Bergische Universität Wuppertal

Fachbereich G: Bildungswissenschaften

Abteilung Für Klinische Psychologie und Psychotherapie

Sleep and Problem Solving In Schizophrenia

PhD. Thesis

Author: Muniarajan Ramakrishnan

Supervisors: Prof. Dr. Gudrun Sartory

Prof. Dr. Reinhard Pietrowsky

Wuppertal, 2011

I dedicate this Doctoral Thesis to my Beloved parents

Die Dissertation kann wie folgt zitiert werden:

urn:nbn:de:hbz:468-20120217-152705-2
[http://nbn-resolving.de/urn/resolver.pl?urn=urn%3Anbn%3Ade%3Ahbz%3A468-20120217-152705-2]

"Knowledge is serene & indestructible wealth; there is nothing else in benefits to compare"

ACKNOWLEDGEMENT

From the depth of my heart, my deepest gratitude and sincere thanks to her ***Excellency Honourable Prof. Dr. Gudrun Sartory*** for all her untiring and innumerable support from the very first day I sent a mail requesting her supervision. She has been the source of spontaneous encouragement. Without her patience, support and provoking suggestions, completion of this would be impossible. My very special thanks go to my co-supervisor ***Prof. Dr. Reinhard Pietrowsky*** for supporting this PhD thesis in all possible ways and in particular for critical reading of this work. His suggestions and valuable comments surely helped vastly to improve this thesis. Furthermore, i thank him for providing me with the opportunity to work at his sleep laboratory. I also would like to thank the other honorable members of my Doctoral committee.

Beside my supervisors and committee, i am tremendously thankful to Honorable PD Dr. Karin Elsesser for her instrumental suggestions, support and cheering up during my difficult times. My sincere thanks to my colleagues and diploma students worked on this project. My deepest thanks to Sonay Bal, Andre Wannemüller and Gabriele Maria Spitzer family. I am grateful to Dr. Janine Hauthal and the CGS team for great support. Last but not least, undoubtedly i am grateful to my parents for educating me, moral support, and unconditional help and for every single thing I have now. I immensely value the time and energy participants of this research study.

Finally, my sincere thanks to the German higher authorities and fabulous people for allowing me to do my doctorate in this beautiful country. They will be remembered for ever. I am appreciating every moment.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Abbreviations

APA - American Psychiatric Association

AMI - Autobiographical Memory Inventory

ANOVA - Analysis of Variance

CANTLAB - Cambridge Neuropsychological Test Automated Battery

CPT – Continuous Performance Test

CT – Computerized Tomography

COWAT - Controlled Oral Word Association Test

CVLT - California Verbal Learning Test

DAS - Disability Assessment Schedule

DSM – Diagnostic and Statistical Manual of Mental Disorders

EEG – Electrocardiography

EMG – Electromyography

EOG – Electrooculography

ERP - Event Related Potential

fMRI - functional Magnetic Resonance Imaging

GABA – Gamma Aminobutyric Acid

ICD – International Classification of Diseases

MWT-B – Multiple Choice Word Comprehension Test

MANOVA - Multivariate Analysis of Variance

MHVS – The Mill Hill Vocabulary Scale

NART IQ – National Adult Reading Test IQ

NREM – non-rapid Eye Movement

NIRS – Near-Infrared Spectroscopy

PANSS - Positive and Negative Syndrome Scale

PET - Positive Emission Tomography

REM - Rapid Eye Movement

SCID - Structured Clinical Interview

SCWT – Stroop Colour-Word Test/Task

SPECT – Single Photon Emission Tomography

SPSS - Statistical Package for the Social Sciences

SWS - Slow Wave Sleep

TOL - Tower of London Test

TMT - Trail Making Test

VLMT - Verbal Learning and Memory Test

WISC – Wisconsin Card Sorting Test

WHO – World Health Organization

WAIS - Wechsler Adult Intelligence Scale

WMS - Wechsler Memory Scale

3-D CTL Test – Three-Dimensional Computerized Tower of London Test

CHAPTER 1

INTRODUCTION

1.1 Schizophrenia

Schizophrenia is a severe mental disorder characterized by disturbances in thinking, sense of self, affect, motivation, behaviour and interpersonal functioning. The pathology of schizophrenia is also heterogeneous. Although social, environmental and genetic risk have been identified as factors that play a role in the development of schizophrenia, the exact etiology still remains unclear (Ferreira, 1961). Currently available treatments can reduce the severity of the symptoms but cannot cure the disorder.

1.1.1 Evolution and Origins of the Concept of Schizophrenia

Schizophrenia was first identified as a disease by Benedict Augustin Morel (1809–1873). Benedict Augustin Morel, a French physician, coined the term "Dementia Praecox" in 1860 to describe a mental disorder which initially struck in young adult age and subsequently lead to degeneration of mental functioning. The term "Dementia Praecox" was further systematically elucidated by German psychiatrist Emil Kraepelin (1856-1926). Dementia praecox, as it was thought to be a degeneration of the brain (Dementia), beginning at a relatively young age (praecox) and ultimately leading to the disintegration of the entire personality. Emil Kraepelin believed biological and genetic malfunction to be the primary causes for this mental disease and thought to that the delusions, hallucinations and bizarre behavioral abnormalities seen in people with schizophrenia could be ultimately traced to a physical abnormality or disease.

Eugen Bleuler (1857-1939), a Swiss psychiatrist, opposed Emil Kraepelin's views that dementia praecox is a disease of the brain or irreversible brain damage. In 1911, he introduced a striking change in both the terminology and understanding of the disorder. He coined the term "Schizophrenia" and suggested that the name of the disease is changed because of its characteristic disorganization of several mental functions. He divided symptoms of schizophrenia into four fundamental symptoms, which he thought were characteristic of schizophrenia. The four As identified by Eugen Bleuler are given below (Table 1.1).

EUGEN BLEULER'S FOUR As
➢ Associational disturbances (Thought Disorder)
➢ Ambivalence (Refers to an underlying emotional attitude with co-existing contradictory impulses (Bleuler 1911)
➢ Affect (Problems in outward expression of emotion) and
➢ Autism (Impaired communication, excessive rigidity and emotional detachment)

Table 1.1 Eugen Bleuler's four As

The influential new perspective on defining schizophrenia features was provided by a German psychiatrist, Kurt Schneider (1887-1967). In 1959, Schneider listed a group of symptoms and called them as "First-Rank symptoms" (Table 1.2). He tried to make the diagnosis of schizophrenia more precise by identifying a certain group of symptoms as being characteristic of schizophrenia. He attempted to identify features that were highly specific to schizophrenia. The characteristic symptoms of schizophrenia chosen by him varied considerably from the basic and fundamental symptoms of Eugen Bleuler. Kurt Schneider emphasised diagnostically differentiating symptoms that could

be precisely observed and occurred frequently to be instrumental in the differential diagnosis (Andreasen & Carpenter, 1993).

SCHNEIDERIAN FIRST-RANK SYMPTOMS
➢ Audible thoughts
➢ Voices heard arguing or discussing or both
➢ Voices heard commenting one's action
➢ Somatic hallucination
➢ Thought withdrawal and other experiences of influenced thought
➢ Thought insertion (The delusion that thoughts are being inserted into one's mind by someone else)
➢ Thought broadcasting or thought diffusion and delusional perception

Table 1.2 Schneiderian First-Rank Symptoms

Schneiderian first-rank symptoms have played a prominent role in the recent diagnostic systems: in International Classification of Diseases (ICD-10) as well as in Diagnostic and Statistical Manual of Mental Disorders DSM-III and DSM-IV. Both ICD-10 and DSM-IV emphasize the presence of the First-Rank symptoms as being symptomatically sufficient for the diagnosis of schizophrenia.

1.1.2 Symptoms of Schizophrenia

The symptoms of schizophrenia vary widely in severity and type from individual to individual (Tandon et al., 2009). Nancy Andreasen (1985) suggested two symptom dimensions as a result of a factor analytic study. She developed measurement scales of symptoms found in factor analytic studies that some heaped together with certain other symptoms occurred. She described one factor called "positive symptoms" - including delusions and hallucinations - and the other factor as "negative symptoms" - language impoverishment and social

withdrawal. The symptoms of schizophrenia fall into two categories "positive" and "negative" symptoms. Overt psychotic behavior such as delusions, hallucinations, disorganized speech and disturbed behavior are called positive symptoms. The positive symptoms are exaggerations or distortions of normal thoughts, emotions and behavior. Positive symptoms serve as signs of presence of very uncommon thoughts and perceptions that involve a loss of contact with reality. Delusions or deeply entrenched false beliefs are the most common disturbance of thought content associated with schizophrenia patients. Hallucinations are false perception not corresponding to the objective stimuli present in the environment. Hallucinations are false perceptions involving one of the five senses although they are auditory ex: patients hear voices in most cases. Although hallucinations do not correspond to actual stimuli, they are real to patients with schizophrenia. Disorganized speech is also one of the common symptoms in schizophrenia. Their language can be grossly distorted to the point of incomprehensibility. Some people with schizophrenia speak with odd intonations and lack the normal expressiveness and gestures common in everyday talk.

Many people with schizophrenia also have negative symptoms. Negative symptoms are those that involve functioning lower than the level of behavior regarded as normal (Halgin & Whitbourne, 2005). The most common negative symptoms are alogia, affective flattening and avolition. Alogia is a loss of words or notable lack of spontaneity or responsiveness in conversation. In affective flattening, an individual seems unresponsive, with relatively motionless body and facial reactions while maintaining minimal eye contact. The symptoms of avolition involve a lack of initiative and unwillingness to act. Many patients with schizophrenia also experience anhedonia, a loss of interest in or ability to experience pleasure from activities that most of people find appealing.

1.1.3 Diagnosis of Schizophrenia – Modern Classifications

The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) (American Psychiatric Association, 1994) and the International Classification of Diseases (ICD-10) (World Health Organization, 1993) provides the criteria for diagnosing schizophrenia and other mental disorders. The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) is most widely used system for diagnosing schizophrenia and other mental disorders. The American psychiatric association presents the criteria for diagnosis of schizophrenia in the "Diagnostic and Statistical Manual of Mental Disorders IV" (Table 1.3). The ICD-10 classification for mental and behavioral disorders also plays a vital role in the diagnosis of schizophrenia and related disorders. The criteria and standard requirements for diagnosis of schizophrenia as per ICD-10 are given below (Table 1.4).

1.1.4 DSM-IV versus ICD-10 Classification Systems

On the surface the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) and the International Classification of Diseases (ICD-10) classifications appears very similar. There are differences exist. Even though efforts have been made to structure the gap between ICD-10 and DSM-IV and push them closer, remarkable differences still remain related to subtypes, definition and duration of schizophrenia and also classification of certain other psychotic disorders classified with schizophrenia. ICD-10 categorizes schizotypal disorder, persistent delusional disorder, acute and transient psychotic disorders, induced delusional disorder and schizoaffective disorder. The Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition- (DSM-IV) does not include the category of schizotypal disorders with psychotic disorders but, categorized under cluster A personality disorders.

Table 1.3 American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders IV

Diagnostic and Statistical Manual For Mental Disorders, Fourth Edition- (DSM-IV) Diagnostic Criteria For Schizophrenia

A) Characteristic symptoms: Two or more for the following, each present for a significant portion of time during a one month period or less if sufficiently treated:
- Delusions.
- Hallucinations.
- Disorganized speech (Ex: Frequent derailment or incoherence).
- Grossly disorganized or catatonic behavior.
- Negative symptoms, that is, affective flattening, alogia or avolition.

Note: Only one criterion- A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.

B) Social/Occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-are are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic or occupational achievement).

C) Duration: Continuous signs of the disturbances persist for at least 6 months. This 6 month period must include at last 1 month of symptoms (or less if successfully treated) that meet Criterion A (that is, active-phase symptoms) and may include prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbances may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated from (for example, odd beliefs, unusual perceptual experiences).

D) Schizoaffective and Mood Disorder exclusion: Schizoaffective Disorder and Mood Disorder with Psychotic Features have been ruled out because either no major depressive, manic or mixed episodes have occurred during active-phase symptoms; their total duration has been brief relative to the duration of the active and residual periods.

E) Substance/General medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance (For example: drug of abuse, a medication) or a general medical condition.

F) Relationship to a Perverse Developmental Disorder: If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of the Schizophrenia is made only if prominent delusions or hallucinations are present for at least a month (Or less if successfully treated).

American Psychiatric Association, Diagnostic and statistical Manual of Mental Disorders IV (APA 1994)

Source: Adapted from American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. IV Edition. Washington, DC: American Psychiatric Association.

Table 1.4 International Classification of Diseases ICD-10 Diagnostic Criteria for Schizophrenia (WHO 1993).

International Classification of Diseases ICD-10 Diagnostic Criteria For Schizophrenia
Either at least one of the syndromes, symptoms, and sign listed below under (1), or at least two of the symptoms and signs listed under (2), Should be present for most of the time during an episode of psychotic illness lasting for at least one month (Or at some time during most of the days): 1) <u>At least one of the following must be present:</u> ➢ a) Thought echo, thought insertion or withdrawal, or thought broadcasting. ➢ b) Delusions of control, influence or passivity, clearly referred to body or limb Movements or specific thoughts, actions or sensations; delusional perception. ➢ c) Hallucinatory voices giving a running commentary on the patient's behavior, or discussing the patient among themselves, or other types of hallucinatory voices coming from some part of the body. ➢ d) Persistent delusions of other kinds that are culturally inappropriate and completely impossible (ex: Being able to control the weather, or being in communication with aliens from another world). 2) <u>Or at least two of the following:</u> ➢ a) Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions without clear affective content, or by persistent over-valued ideas. ➢ b) Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech. ➢ c) Catatonic behavior, such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses. 3) <u>Most Commonly Used Exclusion Criteria:</u> ➢ 1) If the patient also meets criteria for manic episode or depressive episode, the criteria listed under I (1) and I (2) above must have been met before the disturbance of mood developed. ➢ 2) The disorder is not attributable to organic brain disease, or to alcohol or drug-related intoxication, dependence, or withdrawal.
International Classification of Diseases (ICD-10) Diagnostic Criteria for Schizophrenia (WHO 1993)

<u>Source</u>: Adapted from the ICD-10 Classification of Mental and Behavioural Disorders –Diagnostic Criteria for Research – World Health Organization, Geneva (1993).

1.1.5 Subtypes of Schizophrenia

Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) distinguishes between several different types of schizophrenia. The four basic subtypes of schizophrenia described in DSM-IV are paranoid, hebephrenic (disorganized in DSM-IV), catatonic and undifferentiated. The subtypes are distinguished by the combination of symptoms a person experiences.

1.1.5.1 Paranoid Schizophrenia

Paranoid schizophrenia is characterized predominantly by the presence of persecution or grandeur. People with paranoid type are preoccupied with one or more bizarre delusions or have auditory hallucinations, but without disorganized speech or disturbed behavior. People with paranoid type of schizophrenia show limited deterioration of mental aptitude, emotional effect and behavior than other schizophrenic subtypes.

1.1.5.2 Disorganized type

The disorganized type is characterized by an amalgam of symptoms that incorporates disturbed behavior, disorganized speech and irrelevant effect. Disorganized symptoms refer to the presence of confusion in thinking, inability to think clearly, disordered or incoherent speech, and grossly disorganized behavior like rhythmic gestures. Absurd grinning and grimacing are also frequent in patients with disorganized type.

1.1.5.3 Catatonic type

When the prominent symptom in a person with schizophrenia is bizarre motor behaviors or postural or movement abnormalities, the person is diagnosed as having catatonic type. Stuporous catatonia and excited catatonia are two forms

of catatonic schizophrenic subtype. The common characteristic of stuporous and excited catatonia forms is the obvious abnormality of motor behavior. The person with stuporous catatonia may be in a state of absolute stupor or may show a vast decline in extemporaneous movements and activity. Patients with excited catatonia show an extreme psychomotor agitation. Periodic catatonia is an infrequent but fascinating form of catatonia.

1.1.5.4 Undifferentiated type

Undifferentiated type is used when a person shows complex symptoms of schizophrenia such as hallucinations, delusions, incoherence and disturbed behavior, but does not meet the criteria for paranoid or catatonic or disorganized types of schizophrenia.

The other two diagnostic classifications in the schizophrenia spectrum disorders are residual type and schizophreniform disorder.

1.1.5.5 Residual type

Residual type is characterized by a past history of at least one episode of schizophrenia, but no longer does. This diagnosis made when there are prominent negative symptoms or two or more deteriorating characteristic symptoms, but the person currently lacks prominent positive symptoms (ex: hallucinations, delusions, disorganized speech or catatonic behavior).

1.1.5.6 Schizophreniform Disorder

Individuals with schizophreniform disorder have psychotic symptoms that are same as those found in schizophrenia, except for period (Halgin &

Whitbourne, 2005). Schizophreniform disorder symptoms last longer than those of brief psychotic disorder but not so long that the practitioner would diagnose the individual as having schizophrenia. Most importantly, active symptoms last from one to six months. If the symptoms last more than six months, the practitioner is more likely to make the diagnosis of schizophrenia (Halgin & Whitbourne, 2005). Some people with schizophreniform disorder will completely recover and will not suffer in further episodes of psychosis (Walker et al., 2004).

1.1.5.7 Schizoaffective Disorder

Among other psychotic disorders, the diagnosis of schizoaffective disorder made to the individual who experience either major depressive episode, a manic episode or mixed episode at the same time that they meet the diagnosis for schizophrenia (Halgin & Whitbourne, 2005). In this disorder, during the period of active symptoms, there is the duration of minimum two weeks during which the individual does not have prominent mood symptoms but continues to have psychotic symptoms (ex: delusions, hallucinations).

1.1.6 Phases of Schizophrenia

The onset of clinical symptoms of schizophrenia may be sudden or gradual and not dramatic (Walker et al., 2004). There are three phases of schizophrenia. Important to the diagnosis of schizophrenia is a marked disturbance lasting at least six months. During this six-month period is an active phase of symptoms, such as hallucinations, delusions, disorganized speech, disturbed behaviour and negative symptoms (Halgin & Whitbourne, 2005). The active period does not appear without warning signs. Most but not everyone have a prodromal phase, a period earlier to the active phase which people show a gradual deterioration in social and interpersonal functioning. During this phase

individuals may begin to lose interest in their usual pursuit and socially isolate themselves. Prodromal phase is characterized by much maladaptive behaviour, such as eccentricity, poor grooming, inappropriate emotionality, unusual beliefs, odd perceptual experience, inability to work productively and decreased energy (Lieberman et al., 2001; Walker et al., 2004). For many individuals, the active phase is followed by a residual phase (Halgin & Whitbourne, 2005). In residual phase individuals may be listless, have a trouble in concentration and be abjure. Moreover the symptoms in this phase are similar to those of prodromal period.

1.1.7 Epidemiology of Schizophrenia

1.1.7.1 Prevalence

The frequencies of occurrence of a disease are usually given in prevalence or incidence rates. Prevalence is the ratio of the number of occurrences of a disease or disorder to the number of units at risk in the population. The relative amount of people who manifest a disorder or disease at a given point of time is point prevalence. The relative amount of people who manifest a disorder or disease over a definite period of time is period prevalence. The relative amount of the people who have ever manifested a disease or disorder, who are alive on a given day is a life time prevalence. Lifetime morbid risk is the chance factor of an individual developing the disease or disorder during a specific period of their life.

The annual occurrence rate of schizophrenia is 0.2 - 0.4 per 1000, unrelated to gender with a life time prevalence of about 1 percent in the general population (Jablensky, 1999; Carpenter & Buchanan, 1994). McGrath et al. (2008) in their systematic review used 1,721 prevalence estimates from 188 studies (132 general population based studies, 15 migrant studies and 41 studies reported the

prevalence in other special groups) related to the prevalence of schizophrenia. Of that 132 general population studies, they identified 21 for point prevalence, 34 for period prevalence and 24 for life time prevalence. Nine studies for life time morbid risk, 44 studies in patient census derived data. On the basis of combined prevalence data, they found no significant difference between urban or rural or mixed urban and rural sites and no significant difference across periods. They also found that the prevalence and incidence of schizophrenia in migrant was higher compared to the native-born individuals. Their study found a significant difference in distribution of prevalence estimates when sorted by economic status, while developed nations having higher estimates than less developed economies.

1.1.7.2 Gender, Age and Cultural Features

The age of onset in schizophrenia for men is between 18 and 25, whereas modal age of onset for women is between 25 and mid of thirties (Halgin & Whitbourne, 2005). Schizophrenia onset is quite uncommon for individual below 10 years of age or over 40 years. Male is disproportionately large numbers in previous studies of childhood onset schizophrenia (Spencer & Campbell, 1994).

Epidemiological studies reveal that no culture, race or society found to be free from schizophrenia. Schizophrenia represents a serious public health problem (World Health Organisation, 1997). Previous research studies revealed that the rates of schizophrenia are further developed in some ethnic minority groups such as second-generation of Afro-Caribbean people in the United Kingdom (Boydell et al., 2001).

1.1.7.3 Comorbidity

Psychological comorbidities are common among schizophrenia patients. Substance abuse is the most common comorbidity in schizophrenia patients (Strakowski et al., 1993; Rosenthal, 1998; Buckley et al., 2009) includes stimulants, alcohol, hallucinogens, caffeine and tobacco. Patients with schizophrenia are also more likely to be diagnosed with comorbid disorders including anxiety (Sim et al., 2006; Hwang & Bermanzohn, 2001) and depressive disorders (Buckley et al., 2009).

Strakowski et al. (1993) study on comorbidity in psychosis included 102 patients with a first episode psychosis successively hospitalized. They examined the patients for the presence of psychiatric disorders and medical conditions. Patients were diagnosed based on structured Clinical Interview for DSM-III-R and rated weekly on symptom rating scales. They measured final symptom rating scales, duration of hospitalization and prognosis and recovery on the basis on the stands of operationalized criteria. Their study found comorbid diagnoses in 52% of the patients and 37.7% with multiple comorbid diagnoses. Their study reported that the most common comorbid diagnosis was substance abuse. They also reported patients with affective psychoses were notably more likely than those with nonaffective psychoses to have a comorbid substance abuse diagnosis.

1.1.8 Etiology of Schizophrenia

1.1.8.1 Biological Explanations

Biological elucidations of schizophrenia have their origins in writings of Emil Kraepelin (1913). Emil Kraepelin thought of schizophrenia as disease caused by degeneration of brain tissue. Kraepelin idea gave way for later probing of such factors as brain structure and genetics, which are currently contributing to a person's biological vulnerability to schizophrenia.

1.1.8.2 Structural and Functional Brain Abnormalities

Arrival of sophisticated neuroimaging technologies such as computerized tomography, magnet resonance imaging (MRI), single photon emission computed tomography (SPECT), positron emission tomography (PET) and functional magnetic resonance imaging (FMRI) enabled researchers to study the structural and functional abnormalities precisely. The most common structural abnormalities consistently reported findings using computerized tomography has been that brains of individual with schizophrenia have enlarged ventricles, specifically enlargement of lateral ventricles (Chua & McKenna, 1995). In neuroimaging studies hippocampus is repeatedly found to distinguish patients with schizophrenia from normal individuals (Schmajuk, 2001). The advent of magnet resonance imaging scan technique gives higher resolution imaging and distinguishes the brain white matter and gray matter. This allows researchers to study the complex areas of the brain. Several disorders of the brain may lead to psychotic symptoms (Miller & Manson, 2002).

Gur et al. (2000) investigated reduced dorsal and orbital prefrontal gray matter volume in schizophrenia. They performed magnetic resonance imaging (MRI) in 70 schizophrenia patients and 81 normal controls. They quantified gray and white matter volumes of different areas of the prefrontal cortex. They found reduced volume of prefrontal gray matter in patients with schizophrenia.

1.1.8.3 Neurotransmitters

Neurotransmitters are the chemical messengers that allow the brain cells to interact with each other. The thought of neurotransmitter abnormality in schizophrenia dates long back. Earlier neurotransmitter theories concentrated on epinephrine and followed by noradrenaline, glutamate, and serotonin abnormalities in patients with schizophrenia. Despite of all, dopamine gained support and dominates neurotransmitters basis of schizophrenia research. The dopamine hypothesis predicts that the symptoms found in schizophrenia such as hallucinations, delusions and deficits of attention can be attributed to an excessive activity of neurons that mutually exchange information with each other through dopamine transmission (Carlsson, 1988).

The two supporting proofs for this hypothesis were: antipsychotic medications reduce the occurrence of delusions and hallucinations by blocking the dopamine receptor called as D2 receptor. The dopamine receptors D2 involved in schizophrenia (Abi-Dargham et al., 2000). The antipsychotic medications with blocking effects of D2 improve the schizophrenia symptoms (Seeman, 1980). The second proof is that the antipsychotic drugs biochemically related to dopamine such as amphetamines or L-Dopa increases the chances of psychotic symptoms.

Beyond dopamine, blood tests for serotonin levels (Csernansky & Newcomer, 1994) and effects of clozapine in schizophrenia patients (Masellis at al., 1998) show evidence that those abnormalities in serotonin neurotransmitter system likely to play a key role in schizophrenia than early thoughts.

Masellis at al. (1998) study on clinical reactivity to clozapine medication in patients with schizophrenia used pharmacokinetic approach in 185 patients with

schizophrenia who have been likely evaluated for medication clozapine response. Their study demonstrated the vital role of serotonin neurotransmitter system.

Emerging evidence suggests that abnormalities in GABAergic neurons in the prefrontal brain circuits may also play a role in progression of cognitive impairments concord with schizophrenia (Carlsson at al., 2001).

Cholinergic projections to the cortex and the basal forebrain play an intact role in various cognitive processes seem to be impaired in schizophrenia (Robbins, 1997). The current result patterns for cholinergic involvement in schizophrenia are not as abundant as the serotonergic involvement, but still convincing.

1.1.8.4 Genetic Explanations

One of the well grounded finding in schizophrenia is that certain vulnerability to the illness transmitted genetically (Heston, 1966; Gottesman, 1991; Tsuang et al., 2001). The four types of studies in an attempt to assess the contributions of genetics are family and twin studies, adoption studies, high-risk studies and biological marker studies. The family pattern of schizophrenia gives persuasive evidence in favor of biological explanations. Gottesman (1991) in a review of family, twin and adoption studies summarized the compelling evidence of the role of genetics in schizophrenia. The high concordance rate may be derivable preferentially to genetics or member of the family live in the same home.

1.1.8.5 Family and Twin Studies

Twin studies also play a pivotal role in expanding phenotypes outside the limits of clinical presentation, to accommodate promising bio markers (Cardno & Gottesman, 2000). Franzek and Beckmann (1998) study on genetic framework of schizophrenia spectrum psychoses used different diagnostic systems includes, zygosity diagnoses based on molecular genetics methods and a zygosity inventory. They investigated family history, twin concordance, frequency and severity of the birth related complications of 23 dizygotic (DZ) and 22 monozygotic (MZ) twin pairs. They formulated diagnoses as per the DSM-III-R criteria and Leonhard's nosology. They found none of thirty seven monozygotic twins diagnosed as having systematic schizophrenia, although six twenty-five dizygotic index twins received this diagnosis. Their study found that the identical twins have high concordance rate, near to 90 percent. Their study suggests that schizophrenia spectrum psychoses may consist of etiologically and clinically heterogeneous subgroups with various genetic backgrounds.

1.1.8.6 Adoption Studies

Adoption studies provide evidence of disposition for schizophrenia in families mainly due to genetic factors. Adoption studies track the rate of schizophrenia in children brought up by parents with no schizophrenia, but whose biological parents have schizophrenia. Heston (1966) investigated the incidence of schizophrenia in adoptees with biological parents with schizophrenia and without biological parents with schizophrenia. Heston (1966) study found schizophrenia only in the offspring of mothers with schizophrenia. Five of 47 persons born to mothers with schizophrenia were schizophrenic. Further the study found no cases of schizophrenia in 50 control subjects.

Kety (1988) study on the prevalence of schizophrenia in the biological and adoptive relatives of schizophrenia patient adoptees found that biological relatives of adoptees who suffered from schizophrenia had a remarkably higher chance of schizophrenia than the adoptive relatives who reared them.

Kety et al. (1994) study on mental illness in the biological and adoptive relatives of schizophrenia patient's adoptees found that the schizophrenia particularly in their biological relatives and its rates was significantly greater than the biological relatives of the healthy controls.

1.1.8.7 High-Risk Design

Another approach to examining the relative contributions of environmental and genetics factors to schizophrenia is high-risk design (Halgin & Whitbourne, 2005). Keith et al. (1991) in the epidemiologic catchment area study found that the child with one parent with schizophrenia have a higher risk over their life time of becoming schizophrenic in contrast to a very minor chance in the general population.

1.1.8.8 Studies of Biological Markers

Another proposal among the genetic model is the effort by investigators to enroot a mathematical model that would elucidate how the disorder transmits from one generation to another generation (Halgin & Whitbourne, 2005). Very important measures search for biological makers are smooth pursuit movements and sustained attention.

1.1.8.9 Biological Stressors and Vulnerability

Tragic events happen during the prenatal period and delivery may influence the development of schizophrenia among individual who have a genetic vulnerability to schizophrenia. Patients with schizophrenia are more likely to have a history of prenatal complications (McNeil et al., 2000; van Os & Selten, 1998). Investigators examined the pregnancy and birth records of adults given diagnoses of schizophrenia and recognized higher rate of obstetrical complications, pregnancy, delivery and the time after birth (Ohman & Hultman, 1998).

1.1.8.10 Psychosocial Factors

This perspective focus on family systems, system of roles, interactions and patterns of communication in which individual with schizophrenia grew up. The relationship problems in family are thought to give a way to the development of unhealthy emotional responsiveness and cognitive distortions basic to the psychological symptoms of schizophrenia. The stress created by family members mirrored in the index of expressed emotion (EE), which provide a qualitative measure of the amount of emotions to which care takers or family persons speak in ways that reflect critical comments, hostility and emotional over-involvement (Halgin & Whitbourne, 2005). Individuals living in family showing high a level of expressed emotion have more chances to suffer a relapse than individuals who live in low expressed emotion families (Brown et al., 1972; Kavanagh, 1992).

Expressed emotions may enhance neuropsychological deficits in increasing risk of schizophrenia in individuals with genetic vulnerability (Rosenfarb et al., 2000). Keri and Kelemen (2009) study on vulnerability to interpersonal criticism during family transactions in schizophrenia found family

criticism related to disturbance in thinking in patients with schizophrenia with poor attention and immediate memory.

1.2 Schizophrenia and Neurocognitive Dysfunction

The adverse clinical symptoms of devastating disorder schizophrenia primarily thought to affect cognition, but it also usually contributes to chronic problems with emotion and behaviour. Patients with schizophrenia not only suffer by the severity of the symptoms but also by deficits in cognition (Gold & Harvey, 1993). In schizophrenia, cognitive symptoms are present from the very early stage the disorder is first diagnosed. Neurocognitive impairments are fundamental characteristic in patients with schizophrenia (Kraepelin, 1971). Patients with schizophrenia suffer from a wide range of cognitive deficits (Keefe et al., 2006; Carroll, 2000; Green, 1996). Cognitive deficits are a core feature of schizophrenia that includes problems in speed of processing, attention or vigilance, working memory, verbal learning, verbal memory, visual learning, visual memory, reasoning and problem solving, verbal comprehension and social cognition (Nuechterlein et al., 2004; Green, 2006; Wilk et al., 2005). Cognitive deficits vary in degree of severity among patients with schizophrenia. Cognitive deficits can be enormous, severe and are probably present in most if not all patients with schizophrenia (Dickinson et al., 2007). Consistently implicated findings are on memory, attention and executive functions.

1.2.1 Attention Deficits

Attention is selective concentration or focus of cognitive resource on information while ignoring external stimuli. The distinction between different kinds of attention has suggested by number of psychologists. The two main aspects of attention further divided into selective attention and sustained attention (Krabbendam & Jolles, 2003). Selective attention refers to ability or

capacity to pay attention to relevant and necessary information while ignoring the less important. Sustained attention often referred to as vigilance in schizophrenia. Both selective attention and sustained attention deficits are reported in patients with schizophrenia.

Attention deficits have been one of the widely affected cognitive domains in schizophrenia (Goldberg et al., 1993; Brickman et al., 2004; Kenny at al., 1997; Barr, 2001; Mueller et al., 2004; Elvevag & Goldberg, 2000). The Trail Making Test (TMT) is a standardized and widely used test measure of attention, speed and mental flexibility. The Trail Making Test consists of two parts. TMT-A (psychomotor speed) requires a participant to draw lines sequentially connecting twenty five encircled numbers on a sheet of paper. In TMT-B (set-shifting and flexibility) in which, participants alternates between numbers and letters (ex: 1, A, 2, B, 3, C, 4, D, etc). Patients with schizophrenia performed worse in the TMT A&B (Mojtabai et al., 2000).

Horacek et al. (2006) studied about the association between resting brain metabolism and performance on the TMT A&B. They administered the Trail Making Test A & B on forty-two schizophrenia patients and 42 healthy controls. They studied resting brain metabolism by means of (18) FDG positron emission tomography. They found that patients with schizophrenia performed worse on both TMT-A (psychomotor speed) and TMT-B (set-shifting and flexibility). They also found that PET did not predict the performance on the TMT-A, but predicted that for TMT-B. Their study found PET uptake in the superior, middle and inferior frontal lobes bilaterally related with better performance in the TMT-B. Their study demonstrated neurobiological basis for deficient TMT-B performance in patients with schizophrenia.

1.2.1.1 Selective Attention Deficits

The Stroop Colour-Word Test/Task (SCWT) widely used to study selective attention, in which a word can be printed in discrepant colours. Lean on instructions the task is either of three: word reading, colour naming and interference (name of colours printed in conflicting colours). The attention task requires the participant to concentrate selectively on one dimension of stimulus ignoring inappropriate ones (Goldberg & Green, 2002; Krabbendam & Jolles, 2003)

Everett et al. (1989) administered shortened version of the Stroop Colour-Word Test on 22 patients with schizophrenia, 18 non-schizophrenia patients with other psychiatric disorders (Depressed patients) and 22 non-psychiatric control participants. They found all patients showed deficits in all the stroop scales. They also found that patients with schizophrenia showed as much difficulty as non-schizophrenia subjects on limited time selective attention task, but degraded remarkably more when selective attention had to be maintained. They found two different selective attention deficits marked in patients with schizophrenia. They are difficulty in selectively attending to noticeable aspect of complex stimulus and difficulties in maintaining selective attention over time.

Mathalon at al. (2004) studied about the selective attention in schizophrenia. Their study included fifteen patients with schizophrenia and sixteen age and sex matched control subjects. They gave random sequence of equally probable loud and soft speech sounds and bright and dim checkerboard patterns exposed every 800 to 1200 msec. The participants need to press a button in reaction to soft speech sound in auditory attention task. They recorded event-related potential (ERP) to test the unity and time course of auditory attention. They found that patients with schizophrenia actualized an early attentional filter

but failed to sustain selective attention later in the processing stream. They concluded executive control of auditory attention cannot be sustained in patients with schizophrenia.

1.2.1.2 Sustained Attention Deficits

The Continuous Performance Task/Test (CPT) widely used by researchers to assess sustained attention (Krabbendam & Jolles, 2003). The Continuous Performance Test task involves monitoring a random series of letters or digits that represent continuously, frequently at a rate of roughly about one per second. The subject has to detect target stimuli by pressing a response button and should refrain answering to the foils or distracting stimuli (Goldberg & Green., 2002). There are different versions of Continuous Performance Task/Test (CPT) is available. Some versions of CPT are with high processing loads.

Liu et al. (2002) study examined the deficits in sustained attention in schizophrenia in comparison to other disorders. Their study included 41 inpatients with schizophrenia, 22 major depression patients without psychotic features, 22 bipolar without psychotic features and 42 bipolar patients with psychotic features. They have administered the Continuous Performance Test sessions with an undergrad version of the test and a twenty five percent of stimuli degradation version in which the stimulus images visually distorted. They administered CPT to schizophrenia patients and bipolar both at admission and discharge. They standardized the test scores in comparison with scores for a community sample of 345 participants with adjustment for age, sex and education. They found that all patients groups except the group with nonpsychotic major depression were significantly impaired in their ability to differentiate target from non target stimuli. They reported that patients with schizophrenia had the severest impairment followed by the other groups. They

also found, from admission until discharge, CPT test deficits remain unchanged among schizophrenia group. They reported that patients with schizophrenia had a less stringent reply criterion during the degraded continuous performance test. Their study concluded CPT test deficits are lasting vulnerability indicators for schizophrenia.

These studies demonstrate the selective and sustained attention deficits in patients with schizophrenia.

1.2.2 Memory

Memory is a person's ability to store, retaining and recalling the past experiences and information. Short-term memory and long-term memory are two major categories of memory. Short-term memory permits recall for the time period of a few seconds to a minute without practice. The capacity of short-term memory is very restrictive. The information is accessible only for a valid period of time, but not kept indefinitely. Short–term memory foster by brief patterns of neuronal communication, under the influence on frontal and parietal lobes. Long–term memory can store much large quantities of information for conceivably extensive time period. The capacity of long term memory is abundantly large. Long-term memories are preserved by more fixed and permanent changes in brain neural connections. Working memory is the capability frantically to hold information in the mind needed to do complex tasks such as comprehension, learning and reasoning.

Memory impairment is one of the major cognitive domains affected in patients with schizophrenia (McKeena et al., 1995). Several studies reported memory impairment in patients with schizophrenia (Brickman et al., 2004).

Saykin et al. (1991) studied neuropsychological function in schizophrenia. Their study included 36 unmedicated patients with schizophrenia and 36 age-matched control participants. They administered a battery of neuropsychological tests. In their study schizophrenia patients showed generalized impairment relative to healthy controls and a selective deficit in memory.

Kenny et al. (1997) studied cognitive impairments in schizophrenia. Their study included 17 adolescents with schizophrenia and 17 healthy controls. They administered number of neuropsychological tests. They administered the Trigram Recall with Interference Test as a measure of working memory. They reported that the adolescents with schizophrenia have generalized deficits in cognition, which is more pronounced on tests of attention and working memory.

A meta-analysis by Aleman et al. (1999) on memory impairment in schizophrenia included seventy studies that reported measures of long-term memory and short-term memory (Digit Span). They found a significant and stable relation between schizophrenia and memory impairment. They also found that magnitude of memory impairment was not affected by factors like age, medication status, illness duration, symptomatology and positive symptoms. They also found a small significant relation between negative symptoms and memory impairment. Their study demonstrated a reliable association between memory impairment and schizophrenia.

Boeker et al. (2006) study included twenty-two patients with paranoid schizophrenia and twenty-two age and sex matched controls participants. They administered a battery of neuropsychological tests (MWT-B, Trail Making Test A&B, The Tower of London Test, TAP battery of Attention, Wechsler Memory Scale-Revised, German version of Verbal Fluency Test, Autobiographical Memory Inventory-AMI), personality (Temperament and Character Inventory)

and psychopathological scale (PANSS). They have found that patients with schizophrenia showed deficits in executive function, working memory and episodic memory.

Morice and Delahunty (1996) study on frontal and executive impairments in patients with schizophrenia found significant differences in schizophrenia patients compared with the healthy controls in two tests of working memory: alphabet span and sentence span test. They found an impaired memory performance in patients with schizophrenia.

Mueller et al. (2004) study included 100 inpatients with chronic schizophrenia and 62 control participants. They examined neuropsychological deficits and their relationship to clinical symptoms in schizophrenia. They administered various neuropsychological tests. In their study schizophrenia patients showed pronounced cognitive deficits with verbal memory impairments best differentiating schizophrenia patients and healthy controls.

Kravariti et al. (2007) study used z-transformed scores extracted with reference to forty-three control participants to compare cognitive profile and selectivity of cognitive deficits in nineteen recent onset and twenty-three chronic patients with adolescent-onset schizophrenia. In their study, compared with healthy controls both schizophrenia patient groups were impaired in intelligent quotient, verbal memory and planning.

Forbes et al. (2009) systematic review and meta-analysis compared the working memory function in patients with schizophrenia and healthy controls. Their study conducted a meta-analysis on thirty-six measures of phonological, visuospatial and central executive working memory functioning included 441 separate results from 187 different research studies. Their study reported

statistically significant effect sizes for all working memory measures displaying deficit in schizophrenia groups. They found considerable deficits in working memory in schizophrenia groups across all three working domains.

The above studies show memory impairments in patients with schizophrenia.

1.2.3 Executive Functions

"Executive function refers to those capabilities that enable a person to engage in independent, purposive, self serving behaviour successfully" (Lezak, 1995). In cognitive neuropsychology, executive functions are generally defined as set of cognitive functions. Executive functions refer to the brain activity that maintain, co-ordinate, systemize, and incorporate the other functions of the cognitive faculty. Executive function deficits associated with a number of mental disorders especially schizophrenia. Patients with schizophrenia show deficits in executive functions (Brickman et al., 2004; Kenny at al., 1997; Zec, 1995), including poor processing cognitive information, reduced problem-solving skills and abilities as measured by the Tower of London test.

Kenny et al. (1997) study included seventeen adolescent patients with schizophrenia and seventeen healthy controls. They administered a battery of neuropsychological tests. They have assessed executive functions using Wisconsin Card Sorting Test and the maze subtest of the WISC-R. The Wisconsin Card Sorting Task is a measure of cognitive flexibility. Participants have to sort cards according to four conceptual rules. They found a generalized neuropsychological impairment in adolescent patients with schizophrenia including executive functions.

Joshua et al. (2009) investigated executive functions in schizophrenia. Their study included 39 patients with schizophrenia, 40 bipolar disorder patients and 44 control participants. They administered the Hayling Sentence Completion Test on the entire group. The Hayling Sentence Completion Test is a measure of executive functions. The test consists of two sections of fifteen sentences each having the last word missing. In the first section, tester reads sentence loudly and the subject has to complete the sentences, granting a simple measure of speed in response. In the second section, the participant requested to finish the sentences with that word does not fit, yielding measures of response suppression ability and thinking time. In their study patients with schizophrenia significantly impaired in all measures of test compared to the control participants. The performance of schizophrenia patients was related to the higher ratings of cognitive disorganization.

The abstraction of reasoning and problem solving used to epitomize a general accumulation of processes incorporated in logical thinking, planning, mental flexibility, taking suitable actions and preventing irrelevant actions, and choosing appropriate sensory information. The main feature of problem solving activity is a creation of the plan of action to achieve a particular goal (Hayes, 1989). Problem solving is a larger domain of executive function. In general, the very term problem solving refers to efforts and ability to do something or solve problem successfully with skills and strategies. Problem solving is regard as the complex faculty of all intellectual functions. There are no intact solutions for solving the problem. Problem solving depends on the nature and complexity of the problem. Problems with planning are reported in patients with schizophrenia (Kravariti et al., 2007).

Facing problems requires solution. But the action to solve the problem requires proper planning to achieve a certain goal. Problem solving is a mental

process and goal directed behaviour. The abilities required to solve the problem varies depending on the skill sets and confronted problem. Existing knowledge, proper planning, motivation and needs are important characteristics of problem solving.

The Tower of London test (Shallice, 1982) is widely used neuropsychological test measure of planning, sequencing and problem solving. The initial investigations by Shallice used the Tower of London were with patients with lobe damage (Shallice, 1982). In the computerized version of the Tower of London Test, participants presented with the problem in computer where they required rearranging a set of coloured balls in the bottom half of the computer screen, so that the positions matched the goal arrangement presented in the top half of the screen. They consist of varying number tasks with increasing difficulty. The starting position of the balls varied. One trial given to the participants before the test starts. The participants instructed to complete the test as fast as they can with few numbers of moves. The scores are a number of solved tasks and total time taken to complete the Tower of London test. But different studies use different measures and different number of tasks.

Anderson et al. (1996) study on validation and standardization of the Tower of London Test for paediatric population found significant correlations between the Tower of London test and other measures of executive function.

Morris et al. (1995) study on problem solving in schizophrenia included 30 patients with schizophrenia and twenty-seven healthy controls. The participants tested on the Three-Dimensional Computerized Tower of London test (3-D CTL Test). Their study found that patients with schizophrenia as measured with (3-D CTL Test Control) took considerably more moves and solved significantly fewer problems in the ten problem moves than healthy controls. The time taken by

schizophrenia patients was longer than those of healthy controls. They also reported that the response time tends to be longer in schizophrenia patients with negative symptoms. Their study suggests a deficit in problem solving among schizophrenia patients.

