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**Neuropsychiatric Syndromes in the Survivors of Traumatic Brain Injury in  
Oman:  
An examination of disorder of self-neglect**

**Aziz Nasser Hamad Al-Namani**

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## **ABSTRACT**

*Traumatic Brain Injury (TBI) is one of the most challenging public health problems facing the Sultanate of Oman. Each year between 7,500 and 10,000 Omanis (300-400 per 100,000 of the population), suffer a traumatic brain injury (TBI). Despite this extraordinary incidence, little is known about the psychiatric complications of these injuries.*

*The research described in this thesis, measured the prevalence and nature of the psychiatric complications in Omani TBI patients who attended a national Neurosurgical outpatient clinic. The research also identified the predictors of apathy, which is arguably the most common and debilitating complication of TBI, and as a test of both the efficacy of the agent and the follow-up program for brain injured patients, the outcome of Methylphenidate treatment of apathy was determined for the affected patients.*

*A sample of 103 TBI patients was assessed using various psychiatric assessments that included the Hospital Anxiety and Depression Scale (HADS), the Apathy Evaluation Scale (AES), and various cognitive function tests.*

*Eighty-three patients were male and 75% were aged between 15 and 31 years. All, except one patient, were injured in a road traffic accident (RTA). Based on the Glasgow Coma Scale (GCS), fifty-four patients could be categorized as having had a mild brain injury, twelve were moderately injured, and 37 had a severe brain injury. Forty-six were injured within the previous six months, whereas 46 were injured more than a year beforehand.*

*Forty two percent had apathy and 42% were depressed; 40% had anxiety and 35% had fatigue. This is a significantly higher rate than that reported in the general Omani population. However, in the context of any possible cultural differences, it is similar to the rates of psychiatric complications of TBI cited internationally.*

*Among various clinical and demographic factors, the strongest predictor of apathy was the Buschke Selective Reminding Test (BSRT). Apathy in these patients was not associated with either depression or fatigue; that is, all three problems appeared to exist independently. Additionally, the existence and nature of any apathy did not correlate with the severity of the brain injury.*

*The trial of medicine was disrupted by low levels of recruitment, high rates of non-attendance and poor medication compliance, some of which was attributed to side effects. In the small cohort who took Methylphenidate (20 mg ER tablet) for two weeks, an improvement was not only seen in their level of apathy, but also in respect to their depression and fatigue. The improvement of apathy did not reverse following withdrawal of the drug. The improvement of apathy was not explained in this small group by the improvement in depression.*

*Although a plausibility argument can be made for this medicine and some encouraging clinical results were found, the major finding here is that Oman does not have an adequate rehabilitation program for brain-injured patients. This requires urgent address given the incidence of brain injuries cited above and the predominance of young people who are injured.*

*It is possible that the stigma of having a mental illness affected the number of patients who were willing to participate in the study and such attitudes and their vulnerability to modification warrants further study.*

*Conclusion: Psychiatric complications are common in Omani patients with TBI. Early diagnosis and treatment of these complications will improve the quality of life for these patients and their families. There is an urgent need for an effective rehabilitation system for brain-injured patients and in particular, one that ensures adherence to sustained and regular follow-up.*

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## TABLE OF CONTENTS

1. TITLE PAGE	
2. ABSTRACT	III
3. ACKNOWLEDGEMENT	V
4. TABLE OF CONTENTS	VII
5. LIST OF TABLES AND FIGURES	IX
6. SELECTED ABBREVIATION AND ACRONYMS	XI
7. CHAPTER ONE: TRAUMATIC BRAIN INJURY	
a. Introduction	1
b. Epidemiology of Traumatic Brain Injury	7
c. Causes of Traumatic Brain Injury	11
d. Conclusion	17
8. CHAPTER TWO: COGNITIVE, EMOTIONAL AND BEHAVIOURAL IMPAIRMENTS IN PARTICIPANTS WHO HAVE SUSTAINED TRAUMATIC BRAIN INJURY	
a. Introduction	19
b. Psychiatric syndromes in traumatic brain injury	19
c. Factors affecting the presentation of psychiatric complications of TBI	30
d. Studies of psychiatric complications of TBI in Oman	37
e. Aims of the project	39
f. Hypothesis	39
g. Methodology	39
h. Results	44
i. Discussion	54
j. Conclusion	66



9. CHAPTER THREE: APATHY FOLLOWING TRAUMATIC BRAIN INJURY	
a. Introduction	67
b. Aim of the project	79
c. Hypothesis	79
d. Methodology	80
e. Results	81
f. Discussion	95
10. CHAPTER FOUR: THE INEFFECTIVENESS OF TBI REHABILITATION SERVICES IN OMAN	
a. Introduction	101
b. Hypothesis	107
c. Methodology	108
d. Results	113
e. Discussion	120
f. Conclusion	120
11. CHAPTER FIVE: INTEGRATION AND GENERAL DISCUSSION	
a. Theoretical background	133
b. The status of TBI rehabilitation program in Oman	135
c. The aims	137
d. The hypothesis	137
e. The studies	138
f. On conceptual and methodological issues	153
g. Conclusion	155
12. INDIVIDUAL CASE REPORTS	156
13. ASSESSMENT MEASURES	186
14. GRAPHS SHOW DISTRIBUTION OF THE VARIABLES BEFORE AND AFTER TRANSFORMATION	211
15. LIST OF REFERENCES	232

## **LIST OF TABLES AND FIGURES**

- Table 1.1: A Table Shows the Incidence of TBI in Different Countries
- Table 1.2: A Table Shows The Economic Burden of Different Types of Injury Relative To That of All Injuries.
- Table 1.3: A Table Shows The Percentage of Traumatic Brain Injuries That Is Caused By Road Traffic Accidents In Different Countries.
- Table 1.4: A Table Shows The Incidence of Deaths Due To Road Traffic Accidents In Different Countries In 2008.
- Table 1.5: A Table Shows Worldwide Causes of Death and Disability between 1998 and 2020
- Table 2.1: A Table Shows The Prevalence of Psychiatric Complications in Traumatic Brain Injury Patients.
- Table 2.2: A Table Shows the Age at the Time of the Injury for the Studied Group In Comparison With the Overall Omani Population
- Table 2.3: A Table Shows the Educational Level of 103 Omani TBI Patients
- Table 2.4: A Table Shows Past Medical and Psychiatric History of the Participants, (N= 103 Patients Who Had Sustained Traumatic Brain Injury)
- Table 2.5: A Table Shows the Number of Participants on Medication as Treatment or Prophylaxis in a Cohort of 103 TBI Patients
- Table 2.6: A Table Shows the Glasgow Coma Scale (GCS) Scores in 103 TBI Patients
- Table 2.7: A Table Shows the Period of Post-Traumatic Amnesia in 93 TBI Patients
- Table 2.8: A Table Shows the Estimated Pre-Morbid IQ in 103 TBI Patients
- Table 2.9: A Table Shows the Cognitive Performance of TBI Patients In Comparison To Healthy Normal Subjects
- Table 2.10: A Table Shows the Statistical Analysis of the Cognitive Performance Data Cited In Table 2.9
- Table 2.11: A Table Shows the Results of Self-Reporting Questionnaire of 103 TBI Patients
- Table 2.12: A Table Shows the Mood Disorders Identified in the Current Study In Contrast To That Reported In Other Published Studies
- Table 3.1: A Table Shows the Prevalence of Apathy and Depression in Various Neurological Diseases

- Table 3.2: A Table Shows the Prevalence of Apathy in Various Neurological Diseases
- Table 3.3: A Table Shows the Clinical and Demographic Characteristics of 103 Omani TBI Patients
- Table 3.4: A Table Shows the Correlations of Apathy Evaluation Scale With Several Demographics and Neuropsychiatric Variables
- Table 3.5: A Table Shows The First Seven Factors Accounted For Much of The Variability In The AES. Rotated Component Matrix (A)
- Table 3.6: A Table Shows the Total Amount of Variances Explained By the First Fourteen Factors in the Principle Component Analysis
- Table 3.7: A Table Shows The Result of Regression Analysis.
- Table 3.8: A Table of Regression Analysis Shows The Percentage of The Variability In AES Explained By The Model. ANOVA (B).
- Table 3.9: A Table Shows Model Summary (B) of Predictors of AES
- Table 4.1: A Table of the Demographic and Clinical characteristics of the study cohort (n = 43)
- Table 4.2: A Table Shows The Demographic and Clinical Data of Eleven TBI Patients Treated With Methylphenidate.
- Table 4.3: A table shows Apathy Evaluation Scale scores in eleven TBI patients treated with Methylphenidate

### **LIST OF FIGURES**

- Figure 1.1: A Graph Showing the Increase Rate of Injuries with Increase Population and Registered Vehicles
- Figure 3.1: A Graph Shows Glasgow Coma Scale, Disability Rating Scale, and Posttraumatic Amnesia Before and After Transformation
- Figure 4.1: A Flowchart Showing The Drop Out of Patients Through Different Stages of The Study
- Figure 4.2: A Diagram Shows Stages of Helping Victims of Road Traffic Accidents
- Figure 4.3: A Diagram Showing Three Hypothetical Models of Health Care and Its Direct Bearing On Mortality and Disability

## **SELECTED ABBREVIATION AND ACRONYMS**

AES	Apathy Evaluation Scale
BL1	Baseline 1
BL2	Baseline 2
BSRT	Buschke Selective Reminding Test
CT	Computerized Tomography
DLPFC	Dorsolateral Prefrontal Cortex
FAS	Fatigue Assessment Scale
GCS	Glasgow Coma Scale
HADS	Hospital Anxiety and Depression Scale
LOC	loss of consciousness
MRI	Magnetic Resonance Imaging
NPI	Neuropsychiatric inventory
PCS	Post-concussion syndrome
PD	Parkinson's disease
POST1	Post-withdrawal 1
POST2	Post-withdrawal 2
PTA	posttraumatic amnesia
SPM	Standard Progressive Matrices
SAH	Subarachnoid haemorrhage
SPECT	Single Positron Emission Computerized Tomography
TBI	Traumatic brain injury
RTA	Road Traffic Accident
WCST	Wisconsin Card Sorting Task
ROP	Royal Oman Police

# **CHAPTER ONE: TRAUMATIC BRAIN INJURY (TBI)**

## **1.1 INTRODUCTION**

Neuropsychiatric complications are common in traumatic brain injury (TBI) patients. Studies have shown that more than 50% of TBI patients develop a psychiatric disorder and up to 44% of patients suffer from more than one psychiatric disorder (Hibbard MR, 1998). However, most of these studies have been conducted on western populations. There are very few studies in developing countries such as Oman.

The present thesis examines the neuropsychiatric complications of TBI in the Oman population.

Since this study was conducted in the Sultanate of Oman and because the health care system in the country may not be familiar to readers, the first part of this thesis gives background information about the country and the health care delivery system. This is followed by a brief overview of TBI including definitions, proposed mechanisms, causes, risk factors, classification, and mechanisms of TBI relevant to neurobehavioral impairment.

### **1.1.1 Healthcare in Oman**

The Sultanate of Oman is located in the extreme south- east corner of the Arabian Peninsula. It is bordered on the north by the United Arab Emirates (U.A.E.), on the northwest by Saudi Arabia, and on the southwest by the Republic of Yemen. Oman has a total area of approximately 309,500 square kilometres and a coastline of 3,165 km. The Sultanate of Oman has a population of approximately 2.3 million (Al-Naamani & Al-Adawi, 2007).

Oman has had a turbulent past with internal conflict between tribes throughout the 19<sup>th</sup> and early 20<sup>th</sup> centuries. This caused the modernisation of the country to be delayed compared to neighbouring countries.

It was not until relative peace was established by Sultan Said bin Taimur, father of the current Sultan, and the discovery of oil in the 1960s, that Oman began on the road towards modernization (Hill, Muyeed, & Al-Lawati, 2000).

However, since the ascent of His Majesty Sultan Qaboos Bin Said Al-Said to the throne in 1970, Oman has gone through a dramatic socioeconomic transformation. This was only possible because of the wise leadership of His Majesty in seeking peaceful solutions to the internal conflicts, developing the country's infrastructure, and instituting human resource development.

Omani economic indicators have increased significantly in the past three decades. The gross domestic product (GDP) rose from a mere RO 104 million in 1970 to RO 23,185 million in 2008 and the corresponding per capita income of RO 158 rose to RO 7,790 (1 Omani riyal = US\$ 2.597) (Ministry of Health, 2007; Ministry Of National Economy, 2010). Total government expenditure in 2007 was RO 5,880 million of which RO 235 million was spent by the Ministry of Health (4% of Government expenditure) (Ministry Of National Economy, 2010).

Ministry of health expenditure increased from 172.0 million in 2003 to 329.9 million in 2009 (Ministry of Health, 2010). Oman spent 2.4% of its GDP on health in 2008. (WHO, 2010). This compared to 3.6% spent in Bahrain, 2% in Kuwait, 3.3% in Qatar, 3.3% in Saudi Arabia and 2.4% in United Arab Emirates (WHO, 2010). The Government has made a strong commitment to the social sectors with government expenditure increasing steadily between 1981 and 2001. The health sector budget expenditure doubled from 2.6% in 1981 to 5.3% of GDP in 2001 (Ministry of National Economy, 2006).

Health services in Oman are mainly provided by the Ministry of Health; in 2007, this was largely by way of 49 hospitals (4,544 beds). Other five hospitals (601 beds) were provided by the Ministry of Defence, the Royal Oman Police, Petroleum Development of Oman, and Sultan Qaboos University Hospital.

Although the private sector has a smaller role, the government is interested in stimulating its growth. Ministry of Health data showed that there were five private hospitals (178 beds) in 2007 and this is expected to rapidly increase in the following years (Ministry of Health, 2007).

The number of medical staff has also increased in the recent years. The ratio of physicians per 10,000 populations rose from about 0.2 in 1970 to 17.9 in 2007. However, the ratio of general practitioners to specialists has been stable, around 2.0, for the past five years. The ratio of other health care personnel has also been continuously increasing and currently it is 37.9 per 10,000 for nurses, 1.9 per 10,000 population for dentists and 3.3 per 10,000 for pharmacists (Ministry of Health, 2007).

Oman has universal free health care for all its citizens and when it was subjected to international scrutiny, the World Health Organization ranked Oman as the most efficient health care system in the world in terms of outcomes (A Al-Mandhari, Al-Adawi, Al-Zakwani, Al-Shafae, & Eloul, 2008).

Despite these improvements in various health indicators, the current focus is still largely geared towards communicable diseases and malnutrition. In the midst of epidemics of the communicable diseases, there is also a 'silent epidemic' of non-communicable diseases, often precipitated and exacerbated by an individual's behaviour and lifestyle. There is a range of disorders that are often collectively referred to as stress-induced illnesses, which seem to stem from the way people respond to adverse environmental factors. There are also aspects of human behaviour, such as smoking and reckless driving, which can result in serious injury and often fatalities. As the control of communicable diseases improves, the relative health burden due to non-communicable diseases is likely to increase. Therefore, non-communicable "illnesses" such as the sequel of RTAs are likely to contribute disproportionately to the burden of health care in Oman.

It has been estimated that between 300 and 400 per 100,000 population in Oman incur a TBI each year (Al-Naamani & Al-Adawi, 2007). Without long-term care and rehabilitation, these patients left with potentially reversible, but debilitating neuropsychiatric complications. Sadly, most of these victims are young and the most productive members of the society. Therefore, preventing TBI and improving health care delivered to these patients is extremely important for the social and economic development of the country.

### **1.1.2 Definition of Traumatic Brain Injury (TBI)**

Traumatic Brain Injury has been variously defined, depending on the inclusion criteria. Furthermore, TBI is often used synonymously with terms such as “head injury”, “acquired brain injury”, “closed head injury”, “brain injury”, and “concussion” (Williams, 1997). These have resulted in several definitions of TBI.

Conventionally, TBI refers to externally induced physiological disruption of the brain function that can lead to tissue loss or cell death (Fabiano & Daugherty, 1998). These physiological disruptions can be permanent or temporal and might cause psychological or physical disability (Wright, 2005). Morton et al. define TBI as “a sudden and very serious physical damage to the face, skull, scalp, dura or brain caused by a mechanical force that can produce devastating multiple psychosocial, cognitive and physical disabilities” (M. Morton & Wehman, 1995).

The National Head Injury Foundation of The United States of America defines TBI as “an insult to the brain caused by external physical force, that may produce a diminished or altered state of consciousness, which results in impairment of cognitive abilities or physical functioning” (Hamann, 2003).

The insult in TBI is caused by an external physical force that involves the brain being struck in contrast to degenerative or congenital processes (Stratton & Gregory, 1994). As a result of this external force, head injury can either be a closed or a penetrating head injury depending on whether or not the dura matter is breached (Rao & Lyketsos, 2000).

An acquired brain injury is another related term, which is sometimes used interchangeably with TBI. An acquired brain injury is one that occurs after birth and is not hereditary, congenital, or degenerative. The term was adopted by the Brain Injury Association of America In 1997 in order to include internal insults to the brain (e.g. stroke, meningitis, and anoxia) and not only those that were produced by external trauma (Marion & Spiegel, 2000).



### **1.1.3 Classifications of Traumatic Brain Injury (TBI)**

There are four main ways of classifying TBI. The first and the most common classification is based on the nature of the physical trauma and whether the TBI is open or closed. About 90% of all TBI are closed head injuries in which the skull remains intact and the brain is not penetrated (Hammeke, 2003).

The second classification categorises brain injury according to the severity. This depends on the examination of the patient immediately after TBI. In this classification, three main parameters are important. These are the score on the Glasgow Coma Scale (GCS), the duration of loss of consciousness (LOC), and the duration of post-traumatic amnesia (PTA) (M. Kraus, 1999).

The GCS is the most widely used scoring system used in quantifying the level of consciousness following a TBI (Chan, 2010). The scale based on eye opening, verbal response, and the best motor response. The three values are considered both separately and as a sum. The lowest possible GCS is 3 (deep coma or death), while the highest is 15 (a fully awake person) (Teasdale & Jennett, 1974). The GCS was initially developed to measure the depth of coma, but it has been commonly used to assess the severity of TBI (Anna Sundström, 2006).

PTA is a confusion state that occurs immediately after brain injury where the injured patient is not able to remember events occurred after the incident. During this state, the patient will be disoriented to time, place, and person and new events cannot be stored in the memory. Following a suggestion by Rees (Rees, 2003), PTA duration is classified into: No PTA, one day or less, more than one day and less than one week, one to two weeks, two to four weeks, more than four weeks.

Combining GCS, LOC, and PTA, TBI is classified as mild, when the patient has a GCS of 13–15, a LOC of less than 30 minutes, and/or PTA of less than one hour. Patients with moderate TBI have a GCS of 9–12, a LOC of 1–24 hours, and/or PTA of 30 minutes to 24 hours. A GCS of eight or less, a LOC of more 24 hours, and/or PTA of more than one day is classified as severe TBI (Rao & Lyketsos, 2000).

This classification has been found to be useful in predicting the prognosis of moderate and severe TBI, but is not as good in predicting the prognosis of the milder forms of TBI (M. Kraus, 1999). Researchers often use combinations of the above parameters to classify the severity of TBI. Some use only GCS (M. Kraus, 1999), others use LOC and/or PTA (Annegers, Grabow, Kurland, & Laws, 1980).

The third classification depends on neuroimaging findings where the brain injury is classified as focal contusion, hypoxic-ischemic injury, and subdural or epidural hematoma (Asikainen, 2001). In focal cortical contusions, the radiological finding is localized haemorrhage and/or oedema involving the cortical and adjacent areas. In the case of hypoxic-ischemic injuries, small petechial haemorrhages are often seen in the white matter (Bigler, 2010). Subdural and epidural hematomas classically appear in radiological examination as crescent-shaped and lenticular-shaped opacities respectively (Parikh, Koch, & Narayan, 2007).

The fourth classification is based on the time course where a demarcation is made between primary injury, which develops at the time of the impact, and secondary injury, which is caused by subsequent complications.

#### **1.1.4. Mechanisms of Head Injury**

A TBI is caused by a physical force hit on the skull. This force is then transmitted to the brain where it can cause either diffuse or focal brain injury.

Focal brain injury is most common in orbital-frontal and temporal areas of the brain because of the skull's bony protuberances in these areas (Vaishnavi, Rao, & Fann, 2009). This in contrast to diffuse brain injury, which often involves most parts of the brain.

Diffuse brain injury is caused by a relatively rapid movement of the brain within the skull, which causes stretching and tearing of axons (Kamali Nejad & Melissa, 2010). This axonal damage can result in disturbances that range from brief physiological changes to wide spread axonal damage, which is called diffuse axonal injury (DAI) (Brissos & Dias, 2005).

Diffuse axonal injury is “ thought to be responsible for the degree of impairment of consciousness in the acute stage and responsible for the much of the disability in later stages for all types of injury” (Chang & Jang, 2010).

However, the injury to the brain often continues even after the initial impact. This is often called secondary damage and occurs because of several mechanisms such as ischemia, metabolic abnormalities, release of excitatory amino acids, oxidative free-radical production, and disruption of neurotransmitters such as serotonin (Brissos & Dias, 2005).

## **1.2 EPIDEMIOLOGY OF TBI**

Inconsistencies in the definition and classification of TBI, along with discrepancies in data collection, have made the epidemiology of TBI both confusing and difficult to study.

However, several clinical and population-based studies designed to determine the prevalence of brain injury cases, have been undertaken in different parts of the world. These studies have shown a wide variation in the prevalence of TBI across the world, depending on the type of the study, causes of TBI, and the age demographics of that country. A review of these detailed studies is summarised in Table 1.1.

**Table 1.1: A table shows the incidence of TBI in different countries**

<b>Place and reference</b>	<b>Year of the study</b>	<b>Head injury / 100,000</b>
USA (Koskinen & Alaranta, 2008)	2006	403
Australia (Helps, Henley, & Harrison, 2008)	1999-2004	107
UK (Das-Gupta & Turner-Stokes, 2002)	2001	300
South Africa (D. S. Brown & Nell, 1991; Joosub, 2009)	2007	200-316
Germany (Rickels, von Wild, & Wenzlaff, 2010)	2001	332
<b>Oman (Al-Adawi S, 2004)</b>	<b>2002</b>	<b>300-400</b>

Nevertheless, studies have shown that TBI is a major cause of death and disability worldwide (Alves OL, 2001). Experts in the field of TBI have estimated that each year at least 10 million TBI events, serious enough to result in death or hospitalizations, occur worldwide (Levack, Kayes, & Fadyl, 2010; Murray & Lopez, 1996).

Furthermore, it is estimated that there are more than 57 million people worldwide who are living with the sequel of TBI (Murray & Lopez, 1996). Worryingly, many researchers believe these figures to be underestimated because of difficulties in data collection, especially in regard to inclusion and exclusion criteria. In respect to data collection for TBI, many patients with mild TBI may not present to the hospital, and the ones who do, may be discharged from the emergency department without adequate documentation (J. Kraus & McArthur, 1996). Furthermore, severe TBI associated with death at the scene of the accident, or during transport to a hospital, may not be accounted for in data collection processes. Similarly, a TBI may be overlooked in people where the focus of treatment is for other major trauma, such as chest or orthopaedic.

However, there have been some improvements in the outcome of TBI. Recent epidemiological studies have shown that the mortality rate from TBI has decreased (Georgoff, Meghan, Mirza, & Stein, 2010; Zink, 2001). This is thought to be a result of the improvement in road safety, acute care management and emergency services (Marshall, 2000).

Despite any such improvement, the mortality in TBI remains high with an overall mortality rate of 15 to 30 per 100,000 population (McAllister, 1992). It is estimated that 5–10% of victims of traumatic brain injury die, and that approximately 40% of the deaths related to general injury are associated with TBI (Adekoya, Thurman, White, & Webb, 2002; Frankowski, Annegers, & Whitman, 1985). However, the concurrent decline in TBI mortality and an increase in TBI prevalence has inevitably resulted in a significant increase in the number of people living with various complications of TBI (Chestnut, 1999).

In addition to the physical and psychiatric complications of TBI, the financial cost of TBI is also substantial. The annual lifetime costs of TBI in United States was estimated at \$US 60 billion for the year 2000 (Finkelstein, Corso, & Miller, 2006). This amount includes only medical costs and productivity losses for the patients and does not include the value for the poor quality of life and productivity losses for parents and caregivers.

Other studies have shown that TBI causes a relatively greater productivity loss than other injuries (see Table 1.2).

**Table 1.2: A table shows the economic burden of different types of injury relative to that of all injuries.**

<b>Injury</b>	<b>Cost percentage (%)</b>
Traumatic Brain Injury	15.7
Spinal cord injury	1.1
Vertebral column injury	5.7
System-Wide	14.6
Other/Unspecified	13.9
Lower Extremity	13.6
Upper Extremity	15.6
Torso	11.1
Other Head/Neck	8.8

*Source:* Finkelstein, E., Corso, P., & Miller, T. (2006). *The incidence and economic burden of injuries in the United States:* Oxford University Press, USA.

