوى الاصابات المتعدده وقد تم استخدام هذه النوعية من الدراسات فى مرضى الفصام بنجاح.

على خلاف فروع الطب الاخرى لا توجد للامراض النفسية وسيلة معملية للتشخيص ولكن يتم التشخيص عن طريق الملاحظه السريرية . ادى ذلك الى البحث عن وسيله جديدة للتشخيص ولمتابعة المرض.

بعض أقارب المرضى يشتركون معهم فى حمل الجينات المرضية ولا يظهر عليهم المرض وعلى النقيض بعض الاشخاص تظهر عليهم الاعراض المرضية بدون وجود الجين الحامل للمرض .... هذا ادى الى اختيار وسيلة تشخيصية اخرى فى ما بين الجينات المرضية والصوره الخارجية للمرض . واجمع الباحثون على اختيار وسيلة وسطية بين الجينات والمظهر الخارجى للمرض وهى اما الاختبارات المعرفية السيكولوجيه، أوتصوير المخ مثل التصوير المغناطيسى بالرنين.

فى النهاية مرض الاضطراب الوجدانى ثنائى القطب من الامراض المنتشرة وتؤدى الى تدهور فى جوده الحياة للمرضى المصابين بالاضافة الى امكانية اصابة المريض بالادمان او وجود ميول انتحارية لديه. بالأضافه الي ما يؤديه المرض من عبئاً ثقيلاً علي الخدمات الصحيه و علي الأقتصاد القومي ككل.

أدى ذلك إلى غزارة البحث فى هذا المرض من اجل توفير حياة افضل للمريض والوقاية من المضاعفات المرضية الاخرى السابق ذكرها.

فى هذا البحث تم اختيار مجموعة من المرضى المصابون اصابة واحده بعد تمام الشفاء ومقارنتهم بمجموعة اخرى مصابة عدة مرات ايضا بعد الشفاء ومقارنة المجموعتين بمجموعة ضابطة. تم اختيار العينة من المرضى المترددين على العيادات الخارجية بمركز الطب النفسى بمستشفى عين شمس الجامعي. وتم عمل الاختبارات المعرفية التالية ، اختبار وكسلر للذكاء ، اختبار وكسلر للذاكرة ، اختبار تريل أ ، ب للانتباة ، ويسكونسين للوظائف التنفيذية. تم عمل اختبار هميلتون للأكتئاب واختبار ينج للهوس للتأكد من عدم وجود اى اعراض وجدانية مما قد يؤثر فى دقه النتائج.

نتائج البحث :-

- اظهرت نتائج هذا البحث وجود تدهور فى القدرات المعرفية فى المرضى ذوى الاصابة الاولى والاصابة المتعدده مقارنة بالمجموعة الضابطة. وأيضا وجود تدهور فى الاصابة المتعددة اكثر مقارنة بالاصابة الأولى.
- أظهرت نتائج هذا البحث عن تأثر وظيفة الذاكرة اللغوية فى المجموعة الذكورية مقارن بالمجموعة الانثوية . مع عدم وجود فروق في باقي الأختبارات.
- مده المرض لها علاقه عكسيه بالوظائف التنفيذية والأنتباة.
- عدد نوبات الأصابه بالمرض لها علاقه عكسيه بالوظائف التنفيذية.
- السن عند بدايه ظهور الأعراض المرضيه له علاقه عكسيه بالذاكره اللغويه والمرئيه و بالوظائف التنفيذية و الانتباة.

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