Pantelis et al. (1997) study included thirty-six hospitalized patients with chronic schizophrenia. They tested patients using the Computerized Cambridge Neuropsychological Test Automated Battery (CANTLAB) and compared with those data of healthy controls and patients with the neurological disorders, matched age, sex and National Adult Reading Test IQ (NART IQ). The CANTLAB is a computer based cognitive assessment system consisting of a battery of neuropsychological tests (General memory and learning, working memory and executive functions, visual memory, attention and reaction time, semantic or verbal memory, and decision making) administered to the participants using a touch screen computer. They have tested the higher level of planning ability using the CANTLAB Tower of London test. The Tower of London task consisted of total 12 problems: 2 trials for each of the 2 and 3 move solutions and 4 trials for each of the 4 and 5 move solutions. They also recorded measurement of selection (initial movement) and execution (subsequent movement) latencies to estimate motor speed. Their study found that patients with schizophrenia impaired on visuo-spatial memory span compared with other groups. Schizophrenia patients found to be impaired on the spatial working memory. On the Tower of London task, they found that patients with schizophrenia made fewer perfect solutions and took more number of moves for completion. They reported that schizophrenia patients not impaired in their initial thinking (planning latencies), but remarkably prolonged subsequent thinking (execution) latencies. Their study reported an overall deficit of executive functioning in patients with schizophrenia.

Morice & Delahunty (1996) study included 17 patients with schizophrenia and seventeen healthy controls. All participants were administered the National Adult Reading Test (NART) and the eleven subtests of the Wechsler Adult Intelligence Scale –Revised to assess the current and premorbid IQ. They also administered the Wisconsin Card Sorting test (WCST), the Tower of London test (3 each of one-through six move problems) and five tests of short-term memory (Digit Span Forward, Word Span Forward, Digit Span Backward, Alphabet Span and Sentence Span). Their study found working memory deficits in patients with schizophrenia compared with controls. They found no difference in the Tower of London performance in the first three levels of complexity. However, they found a significant difference in the last three levels between patients and controls. Their study suggested that patients with schizophrenia have a deficit in processing complex information.

Zhu et al. (2010) study investigated the functional changes in the prefrontal cortex of forty first episode schizophrenia patients and 40 age and gender-matched healthy controls using multichannel Near-Infrared spectroscopy (NIRS), while performing the Tower of London test. They found that patients with schizophrenia show a significantly decreased activation in the left prefrontal cortex and a poorer performance in the Tower of London test compared with the controls participants. This study confirms deficits in planning ability among patients with schizophrenia. Their study also found the links between reduced left prefrontal activity and test performance.

An extensive review on neurocognitive impairments in patients with schizophrenia are presented below (Table 1.5)

Table 1.5 Deficits found in Specific Neurocognitive Domains in Schizophrenia Patients compared with Healthy Controls, ADHD and Bipolar Disorder.

Study	Participants	Findings
Arango et al., 1999	Schizophrenia patients *N*=85, Healthy Controls *N*=36	Deficits in verbal fluency (Control Oral Word Association Test), memory (Wechsler Memory Scale-Revised), speed of processing and Executive function (Trail Making Test A&B), and selective attention (Stroop Color and Word Test) in patients with schizophrenia.
Øie & Rund, 1999	Schizophrenia patients *N*=19, ADHD patients *N*=20, Healthy controls *N*=30	Deficits in verbal memory (California Verbal Learning Test), visual memory (Kimura Recurring Figures Test), speed of processing (Trail Making Test A&B and WISC-R Digit Span Test), and executive functions (Wisconsin Card Sorting Test, Wechsler Intelligence Scale for Children-Revised similarities) in patients with schizophrenia.
Morrison et al., 2006	Schizophrenia patients *N*=43, Healthy controls *N*=12	Deficits in verbal and non-verbal intelligence in patients with schizophrenia.
Toulopoulou et al., 2003	Schizophrenia patients *N*=25, Schizoaffective disorder *N*=5, Relatives of Schizophrenia patients *N*=115, Healthy controls *N*=66	Deficits in verbal immediate recall, visual memory/learning (Wechsler Memory Scale), working memory (Executive Golf) and Planning (3D-Computerized Tower of London task) in patients with schizophrenia.
Silver et al., 2003	Schizophrenia patients *N*=27, Healthy controls *N*=37	Deficits in working memory (WAIS Digit Span Tests), attention (Continuous Performance Test), and executive functions in patients with schizophrenia.

Kravariti et al., 2003	Schizophrenia patients *N*=42, Healthy Controls *N*=43	Deficits in attention (Wechsler Memory Scale-Revised), verbal memory (Wechsler Memory Scale-Revised), visual memory (Wechsler Memory Scale-Revised), working memory (Executive Golf Task) and executive functions (Computer based Trial Making Task) in patients with schizophrenia.
McClellan et al., 2004	Schizophrenia patients *N*=27,Bipolar patients *N*=22, Psychosis NOS *N*=20	Compared to standardized norms, deficits found in verbal memory (California Verbal Learning Test-Children Version), visual memory (Wide Range Assessment of Memory and Learning), speed of processing (Test of Visual Motor Integration), planning and problem solving (Controlled Oral Word Association) and Executive functions (Wisconsin Card Sorting Test) in patients with schizophrenia.
Ueland et al., 2004	Schizophrenia patients *N*=22, Healthy controls *N*=30	Deficits in working memory (Digit span Backward Task, Wechsler Intelligence Scale for Children-Revised), psychomotor Speed (Digit Symbol WISC-R), Executive functions (Wisconsin Card Sorting Test) and visual memory (Kimura Recurring Figures test) in patients with schizophrenia.
Mueller et al., 2005	Schizophrenia patients *N*=43, Healthy controls *N*=27	Deficits in verbal fluency found in patients with schizophrenia.
Rhinewine et al., 2005	Schizophrenia patients *N*=54, Healthy controls *N*=52	Deficits in verbal memory (California Verbal Memory Test), attention (Trial Making Test-A /Continuous Performance Test) and Executive functions (Wisconsin Card Sorting Test; Trail Making Test-B) in patients with schizophrenia.

Kester et al., 2006	Schizophrenia patients *N*=15, Healthy controls *N*=25	Deficits in planning and problem solving (The Iowa Gambling Task) in patients with schizophrenia.
Rodriguez – Sanchez et al., 2007	Schizophrenia patients *N*=26, healthy controls *N*=28	Deficits in speed of information processing in patients with schizophrenia.
González-Blanch et al., 2007	Schizophrenia patients *N*=131, healthy controls *N*=28	Deficits in speed of processing/executive functions, motor dexterity, motor speed, sustained attention and; verbal learning and memory in patients with schizophrenia.
Landrø and Ueland, 2008	Schizophrenia patients *N*=21, Healthy controls *N*=28	Deficits in verbal learning and verbal fluency in patients with schizophrenia.
Ojeda et al., 2008	Schizophrenia patients *N*=90, healthy controls *N*=30	Deficits in verbal fluency, immediate and delayed memory in patients with schizophrenia.
Sánchez et al., 2009	Schizophrenia patients *N*=95, healthy controls *N*=53	Deficits in verbal memory, working memory, executive functions and processing speed in patients with schizophrenia.
Wobrock et al., 2009	Schizophrenia patients *N*=24, bipolar disorder *N*=18 and healthy controls *N*=23	Deficits in attention, psychomotor performance, verbal working memory, cognitive flexibility and executive functions in patients with schizophrenia.

Noh et al., 2010	Schizophrenia patients *N*=114, healthy controls *N*=120	Deficits in speed of processing, working memory, verbal learning & memory, attention/vigilance and; reasoning & problem solving in patients with schizophrenia
Zilles et al., 2010	Schizophrenia patients *N*=31, healthy controls *N*=47	Deficits in working memory (different working memory tasks) in patients with schizophrenia.

All these research studies indicate overall neurocognitive impairment in a variety of domains in patients with schizophrenia.

1.2.4 Discrepancy in Findings on Neurocognitive Impairment in Schizophrenia

There are some studies that show neuropsychological performances in patients with schizophrenia to be normal. Liu et al. (2006) study included 122 schizophrenia patients and 94 healthy control participants. Participants were administered a comprehensive neuropsychological test battery (Visual spatial ability, verbal ability, verbal memory, execution, visual memory, motor ability, metal control and attention). Their study reported that cognitive deficits were prevalent among schizophrenia patients but is not a common feature.

The neuropsychological performances of a significant minority of patients with schizophrenia are normal (Reichenberg et al., 2009). A study by Palmer et al. (1997) administered a comprehensive neuropsychological test battery to 171 patients with schizophrenia and 63 normal controls. Their study found that 27 percent of the patients were neuropsychologically normal. A study by Holthausen et al. (2002) found 23 out of 118 (19%) patients with first onset schizophrenia are cognitively unimpaired.

1.2.5 Cognitive Impairment and Functional Outcomes in Schizophrenia

Cognitive impairments connected to poor functional outcomes in patients with schizophrenia (Keefe et al., 2006; Green, 1996; Green et al., 2004; Green & Nuechterlein, 1999; Heaton & Pendleton, 1981). The cognitive domains most reliably connected to functional outcome in schizophrenia includes vigilance, immediate or verbal working memory, secondary verbal memory and executive functions (Green et al., 2000). Social problem solving, community outcome and psychosocial skill acquisitions are related functional outcomes (Goldberg & Green, 2002). Patients with schizophrenia often lack the ability to solve the problem left by stressful life events leads to poor quality of life.

Cervellione et al. (2007) study included twenty-six schizophrenia early onset patients and twenty-six healthy controls. They examined by means of a comprehensive neuropsychological test battery, a median of thirteen months after a baseline testing. They examined the stability scores and relationship between baseline performances. In their study, schizophrenia patients impaired across neurocognitive variables at baseline and follow-up compared to healthy control participants. They also found the deficits remained stable over time. Their study found that follow-up social, communication, personal living and community living skills related to the working memory, verbal memory, attention/vigilance at a baseline; and specific cognitive spheres more strongly associated to functional outcomes.

Sánchez et al. (2009) study included 95 patients with schizophrenia and fifty-three healthy control participants. All participants were given a battery of neuropsychological tests includes test for working memory, verbal memory, processing speed and executive functioning. They assessed the functional disability after six months follow-up with the Disability Assessment Schedule

after the neuropsychological and clinical examination. They found that schizophrenia patients perform worse than the healthy controls on all neurocognitive domains. They also found that most neurocognitive domains related with the patients functional disability shown after six months after admission to the study including vocational outcomes, self-care, family contact and social functioning. In their study, performance on processing speed associated to clinical, social and functional outcomes in patients with schizophrenia.

Ojeda et al. (2008) study included 90 hospitalized patients with schizophrenia and thirty healthy control participants. They administered neuropsychological test battery includes tests for verbal memory, verbal fluency, motor speed, processing speed. They examined outcome measures using Disability Assessment Schedule (DAS-WHO) and number of hospitalizations. Their results confirmed the chronicity of clinical symptoms and impairment on functional disability. They found that verbal fluency, immediate and delayed memory predicts the functional outcome. After adding processing speed into regression analyses, the significance in verbal fluency and verbal memory declined significantly. They suggested that processing speed may be a central factor in relation between cognitive symptoms and functional outcomes in patients with chronic schizophrenia.

All these studies show the cognitive deficits in patients with schizophrenia.

1.3 Sleep

"Sleep is the golden chain that ties health and our bodies together"

Thomas Dekker

Sleep is a complex, natural, reversible state occurring at regular intervals generated and regulated by different complex neuronal systems (Norwood & Teofilo Lee-Chiong, 2006; Teofilo Lee-Chiong, 2008). Previously, sleep was considered to be a passive state of brain. This supposition was invalidated by innovative experiments of Bremer in 1930 and it was recognized that sleep is actively produced by activity in particular regions of the brain. In 1937, Loomis et al. was first to notice that sleep is dissimilar during the entire night. Loomis et al. elucidated the different sleep stages based on EEG (Loomis et al., 1937). In 1953, Nathaniel Klietman a professor emeritus in physiology at the University of Chicago along with his student Eugene Aserinsky have been studying sleep difficulties in infants noticed the occurrence of rapid eye movements in sleeping infants (Aserinsky & Kleitman, 1953). This remarkable finding gave way to identify two individual states within sleep: non-rapid eye movement (non-REM) sleep and rapid eye movement (REM) sleep (Latta & Van Cauter, 2002). In 1957, Dement and Klietman in the study on dreaming and stage of sleep tested five subjects, waking them various times during the night (both during REM and NREM sleep) to test their dream recall. Their study found a significant association between REM sleep and dreaming (Dement & Kleitman, 1957).

1.3.1 Polysomnography

Polysomnography is considered as the single most important laboratory technique in a sleep study, using precise electrophysiological techniques (Chakroverty, 2003). Polysomnography consists of electrophysiological recording

of the brain cerebral cortex activity by electroencephalography (EEG), movements of eye by electrooculography (EOG) and muscle tone by electromyography (EMG).

The electroencephalography is considered to be the dynamic electro physiologic procedure that evaluates the functions of the brain. The first electroencephalogram tracing from human was recorded by the German Physiologist Hans Berger in 1928. The electroencephalogram records the electrical activity and waveforms produced by cortical neurons (Westmoreland, 2009). Electrooculography is a procedure for measuring the difference in potentials between the cornea and retina. Electromyography is a procedure for examining and recording electrical activity produced by skeletal muscles. This measurement aids the deduction of REM sleep (Rechtschaffen and Kales, 1968).

The electroencephalogram, electrooculogram and electromyogram have become primary the means of monitoring the stages of human sleep. The recordings obtained can be scored visually as either wakefulness or the various stages of sleep.

1.3.2 Sleep Stages and Scoring

A criterion for scoring the stages of sleep based on EEG was first described by Loomis et al in 1937. They classified different EEG sleep features into 5 levels (A to E) (Davis et al., 1938). K-complex was first described by them in 1938. The etiology of naming as K-complex remains unclear (Ernst Niedermeyer, 2005). The stages of sleep proposed by Loomis et al are shown below in the table 1.6

Table 1.6 Old Terminology of Sleep Stages used by Loomis et al (1937)

A	Interrupted Alpha	Normal waking 10 per second rhythm pattern
B	Low Voltage	Alpha rhythm lost
C	Spindles	Spindles of 14 per sec waves and random delta waves 0.2 per second
D	Spindle plus random	Both types of waves increase in voltage, delta waves become stronger
E	Random	Delta waves continues to increase in voltage and wavelength

The sleep scoring was changed by Dement and Kleitman in 1957 after a serendipitous discovery of REM sleep. Dement and Kleitman classifications of sleep stages were shown below in the table 1.7

Table 1.7 Dement & Kleitman Classification of Sleep Stages.

1	Drowsiness	From alpha dropout to vertex waves
2	Light Sleep	Spindles, vertex waves Complexes
3	Deep Sleep	Much slowing, K - complexes, some spindles
4	Very Deep Sleep	Much slowing, Some K-complexes
REM	REM Sleep	desynchronization with faster frequencies

Dement & Klietman criteria for scoring sleep stages were standardized by Rechtschaffen and Kales in 1968. After Rechtschaffen and Kales manual on sleep stage scoring was published, dramatic changes occurred in human sleep research (Silber et al., 2007). This manual is widely used for the scoring of the sleep stages. Rechtschaffen and Kales manual on sleep stage scoring was show below on table 1.8

Sleep consists of two main states: non-rapid eye movement (non-REM) sleep and rapid eye movement (REM) sleep. Non rapid eye movement (non-REM) sleep is further classified into four stages from the sleep stage 1 to sleep stage 4. Sleep stages 3 and 4 in non-REM are referred to as slow wave sleep (SWS) or deep sleep stage or delta sleep. The non-REM sleep is also called orthodox sleep. The first half of the night is dominated by NREM sleep and REM sleep will be greatest during the rest of the night. REM sleep occurs during the night that changes with NREM sleep for every 90 to 120 Minutes in the night. The arousal thresholds commonly lowest in sleep stage 1 and highest in sleep stage 4. Generally, rapid eye movement sleep and non-REM sleep periods substitute cyclically all over the night (Figure 1.1). The percentage and frequency of sleep stages varies during the night - in the early hours of sleeping slow wave sleep dominates, whereas REM sleep occurs very often in the second part of sleep (Rechtschaffen & Kales., 1968; Susmakova, 2004). REM sleep is also called paradoxical sleep. The sleep architecture will change during the different stages of lifespan of human life.

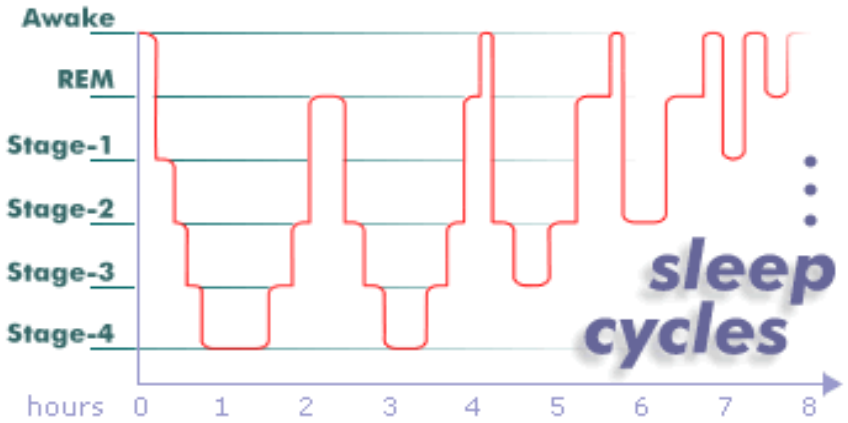


Figure 1.1 Sleep Cycle Associated With Whole Night Sleep

(Picture from *Thinquest* stages of sleep, web: www.thinkquest.org)

Table 1.8 Rechtschaffen & Kales (1968) Scoring Sleep Stages

STAGE	ELECTROENCEPHALOGRAM	ELECTROOCULOGRAM	ELECTROMYOGRAM
STAGE WAKE	* Alpha activity, and/or low voltage, mixed frequency activity.	Often REMs.	Usually not necessarily accompanied by high tonic EMG.
STAGE 1	* A relatively low voltage, mixed frequency EEG without rapid eye movements (REMs) * Decrease in the amount, amplitude and frequency of alpha activity. * Scoring stage 1 requires absolute absence of clearly defined K-complexes and sleep spindles. * Vertex sharp wave may appear in conjunction with high amplitude 2-7 cps activity. The amplitude of the vertex is occasionally as high as 200µV.	Characterized by the presence of slow eye movements each of several seconds duration. Rapid eye movements are absent.	Tonic EMG levels are usually below those of relaxed wakefulness.
STAGE 2	* Low voltage, mixed frequency EEG. * Presence of sleep spindles and (or) k-complexes. * Spindle between 12-14 cycles per second (cps) of at least 0.5 sec. * K-complex-Negative sharp wave immediately followed by a positive component with a total duration should exceed 0.5 second. * Long periods may intervene between sleep spindles and k-complexes. * Absence of sufficient high amplitude, slow activity that defines stages 3 and 4. * If less than 3 minutes of record meeting requirements for stage 1 occur between sleep spindles and or K-Complexes in the absence of movement arousals or pronounced increases in muscle tone, intervening epochs are considered stage 2. The intervening epochs are scored as stage 1 if the interval without sleep spindles or K-complexes lasts minutes or longer.		Low EMG activity.
STAGE 3	* At least 20% but < not more than 50% of the epoch consists waves of 2 cps or slower waves having amplitudes greater than 75 µV from peak to peak.		Low EMG activity.
STAGE 4	* More than 50% of the epoch consists of 2 cps or slower waves having amplitude greater than 75 µV from peak to peak.		Low EMG activity.
STAGE REM	* Relatively low voltage, mixed frequency EEG activity. * Resembles stage 1. Vertex sharp waves are not prominent. * Saw tooth waves may seen. * Absence of sleep spindles and K-complexes.		Low Amplitude electromyogram (EMG).
MOVEMENT TIME	Scoring epoch during which polygraph record is obscured by movements of the subject.	EOG tracings obscured in more than half of the epoch by muscle tension and or amplifier blockings.	The change in pattern may consist either an increase in amplitude of the EMG signal or an amplifier blocking.

Source: Modified and adapted from Rechtsschaffen, A & Kales, A manual Of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Public health service, U.S. Government Printing Office, Washington, D.C., 1968

1.3.2.1 Microstructures of Sleep EEG

Microstructures of sleep relay on quantification of phasic events like K-complexes and spindles. Quantifying the microstructures of sleep like K-complex and spindles would give additional insight about the role of more specific sleep variables (Muzet, 2005). The changes and variances in the occurrence and frequency of sleep related phasic events may be associated with specific psychiatric disorders and may give insight into diagnostic improvements in the prognosis of complex psychiatric disorders (Muzet, 2005).

1.3.2.1.1 K-complexes

K-complexes are frequently seen in sleep stage 2 and prominent feature in non-REM sleep (Rechtschaffen & Kales, 1968; Happe et al., 2002; Muzet, 2005).

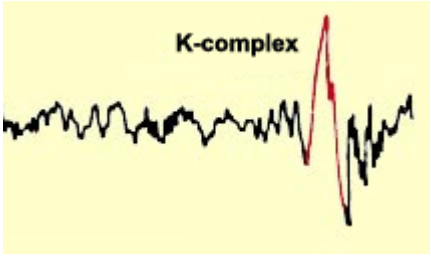


Figure 1.2 Picture of K-complex in sleep EEG

The K-complex is defined as large amplitude greater than 75μV negative-positive wave, exceeding 0.5 sec duration (Rechtschaffen & kales, 1968).

1.3.2.1.2 Neurophysiology of the K-complexes

In sleep stages, the more K-complexes were indicative of deeper sleep (sleep stage2). The K-complexes are more frequent as the proximity of the slow wave sleep increases (Halasz et al., 1977; Colrain, 2005). Different studies explained the functions of K-complexes in variable terms. K-complexes are sleep-

related evoked EEG phenomenon (Colrain & Crowley, 2005). K-complexes might be a sleep protective function (Wauquier et al., 1995; Vetter & Boker, 1962). K-complexes engaged in sleep specific information processing during sleep (Colrain, 2005). K-complex carries characteristics of evoked potentials, which caters subattentive information processing (Muzet, 2005).

Hálasz work long suggested that "K-complexes are complex multifunctional phenomenon of sleeping brain involved in information processing and defence against the arousal effect of sensori stimuli" (Hálasz et al., 2005). Further studies also accepted the view that k-complexes are reflective of a brain state that is conducive to sleep (Wauquier at al., 1995). Given new orientation of research about K-complexes indicated by researchers, it is reasonable to relate sleep specific information processing and sleep protective mechanism.

1.3.2.1.3 Spindles

The presence of sleep spindles is most common in sleep stage 2 NREM sleep (Rechtschaffen and Kales, 1968; Fogel et al., 2007). Sleep spindles been widely employed in sleep research. Sleep spindles and K-complexes are transient phenomena that may intervene between two events without change in sleep stage (Rechtschaffen and Kales, 1968).

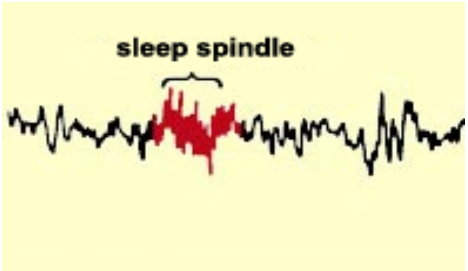


Figure 1.3 Picture of sleep spindle in sleep EEG

1.3.2.1.4 Neurophysiology of Spindles

Sleep spindles are associated with activation of the thalamus (Liu et al., 2008). The sleep spindles are often seen over the central and frontal head regions (Shih et al., 2000). Sleep spindles are consequences of communication between cells in the thalamus and cortex. Spindles are mostly produced in the thalamus that co-ordinates incoming stimuli and sends it along to the cerebral cortex (Ferrarelli et al., 2007; Ferrarelli & Tononi, 2011). Sleep spindle activity is associated with the integration new information into existing knowledge (Tamminen et al., 2010).

Gibbs and Gibbs (1962) study on the correlation of EEG sleep pattern with mental retardation reveals that individuals with mental retardation have unusual spindles. Later studies linked the dysfunctions of thalomacortical loops and abnormal spindles. Fogel et al. (2007) study examined the relationship between spindles and intelligent quotient. Their study found a positive correlation between intelligent quotient and number of spindles. A study by Clemens et al. (2005) on sleep related consolidation found a connection between sleep spindle activity and verbal memory consolidation.

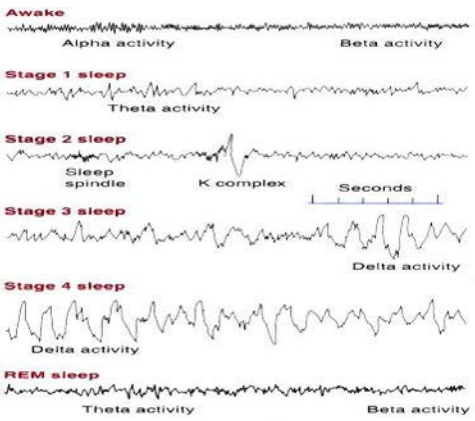


Figure 1.4 Sleep EEG and Wave Patterns of Different Stages (Source: Horne, J. A. (1988) Why We Sleep, The Function of Sleep in Humans and Other Mammals (Oxford University Press, Oxford).

1.3.3 Functions of Sleep

Sleep is one of the most basic and important human drives. During sleep, growth and repair of tissues of the body are thought to occur and energy is conserved and stored (The American Heritage Science Dictionary, 2011). Sleep theories elucidate the important role of sleep for conservation of energy, neural growth and processing, thermoregulation, somatic growth regulation, memory and learning. There are two prominent theories about the functional purpose of sleep - Restoration theory and Ecological theory.

1.3.3.1 Restoration Theory

Restoration theory is also known as recuperative or restitutive theories. Restorative theories are based on the ideas of animals sleep. Sleep offers a chance for the human body to perform biochemical and physiological repairs while dedicating energy to repair and recovery of the human immunological and nervous system for proper functioning. Accordingly, the major function of sleep is to restore tissue and save energy (Oswald, 1966).

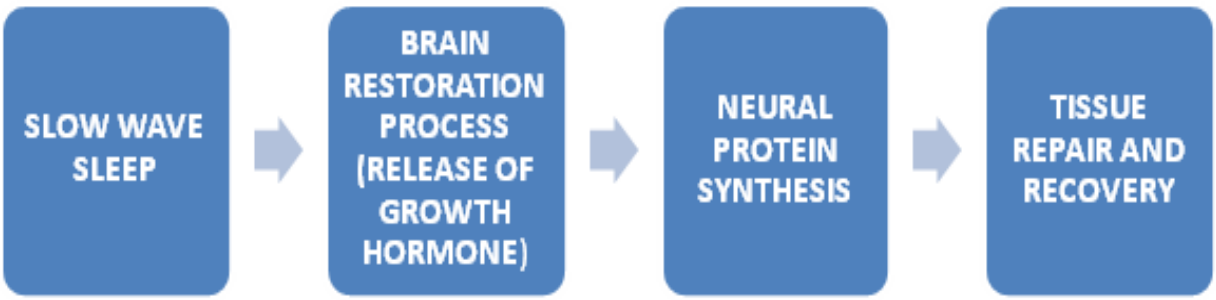


Figure 1.5 Physiological Restorations during Sleep (Oswald, 1966; Oswald & Adam, 1984)

Stern and Morgane (1974) theoretical view of REM sleep function suggests that the function of REM sleep is to restore the level of neurotransmitters after daily activities.

Further empirical evidence in support of restoration theory given by Shapiro and Colleagues in 1981. They performed sleep recordings in marathon runners for 4 successive nights followed by a 92 kilometres run. The study found significant increase in total sleep time and slow wave sleep (SWS) after a metabolic stress. Their finding demonstrates confirmed exercise effect of sleep and support for sleep restoration theory.

Berry and Webb (1983) studied the relationship between sleep and mood variables among 36 male and 39 females. Their study correlated the data of two night sleep recordings with five mood scales of the Lorr Mood Scale administered prior to second night. They compared the correlation of first night sleep and mood variables with those obtained from the same mood variables and second night sleep. It was found that the people who slept well during given night had less anxiety on the next day compared to the people who had poor sleep or disturbed night sleep (Berry & Webb, 1983).

Horne (1988) extends the idea of sleep pioneer Oswald. He developed a theory that incorporates aspects from both adaptive and restorative theories. According to his theory, sleep is divided into essential and optional components. Essential is core sleep consists slow wave sleep (SWS); while optional sleep is sleep stage 1, sleep stage 2 and REM. Core sleep is extremely beneficial for normal functioning of the brain, while time spent on lighter stages (stage 1 and 2) and REM sleep are only optional.

1.3.3.2 Ecological Theory

Ecological theory is also known as behavioural theories. Ecological theory complies with restoration theory in terms of sleep and its purpose. Ecological theory focuses sleep from an evolutionary perspective. The observation of difference in sleep pattern and sleep duration between birds, mammals, animals and man led to evolutionary theory of sleep. Evolutionary theory suggests sleep is not necessary but, serve as an important survival function. Meddis (1975) articulates that sleep pattern in any species depends on the necessity to adapt threats in the environment and dangers. For some animals, sleep serve as function of keeping them fairly immobile and safe from predators. But, species in threat and danger from predators sleep relatively little to remain vigilant. He also suggests that the duration of sleep in species depends on predator avoidance and food requirements. All these theories show the varied functions of sleep.

1.4 Sleep and Schizophrenia

Sleep disturbances are common in patients with schizophrenia (Monti & Monti, 2006; Manoach & Stickgold, 2009), it may either due to distressing symptoms or side effect of antipsychotic medication (Benson, 2008; Monti & Monti, 2006). Sleep disturbances in patients with schizophrenia include difficulty in initiating and maintaining sleep, poor sleep efficiency, reduced total sleep time, day time fatigue that affects day today tasks. Sleep disorders are part of the clinical picture in schizophrenia. Thirty to eighty percent of patients with schizophrenia are found to have sleep disturbances (Cohrs, 2008). There is a unique relationship between the pathology of schizophrenia and poor sleep (Norwood and Lee-Chiong, 2006). In general, sleep appear to worsen during acute episodes (Kupfer et al., 1970), and improves following antipsychotic medication treatment (Krystal et al., 2008), or during remission. However, even

medicated and clinically stable patients subjectively experience chronic sleep disturbances.

Early Studies in Sleep and Schizophrenia

Earlier sleep studies in schizophrenia examined the promising role of REM sleep intrusions in the pathogenesis of schizophrenia (Benson, 2008). REM sleep abnormalities are not consistently replicated in successive studies, so the focus turned to evaluate the other features of sleep architecture like sleep latency, total sleep time, sleep efficiency, sleep stage 3 and 4, slow wave sleep, REM latency and quantification of spindles.

1.4.1 Polysomnographic Features in Schizophrenia

Distinctive sleep patterns may be one of markers in schizophrenia patients. Sleep parameters are divided into three groups: sleep continuity (sleep latency, number of wakening and wake after sleep onset, sleep efficiency, total sleep time), sleep architecture (The percentages of sleep stage 1, 2, 3 and 4, and stage REM), and REM sleep measures (REM latency). An extensive review of sleep parameters impairments in patients with schizophrenia are given below.

1.4.1.1 Sleep Continuity

Number of Wakening and Wake after Sleep Onset

Increased wake time after sleep onset and number of awakening are reported impairments in sleep in patients with schizophrenia. Ganguli et al. (1987) study included 8 young never-medicated schizophrenia patients, 8 with

delusional depression, sixteen non-delusional depression and sixteen healthy controls. They conducted two consecutive nights of polysomnography. They found that patients with schizophrenia show increased wakefulness after sleep onset compared to other groups.

Lauer et al. (1997) polysomnographically examined twenty-two drug-naive patients with schizophrenia, paranoid type and twenty healthy controls. In addition, they assessed the ventricular brain ratio by means of computerized tomography. They found an increased wake time after sleep onset in patients with schizophrenia, specifically during first non-REM period compared to healthy controls.

Yetkin et al. (2011) study on sleep architecture in patients with schizophrenia included thirteen adult male inpatients with schizophrenia, undifferentiated type and an age- and sex-matched group of healthy controls. They conducted polysomnographic recordings. They found more awakenings and increased duration of awakenings after falling asleep among schizophrenia patients compared to the healthy controls.

These studies confirm the poor continuity of sleep in patients with schizophrenia.

1.4.1.1.1 Total Sleep Time

The reduced of total sleep time was observed in patients with schizophrenia. Yetkin et al. (2011) study on sleep architecture in schizophrenia patients included thirteen adult male inpatients with schizophrenia, undifferentiated type and an age- and sex-matched group of healthy controls. They conducted polysomnographic recordings and scored sleep EEG according

to Rechtschaffen and Kales, 1968 standard criteria. They found less total sleep time in patients with schizophrenia compared to the healthy controls.

1.4.1.1.2 Sleep Efficiency

Sleep efficiency is the ratio of time spent asleep to the amount of time spent in bed. Poor sleep efficiency is another impaired sleep parameter reported in patients with schizophrenia. Keshavan et al. (1998) study included thirty unmedicated patients with schizophrenia and thirty age and sex-matched healthy controls. They visually scored sleep data as well as used automated period amplitude analyses and power spectral analyses. They found reduced sleep efficiency in patients with schizophrenia compared to healthy controls.

Yetkin et al. (2011) study on sleep architecture in schizophrenia patients included thirteen adult male inpatients with schizophrenia, undifferentiated type and an age- and sex-matched group of healthy controls. They conducted polysomnographic recordings. They found lower sleep efficiency in patients with schizophrenia compared to healthy controls.

These studies show poor sleep efficiency in patients with schizophrenia.

1.4.1.1.3 Sleep Onset Latency

Sleep onset latency is the length of time taken for the transition of sleep from full wakefulness to sleep stage 1. Increased sleep onset latency is one of impaired sleep parameters reported in patients with schizophrenia. Keshavan et al. (1998) study included thirty unmedicated patients with schizophrenia and thirty age and sex-matched healthy controls. They visually scored sleep data as well as used automated period amplitude analyses and power spectral analyses.

They found longer sleep latency in patients with schizophrenia compared to healthy controls.

Hoffmann et al. (2000) study compared the quantitative EEG measures during non-REM sleep among age-matched symptomatic unmedicated schizophrenia patients, depressed and healthy control men. They included thirteen participants in each group. They scored sleep data according to Rechtschaffen and kales 1968 standard criteria. They found that sleep latency in schizophrenia group was three times longer than healthy controls and twice as long as in depressive group.

Yang and Winkelman (2006) study investigated the relationship between clinical symptom severity and sleep EEG parameters in a relatively diagnostically similar group of patients with schizophrenia. They obtained sleep EEG data in fifteen drug-free inpatients with schizophrenia, undifferentiated type and sex-matched healthy controls. They visually scored sleep EEG data according to Rechtschaffen and kales 1968 standard criteria. Their study reported profound difficulties in sleep initiation in patients with schizophrenia.

Yetkin et al. (2011) study on sleep architecture in patients with schizophrenia included the thirteen adult male inpatients with schizophrenia, undifferentiated type and an age- and sex-matched group of healthy controls. They conducted polysomnographic recordings and scored sleep EEG according to Rechtschaffen and kales 1968 standard criteria. Their study reported longer sleep latency in schizophrenia patients.

These studies show impaired sleep onset latency in patients with schizophrenia.

1.4.1.2 Sleep Architecture

1.4.1.2.1 Slow Wave Sleep

Slow wave sleep is thought to be the most "restorative" sleep. Slow wave sleep was generally found to be decreased in patients with schizophrenia. The most reliable sleep EEG abnormality in schizophrenia is slow wave sleep (SWS) deficit. Keshavan et al. (1998) study compared sleep data of visually scored as well as automated period amplitude analyses and power spectral analyses of thirty unmedicated schizophrenia patients and thirty age and sex-matched healthy controls. They found a decreased visually scored delta sleep in patients with schizophrenia compared to healthy controls.

Yang and Winkelman (2006) study investigated the relationship between clinical symptom severity and sleep EEG parameters in a relatively diagnostically similar group of patients with schizophrenia. They obtained sleep EEG data in fifteen drug-free inpatients with schizophrenia, undifferentiated type and sex-matched healthy controls. They visually scored the sleep EEG data according to Rechtschaffen and kales 1968 standard criteria. They found a profound slow wave sleep deficit in schizophrenia patients compared to the healthy controls.

While these studies show slow wave sleep deficits in patients with schizophrenia. On contrary, Ganguli et al. (1987) and Yetkin et al. (2011) studies on sleep EEG in patients with schizophrenia did not find slow wave sleep deficits in patients with schizophrenia.

1.4.1.3 Stage REM

Reduced percentage of REM sleep also frequently reported in patients with schizophrenia. Evidence for a disinhibition of REM sleep mechanisms is inconsistent. Yetkin et al. (2011) study on sleep architecture in patients with schizophrenia included the thirteen adult male inpatients with schizophrenia, undifferentiated type and an age- and sex-matched group of healthy controls. They conducted polysomnographic recordings. In their study, the percentage of REM sleep was reduced in patients with schizophrenia compared to healthy controls.

1.4.1.4 REM Sleep Measures

1.4.1.4.1 REM Sleep Latency

Reduced REM sleep latency frequently reported in patients with schizophrenia. Poulin et al. (2003) study included eleven patients with acute schizophrenia drug-naive with eleven healthy controls. They scored sleep stages and visually identified the phasic events occur during REM sleep. They found reduced REM sleep latency in patients with schizophrenia compared to the healthy controls.

On contrary, Yetkin et al. (2011) study on sleep architecture found no significant difference in REM sleep latency between schizophrenia patients and healthy controls.

An extensive review on sleep EEG in patients with schizophrenia is presented below in the table 1.9

Table 1.9 Review on Sleep EEG Abnormalities in Patients with Schizophrenia.

Research study	Population	Clinical information	Findings of the study
Kempenaers et al., 1988	Schizophrenia patients *N*=9 Controls *N*=9 Depression *N*=9	Inpatients with schizophrenia.	Poorly efficient sleep due to delayed sleep onset.
Tandon et al., 1992	Schizophrenia patients *N*=40, Controls *N*=15	20 drug-naive patients with schizophrenia, 20 drug free but previously medicated patients with schizophrenia.	Drug naive and previously medicated patients had significantly greater impairment of sleep continuity and shorter REM latency compared with controls
Riemann et al., 1995	Schizophrenia patients *N*=10, Controls *N*=10, Major depressive disorder *N*=10	Inpatients with schizophrenia.	Impairments in sleep efficiency.
Benson et al., 1996	Schizophrenia patients *N*=14, nonpsychiatric comparison subjects *N*= 15	Inpatients with schizophrenia.	In patients with schizophrenia, they found long sleep latencies, reduced sleep efficiency, stage 4 deficit and short REM latency.
Lauer et al., 1997	Schizophrenia patients *N*=22, Controls N=20	Drug-naive patients with schizophrenia-Paranoid type.	Compared with controls patient with schizophrenia showed reduced total sleep time, reduced sleep efficiency,

			reduced sleep stage 2, increased sleep onset latency, more number of awakenings and increased amount of wakening.
Röschke et al. 1998	Schizophrenia patients *N*=11, Controls *N*=11	Inpatients with schizophrenia.	REM Latency.
Keshavan et al., 1998	Schizophrenia patients *N*=30, Controls *N*=30	Unmedicated patients with schizophrenia.	Schizophrenia patients showed Reduced delta sleep, reduced total sleep time, reduced sleep efficiency and sleep latency compared with healthy controls.
Hoffmann et al., 2000	Schizophrenia patients *N*=13, Controls *N*=13 Major depressive disorder *N*=13	Symptomatic but unmedicated patients with schizophrenia.	Sleep latency in patients with schizophrenia was three times longer than normal controls and twice than depressive disorder.
Poulin et al., 2003	Schizophrenia patients *N*=11, Controls *N*=11	Acute schizophrenia never treated with neuroleptics.	Compared with healthy controls, patients with schizophrenia showed: Decreased stage 4, reduced REM sleep latency, difficulty in initiation of sleep.

Yang & Winkelman., 2006	Schizophrenia patients *N*=15, controls *N*=15	Inpatients with schizophrenia.	Profound difficulties in sleep initiation and maintenance, poor sleep efficiency, slow wave sleep deficit and increased REM density among patients with schizophrenia.

1.4.1.5 Microstructures of Sleep EEG in Schizophrenia

While there is sufficient information and significant research on macrostructures of sleep EEG in schizophrenia, not many studies have been conducted on the microstructures of sleep EEG in schizophrenia.

1.4.1.5.1 K-complexes and Schizophrenia

There are no studies reported abnormalities in K-complexes in patients with schizophrenia.

1.4.1.5.2 Spindles and Schizophrenia

Ferrareli et al. (2010) investigated spindle deficits in a larger sample of schizophrenia patients. They performed whole night EEG recordings in 49 patients with schizophrenia, 20 non-schizophrenia patients receiving antipsychotic medication and 44 healthy controls. They assessed slow wave sleep. They reported that the spindle deficits can be reliably established in patients with schizophrenia.

Ferrarelli et al. (2007) engaged with a 256-electrode high density EEG to examine sleep rhythms variations between patients with schizophrenia, healthy controls and people with history of depression. Their study included 17 healthy controls, 18 medicated schizophrenia patients and 15 participants with history of depression. They recorded the first sleep episode of the night with 256-electrode high density EEG and analyzed for variations in EEG power spectra, power topography and sleep specific cortical oscillations. They found a reduced sleep spindle activity, number of spindles, amplitude, duration and integrated spindle activity in schizophrenia patients. A review on sleep EEG microstructures in schizophrenia is presented as follows (Table 1.10).

Table 1.10 Review on Sleep EEG Microstructure abnormalities in Schizophrenia.

Research Study	Population	Clinical Information	Findings
Ferrarelli et al., 2007	Schizophrenia patients *N*=18, Controls *N*=17, Depression *N*=15	Medicated patients with schizophrenia.	Reduced number of spindles, amplitude, duration and integrated spindle activity in schizophrenia patients.
Ferrarelli et al., 2010	Schizophrenia patients *N*=49, Controls *N*=44, Non schizophrenic taking antipsychotic medication *N*=20	Patients with schizophrenia on antipsychotic medication	Patients with schizophrenia showed spindle deficit.

1.4.1.6 Medications and their Effects on Sleep in Schizophrenia

The key treatment to improve sleep in schizophrenia patients is administrating medications that have effects on neurotransmitter systems which play a pivotal role in sleep wake functions (Krystal et al., 2008). Antipsychotic medications often improve and reverse sleep architectural abnormalities in schizophrenia patients (Krystal et al., 2008). Presently used antipsychotic medications are divided into typical and atypical agents (Norwood & Lee-Chiong, 2006). Previous studies have examined the effects of the first generation antipsychotics on sleep of schizophrenia patients by means of polysomnographic methods (Benson, 2008). Empirical studies of the medication effects on sleep in patients with schizophrenia treated with second generation antipsychotics examined the effects of atypical antipsychotics like clozapine, risperidone, olanzapine and paliperidone (Benson, 2008).

Salin-Pascual et al. (1999) examined 20 drug free inpatients with schizophrenia (DSM-IV). They polysomnographicaly tested patients for 5 consecutive nights: 1 adaption night; 2 base line nights (first for sleep disorder screening); and 2 nights with olanzapine medication - atypical antipsychotic (10mg olanzapine, one hour before sleep onset). They found that sleep continuity variables and total sleep time show overall improvement. They found reduced sleep stage 1, while sleep stage 2 and delta wave were significantly enhanced. They also found an increase in Rapid eye movement density by second medication night. They concluded that the total sleep improvement was due to increase in sleep stage 2 and delta sleep.

Lee et al. (2001) study included five patients with schizophrenia and five age and sex-matched healthy controls. All participants underwent nocturnal polysomnography before atypical anti-psychotic agent clozapine therapy, during

early and late clozapine therapy. They monitored serum and cortisol level during each nocturnal polysomnography. In their study, clozapine improved sleep continuity and increased sleep stage 2 from the beginning of therapy.

Neuroleptic withdrawal often associated with sleep disturbances in patients with schizophrenia (Nofzinger et al., 1993). Neylan et al. (1992) study included eighteen clinically stable male patients with schizophrenia taking haloperidol. They examined three nights of polysomography for baseline measures and later after again neuroleptic withdrawal. They obtained sleep measures at the point of relapse (n=9) or after a six weeks drug free period if the patient with schizophrenia continued to remain clinically stable (n=9). They found neuroleptic withdrawal lead to decline REM and non-REM sleep and a reduction of REM latency in both groups. They further reported that relapsers varied from non-relapsers in that they had a significant decrease in sleep efficiency, total sleep time, sleep stage 2 and non-REM sleep. They also reported that the level of psychosis inversely correlated with sleep efficiency, total sleep time; sleep stage 4 in the drug free patients.