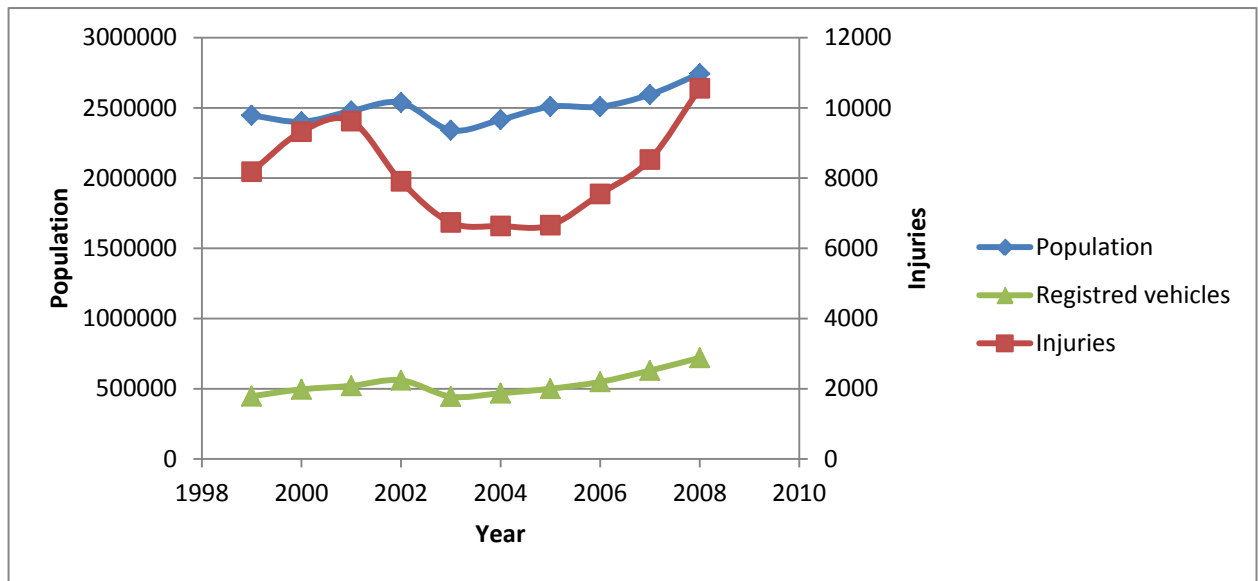
Moreover, TBI patients also suffer from challenging social and economic consequences of their injuries. Studies have found that, on average, 15 years post injury, 75% of head injury patients are not working and 66% need assistance with their activities of daily living (Dawson & Chipman, 1995). However, this particular study was a population-based study that did not include information on the details of the TBI such as the nature and the severity of the injury. Nevertheless, the study clearly indicates the magnitude of the socioeconomic impact of TBI.

Studies examining the functional prognosis of victims of TBI are essential in planning future healthcare in Oman (Al-Naamani & Al-Adawi, 2007; M. Shah, S. Al-Adawi, A. Dorvlo, & D. Burke, 2004).

### **1.2.1. Traumatic Brain Injury (TBI) In Oman**

As reviewed earlier, traumatic brain injuries are the leading cause of death and disability in individuals who are the most productive in their respective society, namely, those who are under 45 years of age (Flaada et al., 2007). If one considers that this age group is at risk, then the situation in Oman is likely to be particularly problematic as almost 90% of the Omani population is within this age group (Economy, 2004). This means that TBI is predictably the leading cause of death and disability for almost 90% of the Omani population. Studies have shown that each year between 300 and 400 people per 100,000 of the Omani population suffer a TBI (Ansari, Akhdar, Mandoorah, & Moutaery, 2000). This situation is predicted to worsen with an increasing number of both registered vehicles and population as shown in figure 1.1.

**Figure 1.1: A graph showing the increase rate of injuries with increase population and registered vehicles**



### 1.2.2 CAUSES OF TRAUMATIC BRAIN INJURY

Several causes of TBI have been identified. These include gunshot wounds, workplace injuries, child abuse, and domestic violence. Other causes of TBI are falls, which cause about 21% of all TBI and violence (12%) (McAllister, 1992). In addition to falls and assaults, blasts have been increasingly recognized as a leading cause of TBI among active duty military personnel in war zones (Scott, Vanderploeg, Belanger, & Scholten, 2005).

Sports and recreational activities are also a major cause of TBI and account for 10% of all TBI (McAllister, 1992). However, it is believed that these injuries are severely underestimated as many people who have a TBI from a recreational activity do not attend medical facilities and hence are not counted.

However, studies have shown that RTAs are the main cause of TBI in many countries and this includes Oman. It has been estimated that RTAs are responsible for 42.1% to 95% of all TBI in the country (Al-Naamani & Al-Adawi, 2007) (see Table 1.3).

**Table 1.3: A Table Shows the Percentage of Traumatic Brain Injuries That Is Caused By Road Traffic Accidents In Different Countries.**

<b>Country (Reference)</b>	<b>Road traffic accident (%)</b>
USA (Kalsbeek et al. 1980)	49
Australia (Selecki et al. 1981)	53
<b>Oman (Al-Adawi et al. 2004)</b>	<b>76</b>
Scotland (Jennet 1996)	24
Taiwan (Lee et el. 1990)	90

### **1.2.3. Road Traffic Accident as the main cause of TBI.**

Though the exact number will never be known, RTAs cause approximately 140,000 injuries and 3,000 deaths worldwide every day (Dahl, 2004).

Unfortunately, road traffic fatalities are predicted to increase by 86% between now and the year 2020 in the Middle East and North African countries (Kopits & Cropper, 2005). RTAs are responsible for 25 per cent of all deaths due to injuries, which is the second leading cause of death among adults aged 15 to 44 years old (Dahl, 2004).

As cited, this is particularly significant for Oman given that the Omani population has a large youth base; about 65% of Omani's are less than 20 years old (Sulaiman, Al-Riyami, Farid, & Ebrahim, 2001).

Sadly, the situation of RTA in Oman is getting worse. The mortality rate from RTAs in Oman was 28 per 100,000 population in 2005, which far exceeded the global average of 19 per 100,000 (Police., 2006) (table 1.4).



This has increased to an extraordinary level of 30 deaths per 100,000 populations in 2008, one of the highest in the world (Police, 2008). Moreover, recent statistics from the Royal Oman Police (ROP) showed that 140 individuals died between 01 January and 13 February 2009 due to RTA (Police, 2009). This is almost three deaths per day, and is a 16% increase over the same period in 2008, which was itself record breaking. As disturbing as these data are, the real toll is even higher as the ROP statistics do not include those who died of their injuries later in hospitals.

**Table 1.4: A Table Shows the Incidence of Deaths Due To Road Traffic Accidents In Different Countries In 2008.**

<b>Road Deaths 2008 (per 100,000 population)</b>	
UK	5.4
US	13
Global Average	19
<b>Oman</b>	<b>30</b>

Source: Salimandsalimah. (2008). *Road crashes*. Salimandsalimah. Retrieved on November 2008, 2008, from the World Wide Web: <http://www.salimandsalimah.org/NewsletterNovember2008.htm>

The magnitude of the problem has stimulated the authorities in Oman, along with other countries in the region, to present their concerns about road safety to the United Nations (Organization, 2004). This resulted in the United Nations General Assembly adopting a special resolution (No 58/9), and prompted the World Health Organization to declare 2004 as the “year of road safety.” In support of this initiative, the Sultan of Oman made the following remarks:

*“ In taking these two important steps, both organizations started the world battle against trauma caused by road accidents, and we hope that all sectors of our societies will cooperate to achieve this noble humanitarian objective “.*

**Qaboos bin Said, Sultan of Oman**

Although mortality is a key indicator of the size of any health problem, including injury, it is important that non-fatal outcomes are measured and included so that the burden of harm arising from RTAs can be accurately determined. For each mortality from RTA, there are dozens of survivors who are left with short-term or permanent disabilities that variously result in ongoing restrictions on their physical functioning, psychosocial well-being, and quality of life.

As cited above, the impact of RTA on individuals and societies is predicted to worsen globally. RTAs were the eighth leading cause of disability-adjusted life years' loss (DALYs) in 2000, and are predicted to become the third leading cause of DALYs by 2020 (Murray & Lopez, 1996; WHO., 2008). Sadly, this will outstrip the diseases, which draw more attention, such as communicable diseases and malnutrition (see Table 1.5).

**Table 1.5: A Table Shows Worldwide Causes of Death and Disability between 1998 and 2020**

<b>1998 - Disease or Injury</b>	<b>2020 - Disease or Injury</b>
Lower respiratory infections	Ischaemic heart disease
HIV/AIDS	Unipolar major depression
Perinatal compromising conditions	<b>Road traffic injuries</b>
Diarrhoeal diseases	Cerebrovascular disease
Unipolar major depression	Chronic obstructive pulmonary disease
Ischaemic heart disease	Low respiratory infections
Cerebrovascular disease	Tuberculosis
Malaria	War
<b>Road traffic injuries</b>	Diarrhoeal diseases
Chronic obstructive pulmonary disease	HIV/AIDS

Source: Murray, C., & Lopez, A. (1996). Global health statistics. Global burden of disease and injury series. Vol. 2. Geneva. *World Health Organization*.

In addition to the huge human and social cost of these injuries, the related economic cost is substantial. It has been estimated that the annual cost of these accidents to the Omani health system is at least R.O. 3.3 million, or 3% of the health budget (Al-Naamani & Al-Adawi, 2007). If the cost of the services and support these patients need in the local community is added, then the figure is much higher. However, no estimate of the quantum is available. Furthermore, this cost is only for moderate and severe injuries, which usually require acute in-patient medical care.

There is also the yet-to-be calculated expenditure of “doctor shopping” where distressed families venture abroad in a desperate attempt to find a “cure” for their injured loved ones.

### **1.3. Studies on Psychiatric complications of TBI**

Unfortunately and worldwide, most research and rehabilitation services have concentrated on the physical complications of TBI (Thomsen, 1987). The consequent behavioural, cognitive, and emotional dysfunction has been largely overlooked.

This inattention to the latter has occurred despite studies showing that, in the long term, neuropsychiatric complications of TBI are the primary determinant of the quality of life for both patients and their relatives. These complications are relatively more persistent, have a greater effect on the burden experienced by the relatives, and have more influence on vocational recovery (Conoley & Sheridan, 2005; Lezak, 1978). According to Brooks (Brooks, 1993), the most important factors predicting the post-rehabilitation adjustment, in addition to the severity of the brain damage, are psychosocial factors, such as the extent to which the patient has insight into their difficulties, the nature of any emotional and behavioural disturbance, and the nature and response of the family. Furthermore, studies have shown that almost 50% of individuals who have sustained a severe TBI have psychiatric complications, while only 10% of them have a physical disability (Glover, 2003).

Studies have shown that psychological complications of TBI are responsible for at least as much disability as physical symptoms (Lishman, 1998). Treatment of these complications should lead to greater ability, improved quality of life and minimise any negative societal impact (Lishman, 1998).

As cited above, recent improvement in acute care management has resulted in a decreased number of patients who die from RTAs and TBIs (Georgoff et al., 2010; Gualtieri & Evans, 1988). Therefore, in addition to neurological disabilities, it is expected to see an increasing number of patients who are suffering from emotional, cognitive and behavioural complications of TBI, (McAllister, 1992).

Unfortunately, the improvement in acute care management has not been accompanied by a progress in the psychological services provided to the survivors of TBI. These services have a scant attention in health budget priorities. As a result, most TBI patients worldwide do not receive psychological services to help them adjusting to newly acquired functional and cognitive limitations. A study by the National Institute of Health found that 85% of brain injury patients did not receive any treatment or psychosocial intervention concerning the long-term difficulties caused by TBI (Brain Injury Resource Center, 2010).

In emerging economies, sometimes known as the 'third World', such as Arabia, the lack of research on the psychiatric complications of brain injury is even more pronounced. In this part of the world, academics and health officials use brain injury data derived from western population studies in planning for rehabilitation services. This should not happen, studies have shown that the presentation, the prevalence, and the course of several psychiatric diseases vary between different cultural groups (Jablensky et al., 2009). There is abundant evidence to suggest that illness or disability is experienced in a socio-cultural content to the extent that the manifestation of disabilities is inescapably social and cultural (Tseng, 2001). Furthermore, the incidence and prevalence of TBI itself is different in the West compared to that in the third World countries. Therefore, it is important to study the nature and the extent of the psychiatric complications of TBI in the Omani population if the local services are to be appropriately configured.

## **1.4 CONCLUSION**

The number of patients who are suffering from various TBI complications in Oman is expected to increase in the coming year. However, there is a national shortfall in neuropsychological and rehabilitation services for these patients, despite the country achieving top ranking in the efficiency of delivering health care services (S Al-Adawi & Burke, 2001).

Apart from few physiotherapy clinics that provide some rehabilitation services, Oman has no fully equipped and functioning rehabilitation centre for brain-injured patients. The development of a centre dedicated to physical and psychological rehabilitation services for patients with TBI should be a top priority for healthcare planners in Oman (S Al-Adawi & Burke, 2001).

This doctoral research has the ambitious but necessary aim of laying the groundwork for such an undertaking. To this end, this thesis examines three aspects of traumatic brain injuries in Oman.

First, the prevalence of neuropsychiatric complications in consecutive Omani TBI patients attending a Neurosurgical centre.

Second, the clinical and demographic correlations of apathy, which is arguably the most common neuropsychiatric complications of TBI.

Third, a study examining the effectiveness of the current TBI rehabilitation services.

## **CHAPTER TWO: COGNITIVE, EMOTIONAL, AND BEHAVIOURAL IMPAIRMENTS IN PARTICIPANTS WHO HAVE SUSTAINED TRAUMATIC BRAIN INJURY**

### **ABSTRACT**

*Previous studies have shown an increase in the prevalence of various cognitive, emotional, and behavioural impairments in TBI patients compared to that of the general population. However, studies of these complications in Arabian population are scant.*

*This study measures the prevalence of these impairments in Omani TBI patients and explores the interrelationship between these impairments and various clinical and demographic characteristics of these patients.*

*One hundred and three TBI patients, who were attending a routine clinical follow up in a Neurosurgical clinic over a six months period, were recruited for the study.*

*The exclusion criteria included a history of psychiatric illness, a history of repeated head injury, a history of neurological illness, and a history of substance abuse.*

*These patients were assessed using various psychiatric measurements that included the Hospital Anxiety and Depression Scale (HADS), the Apathy Evaluation Scale (AES), and various cognitive function scales. Since the cognitive measurements employed in this study have not been validated in Omani populations, the results of these assessments were compared to twenty “healthy control” subjects. The data were then analysed using Wilcoxon’s two independent sample tests.*

*Forty-two percent had apathy, and 42% were depressed; 40% had anxiety and 35% had fatigue. This is a significantly higher rate than that reported in the general Omani population. However, in the context of any possible cultural differences, it is similar to the rates of psychiatric complications of TBI cited internationally. Cognitive performances of these patients were grossly impaired compared to that of the control group.*

*There were no statistically significant correlations between patient's performance in the psychiatric assessments and age at the time of assessment, gender, educational level, age at the time of injury, time since injury, site of the injury the severity of the Brain injury (as measured the Glasgow coma scale (GCS)), present and pre-morbid IQ.*

## **2.1 INTRODUCTION**

Traumatic brain injury (TBI) can result in a wide range of behavioural and psychological symptoms that may or may not be clustered into a specific psychiatric disorder. This chapter describes a study examining the frequency of several neuropsychiatric complications in a series of TBI patients presenting to a Neurosurgical clinic in Oman.

To provide some background, this chapter begins with an outline of the different types of symptoms and neurobehavioral problems that could follow TBI. Then a description of various factors affecting the presentation of psychiatric complications in these patients will be discussed.

## **2.2 PSYCHIATRIC SYNDROMES IN TBI PATIENTS**

Studies have shown that patients with TBI have an increased prevalence of various psychiatric illnesses compared to that of the general population (Hesdorffer, Rauch, & Tamminga, 2009; Taylor & Jung, 1998). Hillbom found that almost one-third of Finnish soldiers who had sustained head injuries during World War II developed psychiatric disorders (C. Corcoran, McAlister TW, Malaspina D, 2005). Other studies have shown that more than 50% of TBI patients develop a psychiatric disorder, and almost half of these patients have more than one psychiatric disorder (Hibbard MR, 1998).

Robert van Reekum did an extensive literature review on the psychiatric complications of TBIs (Table 2.1 and Table 2.12) (R Van Reekum, Cohen, & Wong, 2000). In this review, the average prevalence of psychiatric disorders in TBI patients was reported to vary from 0.7%, in the case of schizophrenia, to 44 % for depression.

**Table 2.1: A Table Shows the Prevalence of Psychiatric Complications in Traumatic Brain Injury Patients.**

<b>Disorder</b>	<b>Total N (#studies)</b>	<b>Max Duration of Follow-Up (yrs.)</b>	<b>N With Disorder</b>	<b>% With Disorder</b>	<b>Relative Risk</b>
Depression	653 (8)	7.5	289	44	7.5
Schizophrenia	302 (4)	4.9	2	0.7	0.5
Post-Traumatic Stress Disorder	441(6)	7.5	62	14.1	1.8
Anxiety Disorder	398 (5)	7.5	36	9.1	2.3
Panic Disorder	282	7.5	26	9.2	5.8
Bipolar Affective Disorder	374	7.5	15	4.2	5.3
Obsessive Compulsive Disorder	282	7.5	18	6.4	2.6
Substance Abuse	168	7.5	37	22	1.3

Adopted from Van Reekum, R., Cohen, T., &Wong, J. (2000). Can traumatic brain injury cause psychiatric disorders? *Journal of Neuropsychiatry and Clinical Neurosciences*, 12 (3), 316.

Brain injury patients usually present with a mixture of symptoms of several disorders and it is rare to find a patient who has a clearly defined disorder. Nevertheless, psychiatric complications in these patients are usually classified as disorders of mood, cognition, behaviour, personality, and post-concussion syndrome (PCS).

### **2.2.1 Mood Disorders**

Mood disorders in patients with TBI were first reported long time ago. Adolf Meyer, in 1904, coined the term, “traumatic insanities,” to describe the mood disorders in TBI patients and suggested an association between the brain lesion and the mood symptoms (Schwarzbold et al., 2008).



Subsequently, several other studies have shown that mood disorders such as anxiety and depression occur after TBI at a greater frequency than that in the general population (Hesdorffer et al., 2009; R. Jorge, Robinson, Starkstein, & Arndt, 1993).

Depression is the most studied mood disorders in TBI patients and is acknowledged to be one of the most common complication in these patients (Seel, Macciocchi, & Kreutzer, 2010). Several studies have shown that 14% to 77% of patients with TBI suffer from depression (Fann, Uomoto, & Katon, 2001; Silver, Hales, & Yudofsky, 2010). In a recent study conducted in Oman, 63% of Omani TBI patients were found to have depression (Al-Adawi et al., 2004). Furthermore, the prevalence of depression, in TBI patients, increases as the time since injury increase (Fleminger, Oliver, Williams, & Evans, 2003). For example, Satz et al. have reported that the prevalence of depression at initial assessment is about 26%; this increases to 31% six months after the injury (Satz et al., 1998).

Other research suggests that depression, in TBI patients, is a complex syndrome with different types depending on the clinical presentation, time since injury, and the site of injury (Handel, Ovitt, Spiro, & Rao, 2007). For example, lesions on the left basal ganglia regions or dorsolateral prefrontal cortex are associated with early onset depression, but this association is not found in late onset depression (Handel et al., 2007).

Depression in these patients usually starts as a feeling of loss, and discouragement that often occurs soon after the injury. Then the patient will start to have symptoms of persistent low mood. About six to twelve months after the injury, the patient will start to have other symptoms of depression such as insomnia, fatigue, suicidal thoughts, and anhedonia (Hinkeldey & Corrigan, 1990; Silver et al., 2010).

The Disease can result in a significant disability and loss of production for societies. The World Health Organization statistics indicate that depression was the fifth leading cause of disability at the turn of this century; it is now the third leading cause of disability and it is predicted to be the second leading cause of disability by 2020 (Murray & Lopez, 1996; WHO, 2008).

Depression is a common cause of functional impairment in the general population and there is substantial evidence that the disease has a similar effect in TBI patients. Rapoport et al. and Fann et al. have reported that TBI patients with depression had poorer functional and psychosocial outcomes than TBI patients without depression (Fann, Katon, Uomoto, &Esselman, 1995; Rapoport, McCullagh, Shammi, & Feinstein, 2005).

Furthermore, the presence of depression in these patients interferes with the much-needed compliance with the rehabilitation processes. In fact, studies have shown that poor cooperation with rehabilitation is a strong indicator of a persistent depressive disorder (Kraus, 1999; Rifshana, 2009).

Additionally, the presence of depression in these patients worsens other TBI complications; it is associated with worsening of post-concussion syndromes (Anderson, 2008; Fann et al., 1995) and impairment of the cognitive functioning (Jorge et al., 2004). Furthermore, patients with depression show more psychological impairment relative to the severity of TBI (Moldover, Goldberg, & Prout, 2004).

However, early diagnosis and treatment of depression in patients with TBI can improve psychosocial and functional outcome of these patients. Studies in other neurological conditions such as stroke have shown that treating depression in these patients can decrease functional impairment, somatic symptoms, and improve illness-beliefs (Fann et al., 2001; Robinson, Bolla-Wilson, Kaplan, Lipsey, & Price, 1986).

The main risk factors for developing depression, post TBI, appear to be a history of psychiatric disorders and poor pre-morbid function (Christianson, 2009; Fedoroff et al., 1992). Injury to the biogenic amine-containing neurons as they pass through the basal ganglia or frontal-subcortical white matter is thought to be the mechanism of developing depression in TBI patients (Rao &Lyketsos, 2000).

Another sequel of TBI, which is symptomatically related to depression, is fatigue. This is defined as “the awareness of a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity” (Aaronson et al., 1999; Michael, 2009).

Fatigue is very common in TBI patients. Studies have shown that the prevalence of fatigue is 21% in mild TBI and up to 73% in more severe cases of TBI (Masson et al., 1996; Riggio & Wong, 2009). Most discouraging, fatigue secondary to a TBI is a chronic problem and not easily amenable to therapeutic interventions. In a sample of individuals with TBI living in the community, 68% were noted to be suffering from fatigue two years post-injury and 73% of patients with TBI had fatigue five years post-injury (Al-Naamani & Al-Adawi, 2007; Olver, Ponsford, & Curran, 1996).

There are no studies, which evaluate the prevalence of fatigue in Omani TBI patients. It is essential for clinicians to recognize fatigue as a common complication of TBI. Unfortunately, most clinicians tend to perceive fatigue as poor compliance or outright laziness (Norrie et al., 2010).

Mania is less frequent in patients with TBI than depression. However, it is much more common in TBI patients than in the general population; as many as 9% of patients with TBI develop mania (Schwarzbold et al., 2008). This is not only significantly greater than in the general population, but it is also higher than that seen in other brain-injured populations (e.g., patients with stroke) (Jorge, Robinson, Starkstein, Arndt et al., 1993).

Mania, in these patients, presents with changes in mood, euphoria, insomnia, impulsivity, and even violent behaviour (Schwarzbold et al., 2008; Stewart & Hemsath, 1988).

A positive family history of mood disorder is a significant risk factor for developing mania in patients with TBI (Rao & Lyketsos, 2000). Similarly, lesions to the right hemispheric limbic structures are often associated with developing mania in patients with TBI (Jorge, Robinson, Starkstein, Arndt et al., 1993; Spiegel, Burgess, Samuels, Laroia, & Kirshenbaum, 2009).

Another common mood disorder in TBI patients is an anxiety disorder. Studies have shown that, between 11 and 70% of TBI patients have an anxiety disorder (Jones et al., 2008). All types of anxiety disorders, such as generalized anxiety disorder, panic disorder, phobic disorders, posttraumatic stress disorder, and obsessive-compulsive disorder are common.

Decreased activity of GABA inhibitory network and increased activity of the aminergic system are thought to be a mechanism of developing anxiety disorders in TBI patients (Rao & Lyketsos, 2000). Anxiety disorders are more common in right hemispheric lesions than left sided lesions (Jorge, Robinson, Starkstein, & Arndt, 1993).

Although mood disorders are the main barriers to functional and social rehabilitation, they are one of the exceptionally few complications of TBI that are potentially treatable (Morton & Wehman, 1995). Therefore, it is essential to improve the understanding of the prevalence of such disorders and how they contribute to functional disability in patients with TBI as this will improve early diagnosis, treatment, and functional outcome.

### **2.2.2 Cognitive Disorders**

Cognitive deficits in patients with TBI are extremely common. Studies have shown that 67% of patients with severe TBI, 32% of mild and 60% of moderate TBI have cognitive impairment (Al-Naamani & Al-Adawi, 2007; Masson et al., 1996).

All domains of cognitive functions, including poor attention (Niemann, Ruff, & Kramer, 1996), poor memory (Richardson, 2002; Wiegner & Donders, 1999), and disturbances of executive functioning such as poor planning, organizing, impaired judgment and impulse control (Brooks, Fos, Greve, & Hammond, 1999; Lezak, 2004; Stuss et al., 1985), have been reported in TBI patients.

Cognitive impairment in these patients is thought to be a direct result of the brain injury (Fann et al. 2001). However, it can also be indirectly caused by other TBI complications such as depression (Kwentus, Hart, Peck, & Kornstein, 1985). Studies in other medical conditions have shown that depression can affect cognitive functioning in these patients (Downhill & Robinson, 1994; Fisher, Sweet, & Pfaelzer-Smith, 1986). However, the term "pseudo dementia" is no longer used in the context of the complex relationship between depression and cognitive function (Cummings, 1989).

Cognitive deficit, in these patients, has been variously classified as delirium (Kwentus et al., 1985; Rao & Lyketsos, 2000), dementia due to head trauma (Capruso & Levin, 1995), amnesic disorder due to head trauma (Capruso & Levin, 1995), or intellectual impairment (Lishman, 2009), depending on the type of symptoms, time of onset and natural history.

In respect to the time course, cognitive impairments in these patients are divided into four phases (Rao & Lyketsos, 2000).

The first phase of cognitive impairment occurs soon after the injury. This is characterised by the loss of consciousness or coma. Then is followed by the second phase where the patient will have a mixture of cognitive and behavioural abnormalities, such as agitation, confusion, and disorientation.

The second phase is associated with an inability to recall events and learn new information. These two phases are sometimes called posttraumatic delirium and they can last for up to one month post injury (Kwentus et al., 1985; Rao & Lyketsos, 2000).

The third phase is characterised by the recovery of the cognitive impairment. This takes place in the first six to twelve months and then there is a plateau in recovery for the next 12 to 24 months.

The fourth is a phase of permanent cognitive impairment. This period is sometimes called "dementia due to head trauma" and characterised by short- and long-term memory impairment, poor attention, impairment of information processing, mental inflexibility, and problems with executive functions.

The prognosis of cognitive impairments in these patients depends on the degree of the head injury, the period of LOC and PTA, and the presence of the brain stem dysfunction (Rao & Lyketsos, 2000). In a meta-analysis study, Schretlen and Shapiro showed that people who have a mild TBI not only rapidly improve, but also reach a baseline within a few months, in contrast to moderate to severe TBI who improve slowly and may not reach a baseline (Schretlen & Shapiro, 2003).

Cognitive impairments are one of the most disabling psychiatric complications of TBI (McCullagh & Feinstein, 2005). In fact, studies have shown that these impairments contribute more to disability than physical impairment (Rapoport et al., 2005).

Apart from natural recovery, there are very few ways to improve the cognitive impairment in these patients. However, patients may experience improvements if they have and are treated for depression (Stoudemire, 1995); treating depression in these patients improves their short-term memory, speed of information processing, attention, and mental flexibility (Fann, Uomoto, & Katon, 2000).

### **2.2.3 Behavioural Disorders**

Behavioural problems associated with TBI have been difficult to classify. These problems have been variously classified as frontal and temporal lobe syndromes (Kraus, 1999), aggressive disorders (Silver, 1994), and as personality changes (Capruso & Levin, 1995).

Injuries to certain areas of the brain have been associated with specific behavioural disorders. For example, a focal injury to the temporal lobes causes memory problems and emotional lability (Gualtieri, 1991); injury to the orbital and frontal areas causes disinhibition, whereas injury to the dorsal part of the frontal lobe causes impairment of executive functions (Duffy, 1994).

### **2.2.4 Psychosis**

The relationship between psychosis and TBI was noted before the 19th century (Corcoran, 2005). Although psychosis in TBI is not as common as mood disorders, it has a devastating effect on recovery and rehabilitation when it occurs.

In the most extensive review of the association between brain injury and psychosis, Davison and Bagley concluded that psychosis in brain-injured subjects is more common than in the general population (Nasrallah, 1981). Studies have shown that up to 10% of patients with TBI develop psychosis (Nasrallah, 1981; Rao & Lyketsos, 2000).

Similarly, studies have shown that 15% of schizophrenic patients have a history of a head injury prior to the development of their psychotic symptoms (Nasrallah, 1981; Rao & Lyketsos, 2000). The majority of these patients do not have a family history of psychotic disorder. This suggests that the head injury is the likely cause of the psychotic symptoms.

The onset of psychosis is variable; recent studies report a mean of four to five years after the TBI (Fujii & Ahmed, 2002). Achte et al. reported the onset of psychotic symptoms ranged from two days to 48 years after injury in their study of World War II veterans; almost 50% reported their first psychotic symptoms ten years or more after the sentinel injury (Achte KA, 1969; C. Corcoran, McAllister, & Malaspina, 2005).

The clinical presentation in these patients is complex and ranges from odd behaviour to schizophrenia-like syndrome. These patients may present with hallucinations, delusions, illogical thinking, ideas of reference, grimacing, and aggressiveness (Thomsen, 1992). The psychotic symptoms in these patients might be acute and transient or chronic and persistent.

Psychotic disorders in brain injury help researchers and scientists to understand primary psychotic disorders such as schizophrenia. For example, there is evidence to suggest that both of these disorders share similar loci where frontal and temporal lobe abnormalities are implicated in the pathogenesis of psychotic symptoms (Fujii, 1996).

### **2.2.5 Personality Changes**

Personality changes are one of the earliest neuropsychiatric complications of TBI documented in the medical literature. Harlows described the most striking personality and behaviour changes after frontal lobe injury in 1848 (Macmillan & Lena, 2010).

The patient, called Phineas P. Gage was a 25-year-old construction supervisor. An iron bar penetrated his frontal lobe. Although subsequently his physical and intellectual impairments recovered totally, his personality dramatically changed. A previously restrained, capable man, Gage became childish, vulgar, inappropriate and impulsive (Castellon, Hinkin, & Satz, 2002). His ex-employers considered the changes so prominent that they refused to re-employ him and to his friends, he was "no longer Gage".

Since that time, personality changes have been reported in between 49% and 80% of TBI patients (Brooks, Campsie, Symington, Beattie, & McKinlay, 1986; McKinlay, Brooks, Bond, Martinage, & Marshall, 1981; Thomsen, 1992). Most common personality changes are borderline (34%), obsessive-compulsive (27%), paranoid (26%), avoidant (26%), and antisocial (21%) (Hibbard, 1998). Although personality changes may appear to be a benign sequel of brain injury, the social and economic burden is considerable as the changes are essentially refractory to treatment.

### **2.2.6 Post-Concussion Syndrome**

Post-concussion syndrome (PCS) is the most common sequel of TBI. Studies have shown that more than 90% of TBI patients suffer from symptoms, which are collectively known as PCS and these include headaches, dizziness, irritability, and difficulties with memory and concentration for days to weeks after the injury (Ryan, 2003) are suffering from PCS.

The disease is often found in mild TBI, but can occur after an injury of any severity (Evans, 1999). However, the syndrome is poorly defined and has caused controversy for years. This started in 1866 when Erichsen reported patients who presented with persistent physical complain after mild brain injuries (Evans, 1999). He suggested that these symptoms were caused by "molecular disarrangement" of the spinal cord caused by the brain injury. The disease was called "railroad spine" because most of the injuries occurred while working on the Prussian railroad.

Rigler, in 1879, refuted this explanation and suggested that the increasing number of these patients was a result of the policy of the Prussian Railroad that started to compensate injured workers (Evans, 1999; Solomon, 2001). He called the condition "compensation neurosis".

Subsequently, Charcot suggested that these symptoms were caused by "psychological factors" (Evans, 1999). The current diagnosis of "post-concussion syndrome" replaced the terms "railroad spine," "compensation neurosis," and "hysteria" in 1934 (Evans, 1999).



However, many questions regarding the syndrome have not yet been answered. For example, it is still not clear why some patients with mild TBI have the PCS while others do not (Levin et al., 1987), furthermore some features of PCS are more prominent in mild TBI than severe TBI (Alexander, 1992).

In an attempt to solve this conundrum, Jacobson describes several factors that can play a role in the pathogenesis of the syndrome (Jacobson, 1995). These factors include a genetic predisposition, motivational factors, stress, and cognitive factors. Other researchers have suggested an association between post-concussive symptoms and prior social difficulties (Fenton, 1993), neuropsychological impairment (King, 1996), brainstem and cortical dysfunction (Watson et al., 1995), personality and coping styles (Middelboe, Birket-Smith, Steen Andersen, & Laue, 1992), and litigation (Binder & Rohling, 1996).

The pathogenesis of this disease is thought to be diffuse axonal injury. However, in most cases, the neurologic examination and various neuropsychological and imaging investigations have been normal. Only few PET and SPECT studies have shown focal defects in these patients (Gray, Ichise, Chung, Kirsh, & Franks, 1992; Langfitt et al., 1986).

Unfortunately, there are no proven pharmacological treatments for Post-concussion syndrome. However, based on studies of other medical diseases, antidepressants are often used in the management of these cases. These studies have shown that if patients with various medical diseases and depression show a reduction of the level of distress and the subjective severity of their physical illness if treated with antidepressants (Borson et al., 1992; Sullivan, Katon, Russo, Dobie, & Sakai, 1993). Similarly, studies also shown that if a patient with a medical condition also have a mood disorder, he will have more physical symptoms, even after controlling for the severity of the medical condition (Lustman, Clouse, & Carney, 1988).

### **2.2.7 Apathy**

In addition to the “classical” psychiatric disorders, such as those shown in Table 2.1, one of the most common and the least well-studied complications of TBI is apathy. The disease is sometimes called aboulia (Al-Adawi, Dawe, & Al-Hussaini, 2000). Studies have shown that almost 50% of patients with TBI have apathy (Van Reekum, Stuss, & Ostrander, 2005).

Aboulia is a term derived from the Greek “boul” (will) and is usually defined “as a lack of will or motivation” (Al-Adawi et al., 2000). Apathy “ refers to a specific neurological syndrome, which manifests as a lack of spontaneity of action and speech, deficiency in initiation, mental and motor slowness, and reduction in an excursion of motion, poor attention, and easy distractibility ” (Al-Adawi et al., 2000).

For clinical purposes, apathy can be defined as “a lack of motivation that is not attributable to diminished level of consciousness, cognitive impairment, or emotional distress” (Kiang, Christensen, Remington, & Kapur, 2003).

Apathy significantly impairs the patient’s compliance with physical rehabilitation and quality of life. Studies have shown that apathy is associated with several negative outcomes such as reduced functional level, distress in caregivers, poor outcome of illness, poor treatment response, and chronicity (Al-Naamani & Al-Adawi, 2007).

The disease will be fully reviewed and analysed in chapter three of this thesis.

### **2.3 Factors Affecting the Presentation of Psychiatric Complications in TBI Patients**

Several factors have been shown to be associated with the presentation of psychiatric complications in patients with TBI. These factors include hereditary predisposition (Visser, Pijl, Stolk, Neeleman, & Rosmalen, 2007), general IQ (O’Toole, 1990; Smith, 1982), age at the time of injury, problems at work or financial instability (Whitlock, 1977), and gender (Flaada et al., 2007). Other pre-morbid factors, which are thought to be important in this regard, are educational level, past medical and psychiatric history, previous brain injury, and any family medical or psychiatric history. As it was pointed out by Symonds: "the response to head injury depends on the kind of head that was injured" (Rao & Lyketsos, 2000).

Most of these factors, affecting the prognosis of TBI itself and, this in turn, affect the presentation of psychiatric complications. The following section will review some of these factors.

### **2.3.1 Age at the Time of Injury**

Age is a crucial factor in TBI studies; most brain injuries occur in individuals aged between 15 and 24 (Collins, 2002). The fact that TBI occurs in younger people is such that there is a relatively greater loss of productive years (Maas AI, 2008). The prognosis of TBI can also be affected by the age at the time of injury (High, 1996). Although some studies found no correlation between age at the time of injury and prognosis, several studies have shown that patients who had TBI at a younger age had poorer prognosis than patients who had TBI later in life (Grosswasser, 1989; Shah, Al-Adawi, & Burke, 2004). Despite several such studies, which clearly show that patients who were younger at the time of injury tend to do worse, clinicians often expect a better prognosis for younger TBI patients (Nybo, 2005).

Given that the bulk of the population is under the age of 20, it is not clear how this fact is affecting the prognosis and complications of TBI in Oman.

### **2.3.2 Gender and Brain Injury**

Clinical studies suggest that there are gender differences in the prevalence of TBI. Studies have shown that TBI is three times more frequent in men (Rao & Lyketsos, 2000; Tait, Anstey, & Butterworth, 2010).

Other studies have shown that men have a fourfold greater risk of fatal brain injury (Rao & Lyketsos, 2000). This large gender difference is thought due to the fact that the main causes of TBI, such as motor vehicle accidents, assaults and gunshot wounds, occur more frequently in men (Rao, 2002).

The gender differences also affect the prognosis of TBI (Bazarian, Blyth, Mookerjee, He, & McDermott, 2010). However, the related findings are inconsistent (Moore, Ashman, Cantor, Krinick, & Spielman, 2010). Some studies suggest that the prognosis of TBI is worse in female patients (Bazarian et al., 2010; Kirkness, 2004). Other studies have shown that there are no gender differences in the outcome of TBI as defined by the number of days to return to work. However, there are significant gender differences in the outcome as measured by the frequency and severity of PCS; females do worse on this outcome of TBI (Bazarian et al., 2010).

In respect of cognitive outcome after TBI, there is also evidence that males perform better than females on measures of attention, whereas females perform better in regard to verbal learning and executive functioning (Moore et al., 2010).

Several explanations have been proposed to account for these gender differences. Several factors that are known to affect the prognosis of TBI, such as pre-morbid IQ, education, employment, and problem solving skills, can also be affected by gender (Lioffi & Wood, 2009; Moore et al., 2010; Rao & Lyketsos, 2000).

Furthermore, studies have shown that the functional organisation of the female brain might be different from that of the male (Farace & Alves, 2000). Women have more bilateral representation of verbal skills and performance IQ. Therefore, females could be affected more by diffuse brain injury (Lioffi & Wood, 2009).

Additionally, epidemiological studies have shown that men and women are different in the way they experience and report illness. The incidences and the prevalence of various psychosomatic illnesses are much higher in females than males. (Lioffi & Wood, 2009; Piccinelli, 2000). Finally, animal studies have shown that while estrogens provide a neuroprotective effect in males, they exacerbate such an injury in females (Emerson, 1993; Lioffi & Wood, 2009).

### **2.3.3 Educational Level and Brain Injury**

Several studies have shown that the level of education has an impact on the development of common diseases (Zhou, Olivier, & Mcdaniel, 2009). For example, studies in the USA have shown that people who have a lower education level are much more likely to have life threatening illness compared to those with had higher education (Zhou et al., 2009).

This is also true in cases of TBI, where an individual's educational background was found to be an influential factor (Whitlock et al., 2003; Wong, Shapiro, Boscardin, & Ettner, 2002). In regard to the incidence of traumatic injury; people with lower levels of education are at greater risk (Hannay, Howieson, Loring, Fischer, & Lezak, 2004). Furthermore, studies have also shown that patients with lower levels of education have poorer rehabilitation outcome (Zafonte, Wood, Harrison-Felix, Millis, & Valena, 2001).

#### **2.3.4 Employment Status**

Employment status can affect the relative risk of having an accident. People who are in the lowest occupational level, as well as those who are unemployed, have four times more risk of RTA (Whitlock et al., 2003).

Post injury employment status is also likely to affect the prognosis of TBI. Studies have shown that patients who are unemployed are more likely to have a poor prognosis of TBI than patients who are employed (Rao & Lyketsos, 2000). Furthermore, patients who are unemployed present more often with psychiatric complications (Rao & Lyketsos, 2000).

Studies in the general medical population have shown that patients who are unemployed present more frequently with mood disorders, such as depression, than patients who are employed (Franulic, Carbonell, Pinto, & Sepulveda, 2004). Similarly, studies in TBI patients have shown that these patients are less likely to be employed if they have psychiatric complications (Franulic et al., 2004).

Finally, employment history by itself can be a useful indicator of the real world functioning of patients with TBI (Sherer et al., 2002). Studies done elsewhere have found that less than 30% of patients with TBI were able to return to work (Björkdahl, 2010; Heiskanen & Sipponen, 1970). Other studies have shown that 50% of patients with severe TBI and 20% of mild TBI were unemployed one year after their head injury (Gordon, 2007; Whiteneck et al., 2001).

#### **2.3.5 Consanguinity**

Traumatic Brain Injury is often triggered by an unintentional injury that affects the head and the organ inside the skull and results in neurobehavioral impairment. Despite brain injuries occurring most often by way of an accident, there is a suggestion that some individuals incur TBI more frequently. One hypothesis is that some sufferers of an acquired brain injury are pre-morbidly accident-prone (Pastor & Reuben, 2006). The researchers also suggest this could be hereditary (Visser et al., 2007).

Consanguinity is very common in Omani society and this has been found to increase the chance of hereditary disorders (Bittles & Hamamy, 2010). Therefore, it is essential to study the effect of consanguinity in the presentation and complications of TBI in Oman.

### **2.3.6 Time since Injury**

Previous studies have shown that the nature and extent of neuropsychiatric complications of TBI change with time after the injury (Dikmen & Reitan, 1977; Fordyce, Roueche, & Prigatano, 1983; Kinsella, Moran, Ford, & Ponsford, 2009; Silver et al., 2010). Neuropsychiatric complications that appear earlier are related to the injury itself while those that appear late are often responses to social and neurological complications of TBI (Silver et al., 2010). Other studies have shown that the severity of depression increases with the time since injury (Silver et al., 2010).

### **2.3.7 Past Medical and Psychiatric History**

Studies have shown that certain physical illnesses appear to increase the rate of the RTA by twofold (Martin-Cantera et al., 2010; Waller, 1965).

The pharmaceutical treatment of mental illness, such as with psycho-stimulants and sedatives, increases the rate of RTA 14 and five times respectively (Glauz & Blackburn, 1975; Martin-Cantera et al., 2010).

Other studies have shown that patients with psychiatric illness report more TBI than the general population (Vassallo, Proctor-Weber, Lebowitz, Curtiss, & Vanderploeg, 2007; Weight, 1998).

Although there is an argument about whether the psychiatric illness causes TBI or the other way around, there is enough evidence to suggest that the presence of a psychiatric disease is a risk factor for TBI (Moore, Terryberry-Spohr, & Hope, 2006). Furthermore, studies also have shown that a pre-injury psychiatric disease can affect recovery after TBI (Bernstein, 1999; Weight, 1998).

Another factor that can play a decisive role in rehabilitation and recovery after a TBI is pre-morbid personality. As cited above, Symonds pointed out that "the response to head injury depends on the kind of head that was injured" (Rao, 2002).

Social factors such as financial instability, poor interpersonal relationships, and marital discord are also crucial in this regard (Rao & Lyketsos, 2000).

### **2.3.8 Past History of Brain Injury**

Several studies have shown that patients with TBI have a higher prevalence of psychiatric illness than the general population (Van Reekum et al., 2000; Weight, 1998). A wide range of psychiatric illnesses has been reported in these patients, including psychosis, depression, anxiety, and apathy.

Nasrallah et al. have reported that 15% of schizophrenia patients had a history of TBI (Nasrallah, 1981). Van Reekum et al. reported that 44% of patients with TBI develop depression (Van Reekum et al., 2000).

### **2.3.9 Family Medical and Psychiatric History**

Studies in the general population have shown that a family history of a psychiatric illness is a predisposing factor to have several psychiatric diseases.

This is also true in the TBI population. For example, a positive family history of mania is a risk factor for developing mania after TBI (Robinson, Boston, Starkstein, & Price, 1988).

### **2.3.10 Site of the Injury**

Several studies have shown different sites of the brain injury are associated with certain neuropsychiatric complications. For example, as cited earlier, depression has been associated with injury in the left basal ganglia and left dorsolateral frontal areas (Rao et al., 2010). Similarly, right hemispheric lesions have been associated with anxiety disorders (Jorge, Robinson, Starkstein, & Arndt, 1993; Silver et al., 2010).

### **2.3.11 Medication**

Several drugs have been routinely used post TBI in order to improve rehabilitation outcome (Wheaton, 2009). Goldstein suggested that if given early after the injury, dopamine agonist drugs could improve the functional outcome of TBI (Goldstein, 2003).

However, some of the drugs that are routinely used in these patients have been shown to impede recovery (Gualtieri & Evans, 1988; Nickels, Schneider, Dombovy, & Wong, 1994).

In addition to assisting recovery, many compounds are used prophylactically. The major impetus for such an undertaking is the prevention of infections and seizures. It is generally considered undesirable for a brain-injured person to have a post-stroke or post-brain injury seizure. Epilepsy has been shown to be an unfavourable prognostic factor for overall functional outcome (Walker & Blumer, 1989).

However, there are two types of seizures in patients with TBI, early and late onset seizure (Al-Adawi, Burke, & Mastronardi, 2006). Early onset seizures occur within the first two weeks of the injury and these have not been found to be associated with higher mortality or poor functional outcome (Al-Adawi et al., 2006). However, some studies have suggested that these early seizures are associated with increase secondary brain injury (Al-Adawi et al., 2006).

There are no studies of the effect of drugs prescribed for the brain-injured patients in Oman.

### **2.3.12 Post-Traumatic Amnesia**

PTA is one of the parameters used to quantify the severity of TBI. It is also often cited as a way of predicting brain injury outcome (Brown et al., 2010; Katz & Alexander, 1994; Wilson, Teasdale, Hadley, Wiedmann, & Lang, 1994).



### **2.3.13 Pre-Injury IQ**

Pre morbid IQ can affect the results of neuropsychological function after TBI in several ways. There are some studies that suggest patients who have a low IQ are more prone to RTA than the general population (O'Toole, 1990; Smith, 1982; Whitley et al., 2010). Other studies suggest that the psychiatric complications after TBI are related to the individual pre-injury IQ (Krpan, 2010; Thomsen, 1992).

### **2.3.14 Severity of TBI**

There are conflicting results on the importance of severity of brain injury in developing psychiatric complications. Some studies showed that severity of TBI might play a role in the development of psychiatric complications (MacGregor et al., 2010). Other studies, such as Sliver et al., showed no association between severity of TBI and depression (Silver et al., 2010).

## **2.4 Studies of Psychiatric Complications of TBI in Oman**

Considering that most of the Omani population is at the high-risk category for non-communicable diseases, including TBI, preliminary studies in Oman suggest that non-intentional injuries are a leading cause of morbidity and mortality. Despite this, very few studies have been done on the psychiatric complications of TBI. Furthermore, previous studies of psychiatric illness among TBI patients in Oman were either a small self-selected cohort and/or only addressed a single diagnosis such as depression (Al-Adawi et al., 2007) or apathy (Al-Adawi et al., 2004).

Moreover, the brain-injured population in this earlier study was recruited from a psychiatric clinic and at a variable time after the injury (Al-Adawi et al., 2004).

The previous Omani studies can be further criticized on the grounds that the studies were not longitudinal and lacked the methodology to identify the functional prognosis of the sequel of TBI. Furthermore, important indicators of severity and prognosis, such as socio-demographic status, were not included.

Finally, the studies did not employ ecologically valid assessment measures, and, the psychometric properties of the measurement used are questionable (Al-Adawi et al., 2007).

The study reported here is an attempt to overcome the limitations of the previous studies. The main aim of this study is to explore the psychiatric sequel of TBI in a relatively large number of patients. These patients were recruited from the Neurosurgical clinics where they attend for both acute and chronic care.

The study also includes all degrees of TBI severity and aims to study different psychiatric complications using standardized and internationally accepted diagnostic methods. An important part of this study will be to determine if psychiatric complications of TBI correlate with age, severity of TBI, and whether the initial clinical presentation predicts functional outcome.

## **2.5 AIMS OF THE PROJECT**

The aims of the present study are to explore the performance of Omani patients who have sustained TBI on various indices of cognitive, emotional, and behavioural functioning and to explore the interrelationship between these indices and various demographic and clinical characteristics of the participants.

## **2.6 HYPOTHESIS**

In view of the above, it is hypothesized that the performance of Omani TBI patients would be significantly impaired compared to that of healthy Omani subjects on various indices of cognitive, emotional, and behavioural functioning.

## **2.7 METHODOLOGY**

As cited in chapter one, the national health care service in Oman is free for its citizens. Tertiary care is largely found in the capital city of Oman, Muscat. This is also true for the services provided to patients with TBI. This service is provided by one centre, The National Neurosurgical Centre, Khoula Hospital, Mina-AL-Fahal, Muscat, Sultanate of Oman. The centre has a national catchment outreach and it is the main point of contact for most patients with TBI.

### **2.7.1 Participants**

#### **2.7.1.1 Sample size.**

Sample size selection depends on a number of factors. It depends on the heterogeneity of the population (Kakinami & Conner, 2010). If the elements of the population are similar as to the parameter being studied then a small sample will give a good result. The sample size also depends on the number of subgroups in the population (Gauderman, 2002). If all subgroups should be represented adequately then a large sample size is needed. The sample size also depends on the phenomenon under study (Kakinami & Conner, 2010). If a rare event is being studied then, to get adequate representation, a large sample size is called for.

The precision to which the statistic or parameter is to be estimated also affects the sample size. The sample size used is a balance between these factors and the cost, in money and time, involved in collecting the data (Noordzij et al., 2010).

It was proposed to estimate proportions to within 0.1 of the true values. When the true proportion is about 0.1, power analysis shows that a sample of size 50 gives a power of 56%. This power reduces to 33% for a sample of size 50 when the proportion is about 0.5. When the sample size is raised to 70, the minimum power is about 75%. Hence, it was proposed a sample of between 70 and 100.

### **2.7.1.2 The Cohort**

The present cohort was recruited from the outpatient clinic of the Neurosurgical department. These were either recent or old TBI patients who were attending the clinic for assessment and management of various physical TBI complications.

Five hundred and forty consecutive patients aged between 15 and 70 years attending the clinic over a six-month period were asked to participate in the study.

Each participating patient underwent careful screening to rule out those who had neurological and psychiatric illnesses prior to their TBI. The exclusion criteria included a history of psychiatric illness, a history of repeated head injury, a history of neurological illness and a history of substance abuse since such clinical populations are likely to confound the result by virtue of having other conditions rather than isolated acquired brain injury. For example, it has been suggested that chronic use of illicit drugs is likely to lead to psychiatric complications that may be independent or additive of acquired brain injury (Buckley & Meyer, 2009).

Similarly, if one has a history of psychiatric illness, then it will not be possible to identify whether a psychiatric complication is due to TBI or to other previous unknown factors.