Chouinard et al. (2004) in their large meta-analysis investigated sleep characteristics in schizophrenia patients without neuroleptic treatment at the time of polysomnography recording. They investigated 20 sleep studies included 652 participants (321 schizophrenia patients and 331 healthy controls) on several sleep parameters including sleep latency, total sleep time, sleep efficiency index, total awake time, sleep stage 2 percentage, sleep stage 4 percentage, slow wave sleep percentage, REM sleep percentage and REM latency. They found that schizophrenia patients have increased sleep latency, decreased total sleep time and decreased sleep efficiency index. In moderator analysis, they reported that sleep problems were worse for the neuroleptic withdrawal group relatively than never treated group. They also found that never treated schizophrenia patients

show significantly increased total awake time and diminished sleep stage 2 percentage. They indicated that sleep disorders may be magnified by residual effects of neuroleptic withdrawal, while rest seemed to be attenuate by neuroleptic treatment.

These studies on consequence of antipsychotic medications in sleep in schizophrenia patients show improvement in sleep architecture and maintenance.

1.4.1.7 Discrepancy and Inconsistency in Sleep EEG Findings in Schizophrenia

The factors that could influence sleep EEG findings in schizophrenia include heterogeneity of duration of illness, diagnoses, patient selection criteria, clinical symptomatology and chronicity of illness. It is evident that sleep EEG findings in schizophrenia patients are inconsistent and discrepant. Some of the reasons for the inconsistency are: the difference in scoring methods, non-standardized diagnostic criterion, several sleep studies have not included habituation night so sleep parameters reported were worse and incomplete adaptation to the change in sleep environment may also one of causative factor for variations. Some other influential variables cannot be denied include, sample selection (inpatient or outpatient), age, gender and co-morbidity.

As discussed above, medications and their effects are also a primary concern. Several studies included patients taking neuroleptics and other antipsychotics which might conceal the true state of sleep. Unmedicated patients tend to have worse sleep compared with the other groups. In some studies, patients were clinically stable while in others they were not.

1.4.1.8 Sleep and Quality of Life in Schizophrenia

Sleep is closely related to every aspect of daily life. Sleep disturbances affects health and reduces the quality of life (Monti & Monti, 2008). Quality of sleep is associated with quality of life in schizophrenia patients.

Ritsner et al. (2004) investigated the relationship between perceived quality of life and subjective sleep quality among patients with schizophrenia. They evaluated 145 schizophrenia patients with measures of symptom severity, emotional distress, adverse effects, quality of life and quality of sleep (Pittsburgh Sleep Quality Index, PSQI). Pittsburgh Sleep Quality Index is one of most standardized measures to evaluate subjective sleep quality, provides a global score and scores seven components. They found that poor sleepers reported lower mean scores on all quality of life domains and were more depressed and distressed, and had more adverse effects to the medications than good sleepers.

1.5 Sleep and Neurocognitive Function

The role of sleep in memory, learning, performance and mood has been extensively studied. There is extensive support for bidirectional relationship between sleep physiology and enhanced cognitive performance. Sleep disturbances and sleep deprivation are known to affect cognition (Chee & Chuah, 2008). Sleep is certainly needed for a proper and well-balanced mental functioning (Stickgold et al., 2001). Lack of proper sleep clearly affects thinking, cognitive and motor performance (Pilcher & Huffcutt, 1996).

1.5.1 Sleep Deprivation and Cognitive Performance

Sleep deprivation affects neurocognitive performance (Harrison & Horne, 2000a; Durmer & Dinges, 2005). Sleep deprivation adversely impairs the higher-

order functioning or executive function (Horne, 1993). Memory tasks are highly negatively influenced by the sleep deprivation.

Pilcher and Huffcutt (1996) in their meta-analysis on effects on sleep deprivation on performance used data from 19 original research studies. Their analysis of 143 study coefficients and a total sample size of 1932 suggest that sleep deprivation robustly worsen human functioning. Their study found that the effects of sleep deprivation on fatigue and related mood states are greater than effects on cognitive or motor performance. They also indicated that partial sleep deprivation has a profound effect on function than effects of long-term or short-term sleep deprivation.

Williamson and Marie Feyer (2000) investigated the performance effects in same participants over 28 hours of sleep deprivation and after measured doses of alcohol up to 0.1% blood alcohol concentration. Their study included 39 participants. They used a randomised cross over control design. They administered several performance tests include the Mackworth Clock Test, simple reaction time, tracking, dual task, Symbol Digit Test, spatial memory search, memory and search test, and grammatical reasoning. Their study found, after 17-19 hours of without sleep test performance was equivalent or worse than that at a blood alcohol concentration of 0.05 %. They also found reaction time speeds up to 50 percent slower for some tests and accuracy were poorer than at this level of blood alcohol. They concluded moderate sleep deprivation impairs the cognitive performance.

Harrison and Horne (2000b) investigated the effects of 36 hour of sleep deprivation on a neuropsychological test of temporal memory. Their study included 40 participants. They have screened and excluded the volunteers with smoking, heavy drinking, participants with sleep or medical problems, epilepsy

patients and participants with migraine. Only moderate consumers of caffeine took part in the study. They assigned participants in randomly within sex to one of four groups: control sleep deprived placebo, control non-sleep deprived with caffeine, sleep deprived with caffeine and sleep deprived with placebo. Caffeine and placebo were given double blind in their study. They have given caffeine or placebo before testing. They gave caffeine to reduce sleepiness. The participants were given tasks consist of colour photographs of unknown faces and had two components: recognition memory and recency discrimination (temporal memory) when previously shown face was presented. Their study found no significant development of recency with caffeine in the sleep deprivation controls. They also found that sleep deprivation groups had a poorer insight into their performance with recency. Their study concluded sleep deprivation impairs temporal memory.

1.5.2 Sleep and Memory

Recent research studies on the effects of sleep on consolidation of memory gained an acceptance. Slow wave sleep is thought to be the most restorative sleep. Both behavioural experiments and physiological studies suggest that slow wave sleep has beneficial effects on memory consolidation (Fowler & Sullivan, 1973; Peigneux et al., 2001). Deep sleep or slow wave sleep has a beneficial effect on the consolidation of declarative memories (Gais & Born, 2004a; Walker, 2009; Plihal & Born, 1999). Whereas, there is no lasting benefit of declarative memory from periods abundant in REM sleep (Gais & Born, 2004a). Both non-REM and REM sleep play a key role in memory consolidation and learning. There is a transformation of information between and within neocortex and hippocampus during sleep that realizes the fixation of memory traces (Stickgold, 1998).

Gais and Born (2004b) studied about sleep and memory consolidation. Their study included 29 healthy men took part in one habituation night and two experimental nights. The subjects were placed on two groups (sleep experimental group *N*=18 and wake control group *N*=11). On each experimental night after electrodes were placed, participants learned two different memory tasks: declarative paired associate word list task and a non-declarative mirror trace task. They woke up test subjects in sleep experiment group three hours after sleep onset. The participants were asked to recall. The subjects in the wake control group were kept awake during the interval between learning and recall measures. The participants also requested to rate their subjective feelings on five point scale and the sleep quality after sleep. Their study demonstrates slow wave sleep related improvement of declarative memory. Their study also demonstrated offline enhancement on a paired-associate wordlist task following sleep, an improvement associated to early night sleep abundant in slow wave sleep.

REM sleep facilitates consolidation of non-declarative memory (Plihal & Born, 1999). Plihal and Born (1999) studied about sleep and memory. Their study consisted of eleven healthy men in experimental sleep group and ten healthy men in wake control group. They administered the Word Stem Priming Task (non-declarative memory) and a mental spatial rotation task (declarative memory) to both groups. The Wordstem priming task were based on 2 lists of words, one serve as a study word list with an explicit learning instructions and other serve as novel word list. They tested repetition priming effects and recall of spatial memory after three hour retention gap, which followed learning and were placed in first half night or second half night. The participants in the sleep group slept concurrently the retention gap, while participants of the wake group were kept awake. Their study reported early retention sleep was overruled by slow wave sleep, whereas REM sleep period prevail during late retention sleep. They

found that behind early retention sleep, recall of spatial memory was greater to that of late retention sleep. Whereas, priming effect was more powerful behind late than early retention sleep. They have suggested that slow wave sleep promotes consolidation of declarative memory and REM sleep helps consolidation of non-declarative memory.

1.5.3 Sleep and Problem Solving

A study by Linde and Bergstrom (1992) investigated sleep loss on performance of complex problem solving tasks compared with exclusively short term memory tasks. Their study consisted of two tasks: first one examined immediate free recall, estimated to reflect the maintenance capability of working memory and the other one was lingual reasoning and problem solving measures, speculated to reflect the processing and monitoring capability of working memory. They kept participants in the experimental group awake and tested on various cognitive measures. Control group was allowed to sleep at home. They have found a remarkable decline in performance left by a sleep loss on Raven's progressive matrices, a problem solving measure. But the control group who have slept well performed higher in the tests. Their study found that there is a significant decline in performance on sleep loss and improved performance following by sleep.

Wagner et al. (2004) study on the effects of sleep on the occurrence of insight used modified version of a mathematical "number reduction task" (Thurstone & Thurstone, 1941) in healthy controls on awake group and sleep group. Participants apply a standard algorithm (consist of two simple rules) for reducing an eight-digit sequence to a final solution. Participants do not know that a simple shortcut exists. The percentage of participants who discover this shortcut or 'hidden rule' when they are retested was 22% in the awake group

versus 60% in the sleep group. They have concluded that sleeping allows the restructuring of new memory representations and facilitates extraction of explicit knowledge and insightful behavior. Striking experimental evidence of process sleep dependant creative insight was splendidly proved.

A study by Cai et al. (2009) investigated the role of rapid eye movement (REM) sleep on creative problem solving using Remote Associate Test (RAT). The RAT is a simple word association test comprise of three words associated by a single concept. Each item requires the participant to combine or associate the three words extract from conjointly remote associate clusters. Their study included seventy-seven healthy participants without any neurological or psychological ailments. The participants were advised to be in the rest during the week prior to testing. They tested all the participants on the RAT twice in 1 day following by analogies. Participants were randomly assigned to a nap or quiet rest group. Participants in the nap group sleep were polysomnographically recorded for 90 minutes or up to two hours in bed, whereas the rest group heard music with polysomnographical monitoring for ninety minutes. Participants were given varied pre-exposure to the creative problem. Their study reported, compared with quiet rest and non-REM sleep, rapid eye movement (REM) sleep enhances creative problem-solving.

1.6 Aim of the Study

Patients with schizophrenia suffer from a wide range of cognitive deficits (Keffe et al., 2006). Sleep deprivation studies in healthy control participants shows sleep deprivation affects neurocognitive performance (Harrison & Horne, 2000a; Durmer & Dinges, 2005) and adversely impairs the higher order functioning or executive functions (Horne, 1993). Moderate sleep deprivation impairs the cognitive performance (Williamson & Marie Feyer, 2000; Harrison &

Horne, 2000b). Memory consolidation studies show the positive effects of sleep on consolidation of memory in healthy controls (Gais & Born, 2004b). In particular slow wave sleep or deep sleep having beneficial effects on declarative memories (Gais & Born, 2004a; Walker, 2009) and REM sleep having beneficial effects on non-declarative memory (Plihal & Born, 1999).

There is evidence of problem solving process being improved by sleep in the healthy controls (Wagner et al., 2004; Linde & Bergstrom, 1992). REM sleep enhances creative problem solving (Cai et al, 2009). Problem solving (Morris et al., 1995; Pantelis et al., 1997; McClellan et al., 2004; Kester et al., 2006; Noh et al., 2010; Zhu et al., 2010) as well as sleep (Sleep continuity, sleep architecture, REM sleep measures and microstructures of sleep) (Monti & Monti, 2006; Manoach & Stickgold, 2009; Yang & Winkelman, 2006; Poulin et al., 2003; Keshavan et al., 1998; Yetkin et al., 2011) has been shown to be impaired in patients with schizophrenia.

To the best of my knowledge there are no reported studies on sleep and problem solving in patients with schizophrenia. The present study aimed at exploring and investigating relationships between sleep and problem solving in patients with schizophrenia.

A consolidation paradigm used to investigate this question ex: participants are tested a day- and night time condition following learning, separated by a week, with half of them being allocated to the night or the day condition first in a balanced design. Sleep parameters examined by means of polysomnography.

1.6.1 Hypotheses

1) Schizophrenia patients show impairment on neuropsychological tests compared with healthy controls.
2) Schizophrenia patients will have impaired sleep parameters compared with controls.
3) Schizophrenia patients will have deficits in problem solving.
4) Night time interval (Post sleep performance) will be more beneficial than day time interval for problem solving.
5) Sleep parameters will be related to problem solving performance in schizophrenia patients.

Title of the Study: *Sleep and problem solving in schizophrenia.*

CHAPTER 2
Methodology

2.1 Place and Period of Study

The data were collected from April 2009 to October 2010 in the Sleep Laboratory, Department of Experimental Psychology, Heinrich Heine University of Düsseldorf, Germany and in the Department of Clinical Psychology and Psychotherapy, University of Wuppertal, Wuppertal, Germany.

2.2 Participants

2.2.1 Schizophrenia Patients

Schizophrenia patients had a mean age of 41.25 years (*SD* = 8.69) and an average of 12 years of education (*SD* = 1.41) (Table 2.1). The patients were 8 males and 12 females. Inclusion criteria were an age of 18 to 55 years, fluency in German, an IQ > 70 and stable medication for the last 2 weeks. Patients met the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for a diagnosis of schizophrenia or schizo-affective disorder was considered for the present study. Diagnoses were ascertained by means of the Structured Clinical Interview for DSM-IV (SCID, German version Wittchen et al., 1997) and the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987).

All patients were screened to exclude substance use or dependence, diagnosed sleep or neurological disorders and benzodiazepine use at the time of the study. Of the twenty schizophrenia patients, 13 had a diagnosis of paranoid schizophrenia, 2 were diagnosed with residual type and 5 had schizoaffective disorder. The majority of patients (*N* = 13) were diagnosed as belonging to the paranoid type (Table 2.2).

Table 2.1 Demographic Data of Schizophrenia Patients

Variable	**Schizophrenia patients** (*N* = 20)
Age	
Mean age (years) (*SD*)	41.25 (8.69)
Sex	
Male	8 (40%)
Female	12 (60%)
Education	
Mean (years) (*SD*)	12 (1.41)

***SD* = Standard Deviation, *N* = Number**

The PANSS positive scale scores were 9 (Min) to 26 (Max) (*M* = 16.55, *SD* = 5), on negative scale scores were (Min) 6 to 30 (Max) (*M* = 14.45, *SD* = 5.69) and on the global psychopathology scale scores were 16 (Min) to 49 (Max) (*M* = 32.50, *SD* = 8.95) (Table 2.2). The duration of illness was measured on the basis of time elapsed since the first diagnosis. This information is based on patient self-report and clinical records.

Table 2.2 Clinical Characteristics of Schizophrenia Patients (*N* = 20)

Diagnosis	
Paranoid schizophrenia (*N*)	13 (65%)
Schizoaffective disorder (*N*)	5 (25%)
Residual type (*N*)	2 (10%)
Duration of illness	
Mean (years) (*SD*)	13.43 (8.36)
Medication	
Atypical antipsychotics (*N*)	15 (75%)
Typical antipsychotics (*N*)	1 (5%)
Typical and atypical antipsychotic (*N*)	4 (20%)
PANSS scores	
Positive scale scores (Mean) (*SD*)	16.55 (5.00)
Negative scale scores (Mean) (*SD*)	14.55 (5.69)
Global psychopathology scale (Mean) (*SD*)	32.50 (8.95)

***SD* = Standard Deviation, *N* = Number**

The information about patient's medication status was documented accordingly. Patients were on different medication protocols - atypical antipsychotic medication (*N* = 15), typical antipsychotics (*N* = 1) and; typical and atypical antipsychotics (*N* = 4).

The patients were recruited from a variety of urban health centres, mainly from the Evangelical Foundation- Tannenhof, Remscheid, Germany.

2.2.2 Healthy Controls

Twelve healthy control participants took part in the study - 4 male and 8 female participants aged from 21 to 50 years (*M* = 37.33, *SD* = 9.01). All participants were screened to exclude substance use or dependence, diagnosed sleep or neurological disorders and benzodiazepine use at the time of the study. The volunteers of healthy control group were recruited from the local campus and nearby universities. The pamphlets explaining the research study were distributed and posted on the university notice boards. The healthy controls were matched by age group, gender, level of education and socioeconomic status of the patient group.

Table 2.3 Demographic Data of Healthy Controls

Variable	**Controls (*N* = 12)**		
Age			
Mean age (*SD*)	37.4 (9.01)		
Range	(21-50)		
Sex	*N*	%	
Men	4	33.3	
Women	8	66.7	
Education			
Mean (years) (*SD*)	12.33 (.99)		

***SD* = Standard Deviation, *N* = Number**

2.2.3 Dropouts and Missing Data

Seven participants were not included in the study (one patient withdrew after the initial assessment, another 3 patients terminated the procedure after the first night in the sleep laboratory and 2 patients and one control participant had to be excluded because of the missing data.

2.2.4 Ethics and Study Approval

Informed consent was obtained from each participant. The study was approved by the ethics committees of the University of Wuppertal & Heinrich Heine University of Düsseldorf, Germany. Participants received a remuneration of 60 Euros.

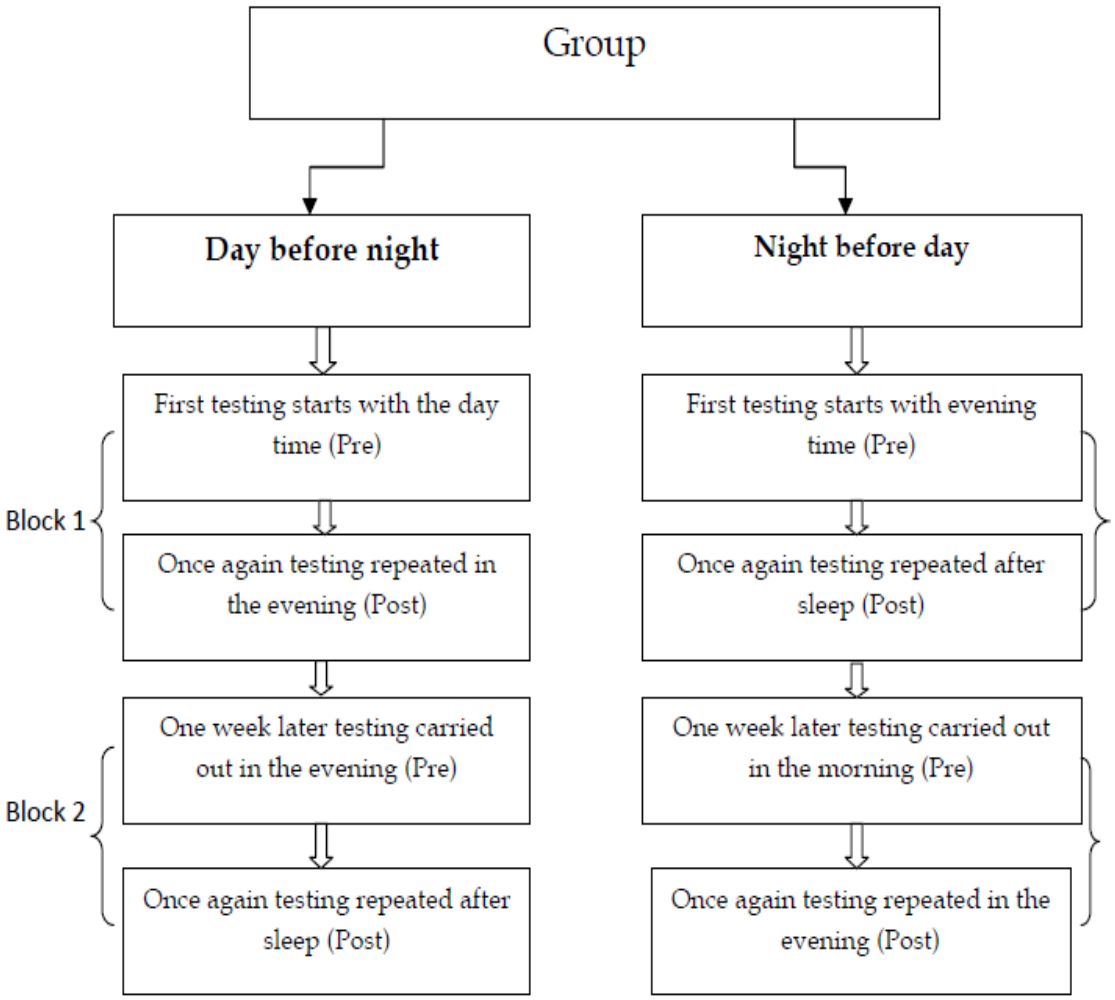
2.3 Research Design

Twenty schizophrenia patients and 12 healthy controls took part in the study. Participants underwent a day- and a night-time condition, separated by a week, with half of them being allocated to the night or the day condition first, in a balanced design. During day condition training occurred in the morning and testing approximately 8 hours later (M = 7.9 hours, SD = .3) in the evening. During the night condition, training occurred in the evening and testing 8 hours later in the morning. There were two versions of experimental task which were randomly presented either first or second time. The description of the research design is explained below in Table 2.4 and Table 2.5

Table 2.4 Description of the Research Design

Status	**Schizophrenia patients** (*N* 20)				**Healthy controls** (*N* 12)			
Group	Day before night *N* =10		Night before day *N*=10		Day before night *N*=6		Night before day *N*=6	
Block	1	2	1	2	1	2	1	2
Pre-post	Pre-post	Pre-post	Pre-post	Pre-post	Pre-post	Pre-post	Pre-post	Pre-post

Table 2.5 Description of the Groups



2.3.1 Combined the Day and Night Condition/Blocks

Preliminary analyses were made as described in the research design (Table 2.4 & Table 2.5). In preliminary analyses is also to check the order effects (Day before night vs. night before day). In later stage, "Day before night" and "night before day"conditions/Blocks were combined respectively to within groups. Combining the "day before night" and "night before day" across the two orders resulted as "Interval" (Day interval vs. Night interval). Day interval vs. Night interval is the main analyses.

2.4 Measures

2.4.1 Structured Clinical Interview for DSM-IV SCID (Wittchen et al., 1997)

The Structured Clinical Interview for DSM-IV (SCID) was developed in 1990. SCID is extensively used in clinical trials and psychiatric research. Structured Clinical Interview for DSM-IV (SCID) is clinician administered diagnostic interview designed for use of professionals in the field of mental health. Structured Clinical Interview - SCID semi structure interview begins with a section on demographic data (ex: age, marital status, educational background, work background) and clinical background (ex: persisting chief complaints, treatment history, past episodes of psychiatric disturbance and present functioning). There are 7 diagnostic modules focused on different diagnostic groups (psychotic, substance abuse, mood, anxiety, somatoform, eating, and adjustment disorders).

All available information like hospital records, hospitalization history, informants and patient observation should be used to rate the Structured Clinical Interview for DSM-IV (SCID). The Structured Clinical Interview for DSM-IV

(SCID) interview approximately takes one hour, but sometimes it may take longer in individuals with severe symptomatology. The Structured Clinical Interview for DSM-IV (SCID) is highly reliable for diagnosis of most of psychiatric disorders.

SCID is divided into different sections, each containing questions about different disorders. For the present research study, module-B (Psychotic and associated symptoms), module-C (differential diagnosis) and module-E (substance use disorders) were administered. Module-B and module-C were used for diagnosis of psychotic disorders, and module-E was used for the assessment of DSM-IV criteria for abuse and alcohol addiction, drugs and medicines.

2.4.2 Positive and Negative Syndrome Scale – PANSS (Kay et al., 1987)

The Positive and Negative Syndrome Scale (PANSS) is common scale in clinical studies for measuring the severity of symptoms in patients with schizophrenia. The PANSS assessment can be completed in 30 to 40 minutes approximately.

The PANSS scale consists of thirty items on three sub scales. Seven items covering positive symptoms (delusions, conceptual disorganization, hallucinations, hyperactivity, grandiosity, suspiciousness /persecution, hostility), seven item covering negative symptoms (blunted effect, poor rapport, emotional withdrawal, passive /apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking) and sixteen covering general psychopathology (somatic concern, guilt feelings, anxiety, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor

attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation and active social avoidance).

Each item was scored on a 7 point item specific Likert scale ranging from 1 to 7. Thus the positive and negative subscales each range from 7 to 49 and the general psychopathology scale from 16 to 112. The reliability for each scale is quite high.

2.4.3 Socio - Demographic Profile

The socio-demographic data were obtained from all participants.

2.5 Neuropsychological Tests

2.5.1 VLMT-Verbal Learning and Memory Test (Helmstaedter at al., 2001)

In order to assess verbal learning, memory and learning potential, a German adaptation of the Rey Auditory Verbal Learning test (Verbaler Lern- und Merkfaehigkeitstest -VLMT; Helmstaedter et al., 2001) was administered. The Verbal Learning and Memory Test require constructive learning and recall of a list of 15 words (List A) over five trials; free recall of this list after each trial is requested. After the five learning trials are complete, a second word list (list B) is presented for free recall to assess the effects of interference, finally unannounced recall of List A is requested after a delay of half an hour, and a recognition trial is performed. Recognition trial requires identification of the words of (list A) out of an orally presented list of fifty words which comprises the words from lists A and B, as well as new distracters words. The verbal learning performance was calculated by summing up the total number of correctly reproduced words over

the five learning trials. A number of scores can be derived. Here we present total number of correctly recalled words immediately and after delay.

2.5.2 Trail Making Test A & B (Reitan et al., 1979)

The Trail Making Test consists of two parts (A and B), each of which contains 15 circles distributed on a sheet of paper. In Part A, each circle contains a number from 1 to 15. After completing the sample test, the participant is instructed to begin at the number 1 and to locate and draw a pencil line to 2, then to 3, and so on until reaching the number 15 as faster as possible. Part B has both numbers and letters within the 15 circles, and the participant is instructed to alternate between them as the numerical and alphabetical sequences progress. The participant begins at 1, locates and draws a line to A, then to 2, then to B, and so on until completing the test. The score for each part of the test is the number of seconds required for completion.

The Trial Making Test Part B is more challenging than Part A. Scoring is expressed in terms of the time in seconds required for completion of each of the two parts of the test. Both parts require perceptual tracking of a sequence and speeded performance, but Part B also requires divided attention. The ratio and difference scores are attempts to elucidate the added task requirements of Part B, and are thought to be purer measures of the more complex divided attention and alternating sequencing tasks required in Part B.

2.5.3. Multiple Choice Word Comprehension Test (MWT-B; Lehr et al 1989)

Verbal intelligence was assessed using the Multiple Choice Word Fluency Test -MWT-B (Mehrfachwahl-Wortschatz-Intelligenz-Test). In a thirty seven item list, containing five words per item (one correct word and four nonsense words),

the participants had to identify the correct word. The number of correct answers was analyzed. Participants asked not to mark the response randomly, if they do not know the answer. The raw scores and IQ value for the MWT-B were given below (Table 2.6).

Table 2.6 Scores for the Multiple Choice Word Fluency Test (MWT-B)

Total Score	Intelligence	Intelligence Quotient (IQ)
0-5	Very low intelligence	≤ 72
6-20	Low intelligence	73-90
21-30	Average intelligence	91-109
31-33	High intelligence	110-127
34-37	Very high intelligence	≥ 128

2.5.4 Digit Symbol Test (Oswald and Fleischmann., 1986)

The Digit Symbol Test, a simplified version of the Oswald and Fleischmann (1986) was used. Nine digits have to be replaced as quickly as possible, with a symbol shown at the top of the page. The score represents the number of correct symbols drawn within 90 seconds. This test measures psychomotor performance, motor persistence, sustained attention, response speed, and visuo-motor coordination. The higher the score, the better the visual acuity and cognitive speed.

2.5.5 Controlled Oral Word Association Test (Benton et al., 1983)

The Controlled Oral Word Association Test used to measure verbal fluency. During this test participants are asked to produce as many words as

possible starting with F, A, S within one minute each. The participants are advised not to use proper names and different forms of the same words. The performance score is the sum of correct words.

2.6 Experimental Task

2.6.1 Tower of London Test (Shallice et al., 1982)

Problem solving was assessed with two versions of the computerized version of the Tower of London test. Participants were presented with a problem in the computer. In this computerized test participants are shown coloured spheres arranged on poles. Displayed are a start position and a goal position and the task is to rearrange the spheres within a set number of moves as fast as possible to attain the goal position. If a task is not completed within the given number of moves it is registered as unsolved. Participants were given an initial practice task which they could carry out as often as they wished to familiarise themselves with the apparatus. There are 15 tasks with increasing difficulty.

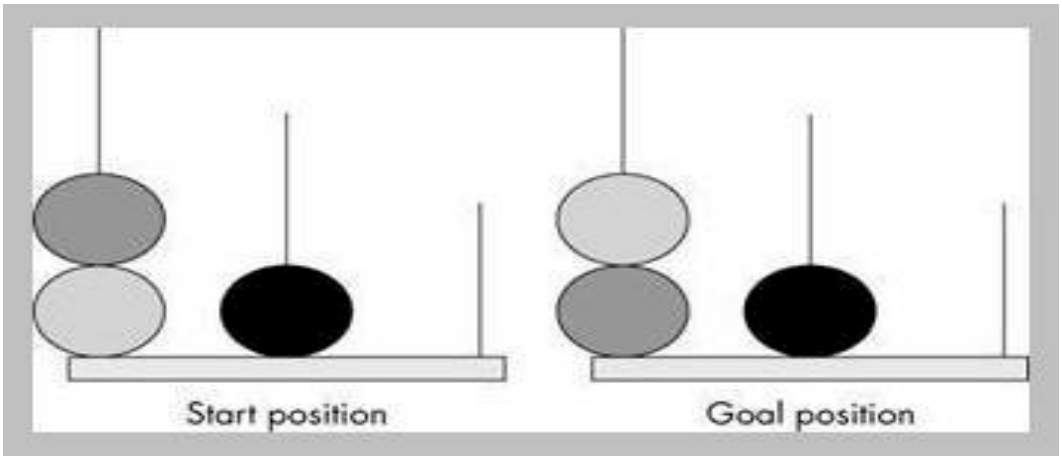


Figure 2.1 Model of the Tower of London Test

Source: Adapted from Psychology Press, Taylor & Francis Group, London
http://www.psypress.com/grome/figures/fig%209.7.jpg

The scores are the number of solved tasks and total time taken to complete the Tower of London test. The Tower of London test (Shallice et al., 1982) is a widely used test measure of planning, sequencing and problem solving. Two versions of the test were used.

2.7 Polysomonography

Prior to retiring at the sleep laboratory, participants were wired for the standard polysomonographic sleep recordings. EEG leads were placed according to the International 10/20 system (Jasper, 1958). Recordings were conducted using the 16 channel polygraph (Biopac MP150 Data acquisition systems and Acqknowledge 3.9.1 software). Biopac MP150 data acquisition system and Acqknowledge 3.9.1 software is an interactive, intuitive program that let instantly view, measure, analyze and transform the data.

Sleep EEG data were sampled at 1000 Hz and band-pass filtered between 1 and 35 Hz for analysis. EOG data were sampled at 1000 Hz and band-pass filtered between 0.05 and 35 Hz and EMG data at 1000 Hz with band-pass filters of 10 and 500 Hz. Additionally, a notch filter was applied.

Sleep EEG files were stored in .acq format. The following recordings were included: electroencephalogram (C3-A2, C4-A1), an electrooculogram (EOG), and a submental chin electromyogram (EMG). EEG electrode placements are briefly explained below.

2.7.1 Electrode Placement

2.7.1.1 EEG Electrode Placement

EEG electrodes (C3 electrode derivation on left central scalp referenced to

the right earlobe & C4 electrode derivation on right central scalp referenced to the left earlobe) were fixed on participants head (Figure 2.2). In order to locate these two points (C3 & C4), a tape measure were applied from the nasion (at top edge of the nose, where the forehead is indented) to the inion (just underneath the occipital condyle, the bump at the back of the head). Half of the total distance is marked with a non permanent black marker. The tape is then placed from the preauricular notch of the left ear through this marked spot to the preauricular notch on the right ear. The mid-point is located again. The intersection of the two measurements locates the vertex. When the vertex is obtained, then 20% of that total distance from ear to ear is recalculated. The distance is then marked from the vertex toward the left ear and the right ear along with the line between the two ears. These are the locations of C3 and C4. Once the appropriate locations are marked, the marking points were cleaned and removed with gel. The conductive paste was used to fix the C3 and C4 electrodes.

2.7.1.2 EOG Electrode Placement

Electrode (E1) is placed approximately 1 cm above and slightly lateral to the outer canthus of one eye and reference electrode on ear lobe (A1). On the second eye movement channel are recorded the potential from an electrode 1cm below and slightly lateral to the outer canthus of the other eye (E2) referred to the earlobe (A1) (Figure 2.2). Both eyes are referenced to the same ear (Rechtschaffen and Kales 1968).

2.7.1.3 EMG Electrode Placement

Two electrodes were placed on the muscle area beneath the chin (submental) (Figure 2.2).

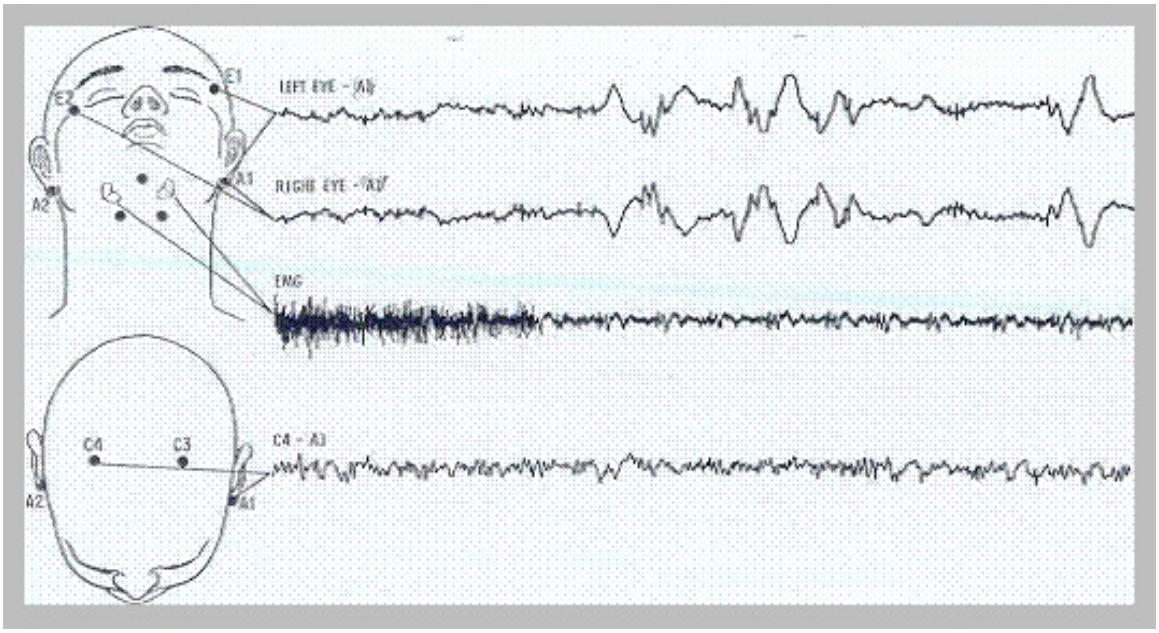


Figure 2.2 Picture Representing Placement of Electrodes

Source: Rechtsschaffen, A & Kales, A manual Of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Public health service, U.S. Government Printing Office, Washington, D.C., 1968

2.7.2 Sleep EEG Scoring

The second night (experimental night) sleep EEG recordings were used for analysis. The sleep data was scored based on the tracings of C3. Thirty-second epochs were staged according to Rechtschaffen - Kales criteria (A Manual of standardized terminology, techniques and scoring system for sleep stages of human subjects). The Rechtschaffen - Kales (1968) criteria for scoring sleep stages were presented in the table 1.8.

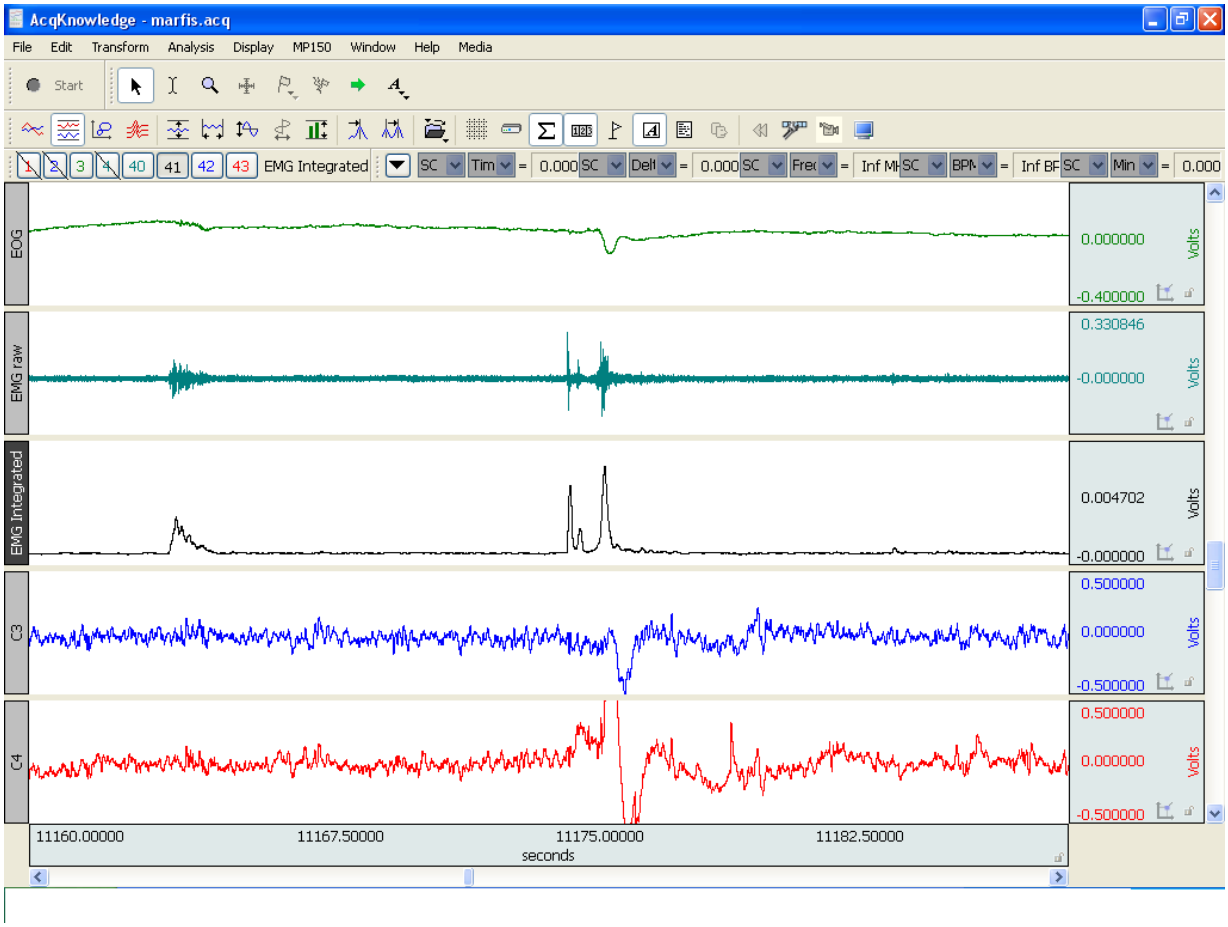


Figure 2.3 Sample Screenshot of Sleep EEG Recorded using Biopac Acqknowledge 3.9.1 Software

The following parameters were analyzed: a) total sleep, defined as the actual time spent asleep; b) sleep latency, defined as the time from lights out until the onsets of three consecutive epochs of sleep stage 1; c) sleep efficiency, was defined as the percentage of time spent asleep divided by the total recording time; d) wake, defined as total time scored as wakefulness between sleep onset and final awakening; e) REM sleep period, defined by not less than 40 epochs of NREM sleep (sleep stage 1 through 4) subtending any two REM periods; f) REM latency, defined as the time from sleep onset until the first epoch of REM sleep; g) sleep stages 1, stage 2, stage 3, stage 4, defined as the number of epochs spent on each stages; h) K-complex, defined as negative sharp wave immediately

followed by a positive component with a total duration more than 0.5 seconds; i) spindles, defined distinct wave patterns 12-14 cycles per second (cps) of at least 0.5 sec.

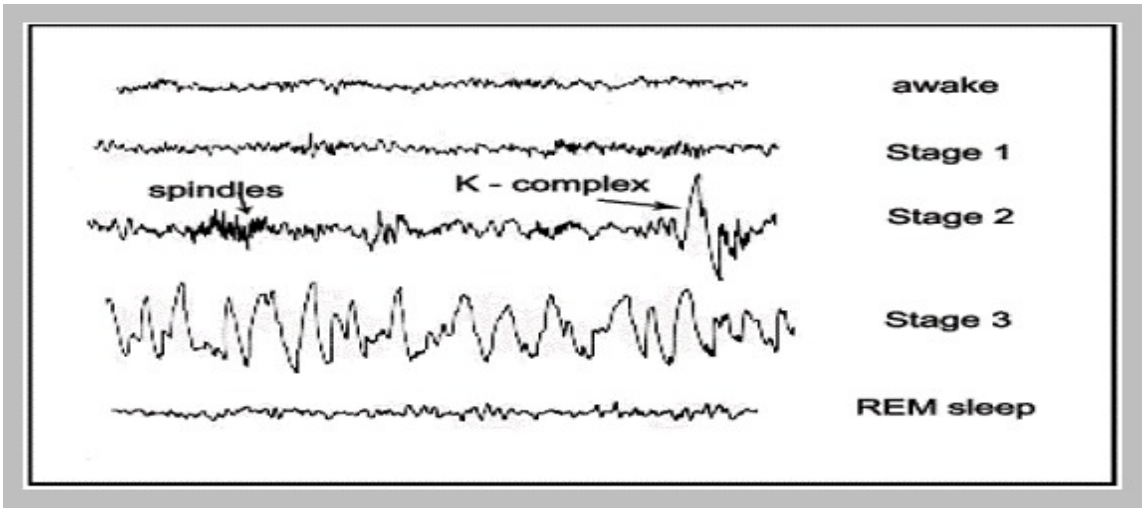


Figure 2.4 Wave Patterns of Different Sleep Stages

After scoring sleep EEG parameters in epochs, sleep parameters were converted from epoch (30 sec) to minutes (min). The time in minutes were calculated for the following sleep parameters: REM (TSR), Non-Rapid eye movement (TSN), total sleep stage 1 (TS1), total sleep stage 2 (TS2), total sleep stage 3 and stage 4 (TS3AND4), total sleep, REM latency, sleep latency, movement time and wake. The sleep architecture also defined in terms of the percentage of sleep time. The percentage was calculated for the following sleep parameters: sleep efficiency, stage 1, stage 2, stage 3 & 4, wake, movement time and total sleep. K-complexes and spindles were defined in terms of number.

2.7.3 Sleep Parameters Examined

The sleep parameters studied in the present study are given below in the table 2.7.

Table 2.7 Sleep Parameters Investigated in the Present Study

TSR (min)	TSN (min)	TS1(min)
TS2 (min)	TS3AND4 (min)	TOTAL SLEEP (min)
REM LATENCY (min)	SLEEP LATENCY (min)	SLEEP EFFECIENCY %
NUMBER OF SPINDLES	NUMBER OF K-COMPLEXES	MOVEMENT TIME (min)
TSW (min)	REM %	NREM %
STAGE 1%	STAGE 2%	STAGE 3 & 4%
WAKE%	MOVEMENT TIME%	TOTAL SLEEP%

REM = Rapid eye Movement, NREM = Non-Rapid eye movement, TSR = Total sleep REM, TSN = Total sleep NREM, TS1 = Total sleep stage 1, TS2 = Total Sleep stage 2, TS3AND4 = Total sleep stage 3 and stage 4, TSW = Total stage wake.

2.8 Procedure

During the first contact patients were administered the standardised interviews to ascertain the diagnosis after which they were given information about the procedure and gave their informed consent. Within the following week they entered either the day interval or the night interval condition. Day-time testing took place in the morning and late afternoon at the Department of Clinical Psychology at the University of Wuppertal or the home of the participants. For the night interval condition participants spent two consecutive nights at the sleep laboratory of the Department of Clinical Psychology, University of Düsseldorf. The first night served to accustom participants to the sleeping conditions while being wired up for polysomnographic recordings.

Testing conditions and groups were briefly explained in research design (Table 2.4) & (Table 2.5). The day testing and night testing procedure is further explained below.

2.8.1 Day Testing

Day-time testing took place in the morning and late afternoon at the Department of Clinical Psychology at the University of Wuppertal or the home of the participants.

2.8.2 Night Testing

On the habituation night, upon arrival of the participant at the sleep laboratory at 21:00 hr, a battery of neuropsychological tests including the Verbal Learning and Memory Test -VLMT, Trial Making test A & B, Multiple Choice Word Comprehension Test (MWT-B), Digit Symbol Test and Controlled Oral Word Association Test were administered. The neuropsychological testing lasts from 40 minutes to one hour.

After the neuropsychological testing, the participant were given time to get ready for sleep. EEG electrodes were fixed on patient head as described above earlier (Figure 2.2). After checking electrode signals the acquisition starts. The participant according to their usual habits at home, freely chose lights out time. The room used for the recording had a comfortable bed, acoustic isolation, controlled temperature and light. The participants were woken up at 6 am in the morning.

The recorded sleep data during the habituation night was not included for the analysis.

Figure 2.5 Shows Sleep Laboratory

On the experimental night, upon arrival of the participant at the sleep laboratory at 21:00 hrs, the Tower of London test was administered. After the testing, just as described above the night testing procedure was the same as during the habituation night. But, the Tower of London test was administered once again to the participant in the morning after awake. The recorded sleep EEG data during the experimental night were used for analysis. The sleep EEG recordings were saved in .acq file format and stored on compact disc with the internal identification number. The recorded sleep data were analysed twice offline by two trained researchers. The scored sleep EEG data were documented in excel file and as well as in a hard copy.

2.9 Statistical Data Analyses

All statistical analyses were carried out using the program Statistical Package for the Social Sciences (SPSS) (PASW statistics 18 release 18.0.0).

2.9.1 Descriptive Measures

T-tests were conducted to assess, group differences with regard to age and education. Sex differences were examined with Chi-square test.

2.9.2 Neuropsychological Test Scores

T-tests for independent samples were conducted to compare the neuropsychological test scores of schizophrenia patients and healthy controls.

2.9.3 Experimental Tasks - Tower of London Test Measures – Preliminary Analyses

In first step preliminary analyses, analyses of variance were carried out to ascertain that none of the independent variables interacted significantly with 'order' (Day before night vs. night before day).

2.9.3.1 Multivariate Analysis of Variance - Schizophrenia Patients versus Healthy Controls

A 2 (Status: schizophrenia patients vs. healthy controls) x 2 (Group: day before night vs. night before day) x 2 (Block: block 1 vs. block 2) x 2 (pre-post: pre vs. post) four-way mixed MANOVA with repeated measures on the last two factors was performed using the number of solved tasks and total time taken as dependant variables. Bonferroni adjustments of p values were used to correct for multiple comparisons. Effect sizes are indicated in terms of η^2**.** All effects are reported as significant at $p < .05$.

2.9.3.2 Multivariate Analysis of Variance - Schizophrenia Patients

A 2 (Group: day before night vs. night before day) x 2 (Block: block 1 vs. block 2) x 2 (Pre-post: pre vs. post) three-way mixed MANOVA with repeated measures on the last two factors was performed using the number of solved tasks and total time taken as dependant variables. Bonferroni adjustments of *p* values were used to correct for multiple comparisons. Effect sizes are indicated in terms of η^2**.** All effects are reported as significant at $p < .05$.

2.9.3.3 Multivariate Analysis of Variance - Healthy Controls

A 2 (Group: day before night vs. night before day) x 2 (Block: block 1 vs. block 2) x 2 (Pre-post: pre vs. post) three-way mixed MANOVA with repeated measures on the last two factors was performed using the number of solved tasks and total time taken as dependant variables. Bonferroni adjustments of *p* values were used to correct for multiple comparisons. Effect sizes are indicated in terms of η^2**.** All effects are reported as significant at $p < .05$.

2.9.4 Experimental Task- Tower of London test measures – Main Analysis (Combined the Day and Night Condition/blocks)

The combined blocks are named as "Interval" (Day interval vs. night interval).

2.9.4.1 Multivariate Analysis of Variance - Day versus Night Interval (Schizophrenia patients vs. healthy controls) Main Analysis

A 2 (Status: schizophrenia patients vs. healthy controls) x 2 (Interval: day interval vs. night interval) x 2 (Pre-post: pre vs. post) three-way mixed MANOVA with repeated measures on the last two factors was performed using

the number of solved tasks and total time taken as dependant variables. Bonferroni adjustments of *p* values were used to correct for multiple comparisons. Effect sizes are indicated in terms of η^2**.** All effects are reported as significant at $p < .05$.

2.9.4.2 Multivariate Analysis of Variance - Day versus Night Interval (Schizophrenia Patients)

A 2 (Interval: day interval vs. night interval) x 2 (Pre-post: pre vs. post) two-way mixed MANOVA with repeated measures was performed using the number of solved tasks and total time taken as dependant variables. Bonferroni adjustments of *p* values were used to correct for multiple comparisons. Effect sizes are indicated in terms of η^2**.** All effects are reported as significant at $p < .05$.

2.9.4.3 Multivariate Analysis of Variance - Day versus Night Interval (Healthy Controls)

A 2 (Interval: day interval vs. night interval) x 2 (pre-post: pre vs. post) two-way mixed MANOVA with repeated measures was performed using the number of solved tasks and total time taken as dependant variables. Bonferroni adjustments of *p* values were used to correct for multiple comparisons. Effect sizes are indicated in terms of η^2**.** All effects are reported as significant at $p < .05$.

2.9.5 Sleep EEG Data

2.9.5.1 Comparison of Sleep EEG Parameters between Patient Group and Control Group

Independent sample t-tests were performed to compare the sleep EEG data of the second night between schizophrenia patients and healthy controls.

2.9.5.2 Correlation of Sleep EEG Parameters and the Tower of London Measures

Pearson product-moment correlation coefficients were computed to assess the relationship between sleep parameters and Tower of London test measures (number of solved tasks and total time taken). The following sleep parameters were examined REM, NREM, total sleep stage 1, total sleep stage 2, total sleep stage 3 and stage 4, total sleep duration, REM latency, sleep latency, sleep efficiency, number of spindles, number of k-complexes, movement time, total stage awake, REM percent, NREM percent, stage 1 percent, stage 2 percent, stage 3 & 4 percent, awake percent, movement time percent and total sleep percent.

CHAPTER 3

RESULTS

3.1 Descriptive Measures

The total sample was comprised of 32 participants. Twenty schizophrenia patients and twelve healthy controls took part in the study.

3.1.1 Schizophrenia Patients

Schizophrenia patients had a mean age of 41.25 years (*SD* = 8.69) and an average of 12 years of education (*SD* = 1.41) (Table 3.1). The patients were 8 men (40%) and 12 women (60%). Of the 20 patients, 13 had a diagnosis of paranoid schizophrenia (65%), 5 were diagnosed with schizoaffective disorder type (25%) and 2 had schizoaffective disorder (10%) (Table 3.1) The majority of patients (*N* = 13) were diagnosed as belonging to the paranoid type (Figure 3.1). The average duration of illness was 13.43 years (*SD* = 8.36).

The mean scores of the PANSS for schizophrenia patients: on positive scale, scores were 9 (Min) to 26 (Max) (*M* = 16.55, *SD* = 5), on negative scale scores were 6 (Min) to 30 (Max) (*M* = 14.45, *SD* = 5.69) and on the global psychopathology scale scores were 16 (Min) to 49 (Max) (*M* = 32.50, *SD* = 8.95) (Table 3.1) (Figure 3.2).

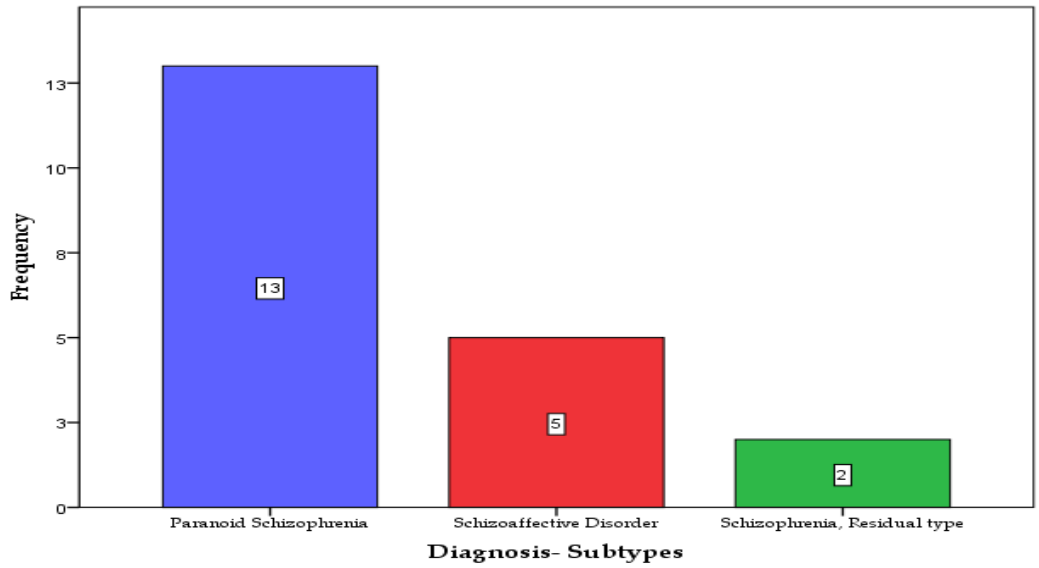


Figure 3.1 Distribution of Diagnostic Subtypes of Schizophrenia patients

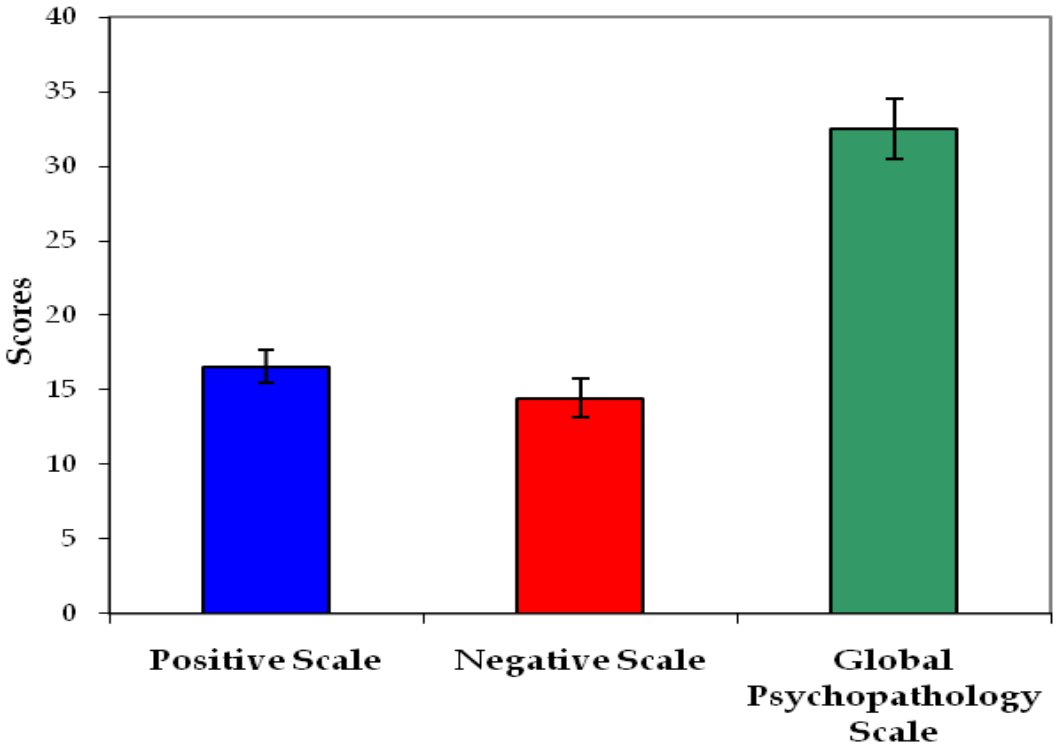


Figure 3.2 PANSS Mean Scores of Schizophrenia Patients

Table 3.1 Demographic and Clinical Characteristics of Schizophrenia Patients and Healthy Controls

Variable	Patients (*N* = 20)			Controls (*N* = 12)		
Age Mean age (years) (*SD*) (Range)	41.25 (8.69) (26-54)			37.4 (9.01) (21-50)		
Sex	***N***	**%**		***N***	**%**	
Men Women	8 12	40 60		4 8	33.3 66.7	
Education Mean (years) (*SD*)	12 (1.41)			12.33 (.99)		
Diagnostic subtypes	***N***	**%**				
Paranoid schizophrenia Schizoaffective disorder Residual type	13 5 2	65 25 10				
Duration of illness Mean (years) (*SD*)	13.43 (8.36)					
Medication	***N***	**%**				
Atypical antipsychotics Typical antipsychotics Typical and atypical antipsychotics	15 1 4	75 5 20				
PANSS scores						
Positive scale scores (Mean) (*SD*) Negative scale scores (Mean) (*SD*) Global psychopathology scale (Mean) (*SD*)	16.55 (5.00) 14.55 (5.69) 32.50 (8.95)					

***SD* = Standard Deviation, *N* = Number; PANSS = Positive and Negative Syndrome Scale**

3.1.2 Healthy Controls

Twelve healthy control participants took part in the study, 4 men (33.3%) and 8 women (66.7%). Participants had a mean age of 37.4 years (*SD* = 9.01) and an average of 12.33 years of education (*SD* = .98) (Table 3.1).

In order to assess possible differences between schizophrenia patients and healthy controls on the demographic measures, *t*-tests were performed. There were no significant differences found between schizophrenia patients and healthy controls with regard to the age and number of school years (age $t(30) = 1.21$, $p = .23$; education $t(30) = -.71$, $p = .47$). For sex differences a Chi-square test was performed (Chi-square = 0.14, $p = .70$).

3.2 Neuropsychological Test Scores

Group means and standard deviations of neuropsychological test scores of the schizophrenia patients and healthy controls are reported in Table 3.2.

3.2.1 Neuropsychological Performance (Schizophrenia Patients versus Healthy Controls)

The neuropsychological test scores of schizophrenia patients ($N = 20$) were compared with those of healthy controls ($N = 12$). Independent samples t-tests were conducted to compare the neuropsychological test scores of schizophrenia patients and healthy controls (Table 3.2). The results showed patients with schizophrenia performed significantly worse than healthy controls on most neuropsychological tests.

Table 3.2 Neuropsychological Test Scores (Schizophrenia Patients vs. Healthy Controls)

Measure	Scores						
	Patients (*N* = 20)		**Controls (*N* = 12)**		**T-tests**		
	Mean	**(*SD*)**	**Mean**	**(*SD*)**	***t***	***df***	***p***
Multiple Choice Word Comprehension test (MWT-B) Raw score	29.10	5.30	30.00	3.69	- .51	30	.60
MWT B – IQ	110.35	14.47	111.58	13.49	- .23	30	.81
Trail Making Test							
TMT A (sec)	46.87	25.75	36.83	16.63	1.20	30	.23
TMT B (sec)	106.42	58.72	63.53	20.93	2.42	30	**.02***
TMT B - TMT A	59.54	51.26	26.61	24.88	2.07	30	**.04***
Digit Symbol Test	43.95	13.82	62.17	9.98	-3.97	30	**.000*****
Controlled Oral Word Association Test	32.60	10.60	44.58	9.53	-3.20	30	**.00****
Verbal Learning and Memory Test –VLMT							
Supra margin (D1)	6.65	2.75	9.67	1.49	-3.47	30	**.00****
Learning performance (D5)	12.10	2.91	14.50	.79	-2.77	30	**.01****
Total Learning performance (∑D1-D5)	49.85	14.13	65.08	4.03	-3.62	30	**.001*****
Recall performance of the interference list (I)	5.75	2.61	9.08	2.50	-3.54	30	**.001*****
Recall performance after interference (D6)	9.75	4.02	13.75	1.13	-3.34	30	**.00****
Recall performance after a time lag (D7)	9.30	3.48	14.08	1.31	-4.54	30	**.000*****
Forgetting to interference (D5-D6)	2.40	1.90	.75	.96	2.78	30	**.00****
Forgotten after a time lag (D5-D7)	2.75	1.91	.42	1.37	3.67	30	**.001*****
Recognition performance (W)	10.80	4.60	14.58	.66	-2.80	30	**.001*****

***p* < .05 * = *p* < .05 ** = *p* < .01, *** = *p* < .001**

3.2.2 Multiple Choice Word Comprehension Test (MWT-B)

There was no significant difference between schizophrenia patients and healthy controls with regard to IQ scores as measured with the Multiple Choice Word Comprehension test (MWT-B) (patients M = 110.35, SD = 14.47; controls M = 111.58, SD = 13.49), $t(30)$ = - .23, p = .81 (Figure 3.3). According to the manual of Multiple Choice Word Comprehension test (MWT-B) intelligent quotients of 110-127 represent high intelligence.

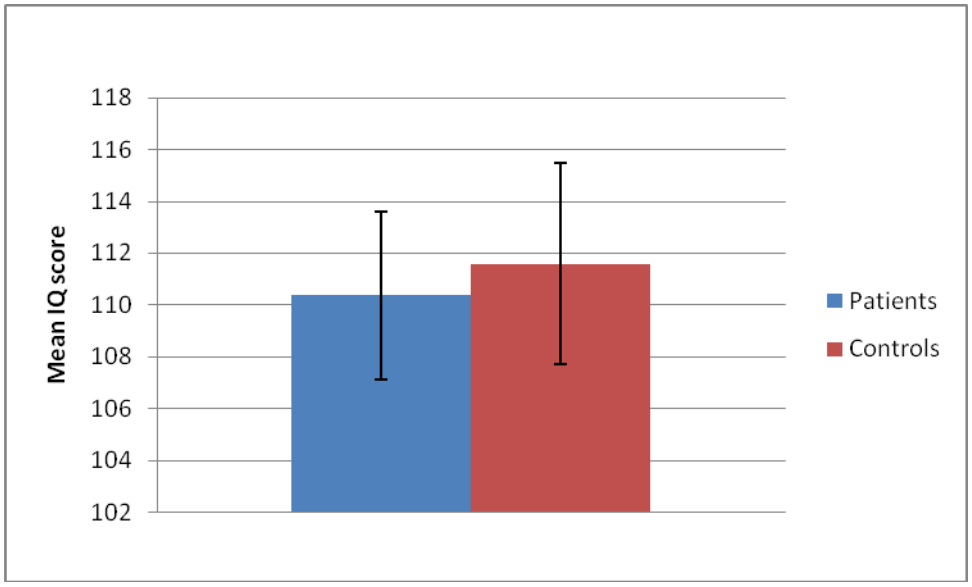


Figure 3.3 Multiple Choice Word Comprehension Test (MWT-B) IQ mean scores of schizophrenia patients and healthy controls (bars represent standard errors)

3.2.3 Trail Making Test

There was no significant difference between schizophrenia patients and healthy controls on the Trail Making Test A (TMT A) (psychomotor speed) (patients M = 46.87, SD = 25.75; controls M = 36.83, SD = 16.63), $t(30)$ = 1.20, p = .23. There was a significant difference between schizophrenia patients and

healthy controls on the Trail Making Test B (TMT B) (set-shifting and flexibility) (patients M = 106.42, SD = 58.72; controls M = 63.53, SD = 20.93), $t(30) = 2.42$, p = .02. Schizophrenia patients had a worse performance with regard to TMT B compared with healthy controls. There was also a significant difference between schizophrenia patients and healthy controls with regard to Trail Making B - A (TMT B - TMT A) difference scores (patients M = 59.54, SD = 51.26; controls M = 26.61, SD = 24.88), $t(30) = 2.07$, p = .04 (Figure 3.4).

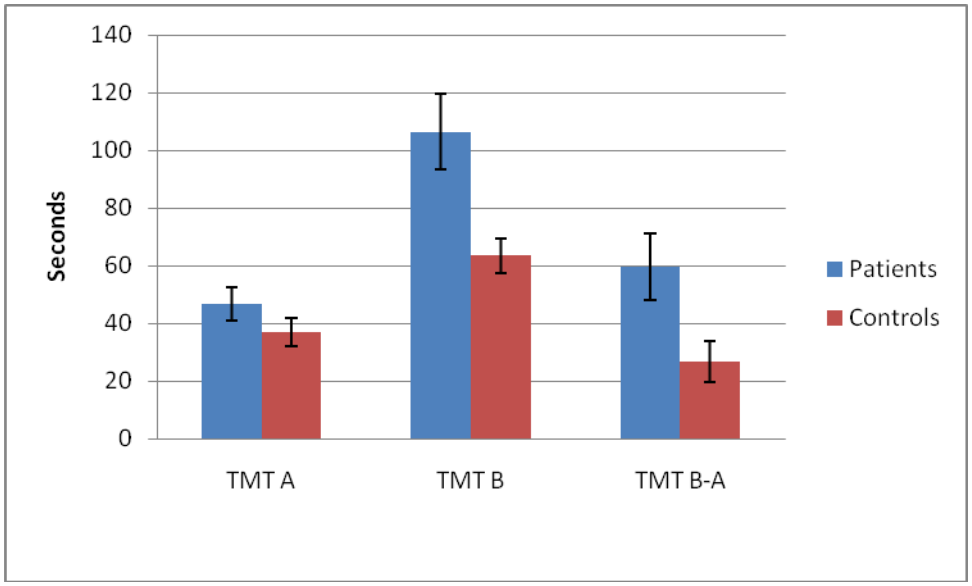


Figure 3.4 Trail Making Test mean scores of schizophrenia patients and healthy controls (bars represent standard errors).

3.2.4 Digit Symbol Test

There was a highly significant difference between schizophrenia patients and healthy controls with regard to the Digit Symbol Test (sustained attention) (patients M = 43.95, SD = 13.82; controls M = 62.17, SD = 9.98), $t(30) = -3.97$, p = .000 (Figure 3.5). The result shows that schizophrenia patients replace fewer symbols than healthy controls in the given time.

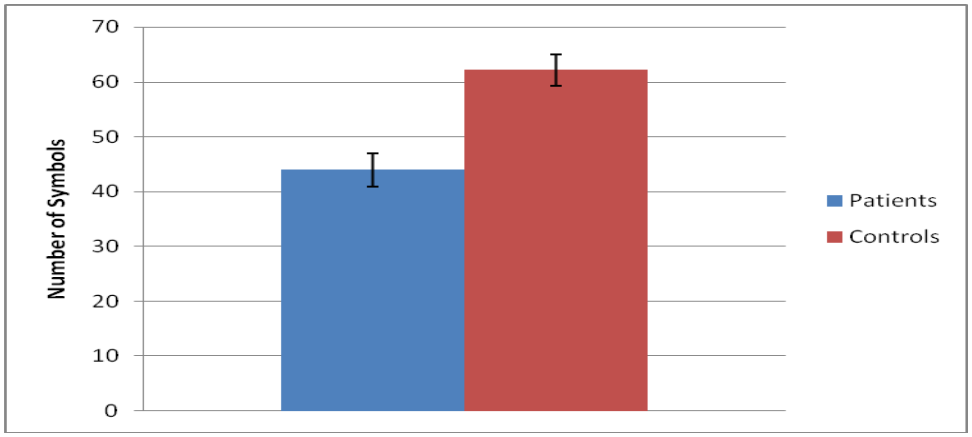


Figure 3.5 Digit Symbol Test mean scores of schizophrenia patients and healthy controls (bars represent standard errors)

3.2.5 Controlled Oral Word Association Test

There was a significant difference between schizophrenia patients and healthy controls with regard to the Controlled Oral Word Association Test (verbal fluency) (patients M = 32.60, SD = 10.60; controls M = 44.58, SD = 9.53), $t(30)$ = -3.20, p = .00 (Figure 3.6). Patients with schizophrenia produce fewer words.

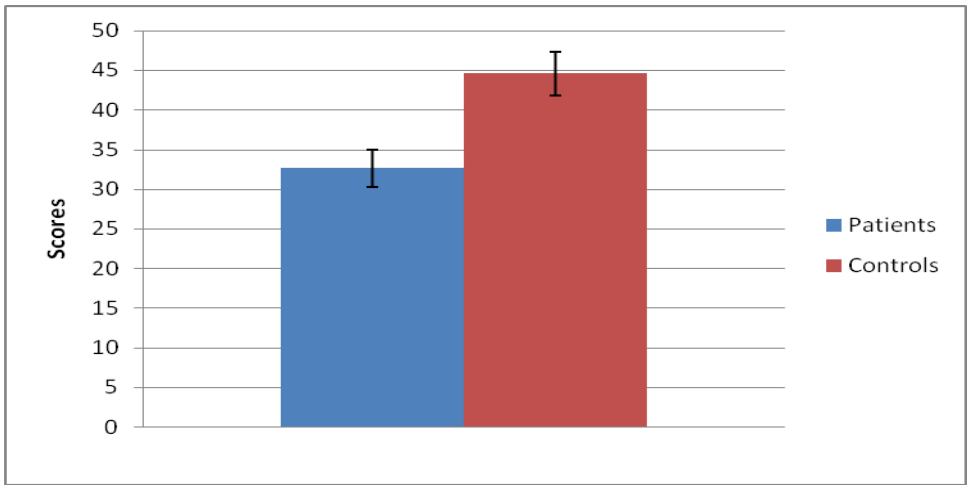


Figure 3.6 Controlled Oral Word Association Test mean scores of schizophrenia patients and healthy controls (bars represent standard errors)

3.2.6 Verbal Learning and Memory Test –VLMT

There were significant differences between schizophrenia patients and healthy controls with regard to all the domains of the Verbal Learning and Memory test (Verbal memory) – VLMT: On supra margin (D1), (patients *M* = 6.65, *SD* = 2.75; controls *M* = 9.67, *SD* = 1.49), *t*(30) = -3.47, *p* = .00 ; learning performance (D5) (patients *M* = 12.10, *SD* = 2.91; controls *M* = 14.50, *SD* = .79), *t*(30) = -2.77, *p* = .01; total learning performance (∑ D1-D5) (patients *M* = 49.85, *SD* = 14.13; controls *M* = 65.08, *SD* = 4.03), *t*(30) = -3.62, *p* = .001; recall performance of the interference list (I) (patients *M* = 5.75, *SD* = 2.61; controls *M* = 9.08, *SD* = 2.50), *t*(30) = -3.54, *p* = .001; recall performance after interference (D6), (patients *M* = 9.75, *SD* = 4.02; controls *M* = 13.75, *SD* = 1.13), *t*(30) = -3.34, *p* = .00; recall performance after time lag (D7), (patients *M* = 9.30, *SD* = 3.48; controls *M* = 14.08, *SD* = 1.31), *t*(30) = -4.54, *p* = .000; forgetting to interference (D5-D6), (patients *M* = 2.40, *SD* = 1.90; controls *M* = .75, *SD* = .96), *t*(30) = 2.74, *p* = .00; forgotten after time lag, (D5-D7) (patients *M* = 2.75, *SD* = 1.91; controls *M* = .42, *SD* = 1.37), *t*(30) = 3.67, *p* = .001 and recognition performance (W), (patients *M* = 10.80, *SD* = 4.60; controls *M* = 14.58, *SD* = .66), *t*(30) = -2.80, *p* =

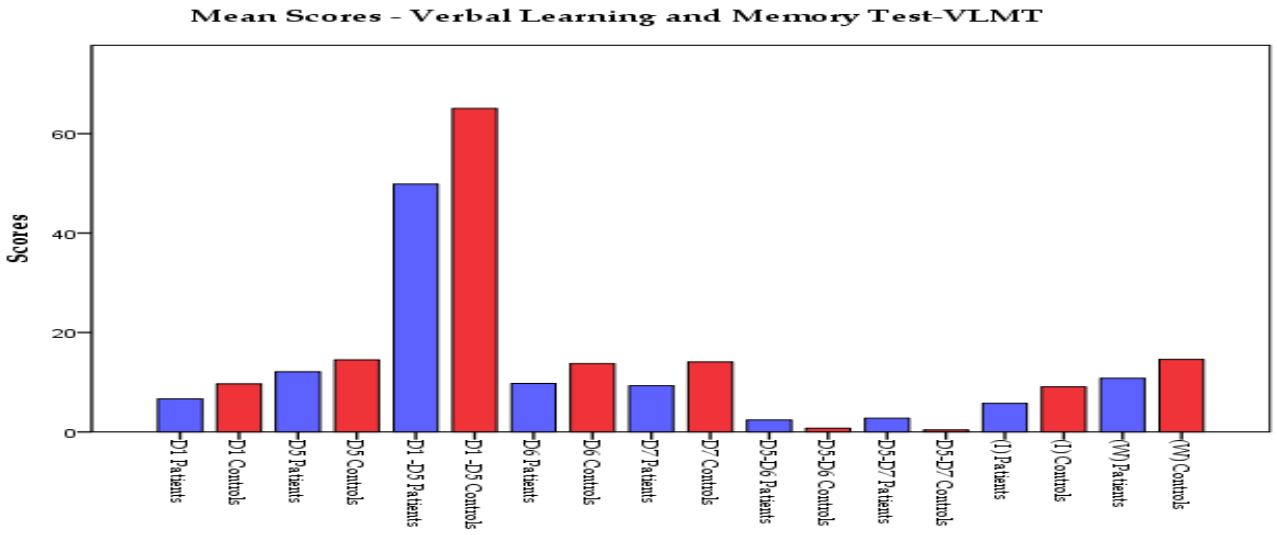


Figure 3.7 Verbal Learning and Memory Test – VLMT mean scores of schizophrenia patients and healthy controls

Summary

Schizophrenia patients showed poorer performance on many variables of neuropsychological tests. Highly significant difference was found in the Digit Symbol Test (sustained attention, speed of processing and visuo-motor co-ordination) and Verbal Learning and Memory Test (memory and learning potential). There was a significant group difference with regard to Control Oral Word Association test (verbal fluency). There was no significant group difference with regard to the Multiple Choice Word Comprehension test (Verbal intelligence) and Trail Making Test – A (attention and psychomotor speed).

3.3 Tower of London Test Measures

In first step of a preliminary analyses, analyses of variance were carried out to ascertain that none of the independent variables interacted significantly with 'order' (Day before night vs. night before day) (see **Appendix A and Appendix B**). As there were no significant interaction effects the "day before night" and "night before day" conditions/blocks were combined respectively to, within groups. The combined blocks were named as "Interval" (Day vs. night interval).

Day versus night interval mean scores and standard deviations for schizophrenia patients and healthy controls for measures of the Tower of London are presented in Table 3.3 and Table 3.4 respectively. The mean score figures were presented in **Appendix A**.

Table 3.3 Mean Scores for the Measures of the Tower of London - Day versus Night Interval (Number of solved tasks)

Day vs. night interval		Number of Solved Tasks					
		Patients *N* = 20			Controls *N* = 12		
		M	*SD*	(Range)	*M*	*SD*	(Range)
Day interval	Pre	10.05	3.36	(1-14)	10.50	2.15	(7-14)
	Post	10.90	2.25	(3-14)	11.16	2.28	(8-15)
Night interval	Pre	9.95	2.41	(5-15)	11.00	1.59	(8-13)
	Post	10.65	2.34	(5-15)	11.66	1.43	(10-14)

***M* = Mean, *SD* = Standard Deviation, *N* = Number**

Table 3.4 Mean Scores for the Measures of the Tower of London- Day versus Night Interval (Total time taken)

Day vs. Night performance		Total Time Taken					
		Patients *N* = 20			Controls *N* = 12		
		M	*SD*	(Range)	*M*	*SD*	(Range)
Day interval	Pre	579.28	372.80	(276-1803)	307.54	106.04	(162-526)
	Post	504.61	291.24	(276-1499)	254.78	72.12	(149-371)
Night interval	Pre	565.01	222.36	(264-1120)	303.87	113.15	(138-538)
	Post	478.26	182.35	(255-920)	254.64	87.43	(123-407)

***M* = Mean, *SD* = Standard Deviation, *N* = Number**

3.3.1 Results of the Multivariate Analysis of Variance for the Measures of the Tower of London - Day versus Night Interval (Patients vs. Healthy Controls)

A 2 (Status: schizophrenia patients vs. healthy controls) x 2 (Interval: day interval vs. night interval) x 2 (Pre-post: pre vs. post) three-way mixed MANOVA with repeated measures on the last two factors was performed using the number of solved tasks and total time taken as dependent variables. The results are presented in Table 3.5.

Table 3.5 Results of the Multivariate and Univariate Results for the Measures of the Tower of London – (Day vs. Night Interval) (Patients vs. Controls)

Source	F (2, 29)	*p*	η^2
Status (Patients vs. controls)	**6.2**	**.00****	**.30**
Interval (Day vs. night)	**.11**	**.89**	**.00**
Interval x Status	**.49**	**.61**	**.03**
Pre-post	**20.19**	**.000*****	**.58**
Pre-post x Status	**.95**	**.39**	**.06**
Interval x Pre-post	**.04**	**.95**	**.00**
Interval x Pre-post x Status	**.11**	**.89**	**.00**
Measure: Number of solved tasks	**F (1, 30)**		
Status	**.98**	**.32**	**.03**
Interval	**.18**	**.67**	**.00**
Interval x Status	**3.41**	**.38**	**.02**
Pre-post	**6.69**	**.01****	**.18**
Pre-post x Status	**.03**	**.84**	**.00**
Interval x Pre-post	**.01**	**.89**	**.00**
Interval x Pre-post x Status	**.01**	**.89**	**.00**
Measure: Total time taken	**F (1, 30)**		
Status	**11.81**	**.00****	**.28**
Interval	**.09**	**.76**	**.00**
Interval x Status	**.06**	**.80**	**.00**
Pre-post	**38.87**	**.000*****	**.56**
Pre-post x Status	**1.97**	**.17**	**.06**
Interval x Pre-post	**.03**	**.85**	**.00**
Interval x Pre-post x Status	**.10**	**.74**	**.00**

*** = $p < .05$; ** = $p < .01$; *** = $p < .001$**

Effects of the MANOVA

Main Effects

There was a significant main effect of status $F(2, 29) = 6.2$, $p = .00$, partial eta squared = .30. There was also a highly significant main effect of Pre-post $F(2, 29) = 20.19$, $p = .000$, partial eta squared = .58. The main effect of day vs. night interval was not significant $F(2, 29) = .11$, $p = .89$, partial eta squared = .00. There was no significant difference between day and night intervals.

Interaction Effects

There were no significant interaction effects. Univariate results were examined on the dependent variables number of solved tasks and total time taken separately.

Effects of the ANOVA

Number of Solved Tasks

Main Effects

There was a significant main effect of pre-post with regard to number of solved tasks $M = 10.37$ vs. 11.09, $F(1, 30) = 6.69$, $p = .01$, partial eta squared = .18. The number of solved tasks significantly increased in the post test measurement (Figure 3.8). The other main effects were not significant.

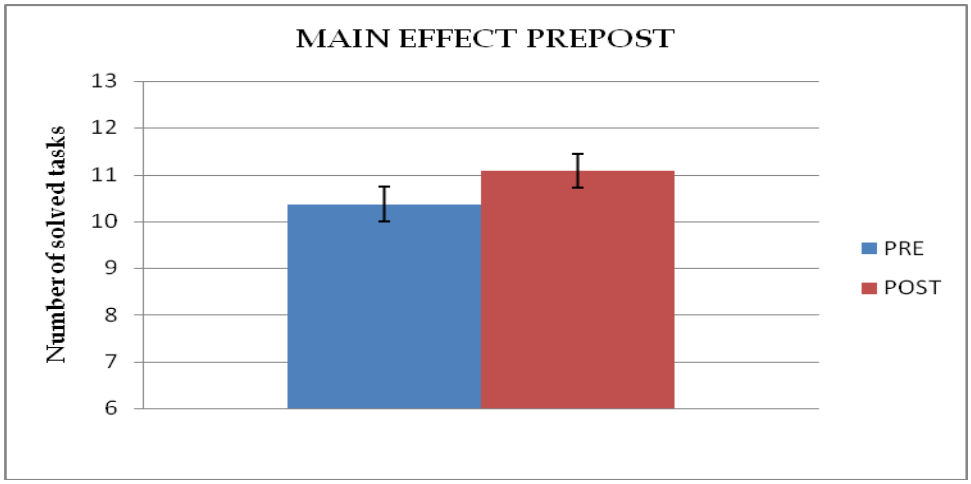


Figure 3.8 Main effect of pre-post with regard to number of solved tasks in the Tower of London test (bars represent standard errors)

Interaction effects

There were no significant interaction effects.

Total time taken

Main effects

There was a significant main effect of status with regard to total time taken M = 531.79 vs. 280.21, $F(1, 30) = 11.81$, $p = .00$. Schizophrenia patients took significantly longer to complete the tower of London test than healthy controls (Figure 3.9). There was a highly significant main effect of pre-post with regard to total time taken $M = 438.92$ vs. 373.07, $F(1, 30) = 38.87$, $p = .000$, partial eta squared = .56. The time taken to complete the Tower of London test significantly reduced in the post test measurement (Figure 3.10). The other main effects were not significant.

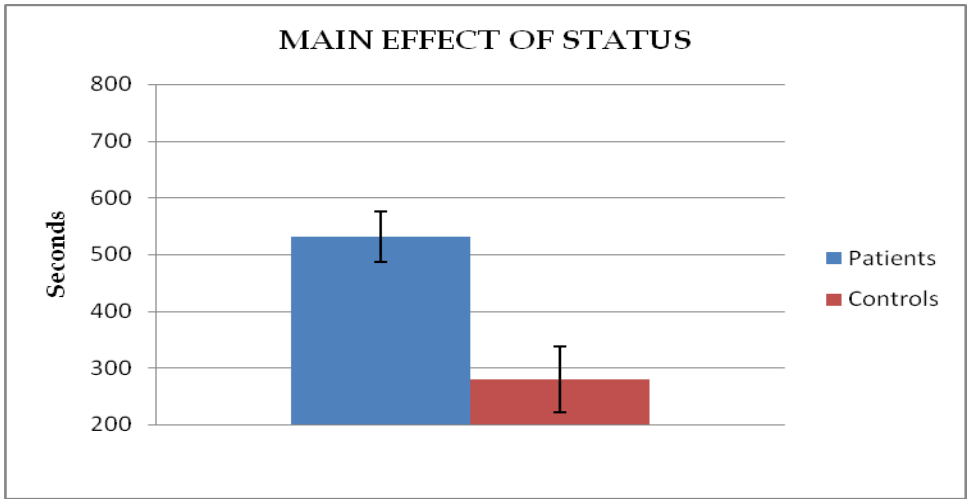


Figure 3.9 Significant main effect of status with regard to total time taken in the Tower of London test (bars represent standard errors)

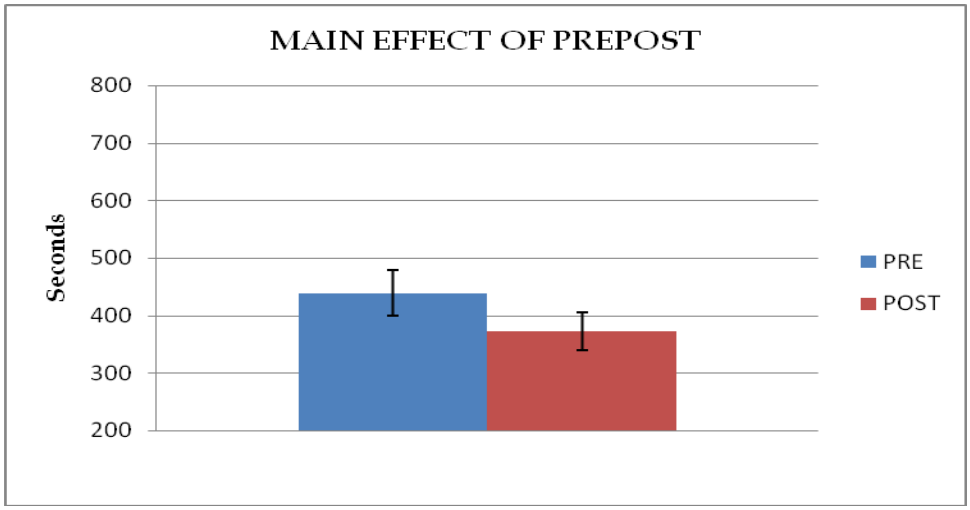


Figure 3.10 Highly significant main effect of Pre-post with regard to total time taken in the Tower of London test (bars represent standard errors)

Interaction effects

There were no significant interaction effects.

Summary

Patients took significantly longer time compared with healthy controls in the Tower of London test. There was an increase in performance with regard to the number of solved tasks and total time taken in the post test measurement. There was no significant difference between night interval performances compared with day interval performance in both groups

3.3.2 Results of the Multivariate and Univariate Analyses of Variance for the Measures of the Tower of London- Day versus Night Interval (Schizophrenia Patients)

A 2 (Interval: day interval vs. night interval) x 2 (Pre-post: pre vs. post) two-way mixed MANOVA with repeated measures was performed using the number of solved tasks and total time taken as dependent variables. The results are presented in Table 3.6.

Table 3.6 Results of the Multivariate and Univariate Analyses of Variance for the Measures of the Tower of London- Day versus Night Interval (Schizophrenia Patients)

Source	F (2, 18)	*p*	η^2
Interval (Day vs. night)	**.17**	**.84**	**.01**
Pre-post	**13.26**	**.000*** **	**.59**
Interval x Pre-post	**.17**	**.83**	**.01**
Measure: Number of solved tasks	**(1, 19)**		
Interval	**.11**	**.73**	**.00**
Pre-post	**4.3**	**.05***	**.18**
Interval x Pre-post	**.04**	**.83**	**.00**
Measure: Total time taken	**(1, 19)**		
Interval	**.14**	**.70**	**.00**
Pre-post	**26.46**	**.000*** **	**.58**
Interval x Pre-post	**.13**	**.71**	**.00**

*** = $p < .05$; ** = $p < .01$; *** = $p < .001$**

Main Effects of the MANOVA

Main Effects

There was a highly significant main effect of pre-post $F(2, 18) = 13.26$, $p = .000$, partial eta squared = .59. There was a significant increase in performance from pre to the post test measures. Schizophrenia patients solved more tasks and took significantly less time to complete the Tower of London Test in the post test measurement.

Interaction Effects

Interval by pre-post interaction was not significant.

Univariate results were examined on the dependent variables number of solved tasks and total time taken separately.

Effects of the ANOVA

Number of Solved Tasks

Main Effects

There was a significant main effect of pre-post with regard to number of solved tasks $M = 10.00$ vs. 10.77, $F(1, 19) = 4.3$, $p = .05$, partial eta squared = .18. Schizophrenia patients improved in the post test measurement with regard to number of solved tasks (Figure 3.11). The main effect of interval was not significant $F(1, 19) = .11$, $p = .73$, partial eta squared = .00

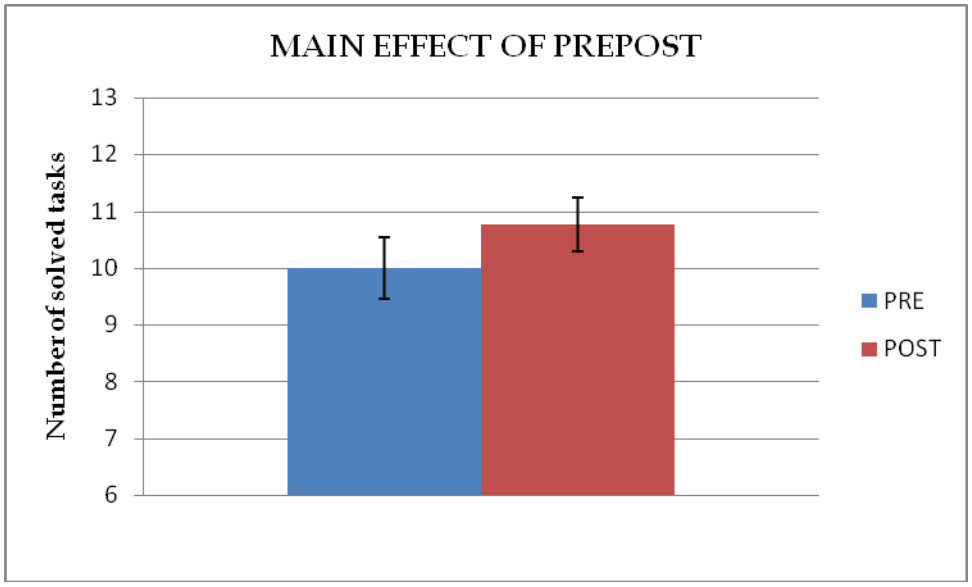


Figure 3.11 Main effect of pre-post with regard to number of solved tasks in the Tower of London test (bars represent standard errors)

Interaction Effects

Interval by pre-post interaction was not significant $F(1, 19) = 0.4$, $p = .83$, partial eta squared = .00

Total Time Taken

Main Effects

There was a highly significant main effect of pre-post $M = 572.14$ vs. 491.43, $F(1, 19) = 26.46$, $p = .000$, partial eta squared = .58. Schizophrenia patients took less time in the post test measures of the Tower of London test (Figure 3.12). The main effect of interval was not significant $F(1, 19) = .14$, $p = .70$, partial eta squared = .00.