In addition to the patients group, controlled “healthy” participants were also recruited. This was necessary since the cognitive assessment measures used in this study lack psychometric properties for Omani population. Therefore, in order to find out whether Omani TBI patients have impairments in the cognitive functions; controlled “healthy” subjects were recruited.

However, these controlled subjects were recruited from the orthopaedic clinic to rule out the possibility that the expected cognitive impairment observed in TBI patient is due to the general effect of being ill rather than a specific result of the brain injury. The inclusion criteria were any patient attending a routine orthopaedic clinic, aged between 15 and 70 years. The exclusion criteria included a history of psychiatric illness, a history of brain injury and a history of substance abuse.

Unfortunately, most patients in the orthopaedic clinic were also involved in an RTA, therefore, were excluded from the study for the fear that they might also have “hidden” brain injury. As a result, only twenty patients were found to be suitable and willing to participate as “normal” control subject. However, these patients were found to be an exact match to the TBI patients in terms of age and sex.

Ethical consent for the study was obtained from the ethical committee of Sultan Qaboos University and all subjects were required to give written consent. In case the subject could not make a meaningful response or rendered incapable due to psychomotor impairment, the caregivers were asked to consent as per regulation of such endeavour in Oman.

## **2.7.2 Data Collection**

### **2.7.2.1 Demographic and Clinical Information**

The socio-demographic data collected were age, gender, educational level, and employment status; as well as injury-related data, such as the age at the time of injury, past medical and psychiatric history, prior incidents of brain injury, family medical and psychiatric history, neuro-imaging data by way of either computed tomography (CT) or magnetic resonance imaging (MRI), and current medications. Most data were obtained from the attending clinical team, the patient’s medical record or directly from the patient and accompanying family members.

One hundred and three consecutive TBI patients met the inclusion criteria for this study. These patients were assessed with the measures listed below. This was only done when their cognitive and emotional function was stable such that they could make consistent and meaningful responses. This status was determined by the attending clinical team (doctors, nurses, and therapists).

### **2.7.2.2 Assessment Measures**

Various well-established neuropsychological assessments were used in order to assess cognitive, behavioural, and emotional complications of TBI.

However, it was not possible to perform a complete assessment on every patient. For example, patients with visual impairment or language difficulties could not be given a self-rated assessment. However, every attempt was made to gather the information by reading the questions to the participant.

The assessments were administered by the author in a Neurosurgical clinic room. This was done in one session and took about one to two hours depending on the number of assessments administered.

Psychiatric functioning was screened using semi-structured interviews, CIDI based on the International Classification of Disease (ICD-10) (WHO 1993). In addition, the Hospital Anxiety and Depression Scale (Zigmond and Snaith 1983) were used to screen for the presence of affective dysfunction. These particular assessment measures have been chosen because their psychometric properties have been established in the Arabic speaking population (Malasi, Mirza et al. 1991).

Cognitive assessment, such as the modified Wisconsin Card Sorting Test, Buschke Selective Reminding Test (Buschke & Fuld, 1974) and Digit Span (Wechsler, 1981) were also administered to assess concentration and attention, and effortful cognitive functioning. These clinical scales are not verbal or language-based and are thought to be independent of culture (Duchesne et al., 2010).

A summary of the assessments used is described below; a detailed review of each of these assessments is in the appendix to this thesis.

## LEVEL OF DISABILITY

1. The Disability Rating Scale (DRS) (Rappaport, Hall, Hopkins, Belleza, & Cope, 1982).
2. The Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974)
3. Post-traumatic amnesia

## NEUROBEHAVIORAL FUNCTIONING

1. Post-concussion syndrome (Physical, Cognitive & Emotional symptoms)
2. Neuropsychiatric inventory (Cummings et al., 1994)
3. Apathy Evaluation Scale (Marin, Biedrzycki, & Firinciogullari, 1991)
4. Fatigue Assessment Scale (Michielsen, De Vries, & Van Heck, 2003)
5. Competency Rating Scale (Hart, 2000)

## THE COGNITIVE FUNCTION TESTS

1. GENERAL IQ.
  - 1.1. Pre-morbid IQ.
  - 1.2. Present IQ. Raven's Standard Progressive Matrices (Raven, 2000).
2. TESTS OF FRONTAL-SUBCORTICAL FUNCTIONS
  - 2.1. Test Of Deductive Reasoning And Mental Flexibility: Modified Wisconsin Card-Sorting Test (WCST) (Nelson, 1976).
  - 2.2. Verbal Fluency Controlled Oral Word Association Test (Benton, 1968).
  - 2.3. Tower Of London (Shallice, 1982).
3. TESTS OF ATTENTION AND MEMORY FUNCTIONS
  - 3.1. Digit Span Wechsler Adult Intelligence Scale sub-test (Wechsler, 1981).
  - 3.2. Buschke Selective Reminding Test (Buschke & Fuld, 1974).

## PSYCHIATRIC STATUS

1. Self-Reporting Questionnaire
2. Hospital Anxiety and Depression Scale

## 2.8 RESULTS

### 2.8.1 Demographic and Clinical Information

#### 2.8.1.1 Present Age

One hundred and three patients were included in the study. The age range of the 103 patients was 15-70 years (mean=30).

#### 2.8.1.2 Age at the time of injury

The largest percentage of TBI (31%) in this sample, occurred in people who were in the age group of 20 to 24 years old as shown in table 2.2.

**Table 2.2: A Table Shows The Age At The Time of The Injury For The Studied Group In Comparison With The Overall Omani Population.**

Age Group	Percent with TBI	Percentage of Omani Population at that age group
5-9	2	10.8
10-14	2	11.7
15-19	20.4	13.5
20-24	32	13.2
25-29	16.5	11.2
30-34	5.9	8.2
35-39	4	5.1
40-44	1	3.9
45-49	2.9	2.7
50-54	6.8	2.2
55-59	2	1.6
60-64	2.9	1.5
65-70	2	0.9



### **2.8.1.3 Gender**

Eighty-three (80.6%) patients were male.

### **2.8.1.4 Educational level**

The majority of patients in this study, 37 (35.9%), had undertaken secondary education.

**Table 2.3: A Table Shows the Educational Level of 103 Omani TBI Patients**

	<b>N</b>	<b>%</b>
Koranic education*	17	16.5
Primary education	32	31.1
Secondary education	37	35.9
Some college education	8	7.8
Completed college education	2	1.9
Graduate education	3	2.9
Still student	4	3.9
<b>Total</b>	<b>103</b>	<b>100.0</b>

\*Traditional Islamic teaching school

### **2.8.1.5 Employment status**

At the time of the injury, twenty patients were unemployed, 45 were employed, and 31 were still students.

### **2.8.1.6 Consanguinity**

Twenty-nine subjects were born from consanguineous parents while 73 came from unrelated parents.

### ***2.8.1.7. Time period from the time of injury to the first assessment date in months***

The subjects were tested at a mean of 22 months following the head injury. (SD=40, range= 1 day – 252 months).

### ***2.8.1.8. Past medical and psychiatric history***

The majority of the patients (96%) had no significant past medical history. One patient had epilepsy. One had sickle cell disease, one had hepatitis B, and one had poliomyelitis.

**Table 2.4 A Table Shows Past Medical and Psychiatric History of the Participants, (N= 103 Patients Who Had Sustained Traumatic Brain Injury)**

	N	%
Healthy/Normal	95	96
Epilepsy	1	1.0
Hepatitis B	1	1.0
Poliomyelitis	1	1.0
Sickle cell disease	1	1.0

### ***2.8.1.9 Family medical and psychiatric history***

No patient declared a family medical or psychiatric history, except for one patient who had a brother with schizophrenia.

### ***2.8.1.10 Neuroimaging data with CT or MRI***

All 103 patients had either CT or MRI findings; 33 (32%) had mainly left sided injury, 21 (20%) had right-sided injury, 29 (28%) had a bilateral head injury and 20 (20%) had normal Neuro-imaging data.

### **2.8.1.11 Current medications**

The majority of participants (n= 88; 85.4%) were not taking any medications. The remaining eight were taking the various compounds listed in Table 2.5.

**Table 2.5 A Table shows the Number of Participants on Medication as Treatment or Prophylaxis in a Cohort of 103 TBI Patients**

<b>Medicine</b>	<b>N</b>	<b>%</b>
None	88	85.4
Amitriptyline	1	1.0
Amoxicillin	1	1.0
Carbamazepine	2	1.9
Lamotrigine	1	1.0
Multivitamins	1	1.0
Phenytoin	8	7.8
Piracetam	1	1.0

### **2.8.1.12 Anti-seizure medication**

As shown in the above table, 11 patients were on anti-seizure medication.

## **2.8.2 Level of Disability**

### **2.8.2.1 Disability Rating Scale (Total Score)**

Using the DRS, only one patient (1%) fulfilled the criteria for severe disability. Four patients were indicated to have a moderately severe disability. Eight had a moderate disability, 14 had partial disability, and 23 had a mild disability. The rest (n = 48) did not score in the disabled range.

### 2.8.2.2 Glasgow Coma Scale

According to the GCS scores, 54 had sustained a mild head injury, 12 had a moderate head injury, and 37 had a severe head injury.

**Table 2.6: A table shows the Glasgow coma scale (GCS) scores in 103 TBI patients**

Severity of TBI	GCS scores	Frequency	Percent
Severe	3	9	35.9
	4	3	
	5	5	
	6	2	
	7	11	
	8	7	
Moderate	10	7	11.7
	11	3	
	12	2	
Mild	13	10	52.4
	14	6	
	15	38	

**NB: Operational definition of brain injury is classified as ‘severe’ (GCS ≤ 8), ‘moderate’ (GCS 9 – 12), ‘mild (GCS ≥ 13).**

### 2.8.2.3 Post-traumatic amnesia

Following the suggestion by Rees (Rees, 2003) and others (Kosch, Browne, King, Fitzgerald, & Cameron, 2010), PTA in this study was classified as a gradient from those who have no PTA to severe type that persist for more than four weeks. PTA was recorded retrospectively from medical notes.

As shown in the Table 2.8, the period of PTA could be determined in 93 subjects. Among these, 29 (31.2%) were recorded to have not incurred any PTA and, at the other extreme, 21 (22.6%) had more than 4 weeks of PTA.

**Table 2.7: A Table shows the Period of Post-Traumatic Amnesia in 93 TBI Patients**

<b>Post-traumatic amnesia</b>	<b>N</b>	<b>%</b>
No PTA	29	31.2
1 day or less	13	14
More than 1 day, less than 1 week	5	5.4
1-2 weeks	10	10.8
2-4 weeks	15	16.1
More than 4 weeks	21	22.6
<b>Total</b>	<b>93</b>	<b>100.0</b>

### **2.8.3 Cognitive Tests**

#### ***2.8.3.1 General Intellectual Functioning***

The raw score of Standard Progressive Matrices was calculated to give an IQ. For brevity, the IQ equivalent of these patients ranged from 20 to 110 (severe to high average mental retardation). The mean IQ was 80 (low average) (Yehia, 2003).

In addition to assessing the current cognitive functioning, an estimate of pre-morbid intellectual functioning was also sought. Because there were no IQ records for any of the patients prior to the accident as detailed in the methodology section, developmental history and academic achievement were used to estimate the patient's pre-morbid intellectual functioning. This assessment measure is detailed in the Appendix

Based on these indices, and according to their school performance, almost 84% had an average pre-morbid intellectual ability. Thirteen percent had below average intellectual ability because they had poor performance in the national examinations.

**Table 2.8: A Table shows the Estimated Pre-Morbid IQ in 103 TBI Patients**

<b>Pre-morbid IQ estimate</b>	<b>N</b>	<b>%</b>
Below average	13	12.6
Average	86	83.5
Above-average	4	3.9
<b>Total</b>	<b>103</b>	<b>100.0</b>

Commonly used cognitive tests were employed in this study in order to identify cognitive impairment in this cohort of TBI patients. Because there are no local norms for these cognitive tests, ‘‘healthy’’ subjects were recruited as controls.

In terms of cognitive impairment, the TBI patients appear to be impaired on all the cognitive measures employed. Table 2.9 lists the summary statistics of Omani patients with TBI compared to the control group. As an illustration of the differences, on the verbal fluency-total score, the average score of the healthy controls was 24.3, while the TBI patients managed only 15.9.

**Table 2.9: A Table shows the Cognitive Performance of TBI Patients In Comparison To Healthy Normal Subjects.**

	Subject type	N	Mean	Standard Deviation
Present age	TBI patient	103	29.7087	13.95064
	Healthy control	20	32.4500	9.45613
Verbal fluency-total score	TBI patient	101	15.93	7.873
	Healthy control	20	24.30	6.538
Tower of London- Number of problems solved out of 12	TBI patient	103	7.66	2.190
	Healthy control	20	11.45	0.999
Standard Progressive matrices-Current IQ	TBI patient	100	28.62	5.436
	Healthy control	20	43.25	6.703
Buschke Selective Reminding Test (BSRT)	TBI patient	103	12.87	4.432
	Healthy control	20	26.05	6.100
Digit Span Total (FORWARD)	TBI patient	96	4.49	1.563
	Healthy control	20	5.65	1.226
Digit Span Total (BACKWARD)	TBI patient	96	2.51	1.005
	Healthy control	20	3.95	0.999
Wisconsin Card Sorting Test-Number of correct categories	TBI patient	101	2.94	1.964
	Healthy control	20	7.95	0.224
Wisconsin Card Sorting Test -Total number of errors	TBI patient	101	8.69	8.130
	Healthy control	20	2.45	1.191
Wisconsin Card Sorting Test -Perseverative errors	TBI patient	101	8.43	8.392
	Healthy control	20	0.55	0.686

When Lilliefors's normality test was applied, most of the variables were not normally distributed. Hence, to test for equality of means of the parameters, Wilcoxon's two independent sample tests were used. The results of this assessment are shown in table 2.10.

There is a significant difference between the TBI patients and the healthy control in all the parameters except in the present age where the two groups can be considered of similar age.

**Table 2.10: A Table shows the Statistical Analysis of the Cognitive Performance Data Cited in Table 2.9.**

	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
Present age	749.000	6105.000	-1.928	0.054
Verbal fluency	403.000	5554.000	-4.257	0.000
Tower of London- Number of problems solved out of 12	117.500	5473.500	-6.323	0.000
Standard Progressive matrices	80.500	5130.500	-6.492	0.000
Buschke Selective Reminding Test (BSRT)	48.000	5404.000	-6.748	0.000
Digit Span Total (FORWARD)	539.000	5195.000	-3.146	0.002
Digit Span Total ( BACKWARD)	268.500	4924.500	-5.396	0.000
Wisconsin-Number of correct categories	0.000	5151.000	-7.143	0.000
Wisconsin -Total number of errors	621.500	831.500	-2.724	0.006
Wisconsin -Perseverative errors	386.000	596.000	-4.414	0.000

*a Grouping Variable: subject type*

The two groups are significantly different on all these parameters (p-values are less than 0.01).



## 2.8.4 Psychiatric Functioning

### 2.8.4.1 Self Reporting Questionnaire

Sixty-six had a higher probability of having a psychiatric illness and 23 had a lower probability of having a psychiatric illness.

**Table 2.11: A table shows the Results of Self-Reporting Questionnaire of 103 TBI Patients**

Self-Reporting Questionnaire -first 20 items	N	%
Lower Range	23	22.3
Middle Range	14	13.6
High Range	66	64.1
Total	103	100

### 2.8.4.2 Hospital Anxiety and Depression Scale (HADS)

Assessing depression using (HADS), 56 patients were not depressed, 19 had mild depression, 20 had moderate, and four had severe depression.

Using the HADS anxiety subscale, 58 patients had no anxiety, 17 had mild anxiety, 18 had moderate, and six had severe anxiety.

## 2.8.5 Neurobehavioral Functioning

### 2.8.5.1 Post-concussion syndrome (Physical, Cognitive & Emotional symptoms)

In this study, 50 patients were found to have several physical post-concussion symptoms, 26 had a single post-concussion syndrome, and 23 had no post-concussion syndrome.

### 2.8.5.2 Fatigue Assessment Scale

Five patients had severe fatigue, 16 had moderate fatigue, 15 had mild fatigue, and 67 had no fatigue.

### **2.8.5.3 Apathy Evaluation Scale**

Using AES, 58 patients had no apathy, 30 had mild, 12 had moderate and one had severe apathy.

### **2.8.5.4 Neuropsychiatric Inventory (NPI)**

This assessment was used here only to identify the cases of depression, anxiety, and apathy. In terms of specific psychiatric illness and based on the NPI, 59 patients had no depression, 21 had mild depression, eleven had moderate and three had severe depression.

Similarly, 82 patients had no anxiety, eight had mild anxiety, two had moderate and two had severe anxiety. Seventy-five patients had no apathy, seven had mild apathy, four had moderate and eight had severe apathy according to the NPI.

## **2.9 DISCUSSION**

The main purpose of this study was to establish the prevalence of psychiatric complications in Omani TBI patients attending a Neurosurgical clinic.

Psychiatric complications in these patients are complex, as is the extent of potential post-TBI psychiatric syndromes; consequently, this study focused on some of the complications such as depression, anxiety, and apathy. Other psychiatric functioning, such as personality and psychotic disorders, were beyond the scope of the current study.

To find out the general psychological morbidity, a self-reporting questionnaire (SRQ) (Beusenberg & Orley, 1994) was used. This test consists of 24 short questions concerning the main symptoms of mental disorders. The patient can respond either 'yes' or 'no' to each question. This assessment has been established as a psychiatric case-finding instrument for detection of psychiatric patients among visitors to health care facilities (Al-Subaie et al., 1998).

Sixty-six of the 103 patients had a high probability of having a psychiatric illness (Table 12). This was supported by the frequency of high scores on both the anxiety (39.8%) and depression subscale (41.7%) of the HADS, in addition to a higher percentage of patients exceeding the threshold for apathy (41.7%) on the Apathy Evaluation scale.

Specific mood disorders such as depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). Forty-three of the 103 TBI patients (41.7%) scored greater than seven cut off, suggesting there is indication of presence of depression (Table 2.12). This is much greater than the prevalence of depression in the general population, which is estimated to be between 2-14 % (p-value<0.001) (Sher, Kahn, & Oquendo, 2010).

Several studies have shown that 14% to 77% of TBI patients suffer from major depressive disorder (Fann et al., 1995; Thombs, Bresnick, & Magyar-Russell, 2006) (Table 2.12). The wide range of TBI patients with depression is because of the different format of the studies. Some are clinical samples and others are community-based studies. Furthermore, the scales used in these studies are also different.

There is controversy whether depression in such a population is an integral part of the traumatic neurological event or a reaction to disability (Silver et al., 2010). There is also a suggestion that disorders such as 'depression' may not present in the same way in different cultures (Al-Adawi et al., 2007).

A recent study conducted in Oman found the prevalence of depression in Omani patients with TBI to be slightly higher (57.4%) (Al-Adawi et al., 2007). However, the setting of the study and the instrument used were different. In that study, the subjects were TBI patients who had been referred to a psychiatric clinic for evaluation and treatment of a psychiatric illness. Therefore, patients with a psychiatric illness such as depression would be overrepresented. Additionally, the Composite International Diagnostic Interview (CIDI) (WHO, 1993) was used to diagnose depression and it was found that HADS, which is used in the current study, is less sensitive than the CIDI for depression (Al-Adawi et al., 2007).

Similarly, anxiety was assessed using the anxiety subscale of the HADS. Forty-one patients (40%) had anxiety (Table 2.12), which is significantly more than the cases of anxiety reported in the general population (5.3%) (Wittchen & Hoyer, 2001).

An earlier study in Oman reported that the rate of anxiety in patients with TBI is 50% (Al-Adawi et al., 2007). This is higher than that found in the current study because the patients in the earlier study were recruited from a psychiatric clinic. Additionally the HADS, which was used in this current study, was found to be less sensitive for the diagnosis of anxiety in this population than the CIDI (Al-Adawi et al., 2007).

Studies elsewhere have found that between eleven and 70% of patients with TBI have anxiety disorders (Rao, 2002).

Fatigue was assessed using the Fatigue Assessment Scale (FAS) (Michielsen et al., 2003). The present study used a score of 21 or greater as an indication of clinical fatigue as suggested by De Vries et al. (De Vries, Michielsen, Van Heck, & Drent, 2004). Thirty-six of the 103 TBI patients (35%) had fatigue by this definition. Fatigue in patients with TBI is common and has been reported to affect between 21 and 73 % of TBI patients (Elovic, Dobrovic, & Fellus, 2005).

Post-concussion syndrome is one of the most common and difficult problems to manage in patients with TBI. Almost 90% of patients with TBI suffer from PCS (Ryan, 2003). In this study, 76 of the 103 (74%) had physical post-concussion symptoms.

The Apathy Evaluation Scale (AES) (Marin et al., 1991) has been designed to indicate whether or not a particular patient is apathetic. For this study, a cutoff score of 34 or greater was used to define the presence of apathy (Al-Adawi et al., 1998; Glenn et al., 2002; Isella et al., 2002).

Forty-three of the 103 brain injury patients (42%) had apathy by this definition (Table 2.12). Studies elsewhere have shown that between 46.4% and 71.1 % of TBI patients have apathy (Van Reekum et al., 2005).

However, previous studies in Oman showed the rate of apathy in Omani patients with TBI to be much lower, 20%, than the rate in the current study (Al-Adawi et al., 2004). This could be because the subjects in the previous study were recruited from a psychiatric clinic. This clinic would have less apathetic patients because patients with apathy usually do not complain of their symptoms (Al-Adawi et al., 2004). Therefore, they are less likely to be referred to a psychiatric clinic than patients with post-concussion symptoms are, for example.

The Neuropsychiatric Inventory (Cummings et al., 1994) usually is employed to assess 12 behavioural disturbances occurring after neurological events: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor activity, night time behaviours and appetite/eating. However, in this study, it was employed to assess only Apathy, Depression, and Anxiety.

In this test, the patients were asked if they felt depressed. If the answer was yes, then they were asked to rate their depression, whether it was mild, moderate or severe.

Fifty-nine (62.8%) patients out of 94 responded as not having depression, 21 (22.3%) had mild depression, 11 (11.7%) had moderate and three (3.2%) had severe depression.

If these results are compared with those from the HADS (depression subscale), where 57% of patients had no depression, 19% had mild depression, 20% had moderate and 4% had severe depression, it is clear that patients who have moderate to severe depression are less likely to report this and even when asked a direct question about whether they have depression. This means that their depression can only be reliably diagnosed by a standard depression test such as the HADS.

Possible explanations for the under-reporting include that these patients consider their depression to be a normal reaction to their brain injury and or that there is a reluctance to admit being depressed because of the stigma of having depression in this society (Al-Busaidi, 2010).

This illustrates the importance of doing formal psychometric tests when screening for mood disorders in TBI and other related patient populations.

Similarly, when screening for anxiety, the patients were asked if they felt anxious. If the answer was yes, then they were asked to rate their anxiety as to whether it was mild, moderate or severe. Eighty-two (87.2%) patients had no anxiety, eight (8.5%) had mild anxiety, two (2.1%) had moderate and another two (2.1%) had severe anxiety.

If these data are compared to the HADS anxiety subscale, (Table 2.5), in which fifty-eight (56.3%) patients had no anxiety, 17 (16.5%) had mild anxiety, 18 (17.5%) had moderate and six (5.8%) had severe anxiety, it is again clear that it is difficult to identify people who have a substantive problem of anxiety unless formal psychometric testing is undertaken.

However, in case of anxiety, the results are surprising. It is usually assumed that patients with anxiety would be likely to admit if they had anxiety symptoms, as such symptoms are usually physical symptoms (e.g. tremor, palpitations and sweating).

Again, a possible explanation here is that this under-reporting in response to a direct question could arise because of the perceived stigma of having a psychiatric illness (Al-Busaidi, 2010).

Apathy was screened for by using the NPI Apathy/indifference subscale, in addition to the standard Apathy Evaluation Scale (AES). In the latter test, patients were asked if they felt apathetic. If the answer was yes, then they were asked to rate their apathy as to whether it was mild, moderate or severe. Seventy-five (79.8%) patients had no apathy, seven (7.4%) had mild apathy, four (4.3%) had moderate and eight (8.5%) had severe apathy.

If these results are compared with those obtained on the AES, where 58 (56.3%) of patients had no apathy, 30 (29.1%) had mild, twelve (11.7%) had moderate and one (1%) had severe apathy, it is again clear that TBI patients often do not admit to substantive mental health problems and that the only reliable way to identify patients with mild or moderate apathy is to use a formal psychometric tool such as the AES.

**Table 2.12 A Table Shows the Mood Disorders Identified in the Current Study In Contrast To That Reported In Other Published Studies**

<b>Disorder</b>	<b>Total N (#studies)</b>	<b>% With Disorder</b>	<b>This study Total</b>	<b>% with disorder</b>
Depression	653 (8)	44	99	41.7
Anxiety Disorder	398 (5)	11-70	99	39.8
Apathy	304 (3)	46.7	101	41.7
Fatigue		21-73	103	35

Adopted from: Van Reekum, R., Cohen, T., & Wong, J. (2000). Can traumatic brain injury cause psychiatric disorders? *Journal of Neuropsychiatry and Clinical Neurosciences*, 12 (3), 316.

Previous studies have shown that cognitive impairments are among the most disabling complications of TBI and cause more disability than physical impairments (Brooks, McKinlay, Symington, Beattie, & Campsie, 1987; McCullagh & Feinstein, 2005).

Most of the cognitive tests have been previously validated in Euro-American population. Apparently, no psychometric property of the presently employed tools that are used as cognitive tests have been reported or validated in non-Western populations and in this regard, Oman is no exception.