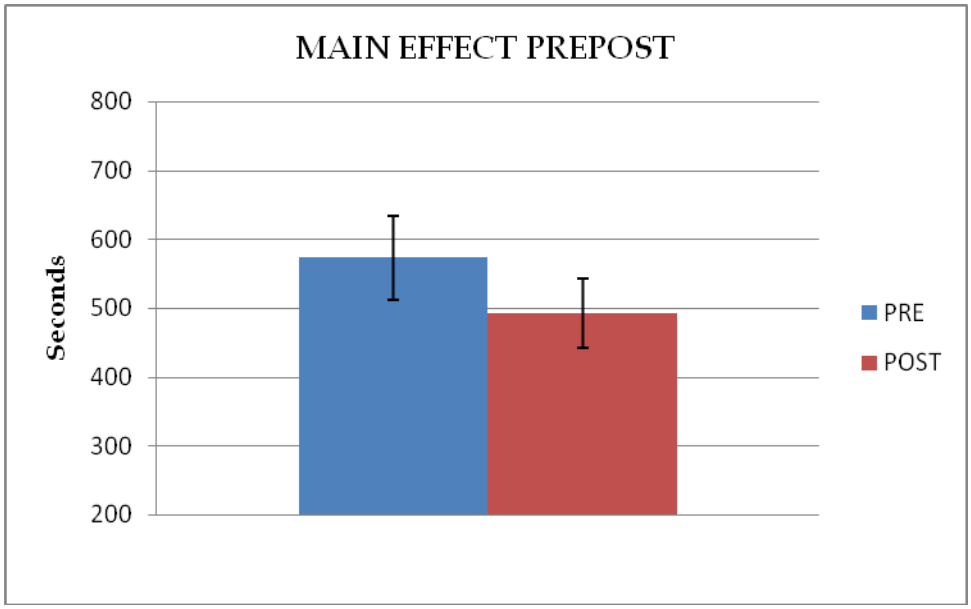


Figure 3.12 Main effect of pre-post with regard to total time taken in the Tower of London test (bars represent standard errors)

Interaction Effects

Performance by pre-post interaction was not significant $F(1, 19) = .13$, $p = .71$, partial eta squared = .00.

Summary

There was no significant difference between day and night intervals in schizophrenia patients. Compared with pre test measures, in the post test measures schizophrenia patients solved more tasks and took significantly less time to complete the Tower of London Test.

3.3.3 Results of the Multivariate and Univariate Analyses of Variance for the Measures of the Tower of London – Day versus Night Interval (Healthy Controls)

A 2 (Interval: day interval vs. night interval) x 2 (pre-post: pre vs. post) two-way mixed MANOVA with repeated measures was performed using the number of solved tasks and total time taken as dependent variables. The results are presented in Table 3.07.

Table 3.7 Results of Multivariate and Univariate analyses of Variance for the Measures of the Tower of London – Day versus Night Interval (Healthy Controls).

Factor	F (2, 10)	*p*	η^2
Interval (Day versus night)	**.47**	**.63**	**.08**
Pre-post	**23.96**	**.000*** **	**.82**
Interval x Pre-post	**.00**	**.99**	**.00**
Measure: Number of solved tasks	**F (1, 11)**		
Interval	**1.03**	**.33**	**.08**
Pre-post	**3.32**	**.09**	**.23**
Interval x Pre-post	**.00**	**1.0**	**.00**
Measure: Total time taken	**F (1, 11)**		
Interval	**.00**	**.94**	**.00**
Pre-post	**49.92**	**.000*** **	**.81**
Interval x Pre-post	**.01**	**.90**	**.00**

*** = $p < .05$; ** = $p < .01$; *** = $p < .001$**

Effects in the MANOVA

Main Effects

There was no significant main effect of interval $F(2, 10) = .47$, $p = .63$, partial eta squared = .08. But there was a highly significant main effect of pre-post $F(2, 10) = 23.96$, $p = .000$, partial eta squared = .89. Control participants took significantly less time to complete the Tower of London test in the post test measures.

Interaction Effects

The interaction effect of interval by pre-post was not significant $F(2, 10) = .00$, $p = .99$, partial eta squared = .00.

Effects of the ANOVA

Univariate results were examined on the dependent variables number of solved tasks and total time taken separately.

Number of Solved Tasks

Main Effects

There was no significant main effect of interval $F(1, 11) = 1.03$, $p = .33$, partial eta squared = .08. The main effect of pre-post on number of solved tasks was also not significant $F(1, 11) = 3.32$, $p = .09$, partial eta squared = .23

Interaction Effects

The interaction effect of interval by pre-post with regard to number of solved tasks was not significant $F(1, 11) = .00$, $p = 1.0$, partial eta squared = .00.

Total Time Taken

Main Effects

There was no significant main effect of interval $F(1, 11) = .00$, $p = .94$, partial eta squared = .00. But, there was a highly significant main effect of pre-post on total time taken $M = 305.70$ vs. 254.71, $F(1, 11) = 49.92$, $p = .000$, partial eta squared = .81. Control participants took significantly took less time to complete the Tower of London test in the post test measurement (Figure 3.13).

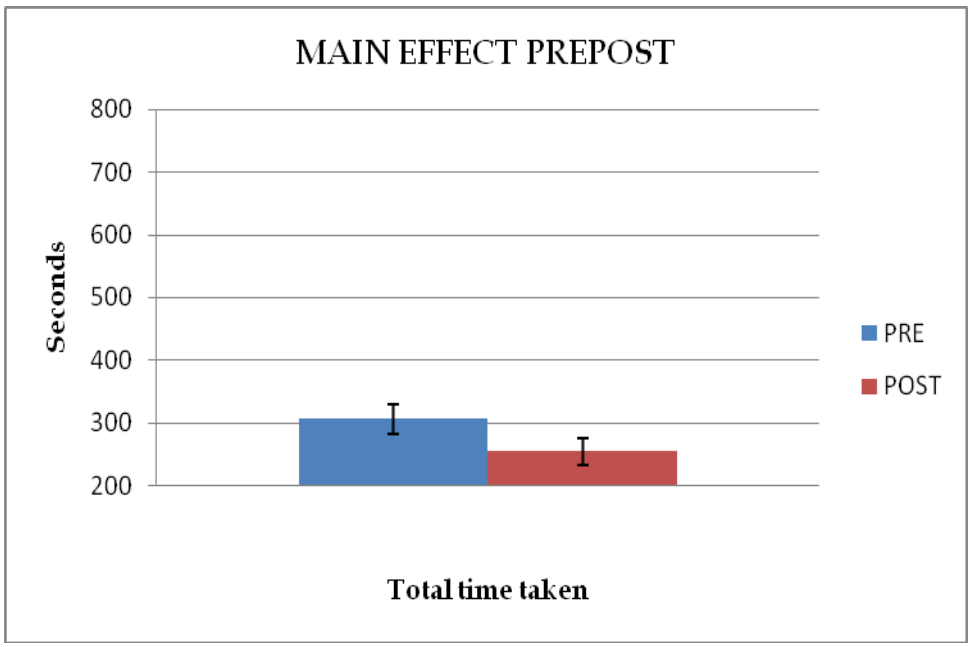


Figure 3.13 Highly significant main effect of Pre-post with regard to total time taken in the Tower of London test (bars represent standard errors)

Interaction Effects

The interaction effect of interval by pre-post with regard to total time taken was not significant $F(1, 11) = .01$, $p = .90$, partial eta squared = .00.

Summary

There was no significant difference between day and night interval performances in the healthy controls. Healthy control participants took significantly took less time to complete the Tower of London test in the post test measurement.

3.4 Sleep EEG Results

Group means of sleep EEG parameters of schizophrenia patients and healthy controls were reported in Table 3.8.

Table 3.8 Comparison of Sleep EEG Parameters – Schizophrenia Patients vs. Healthy Controls

Measure	Score								
	Patients (*N* = 20)			Controls (*N* = 12)			T- tests		
	Range	Mean	*SD*	Range	Mean	*SD*	*t*	*df*	*p*
TSR (min)	22-147	77.25	32.33	45-143	82.62	26.97	- .84	30	.40
TSN (min)	250-377	312.65	39.92	170-360	306.33	49.53	.39	30	.69
TS1 (min)	28-241	96.45	56.74	3-177	62.70	44.94	1.75	30	.09
TS2 (min)	54-223	125.45	48.41	94-226	141.91	42.74	- .97	30	.33
TS3 AND4 (min)	17-210	90.87	59.77	28-179	102.25	48.99	- .55	30	.58
TOTAL SLEEP (min)	299-437	386.77	37.95	215-446	405.50	62.57	- .05	30	.29
REM LATENCY (min)	65-263	141.05	45.19	62-269	127.50	51.74	.77	30	.44
SLEEP LATENCY (min)	8-59	26.60	14.40	9-95	43.54	28.96	-2.21	30	**.03***
SLEEP EFFECIENCY %	72-96	85.46	7.08	48-95	85.13	12.66	.09	30	.92
NO OF SPINDLES	0-97	15.95	24.53	0-49	17.16	15.35	- .15	30	.87
NUMBER OF K-COMPLEXES	10-131	65.85	30.03	14-109	63.41	27.58	.22	30	.82
MOVEMENT TIME	0-11	2.52	2.83	0-9	2.20	2.34	.32	30	.74
TSW (min)	9-118	58.05	33.20	4-234	74.95	57.07	-1.06	30	.29
REM %	8-36	19.76	7.67	12-36	21.35	5.55	- .62	30	.53
NREM %	65-95	81.01	8.27	67-88	75.79	6.45	1.86	30	.07
STAGE 1 %	7-63	25.30	15.35	1-41	15.53	10.33	1.94	30	.06
STAGE 2 %	17-56	32.50	12.47	21-53	35.70	10.85	- .73	30	.46
STAGE 3 & 4 %	5-49	23.23	14.52	12-44	24.68	10.85	- .29	30	.76
WAKE %	3-38	15.83	10.51	1-109	22.31	28.11	- .93	30	.35
MOVEMENT TIME %	0-4	.67	.80	0-3	.57	.61	.36	30	.71
TOTAL SLEEP %	63-91	80.57	7.90	45-93	84.47	13.03	-1.05	30	.29

REM = Rapid eye Movement, NREM = Non-Rapid eye movement, TSR = Total sleep REM, TSN = Total sleep NREM, TS1 = Total sleep stage 1, TS2 = Total Sleep stage 2, TS3AND4 = Total sleep stage 3 and stage 4, TSW = Total stage wake.

* ***Sig .05* (2 –Tailed) $p < .05$**

3.4.1 Sleep EEG Parameters (Schizophrenia Patients vs. Healthy Controls)

Independent samples t-tests were performed to compare the sleep EEG parameters between schizophrenia patients and healthy controls. The results were presented in Table 3.8. There was a significant difference between the schizophrenia patients and healthy controls with regard to sleep latency (patients M = 26.60, SD = 14.40; controls M = 43.54, SD = 28.96), $t(30)$ = -2.21, p = .03 (Figure 3.14). Schizophrenia patients had short sleep latency. There were marginally significant difference with regard to sleep stage 1 (TS1), NREM percentage and stage 1 percentage.

There were no significant differences between schizophrenia patients and healthy controls with regard to other sleep parameters like sleep REM (TSR), Non-Rapid eye movement (TSN), total sleep stage 2 (TS2), total sleep stage 3 and stage 4 (TS3AND4), total sleep, REM latency, sleep efficiency, number of spindles, number of K-complexes , movement time, total stage wake (TSW), REM %, stage 2 %, stage 3 & 4 %, wake %, movement time % and total sleep %.

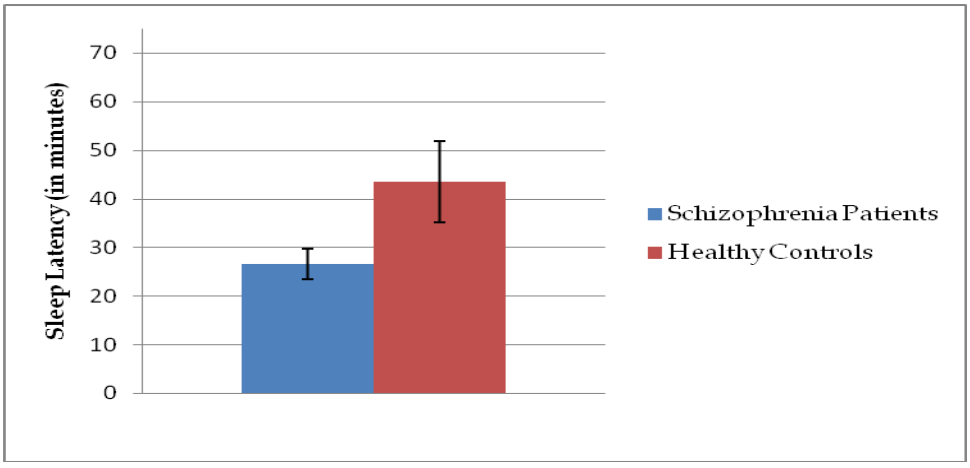


Figure 3.14 Mean of sleep latency in schizophrenia patients and healthy controls (bars represent standard errors)

Summary

The comparison of sleep EEG parameters between schizophrenia patients and healthy controls showed a significant difference in sleep latency and marginal significant in sleep stage 1 and sleep stage 1 percentage; and non-rapid eye movement percentage (NREM %). Schizophrenia patients had shorter sleep latency. Patients and healthy controls does not differed significantly with regard to other sleep parameters like sleep REM (TSR), Non-Rapid eye movement (TSN), total sleep stage 2 (TS2), total sleep stage 3 and stage 4 (TS3AND4), total sleep, REM latency, sleep efficiency, number of spindles, number of K-complexes , movement time, total stage wake (TSW), REM %, stage 2 %, stage 3 & 4 %, wake %, movement time % and total sleep %.

3.4.2 Correlation between Sleep Parameters and the Tower of London Test Measures

Pearson product-moment correlation coefficients were computed to assess the relationship between sleep parameters and the Tower of London test measures (number of solved tasks and total time taken). The correlation analysis results of schizophrenia patients and healthy controls were presented below in Table 3.9 and Table 3.10

Table 3.9 Correlation between Sleep Parameters and the Tower of London Measures (Schizophrenia Patients) *N* = 20

Measure	Number of solved tasks (night -pre)	Number of solved Tasks (night -post)	Total time taken (night -pre)	Total time taken (night-post)
TSR (min)				
r	.13	.14	-.01	-.06
p	.57	.53	.94	.77
TSN (min)				
r	.01	.04	-.28	-.31
p	.95	.86	.21	.18
TS1 (min)				
r	-.18	-.50*****	.16	.21
p	.43	.02	.49	.37
TS2 (min)				
r	.27	.33	.26	.18
p	.24	.15	.26	.43
TS3AND4 (min)				
r	-.03	.24	-.56*****	-.55*****
p	.88	.29	.01	.01
Total Sleep (min)				
r	.10	.14	-.35	-.39
p	.67	.54	.12	.08
REM Latency (min)				
r	-.03	-.23	-.11	-.03
p	.88	.32	.62	.88
Sleep Latency (min)				
r	-.13	-.07	.09	.04
p	.57	.75	.69	.85
Sleep Efficiency %				
r	.27	.31	-.21	-.24
p	.24	.17	.36	.30
Number of Spindles				
r	.09	-.06	.15	.08
p	.69	.77	.51	.72
Number of K-complexes				
r	.56	.63******	-.08	-.03
p	.01	.00	.73	.88
Movement Time (min)				
r	.04	.06	-.34	-.28
p	.84	.78	.14	.21
Total stage Wake (min)				
r	-.27	-.27	.24	.27
p	.24	.24	.29	.24
REM%				
r	-.11	.10	.04	-.01
p	.64	.64	.84	.96
NREM %				
r	-.07	-.07	-.00	.02
p	.76	.75	.98	.91
Stage 1 %				
r	-.18	-.51*****	.20	.26
p	.43	.02	.39	.25
Stage 2 %				
r	.27	.32	.36	.31
p	.24	.16	.11	.18
Stage 3 & 4 %				
r	-.07	.22	-.53	-.54*****
p	.74	.33	.01	.01
Wake %				
r	-.22	-.21	.26	.30
p	.33	.36	.26	.18
Movement Time %				
r	.24	.04	-.30	-.25
p	.91	.84	.19	.27
Total Sleep %				
r	.10	.14	-.35	-.39
p	.67	.54	.12	.08

***** Correlation is significant at the 0.05 level (2-tailed), ****** Correlation is significant at the 0.01 level (2-tailed)

Table 3.10 Correlation between Sleep Parameters and the Tower of London Measures (Healthy Controls) *N* = 12

Measure	Number of solved tasks (night-pre)	Number of solved Tasks (night-post)	Total time taken (night-pre)	Total time taken (Night-post)
TSR (min)				
r	.11	-.04	-.05	-.03
p	.73	.89	.87	.92
TSN (min)				
r	-.26	-.11	.27	.21
p	.40	.72	.39	.49
TS1 (min)				
r	-.40	-.17	.35	.30
p	.18	.58	.25	.33
TS2 (min)				
r	.07	-.20	-.40	-.27
p	.82	.52	.19	.38
TS3AND4 (min)				
r	.03	.23	.28	.18
p	.90	.46	.36	.57
Total Sleep (min)				
r	-.29	-.12	.44	.44
p	.34	.70	.14	.14
REM Latency (min)				
r	.02	.07	.09	.17
p	.94	.82	.77	.58
Sleep Latency (min)				
r	.19	.20	-.08	.00
p	.53	.52	.80	.98
Sleep Efficiency %				
r	-.29	-.12	.46	.44
p	.34	.69	.12	.15
Number of Spindles				
r	.27	.15	-.68*****	-.70*****
p	.39	.62	.03	.01
Number of K-complexes				
r	-.37	-.12	-.34	-.14
p	.23	.69	.27	.66
Movement Time (min)				
r	-.04	-.09	-.20	-.01
p	.88	.76	.52	.95
Total stage Wake (min)				
r	.22	.12	-.15	-.10
p	.49	.70	.62	.74
REM%				
r	.29	.02	-.30	-.28
p	.35	.94	.33	.37
NREM%				
r	.04	.00	-29	-.38
p	.89	.97	.35	.21
Stage 1 %				
r	-.33	-.14	.24	.18
p	.28	.66	.44	.55
Stage 2 %				
r	.23	-.12	-.62*****	-.50
p	.45	.69	.03	.09
Stage 3 & 4 %				
r	.10	.27	.21	.09
p	.74	.38	.51	.78
Wake %				
r	.22	.10	-.28	-.27
p	.47	.74	.36	.39
Movement Time %				
r	.02	-.06	-.26	-.09
p	.93	.84	.40	.77
Total Sleep %				
r	-.29	-.12	.44	.44
p	.34	.70	.14	.14

* Correlation is significant at the 0.05 level (2-tailed), ** Correlation is significant at the 0.01 level (2-tailed)

3.4.3 Correlation - Schizophrenia Patients

3.4.3.1 Number of Solved Tasks

There was a significant negative correlation between the number of solved tasks (night-post) and total sleep stage 1 (TS1), r = - .50, n = 20, p = .02 (Figure 3.15). There was a highly significant positive correlation between the number of solved tasks (night-post) and the number of K-complexes r = .63, n = 20, p = .00 (Figure 3.16). Number of solved tasks (night-post) also negatively correlated with stage 1 %, r = - .51, n = 20, p = .02 (Figure 3.17).

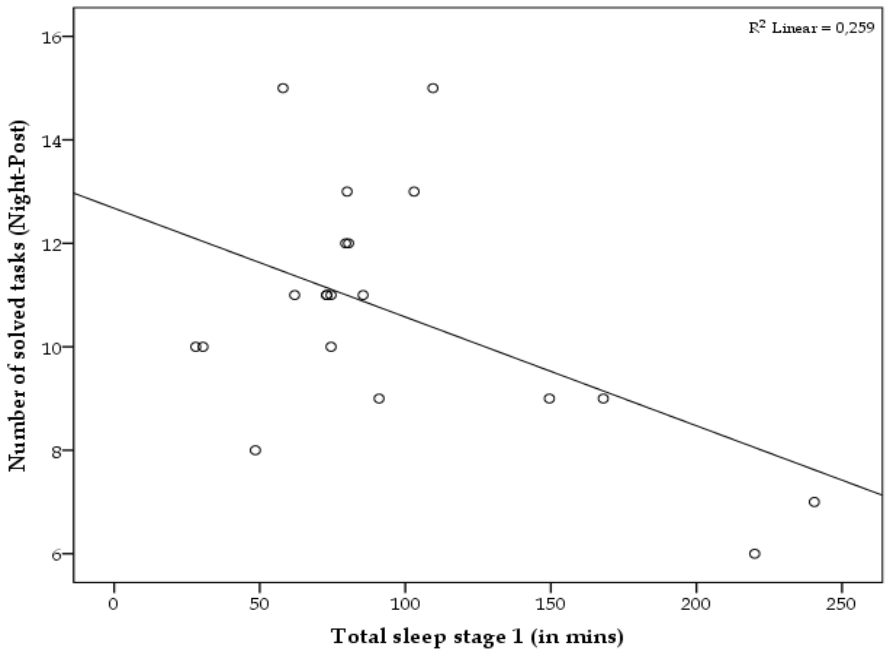


Figure 3.15 Scatterplot of total sleep stage 1 (min) related to number of solved tasks (night-post) in 20 schizophrenia patients (r = - .50, p = .02). Less minutes of total sleep stage 1 was related to a higher number of solved tasks in the Tower of London test.

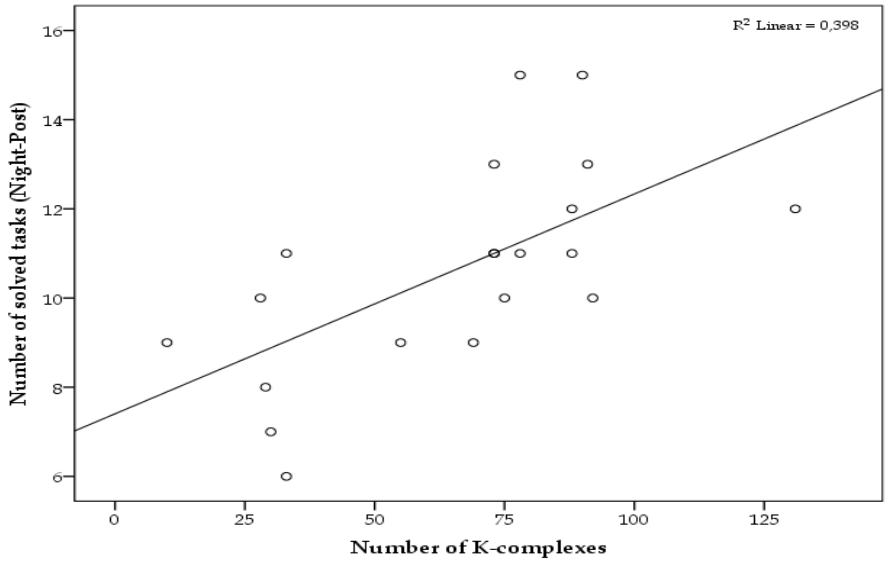


Figure 3.16 Scatterplot of number of k-complexes related to number of solved tasks (night-post) in 20 schizophrenia patients (*r* = .63, *p* = .00). A greater number of K-complexes were related to a higher number of solved tasks in the Tower of London test.

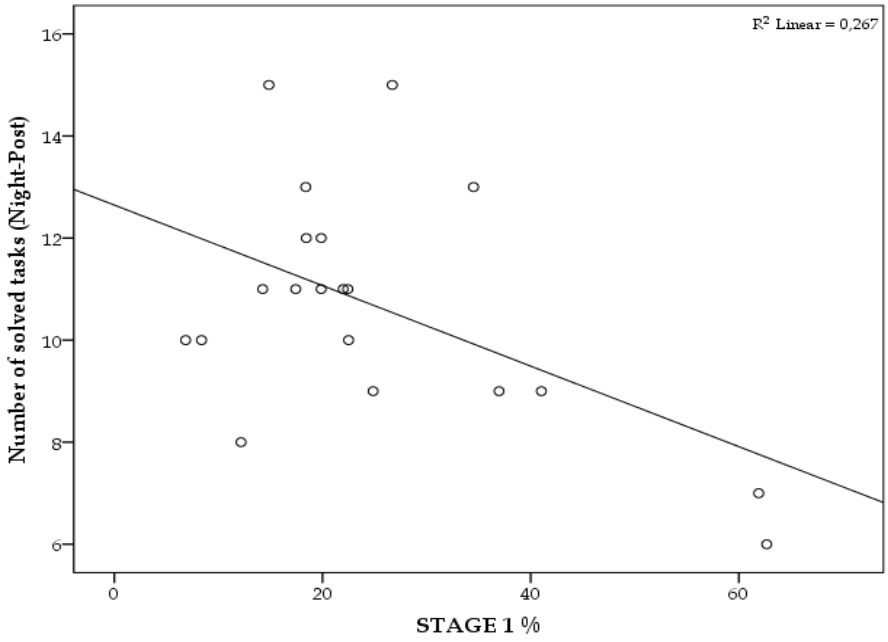


Figure 3.17 Scatterplot of stage 1 as a percentage of total time related to number of solved tasks (night-post) in 20 schizophrenia patients (*r* = - .51, *p* = .02). A lower percentage of stage 1 was related to a higher number of solved tasks in the Tower of London test.

3.4.3.2 Total Time Taken

There was a negative correlation between total time taken (night-pre) and total sleep stage 3 and stage 4 (TS3AND4), r = - .56, n = 20, p = .01 (Figure 3.18). There was also a negative correlation between total time taken (night-post) and total sleep stage 3 and stage 4 (TS3AND4), r = - .55, n = 20, p = .01 (Figure 3.19). There was also a negative correlation between total time taken (night-post) and stage 3 & 4 %, r = - .54, n = 20, p = .01 (Figure 3.20).

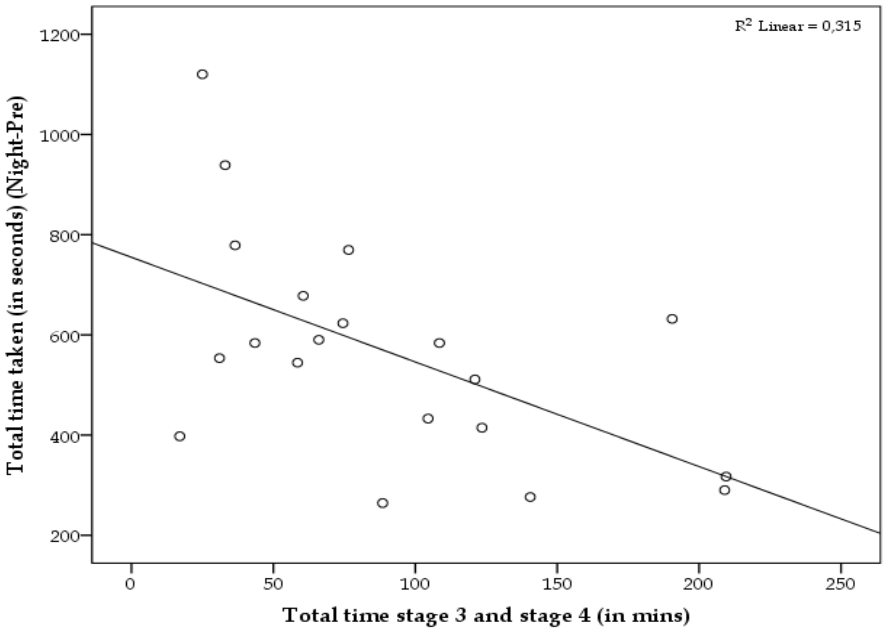


Figure 3.18 Scatterplot of total sleep stage 3 and stage 4 (min) related to total time taken (night-pre) in 20 schizophrenia patients (r = - .56, p = .01). Less time total sleep stage 3 and stage 4 was related to more time taken in the Tower of London test.

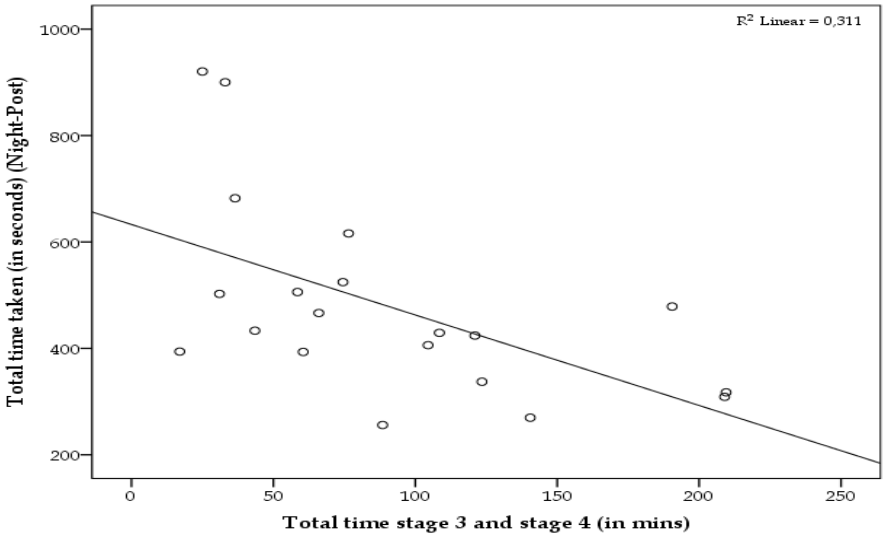


Figure 3.19 Scatterplot of total sleep stage 3 and stage 4 (min) related to total time taken (night-post) in 20 schizophrenia patients (*r* = - .55, *p* = .01). Less duration of total sleep stage 3 and stage 4 was related to more time taken in the Tower of London test.

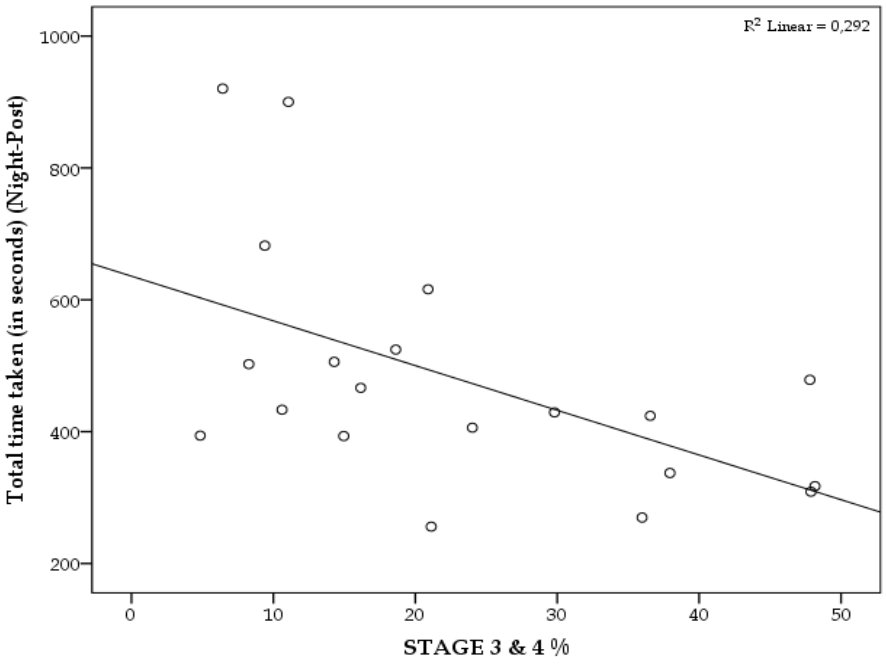


Figure 3.20 Scatterplot of stage 3 & 4 as a percentage of total sleep time related to total time taken (night-post) in 20 schizophrenia patients (*r* = - .54, *p* = .01). Small percentage of stage 3 & 4 was related to more time taken in the Tower of London test.

Summary

The relationship between sleep parameters and the Tower of London test performance was evaluated. Some performance measures were differentially correlated to sleep specific variables. Schizophrenia patients showed a negative correlation between sleep stage 1 and sleep stage 1 percentage with number of solved tasks. This finding suggests that the less time patient spent on sleep stage 1, the more tasks they solve. There was a significant positive correlation between the total number of K-complexes and the number of solved tasks in the Tower of London test. This finding shows the more K-complexes, the more tasks were solved. In schizophrenia patients sleep stage 3 and 4 and its percentage negatively correlated with total time taken to complete the Tower of London test. This finding shows the less time spent on stage 3 and 4, the longer it took to complete the Tower of London test.

3.4.4 Correlation - Healthy Controls

3.4.4.1 Number of Solved Tasks

The number of solved tasks did not significantly correlate with regard to sleep parameters like total sleep REM (TSR), total sleep NREM (TSN), sleep stage 1 (TS1), sleep stage 2 (TS2), sleep stage 3 and 4 (TS3AND4), total sleep, REM latency, sleep efficiency, number of sleep spindles, number of K-complexes, movement time, total stage wake (TSW), REM %, stage 1 %, stage 2 %, stage 3 and 4 %, wake %, movement time % and total sleep%.

3.4.4.2 Total Time Taken

There was a negative correlation between total time taken (night-pre) and number of spindles, r = - .68, n = 12, p = .03 (Figure 3.21). There was also a negative correlation between total time taken (night-post) and number of

spindles, r = - .70, n = 12, p = .01 (Figure 3.22). Total time taken (night-pre) negatively correlated with Stage 2 %, r = - .62, n = 12, p = .03 (Figure 3.23).

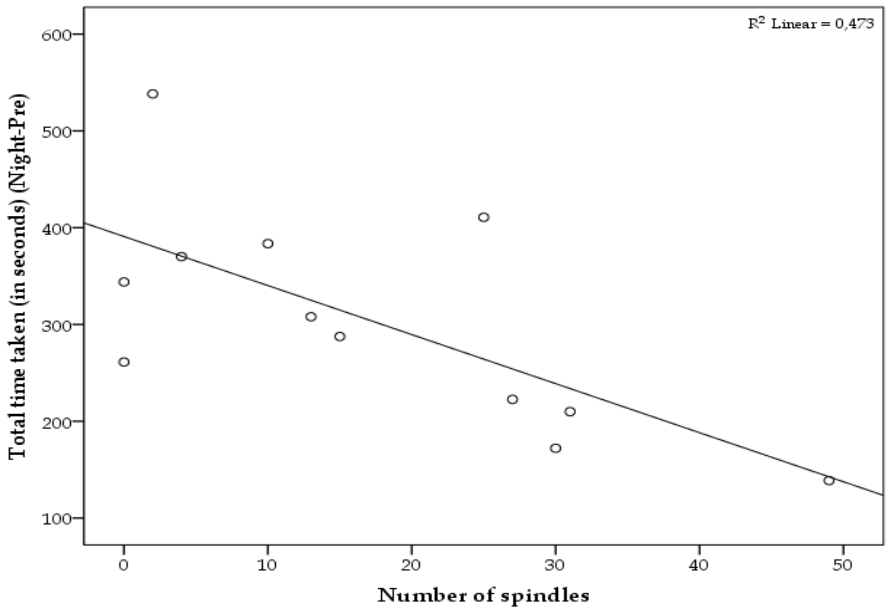


Figure 3.21 Scatterplot of number of spindles related to total time taken (night-pre) in 12 healthy controls (r = - .68, p = .03). Less number of spindles was related to more time taken.

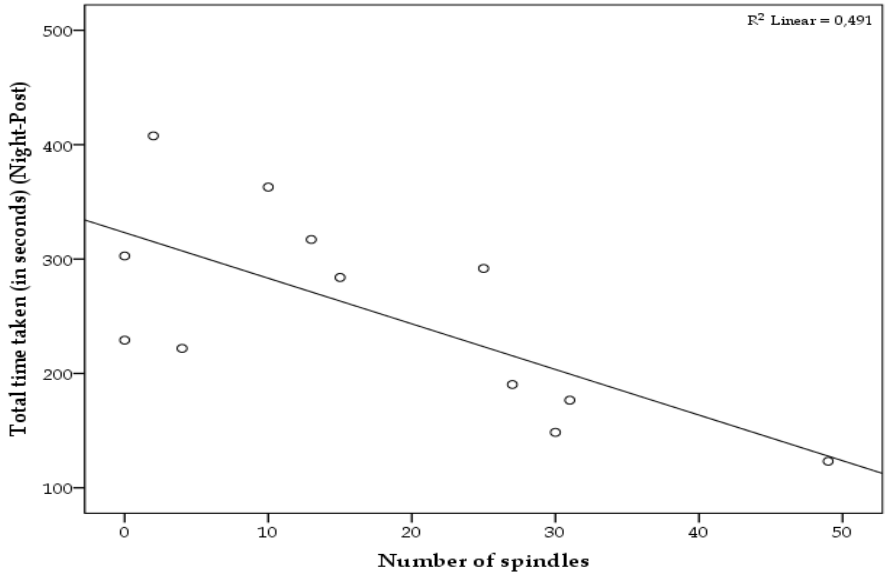


Figure 3.22 Scatterplot of number of spindles related to the total time taken (night-post) in healthy controls (r = - .70, p = .01). Fewer spindles were related with more time taken.

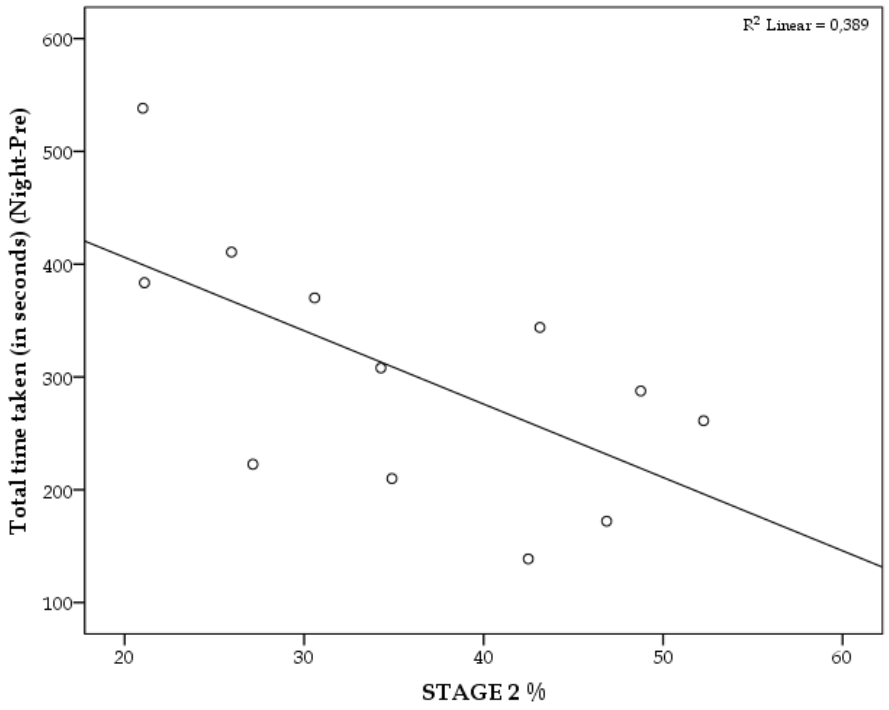


Figure 3.23 Scatterplot of stage 2 as a percentage of total sleep time related to total time taken (night-pre) in 12 healthy controls (*r* = - .62, *p* = .03). A smaller percentage of stage 2 percent was related to more time taken.

Summary

The relationship between sleep parameters and the Tower of London test performance was evaluated. Some performance measures were differentially correlated to sleep specific variables. In healthy controls, a smaller number of spindles were negatively correlated with more total time taken to complete the Tower of London test. The less number of spindles, the healthy controls took longer to complete the Tower of London test. A smaller percentage of sleep stage 2 % was related to more time taken to complete the Tower of London test.

CHAPTER 4

DISCUSSION

There is evidence of problem solving process being improved by sleep. Problem solving as well as sleep have been shown to be impaired in patients with schizophrenia. The present study aimed at investigating relationship between the two domains. The principal findings of the current investigation were listed below. There was no advantage to night time interval compared to day time interval for improved problem solving performance in both groups. Compared with the healthy controls, schizophrenia patients performed generally worse on the experimental tasks. Schizophrenia patients as well as healthy controls improved their performance in the second measurement occasion. Compared to control participants, schizophrenia patients were impaired in their performance of neuropsychological tests and took significantly longer to complete the Tower of London test. Shorter sleep onset latency was observed in schizophrenia patients. There was a marginal significant in sleep stage1 and sleep stage 1 percentage; and non-rapid eye movement percentage (NREM %). There were no significant differences between schizophrenia patients and healthy controls with regard to other sleep parameters.

To explore our hypothesis that sleep specific parameters contribute to the beneficial effects in problem solving measures, we examined the relationship between sleep parameters and the Tower of London test, the major findings in the patient group were: 1) less sleep stage 1 (min) and its percentage was related to a higher number of solved tasks; 2) a greater number of K-complexes were related to a higher number of solved tasks; 3) less minutes of sleep stage 3 & 4 (min) and its percentage were related to more time taken to complete the Tower of London test. No comparable results were observed for the healthy controls. In

the healthy control group, the major findings were: 1) fewer sleep spindles were related to more time taken to complete the Tower of London test 2) a smaller percentage of sleep stage 2 was related to more time taken to complete the Tower of London test.

4.1 Neuropsychology

Neurocognitive impairments are fundamental characteristics in patients with schizophrenia. Patients with schizophrenia suffer from a wide range of cognitive deficits (keefe et al., 2006). In the present study overall, schizophrenia patients exhibited poorer performance on many variables of neuropsychological assessments. Among the neuropsychological functions assessed in the present study, highly significant differences between schizophrenia patients and healthy controls were found in areas of sustained attention, verbal memory, working memory, verbal fluency, problem solving and executive functions.

There was no significant difference between schizophrenia patients and healthy controls with regard to Trail Making Test-A (attention and psychomotor speed). Our study did not replicate the finding of deficits in TMT-A in schizophrenia patients (Horacek et al., 2006). Their study sample included young schizophrenia patients with a mean age of 24.3 years. But in the present study, the mean age of patients was 41.25 years. This might be one the reason for the differences. There was a significant difference with regard to the Trial Making Test-B. Schizophrenia patients took longer to complete the Trial Making Test-B (Mental flexibility and executive functions) compared to the healthy controls. The Trial Making Test-B is thought to require executive control and mental flexibility. Our study replicates the finding of executive function deficits in patients with schizophrenia (Brickman et al., 2004; Rhinewine et al., 2005; Arngo et al., 1999). The inadequacy to plan effectively, added to longer fixation and

lacking planning sequence and accomplishing was established piece of evidence as the centre neuropsychological substrate for the Trail Making Test (TMT) deficits in patients with schizophrenia (Wölwer & Gaebel, 2002).

Schizophrenia patients and healthy controls did not differ significantly in verbal intelligence (Multiple Choice Word Comprehension Test- MWT-B). Morrison et al. (2006) study have reported verbal intelligence deficit in patients with schizophrenia. The present study did not confirm the finding of verbal intelligence deficit in patients with schizophrenia. Their study was a long time study with baseline and follow-up over an average of thirty three years. Their study used the Mill Hill Vocabulary Scale (MHVS) diagnostic instrument to assess verbal intelligence. This might be the reasons for the differences. Schizophrenia patients performed significantly worse than the healthy controls on the test of sustained attention, speed of processing and visuo-motor co-ordination (Digit Symbol Test). There was a highly significant difference between schizophrenia patients and healthy controls on this test. The present study result replicates the finding of sustained attention deficits in patients with schizophrenia (Liu et al., 2002). There was a significant difference between schizophrenia patients and healthy controls on a test of verbal fluency (Controlled Oral Word Association Test). Schizophrenia patients showed a deficit in verbal fluency. Our study confirms the finding of verbal fluency deficits in patients with schizophrenia (Landrø & Ueland, 2008).

There was a highly significant difference between schizophrenia patients and healthy controls on measures of memory and learning potential (Verbal Learning and Memory Test). Schizophrenia patients show a deficit in memory and learning potential. The present study confirms previous finding of pronounced memory impairments in patients with schizophrenia (Sartory et al.,

2001, Mueller et al., 2004; Kravariti et al., 2007; Boker et al., 2006; Aleman et al., 1999).

Summary

Summarizing our findings, patients with schizophrenia showed deficits as compared to healthy controls in a number of tasks that seem to tap higher levels of cognitive functioning. Patients with schizophrenia exhibit more neurological signs than healthy control participants. Neurocognitive deficits are well documented in patients with schizophrenia. In the present study sustained attention deficits are more pronounced in patients with schizophrenia. Memory impairments also appear to be highly evident in patients with schizophrenia. Information processing speed may also be regarded as a one of most affected cognitive domain in patients with schizophrenia. Taken together, the present findings on neuropsychological tests confirm the fact that patients with schizophrenia have neuropsychological impairments (Mojtabai et al., 2000; Wilk & Gold, 2005).

4.2 Results of the Tower of London Test Measures

4.2.1 Schizophrenia Patients vs. Healthy Controls (Day vs. Night Performance)

Schizophrenia patients performed generally worse on the experimental task compared to the healthy controls and both groups showed learning on the tasks (ex: they performed better in the second measurement compared to the first measurement). There was no advantage to night-time interval compared to the day-time interval in schizophrenia patients as well as in healthy controls. In general sleep had no effect on the task performance in contrast to a comparable time of wakefulness in both groups. Compared with the control participants,

schizophrenia patients took significantly longer time to complete the Tower of London test. Schizophrenia patients took average of 532 seconds, whereas control participants took 281 seconds to complete the Tower of London test. There was no significant difference on the number of solved tasks between schizophrenia patients and healthy controls. Compared to pre-test measurement, in post-test measurement schizophrenia patients as well as healthy controls solved more tasks and took significantly less time to complete the Tower of London test.

The findings of the present study in the direction of sleep and improved performance failed to confirm the findings of the research study by Wagner et al. (2004). Wagner et al. (2004) study on the effects of sleep on the occurrence of insight in healthy controls used a modified version of a mathematical "number reduction task" (Turnstone & Thurstone, 1941) in healthy controls on awake group and sleep group. Participants apply a standard algorithm (consisting of two simple rules) for reducing an eight-digit sequence to a final solution. Participants do not know that a simple shortcut exists. The percentage of participants who discover the shortcut or 'hidden rule' when they are retested was 22% in the awake group versus 60% in the sleep group. They have concluded that sleeping allows the restructuring of new memory representations and facilitates extraction of explicit knowledge and insightful behavior. There may be three reasons why the present results differ: (1) the type of tasks used is different from the present study (2) type of assessment also differs and; (3) control condition kept awake: keeping awake at night leads to deterioration in performance.

The present study finding is not in line with the evidence of beneficial effect of sleep on improved problem solving performance. A study by Linde and Bergstrom (1992) investigated sleep loss on performance of complex tasks

problem solving compared with exclusively short term memory tasks. Their study included two tasks: first one examined immediate free recall, estimated to reflect the maintenance capability of working memory and the other one was lingual reasoning and problem solving measures, speculated to reflect the processing and monitoring capability of working memory. They have kept the participants in the experimental group awake and tested on various cognitive measures. Control group was allowed to sleep at home. They found a remarkable decline in performance left by a sleep loss on Raven's progressive matrices, a problem solving measure. They also found that the control group who have slept well performed higher in the tests. Their study reported that there is a significant decline in performance on sleep loss and improved performance when followed by sleep. There are some of the possible reasons for the failure of a sleep induced improved performance in the present study. Firstly, type of task they used is different from the present study. Secondly, they kept the experimental group awake. The type of assessment is very different from the present study. Sleep and improved performance are not a very robust phenomenon. It depends on the type of learning and the time interval between learning and sleep. Thus, it may be possible that same of the other factors influencing the sleep and improved problem solving effect did prevent or override this effect.

Incomplete adaption to the sleep laboratory environment may also be one of the reasons why our participants did not explicitly show overall beneficial post sleep performance in the Tower of London test. Secondly the present research study sample is too low to draw any such authentic conclusion.

4.2.2 Schizophrenia Patients (Day Interval vs. Night Interval Performance)

There was no significant difference in the Tower of London test performance between night time and day time interval. There was no advantage

to the night time interval compared with the day time interval. Schizophrenia patients significantly improved in post-test measures of the Tower of London test. In post-test measures, schizophrenia patients solved more tasks and took less time to complete the Tower of London test.

4.2.3 Healthy Controls (Day Interval vs. Night Interval Performance)

There was no significant difference in the Tower of London test performance between night time interval and day time interval. There was no advantage to the night time interval compared with the day time interval for the healthy controls as well. There was no significant difference on the number of solved tasks in the Tower of London test between pre-test and post-test measures. But there was a significant difference in total time taken between pre-test and post-test measures. In the post-test measurement the total time taken to complete the test is drastically reduced.

Summary

Schizophrenia patients performed generally worse on the experimental task (The Tower of London Test) compared to the healthy controls and both groups showed learning on the tasks. There was an increase in performance in both the groups in the second measurement occasion. Generally sleep had no effect on task performance in contrast to a comparable time of wakefulness in both groups. There was no advantage to night time interval compared with the day time interval in both groups. Compared to the healthy controls, schizophrenia patients took significantly longer time to complete the Tower of London test.

4.3 Comparison of Sleep EEG Parameters – Schizophrenia vs. Healthy Controls

The comparison of sleep EEG parameters between the two groups shows a significant difference in sleep onset latency. Schizophrenia patients had shorter sleep onset latency. There was a marginal significant difference in sleep stage 1, sleep stage 1 percentage and Non-rapid eye movement percentage (NREM %). The present study did not show the characteristic features of sleep disturbance reported in the previous research studies in patients with schizophrenia. We failed to find significant differences with regard to the other sleep parameters.

Previous sleep studies in schizophrenia patients have compared sleep latency between schizophrenia patients and healthy controls (Keshavan et al., 1998; Lauer et al., 1997; Yetkin et al., 2011) have shown increased sleep latency in patients with schizophrenia. The present study did not confirm the finding. In the present study sleep latency significantly differ between schizophrenia patients and healthy controls. Shorter sleep onset latency was observed in schizophrenia patients. However, this may be attributed to the sleep-promoting effect of the neuroleptic medication patients have taken.

A study by Yetkin et al. (2011) on sleep architecture in patients with schizophrenia reported poor sleep efficiency in patients with schizophrenia. The present study results did not replicates the finding of poor sleep efficiency in patients with schizophrenia. The present study did not find a significant difference in sleep efficiency between schizophrenia patients and healthy controls. Their study included only male inpatients with schizophrenia. The difference in sleep efficiency may be because of this reason. There was a marginal significant difference in sleep stage 1 and its percentage (Stage 1 and stage 1%) between schizophrenia patients and healthy controls.

The present study did not find a significant difference in sleep stage 2 percent (Stage 2%) between schizophrenia patients and healthy controls. The present finding is consistent with some previous research studies (Benson et al., 1996; Ganguli et al., 1987; Jus et al., 1973; Riemann et al., 1995; Yetkin et al., 2011) found no significant differences in sleep stage 2 percent in schizophrenia patients. A study by Ferrarelli et al. (2007) examined sleep rhythms variations between schizophrenia patients and healthy controls also found no difference in sleep stage 2 in schizophrenia patients.

Slow wave sleep deficit claimed to be typical for schizophrenia patients. Previous studies have shown a reduction of slow wave sleep in patients with schizophrenia (Caldwell & Domino., 1967; Keshavan et al., 1998; Poulin at al., 2003; Hiatt et al., 1985). However in the present study we did not find slow wave sleep deficit in patients with schizophrenia. There was no significant difference between schizophrenia patients and healthy controls in either on sleep stage 3 and 4 (TS3AND4) or sleep stage 3 and 4 percentage. The present study confirms the finding of Ganguli et al. (1987) study. Their study found slow-wave sleep percent of schizophrenia patients was similar to that seen in the healthy controls. The present study also confirms the finding of Tandon et al. (1992). Their study has found no difference in slow-wave sleep between schizophrenia patients and normal controls. A study by Lauer et al. (1997) also found no difference in slow wave sleep percentage between schizophrenia patients and healthy controls. Ferrarelli et al. (2010) and Yetkin et al., (2011) studies also found no slow wave sleep deficits in schizophrenia patients compared to the control participants.

Poulin at al. (2003) study have compared REM latency between schizophrenia patients and healthy controls reported reduced REM latency in schizophrenia patients. In the present study REM latency did not differ significantly between patients with schizophrenia patients and healthy controls.

Their study included acute schizophrenia patients never treated with neuroleptics. But in the present study, patients were mildly symptomatically affected and were on medications. So the differences in finding may be due to this reason. But the present study confirms the finding of Ganguli et al. (1987) study. Their study found no difference in sleep REM latency in schizophrenia patients compared with control participants. The present study also confirms Caldwell and Domino (1967) and Yetkin et al. (2011) study. Their studies also observed no reduction in REM latency in patients with schizophrenia.

Previous studies have compared the REM percent between schizophrenia patients and healthy controls (Benson et al., 1996; Ganguli et al., 1987; Jus et al., 1973; Keshavan et al., 1998., Riemann et al., 1995; Yang & Winkelman., 2005) found no significant difference in REM percent. The present study confirms the finding. In the present study, REM percentage did not differ between schizophrenia patients and healthy controls.

In the present study, total sleep time did not differ between schizophrenia patients and healthy controls. The present finding is consistent with the finding of Hoffmann et al. (2000). Their study found no difference in total sleep time between schizophrenia patients and healthy controls. But the present finding is inconsistent with the report of Keshavan et al. (1998) study. Their study found decreased total sleep time in schizophrenia patients compared to healthy controls. Keshavan et al. (1998) study included unmedicated schizophrenia patients. This may be one of the reasons for the differences in total sleep time.

Macrostructures of sleep EEG rely on successful sleep epochs. The sleep EEG scores characterization by stages and epochs are macrostructures of the sleep (Muzet, 2005). Macrostructures of sleep are highly investigated domain. In clinical electrophysiology, both the macro and microstructures of sleep are

clinically relevant. But hardly few studied about the microstructures of sleep of EEG in patients with schizophrenia (K-complex and spindles).

Ferrarelli et al. (2007) engaged 256-electrode high density EEG to examine whether sleep rhythms vary between patients with schizophrenia, healthy controls and people with history of depression. They found spindle deficits in patients with patients with schizophrenia. Another study by Ferrarelli et al. (2010) also reported sleep spindle deficits in schizophrenia patients and suggested impairments in specific neuronal circuits. In the present study, number of spindles did not differ significantly between schizophrenia patients and healthy controls. We did not find reduced sleep spindle activity in schizophrenia patients. There are a number of possible reasons for the differences in the present study. The present study used Rechtscaffen and kales, 1968 manual for scoring sleep stages and used 16 channels polygraph. Ferrarelli et al. (2007) study had used 256-electrode high density EEG and used different scoring methods. Ferrarelli et al. (2010) also used 256-electrode high density EEG. These may be some of the possible reasons for the differences.

K-complexes are well known to be a hallmark of sleep stage 2 (Happe et al., 2002). There are no reported abnormalities in K-complexes in patients with schizophrenia. The present study did not find significant differences in the number of K-complexes between schizophrenia patients and healthy controls.

Summary

Sleep parameters did not substantially differ between schizophrenia patients and healthy controls, except to shorter sleep onset latency in schizophrenia patients. If we see the overall sleep parameters in the present study, schizophrenia patients did not show worse or classical symptoms

consistently reported in previous sleep studies on schizophrenia. One of the primary reasons is, the present study included medicated and clinically stable patients with schizophrenia. The clinical rating scales confirmed the diagnosis of the schizophrenia patients and showed that they were only mildly symptomatically affected. The present study patient sample population did not included in-patients with schizophrenia. Some of the reasons why sleep studies on patients with schizophrenia failed to generate consistent findings were, some previous studies did not include habituation night so the results on sleep parameters were worse. Sleep EEG findings are influenced by treatment and phases of illness, problems with diagnostic procedure, difference in scoring methods, confound of age, confound of gender, degree of chronicity, schizophrenia subtypes and effects of the medication.

4.4 Correlation between Sleep Parameters and the Tower of London Test

The relationship between sleep parameters and problem solving (the Tower of London test) was evaluated in schizophrenia patients and healthy controls. Some performance measures were differentially correlated with specific sleep parameters. Schizophrenia patients showed a negative correlation between stage 1 sleep and its percent with the number of solved tasks in the Tower of London test. This finding suggest that if less time schizophrenia patient spent on stage 1 sleep, the more they solve tasks in the Tower of London test. No comparable results were observed for the healthy controls.

In schizophrenia patients we observed a significant strong positive relationship between the total number of K-complexes and number of solved tasks in the Tower of London test. No comparable results were observed for the healthy controls. This finding suggests when the number of K-complexes are more, the more tasks they solve problems in the Tower of London test. The

correlation between the number of K-complexes and performance after sleep in schizophrenia patients shows that processes during stage 2 sleep, in which the K-complexes predominantly occurs may be beneficial for the neuropsychological performance. K-complexes occur spontaneously but often are elicited by external or internal stimulation. They are assumed to suppress or indicate the suppression of cortical arousal evoked by stimulation or waking state activation like learning (Tononi & Cirelli, 2006). In sleep stages more K-complexes were indicative of deeper sleep and are more frequent as the proximity of the slow wave sleep (SWS) increases (Colrain, 2005; Halász et al., 1977). K-complexes possibly generated through an extra-thalamic or non-specific thalamic pathway (Colrain & Crowley, 2005). With regard to the latter function, K-complexes are proposed to be correlated to memory consolidation during sleep. Particularly, K-complexes are assumed to represent cortical down-state during sleep which is essential for a repeated practise of encoded memory engrams (Cash et al., 2009). K-complexes in humans have been shown to be identical to down-states in the slow wave sleep which are assumed to play a pivotal role in memory consolidation due to the replay of transient hippocampus-based activity into long term memory engrams (Cash et al., 2009). The higher the number of K-complexes, the more synaptic downscaling occurred and the better the encoded memory engrams can be consolidated. Thus it can be reasonable to assume that the correlation of a higher number of K-complexes with a better performance following these K-complexes in patients indicates that the schizophrenia patients did incurred benefit from a more extensive downscaling of synaptic activity (Tononi & Cirelli, 2006), although this effect was not strong enough for a general improvement compared to wakefulness.

K-complexes in some of previous studies are explained in terms of arousal phenomenon (Roth et al., 1956). Some of previous studies suggest K-complexes maybe involved in sleep protective mechanism (Wauquier et al., 2009; 1995;

Muzet, 2005; Vetter & Boker, 1962). Some other reviews suggest K-complexes may engage in sleep specific information processing during sleep (Halász, 2005; Muzet, 2005).

In schizophrenia patients sleep stage 3 and 4 (slow wave sleep or deep sleep or delta sleep) and its percentage negatively correlated with a total time taken to complete the Tower of London test. The result pattern suggests that if patients spend less time on sleep stage 3 and 4 (SWS), the longer they took to complete the Tower of London test. Slow wave sleep (SWS) often referred to as deep sleep and thought to be the most restorative sleep.

Among the healthy controls the number of spindles negatively correlated with a total time taken to complete the Tower of London test. This finding suggests that if the number of spindles is less; the longer the participants took to complete the Tower of London test. Sleep spindles are widely studied in the sleep research. However, no study found a correlation between the number of spindles and problem solving performance.

Among human sleep spindle activity are inferred to be related with memory consolidation (Gais et al., 2002; Clemens et al., 2005; Walker et al., 2002). Increased sleep stage 2 spindle activity is related to an increase in recall performance and thus, may reflect memory consolidation (Schabus et al., 2004). Sleep spindle activity may be associated with improved cognitive performance (Schabus et al., 2006). The function of the sleep spindle is associated to memory consolidation and intellectual ability (Fogel & Smith, 2011). These different findings on IQ and memory domains suggest the link between the sleep spindles and cognitive performances.

4.5 Hypotheses and Results at a Glance

Schizophrenia patients show impairment on neuropsychological tests compared with the healthy controls	⇨	Support for this hypothesis found as schizophrenia patients performed worse in most neuropsychological tests
Schizophrenia patients will have impaired sleep parameters compared with healthy controls	⇨	Support for this hypothesis was not found, as patients and controls do not differ significantly in sleep parameters except sleep Latency
Schizophrenia patients will have deficits in problem solving	⇨	Support for this hypothesis partially found as patients took longer to complete the Tower of London test
Night time interval (post sleep performance) will be more beneficial than day time interval for problem solving	⇨	Support for this hypothesis not found as interval is not significant
Specific sleep parameters will be related to improved problem solving performance in schizophrenia patients	⇨	Support for this hypothesis found as the number of K-complexes related to measures of the Tower of London test

4.6 Conclusions

The present study shows that patients with schizophrenia suffer from a wide range of cognitive deficits including sustained attention, verbal memory,

working memory, long term memory, verbal fluency, problem solving and executive functions. Sustained attention, speed of processing and working memory deficits are more pronounced in patients with schizophrenia. Schizophrenia patients took significantly longer to complete the Tower of London test.

Compared to the healthy controls, schizophrenia patients performed generally worse on the Tower of London test. Both groups showed learning on the tasks ex: they performed better in second compared to the first measurement. In general sleep had no effect on task performance in contrast to the comparable time of wakefulness in both groups. There was no advantage of night time interval compared to the day time interval for improved problem solving in both groups.

Sleep parameters did not substantially differ between schizophrenia patients and healthy controls, except shorter sleep onset latency in schizophrenia patients. The latter showed a marginally longer percentage of sleep stage 1 than the healthy controls. There were no other significant group differences with regard to sleep continuity (number of wakening and wake after sleep onset, sleep efficiency, total sleep time), sleep architecture (The percentages of sleep stage 2, 3 and 4, and stage REM), and REM sleep measures (REM latency).

However, some performance measures were differently correlated to specific sleep parameters. Sleep specific parameter, the number of K-complexes, somewhat had a beneficial effect for problem solving in patients with schizophrenia. Although this effect did not enhance total performance of the schizophrenia patients, the result shows that within the cognitive impairment of schizophrenia patients, beneficial effects of sleep can be assessed. These promoting effects of sleep were however too weak to generally enhance the

performance measures compared to a time of wakefulness or compared to healthy control participants. The overall results indicate different modes of problem solving associated to sleep in schizophrenia patients and healthy controls.

4.7 Limitations of the Present Study

There are several limitations of this study. The present study sample did not include inpatients with schizophrenia. The sample included clinically stable and mildly symptomatically affected outpatients with schizophrenia. The sample size is limited to draw any major strong conclusions. Since there is no previous study done on sleep and problem solving in patients with schizophrenia, this study on sleep and problem solving is more exploratory. We took extreme care to report and interpret the findings.

4.8 Future Directions of Research

Future study has to be conducted on large sample size investigating the microstructures of sleep EEG.

SUMMARY

There is an evidence of problem solving process being improved by sleep in the healthy controls. Previous studies show REM sleep enhances creative problem solving and slow wave sleep is also shown to have positive effects for problem solving process. Problem solving as well as sleep has been shown to be impaired in schizophrenia patients. The present study aimed at exploring and investigating relationships between sleep and problem solving in patients with schizophrenia.

A consolidation paradigm was used to investigate the question. Participants were tested a day- and night-time condition following learning, separated by a week, with half of them being allocated to the night or the day condition first in a balanced design. Sleep parameters examined by means of a whole night polysomnography.

The present study shows that patients with schizophrenia suffer from a wide range of cognitive deficits including sustained attention, verbal memory, working memory, long term memory, verbal fluency, problem solving and executive functions. Sustained attention, speed of processing and working memory deficits are more pronounced in patients with schizophrenia. Schizophrenia patients performed generally worse in the Tower of London test compared to the healthy controls. Patients took significantly longer to complete the Tower of London test. In general, sleep had no effect on task performance in contrast to a comparable wakefulness in both groups. Sleep parameters did not substantially differ between schizophrenia patients and healthy controls, except shorter sleep onset latency in the patients. Some performance measures were differently correlated to specific sleep parameters. In the patients, a higher number of K-complexes were associated with a higher number of solved tasks in

the Tower of London following sleep. In addition, a less time spent in slow wave sleep was associated with a more time taken to solve the Tower of London tasks. No comparable results were observed for the healthy controls. In the controls, less number of sleep spindles was associated with more total time taken in the Tower of London test.

In sum, the present study revealed that sleep specific parameter the number of K-complexes had a beneficial effect on problem solving in patients with schizophrenia. Although this effect did not enhance total performance of the schizophrenia patients, the result pattern indicate that within the cognitive impairment of patients with schizophrenia, beneficial effects of sleep can be assessed. These promoting effects of sleep were nevertheless too weak to generally enhance the performance measures compared to a time of wakefulness or compared to the healthy controls. Nonetheless, they probably point to schizophrenia specific process during sleep, which may be helpful for the understanding of cognitive disturbances of this disorder. The overall results indicate different modes of problem solving associated to sleep in schizophrenia patients and healthy controls.

References

Abi-Dargham, A., Rodenhiser, J., Printz, D., Zea-Ponce, Y., Gil, R., Kegeles, L. S., Weiss, R., Cooper, T. B., Mann, J. J., Van Heertum, R. L., Gorman, J. M., & Laruelle, M. (2000). Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America, 97*(14), 8104-8105.

Aleman, A., Hijman, R., de Haan, E. H. F., & Kahn, R. S. (1999). Memory impairment in schizophrenia: a meta-analysis. *American Journal of Psychiatry, 156*(9), 1358-1366.

American Psychiatric Association. (1994). Diagnostic and statistical manual of mental disorders (4th ed). Washington, DC

Anderson, P., Anderson, V., & Lajoie, G. (1996). The tower of London test: Validation and standardization for pediatric populations. *The Clinical Neuropsychologist, 10*(1), 54-65.

Andreasen, N. C., & Carpenter, W. T. (1993). Diagnosis and classification of schizophrenia. *Schizophrenia Bulletin, 19*(2), 199-214.

Arango, C., Bartko, J. J., Gold, J. M., & Buchanan, R. W. (1999). Prediction of neuropsychological performance by neurological signs in schizophrenia. *American Journal of Psychiatry, 156*, 1349-1357.

Aserinsky, E., & Kleitman, N. (1953). Regularly occurring periods of eye motility, and concomitant phenomena during sleep. *Science, 118*, 273-274.

Barr, W. B. (2001). Schizophrenia and attention deficit disorder. Two complex disorders of attention. *Annals New York Academy of Sciences, 931*, 239-250.

Benson, K. L., Sullivan, E. V., Lim, K. O., Lauriello, J., Zarcone, V., & Pfefferbaum, A. (1996). Slow wave sleep and computed tomographic measures of brain morphology in schizophrenia. *Psychiatry Research, 60*, 125-134.

Benson, K. L. (2008). Sleep in schizophrenia. *Sleep Medicine Clinics, 3*(2), 251-260.

Benton, A. L., Hamsher, K., & Sivan, A. B. (1983). Multilingual aphasia examination (3rd ed.). Iowa City: *AJA Associates*.

Berry, D. T., & Webb, W. B. (1983). State measures and sleep stages. *Psychological Reports, 52*(3), 807-812.

Biopac MP150 (*BIOPAC Systems Inc*, Goleta, CA)

Boeker, H., Kleiser, M., Lehman, D., Jaenke, L., Bogerts, B., & Northoff, G. (2006). Executive dysfunction, self, and ego pathology in schizophrenia: an exploratory study of neuropsycholoy and personality. *Comprehensive Psychiatry, 47*, 7-19.

Boydell, J., van Os, J., McKenzie, K., Allardyce, J., Goel, R., McCreadie, R. G., & Murray, R. M. (2001). Incidence of schizophrenia in ethnic minorities in London: ecological study into interactions with environment. *BMJ, 323*, 1336-1338.

Brickman, A. M., Buchsbaum, M. S., Bloom, R., Bokhoven, P., Paul-Odouard, R., Haznedar, M. M., Dahlman, K. L., Hazlett, E. A., Aronowitz, J., Heath, D., & Shihabuddin, L. (2004). Neuropsychological functioning in first-break, never-medicated adolescents with psychosis. *Journal of Nervous and Mental Disease, 192*, 615-622.

Brown, G. W., Birley, J. L., & Wing, J. K. (1972). Influence of family life on the course of schizophrenic disorders: a replication. *The British Journal of Psychiatry, 121*, 241-258.

Buckley, P. F., Miller, B. J., Lehrer, D. S., & Castle, D. J. (2009). Psychiatric comorbidities and schizophrenia. *Schizophrenia Bulletin, 35*(2), 383-402.

Cai, D. J., Mednick, S. A., Harrison, E. M., Kanady, J. C., & Mednick, S. C. (2009). REM, not incubation, improves creativity by priming associative networks. *PNAS, 106*(25), 10130-10134.

Caldwell, D. F., & Domino, E. F. (1967). Electroencephalographic and eye movement patterns during sleep in chronic schizophrenic patients. *Electroencephalography and clinical Neurophysiology, 22*, 414-420.

Cardno, A. G. and Gottesman, I. I. (2000), Twin studies of schizophrenia: From bow-and-arrow concordances to Star Wars Mx and functional genomics. *American Journal of Medical Genetics*, 97: 12–17.

Carlsson, A. (1988). The current status of the dopamine hypothesis of schizophrenia. *Neurophsychopharmacology, 1*(3), 179-186.

Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML. (2001)

Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Annu Rev Pharmacol Toxicol* 41:237-260

Carpenter, W. T. Jr., & Buchanan, R. W. (1994). Schizophrenia. *New England Journal of Medicine, 330*, 681-690.

Cash, S. S., Halgren, E., Dehghani, N., Rossetti, A. O., Thesen, T., Wang, C., Devinsky, O., Kuzniecky, R., Doyle, W., Madsen, J. R., Bromfield, E., Eröss, L., Halasz, P., Karmos, G., Csercsa, R., Wittner, L., & Ulbert, I. (2009). The human k-complex represents an isolated cortical down-state. *Science, 324*, 1084-1087.

Cervellione, K. L., Burdick, K. E., Cottone, J. G., Rhinewine, J. P., & Kumra, S. (2007). Neurocognitive deficits in adolescents with schizophrenia: longitudinal stability and predictive utility for short-term function outcome. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(7), 867-878.

Chokroverty, S, Movement Disorders, *Handbook of Clinical Neurophysiology*. Vol No 1. Hallett (Ed), 2003. P 139

Chouinard, S., Poulin, J., Stip, E., & Godbout, R. (2004). Sleep in untreated patients with schizophrenia: a meta-analysis. *Schizophrenia Bulletin, 30*(4), 957-967.

Chua, S. E., & McKenna, P. J. (1995). Schizophrenia – a brain disease? A critical review of structural and functional cerebral abnormality in the disorder. *The British Journal of Psychiatry, 166*, 563-582.

Clemens, Z., Fabó, D., & Halász, P. (2005). Overnight verbal memory retention correlates with the number of sleep spindles. *Neuroscience, 132*, 529-535.

Cohrs, S. (2008). Sleep disturbances in patients with schizophrenia: Impact and effect of antipsychotics. *CNS Drugs, 22*(11), 939-962.

Colrain, I. M., & Crowley, K. E. (2005). Evoked potentials during non-REM sleep: utility and functional significance. *Handbook of Clinical Neurophysiology, 6*, 125-135.

Colrain, I. M. (2005). The K-complex: a 7-decade history. *SLEEP, 28*(2), 255-273.

Csernansky JG, Newcomer JW: Are there neurochemical indicators of risk for schizophrenia? *Schizophr Bull*, 1994, 20(1):76-88.

Davis, H., Davis, P. A., Loomis, A. L., Harvey, E. N., & Hobart, G. (1938). Human brain potentials during the onset of sleep. *Journal of Neurophysiology, 1*, 34-38.

Dement, W., & Kleitman, N. (1957). The relation of eye movements during sleep to dream activity: an objective method for the study of dreaming. *Journal of Experimental Psychology, 53*(5), 339-346.

Dickinson, D., Ramsey, M. E., & Gold, J. M. (2007). Overlooking the obvious. A meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Arch Gen Psychiatry*, 64, 532-542.

Durmer, J. S., & Dinges, D. F. (2005). Neurocognitive consequences of sleep deprivation. *Seminars in Neurology, 25*(1), 117-129.

Elvevåg, B., & Goldberg, T. E. (2000). Cognitive impairment in schizophrenia is the core of the disorder. *Critical Reviews in Neurobiology, 14*(1), 1-21.

Everett, J., Laplante, L., & Thomas, J. (1989). The selective attention deficit in schizophrenia. Limited resources of cognitive fatigue? *Journal of Nervous and Mental Diseases, 177*(12), 735-738.

Ferrarelli, F., & Tononi, G. (2011). The thalamic reticular nucleus and schizophrenia. *Schizophrenia Bulletin, 37*(2), 306-315.

Ferrarelli, F., Peterson, M. J., Sarasso, S., Riedner, B. A., Murphy, M. J., Benca, R. M., Bria, P., Kalin, N., & Tonomi, G. (2010). Thalamic dysfunction in schizophrenia suggested by whole-night deficits in slow and fast spindles. *American Journal of Psychiatry*, 167, 1339-1348.

Ferrarelli, F., Huber, R., Peterson, M. J., Massimini, M., Murphy, M., Riedner, B. A., Watson, A., Bria, P., & Tononi, G. (2007). Reduced sleep spindle activity in schizophrenia patients. *American Journal of Psychiatry, 164*, 483-492.

Ferreira, A. J. (1961). The etiology of schizophrenia. *California Medicine, 94*(6), 369-377.

Fogel, S. M., & Smith, C. T. (2011). The function of the sleep spindle: a physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. *Neuroscience and Biobehavioral Reviews, 35*(5), 1154-1165.

Fogel, S. M., Nader, R., Cote, K. A., & Smith, C. T. (2007). Sleep spindles and learning potential. *Behavioral Neuroscience, 121*(1), 1-10.

Forbes, N. F., Carrick, L. A., McIntosh, A. M., & Lawrie, S. M. (2009). Working memory in schizophrenia: a meta-analysis. *Psychological Medicine, 39*(6), 889-905.

Flower, M. J., Sullivan, M. J., & Ekstrand, B. R. (1973). Sleep and memory. *Science, 179*, 302-304.

Franzek E, Beckmann H: Different genetic background of schizophrenia spectrum psychoses: a twin study. *Am J Psychiatry* 1998; 155:76–83

Gais, S., & Born, J. (2004a). Declarative memory consolidation: mechanisms acting during human sleep. *Learning and Memory, 11*, 679-685.

Gais, S., & Born, J. (2004b). Low acetylcholine during slow-wave sleep is critical for declarative memory consolidation. *Proceedings of the National Academy of Sciences of the United States of America, 101*(7), 2140-2144.

Ganguli, R., Reynolds, C. F., & Kupfer, D. J. (1987). Electroencephalographics sleep in young, never medicated schizophrenics. *Archives of General Psychiatry, 44*(1), 36-44.

Gibbs, E. L., & Gibbs, F. A. (1962). Extreme spindles: correlation of electroencephalographic sleep pattern with mental retardation. *Science, 138*, 1106-1107.

Gold, J. M., & Harvey, P. D. (1993). Cognitive deficits in schizophrenia. *Psychiatric Clinics of North America, 16*(2), 295-312.

Goldberg, T. E., Gold, J. M., Greenberg, R., Griffin, S., Schulze, S. C., Pickar, D., Kleinmann, J. E., & Weinberger, D. R. (1993). Contrasts between patients with affective disorders and patients with schizophrenia on a neuropsychological test battery. *American Journal of Psychiatry, 150*(9), 1355-1362.

Goldberg, T. E., & Green, M. F. (2002). Neurocognitive functioning in patients with schizophrenia: an overview. In K. L. Davis, D. Charney, J. T. Coyle, & C. Nemeroff (Eds.), *Neuropsychopharmacology: The Fifth Generation of Progress: An Official Publication of the American College of Neuropsychopharmacology*. Lippincott Williams & Wilkins: Philadelphia.

Gonzáles-Blanch, C., Crespo-Facorro, B., Alvarez-Jiménez, M., Rodríguez-Sánchez, J. M., Pelayo-Teán, J. M., Pérez-Iglesias, R., & Vázquez-Barquero, J. L. (2007). Cognitive dimensions in first-episode schizophrenia spectrum disorders. *Journal of Psychiatric Research, 41*(11), 968-977.

Gottesman, I. I. (1991). *Psychiatric genesis: the origins of madness*. Freeman: New York.

Green, M. F., & Nuechterlein, K. H. (1999). Should schizophrenia be treated as a neurocognitive disorder? *Schizophrenia Bulletin, 25*(2), 309-318.

Green, M. F., Kern, R. S., & Heaton, R. K. (2004). Longitudinal studies of cognitive and functional outcome in schizophrenia: implications for MATRICS. *Schizophrenia Research, 72*(1), 41-51.

Green, M. F., Kern, R. S., Braff, D. L., & Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the „right stuff“? *Schizophrenia Bulletin, 26*(1), 119-136.

Green, M. F. (2006). Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *Journal of Clinical Psychiatry, 67*(9), 3-8.

Green, M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *American Journal of Psychiatry, 153*, 321-330.

Gur, R. E., Cowell, P. E., Latshaw, A., Turetsky, B. I., Grossman, R. I., Arnold, S. E., Bilker, W. B., & Gur, R. C. (2000). Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Archives of General Psychiatry, 57*, 761-768.

Halász, P., Rajna, P., Pál, I., Balogh, A., & Dévényi, É. (1977). Spontaneous and evoked synchronization reactions in sleep. *Activitas Nervosa Superior, 19*, 211-212.

Halgin, R.P., & Whitbourne, S.K. (2005) *Abnormal Psychology: Clinical perspectives on psychological disorders*, Fourth Edition. McGraw Hill.

Halász, P. (2005). K-complex, a reactive EEG graphoelement of NREM sleep: an old chap in a new garment. *Sleep Medicine Reviews, 9*(5), 391-412.

Harrison, Y., & Horne, J. A. (2000a). The impact of sleep deprivation on decision making: a review. *Journal of Experimental Psychology, 6*(3), 236-249.

Harrison, Y., & Horne, J. A. (2000b). Sleep loss and temporal memory. *The Quarterly Journal of Experimental Psychology, 53*(1), 271-279.

Happe, S.; Anderer, P.; Gruber, G.; Klösch, G.; Saletu, B.; Zeitlhofer, J. (2002). Scalp topography of the spontaneous K-complex and of delta-waves in human sleep. *Brain Topography.* 15(1):43–9.

Hayes, J. R. (1989). *The complete problem solver* (2nd ed.). Hillsdale, NJ: *Lawrence Erlbaum Associate*s.

Heaton, R. K., & Pendleton, M. G. (1981). Use of neuropsychological tests to predict adult patients' everyday functioning. *Journal of Consulting and Clinical Psychology, 49*(6), 807-821.

Helmstaedter C, Lendt M, Lux S (2001). VLMT—verbaler Lern- und Merkfähigkeitstest. *Hogrefe Verlag: Beltz Test GmbH*.

Heston, L. L. (1966). Psychiatric disorders in foster home reared children of schizophrenic mothers. *The British Journal of Psychiatry, 112*(489), 819-825.

Hiatt, J. F., Floyd, T. C., Katz, P. H., & Feinberg, I. (1985). Further evidence of abnormal non-rapid-eye-movement sleep in schizophrenia. *Archive of General Psychiatry, 42*(8), 797-802.

Hoffmann, R., Hendrickse, W., Rush, A. J., Armitage, R. (2000). Slow-wave activity during non-REM sleep in men with schizophrenia and major depressive disorder. *Psychiatry Research, 95*, 215-225.

Holthausen, E. A. E., Wiersma, D., Sitskoorn, M. M., Hijman, R., Dingemans, P. M., Schene, A. H., & van den Bosch, R. J. (2002). Schizophrenic patients without neuropsychological deficits: subgroup, disease severity or cognitive comprehension? *Psychiatry Research, 112*, 1-11.

Horacek, J., Dockery, C., Kopecek, M., Spaniel, F., Novak, T., Tislerova, B., Klirova, M., Palenicek, T., & Höschl, C. (2006). Regional brain metabolism as the predictor of performance on the Trail Making Test in schizophrenia. A18FDG PET covariation study. *Neuroendocrinology Letters, 27*(5), 587-594.

Horne, J. A. (1988) Why We Sleep, The Function of Sleep in Humans and Other Mammals (*Oxford University Press*, Oxford).

Horne, J. A. (1993). Human sleep, sleep loss and behavior: implications for the prefrontal cortex and psychiatric disorder. *British Journal of Psychiatry, 162*, 413-419.

Hwang, M. Y., & Bermanzohn, P. C. (2001). Schizophrenia and comorbid conditions: diagnosis and treatment. *American Psychiatric Press*: Washington D.C.

Jablensky, A. (1999). Schizophrenia: epidemiology. *Current Opinion in Psychiatry, 12*, 19- 28.

Jasper HH. The ten-twenty electrode system of the International Federation. EEG *Clin Neurophysiol* 1958; 10:371–375.

Joshua, N., Gorgos, A., & Rossell, S. (2009). Executive functioning in schizophrenia: a thorough examination of performance on the Hayling

Sentence Completion Test compared to psychiatric and non-psychiatric controls. *Schizophrenia Research, 114*,84-90.

John G. Csernansky and John W. Newcomer, Are There Neurochemical Indicators of Risk for Schizophrenia? *Schizophr Bull (1994) 20(1): 75-88 doi:10.1093/schbul/20.1.75*

Jus, K., Bouchard, M., Jus, A. K., Villeneuve, A., & Lachance, R. (1973). Sleep EEG studies in untreated, long-term schizophrenic patients. *Arch Gen Psychiatry, 29*(3), 386-390.

Kavanagh, D. J. (1992). Recent developments in expressed emotion and schizophrenia. *The British Journal of Psychiatry, 160*, 601-620.

Kay SR, Opler LA, Fishbein A (1987) Positive and Negative Syndrome Scale (PANSS) rating manual. *Social and Behavioral Sciences Documents*, San Rafael, Calif.

Keefe, R. S. E., Bilder, R. M., Harvey, P. D., Davis, S. M., Palmer, B. W., Gold, J. M., Meltzer, H. Y., Green, M. F., Miller, D. D., Canive, J. M., Adler, L. W., Manschreck, T. C., Swartz, M., Rosenheck, R., Perkins, D. O., Walker, T. M., Stroup, T. S., McEvoy, J. P., & Lieberman, J. A. (2006). Baseline neurocognitive deficits in the CATIE schizophrenia trial. *Neuropsychopharmacology, 31*, 2033-2046.

Keith, S. J., Regier, D. A., & Rae, *D. S.* (*1991*). *Schizophrenic disorders. In L. N. Robins & D. A. Regier* (*Eds.*). *Psychiatric disorders in America*: *The Epidemiologic Catchment Area Study* (pp. 33–52).

Kempenaers, C., Kerkhofs, M., Linkowski, P., & Mendlewicz, J. (1988). Sleep EEG variables in young schizophrenic and depressive patients. *Biological Psychiatry, 24*(7), 833-838.

Kenny, J. T., Friedman, L., Findling, R. L., Swales, T. P., Strauss, M. E., Jesberger, J. A., & Schulz, S. C. (1997). Cognitive impairment in adolescents with schizophrenia. *American Journal of Psychiatry, 154*, 1613-1615.

Kéri, S., & Kelemen, O. (2009). The role of attention and immediate memory in vulnerability to interpersonal criticism during family transactions in schizophrenia. *British Journal of Clinical Psychology, 48*, 21-29.

Keshavan, M. S., Reynolds, C. F., Miewald, J. M., Montrose, D. M., Sweeney, J. A., Vasko, R. C., & Kupfer, D. J. (1998). Sleep deficits in schizophrenia. *Arch Gen Psychiatry, 55*, 443-448.

Kester, H. M., Sevy, S., Yechiam, E., Burdick, K. E., Cervellione, K. L., & Kumra, S. (2006). Decision-making impairments in adolescents with early-onset schizophrenia. *Schizophrenia Research, 85*, 113-123.

Kety, S. S. (1988). Schizophrenic illness in the families of schizophrenic adoptees: findings from the Danish national sample. *Schizophrenia Bulletin, 14*(2), 217-222.

Kety, S. S., Wender, P. H., Jacobsen, B., Ingraham, L. J., Janson, L., Faber, B., & Kinney, D. K. (1994). Mental illness in the biological and adoptive relatives of schizophrenic adoptees. *Arch Gen Psychiatry, 51*(6), 442-455.

Krabbendam, L., & Jolles, J. (2003) The Neuropsychology of Schizophrenia. In H. D'Haenen, J. A. den Boer, & P. Willner (Eds.) *Biological Psychiatry*. John Wiley & Sons, Ltd, Chichester, UK.

Kraepelin, E. (1971). *Dementia praecox and paraphrenia*. Huntington, NY: Robert E Krieger Publishing Co.

Kravariti, E., Morris, R. G., Rabe-Hesketh, S., Murray, R. M., & Frangon, S. (2003). The Maudsley early-onset schizophrenia study: cognitive function in adolescent-onset schizophrenia. *Schizophrenia Research, 65*, 95-103.

Kravariti, E., Morris, R. G., Rabe-Hesketh, S., Murray, R. M., & Frangon, S. (2007). Comparative profile analysis of cognitive function in recent-onset and chronic patients with adolescent-onset schizophrenia. *Schizophrenia Research, 94*, 240-244.

Krystal, A., Goforth, H., & Roth, T. (2008). Effects of antipsychotic medications on sleep in schizophrenia. *International Clinical Psychopharmacology, 23*(3), 150-160.

Kupfer, D. J., Wyatt, R. J., Scott, J., & Snyder, F. (1970). Sleep disturbance in acute schizophrenic patients. *American Journal of Psychiatry, 126*, 1213-1223.

Landrø, N. L., & Ueland, T. (2008). Verbal memory and verbal fluency in adolescents with schizophrenia spectrum disorders. *Psychiatry and Clinical Neurosciences, 62*, 653-661.

Latta, F., & van Cauter, E. (2002). Sleep and biological clocks. In M. Gallagher, & R. Nelson (Eds.), *Handbook of Psychology, Volume 3: Biological Psychology*. Hoboken, NJ, US: John Wiley & Sons Inc.

Lauer, C. J., Schreiber, W., Pollmächer, T., Holsboer, F., & Krieg, J.-C. (1997). Sleep in schizophrenia: a polysomnographic study on drug-naive patients. *Neuropsychopharmacology, 16,* 51-60.

Lehrl, S., 1989. Manual Zum MWT-B. *Fachbuchgesellschaft,* Erlangen.

Lee, J. H., Woo, J. I., & Meltzer, H. Y. (2001). Effects of clozapine on sleep measures and sleep-associated changes in growth hormone and cortisol in patients with schizophrenia. *Psychiatry Research, 103*, 157-166.

Lieberman, J.A.; Perkins, D.; Belger, A.; Chakos, M.; Jarskog, F; Boteva, K.; and Gilmore, J. The early stages of schizophrenia: Speculations on pathogenesis, pathophysiology, and therapeutic approaches. *Biological Psychiatry,* 50:884-897, 2001.

Norwood & Teofilo Lee-Chiong, T.L. (2006). *Sleep: a comprehensive handbook*. New York: Wiley-Liss.

Lezak, M. D. (1995). Neuropsychological Assessment (3rd ed.). New York: *Oxford University Press*.

Linde, L., & Bergström, M. (1992). The effect of one night without sleep on problem-solving and immediate recall. *Psychological Research, 54*, 127-136.

Liu, S. K., Chiu, C.-H., Chang, C.-J., Hwang, T.-J., Hwu, H.-G., & Chen, W. J. (2002). Deficits in sustained attention schizophrenia and affective disorders: stable versus state-dependent markers. *American Journal of Psychiatry, 159*, 975-982.

Liu, S. K., Hsieh, M.-H., Huang, T.-J., Liu, C.-M., Liu, C.-C., Hua, M.-S., Chen, W. J., & Hwu, H.-G. (2006). Patterns and clinical correlates of neuropsychologic deficits in patients with schizophrenia. *Journal of the Formosan Medical Association, 105*(12), 978-991.