It was therefore essential to compare the performance of victims of TBI with so-called healthy Omani subjects. These controls were recruited from an orthopaedic clinic. All efforts were made to rule out the possibility of any of these controls having any history of psychiatric illness or of brain injury. However, this cannot be completely ruled out, as still there is a possibility of these controls having had an unnoticed mild brain injury.

Nevertheless, these brain-injured patients were found to be relatively and significantly impaired in all of the cognitive functioning tests employed here. This demonstrates that the TBI patients have subtle, but debilitating cognitive impairment.

### **2.9.1 Demographic and Clinical Information**

The detailed analysis of how the demographic and clinical characteristics of these patients affected the presentation of psychiatric complications of TBI is beyond the scope of this study. However, some of the findings are worth mentioning.

#### **2.9.1.1 Age at Time of Assessment**

Age at the time of assessment is an important factor in regard to psychiatric complications of TBI. Studies have shown that these complications differ depending on the age of the patient. For example, it has been found that the cognitive performance of young TBI patients is better than middle aged (mean=49 years) TBI patients and the performance of middle-aged TBI patients is similar to that of older (mean=70 years) healthy control subjects (Klein, Houx, & Jolles, 1996).

It has been also reported that psychiatric complications of TBI are more prevalent in older individuals (Johnstone, Childers, & Hoerner, 1998).

In this study, the correlation between age at the time of assessment and depression, anxiety and apathy was not statically significant ( $p > 0.05$ ). This could be because the majority of patients in this study (75%) were young aged between 15 and 31 years. The older patients were underrepresented in this sample.

#### **2.9.1.2 Gender**

Studies have shown that men have twice the risk of TBI and a fourfold risk of fatal brain injury (Flaada et al., 2007; Rao & Lyketsos, 2000). In this study, almost 81% of the subjects were male.

Some studies suggest that the prognosis of TBI is worse in females (Kirkness CJ, 2004). However, in this study, there was no significant correlation between the disability rating scale (DRS) and gender ( $p = 0.97$ ). This could be because male subjects are over represented in this sample.



### **2.9.1.3 Educational Level**

In this study, it was found that the secondary education level was the highest level of education reached before the injury for the (35.9%) of patients. This is similar to the percentage of Omanis who have had secondary education in general population. According to the National Health Survey 2000, 48.6% had secondary level education or higher.

Therefore, the results here do not support those studies published elsewhere that suggest that people with lower levels of education are at greater risk of TBI (Hannay et al., 2004). However, this conclusion should be made with caution given the small number of study group.

### **2.9.1.4 Age at the Time of Injury**

Thirty three percent of patients (33%) who had TBI in this study were younger than 24 years at the time of the injury. However, only 13% of the Omani population are in that age range. This is consistent with data from studies done elsewhere, which have shown that most head injury victims are young (Flaada et al., 2007).

This is also crucial in terms of prognosis as patients who were injured at a younger age are at greater risk of injury sequel (Taylor & Alden, 1997). There were no statistically significant correlations between age at the time of injury and depression ( $r = -0.005$ ,  $p = 0.9$ ) or disability scale ( $r = -0.06$ ,  $p = 0.6$ ).

This contradicts studies cited earlier, which showed that the younger age at time of injury, the more disability. A possible reason for the discrepancy is that although there was a wide range of ages at the time of injury, 5-70 years, almost 50% had their injury between the ages 15-24.

### **2.9.1.5 Time since Injury**

Time since injury is another important factor in terms of the neuropsychiatric complications of TBI. As cited above, previous studies have shown that the nature and extent of the neuropsychiatric complications of TBI change with time after the injury (Dikmen & Reitan, 1977; Fordyce et al., 1983; Kinsella et al., 2009). Therefore, any reports of neuropsychiatric problems should be seen in the context of time elapsed after injury.

Previous studies have shown that the severity of depression increases with increase in time since injury (Silver et al., 2010). In this study, it was also found that the severity of depression increases with an increase in time since the injury. However the correlation was not statistically significant ( $r = 0.17$   $p = 0.16$ ).

### **2.9.1.6 Family Medical and Psychiatric History**

A family history of psychiatric illness predisposes to having a mental illness. In order to make sure that these patients had no other predisposing factors to the development of a psychiatric history, apart from the sentinel head injury, it was important to exclude patients with any family history of mental illness.

One hundred and two patients denied any family medical or psychiatric history, and one had a brother with schizophrenia. Given the absence of a personal and family past history of mental health and TBI, the psychiatric complications in these patients are more likely due to the TBI.

### **2.9.1.7 Radiological Findings**

As cited earlier, several studies have shown that a particular site of head injury is associated with certain neuropsychiatric complications. For example, depression has been associated with injury in the left basal ganglia and left dorsolateral frontal areas (Rao et al., 2010).

Similarly, right hemispheric lesions have been associated with anxiety disorders (Jorge, Robinson, Starkstein, & Arndt, 1993; Silver et al., 2010).

In this study, lesions were sited on the right side in 20%, on the left in 32%, 28% were bilateral and 20% had normal radiological findings. It follows that, the neuropsychiatric complications of TBI in these 103 patients were not affected by any predominance of specific hemispheric lesions.

In this study, it was found that 80% of the patients had radiological findings despite the fact that most of them (50%) had a mild TBI according to GCS scores. This could be explained by the fact that these patients were referred from peripheral hospitals. Therefore, only patients with radiological findings were likely to be referred regardless of the GCS scores. Hence the high percentage of patients with radiological findings. However, this finding also questions the credibility of GCS as an assessment of the severity of TBI.

Similarly, the majority of TBI patients have been shown to have diffuse brain injury (Ghajar, 2010). This was also the case here, where according to the radiology reports, 45% of the patient had this type of brain injury. The next most common was a frontal lobe injury (25%). Again, previous studies have shown that frontal lobe injury is frequent in TBI (Taber, Warden, & Hurley, 2006).

#### **2.9.1.8 Glasgow Coma Scale (GCS)**

Where available, the GCS was used in this study for classifying the severity of head injury. A GCS score of 13 to 15 was considered mild, nine to twelve was considered moderate, and eight or less was considered severe. The sample of 103 patients was found to be relatively heterogeneous; 12% of patients had a moderate head injury, and 52% and 36% had mild and severe head injuries respectively. Generally, mild TBI is more common than severe brain injury (Kraus et al., 2007). However, in this study, severe brain injury was more common.

One reason for this observation could be that these patients were recruited from a Neurosurgical outpatient clinic at which mild TBI patients were less likely to attend.

In this study, it was found that patients with severe brain injury had higher rates of depression, anxiety, and apathy. However, these associations were not statistically significant ( $p > 0.05$ ). Studies on the relationship between the severity of TBI and subsequent psychiatric complications are inconsistent. Some studies show a positive relationship and others shows no relationship (Fann et al., 2004).

## **2.9.2 General IQ**

### **2.9.2.1 Standard Progressive Matrices-Current**

It is crucial to estimate the patients' IQ so that the extent and specificity of psychological impairments of TBI patients can be assessed. Standard Progressive Matrices (SPM) was used for this purpose (Raven, 2000). Patients had an IQ equivalent of 20 to 110 (severe mental retardation to – high average). The mean IQ was 80 (low average) (Yehia, 2003).

This was also found in other similar studies (Lezak, 2004; Pivonka-Jones, Johnson, Randall, & Ashwal, 2014). These studies showed that the IQ usually drop immediately after moderate to severe brain injury, then the IQ significantly increases during the first six months. The studies also found that most of head injury patients have an average IQ (Lezak, 2004; Pivonka-Jones et al., 2014). Given the fact that most of our patients were assessed after 6 months of the injury therefore their IQ showed improvement.

Some studies have found an association between apathy and lower IQ (Van Reekum et al., 2005). However, others have not found this association (Anja et al., 2009). In this study, IQ was poorly associated with apathy ( $r = -0.09$ ,  $p = 0.37$ ), and depression ( $r = -0.16$ ,  $p = 0.2$ ).

### **2.9.2.2 Pre-morbid IQ estimate**

It has been suggested that patients who have a low IQ are prone to RTA (O'Toole, 1990; Smith DI, 1982). However, in this study, we found that almost 80% of these TBI patients had an average pre-morbid IQ. In addition, the psychiatric complications of TBI appear to be related to the individual's pre-injury IQ (Thomsen, 1992). In this study, we did not find a significant difference between the subjects who had an above average IQ and those that were below average, in terms of subsequent psychiatric complications ( $p = 0.8$ ).

## **2.10 LIMITATIONS OF THE CURRENT STUDY**

Generalisations from this study should be made cautiously because of the following limitations. The main limitation of this study is that the sample was recruited from the Neurosurgical outpatient clinic. Therefore, it may not be representative of Omani TBI patients.

However, the health care system in Oman is centralized. Until recently, all patients with TBI were referred to the Neurosurgical clinic at Khoula Hospital. Therefore, this sample can be considered as a representative sample of patients with TBI in Oman. However, the sample still has fewer mild type of TBI than would be expected and the most severe and chronic patients are not likely to be attending the clinic because of limitations on their mobility.

Another limitation is the reliability of some of the data that was taken from medical records, such as GCS scores as this was assessed by different physicians and some of the data were missing. Additionally, the sample size was a small and heterogeneous cohort with variations in severity of TBI, and time since injury.

Furthermore, although the control group matched with the TBI population group in the demographic background, there were not matched in the number of subjects. Only twenty “healthy” control subjects were used to compare the cognitive performance of 103 patients. However, it was clear that the cognitive performances of the TBI patients were significantly impaired compared to the healthy control.

Stigma of mental illness might also affect the results. Although one of the exclusion criteria for the study was past psychiatric history, because of the stigma, some patients might not have admitted having a history of psychiatric illness. Therefore, these patients were wrongly included in the study.

The validity of some of the assessment measures used here such as HADS and AES is also questionable. Furthermore, although the assessments were translated into the Arabic language, some of the meanings could have been lost in the translation process.

Because of cognitive impairment, the questioners were read to patients rather than the patients reading the questions themselves. It is possible that the patients were reluctant to reveal some of the sensitive issues, especially with high stigma of mental illness in the society.

Despite these limitations, the findings from this study can provide a basis for future studies that could be done with larger numbers of patients, longitudinal follow-up and, comparison with culturally validated assessment measures.

## **2.11 CONCLUSION**

Cognitive, emotional, and behavioural impairments are common in Omani TBI patients. Previous studies have shown that these problems are a source of significant distress and disability for both patients and their families.

Since effective treatment of these complications can improve the outcome and the quality of life, there is an urgent need for research on the epidemiology, pathophysiology, and treatment of psychiatric complications in these patients.

This will help in the development of a more comprehensive TBI rehabilitation framework within the country.

## **CHAPTER THREE: APATHY FOLLOWING TRAUMATIC BRAIN INJURY**

### **ABSTRACT**

*Poor motivation, described semantically here as Apathy, is one of the most common psychiatric complications of Traumatic Brain Injury (TBI). This chapter addresses the clinical indices of Apathy in 103 consecutive Omani TBI patients aged between 15 and 70 who attended a Neurosurgical follow-up clinic. Patients consenting to the study underwent various neuropsychiatric assessments. The data were then analysed using factor analysis, correlation and multiple regression techniques. The main finding was that frontal system cognitive impairment is the best predictor of apathy in these patients. This is consistent with the hypothesis that impaired motivation may be due to a disruption of the limbic-frontal-subcortical circuits.*

### **3.1 INTRODUCTION**

As reviewed in chapter two of this thesis, psychiatric complications are extremely common in patients with TBI. In addition to classical psychiatric disorders such as depression and anxiety, one of the most common, distressing and least well studied complication in these patients is Apathy (S Al-Adawi, Dawe, & Al-Hussaini, 2000).

Apathy is defined as “ a lack of motivation that is not attributable to a diminished level of consciousness, cognitive impairment or emotional distress” (Kiang, Christensen, Remington, & Kapur, 2003).

This chapter will further analyse the concept of apathy in Omani TBI patients. The study will explore the interrelationship between apathy and other behavioural, emotional, and cognitive sequel of brain injury. First, the definitions of apathy and concepts that often associated with motivation will be reviewed.

### 3.1.1 Definition of Apathy

The word *apathy* is derived from the Greek word *pathos* or passions (Chatterjee A & Fahn S, 2002; Fahn, 2005). A lack of passion or emotion is therefore called apathy. However, the term has been used not only to refer to a lack of emotion but also to a lack of motivation (Chatterjee A & Fahn S, 2002; Fahn, 2005).

Another term, which is usually used interchangeably with apathy, is Aboulia. Aboulia or abulia, is a term derived from the Greek word “boul” or (will); therefore, aboulia is defined as a lack of will. In Neuropsychiatry, aboulia is often associated with psychomotor retardation (S Al-Adawi, Dawe, et al., 2000).

Another term that is related to the concept of motivation is ‘conation’. The term refers to purposeful striving toward and the willing of task completion (Reitan & Wolfson, 2005). Historically, conation, together with cognition and affection were considered to be the basic three elements of mental functioning. However, recently the term is hardly used or referred to in the clinical literature.

Nevertheless, some studies have suggested that conation is frequently impaired in patients with brain injury (Reitan & Wolfson, 2005). This impairment might present as apathy.

The concept of apathy started more than 2,000 years ago when the Greek philosophers wrote about being *apathous*. This meant free from passions and was considered to be the only way to a happy life (S. E. Starkstein & Leentjens, 2008). Extreme emotions and passions were thought to prevent the brain from rational thinking and thus led to irrational behaviour. During the Renaissance, the term “Apathy” was used to refer to a state of freedom from passions. At that time, apathy was considered a preferred human lifestyle rather than a disorder. Later, by the early 19th century, the term apathy was used to refer to a state of “physiological and psychological non-reactivity” (S. E. Starkstein & Leentjens, 2008).

Subsequently, in 1991, Marin proposed to classify apathy as a specific neuropsychiatric syndrome, “characterised by diminished goal-directed behaviour, diminished goal-directed cognition, and decreased emotional concomitants of goal directed behaviour” (S. E. Starkstein & Leentjens, 2008).



Clinically, diminished goal-directed behaviour may present as a lack of effort, and persistence in the therapy tasks as well as in the time spent socialising. Diminished goal-directed cognition may present as a decreased interest in learning new things, lack of plans and goals, lack of concern about one's own health or functional status; and, finally, reduced emotional concomitants of goal directed behaviours may be indicated by flattened affect, and emotional indifference (S. E. Starkstein & Leentjens, 2008).

Marin defines apathy as a sequel of neuropsychiatric illnesses, such as Alzheimer's disease (AD), dementia, and TBI, rather than as a sign of emotional distress. For clinical purposes, Marin defined apathy "as a lack of motivation that is not attributable to a diminished level of consciousness, cognitive impairment or emotional distress" (Kiang et al., 2003).

Although the definition of apathy sounds straightforward, there is considerable debate about the definition and the nature of the disorder. Marin's definition of apathy suggests that apathy is a disorder of drive and motivation (Marin & Wilkosz, 2005).

Other definitions of apathy conceptualise apathy as a disorder of feelings and/or expression of emotions. For example, Sims defined apathy as "the absence of feeling that frequently occurs together with a lack of emotional sensitivity and flattening of affective response" (S. E. Starkstein & Leentjens, 2008). Furthermore, Levy and Dubois recently offered a more behavioural definition of apathy where they defined apathy as "a behavioural syndrome consisting of a reduction of self-generated voluntary and purposeful behavioural" (S. E. Starkstein & Leentjens, 2008).

Drubach et al suggested a more inclusive definition of Apathy (Drubach, Zeilig, Perez, Peralta, & Makley, 1995). They defined apathy as "a specific neurological syndrome, which manifests as a lack of spontaneity of action and speech, deficiency in initiation, inertia, mental and motor slowness, a reduction in an excursion of motion, poor attention and easy distractibility" (S Al-Adawi, Al-Naamani, et al., 2000).

This slowing in performance has been described in the literature using various terms such as bradykinesia, catatonia, and anhedonia. Other authors have used various terms such as "reward deficiency syndrome" (Robert et al., 2009), "dopamine deficiency syndrome" (Wolters, van der Werf, & van den Heuvel, 2008), and "amotivational syndrome" (Harris, Eng, Kowatch, Delgado, & Saldaña, 2010) to describe a group of related symptoms where poor motivation is the main feature.

Although there are conflicting views as to whether apathy should be considered as a primary disorder of emotion, a disorder of drive and motivations, or both, the most widely used definition includes behavioural and cognitive dimensions (S. E. Starkstein & Leentjens, 2008). Most recently, Van Reekum and colleagues proposed a similar definition of apathy which incorporate the emotional, cognitive and behavioural domains (S. Starkstein & Brockman, 2010; Robert Van Reekum, Stuss, & Ostrander, 2005).

Caplan has suggested “three criteria for the diagnosis of apathy: (I) decreased spontaneity in activity and speech; (ii) prolonged latency in responding to queries, directions and other stimuli; and (iii) reduced ability to persist with a task” (Drubach et al., 1995).

In regard to the current classification systems of psychiatric disorders, there is no mentioning of the term apathy in the International Classification of Diseases (ICD) -10 (WHO., 1993). However, in the Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> Edn, DSM-IV, the term apathy is used, not as a distinct disorder, but as a subtype of personality changes due to a general medical disorder (American Psychiatric Association, 1994).

### **3.1.2 Apathy and Depression**

Historically, poor motivation has been associated with depression. Earlier this century, Stoddard described depressive patients as being characterized by “... Generalized slowing and difficulty in getting started” (Bermanzohn & Siris, 1992). This ‘psychomotor retardation’ may be construed as reflecting impaired motivation.

Furthermore, according to both DSM-IV and ICD-10, a patient can be diagnosed with depression, even if he has no symptom of a depressed mood provided that he has a loss of interest or pleasure.

Therefore, a question arises as to whether apathetic patients can be consistently distinguished from patients with depression.

Several studies have suggested that these two syndromes are different (see table 3.1). For example, Kant et al examined the prevalence of apathy in 83 consecutive brain injury patients attending a neuropsychiatric clinic. In this study, 71% of these patients were found to have apathy, but only 60% had depression; this means that 11% of these patients had isolated apathy (Kant, Duffy, & Pivovarnik, 1998).

Similar findings were found in other diseases such as Alzheimer diseases (AD) (S. Starkstein, Petracca, Chemerinski, & Kremer, 2001), Parkinson’s disease (Sergio E Starkstein et al., 1992), and post stroke (Okada, Kobayashi, Yamagata, Takahashi, & Yamaguchi, 1997).

Other studies have shown that in patients with Parkinson’s disease, apathy and depression together is more frequent than depression in isolation (Dujardin et al., 2007).

**Table 3.1: A table shows the prevalence of apathy and depression in various neurological diseases**

Author	Disorder	N. Patients	Apathy	Depression	Pure Apathy
(S. Starkstein et al., 2001)	AD	319	37 (%)	24 (%)	13 (%)
(S. Starkstein et al., 1992)	Parkinson’s	50	42 (%)	30 (%)	12 (%)
(Okada et al., 1997)	Post stroke	40	50 (%)	20 (%)	30 (%)
(Kant et al., 1998)	TBI	83	71 (%)	60 (%)	11 (%)

Adopted from Van Reekum, R., Stuss, D. T., & Ostrander, L. (2005). Apathy: Why Care? *J Neuropsychiatry Clin Neurosci*, 17(1), 7-19.

Pharmacological studies also suggested that apathy and depression are different diseases. In a study of vascular dementia patients who were treated with Methylphenidate, “there was no association between apathy and depression before treatment, and neither did the level of depression decrease as apathy improved with treatment” (Robert Van Reekum et al., 2005). Similarly, in another treatment study of patients with post-TBI, apathy improved while depression did not in response to Bromocriptine (Powell, al-Adawi, Morgan, & Greenwood, 1996).

Finally, in a study analysing the correlation between variables of the Neuro psychiatric inventory (NPI), depression was not found to be correlated with apathy (Patten, 2001).

Separating apathetic and depressed patients is clinically significant, as these two disorders have been speculated to respond to different interventions (Butterfield, Cimino, Oelke, Hauser, & Sanchez-Ramos, 2010; Landes, Sperry, Strauss, & Geldmacher, 2001).

### **3.1.3 Apathy and Hedonism**

Pertinent to this view, the concept of will and motivation has been associated with philosophical ideas of hedonism. Hedonism is derived from the Greek word ‘hedone’, meaning ‘delight’, ‘enjoyment’, or ‘pleasure’.

The notion that hedonic mechanisms might provide direction to behaviour is credited originally to the ancient Greeks, who suggested that pleasure and pain are two fundamental forces governing behaviour (Bozarth, 1994); humans then, are thought to have an intrinsic tendency to seek pleasure and avoid pain.

The behaviour is thus determined by the anticipated consequences of their actions (i.e. how much pleasure they derive or anticipate to deriving).

In the psychological literature, hedonism is often equated with the seeking of pleasure, reward, or positive reinforcement. It has been applied, both explicitly and implicitly, in formulating the theory that behaviour is regulated by pleasure and pain.

Clinically, anhedonia is defined as “an inability to experience pleasure as manifested in facial expression, speech, behaviour, lifestyle and the individual’s account of personal experience” (S. E. Starkstein & Leentjens, 2008).

The relationship between Apathy and anhedonia depends on the initial definition of apathy; whether apathy is a primary emotional or behavioural disorder. If apathy is considered an emotional disorder, then anhedonia should be a compulsory diagnostic criterion. However, if apathy is defined as a behavioural disorder, then anhedonia may not be a necessary diagnostic criterion.

The concept of anhedonia also provides more evidence that depression and apathy are distinct disorders. Studies have found that anhedonia is more characteristic of depression than apathy in patients with dementia (Butterfield et al., 2010). However, other studies suggested that anhedonia is more related to apathy than depression (Butterfield et al., 2010).

Surprisingly, the concept of pleasure and anhedonia has not been explored in the context of apathy in TBI patients (Butterfield et al., 2010). Relevant study is overdue, and it may be useful to consider a counter-concept of hedonism, by way of the association of anhedonia with the clinical indices of apathy.

### **3.1.4 Apathy and Neurocognitive Functioning**

In addition to the disabling neurological and affective dysfunction, survivors of TBI often have various cognitive impairments (Coetzer, 2010; Geraldina et al., 2003). These impairments frequently involve cognitive functions that essential to effective goal-directed behaviour.

Such patients usually show characteristics of frontal lobe pathology, including excessive or diminished cortical and behavioural arousal, difficulty in planning or initiating activity, severe apathy or euphoria, disinhibition, and a reduced ability to monitor and control thought, speech, and actions (Fuster, 1989; Ross & Hoaken, 2010; Stuss & Alexander, 2000).

The "frontal lobe syndrome" also entails a characteristic disintegration of cognitive functions, which include a lack of mental flexibility, disturbances of concentration and memory, and a general failure to apply sensible problem-solving strategies.

Several studies have shown that apathy is associated with the frontal system cognitive dysfunction (Witgert et al., 2010). For example, AD patients with apathy were found to have a decrease in the performance of several cognitive function assessments such as the BSRT (total and delayed), Boston Naming Test, Wisconsin Card Sorting Test, the Purdue Pegboard, and verbal fluency (Robert Van Reekum et al., 2005). These assessments measures are known to assess the cognitive functions of the frontal lobe system.

Similarly, other studies have shown that the improvement in verbal fluency, Trails B performance, digit span, and BSRT occur concurrently with a resolution of apathy in response to treatment with Amantadine and Bromocriptine (Powell et al., 1996; Robert Van Reekum et al., 2005).

Several other studies show a significant association between executive function and apathy (Robert Van Reekum et al., 2005). Ponsford et al. compared the performance on several attention tests of 47 survivors of severe brain injury within a year of injury and compared them to a group of 30 orthopaedic clinic patients (Ponsford & Kinsella, 1992). It was concluded that the sequel of brain injury includes frontal lobe dysfunction. Furthermore, this dysfunction is present even in patients whose CT scans demonstrate no focal lesions the frontal lobe.

Although there are strong evidences for association between Apathy and cognitive dysfunction, there are conflicting opinions whether it is the cognitive dysfunction that causes the apathy or if the apathy causes the cognitive dysfunction. However, the general conclusion is that primary cognitive deficits do not usually cause apathy. For example, studies have shown that almost half of patients with primary cognitive impairment do not have Apathy (S. Starkstein et al., 2001).

Again, more study is needed to see if TBI-induced cognitive impairments exist in different cultures as little data from cross-cultural samples are available, and it is not clear if these broad spectrums of impairment contribute to a disorder of self-neglect.

### **3.1.5 Prevalence of Apathy**

Studies have shown that apathy is common in several neuropsychiatric disorders. In an extensive literature review on apathy, Van Reekum et al reported that 61% of TBI patients, 55% of patients with Alzheimer disease, and 41% of patients with lesion on the basal ganglia have apathy as it is shown in Table 3.2.

**Table 3.2: A table shows the prevalence of apathy in various neurological diseases**

Disorder	Total N (# studies)	# With Disorder	% With Disorder
Alzheimer diseases	1355(16)	752	55.5
TBI	129(4)	210	61.4
Basal ganglia l lesions	589 (12)	239	40.6
HIV	181(2)	54	29.8

Source: Van Reekum Robert, Stuss, D. T., & Ostrander, L. (2005). Apathy: Why Care? *J Neuropsychiatric Clin Neurosci*, 17(1), 7-19.

The Van Reekum et al. study also noted that regardless of the nature of the original illness, diseases that mainly affecting the cortex, such as AD and TBIs, have about 60% prevalence of apathy, while diseases that involve sub cortical structures have a point prevalence of only 40% (Robert Van Reekum et al., 2005). This suggests that the location of the brain pathology might be more influential than the nature of the pathology itself in terms of generating apathy.

Previous studies examining the prevalence of apathy in Omani TBI patients found that 18% to 90% of these patients have apathy (S Al-Adawi et al., 2007).

### **3.1.6 The Anatomy of Apathy**

It seems reasonable then to argue that there is an anatomical basis for impaired motivation. As Hippocrates suggested: *"From nothing else but the brain come joy, delights, laughter and sports, sorrows, grieve, despondency, and lamentations...madness and delirium...fears and frights which assail us...thoughts that will not come, forgotten duties, and eccentricities... All these things we endure from the brain..."* Hippocrates, *On the Sacred Disease*, 4<sup>th</sup> century B.C.

As discussed earlier, most studies indicate that mainly the frontal lobe is involved in cases of apathy.

It has been often reported that frontal lobe damage produces excessive or diminished arousal, apathetic behaviour, impairment of planning and initiating activity, euphoria, disinhibition, and reduced ability to monitor speech and actions (Fuster, 1989; Ross & Hoaken, 2010; Sundar & Adwani, 2010).

In addition to the frontal cortex, subcortical areas such as hypothalamic nuclei (Krahulik, Zapletalova, Frysak, & Vaverka, 2010; Salloway & Cummings, 1996), substantia nigra (Ehrt, Pedersen, & Aarsland, 2010; Freeman & Watts, 1942), and basal ganglia (Chakravarthy, Joseph, & Bapi, 2010; Galynker et al., 1997) have also been implicated in the pathogenesis of apathy.

Furthermore, previous studies have shown that diseases with similar symptoms to apathy, such as depression and negative schizophrenia have been associated with dysfunction in the dopaminergic brain circuit linking sub cortical and frontal structures (Ehrt et al., 2010).

Similarly, focal injuries to cortical--subcortical circuitry has been associated with apathetic symptoms (Jahanshahi, 1998; Koziol & Budding, 2009).

### **3.1.7 SPECT Findings in Patients with Apathy**

Neuro-imaging studies shed more light on the functional anatomy of apathy. Several Neuro-imaging studies of depressed patients with psychomotor retardation show reduction of metabolic activity in the frontal cortex (Baxter Jr et al., 1989). More recently, positron emission tomography (PET) studies of depressed patients with psychomotor retardation, showed a reduction of activity in the left dorsolateral prefrontal cortex (LDPFC), a region which has been consistently linked with the mediation of effortful and voluntary information processing (Bench, Friston, Brown, Frackowiak, & Dolan, 2009; Viviani et al., 2010).

An interesting finding from these studies is that the cortical structures do not have to be directly injured in order to show impairment. Di-Piero et al studied a patient with a small haemorrhage in the left globus pallidus (Di Piero, Chollet, Dolan, Thomas, & Frackowiak, 1990). Ten days after the stroke, PET scans revealed reduced metabolism in the cortex.



Consistent with these findings, Sultzer et al examined patients with intact cerebral cortices and found cortical metabolism, as measured by 18F-fluorodeoxyglucose positron emission tomography, to be inversely proportional to the size of the subcortical lesions measured by MRI (Sultzer et al., 1995). Similarly, Szekely et al found that patients with medial thalamic lesions had prominent frontal cortical metabolic deficits (Szekely et al., 1991).

In a case study by Metter et al., 18F-fluorodeoxyglucose-PET revealed a large area of hypometabolism in the left lateral frontal cortex in a patient with a lacunar infarct of the genu of the left internal capsule (Metter et al., 1985). In this patient, cortical architecture in the metabolically depressed regions was normal on histological examination. Recent studies have also confirmed the above findings (Sharma, Zimmermann Meinzingen, & Johanson, 2010).

The term diaschisis has been used to describe these remote effects of focal brain lesions (Baranova, Whiting, & Hamm, 2006). Thus, the observed 'subcortical' diaschisis may reflect a persistent compromise of the functional relationship between subcortical nuclei and the cerebral cortex. This may explain why brain injury that does not involve the frontal cortex, sometimes leads to impairments of motivation.

Neuro-imaging studies have also shown that the impairment these patients have is not temporal and can last for years. A SPECT study by Goldenberg et al. showed that, in comparison to normal controls, 36 survivors of severe head injuries had lower cerebral blood flow bilaterally in the orbital, frontal and basal ganglia regions more than three years after their injuries (Goldenberg, Oder, Spatt, & Podreka, 1992).

However, other studies showed that these SPECT findings improve when the patient is treated with a psycho-stimulant (Robert Van Reekum et al., 2005; Watanabe et al., 1995).

Another important conclusion from Neuro-imaging studies is that these data are consistent with a model of reduced dopaminergic function in apathy and depression because the frontal cortex is rich in dopaminergic innervations (D'haenen & Bossuyt, 1994; Lehto et al., 2008).

### **3.1.8 Apathy and Cross-Cultural Psychiatry**

The effects of culture on neuropsychiatric symptoms are well described (Kleinman, 1987; Napoles, Chadiha, Eversley, & Moreno-John, 2010; Vilalta-Franch et al., 1999). In the Arab world, disturbance of mood is often thought to manifest in somatic metaphor (S Al-Adawi et al., 2004; Al-Lawati et al., 2000). This contrasts to a predominance of cognitive metaphor among the Westernised world.

In this society, depressed patients will present with various somatic complaints such as headache and abdominal pain. This could be because of the stigma of having a mental illness makes patients feels more comfortable to talk about physical symptoms rather than emotional difficulties.

Additionally, in the Arab world it is believed that mental illnesses are caused by supernatural forces. Therefore, the proper place for treatment of these illnesses is with traditional healers rather than with conventional medicine.

Cross-cultural studies of apathy also show that this disorder is experienced differently in different cultures. For example, examining cross-cultural levels of distress among relatives of patients with Alzheimer Disease, Pang et al. (Pang et al., 2002) have shown that, in contrast to their American counterparts, aboulia like disorders in Chinese culture are “unlikely to be viewed by that society with contempt or as a social burden” (S Al-Adawi et al., 2004).

As cultures attach different meanings to life, and thus conceive reality differently, it would be fascinating to examine the relevance of the concept of aboulia in Oman where the collective identity of the family and tribal affiliations appear to be central to individual identity and function.

Furthermore, seeking treatment in this society is not only a social but also a religious obligation. Hence, it will be appealing to see how these beliefs might affect Omani TBI patients, who usually have low motivation for treatment.

From this background, it is clear that apathy has been related to various affective, cognitive, anatomical, and socio-demographic factors. Knowledge of these factors, and how they are associated with apathy, will enhance understanding of the pathogenesis of apathy.

This study will examine the concept of apathy in Omani TBI patients. In particular, the study will determine the best predictors of apathy among various clinical and demographic factors that are frequently reported in patients with TBI. Such a study has not been undertaken anywhere in the Arab world.

### **3.2 AIM OF THE PROJECT**

1. To establish the prevalence of apathy in Omani TBI patients attending a Neurosurgical outpatient clinic.
2. To examine the presence of other psychiatric disorders, which have been related to the concept of Apathy.
3. To explore the relationship between apathy and various clinical and demographic characteristics of patients with TBI.

### **3.3 HYPOTHESIS**

In view of the above background, it is hypothesised that:

1. Apathy is a common neuropsychiatric complication of TBI in Oman.
2. Apathy in patients with TBI is independent of affective dysfunctions such depression and fatigue.
3. Apathy is associated with neurocognitive impairments of mental activities that require effort.
4. Apathy is associated with frontal lobe system dysfunction.

### **3.4 METHODOLOGY**

This study is an extension of the study described in Chapter Two, and consequently, the methods for recruitment of participants and recording of demographic and other information is outlined in chapter two.

In brief, 103 patients presenting sequentially to a Neurosurgical follow up clinic underwent a range of neuropsychiatric and neuropsychological tests. The assessment measures are detailed on page 186.

From theoretical perspective as outline in the earlier chapters, the variable of main interest for this study was apathy as measured by the Apathy Evaluation Scale (AES) (Marin et al., 1991). It was speculated that lack of willed action or apathy tend to have negative repercussions on various cognitive, emotional and behavioural repertoire.

#### **3.4.1 Data Analysis**

Descriptive analysis was used to analyse 42 clinical and demographic characteristics, as detailed in chapter two of this thesis.

To investigate the potential relationships between these characteristics with the AES, Pearson's product-moment correlation coefficients were computed. A conservative Bonferroni correction was applied for deciding statistical significance. Therefore, (p-value) has to be lower than 0.001 (0.05/42) in order to be accepted as significant.

The Shapiro-Wilk (SW) and Kolmogorov-Smirnov (KS) tests for normality were used used to check for normality. If a variable is found to be non-normal, then the following transformations were tried, log base 10, log base e, square root and fourth roots.

Principal component analysis was used to group variables as a mean of data reduction.

Eigenvalues of more than one were used as the method to decide on the number of factors to be included in the multiple regression analysis. Fourteen factors had eigenvalues greater than one in the principal components analysis. These factors were entered as predictors in a stepwise multiple regression with the Apathy Evaluation Scale as the dependent variable.

All analyses were performed using SPSS for Windows version 15.0. (SPSS Inc.).

## **3.5 RESULTS**

### **3.5.1 Social-Demographic and Clinical Characteristics**

The demographic and clinical information such as age, sex, time since the injury and radiological findings of these patients are presented in Table 3.3.

As expected, given that the majority of the Omani population is relatively young, the majority of the TBI subjects in this study were also young, age ranged from 15 to 25 years.

In terms of education, the majority achieved the lower end of education (primary and secondary school) or were still attending an educational setting.

In terms of employment, the majority were still students. RTAs were the cause of TBI in all except one patient who had TBI due to falling down from a camel.

The remaining clinical data is shown in Table 3.3.

**Table 3.3: A Table Shows the Clinical and Demographic Characteristics of 103 Omani TBI Patients**

Parameter		No. of Patients	% of patients
Gender	Male	83	80.6
	Female	20	19.4
Age at the time of injury	15-25	64	62
	26-35	18	18
	36-45	3	3
	46-70	17	17
Time since injury	≤ 1 month	12	12
	More than one month and less than one year	45	42
	≥ 1 year	46	45
Education	Koranic education	17	16.5
	Primary	32	31.1
	Secondary	37	35.9
	Primary	8	7.8
	Some college	2	1.9
	Completed college	3	2.9
	Still students	4	3.9
Employment	Employed	45	45.0
	Unemployed	20	20
	Full time homemaker	4	4
	Student	31	31
Consanguinity	Yes	29	28
	No	73	71
History of acquired brain injury	Yes	0	0
	No	103	100
Injury severity (GCS)	GCS (mild; 13 to 15)	54	52.4
	GCS (moderate; 9 to 12)	12	11.7
	GCS (severe; less than 8)	37	35.9
Motor/Paralysis	No paresis/not classified	52	50.5
	Left-sided	29	28.2
	Right-sided	14	13.6
	Quadriparesis	3	4.9
Left vs. Right handedness	Right	73	70.9
	Left	30	29.1
Site of injury (Left vs. Right)	Normal	20	19.4
	Right side	21	20.4
	Left side	33	32
	Bilateral	29	28.2
Time since the injury	< 6 months	46	44.7
	7 to 12 months	11	10.6
	> 12 month	46	44.7
Neuroimaging data with CT or MRI	Diffused	46	46.5
	Bilateral frontal hematoma	30	30.3
	Focal	6	6.1
	Normal	17	17.2

*CT = Computed Tomography Imaging; MRI = magnetic resonance imaging; GCS = Glasgow Coma Scale*

### **3.5.2 Psychiatric Functioning**

The results of these assessments are detailed in chapter two of this thesis.

#### ***3.5.2.1 Self-Reporting Questionnaire***

To find out the probability of having a mental illness, a self-reporting questionnaire (SRQ) (Beusenberg & Orley, 1994) was used. This test consists of 24 short questions related to the main symptoms of mental disorders. The patient can respond either 'yes' or 'no' to each question. This assessment has been used for detection of psychiatric patients among visitors of health care facilities. However, it determines the prevalence of 'conspicuous psychiatric morbidity' (CPM) rather than a specific diagnosis. The assessment has been validated in various developing countries (Al-Subaie, Mohammed, & Al-Malik, 1998).

Sixty-six (64.1%) had a high probability and 23 had a lower probability of having a psychiatric illness.

#### ***3.5.2.2 Hospital Anxiety and Depression Scale***

Assessing depression using the HADS, 56 (56.6%) patients had no depression, 19 had mild depression, 20 had moderate, and four had severe depression.

Using the HADS anxiety subscale, fifty-eight (56.3%) of patients had no anxiety, 17 had mild anxiety, 18 had moderate and six had severe anxiety.

### **3.5.3 Neurobehavioral Functioning**

#### ***3.5.3.1 Post-concussion syndrome (PCS) (physical, cognitive, and emotional symptoms)***

In this study, 76 patients had physical PCS, 57 had cognitive PCS, and 51 had emotional PCS. Among the physical PCS, 50 patients were found to have multiple post-concussion symptoms, 26 had a single post-concussion symptom, and 23 had no post-concussion symptoms. In general, memory impairment was the most common single symptoms, found in 56 patients, followed by headache in 51 patients.

### **3.5.3.2 Fatigue Assessment Scale**

Five (4.9%) patients had severe fatigue; 16 had moderate fatigue; 15 had mild fatigue, and 67 had no fatigue.

### **3.5.3.3 Apathy Evaluation Scale**

Using the AES, 58 (56.3%) of patients had no apathy, 30 had mild, 12 had moderate, and one had severe apathy.

### **3.5.3.4 Neuropsychiatric Inventory (NPI)**

In terms of specific psychiatric illness, 59 (62.8%) of patients had no depression, 21 had mild depression, 11 had moderate and 3 had severe depression according to the NPI. Similarly, eighty-two (87.2%) patients had no anxiety, eight had mild anxiety, two had moderate and two (2.1%) had severe anxiety according to NPI.

According to the NPI, 75 (79.8%) of patients had no apathy, seven had mild apathy, four had moderate, and eight had severe apathy.

## **3.5.4 Predictors of Apathy (Apathy Evaluation Scale)**

To investigate the potential relationships with the AES, Pearson's product-moment correlation coefficients were computed. However, because of the large number of variables ( $n = 42$ ) analysed for a small number of subjects (103), the conservative Bonferroni correction was used for deciding statistical significance. Therefore, (p-value) has to be lower than 0.001 ( $0.05/42$ ) in order to be accepted as significant.

Among these variables, only Fatigue Assessment Scale had a statistically significant positive correlation with AES as shown in Table 3.4.



**Table 3.4: A Table shows the Correlations of Apathy Evaluation Scale with several Demographics and Neuropsychiatric variables.**

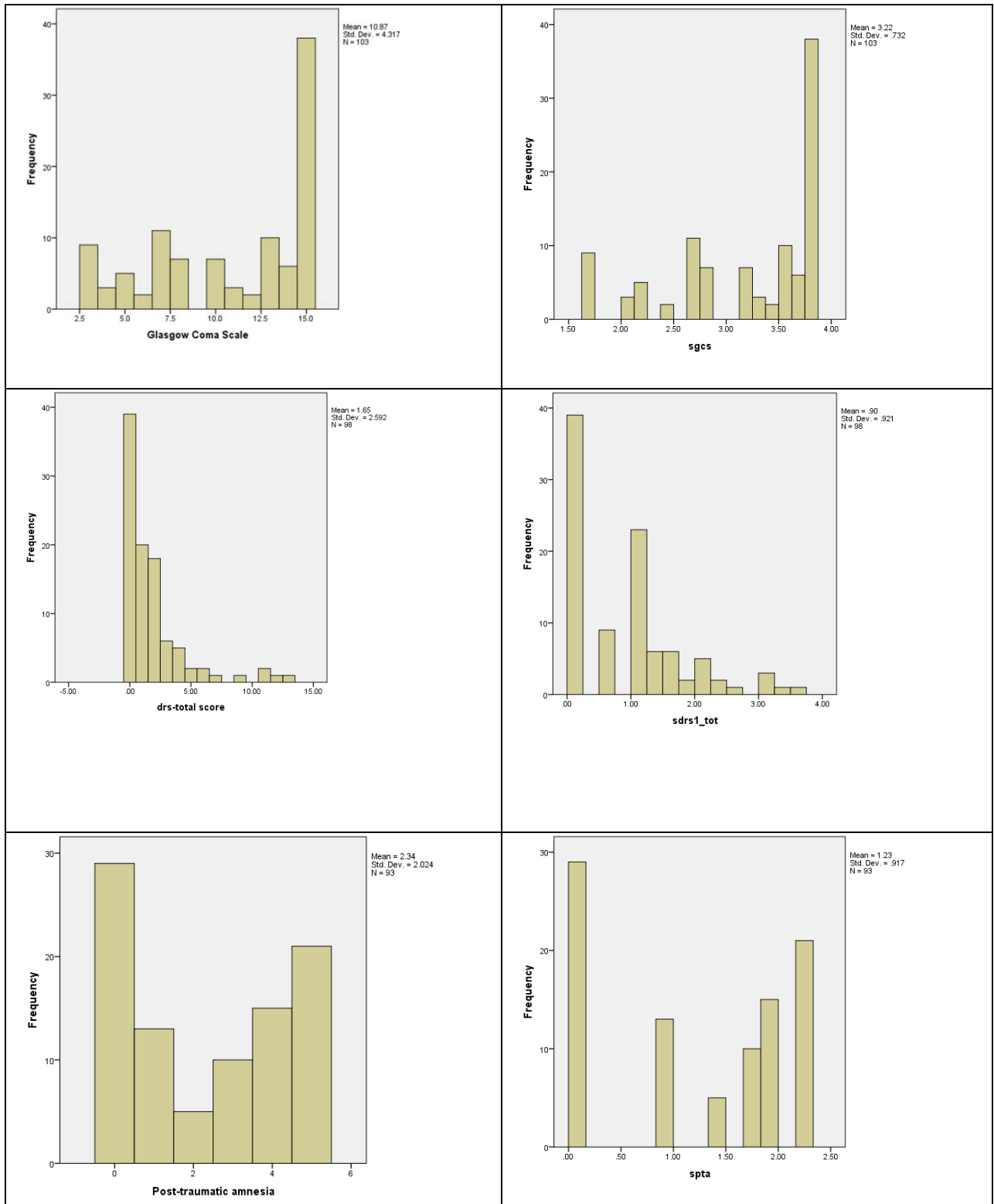
Measure	Correlation with Apathy Evaluation Scale		
	R	P-value (Not corrected)	N
<b>DEMOGRAPHIC INFORMATION AND CLINICAL INFORMATION</b>			
1. Present age	-0.138	0.169	101
2. Educational level	0.047	0.64	101
3. Age at the time of injury	-0.138	0.170	101
4. Time period from the time of injury to the first assessment date in months	-0.006	0.952	101
<b>LEVEL OF DISABILITY</b>			
5. Disability Rating Scale _Total score	-0.096	0.349	97
6. Glasgow Coma Scale	0.024	0.811	101
7. Post-traumatic amnesia	0.085	0.423	101
<b>COGNITIVE TESTS</b>			
8. Buschke Selective Reminding Test (BSRT)	0.161	0.108	101
9. Verbal fluency-total score	-0.014	0.892	99
10. WCST-Number of correct categories	0.123	0.223	99
11. WCST- Total number of errors	0.051	0.616	99
12. WCST-Perseverative errors	0.051	0.618	99
13. Tower of London	-0.070	0.489	101
14. Digit Span (Forward)	0.026	0.803	94
15. Digit Span (Backward)	-0.106	0.309	94
16. IQ Raven's Coloured Progressive matrices-Current IQ	-0.002	0.984	98
17. Premorbid IQ estimate	-0.026	0.797	101
<b>PSYCHIATRIC FUNCTIONING</b>			
18. SRQ First 20 questions.	-0.097	0.334	101
19. SRQ Psychotic items.	-0.057	0.574	101
20. SRQ Total Score.	-0.090	0.370	101
21. HADS Depression Subscale.	0.142	0.164	97
22. HADS Anxiety Subscale.	0.117	0.255	97

NEUROBEHAVIORAL FUNCTIONING			
23. PCS (Physical symptoms)	-0.130	0.203	98
24. PCS (Cognitive symptoms)	-0.053	0.599	101
25. PCS (Emotional symptoms)	-.006	0.949	101
26. NPI: Delusions	-.138	0.170	101
27. NPI: Hallucinations	0.302	0.002	101
28. NPI: Agitation / aggression	0.068	0.498	101
29. NPI: Depression	-0.013	0.896	101
30. NPI: Anxiety	0.146	0.144	101
31. NPI: Elation/Euphoria	0.257	0.010	101
32. NPI: Apathy	0.093	0.357	101
33. NPI: Disinhibition	0.092	0.362	101
34. NPI: Irritability	-0.011	0.910	101
35. NPI: Motor disturbance	0.009	0.928	101
36. NPI: Night time behaviours	0.141	0.160	101
37. NPI: Appetite/Eating	0.123	0.22	101
38. NPI: Total NPI	0.221	0.026	101
39. Fatigue Assessment Scale	0.313	0.001	101
40. CRS (Patients form)	-0.024	0.822	92
41. CRS (Clinical Form)	0.031	0.760	101
42. CRS (Attendant Form)	0.051	0.624	95

### ***3.5.4.1 Data Reduction: Principal-Components Analysis***

Normality test was performed using the Shapiro-Wilk (SW) and Kolmogorov-Smirnov (KS) tests. However, no transformation was found to give normality in any of the variables except log e (Apathy Evaluation Scale, (AES), log e (Time since injury), and square root (Hospital Anxiety and Depression Scale, Anxiety subscale). Some of the transformation graphs are shown here (Graph: 4.1), the complete set of graphs can be found in the appendix

**Figure 3.1: A Graph shows Glasgow Coma Scale, Disability Rating Scale, and posttraumatic Amnesia before and after transformation.**



Multiple linear regression analyses were used to determine the variables most predictive of apathy. However, because of the large number of variables and as most of them are conceptually related (BSRT and WCST), principal-components analysis was used to group related variables. This was used as a mean of data reduction.

Several original variables were not analysed in the principal-components analysis because they were regarded as not significant in this study such as (e.g. Gender, employment status). These lead to a reduction of the number of variables to 42 variables.

A commonly held view is that principal component analysis requires a subject: variable ratio to be at least 4:1 or 5:1. However, some researchers consider this a conservative ratio (Hair Jr, Anderson, Tatham, & William, 1995). In fact, Kline et al demonstrated empirically that even a subject: variable ratio as low as 3:1 can produce factors similar to those produced with ratios as high as 20:1 (Kline & Barrett, 1983). However, findings from smaller subject: variable ratios should be interpreted cautiously.

In view of the relatively small sample tested here, it was important to exclude as few of the subjects as possible. Eleven subjects had at least one data point missing, reducing the sample with complete data to only 92. Two approaches to this problem of missing data were considered. The first is to use mean substitution; however, this can lead to an inflated variance in the first component (Savournin, Evans, Hirst, & Watson, 1995). An alternative approach is to delete the data pair wise at the stage of calculating the inter-item correlation matrix prior to the component analysis. However, with the present data, the matrix produced failed to be definite. Therefore list wise deletion was identified as the preferred approach of capitalising on the available data without introducing severe distortions. This reduced the number of subjects analysed in multiple regression analysis of 62 subjects.

Variables with eigenvalues greater than one in the principal components analysis were subjected to Varimax rotation. Fourteen factors had eigenvalues greater than one accounting almost 79% of the variation.

The relatively large number of factors is an indication of the low correlation between most of the variables. The results of that rotation are shown in Table 3.5 and Table 3.6.

**Table 3.5: A table shows the first seven factors accounted for much of the variability in the Apathy Evaluation Scale. Rotated Component Matrix (a)**

	Component													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
NPI: Disinhibition:	.884													
WCST -Perseverative errors	.845													
WCST-Number of correct categories	-.693													
WCST -Total number of errors	.541													
NPI: Delusions:	.525													
CRS (Relative)		.967												
CRS (Clinician Form)		.963												
CRS (Patients form)		-.809												
HADS (Anxiety)			.837											
HADS (Depression)			.804											
FAS scale 1 results			.663											
Digit Span Total (BACKWARD)				.814										
Digit Span Total (FORWARD)				.806										
Tower of London- Number of problems solved out of 12				.795										
SRQ - Total Score					.949									
SRQ -First 20 items					.910									
SRQ - Psychotic items					.707									
Present age						.949								
Age at the time of injury						.929								
PCS – emotional symptoms							.763							
PCS -Cognitive symptoms							.760							
PCS -Physical symptoms							.521							
NPI anxiety severity								.805						
Time period from the time of injury to the first assessment date in months								.769						
NPI depression severity								.618						
NPI apathy severity									.862					
DRS-total score									.542					
Buschke Selective Reminding Test (BSRT)										.722				
NPI: Elation/Euphoria:										.576				
NPI: Appetite/Eating:										.485				
Raven's Coloured Progressive matrices-Current IQ										.418				
Glasgow Coma Scale											-.631			
Premorbid IQ estimate											.581			
NPI: Agitation. Aggression:											.580			
NPI: Motor disturbance:												.871		
NPI: Hallucinations:										.429	.461			
Verbal fluency-total score													.839	
NPI: Nighttime behaviours:														.702
Post-traumatic amnesia														-.501

Extraction Method: Principal Component Analysis.

Rotation Method: Varimax with Kaiser Normalization. A Rotation converged in 45 iterations.

Factor one was related most closely to all three subsets of the Wisconsin Card Sorting Test (perseverative errors, number of correct categories, and the total number of errors). Therefore, this component was labelled The Frontal Lobe Function Factor.