Liu, C.-H., Guo, Y. P., Meng, X.-K., Yu, Y.-Q., Xiong, Y., Gao, L.-X., Chan, Y.-S., & He, J. (2008). Spindle oscillations are generated in the dorsal thalamus and modulated by the thalamic reticular nucleus. *Nature Preceding*, retrieved from http://hdl.handle.net/10101/npre.2008.2313.1 (19.09.2008).

Loomis, A. L., Harvey, E. N., & Hobart, G. A. (1937). Cerebral states during sleep, as studied by human brain potentials. *Journal of Experimental Psychology, 21*(2), 127-144.

Manoach, D.S. & Stickgold, R. (2009) Does abnormal sleep impair memory consolidation in schizophrenia?. *Front. Hum. Neurosci.,* 3, 1–8.

Mathalon, D. H., Heinks, T., & Ford, J. M. (2004). Selective attention on schizophrenia: sparing and loss of executive control. *American Journal of Psychiatry, 161*, 872-881.

Masellis M, Basile V, Meltzer HY, Lieberman JA, Sevy S, Macciardi FM, Cola P,

Howard A, Badri F, Nothen MM, Kalow W, Kennedy JL: Serotonin subtype 2 receptor genes and clinical response to clozapine in schizophrenia patients. *Neuropsychopharmacology* 1998; 19:123-132

McClellan, J., Prezbindowski, A., Breiger, D., & McCurry, C. (2004). Neuropsychological functioning in early onset psychotic disorders. *Schizophrenia Research, 68*(1), 21-26.

McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiological Review, 30*, 67-76.

McKenna, P., Clare, L., & Baddeley, A. D. (1995). Schizophrenia, In A. D. Baddely, B. A. Wilson, & F. N. Watts (Eds.), *Handbook of Memory Disorders*. New York: Wiley.

McNeil TF, Cantor−Graae E, Ismail B: Obstetric complications and congenital malformation in schizophrenia. *Brain Research Reviews* 2000; 31:166−178

Meddis, R. (1975). On the function of sleep. *Animal Behavior, 23*, 676-691.

Miller, R., & Mason, S. E. (2002). Diagnosis – Schizophrenia: a comprehensive resource for patients, families and helping professionals. New York: *Columbia University Press*.

Mojtabai, R., Bromet, E. J., Harvey, P. D., Carlson, G. A., Craig, T. J., & Fenning, S. (2000). Neuropsychological differences between first-admission schizophrenia and psychotic affective disorders. *American Journal of Psychiatry, 157*, 1453-1460.

Monti, J. M., & Monti, D. (2006) Sleep and antipsychotic drugs in schizophrenia patients. In M. Lader, D. P. Cardinali, & S. R. Pandi-Perumal (Eds.), *Sleep and Sleep Disorders*. New York: Springer Science + Business Media.

Monti, J. M., & Monti, D. (2008). Human sleep: an overview. In J. C. Verster, S. R. Pandi-Perumal, & D. Streiner (Eds.), *Sleep and quality of life in clinical medicine*. Totowa, NJ: Humana Press.

Morice, R., & Delahunty, A. (1996). Frontal/executive impairments in schizophrenia. *Schizophrenia Bulletin, 22*, 125-137.

Morris, R. G., Rushe, T., Woodruffe, P. W. R., & Murray, R. M. (1995). Problem solving in schizophrenia: a specific deficit in planning ability. *Schizophrenia Research, 14*, 235-246.

Morrison, G., O'Carroll, R., & McCreadie, R. (2006). Long-term course of cognitive impairment in schizophrenia. *The British Journal of Psychiatry, 189*, 556-557.

Müller, B. W., Sartory, G., & Bender, S. (2004). Neuropsychological deficits and concomitant clinical symptoms in schizophrenia. *European Psychologist, 9*(2), 96-106.

Müller, U., Werheid, K., Hammerstein, E., Jungmann, S., & Becker, T. (2005). Prefrontal cognitive deficits in patients with schizophrenia treated with atypical or conventional antipsychotics. *European Psychiatry, 20*, 70-73.

Muzet, A. (2005). Alteration of sleep microstructure in psychiatric disorders. *Dialogues in Clinical Neuroscience, 7*(4), 315-321.

Nancy C. Andreasen: Positive vs. Negative Schizophrenia: A Critical Evaluation *Schizophr Bull (1985) 11(3): 380-389*

Neylan, T. C., van Kammen, D. P., Kelley, M. E., & Peters, J. L. (1992). Sleep in schizophrenic patients on and off haloperidol therapy. *Arch Gen Psychiatry, 49*(8), 643-649.

Niedermeyer, E. (2005). Sleep and EEG. In E. Niedermeyer & F. H. Lopes da Silva (Eds.), *Electroencephalography: basic principles, clinical applications, and related fields*. Lippincott Williams & Wilkins: Philadelphia.

Nofzinger, E. A., van Kammen, D. P., Gilbertson, M. W., Gurklis, J. A., & Peters, J. L. (1993). Electroencephalographic sleep in clinically stable schizophrenic patients: two-weeks versus six-weeks neuroleptic-free. *Biological Psychiatry, 33*, 829-835.

Noh, J., Kim, J.-H., Hong, K. S., Lee, D., & Yoon, S. C. (2010). Factor structure of the neurocognitive tests: an application of the confirmative factor analysis in stabilized schizophrenia patients. *Journal of Korean Medical Science, 25*, 276-282.

Nuechterlein, K. H., Barch, D. M., Gold, J. M., Goldberg, T. E., Green, M. F., & Heaton, R. K. (2004). Identification of seperable cognitive factors in schizophrenia. *Schizophrenia Research, 72*, 29-39.

Öhman, Arne; Hultman, Christina M: Electrodermal activity and obstetric

complications in schizophrenia. *Journal of Abnormal Psychology*, Vol 107(2), May 1998, 228-237

Øie, M., Rund, B. R. (1999). Neuropsychological deficits in adolescent-onset schizophrenia compared with attention deficit hyperactivity disorder. *American Journal of Psychiatry, 156*, 1216-1222.

Ojeda, N., Pena, J., Sànchez, P., Elizagárate, E., & Ezcurra, J. (2008). Processing speed mediates the relationship between verbal memory, verbal fluency, and functional outcome in chronic schizophrenia. *Schizophrenia Research, 101*, 225-233.

Oswald, I. (1966). *Sleep*. Penguin: Harmondsworth.

Oswald, W.D., Fleischmann, U.M., 1986. Handbuch NAI (Nuernberger Alters-Inventar). *Universitaet Erlangen*, Nuernberg.

Oswald, I., & Adam, K. (1984). Sleep helps healing. *British medical journal, 289*, 1400-1401.

Palmer, B. W., Heaton, R. K., Paulsen, J. S., Kuck, J., Braff, D., Harris, M. J., Zisook, S., & Jeste, D. V. (1997). Is it possible to be schizophrenic yet neuropsychologically normal? *Neuropsychology, 11*(3), 437-446.

Pantelis, C., Barnes, T. R. E., Nelson, H. E., Tanner, S., Weatherley, L., Owen, A. M., Robbins, T. W. (1997). Frontal-striatal cognitive deficits in patients with chronic schizophrenia. *Brain, 120,* 1823-1843.

Peigneux, P., Laureys, S., Delbeuck, X., & Maquet, P. (2001). Sleeping brain, learning brain. The role of sleep for memory systems. *NeuroReport, 12*(18), 111-124.

Pilcher, J. J., & Huffcutt, A. I. (1996). Effects of sleep deprivation on performance: a meta-analysis. *Sleep, 19*(4), 318-326.

Plihal, W., & Born, J. (1999). Effects of early and late nocturnal sleep of priming and spatial memory. *Psychophysiology, 36*, 571-582.

Poulin, J., Daoust, A.-M., Forest, G., Stip, E., & Godbout, R. (2003). Sleep architecture and its clinical correlates in first episode and neuroleptic-naive patients with schizophrenia. *Schizophrenia Research, 62*(1-2), 147-153.

Rechtsschaffen, A & Kales, A manual Of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Public health service, U.S. Government Printing Office, Washington, D.C., 1968

Reichenberg, A., Harvey, P. D., Bowie, C. R., Mojtabai, R., Rabinowitz, J., Heaton, R. K., & Bromet, E. (2009). Neuropsychological function and dysfunction in schizophrenia and psychotic affective disorders. *Schizophrenia Bulletin, 35*(5), 1022-1029.

Reitan, R.M., 1979. Trail Making Test. Manual for Administration and Scoring. *Reitan Neuropsychology Laboratory*, South Tucson: Reitan.

Rhinewine, J. P., Lencz, R., Thaden, E. P., Cervellione, K. L., Burdick, K. E., Henderson, I., Bhaskar, S., Keehlisen, L., Kane, J., Kohn, N., Fisch, G. S., Bilder, R. M., & Kumra, S. (2005). Neurocognitive profiles in adolescents

with early-onset schizophrenia: clinical correlates. *Biological Psychiatry, 58*(9), 705-712.

Riemann, D., Kammerer, J., Löw, H., & Schmidt, M. H. (1995). Sleep in adolescents with primary major depression and schizophrenia: a pilot study. *Journal of Child Psychology and Psychiatry, 36*(2), 313-326.

Ritsner, M., Kurs, R., Ponizovsky, A., & Hadjez, J. (2004). Perceived quality of life in schizophrenia: relationships to sleep quality. *Quality of Life Research, 13*(4), 783-791

Robbins TW. Arousal systems and attentional processes. *Biological Psychology* 1997; 45: 57-71.

Rodriguez-Sánchez, J. M., Crespo-Farorro, B., González-Blacn, C., Perez-Iglesias, R., & Vásquez-Barquero, J. L. (2007). Cognitive dysfunction in first-episode psychosis: the processing speed hypothesis. *The British Journal of Psychiatry, 191*, 107-110.

Ronan O'Carroll,Cognitive impairment in schizophrenia *Advances in Psychiatric Treatment (2000), vol. 6,* pp. 161–168

Röschke, J., Wagner, P., Mann, K., Prentice-Cuntz, T., & Frank, C. (1998). An analysis of the brain's transfer properties in schizophrenia: amplitude frequency characteristics and evoked potentials during sleep. *Biological Psychiatry, 43*, 503-510.

Rosenfarb, I. S., Nuechterlein, K. H., Goldstein, M. J., & Subotnik, K. L. (2000). Neurocognitive vulnerability, interpersonal criticism, and the emergence

of unusual thinking by schizophrenic patients during family transactions. *Arch Gen Psychiatry, 57*, 1174-1179.

Rosenthal, R. N. (1998). Is schizophrenia addiction prone? *Current Opinion in Psychiatry, 11*(1), 45-48.

Roth, M., Shaw, J., & Green, J. (1955). The form, voltage distribution and physiological significance of the k-complex. *Electroencephalography and Clinical Neurophysiology, 8*(3), 385-402.

Salin-Pascual, R. J., Herrera-Estrella, M., Galicia-Polo, L., & Rosas Laurrabaquio, M. (1999). Olanzapine acute administration in schizophrenic patients increases delta sleep and sleep efficiency. *Biological Psychiatry, 46*, 141-143.

Sánchez, P., Ojeda, N., Peña, J., Elizagárate, E., Yoller, A. B., Gutiérrez, M., & Ezcurra, J. (2009). Predictors of longitudinal changes in schizophrenia: the role of processing speed. *Journal of Clinical Psychiatry, 70*(6), 888-896.

Sartory, G., Thom, A., Griese, J., Young, D., Butorac, M., Pokraja-Bulian, A., & Sendula, M. (2001). Lack of insight and concomitant neuropsychological deficits in schizophrenia. *Zeitschrift für Neuropsychologie, 12*(1), 54-60.

Saykin, A. J., Gur, R. C., Gur, R. E., Mozley, P. D., Mozley, L. H., Resnick, S. M., Kester, D. B., & Stafiniak, P. (1991). Neuropsychological function in schizophrenia. Selective impairment in memory and learning. *Arch Gen Psychiatry, 48*(7), 618-624.

Schabus, M., Gruber, G., Paraptics, S., Sauter, C., Klösch, G., Anderer, P., Klimesch, W., Saletu, B., & Zeitlhofer, J. (2004). Sleep spindles and their significance for declarative memory consolidation. *Sleep, 27*(8), 1479-1485.

Schabus, M., Hödlmoser, K., Gruber, G., Sauter, C., Anderer, P., Klösch, G., Parapetics, S., Saletu, B., Klimesch, W., & Zeitlhofer, J. (2006). Sleep spindle-related activity in the human EEG and its relation to general cognitive and learning abilities. *European Journal of Neuroscience, 23*, 1738-1746.

Schmajuk, N. A. (2001). Hippocampal dysfunction in schizophrenia. *Hippocampus, 11*, 599-613.

Seeman, P. (1980). Brain dopamine receptors. *Pharmacological Review, 32*, 229-313.

Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London: Series B, Biological Sciences, 298*(1089), 199–209.

Shapiro, C. M., Bortz, R., Mitchell, D., Bartel, P., & Jooste, P. (1981). Slow-wave sleep: a recovery period after exercise. *Science, 214*, 1253-1254.

Shih, J. J., Weisend, M. P., Davis, J. T., Huang, M. (2000). Magnetoencephalographic characterization of sleep spindles in humans. *Journal of Clinical Neurophysiology, 17*(2), 224-231.

Silber, M. H., Ancoli-Israel, S., Bonnet, M. H., Chokrocerly, S., Grigg-Damberger, M., Hirshkowitz, M., Kapen, S., Keenan, S. A., Kryger, M. H., Penzel, T., Pressman, M. R:, & Iber, C. (2007). The visual scoring of sleep in adults. *Journal of Clinical Sleep Medicine, 3*(2), 121-131.

Silver, H., Feldman, P., Bilker, W., & Gur, R. C. (2003). Working memory deficit as a core neuropsychological dysfunction in schizophrenia. *American Journal of Psychiatry, 160*, 1809-1816.

Sim, K., Chua, T. H., Chan, Y. H., Mahendran, R., Chong, S. A. (2006). Psychiatric comorbidity in first episode schizophrenia: a 2 year, longitudinal outcome study. *Journal of Psychiatric Research, 40*(7), 656-663.

Spencer, E. K., & Campbell, M. (1994). Children with schizophrenia: diagnosis, phenomenology, and pharmacotherapy. *Schizophrenia Bulletin, 20*(4), 713-725.

Stern, W. C., & Morgane, P. J. (1974). Theroretical view of REM sleep function: maintenance of catecholamine systems in the central nervous system. *Behavioral Biology, 11*, 1-32.

Stickgold, R. (1998). Sleep: off-line memory reprocessing. *Trends in Cognitive Sciences, 2*(12), 484-492.

Stickgold, R., Hobson, J.A., Fosse, R., and Fosse, M. (2001). Sleep, learning, and dreams: off-line memory reprocessing. *Science 294* 1052–1057.

Strakowski SM, Tohen M, Stoll AL, et al. Comorbidity in psychosis at first hospitalization. *Am J Psychiatry* 1993;150:752-7.

Susmakova, K. (2004). Human sleep and sleep EEG. *Measurement Science Review, 4*(2), 59-74.

Tamminen, J., Payne, J. D., Stickgold, R., Wamsley, E. J., & Gareth, M. (2010). Sleep spindle activity is associated with the integration of new memories and existing knowledge. *Journal of Neuroscience, 30*(43), 14356-14360.

Tandon, R., Nasrallah, H. A., & Keshavan, M. S. (2009). Schizophrenia, "just the facts" 4. Clinical features and conceptualization. *Schizophrenia Research*, 110, 1-23.

Tandon, R., Shipley, J. E., Taylor, S., Greden, J. F., Eiser, A., DeQuardo, J., & Goodson, J. (1992). Electroencephalographic sleep abnormalities in schizophrenia. *Arch Gen Psychiatry, 49*(3), 185-194.

Teofilo L. Lee-Chiong, Sleep Medicine (2008): Essentials and Review, *Oxford University press*.

The American Heritage® Science Dictionary. Source location: Houghton Mifflin Company. http://dictionary.reference.com/browse/sleep. Available: http://dictionary.reference.com. Accessed: October 03, 2011.

Thurstone, L. L., & Thurstone, T. G. (1941). *Factorial studies of intelligence*. University of Chicago Press: Chicago.

Tononi, G. & Cirelli, C. (2006). Sleep function and synaptic homeostasis. *Sleep Medicine* Reviews, 10, 49-62.

Toulopoulou, T., Morris, R. G., Rabe-Hesketh, S., & Murray, R. M. Selectivity of verbal memory deficits in schizophrenic patients and their relatives. (2003). *American Journal of Medical Genetics Part B (Neuropsychiatric Genetics), 116*, 1-7.

Tsuang, M. T., Stone, W. S., & Faraone, S. V. (2001). Genes, environment and schizophrenia. *The British Journal of Psychiatry, 178*, 18-24.

Ueland, T., Øie, M., Landrø, N. I., & Rund, B. R. (2004). Cognitive functioning in adolescents with schizophrenia spectrum disorders. Psychiatry Research, 126(3), 229-239.

van Os J, Selten JP (1998) Prenatal exposure to maternal stress and subsequent schizophrenia : The May 1940 invasion of The Netherlands. *British Journal of Psychiatry*, Vol 172, Apr 1998, 324-326

Vetter, K., & Boker, W. (1962). Zur Funktion des K-Komplexes im Schlaf-Elektroencephalogramm. *Nervenarzt, 33*, 390-394.

Wagner, U., Gais, S., Haider, H., Verleger, R., & Born, J. (2004). Sleep inspires insight. *Nature, 427*(22), 352-355.

Walker, E., Kestler, L., Bollini, A., & Hochman, K. M. (2004). Schizophrenia: etiology and course. *Annual Review of Psychology, 55*, 401-430.

Walker, M. P., Brakefield, T., Morgan, A., Hobson, J. A., & Stickgold, R. (2002). Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron, 35*, 205-211.

Walker MP. The role of sleep in cognition and emotion. Ann N Y *Acad Sci 2009*;1156:168-197.

Wauquier, A., Aloe, L., & Declerck, A. (1995). K-complexes: are they signs of arousal or sleep protective? Journal of Sleep Research, 4(3), 138-143.

Westmoreland, (2009). Clinical Neurophysiology. In J. R. Daube, & D. I. Rubin (Eds.) *Clinical neurophysiology*. Oxford University Press: Oxford.

Wilk, C. M., Gold, J. M., McMahon, R. P., Humber, K., Iannone, V. N., & Buchanan, R. W. (2005). No, it is not possible to be schizophrenic yet neuropsychologically normal. *Neuropsychology, 19*(6), 778-786.

Williamson, A. M., & Feyer, A.-M. (2000). Moderate sleep deprivation produces impairments in cognitive and motor performance equivalent to legally prescribed levels of alcohol intoxication. Occupational Environment Medicine, 57, 649-655.

Wittchen HU, Zaudig M, Fydrich T (1997). SKID-I/II: Strukturiertes klinisches Interview für DSM-IV. *Hogrefe*: Göttingen.

Wobrock, T., Ecker, U. K., Scherk, H., Schneider-Axmann, T., Falkai, P., & Gruber, O. (2009). Cognitive impairment of executive function as a core symptom of schizophrenia. *Word Journal of Biological Psychiatry, 10*(4), 442-451.

Wölwer W, Gaebel W: Impaired trail-making test-B performance in patients with acute schizophrenia is related to inefficient sequencing of planning and acting. *J Psychiatr Res* 2002;36:407–416.

World health organization (1993) The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. Geneva: WHO.

World Health Organisation. Schizophrenia & Public Health. Geneva (Switzerland): *World Health Organisation*; 1997. 41p, p1.

Yang, C., & Winkelman, J. W. (2006). Clinical significance of sleep EEG abnormalities in chronic schizophrenia. *Schizophrenia Research, 82*, 251-260.

Yetkin, S., Aydin, H., Özgen, F., Sütcigil, L., Bozkurt, A. (2011). Sleep architecture in schizophrenia patients. *Turkish Journal of Psychiatry, 22*(1), 1-8.

Zec, R. F. (1995). Neuropsychology of schizophrenia according to Kraepelin: disorders of volition and executive functioning. *European Archives of Psychiatry and Clinical Neuroscience, 245*, 216-233.

Zhu, Y., Liu, X., Wang, H., Jiang, T., Fang, Y., Hu, H., Wang, G., Wang, X., Liu, Z., & Zhang, K. (2010). Reduced prefrontal activation during Tower of London in first-episode schizophrenia: a multi-channel near-infrared spectroscopy study. *Neuroscience Letters, 478*(3), 136-140.

Zilles, D., Gruber, E., Falkai, P., & Gruber, O. (2010). Patients with schizophrenia show deficits of working memory maintenance components in circuit-specific tasks. *European Archives of Psychiatry and Clinical Neuroscience, 260*, 519-525.

Appendix A

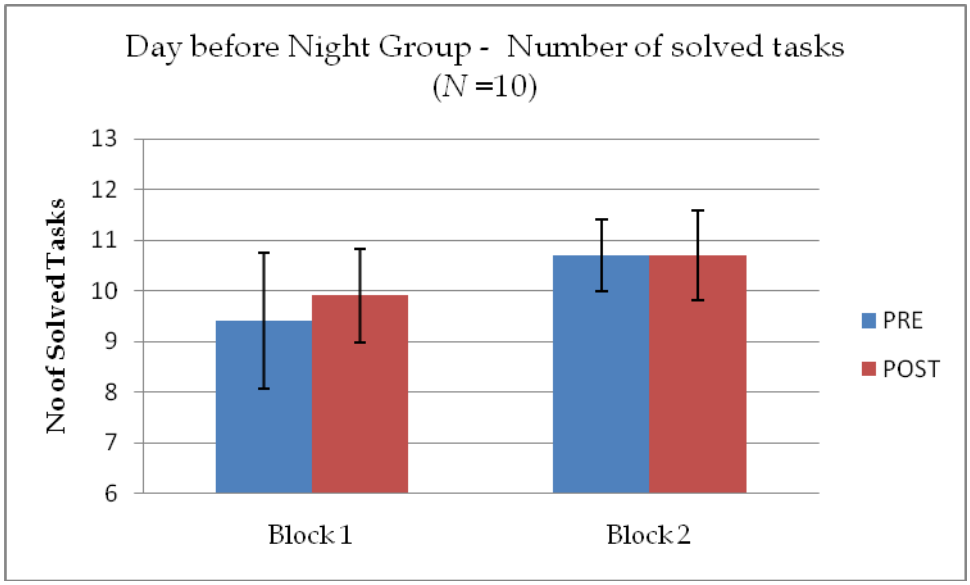


Figure A1 Mean scores of number of solved tasks in the Tower of London test - Day before night group - Schizophrenia patients (bars represent standard errors)

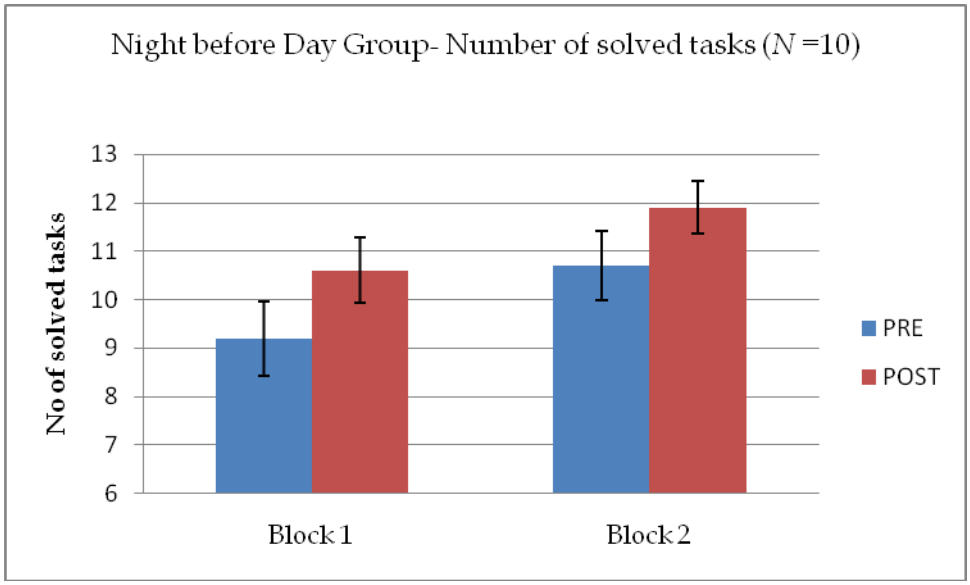


Figure A2 Mean scores of number of solved tasks in the Tower of London test – Night before day group - Schizophrenia patients (bars represent standard errors)

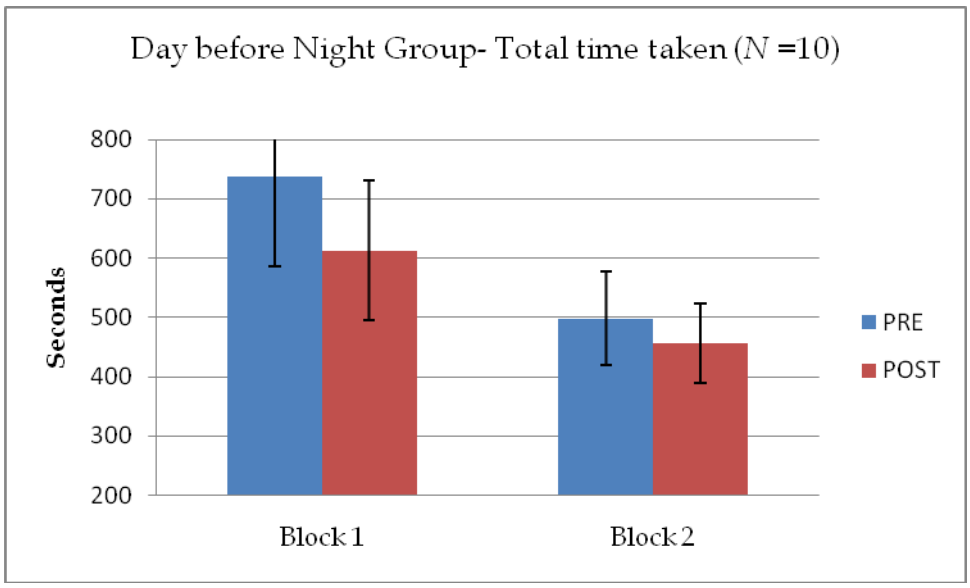


Figure A3 Mean scores of total time taken in the Tower of London test – Day before night group - Schizophrenia patients (bars represent standard errors)

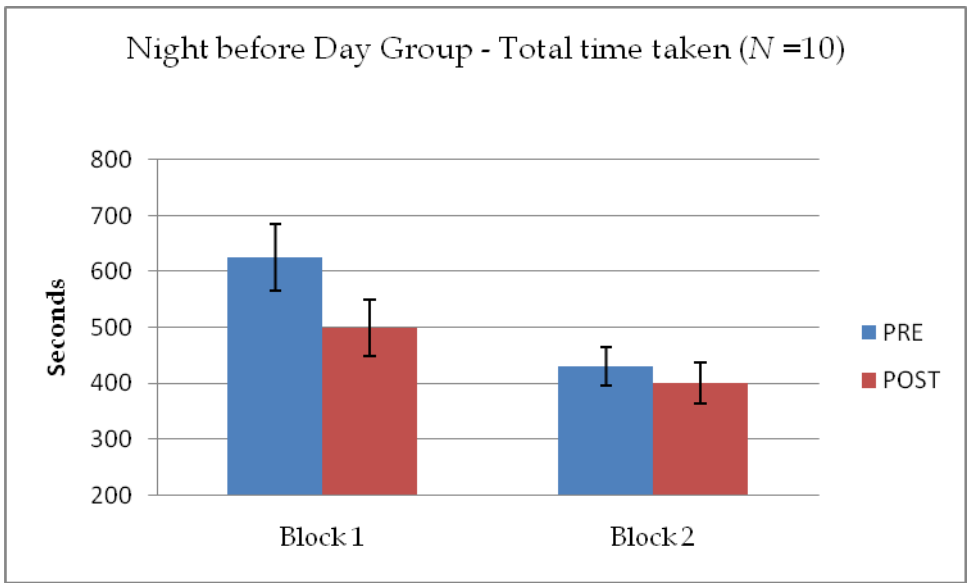


Figure A4 Mean scores of total time taken in the Tower of London test – Night before day group - Schizophrenia patients (bars represent standard errors)

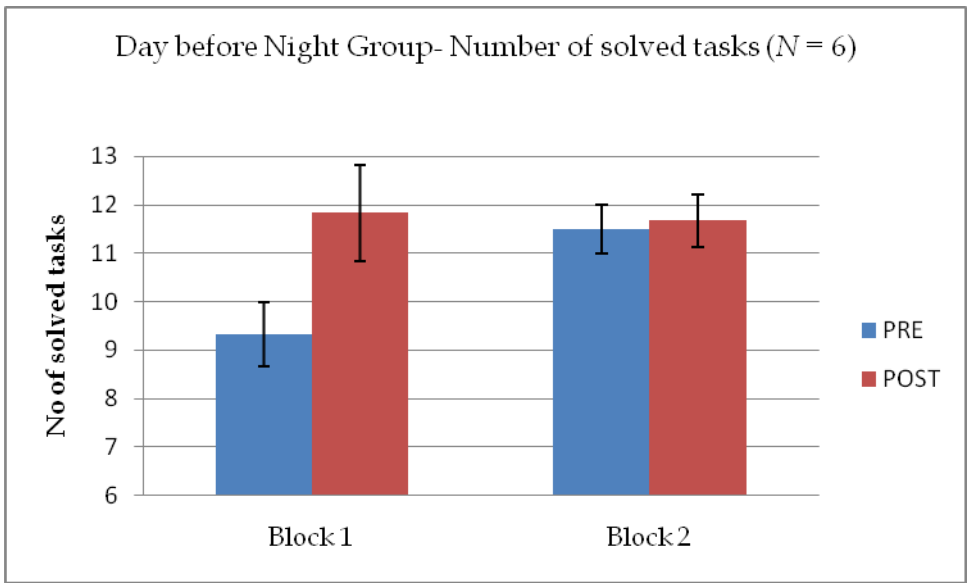


Figure A5 Mean scores of number of solved tasks in the Tower of London test – Day before night group - Healthy controls (bars represent standard errors)

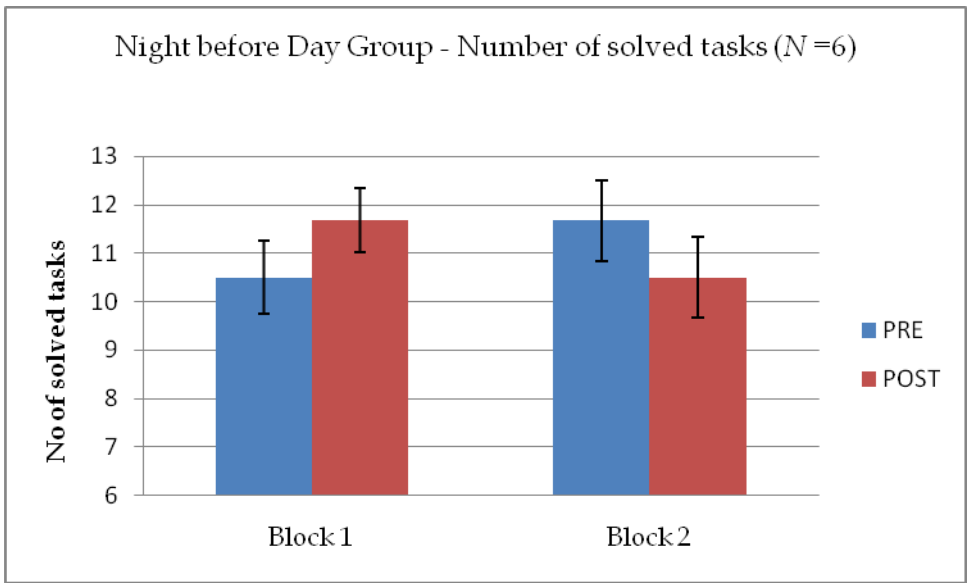


Figure A6 Mean scores of number of solved tasks in the Tower of London test – Night before day group - Healthy controls (bars represent standard errors)

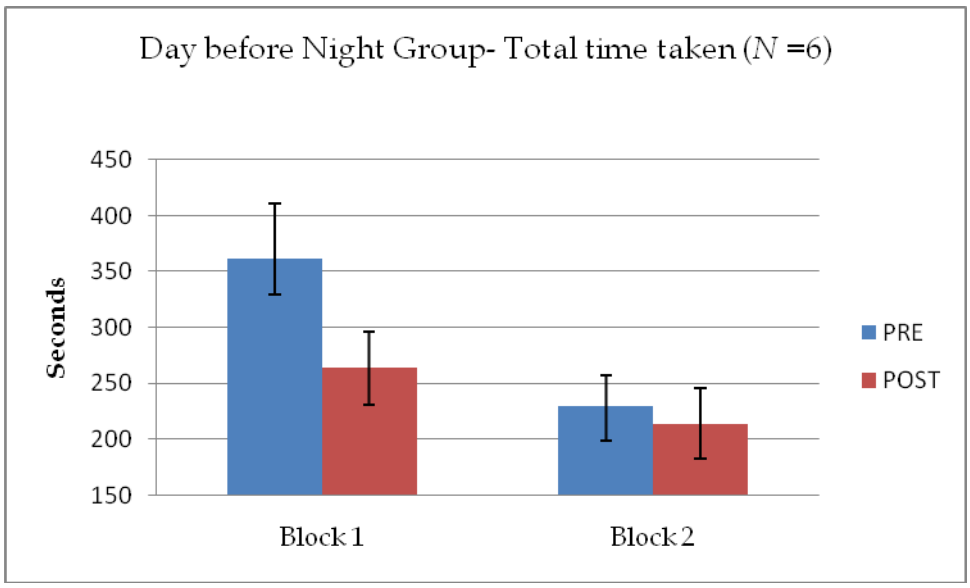


Figure A7 Mean scores of total time taken in the Tower of London test – Day before night group - Healthy controls (bars represent standard errors)

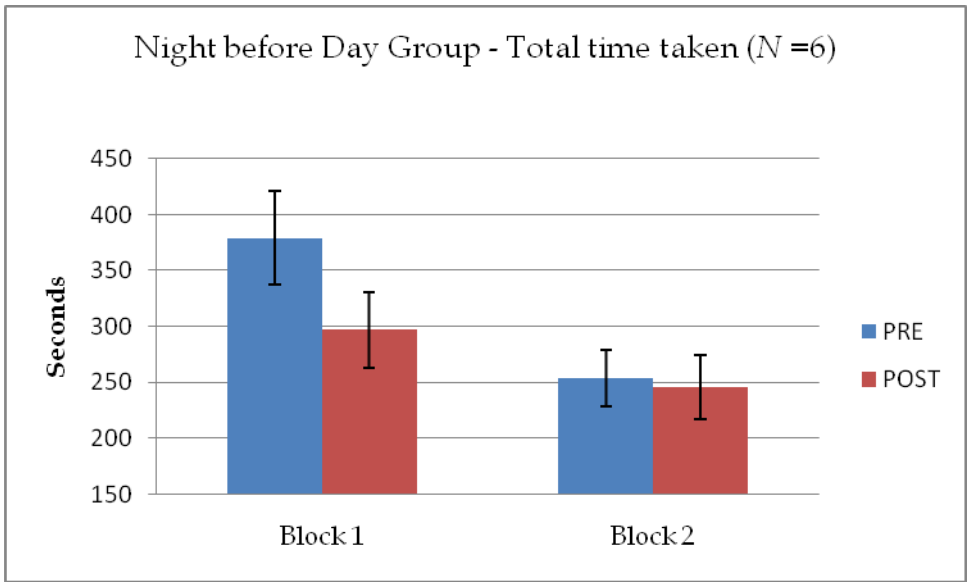


Figure A8 Mean scores of total time taken in the Tower of London test – Night before day group - Healthy controls (bars represent standard errors)

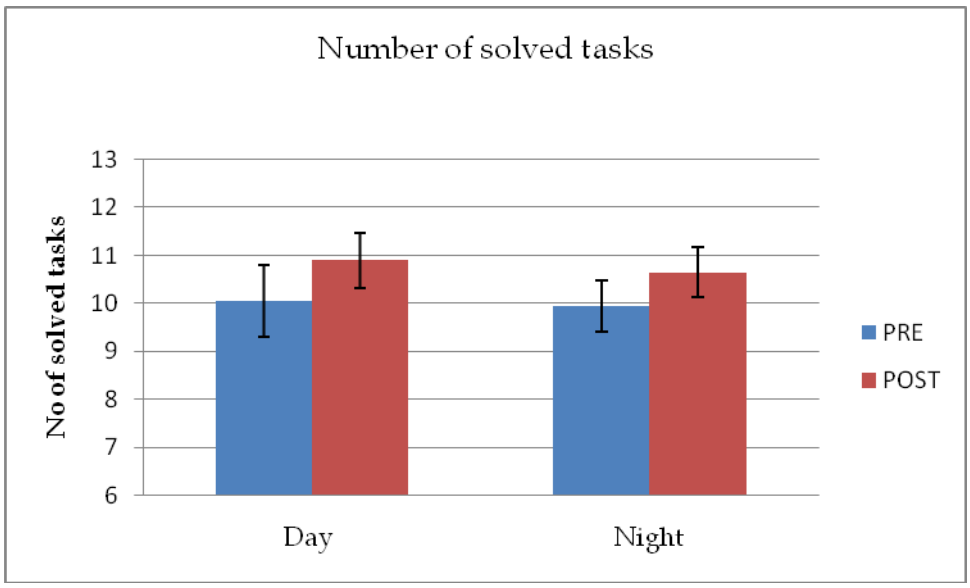


Figure A9 Mean scores of number of solved tasks in the Tower of London test - Day vs. night interval – (Schizophrenia patients) (bars represent standard errors)

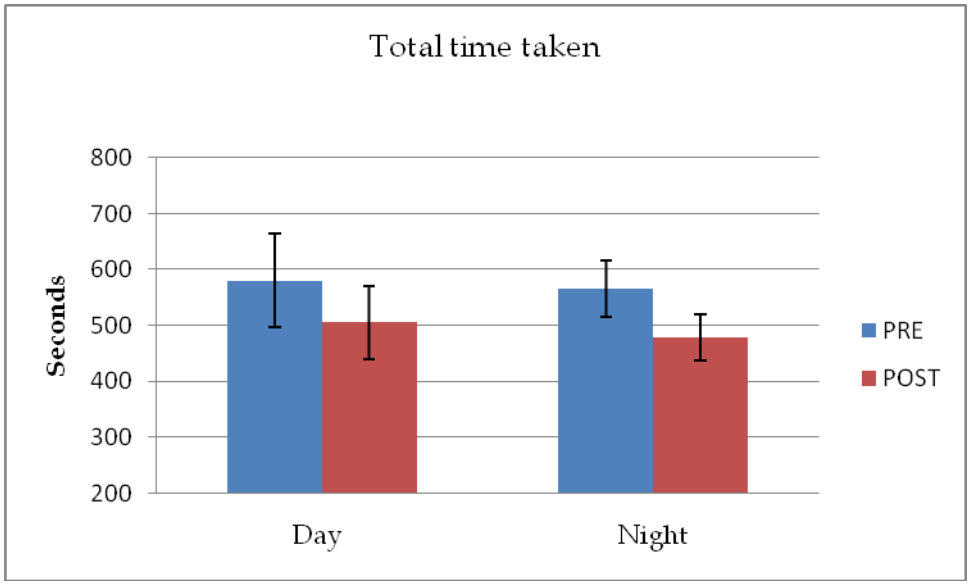


Figure A10 Mean scores of total time taken in the Tower of London test - Day vs. night interval – (Schizophrenia patients) (bars represent standard errors)

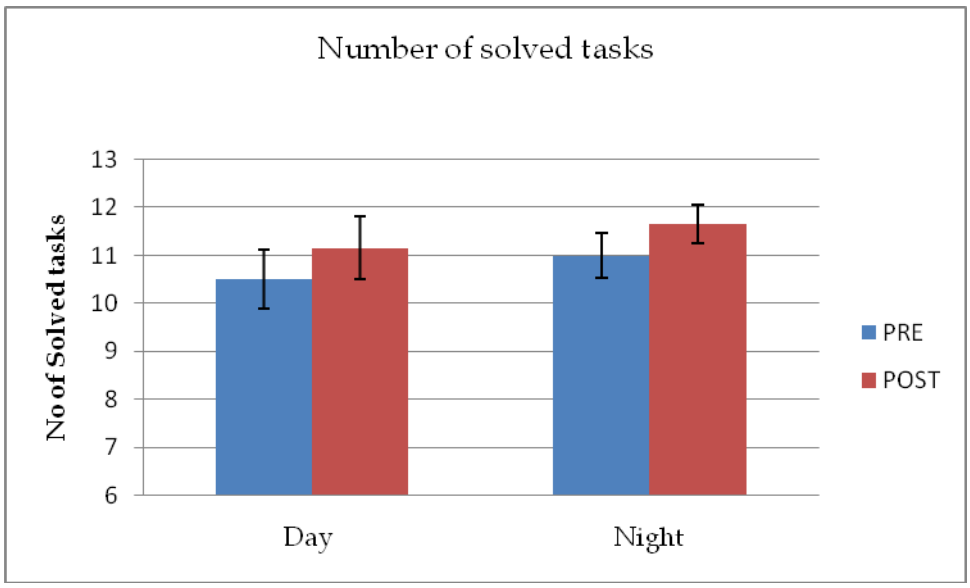


Figure A11 Mean scores of number of solved tasks in the Tower of London test - Day vs. night interval – (Healthy controls) (bars represent standard errors)

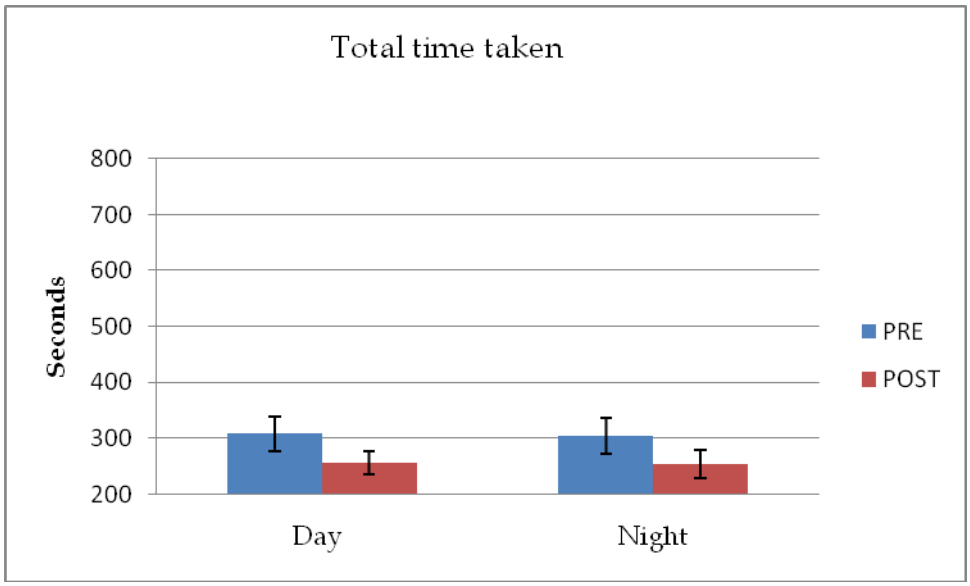


Figure A12 Mean scores of total time taken in the Tower of London test - Day vs. night interval – (Healthy controls) (bars represent standard errors)

Appendix B

B1 Experimental Task Results – Tower of London Measures – Preliminary Analyses.