Factor two was related most closely to the three subsets of the Patient Competency Rating Scale (attendant, clinical, and patient forms). Therefore, this factor was called The Competency Factor.

Factor three was related most closely to both subsets of HADS (Anxiety and Depression) and followed by the Fatigue Assessment Scale. This factor was called The Mood Factor.

Factor four was related most closely to the two subsets of digit span (backward and forward) followed by the Tower of London scale. Therefore, this factor was called The Attention and Memory Factor.

Factor five was related most closely to the self-reporting questionnaire. This factor was called General Mental Health Factor.

Factor six was related most closely to age at the time of injury and age at the time of assessment. This factor was called Age Factor.

Factor seven was most closely related to the post-concussion syndrome assessment. This factor was called Post-Concussion Syndrome Factor.

Each of the components accounted for the following amount of variance in the Apathy Evaluation Scale: Frontal lobe function factor = 8.0%; Competency Factor = 7.4%; Mood factor = 6.8%; Attention and memory factor = 6.8%; General mental health factor = 6.4%; Age factor = 5.9% and Post-concussion syndrome factor = 5.7% as shown in Table 3.6.

**Table 3.6: A table shows the total amount of variances explained by the first fourteen factors in the principle component analysis**

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
	Total	% of Variance	The Cumulative %	Total	% of Variance	The Cumulative %	Total	% of Variance	The Cumulative %
1	4.599	10.949	10.949	4.599	10.949	10.949	3.357	7.992	7.992
2	4.491	10.692	21.641	4.491	10.692	21.641	3.128	7.448	15.440
3	3.511	8.359	30.000	3.511	8.359	30.000	2.877	6.850	22.290
4	2.976	7.087	37.087	2.976	7.087	37.087	2.864	6.820	29.110
5	2.762	6.575	43.662	2.762	6.575	43.662	2.694	6.413	35.523
6	2.547	6.064	49.726	2.547	6.064	49.726	2.466	5.872	41.396
7	2.211	5.265	54.991	2.211	5.265	54.991	2.409	5.735	47.130
8	1.860	4.429	59.420	1.860	4.429	59.420	2.314	5.510	52.640
9	1.802	4.290	63.710	1.802	4.290	63.710	2.113	5.030	57.671
10	1.486	3.538	67.248	1.486	3.538	67.248	1.995	4.751	62.421
11	1.402	3.337	70.585	1.402	3.337	70.585	1.882	4.480	66.901
12	1.291	3.073	73.658	1.291	3.073	73.658	1.842	4.387	71.288
13	1.119	2.663	76.321	1.119	2.663	76.321	1.603	3.818	75.106
14	1.077	2.565	78.886	1.077	2.565	78.886	1.588	3.780	78.886

Extraction Method: Principal Component Analysis.

#### ***3.5.4.2 Relationship of Factor Scores to Apathy Evaluation Scale: Multiple Regression Analysis***

The fourteen factors, which had eigenvalues greater than one in the principle components analysis, were entered as predictors in multiple regression analysis with the Apathy Evaluation Scale as the dependent variable. The results of this analysis are shown in table (3.7).

Factor 10 emerged as the first predictor ( $t = 2.85$ ,  $p = 0.007$ ). This factor was related most closely to BSRT. Therefore, this factor was called the Working Memory Factor.

The remaining factors were not statistically significant contributors, but, the next greatest contribution was made by Factor two ( $t = 1.57$ ,  $p = 0.124$ ). This factor was called the Competency Factor. None of the remaining factors made any significant improvement in the regression, even when the probability of entry and removal were set high at 0.35 and 0.4 respectively (Table 3.7 and table 3.8).



**Table 3.7: A table shows the result of regression analysis**

Model	Unstandardized Coefficients		Standardized Coefficients	T	Sig.	Correlations			Collinearity statistics	
	B	Std. Error	Beta			Zero-order	Partial	Part	Tolerance	VIF
(Constant)	34.909	1.394		25.041	0.000					
REGR factor score 1 for analysis 1	-1.241	1.415	-0.109	-0.877	0.385	-0.109	-0.127	-0.109	0.997	1.003
REGR factor score 2 for analysis 1	2.204	1.407	.195	1.566	0.124	0.201	0.223	0.195	0.998	1.002
REGR factor score 3 for analysis 1	1.981	1.393	0.177	1.422	0.162	0.177	0.203	0.177	1.000	1.000
REGR factor scores 4 for analysis 1	-0.457	1.395	-0.041	-0.328	0.744	-0.042	-0.048	-0.041	1.000	1.000
REGR factor score 5 for analysis 1	-0.628	1.400	-0.056	-0.449	0.656	-0.058	-0.065	-0.056	0.999	1.001
REGR factor scores 6 for analysis 1	-1.501	1.399	-0.134	-1.072	0.289	-0.136	-0.155	-0.133	0.999	1.001
REGR factor score 7 for analysis 1	-0.117	1.393	-0.010	-0.084	0.933	-0.010	-0.012	-0.010	1.000	1.000
REGR factor scores 8 for analysis 1	0.628	1.393	0.056	0.450	0.654	0.056	0.066	0.056	1.000	1.000
REGR factor score 9 for analysis 1	0.826	1.394	0.074	0.592	0.556	0.073	0.086	0.074	1.000	1.000
REGR factor score 10 for analysis 1	3.984	1.399	0.355	2.848	0.007	0.356	0.384	0.354	0.999	1.001
REGR factor score 11 for analysis 1	-1.547	1.393	-0.138	-1.110	0.273	-0.138	-0.160	-0.138	1.000	1.000
REGR factor score 12 for analysis 1	1.176	1.396	0.105	0.842	0.404	0.104	0.122	0.105	0.999	1.001
REGR factor score 13 for analysis 1	-0.164	1.393	-0.015	-0.118	0.907	-0.015	-0.017	-0.015	1.000	1.000
REGR factor score 14 for analysis 1	-0.373	1.420	-0.033	-0.262	0.794	-0.037	-0.038	-0.033	0.997	1.003

a Dependent Variable: apathy evaluation scale patients

The acceptability of the model from a statistical perspective was assessed using ANOVA analysis (Table 3.8). The assessment showed that although not statistically significant, the sum of squares indicates that the model explains more than one third of the variation in the Apathy Evaluation Scale.

**Table 3.8: A table of regression analysis shows acceptability of the model from a statistical perspective. ANOVA**

Model		Sum of Squares	Df	The Mean Square	F	Sig.
1	Regression	2110.381	14	150.741	1.254	0.271
	Residual	5651.361	47	120.242		
	Total	7761.742	61			

This table shows that the multiple correlation coefficient (R) is large (0.521) (table 3.9). This indicates a strong linear correlation between the observed and model-predicted values of the Apathy Evaluation Scale.

**Table 3.9: A table shows the model summary (b) of predictors of AES.**

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.521 <sup>a</sup>	0.272	0.055	10.965

### 3.6 DISCUSSION

As reviewed earlier, several demographic and clinical variables of patients with TBI have been reported to be strongly correlated with apathy (Anja et al., 2009; R. E. Jorge, Starkstein, & Robinson, 2010; Marin RS, 1996; Robert Van Reekum et al., 2005; Witgert et al., 2010). Knowledge of these factors, and how they are correlated with apathy, will improve understanding of the pathogenesis of Apathy. This will also enhance the understanding of other disorders of motivation such as Parkinson's disease, Schizophrenia with negative symptoms and retarded Depression.

The first aim of this study was to find the prevalence of apathy and other psychiatric complications of TBI that have been reported to be associated with apathy. One hundred and three patients were screened for various psychiatric complications as detailed in Chapter two of this thesis. Among these, 43.4% were found to have depression, 43.7% had anxiety, 33% had fatigue, and 42% had apathy.

The second aim was to determine the best predictors of apathy among various clinical and demographic factors. Multiple regression analysis was used for this purpose. The results of the analysis showed that only the Buschke Selective Reminding Test (BSRT) accounted for a significant amount of the variability in the Apathy Evaluation Scale (AES). BSRT is a cognitive assessment that was found to be sensitive to 'frontal lobe system impairments (Lezak, 2004). Therefore, the findings of this study confirm the main hypotheses of this study that apathy in TBI patients would be associated with cognitive impairments associated with frontal lobe system.

However, another cognitive assessment which is also associated with frontal lobe system, WCST, failed to make any significant contribution to AES (Lezak, 2004). This suggests a functional separation between cognitive functions concerned with learning new information (as assessed by BSRT) and those concerned with deductive reasoning and mental flexibility (WCST).

It is notable that BSRT is an effortful task, in that learning and recall can be enhanced by application of encoding and / or retrieval strategies, and / or rehearsal. Therefore, this task is much more likely to be impaired in patients with apathy. However, this could also mean that WCST is less sensitive to frontal lobe impairment as suggested by others (Anderson, Damasio, Jones, & Tranel, 1991; Mountain & Snow, 1993).

It is also fascinating to note that both BSRT and WCST were not grouped together in the principle component analysis.

The rest of the variables, notably the mood factors, did not have a significant contribution to the variability of AES. This also confirms the second hypothesis of this study that apathy is independent of affective dysfunction. However, this finding is interesting because despite significant overlaps between the behaviours one would expect to be related to poor motivation and low mood, the separation observed here suggests that the pathogenesis of poor motivation and subjective symptoms of depression may involve different mechanisms. This also contradicts the opinion that poor motivation, which is frequently seen in TBI patients, is simply secondary to depression (Butterfield et al., 2010; S. Starkstein & Brockman, 2010).

Although it was not statistically significant and did not contribute significantly to the variance of AES, the Patient Competency Rating Scale (PCRS) (attendant, clinical, and patient forms) was the next best predictor of AES after BSRT. The primary purpose of the PCRS is to evaluate self-awareness “the ability to appraise one's current strengths and weaknesses following traumatic brain injury” (Prigatano, 1986). PCRS is a 30-item self-report instrument that asks the subject to use a 5-point Likert scale to rate their degree of difficulty on a variety of tasks and functions. Total scores range from 30 to 150, with higher scores indicating greater competency. The subject's responses are compared to those of a significant-other (e.g. a relative or therapist) who rates the subject on the identical items. Impaired self-awareness may be inferred from discrepancies between the two ratings, such that the subject overestimates their abilities compared to the other informant.

In this sample, the scores were recorded as a total score for each form (attendant, clinical, and patient forms). The direction of the relationship between AES and PCRS in the multiple regression scale was positive. This means that the more competent (in total score) the patient is, the less apathetic they are. This was also confirmed looking at the individual's scores that showed a positive correlation between the PCRS (self-reports) and apathy. This means that the less competent the patients evaluated themselves, the more apathetic they were. However, this was not the case looking at the attendant and the clinical forms of PCRS which showed that the less competent the patient is, the less apathetic they are. This suggests that in the pathogenesis of apathy, how patient perceive himself to be competent is much more crucial than the attendant evaluation.

Although it was not statistically significant after applying the conservative Bonferroni correction, one of the surprising findings of this study was the positive correlation between elation/euphoria, hallucination and apathy. This could be because, in cases of elation and hallucination, patients realize that they have a severe mental illness. As a result, they become apathetic, especially that self-awareness was also found to be contributing much to the Apathy Evaluation Scale. This means that the more the patients become aware of the severity of their illness, the more apathetic they become.

Another surprising finding of this study is that the severity of TBI did not make much contribution to the AES. Although this has been reported elsewhere (Rehabil, 2010), one would expect apathy to be correlated with the severity of TBI. Even more interestingly, the direction of the relationship between the severity of TBI (GCS score) and AES was positive. This means the higher the score of GCS (less severe TBI) the more apathetic the person become.

This could arise because the assessments of the severity of TBI and the apathy evaluation were done on different occasions (i.e. the severity of TBI was assessed at the time of injury while apathy was assessed at the subsequent visits to the outpatient Neurosurgical department). However, another explanation could be that, in case of severe brain injury, the cognitive awareness of the level of disability is impaired in these patients. This cognitive function could be crucial in the pathogenesis of apathy as discussed earlier.

Previous studies in stroke patients showed that older patients are more likely to have apathy than younger patients are (Sagen et al., 2010; Robert Van Reekum et al., 2005). In this study, the age factor failed to make any significant contribution to the variance of AES. Even more interestingly, the direction of the relationship was negative. This means that the older patients are less likely to have apathy than younger TBI patients are. Again, this could also be because with increased age these patients lose cognitive abilities, such as awareness of the level of disability, some of which might be decisive in the development of apathy.

### **3.7 CONCLUSION**

The findings from this study confirm the hypothesis made in the introduction. However, these findings should be treated cautiously pending replication. Particularly, that most of the variables were non-normal, and no simple transformation could make them normal. Hence, the results give an indication of what the real situation may be.

The small number of the subjects in the study and a further reduction of sample size due to missing data for many of the participants may limit the reliability of the findings. Unfortunately, this is often the case when doing research with patients whose brain injury is diverse and severe.

A recommendation for future studies is to study the predictors of apathy in a larger number of subjects. An increase in sample size may alleviate some of the distributional concerns. Since most variables were non-normal, it will be interesting for the future study to analyse the data using non-parametric regression.

It will also be appealing to study the association with apathy in other populations, such as in orthopaedic patients and to use other affective scales as some investigators have recently suggested that HADS may not be effective in the diagnosis of depression in Omani patients with TBI (S Al-Adawi et al., 2007).

## **CHAPTER FOUR: THE INEFFECTIVENESS OF TBI REHABILITATION SERVICES IN OMAN**

Originally, this chapter was going to present the findings of a study looking at the effect of methylphenidate on apathy in post TBI patients.

However, as the attempted trial proceeded it became obvious that the numbers required were falling way below those that had been anticipated. It was realised that this failure was in part due to the inability of rehabilitation services to provide an appropriate level of follow-up and support for Oman TBI patients with psychiatric complications. Further, a number of other social and cultural influences may have exerted an influence.

Hence, instead of merely reporting the results of the clinical drug study, a decision was made to use the problems with implementing the study, to examine the adequacy of rehabilitation services provided to people with moderate to severe forms of TBI in Oman.

Because the original focus was on the methylphenidate trial, justification for this as a drug study is still provided, as is a description of the study design and some of the results.

The discussion of the results, and the very low completion rate, provides the opportunity for reflection on the reasons for this, and the service provision, social and cultural factors that may have contributed to the difficulties in completing this study.

On this ground, the initial employment of this study, to evaluate the effectiveness of Methylphenidate in the treatment of Apathy, became a tool to assess the overall status of TBI rehabilitation program in Oman.

## **ABSTRACT**

*Chapter two and three of this thesis have demonstrated that psychiatric complications, including apathy, are extremely common among Omani TBI patients. Therefore, in order to be effective, any rehabilitation program for these patients should include psychiatric services. The system should also be able to test any novel treatment in this developing field of Medicine.*

*As reviewed earlier, Oman does not have a multidisciplinary TBI rehabilitation centre. TBI patients, attending regular Neurosurgical or physiotherapy follow-ups and found to have a psychiatric complication, are referred to Ibn Sina Hospital or Sultan Qaboos University Hospital (SQUH) for further evaluation and management of the psychiatric complications.*

*The aim of this study was to assess the effectiveness of the rehabilitation services provided for Omani TBI patients with psychiatric complications.*

*To test these services two aspects of services delivery were chosen. The first was the capacity of the services to maintain TBI patients with psychiatric complications on regular psychiatric follow-ups at SQUH. The second aspect was to assess the ability of the system to enable a basic drug trial on the psychiatric complications of TBI. These were assessed as part of an attempt to perform a research study, initiated to examine the effects of Methylphenidate on the functioning of apathetic TBI patients. This study was chosen as tests of the rehabilitation system, in the belief that, in a well-functioning service, the studies should be able to be successfully completed.*

*The study was a follow-up to the work presented in earlier chapters of this thesis. Forty-three apathetic, TBI patients who were attending a regular Neurosurgical clinic, were included in the study. These patients were assessed for mood, fatigue, and cognitive functions, in addition to apathy. The patients were then asked to attend regular follow up and management of their apathy at the psychiatric clinic of SQUH. After repeated baseline measurements, Methylphenidate SR 20 mg was started and gradually increased over four weeks.*

*Assessments were repeated during the maintenance period and after the drugs were withdrawn. Patients who attended the psychiatric clinic and adhered to the prescribed treatment were analysed.*



*Out of the forty-three, only three patients could complete the study. The remaining patients dropped out during different stages of the study. Therefore, it was unreasonable to complete the natural observation on the effect of Methylphenidate in these patients.*

*The trial showed that the current TBI rehabilitation system in Oman is not sufficiently organized to provide the required psychiatric services for TBI patients. The study also revealed that the system could not even accommodate a basic drug administration and follow up regimen.*

*This demonstrated the limitations and ineffectiveness of the current rehabilitation system. Changes to the administration and delivery systems must be made if patients with TBI are to receive appropriate treatment.*

#### **4.1 INTRODUCTION**

As reviewed in chapters one and two of this thesis, Oman has one of the highest prevalence of TBI patients in the world (Al-Reesi et al., 2012).

The number of these patients is predicted to increase in the coming years because of the increasing in number of Oman population, Road Traffic Accidents (RTAs) and concurrent improvement in Emergency services and Neurosurgical interventions (Al-Naamani & Al-Adawi, 2007).

As demonstrated in chapter three of this thesis, neuropsychiatric complications are particularly common in Omani TBI patients. This situation warrants a comprehensive, multidisciplinary TBI rehabilitation program.

According to WHO, rehabilitation is “a process aimed at enabling disabled patients to reach and maintain their optimal physical, sensory, intellectual, psychological, and social functional levels. Rehabilitation provides disabled people with the tools they need to attain independence and self-determination” (Ravnborg, 2012).

In cases of more severe brain injury, rehabilitation often consists of two phases. The first is the inpatient stage that usually takes one to three months post injury. Although the focus in this phase is on Neurosurgical interventions, it is also the phase where detailed analysis of functional impairments is done, and an individualized program based on the needs of the patient is planned. In this phase, the patient is also prepared for the outpatient, often long-term, rehabilitation process.

The second phase is the outpatient or community phase that may last for more than two years, depending on the severity of the injury, the disability and the age of the patient. The second phase is the phase that focuses directly on enabling the brain-injured person to re-integrate into society as fully as possible. In this phase, rehabilitation ideally consists of varied and multiple interventions, including surgical, nursing, occupational therapy, speech, physical, and psychological care.

The aim of a TBI rehabilitation program is to help patients return as much as possible to his or her pre-morbid functioning. As reviewed earlier, this is not only restricted to physical functioning, but also to psychological and occupational functioning. In fact, studies have shown that the rehabilitation process is likely to fail if the psychological and vocational domains are not addressed (Gupta & Taly, 2012).

As a result, many TBI rehabilitation programs worldwide adopted a comprehensive, bio psychosocial rehabilitation programs. These rehabilitation systems often consist of various interventions, including surgical, occupational, speech, physical, and psychological care (Cernich, Kurtz, Mordecai, & Ryan, 2010; Vas, Chapman, Cook, Elliott, & Keebler, 2011).

Studies have shown that these comprehensive programs does not only improve rehabilitation outcome, but also are found to be cost effective (Caracuel et al., 2012; Schönbergera, Humle, Zeeman, & Teasdale, 2006). A study of 145 TBI patients showed that the estimated savings in care costs following rehabilitation was over 40,500 (USD) per year (L. Turner-Stokes, 2008).

Another study showed that the spending in health and social care for patients attending a rehabilitation program was recouped in 5 years (Murphy et al., 2006). This is because the cost of not rehabilitating TBI patients is significant given the fact that most of these patients are young and productive members of societies, with relatively normal life expectancy.

Recently there have been considerable improvements in the TBI rehabilitation programs. Several new intervention methods such as task-specific training for cognitive impairments have been added (Hartley et al., 2011; Walker, Bell, & Watanabe, 2012). In psychopharmacological development, new compounds such as Methylphenidate, have been added to rehabilitation programs and found to improve the outcome (Hartley et al., 2011; Walker et al., 2012).

Therefore, an effective rehabilitation system should not only have all the necessary subspecialties such as speech therapy, physical therapy, and psychiatric services, but also a system where innovative models of care can be tested.

The question here is whether the current rehabilitation system in Oman is sufficiently organized for such an approach.

The rehabilitation services in Oman consist of physiotherapy departments in hospitals scattered around the country. These departments usually get involved with a TBI patient only after the patient has been discharged from a Neurosurgical ward.

The programs do not have any psychosocial or psychiatric input. However, patients who are found to have a psychiatric illness, such as apathy or depression, are referred to a psychiatric clinic either to the behavioural medicine department at Sultan Qaboos University Hospital where this study was conducted, or to another tertiary care mental health hospital, Ibn Sina Hospital. Both of these hospitals are in the capital city of Oman where patients are referred from all over the country.

This study assesses the effectiveness of the current TBI rehabilitation system in Oman for taking care of TBI patients with psychiatric complications. The study uses the ability to maintain apathetic TBI patients in a study on the effect of Methylphenidate in treating apathy as an indicator for the effectiveness of the rehabilitation system.

The study is further reported later in this chapter. However, as background, the chapter first reviews the studies on Methylphenidate treatment of apathy.

#### **4.1.2 Studies on Methylphenidate Treatment of Apathy**

Apathy is defined as “a lack of motivation that is not attributable to a diminished level of consciousness, cognitive impairment or emotional distress” (Kiang et al., 2003).

Apathy is common in a number of neurological conditions and it has been associated with various adverse outcomes such as poor quality of life (Kipps, Mioshi, & Hodges, 2009), poor compliance with the rehabilitation program (Robert Van Reekum et al., 2005), and a tendency to follow a chronic course (R. E. Jorge et al., 2010). These are likely to increase distress in caregivers and burden the society and the health care system in general. As a result, several drugs have been studied as potential treatments of apathy (Ishizaki & Mimura, 2011; Marin & Wilkosz, 2005). Of these, Methylphenidate is the most studied (Padala et al., 2010).

Methylphenidate is a psycho-stimulant that is structurally related to Amphetamine (Mehta et al., 2000). However, unlike Amphetamine, Methylphenidate has a greater effect on mental than on motor activities (Hoffman, 2001). The drug was first manufactured, in 1944, to be used as a stimulant for a reversal of coma due to barbiturate abuse.

The biological mechanisms by which methylphenidate exercises its behavioural effect has yet to be established. In preclinical literature, methylphenidate has been suggested to trigger a cascade of various neurotransmitters including dopamine, norepinephrine, and glutamate (Findling & Dogin, 1998). However, the prevailing theory, regarding the mechanism of action of Methylphenidate, is that it binds to the dopamine receptors in the pre-synaptic cell membrane. This blocks dopamine re-uptake and increases extracellular dopamine levels (T. D. Challman & J. J. Lipsky, 2000). Methylphenidate also inhibits norepinephrine reuptake and has a similar, but weaker, effect on serotonin reuptake (Segal, 1997).

As reviewed earlier, several studies have been conducted to evaluate the effectiveness of Methylphenidate in treating apathy. However, these studies have several methodological shortcomings.

Van Reekum et al. (Robert Van Reekum et al., 2005) attempted to identify all studies on the treatment of apathy with Methylphenidate. In this review, it was reported that Methylphenidate has been tried as a treatment of apathy in a total of 225 patients. These patients had Apathy secondary to various neurological conditions. The number of patients in the individual studies was between one and ten. The dose used in these studies was between 5 and 60 mg/day (Robert Van Reekum et al., 2005; Weinberg, Auerbach, & Moore, 1987).

Consistent with this variety, the treatment duration of Methylphenidate also differs significantly between studies. Most of the studies were of short duration, and the subjects were assessed using different types of scales or clinical observation (Van Reekum et al., 2005).

These studies could be further criticized in terms of the number of patients used. Most of these studies were single case studies or small series of patients (Marin & Wilkosz, 2005; Van Reekum et al., 2005).

Additionally, these studies have included patients with mixed age ranges and gender distributions. Many of them have failed to control for spontaneous recovery and, perhaps most importantly, most studies used subjective measures to assess for apathy, only one study used the standard Apathy Evaluation Scale (AES) (Padala, Burke, Bhatia, & Petty, 2007).

The discrepancies in these studies have caused uncertainty about the effectiveness of the drug in treating apathy. In a more recent study of pharmacological treatment of apathy, the reviewers found 'limited and inconsistent evidence for the efficacy' of this drug in the treatment of apathy (Drijgers, Aalten, Winogrodzka, Verhey, & Leentjens, 2009).

In addition to its effect on Apathy, Methylphenidate has also been used in the Pharmacological rehabilitation of TBI patients. Several decades of trials in TBI rehabilitation have concluded that psycho-stimulants can be extremely useful in helping patients to recover from TBI. The drugs have been found to have a heuristic value in restoring lost function and kick-starting the afflicted individual towards pre-morbid functioning level and improved quality of life (Waldron-Perrine, Hanks, & Perrine, 2008).

It is possible that Methylphenidate may 'activate' and motivate brain-injured patient, particularly those with Apathy, to become fully engaged and benefit from rehabilitation regiment (Walker et al., 2012). This is likely to contribute to re-learning or re-training of lost function (Butler & Willett, 2010). In emerging Neuroscience, this may involve reactivating neural pathways or training new neural pathways to recover or improve cognitive, behaviour and emotional functioning that has been adversely impacted by trauma (DeMarchi et al., 2005; Tenovuo, 2006).

Thus, there is growing interest in 'pharmaco-rehabilitation' within the field of rehabilitation (Hartley et al., 2011). However, these drugs are often used as adjunct therapy to speech therapy, physical therapy, and occupational therapy (Cope, 1995; Gentleman, 2001).