The mean scores and standard deviations of schizophrenia patients and healthy controls of the measures of the Tower of London are presented in Table B1 and Table B2. The figures of mean scores for the Tower of London measures were presented in Appendix A

Table B1 Mean scores for the measures of the Tower of London – Number of solved tasks

			Number of Solved Tasks					
			Schizophrenia Patients			Healthy Controls		
			M	*SD*	(Range)	*M*	*SD*	(Range)
Day Before Night Group Patients *N* = 10, Controls *N*= 6	Day Block 1	Pre	9.40	4.28	(1-14)	9.33	1.63	(7-11)
		Post	9.90	2.92	(3-14)	11.83	2.48	(8-15)
	Night Block 2	Pre	10.70	2.26	(8-15)	11.50	1.22	(10-13)
		Post	10.70	2.79	(6-15)	11.67	1.36	(10-14)
Night Before Day Group patients *N* =10, Controls *N* = 6	Night Block 1	Pre	9.20	.77	(5-12)	10.50	1.87	(8-13)
		Post	10.60	.61	(8-15)	11.67	1.63	(10-14)
	Day Block 2	Pre	10.70	.70	(7-14)	11.67	2.06	(8-14)
		Post	11.90	.54	(9-14)	10.50	2.07	(8-13)

M = Mean, *SD* = Standard Deviation, *N* = Number

Table B2 Mean scores for the measures of the Tower of London – Total time taken

			Total Time Taken					
			Schizophrenia Patients			Healthy Controls		
			M	*SD*	(Range)	*M*	*SD*	(Range)
Day Before Night Group Patients *N* = 10, Controls *N* = 6	Day Block 1	Pre	736.94	475.40	(312-1803)	361.56	118.25	(229-526)
		Post	612.01	373.96	(288-1499)	263.73	79.83	(165-371)
	Night Block 2	Pre	497.95	249.89	(264-938)	229.58	67.03	(138-308)
		Post	456.46	210.43	(255-900)	213.06	77.03	(123-317)
Night Before Day Group Patients *N* = 10, Controls *N* = 6	Night Block 1	Pre	625.10	188.46	(414-1120)	378.16	102.11	(222-538)
		Post	498.57	158.83	(337-920)	296.21	82.07	(190-407)
	Day Block 2	Pre	429.61	108.88	(276-641)	253.51	61.22	(162-307)
		Post	399.68	116.47	(276-643)	245.83	69.85	(149-320)

***M* = Mean, *SD* = Standard Deviation, *N* = Number**

B 1.1 Results of Multivariate and Univariate Analyses of Variance for the Measures of the Tower of London (Schizophrenia Patients versus Healthy Controls)

A 2 (Status: schizophrenia patients vs. healthy controls) x 2 (Group: day before night vs. night before day) x 2 (Block: block 1 vs. block 2) x 2 (pre-post: pre vs. post) four-way mixed MANOVA with repeated measures on the last two factors was performed using the number of solved tasks and total time taken as dependent variables. The multivariate and univariate results are presented in Table B3 and Table B4 respectively.

Table B3 Results of multivariate analyses of variance of the measures of the Tower of London (Schizophrenia patients vs. healthy controls)

Effect	F (2, 27)	*p*	η^2
Group (Day Night / Night Day)	.12	.88	.00
Status (Patients vs. controls)	6.0	.00**	.30
Group x Status	.33	.72	.02
Block	22.93	.000***	.62
Block x Group	.36	.69	.02
Block x Status	2.68	.08	.16
Block x Group x Status	.50	.61	.03
Pre-post	19.22	.000***	.58
Pre-post x Group	.09	.90	.00
Pre-post x Status	.89	.42	.06
Pre-post x Group x Status	2.44	.10	.15
Block x Pre-post	10.33	.000***	.43
Block x Pre-post x Group	.02	.97	.00
Block x Pre-post x Status	2.60	.09	.16
Block x Pre-post x Group x Status	.07	.92	.00

* = $p < .05$; ** = $p < .01$; *** = $p < .001$

Table B4 Univariate analysis of variance results for the measures of the Tower of London (Schizophrenia patients vs. healthy controls)

Source	F (1, 28)	*p*	η^2
Measure : Number of solved tasks			
Group (Day Night / Night Day)	.08	.77	.00
Status (Patients vs. controls)	.92	.34	.03
Group x Status	.08	.77	.00
Block	6.4	.01**	.18
Block x Group	.23	.63	.00
Block x Status	1.14	.29	.03
Block x Group x Status	.99	.32	.03
Pre-post	7.3	.01**	.20
Pre-post x Group	.07	.79	.00
Pre-post x Status	.04	.84	.00
Pre-post x Group x Status	5.0	.03*	.15
Block x Pre-post	6.9	.01**	.19
Block x Pre-post x Group	.02	.88	.00
Block x Pre-post x Status	3.8	.06	.12
Block x Pre-post x Group x Status	.02	.88	.00
Measure : Total time taken			
Group (Day Night / Night Day)	.16	.68	.06
Status (Patient vs. controls)	11.43	.00**	.29
Group x Status	.58	.45	.02
Block	29.75	.000***	.51
Block x Group	.31	.57	.01
Block x Status	2.98	.09	.09
Block x Group x Status	.23	.63	.00
Pre-post	36.51	.000***	.56
Pre-post x Group	.15	.69	.00
Pre-post x Status	1.85	.18	.06
Pre-post x Group x Status	.02	.86	.00
Block x Pre-post	20.77	.000***	.42
Block x Pre-post x Group	.00	.93	.00
Block x Pre-post x Status	.11	.74	.00
Block x Pre-post x Group x Status	.07	.78	.00

*** = $p < .05$; ** = $p < .01$; *** = $p < .001$**

Effects of the MANOVA

Main Effects

The main effect of the group was not significant $F(2, 27) = .12$, $p = .88$, partial eta squared = .30 showing day before night or night before day condition

does not differ significantly. There was a significant main effect of status $F(2, 27) = 6.0$, $p = .00$, partial eta squared = .30 with patients showing a poorer performance than control participants. There was a highly significant main effect of block $F(2, 27) = 22.93$, $p = .000$, partial eta squared = .62. Compared to the block 1, in block 2 schizophrenia patients as well healthy controls solved more tasks and took significantly less time to complete the Tower of London test. The main effect of pre-post was also highly significant $F(2, 27) = 19.22$, $p = .000$, partial eta squared = .58. There was an increase in performance from pre to post test measures of the Tower of London test.

Interaction Effects

The block by pre-post interaction was highly significant $F(2, 27) = 10.33$, $p = .000$, partial eta squared = .43. The other interaction effects were not significant.

Further to probe statistically significant effects, univariate results were examined on the dependent variables number of solved tasks and total time taken separately.

Effects of the ANOVA

Number of Solved Tasks

Main Effects

There was a significant main effect of block with regard to number of solved tasks $M = 10.30$ vs. 11.16, $F(1, 28) = 6.4$, $p = .01$, partial eta squared = .18. Compared with block 1, in block 2 measures both patients and control participants solved more number of tasks (Figure B1). There was also a

significant main effect of pre-post with regard to number of solved tasks *M* = 10.37 vs. 11.09, *F*(1, 28) = 7.3, *p* = .01, partial eta squared = .20. Schizophrenia patients as well as healthy controls solved more number of tasks in the post test measures (Figure B2). The other main effects were not significant.

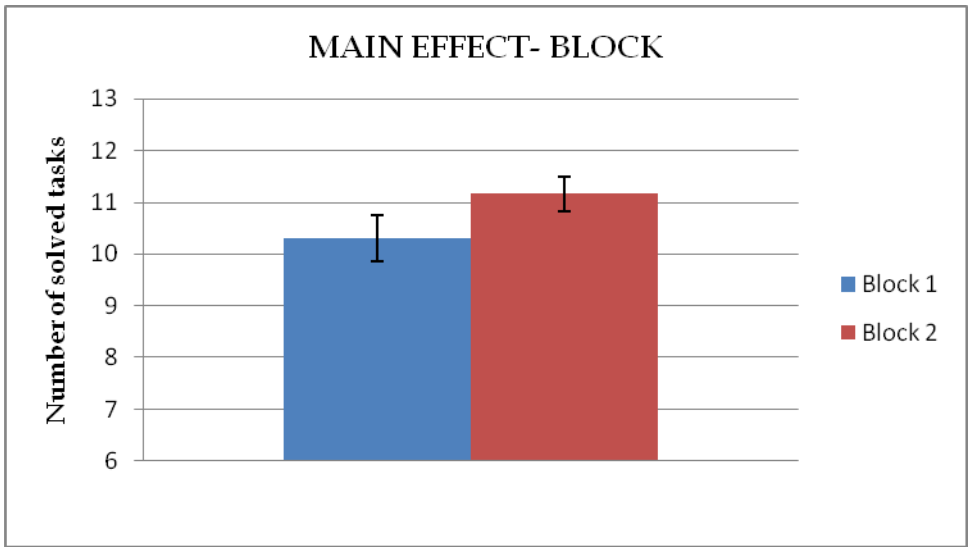


Figure B1 Mean number of solved tasks in the Tower of London test at two measurement occasions (bars represent standard errors)

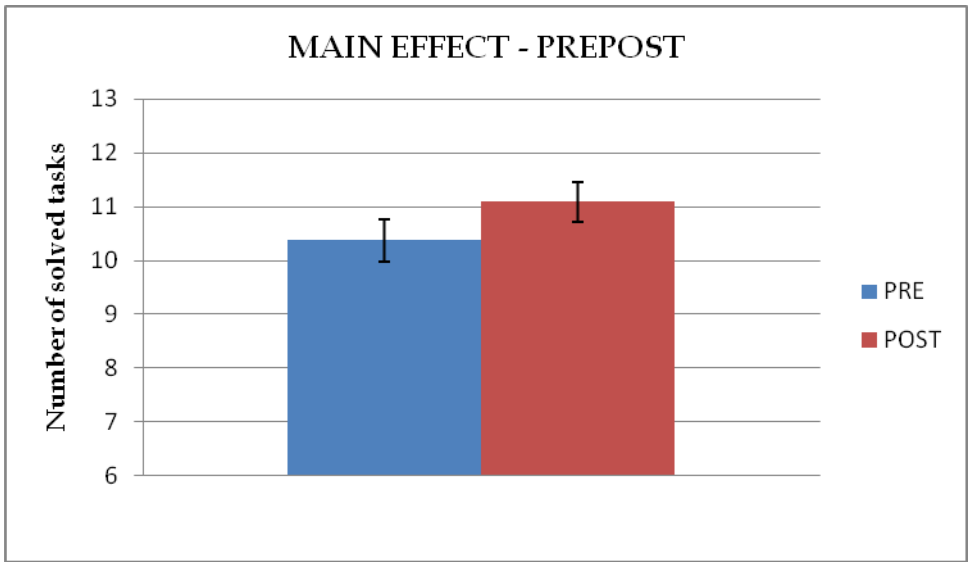


Figure B2 Mean number of solved tasks in the Tower of London test at pre-post measures (bars represent standard errors)

Interaction effects

The interaction effect of pre-post by group by status was significant $F(1, 28) = 5.0$, $p = .03$, partial eta squared = .15. Schizophrenia patients solved more tasks in the post test measures of the night time condition (Figure B3), whereas healthy controls solved more tasks in the post test measures of day time condition (Figure B4). The interaction effect of block by pre-post was also significant $F(1, 28) = 6.9$, $p = .01$, partial eta squared = .19. There was an increase in number of solved tasks in block 1 from pre to post test measures, whereas in the block 2 the number of solved tasks from pre to post test measures are relatively low (Figure B5). All other interaction effects were not significant.

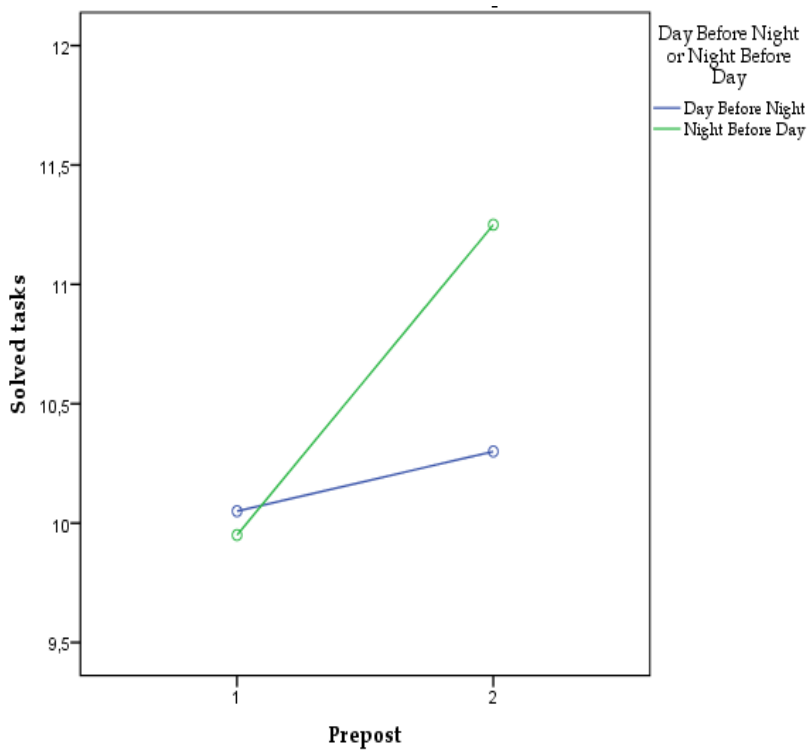


Figure B3 Schizophrenia patients solved a greater number of tasks in the Tower of London test in the post test measures of night time condition – Pre-post by group by status interactions (Schizophrenia patients)

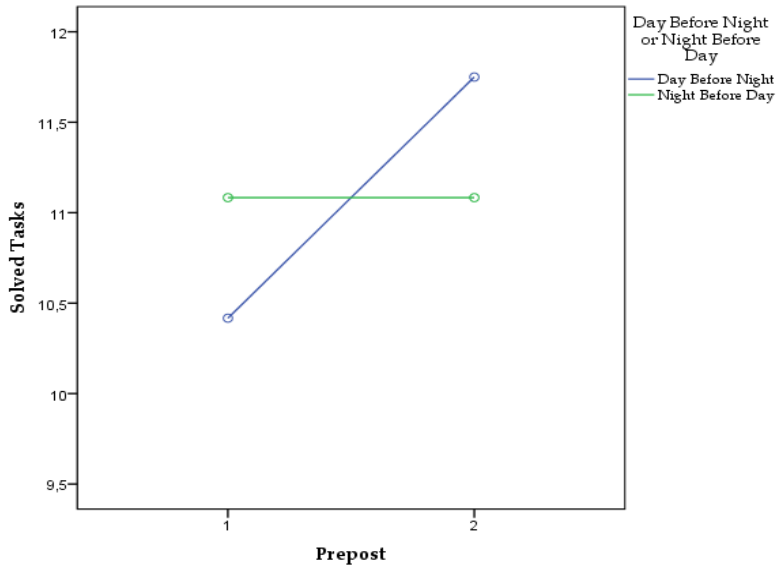


Figure B4 Healthy controls solved a greater number of tasks in the Tower of London test during the day (Post test measures). Number of solved tasks increased from pre to post day measures. Pre-post by group by status interactions (Healthy controls)

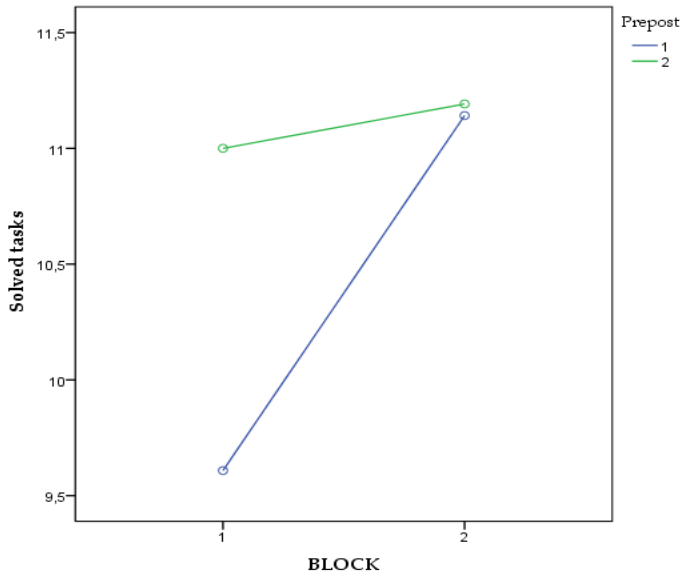


Figure B5 Block by pre-post interactions (number of Solved tasks) in the Tower of London test. In block 1 total number of solved tasks increased from pre to post measure. But in block 2 there is not much increase in number of solved tasks from pre to post measures.

Total Time Taken

Main Effects

There was a significant main effect of status on total time taken *M* 532.04 vs. 280.21, $F(1, 28) = 11.43$, $p = .00$, partial eta squared = .29. Schizophrenia patients took longer to complete the Tower of London test compared with the healthy controls (Figure B6). There was a highly significant main effect of block on total time taken *M* = 471.53 vs. 340.71, $F(1, 28) = 29.75$, $p = .000$, partial eta squared = .51. Compared with block 1, in block 2 the time taken to complete the Tower of London test significantly reduced (Figure B7). The main effect of pre-post on total time taken was also highly significant *M* = 439.05 vs. 373.19 $F(1, 28) = 36.51$, $p = .000$, partial eta squared = .56. Compared with pre test measures, in post test measures both patients and healthy controls took significantly less time to complete the Tower of London test (Figure B8). The other main effects were not significant.

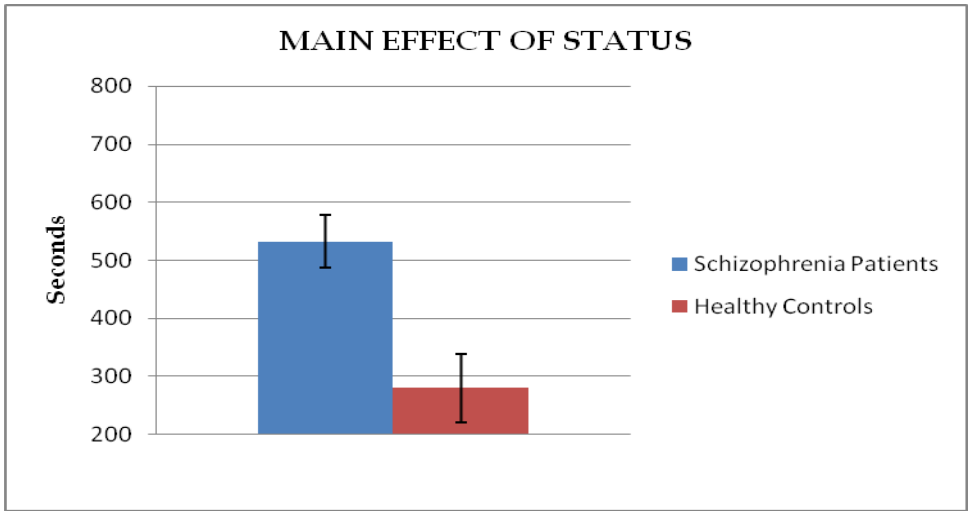


Figure B6 Main effect of status with regard to total time taken in the Tower of London test. Compared with healthy controls schizophrenia patients took significantly longer to complete the Tower of London test (bars represent standard errors)

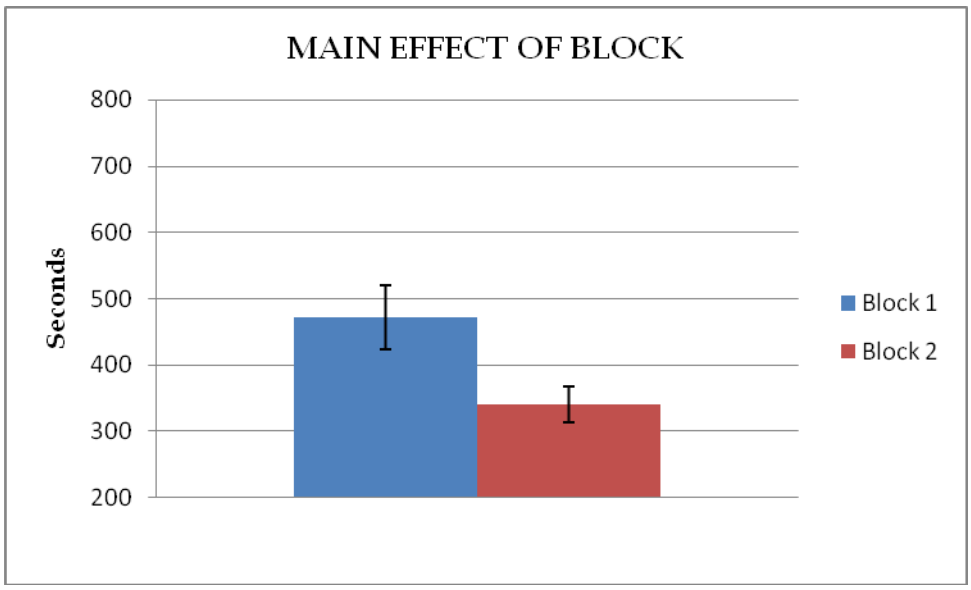


Figure B7 Highly significant main effect of block with regard to total time taken in the Tower of London test (bars represent standard errors). Participants took longer to complete the test in the first block.

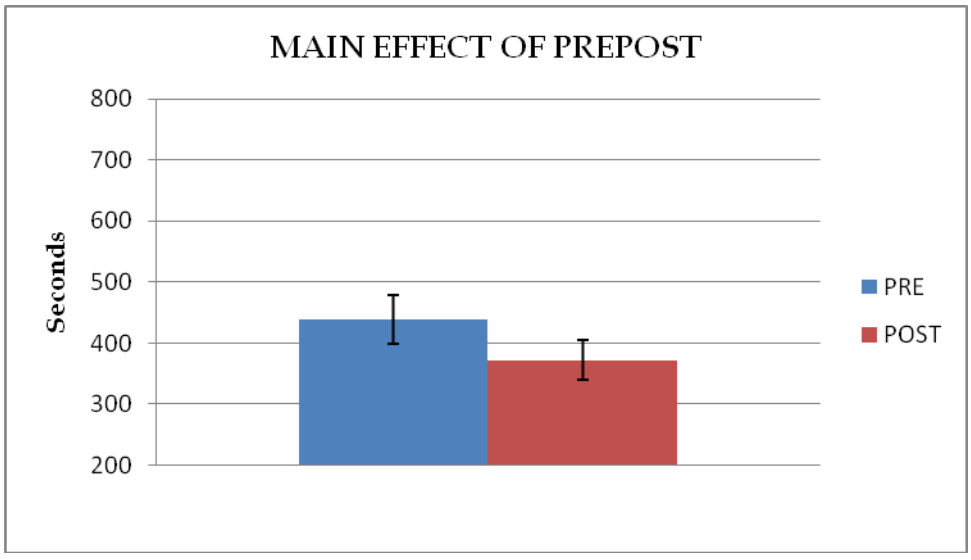


Figure B8 Highly significant main effect of pre-post with regard to total time taken in the Tower of London test (bars represent standard errors)

Interaction Effects

The interaction effect of block by pre-post on total time taken was significant $F(1, 28) = 20.77$, $p = .000$, partial eta squared = .42. In both the blocks total time taken significantly reduced in the post test measures (Figure 3.16). All the other interaction effects were not significant.

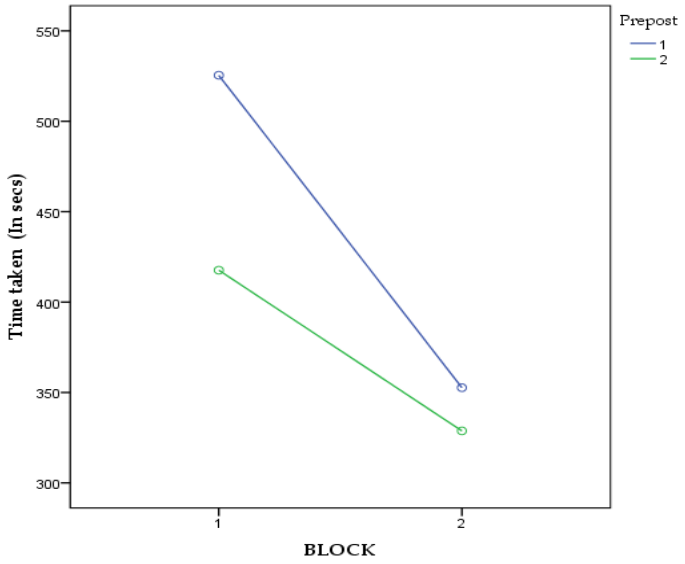


Figure B9 Block by pre-post interactions (total time taken) in the Tower of London test. In both blocks total time taken significantly reduced in post measures.

Summary

Compared with the control participants, schizophrenia patients took significantly longer to complete the Tower of London test. There were no significant difference between patients and controls with regard to number of solved tasks. Compared to the block 1, there is an increase in performance in the block 2 with regard to number of solved tasks and time taken to complete the Tower of London test. Schizophrenia patients solved more tasks in the post measures of the night time condition. Healthy controls solved more tasks on post

test measures of the day time condition. Schizophrenia patient's as well healthy controls showed an improved performance from pre test measure to the post test measures.

B 1.2 Results of the Multivariate Analyses of Variance for the Measures of the Tower of London (Schizophrenia Patients)

A 2 (Group: day before night vs. night before day) x 2 (Block: block 1 vs. block 2) x 2 (Pre-post: pre vs. post) three-way mixed MANOVA with repeated measures on the last two factors was performed using the number of solved tasks and total time taken as dependent variables. The results are presented in Table B5

Table B5 Results of the Multivariate and Univariate Analyses of Variance for the Measures of the Tower of London (Schizophrenia Patients)

Source	F (2, 17)	*p*	η^2
Group (Day Night / Night Day)	**.39**	**.67**	**.04**
Block	**19.98**	**.000*** **	**.72**
Block x Group	**.24**	**.78**	**.02**
Pre-post	**12.54**	**.000*** **	**.59**
Pre-post x Group	**1.09**	**.35**	**.11**
Block x Pre-post	**6.98**	**.00** **	**.45**
Block x Pre-post x Group	**.12**	**.88**	**.01**
Measure: Number of solved tasks	**F (1, 18)**		
Group (Day Night / Night Day)	**.18**	**.67**	**.01**
Block	**7.9**	**.01** **	**.30**
Block x Group	**.16**	**.69**	**.00**
Pre-post	**4.62**	**.04***	**.20**
Pre-post x Group	**2.12**	**.16**	**.10**
Block x pre-post	**.24**	**.62**	**.14**
Block x Pre-post x Group	**.04**	**.83**	**.00**

Measure : Total time taken	F (1, 18)		
Group (Day Night / Night Day)	.62	.43	.03
Block	22.80	.000***	.55
Block x Group	.48	.49	.02
Pre-post	25.12	.000***	.58
Pre-post x Group	.02	.87	.00
Block x Pre-post	11.48	.00**	.39
Block x Pre-post x Group	.06	.80	.00

*** = p < .05; ** = p < .01; *** = p < .001**

Effects of the MANOVA

Main Effects

There was a highly significant main effect of block $F(2, 17) = 19.98$, $p = .000$, partial eta squared = .72. Schizophrenia patients solved more tasks and took significantly less time to complete the Tower of London test. There was also a highly significant main effect of Pre-post $F(2, 17) = 12.54$, $p = .000$, partial eta squared = .59. There is an increase in performance from pre test to post test measures with regard to number of solved tasks and total time taken. The other main effects were not significant.

Interaction Effects

The block by pre-post interaction was significant $F(2, 17) = 6.98$, $p = .00$, partial eta squared = .45. All other interaction effects were not significant.

Further to probe statistically significant effects, univariate results were examined on dependent variables solved tasks and total time taken separately.

Effects of the ANOVA

Number of Solved Tasks

Main Effects

There was a significant main effect of block with regard to number of solved tasks M = 9.77 vs. 11.00, $F(1, 18) = 7.9$, p = .01, partial eta squared = .30. Schizophrenia patients solved more number of tasks in block 2 (Figure B10). There was a marginally significant main effect of Pre-post with regard to number of solved tasks M = 10.00 vs. 10.77 $F(1, 18) = 4.62$, p = .04, partial eta squared = .20. There was a minimal increase in performance from pre to post test measures with regard to number of solved tasks (Figure B11). The other main effects were not significant.

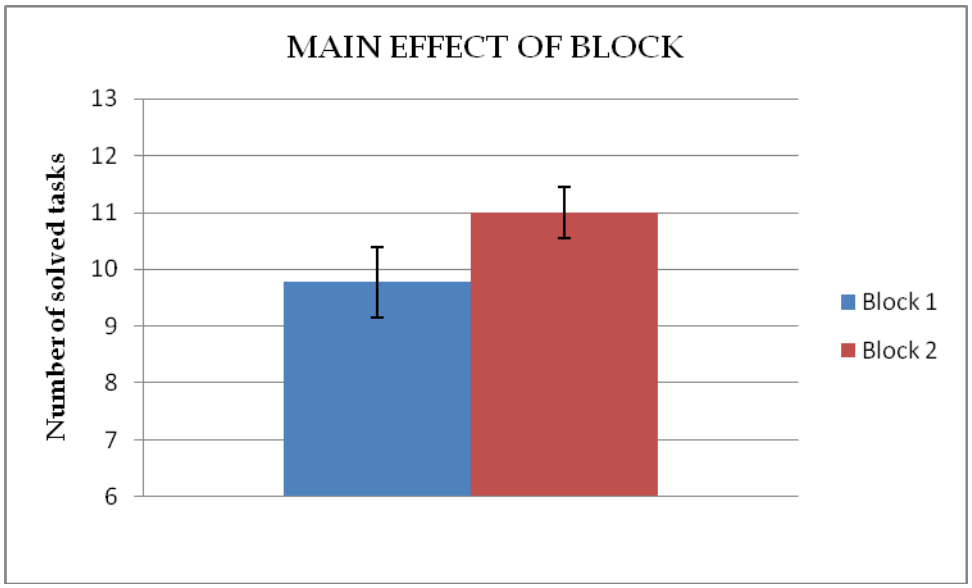


Figure B10 Main effect of block with regard to number of solved tasks in the Tower of London test (bars represent standard errors)

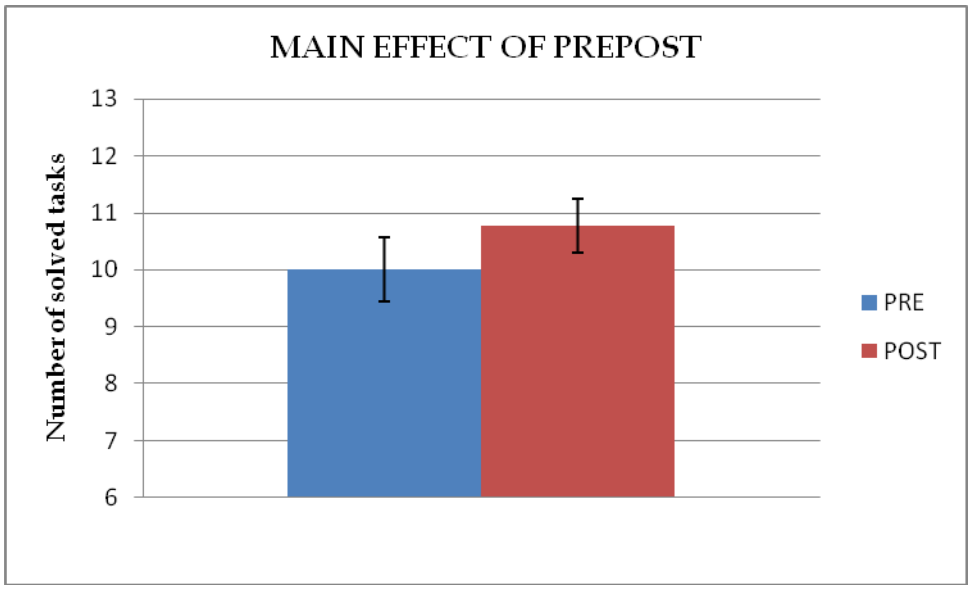


Figure B11 Marginally significant main effect of pre-post with regard to number of solved tasks in the Tower of London test (bars represent standard errors)

Interaction effects

There were no significant interaction effects.

Total Time Taken

Main Effects

There was a highly significant main effect of block with regard to total time taken M = 618.15 vs. 445.92, $F(1, 18) = 22.80$, p = .000, partial eta squared = .55 showing a reduced time taken in block 2 (Figure B12). There was also a highly significant main effect of pre-post with regard to total time taken M = 572 vs. 491, $F(1, 18) = 25.12$, p = .000, partial eta squared = .58 showing a reduced time taken

during post test measures (Figure B13). The other main effects were not significant.

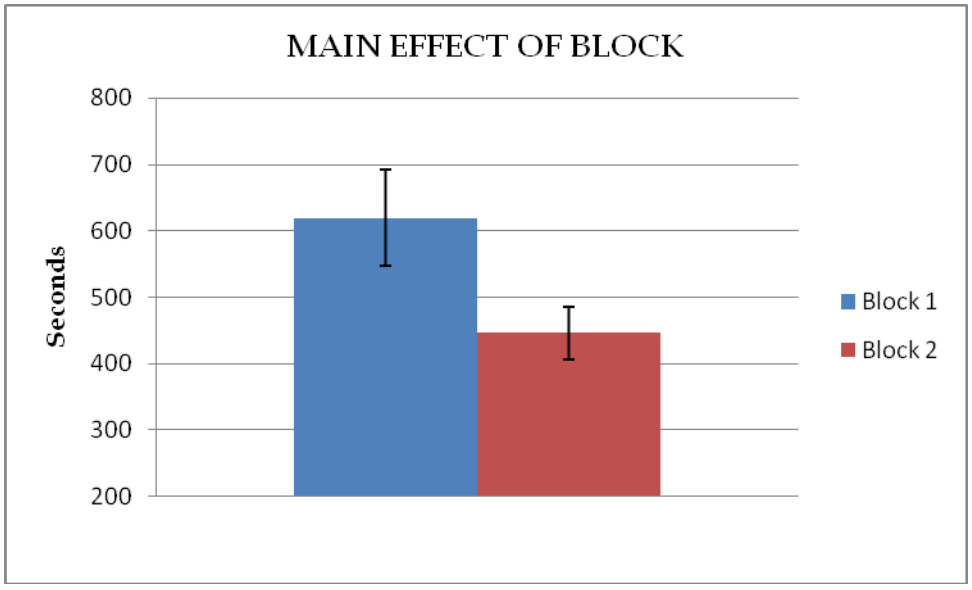


Figure B12 Highly significant main effect of block with regard to total time taken in the Tower of London test (bars represent standard errors)

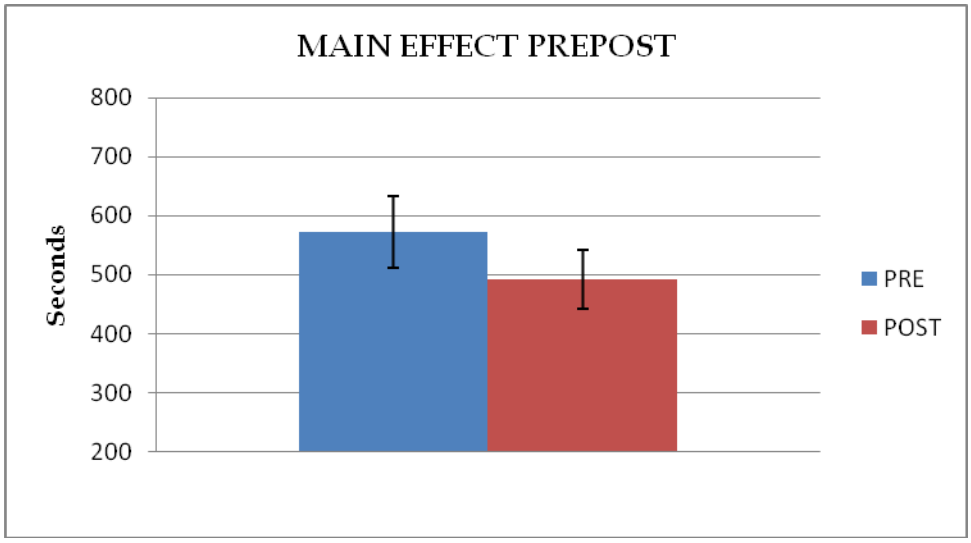


Figure B13 Highly significant main effect of Pre-post with regard to total time taken in the Tower of London test (bars represent standard errors)

Interaction Effects

The interaction effect of block by pre-post with regard to total time taken was significant $F(1, 18) = 11.48$, $p = .00$, partial eta squared = .39. All other interaction effects were not significant.

Summary

There is no significant difference in the Tower of London test performance between day time condition and night time condition. Patients significantly improved in the Block 2 in the Tower of London test. Patients solved more number of tasks and took significantly less time to complete the Tower of London test in Block 2. Pre to post test performance were evident among patient group.

B 1.3 Results of the Multivariate and Univariate Analyses of Variance for the Measures of the Tower of London (Healthy Controls)

A 2 (Group: day before night vs. night before day) x 2 (Block: block 1 vs. block 2) x 2 (Pre-post: pre vs. post) three-way mixed MANOVA with repeated measures on the last two factors was performed using the number of solved tasks and total time taken as dependent variables. The results are presented in Table B7

Table B6 Results of the multivariate and univariate analyses of variance for the measures of the Tower of London (Healthy controls)

Source	F (2, 9)	*p*	η^2
Group (Day Night / Night Day)	.15	.86	.03
Block	37.39	.000***	.89
Block x Group	.62	.57	.12
Pre-post	26.36	.000***	.85
Pre-post x Group	2.56	.13	.36
Block x Pre-post	44.65	.000***	.90
Block x Pre-post x Group	.03	.96	.00
Measure: Number of solved tasks	**F (1, 10)**		
Group (Day Night / Night Day)	.00	1.0	.00
Block	1.0	.33	.09
Block x Group	1.0	.33	.09
Pre-post	4.3	.06	.30
Pre-post x Group	4.32	.06	.30
Block x Pre-post	16.89	.00**	.62
Block x Pre-post x Group	.00	1.0	.00
Measure : Total time taken	**F (1,10)**		
Group (Day Night / Night Day)	.33	.57	.03
Block	64.18	.000***	.86
Block x Group	.02	.86	.00
Pre-post	48.62	.000***	.82
Pre-post x Group	.71	.41	.06
Block x Pre-post	23.65	.00**	.70
Block x Pre-post x Group	.04	.83	.00

* = $p < .05$; ** = $p < .01$; *** = $p < .001$

Effects of the MANOVA

Main Effects

There was a highly significant main effect of block $F(2, 9) = 37.39$, $p = .000$, partial eta squared = .89. This effect shows control participants solved more tasks and significantly less time to complete the Tower of London test during the

second measurement occasion. There was also a highly significant main effect of pre-post $F(2, 9) = 26.36$, $p = .000$, partial eta squared = .85. This effect shows an increased performance during the post test measures with regard to number of solved tasks and total time taken to complete the Tower of London test.

Interaction Effects

The block by pre-post interaction was highly significant $F(2, 9) = 44.65$, $p = .000$, partial eta squared = .90. The other interaction effects were not significant.

Further to probe statistically significant effects, univariate results were examined on dependent variables solved tasks and total time taken separately.

Effects of the ANOVA

Number of Solved Tasks

Main effects

There were no significant main effects with regard to number of solved tasks.

Interaction Effects

The interaction effect of block by pre-post was significant $F(1, 10) = 16.89$, $p = .00$, partial eta squared = .62. The other interaction effects were not significant.

Total Time Taken

Main Effects

There was a highly significant main effect of block on total time taken *M* = 325 vs. 236, *F*(1, 10) = 64.18, *p* = .000, partial eta squared = .86 with controls showing reduced time taken to complete the Tower of London test during second measurement occasion (Figure B14). Nevertheless, the main effect of pre-post on total time taken was also highly significant *M* = 325 vs. 236, *F*(1, 10) = 48.62, *p* = .000, partial eta squared = .82 with control participants showing a reduced time taken during post test measures (Figure B15).

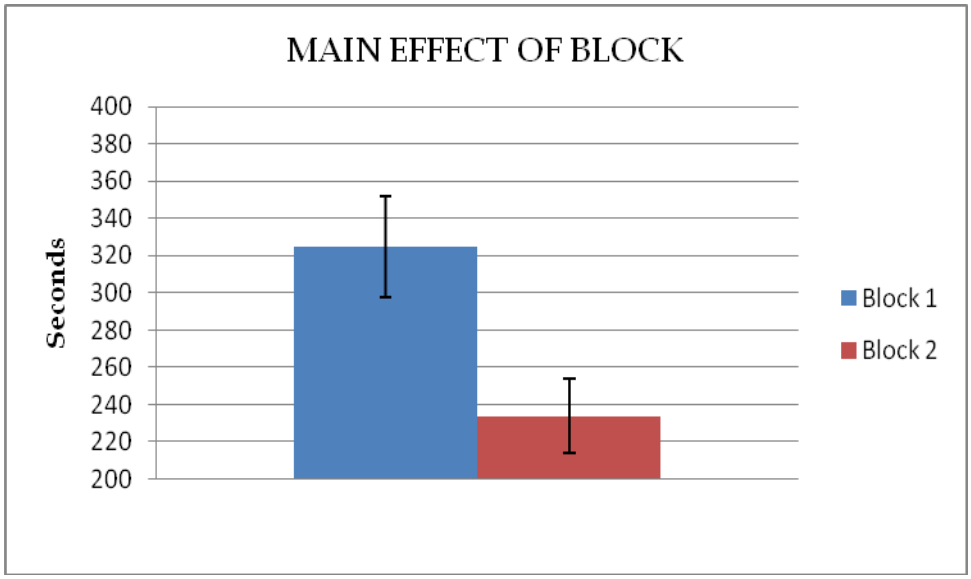


Figure B14 Highly significant main effect of block with regard to total time taken in the Tower of London test (bars represent standard errors)

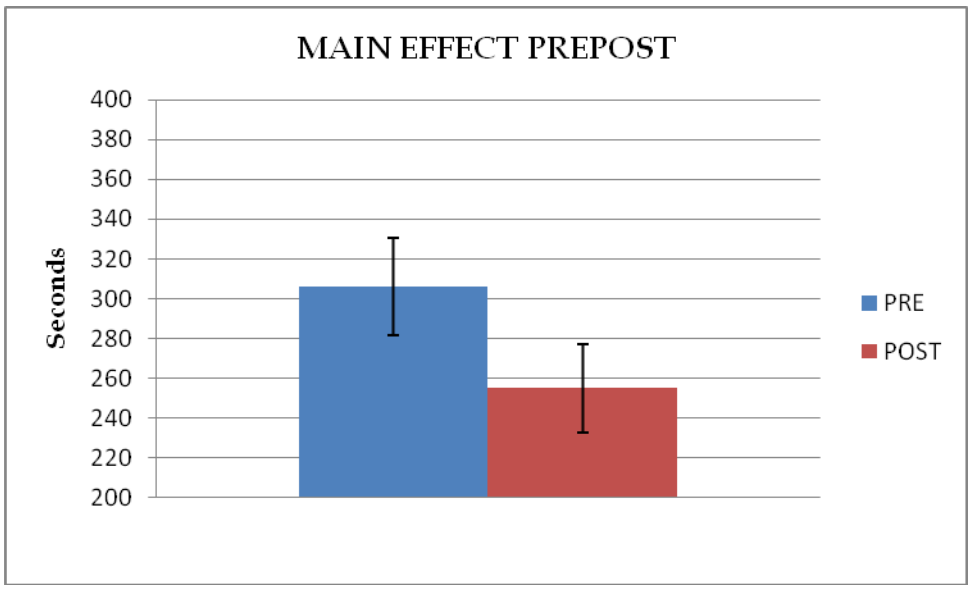


Figure B15 Highly significant Main effect of pre-post with regard to total time taken in the Tower of London test (bars represent standard errors)

Interaction Effects

The interaction effect of block by pre-post on total time taken measure was significant $F(1, 10) = 23.65$, $p = .00$, partial eta squared = .70. All other interaction effects were not significant.

Summary

There was no significant difference in the Tower of London test performance between day time and night time condition. There was no significant difference with regard to the number of solved tasks in the Tower of London test, but there was a significant difference with regard to total time taken to complete the test.

APPENDIX C

POSITIVE and NEGATIVE SYNDROME SCALE for SCHIZOPHRENIA (PANSS)

Instructions: Check one appropriate rating for each item following the specified clinical interview. Refer to the Rating Manual in the Reference Book for item definitions and descriptions of anchoring points.

1= absent 2= minimal 3= mild 4= moderate 5= moderate severe 6= severe 7= extreme

1. POSITIVE SUBSCALE

P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganization	1	2	3	4	5	6	7
P3	Hallucinatory behavior	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspicious/persecution	1	2	3	4	5	6	7
P7	hostility	1	2	3	4	5	6	7

Subtotal: _____

2. NEGATIVE SUBSCALE

N1	Blunted Affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	Passive/apathetic.	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7

Subtotal: _____

3. GENERAL PSYCHOPATHOLOGY SUBSCALE

G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7

G12	Lack of judgment & insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

Subtotal: _____

Total PANSS score (this is the sum of the 3 subtotals): _____