To summarize, several studies suggested that Methylphenidate could be effective in treating apathy. The drug has recently regained ground to be the promising compound to promote recovery in brain-injured population. However, the efficacy of Methylphenidate has not been conclusive.

The author of this thesis did a literature search using Methylphenidate, apathy and TBI as search terms and found no research reports designed specifically to evaluate the treatment of apathy in TBI. Most studies either have assessed the effectiveness of Methylphenidate in treating various neuropsychiatric complications of TBI, including apathy, or have been used to treat patients who have apathy secondary to causes other than TBI. Furthermore, there were no studies on the Arab / Islamic brain injured population.

Lane-Brown et al. did a systemic review of the intervention for Apathy after TBI. In this review only one randomised controlled trial (RCT) of interventions specifically targeting apathy in TBI patients was found. However, the treatment was cranial Electrotherapy stimulation (CES) (Lane-Brown & Tate, 2009).

Based on this assessment of the literature, an original aim of this study was an attempt to study the effectiveness of Methylphenidate in treating Apathy in an Omani TBI population. The study was designed to use quantitative measures of symptoms in patients with apathy during and after treatment with Methylphenidate.

The study attempted to address some of the problems in earlier studies. This was done by recruiting a relatively larger number of subjects, limiting the study to TBI patients with apathy, recruiting patients sequentially, using well-recognized outcome measurement instruments, and repeated baseline measures in order to control for spontaneous recovery.

Although ideally the study could have been placebo controlled, given the paucity of information in the area, it was thought that a single-case methodology, AABAA design, based on repeated measures would be appropriate for such study.

#### **4.2 THE AIM OF THE STUDY**

The aim of this study is to assess the effectiveness of the current TBI rehabilitation system in Oman, and whether the system enables:

1. Omani TBI patients with psychiatric complications to have the required psychiatric, long-term, regular follow-ups and reviews
2. A comprehensive bio psychosocial rehabilitation program for TBI patients
3. Testing of alternative and/or novel treatment approach for TBI patients using the methylphenidate study as an example

#### **4.3 HYPOTHESES**

1. The TBI Rehabilitation system in Oman is not sufficiently organised to enable Omani TBI patients with psychiatric complications to have adequate, regular, and long-term follow-ups and reviews
2. The current TBI rehabilitation system in Oman is not effective as it is not capable of a comprehensive bio psychosocial rehabilitation program.
3. The Rehabilitation program is not sufficiently organised to allow the adequate performance of any study on the treatment of psychiatric complications of TBI.

## **4.4 METHODOLOGY**

### **4.4.1 Study Design:**

#### **4.4.1.1 To assess the ability to maintain TBI patients with psychiatric complications on regular psychiatric follow up and reviews.**

This study was a natural observation of the current arrangements for taking care of TBI patients with psychiatric complications in Oman.

As reviewed earlier, Oman does not have a multidisciplinary TBI rehabilitation centre. TBI patients, attending a regular Neurosurgical or physiotherapy follow-up and found to have a psychiatric complication, are referred to Ibn Sina Hospital or Sultan Qaboos University Hospital (SQUH) for further assessment and management of the psychiatric complication.

For this study, Apathy was chosen as an example of a psychiatric complication in TBI patient and these patients were referred to SQUH for assessments and management of the psychiatric complication.

The study is part of that described in chapters two and three in which 103 TBI patients of both sexes were studied. These were selected from consecutive TBI patients, aged between 15 and 70, and who attended an outpatient department (OPD) at The National Neurosurgical Centre, Khoula Hospital, Mina-AL-Fahal, Muscat, Sultanate of Oman.

Each participating patient underwent careful screening to rule out those with neurological and psychiatric illnesses prior to TBI. The exclusion criteria included a history of psychiatric illness, a history of repeated TBI, a history of neurological illness and a history of substance abuse.

In order to find out patients with Apathy, AES was used for this purpose. One hundred and one patients out of the 103 were able to perform the AES. All patients who scored more than 38 points were considered to have apathy (Marin, 1996). Among the one hundred and one patients, forty-three patients were found to have apathy (BL-1).



All these forty-three patients were asked to give consent for the study and asked to attend the psychiatric clinic at Sultan Qaboos University Hospital for further assessment and management.

Ethical consent for the study was obtained from the ethical committee of Sultan Qaboos University, and all subjects were required to give written consent. In case the subject could not make meaning response or rendered incapable due to psychomotor impairment, the caregivers were asked to consent as per regulation of such endeavour in Oman. The number of patients who gave consent for the study and willing to attend the psychiatric clinic and adhere to the prescribed treatment were calculated.

#### **4.4.1.2 Study Design to Assess the Effectiveness of Methylphenidate for the Treatment of Apathy in TBI Patients.**

A single-case methodology, AABAA design, based on repeated measures was used (Lindsay & Stoffelmayr, 1976). The design is shown schematically below.

A: BASELINE 1 (BL-1)

A: BASELINE 2 (BL-2)

B: METHYLPHENIDATE (METHYL)

A; POST-WITHDRAWAL 1 (POST-1)

A: POST-WITHDRAWAL 2 (POST-2)

Patients who attended at SQUH were re-assessed using AES to find out those who still have apathy (BL-2).

Those who were found to have apathy at the second assessment were asked to give another consent for the treatment study and started on Methylphenidate 20 mg.

These patients were asked to come for re-assessment after two weeks of starting the drug. The dose was incremented every two weeks until the patient improves in terms of apathy (METHYL) or developed side effects.

Patients who improved in the apathy scores were asked to stop the medicine, then re-assessed after two weeks (POST-1) and then after 4 weeks of stopping the medicine (POST-2).

Such research protocol allows experimenters to observe behaviour before treatment, during treatment and after treatment. There are indications that the AABAA study design, tend to circumvent most of the limitations of the previous methodological approach that have been used for TBI patients a number of whom are likely to have spontaneous recovery (Powell et al., 1996).

In the presentation of data, assessment measures for apathy, affective and cognitive assessments were presented. These included AES, HADS, FAS, and cognitive assessments such as Modified card sorting test, Buschke Selective reminding test and Digit Span. However, the main assessment was AES.

The data were presented at the following occasions: two baseline assessments (BL-1 and BL-2); the assessments when the patient was stabilised at a maximum methylphenidate dose (METHYL) which varied for individual patients between 20 and 40 mg; and the two post-withdrawal assessments (POST-1 and POST-2).

Additionally, the numbers of patients who consent for the study, took the medicine, and then came for follow up were calculated.

#### **4.3.4. Drug Regimen**

After repeated baseline assessments (BL-1 and BL-2), Methylphenidate was started.

Methylphenidate is a fast acting drug and reaches peak plasma concentrations between one and three hours after a standard oral dose (T. Challman & J. Lipsky, 2000). However, it also has a short half –life of about 1.5 to 2.5 hours (T. Challman & J. Lipsky, 2000).

As a result, Methylphenidate has to be taken at least twice a day in order to maintain its effectiveness. Methylphenidate, however, is available in a 20-mg sustained release tablet, in addition to the standard 5 mg, 10 mg, and 20 mg tablets.

Previous studies have used doses that ranged between five and 60 mg/day (Robert Van Reekum et al., 2005). Lu et al. (Lu, Gary, Neimeier, Ward, & Lapane, 2012) suggested the use of up to 1 mg/kg/day. Such dosage has been successfully used in other disorders (Robert Van Reekum et al., 2005). Lee et al. (Lee et al., 2005) started Methylphenidate at 5 mg/day and gradually increased this by 2.5 mg every day until 20 mg/day.

However, others have suggested starting with a larger dose, such as 20 mg once to three times a day, especially with the sustained release formulation (T. Challman & J. Lipsky, 2000).

In this study, the 20 mg sustained release was used. This formula has been shown to have a longer plasma half-life, and the time to reach peak plasma concentrations is longer (Birmaher, Greenhill, Cooper, Fried, & Maminski, 1989). Therefore, it is easier to take the tablet, as is taken only once a day. However, this also meant that the patient will have a higher starting dose and these would increase the side effects as detailed in the discussion.

#### **4.3.2 Measurements**

The assessment measures are detailed in the Appendix.

Apathy was assessed using the Apathy Evaluation Scale (AES) (S Al-Adawi et al., 2004; Clarke et al., 2011).

The AES is an 18 questions tool, which has scores ranging from 18-72; the higher the score the greater degree of apathy. The scale has three equivalent forms. One form to be used by patients, one for the clinician, and the third for the informant. The assessment has been found to have good internal consistency, and test-retest reliability. The assessment has also been shown to differentiate apathy from depression (Marin, 1996).

In this study, the clinician form was used with input from the patient, and when possible from the informant. This is because of the nature of TBI patients that most of them will not be able to complete the forms. To the best knowledge of the authors, this is the first time the scale has been used in this way.

A cutoff score of > 38 was used to detect clinical apathy as suggested by Marin (Marin, 1996).

As reviewed in chapter three, apathy in TBI patients may be associated with or secondary to other deficits, in particular affective and cognitive disorders. Therefore, any study of the psychopharmacological intervention for apathy will not be completed unless these deficits are also analysed.

Affective measures, such as the Self Reporting Questionnaire (SQ.) and The Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983), were also administered at each assessment, to determine whether or not changes in the indices of Apathy were accompanied by alterations in anxiety and depression. Similarly, the Fatigue Assessment Scale (FAS) (Michielsen, De Vries, Van Heck, Van de Vijver, & Sijtsma, 2004) was administered to find out whether or not diminished motivation was associated with fatigue.

Cognitive assessment, such as the modified Wisconsin Card Sorting Test, Buschke Selective Reminding Test (Buschke & Fuld, 1974) and Digit Span (Wechsler, 1981) were also administered to assess concentration, attention, and effortful cognitive functioning. These tests were chosen because they are not verbal, or language based and are thought to be independent of culture (Duchesne et al., 2010).

The assessments were administered by the author in a psychiatric clinic consultation room. This was done in one session, and took about one to two hours depending on the cognitive abilities of the patients.

#### **4.3.5 Data Analysis**

The statistical package SPSS 15 was used for analysing the data. Nonparametric analyses using the Wilcoxon rank sum test were employed to determine the changes of apathy, affective and cognitive assessments in the following occasions:

A: BASELINE 1 (BL-1)

A: BASELINE 2 (BL-2)

B: METHYLPHENIDATE (METHYL)

A; POST-WITHDRAWAL 1 (POST-1)

A: POST-WITHDRAWAL 2 (POST-2)

Because previous studies suggested that Methylphenidate would lead to improvement in apathy and other scores, 1-tailed tests of significance were used for the results following Methylphenidate administration. The changes during the baseline period and post withdrawal could not be anticipated. Therefore, two-tailed tests were used.

#### **4.4 RESULTS**

Forty three out of 101 (43%) patients, who were assessed at assessment one, had apathy (BL1). All these forty-three patients consented to the study. The demographic and clinical characteristics of these patients are detailed in table 4.1. Most of these data were obtained from the patient's medical records. Therefore, some data were missing as shown in table 4.1.

Eighty three percent were male; their mean age was 27 years. Thirty-nine percent of these patients had a brain injury more than 1 year prior to the assessment. Thirty percent had mild TBI and 35% had severe TBI. Seventy percent had abnormal Brain scan and 16% had normal neuroimaging scan.

**Table 4.1: A Table of the Demographic and Clinical characteristics of the study cohort (n = 43)**

Parameter	Characteristic	Number	Percentage
Gender	Male	36	83
	Female	7	16
Age (years)	Mean $\pm$ SD	27 $\pm$ 11 years	
	Median	25 years	
	Range	15-70 years	
Time since injury	$\leq$ One month	4	9
	One month to one year	22	51
	One year and above	17	39
	Mean $\pm$ SD	21 $\pm$ 45 Months	
	Median	7 Months	
	Range	1- 252 Months	
Education	Koranic education	4	9.3
	Primary	15	35
	Secondary	18	42
	Some college	3	7
	Completed college	1	2.3
	Graduate education	2	4.7
Employment	Unemployed/Full-time homemaker	12	29
	Employed	21	49
	Student	6	14
Injury severity (Glasgow Coma Scale)	GCS (mild; 13 to 15)	13	30
	GCS (moderate; 9-12)	6	14
	GCS (Severe; 8 or below)	15	35
Site of injury (left vs. Right)	Could not be determined (No scans or Normal scans)	10	23
	Right side	6	14
	Left side	10	23
	Bilateral	12	28
Neuroimaging data with CT or MRI	Abnormal	30	70
	Normal	7	16
	Not Done	6	14

CT= Computed Tomography Imaging; MRI= magnetic resonance imaging;

GCS = Glasgow Coma Scale; SD=Standard deviation

Out of the forty-three, only twenty-six attended the psychiatric clinic at the SQUH. An independent samples t-test was used to investigate whether there was a significant difference between patients who attended and those who did not attend, in relation to their Apathy scores. The test revealed no statistically significant difference between the two groups ( $t = 0.734$ ,  $df = 41$ ,  $p = 0.47$ ). Those who attended ( $M = 43$ ,  $SD = 8$ ) scored slightly lower levels of Apathy than those who did not attend ( $M = 44$ ,  $SD = 8$ ).

Chi-square statistic was used to compare patients who attended and those who did not attend in terms of the demographic and clinical variables such as gender, time since injury, injury severity, estimated pre-morbid IQ, educational level, employment, degree of disability and depression. The results showed no statistical difference between the two groups ( $p > 0.05$ ).

The time between assessment one and two ranged from 13 to 773 days (mean = 281 days). However, there were no statistically significant changes in the level of apathy at BL-1 and BL-2 ( $p > 0.05$ ) using the Wilcoxon rank sum test.

Among the twenty-six patients, twenty-four had apathy at the second assessment. These twenty-four patients were asked to sign a consent form and to come back for starting Methylphenidate. Although all twenty-four patients consented, only eleven patients came back for the Methylphenidate trial (BL2).

In the coming section of this thesis, the group data of the eleven patients will be presented and analysed. Individual case histories are detailed in the appendix.

Of the eleven patients, ten were male. Their ages ranged from 16 to 37 years. Patients' demographic and clinical details are cited in Table 4.2.

**Table 4.2: A table shows the demographic and clinical data of eleven TBI patients treated with Methylphenidate.**

The Patient Name	Age/Sex	Severity of TBI	Months Since Injury	CT Brain Results	SPECT Results	Severity of Apathy
A. A	19/M	Severe	14	Multiple Contusion, Diffuse Axonal Injury	Perfusion defect in the frontal, parietal, occipital and temporal region of the left hemisphere	Mild
F.F	31/F	Severe	7	Left Temporal and parietal contusion, Generalized Oedema	Low perfusion on the posterior part of the left hemisphere	Severe
H.Z	26 /M	Moderate	6	Normal	Not Done	Mild
H.R	23/M	Severe	6	Right Frontal Extra Dural Haemorrhage	Perfusion defect on the right frontal, parietal region	Moderate
H. A	37/M	Not recorded	3	Normal	Normal	Mild
I.H.	21/M	Severe	1	Normal	Not Done	Mild
M.J.	19/M	Severe	168	Could not be determined	Low perfusion at the right temporal lobe	Mild
N.H	29/M	Mild	5	Could not be determined	Normal	Moderate
Q.H.	22/M	Moderate	13	Bleeding at Corpus Callosum	Not Done	Mild
S.J.	29/M	Mild	1	Bleeding in the right ventricular space	Not Done	Mild
S.H.	16/M	Severe	4	Left Frontal Haemorrhage	Not Done	Mild

All, except one patient, had a TBI due to RTA. Six had severe brain injury; two had moderate and two had a mild brain injury. Three patients had a normal CT Brain at the time of injury, and one had diffuse axonal injury as shown.

The time elapsed after the injury ranged from one to 168 months. However, for almost 82%, the period was less than twelve months.



It was necessary to assess whether there was a significant difference between patients who came back to start Methylphenidate and patients who did not come, in relation to their apathy scores. An independent samples t-test was conducted for this purpose.

There were no statistical differences between the two groups ( $t = 0.18$ ,  $df = 22$ ,  $p = 0.8$ ). Those who took Methylphenidate ( $M = 44$ ,  $SD = 9$ ) scored slightly higher levels of Apathy than those who did not take the drug ( $M = 43$ ,  $SD = 10$ ).

Similarly, there were no statistical difference between the two groups in terms of other demographic and clinical variables such as gender, time since injury, injury severity, estimated premorbid IQ, educational level, employment, degree of disability and depression, using chi-square statistic ( $p > 0.05$ ).

These eleven patients were started on Methylphenidate ER 20 mg once daily and asked to come for re-assessment after two weeks of starting the medicines.

Among the eleven patients, three did not come for follow up and three could not tolerate the medicine. Therefore, these six patients were dropped out from the study as shown in Table 4.3.

Among the remaining five, four showed improvement in their apathy score (METHYL). The remaining one patient did not show any improvement despite increase the dose to 40 mg. Hence the medicine was stopped.

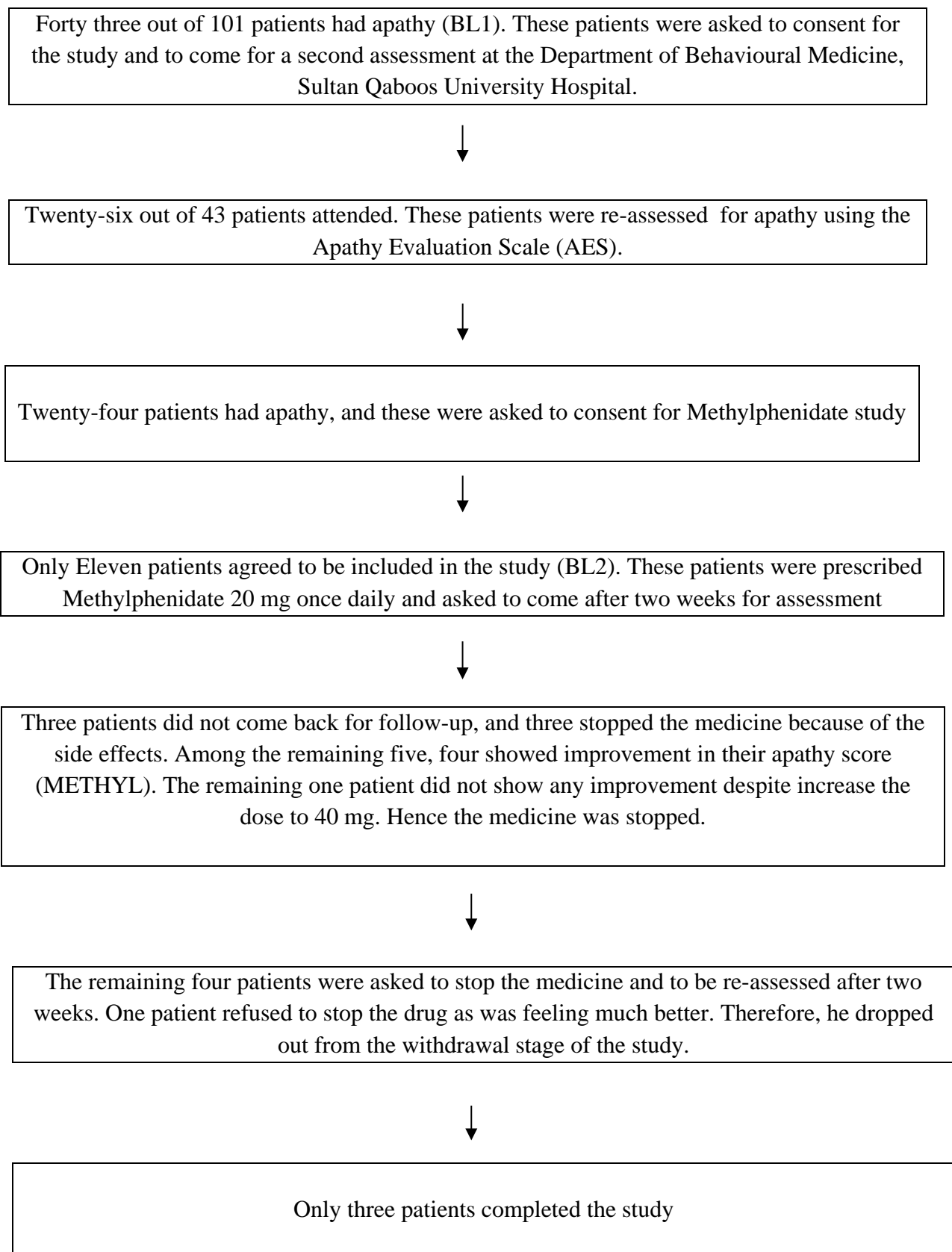
The four patients, who had improvement in their Apathy scores, were asked to stop the medicine and to be re- assessed again after two weeks (POST1). However, one patient refused to stop the medicine. Therefore, he was dropped out of the study.

The remaining three patients were asked to come for re-assessment after four weeks of stopping the medicine (POST2). Apathy scores in these patients did not reverse despite four weeks of stopping the medicine as shown in table 4.3.

**Table 4.3: A table of Apathy Evaluation Scale scores in eleven TBI patients treated with Methylphenidate**

<b>Name</b>	<b>BL1</b>	<b>BL2</b>	<b>METHYL</b>	<b>POST1</b>	<b>POST2</b>
<b>A. A</b>	Mild (42)	Mild (40)	Did not come back for follow up		
<b>F.F</b>	Severe (66)	Severe (65)	Severe (69)	Severe (66)	Severe (66)
<b>H.Z</b>	Mild (47)	Mild (43)	Did not come back for follow up		
<b>H.R</b>	Moderate (48)	Moderate (48)	Could not tolerate the drug		
<b>H. A</b>	Mild (40)	Mild (45)	Normal (30)	Normal (33)	Mild (40)
<b>I.H.</b>	Mild (36)	Mild (34)	Normal (29)	Normal (30)	Normal (30)
<b>M.J.</b>	Mild (34)	Mild (35)	Normal (25)	Normal (23)	Normal (25)
<b>N.H</b>	Moderate (50)	Moderate (49)	Severe (51)	Took only four tabs	
<b>Q.H.</b>	Mild (45)	Mild (42)	Could not tolerate the drug		
<b>S.J.</b>	Mild (36)	Mild (34)	Did not come back for follow up		
<b>S.H.</b>	Mild (44)	Mild (46)	Normal (30)	Refused to stop the drug	
<b>MEAN</b>	Mild (44.3)	Mild (43.7)	Mild (39)	Mild (38)	Mild (40.2)

**Figure 4.1: A Flowchart Showing the Drop Out Of Patients through Different Stages of the Study.**



## 4.5 DISCUSSION

The high number of road traffic accidents in Oman has resulted in many young Omanis surviving with various TBI disabilities (S Al-Adawi et al., 2007; S Al-Adawi et al., 2004; Al-Reesi et al., 2012; Al-Sharbati, Zaidan, Dorvlo, & Al-Adawi, 2011; Shahbaz, 2007).

The preceding chapters of this thesis have demonstrated that neurobehavioral symptoms, including apathy, are common among TBI population in Oman. Therefore, a rehabilitation program for these patients should include psychiatric input. The system should also be able to test any novel treatment for psychiatric complications in TBI patients.

This chapter has embarked on a study to assess whether the current TBI rehabilitation program in Oman is able to provide a comprehensive bio psychosocial rehabilitation program and whether the system enables for testing of a novel treatment approach for these patients. The Methylphenidate study was used to assess these capabilities. Drawing from such challenging study, the related aim is to assess the effectiveness of methylphenidate in treating Apathy in Omani TBI patients.

Forty-three patients who were found to have apathy, according to Apathy Evaluation Scale done in the Neurosurgical outpatient department, were included in this study. These patients were asked to come for the second assessment at Behavioural Medicine Department at Sultan Qaboos University Hospital.

As reviewed earlier, this is the usual practice here in Oman. The Brain injury rehabilitation centre does not have psychiatric input. Therefore, TBI patients who were found to have a psychiatric illness are referred to another hospital for psychiatric intervention. Unfortunately, only 26 patients attended the psychiatric clinic.

As discussed in chapter two, stigma toward mental illness is extremely high in this society. For most patients in Oman, it is much easier to accept having a physical illness rather a mental illness. As a result, only few patients were willing to come for the second assessment in the psychiatric clinic.

Even those few who attended for the second assessment, it was difficult to convince them to participate in the drug trial. Only eleven patients agreed. Generally, the idea of participating in a drug trial in Oman is new and not well accepted. Especially that there is a lack of trust between individuals in the society, and the health care system (Al-Adawi & Burke, 2001).

Additionally, the stigma of taking Methylphenidate from mental health clinic has made recruiting patient for this study even more difficult. The medicine could have been accepted easier if it was given in the Neurosurgical clinic.

Out of the eleven patients who agreed to participate in the drug trials, three patients did not come for follow up after taking the drug and three stopped the drug because of the side effects.

Among the three who reported side effects, one patient (H.R) took only two tablets, then he started to feel giddy, and was not able to walk properly. These symptoms disappear after stopping Methylphenidate. Two weeks after stopping the drug he started to have episodes of falling down with a loss of consciousness; there was no urine or stool incontinence. The patient denied history of fits.

The second patient, QH, took only one Methylphenidate tablet and then he started to feel giddy, tremor and generalized body weakness after 1 hour of taking the medicine.

The third case (NH), felt better initially after taking Methylphenidate. However, the patient then stopped the medication after 4 days because of loss of appetite and irritability.

Among the remaining four, one more patient dropped out of the study at the withdrawal stage (POST1). This patient (SH) had a dramatic improvement in his symptoms and refused to stop the drug.

The fact that the majority of patients were lost to follow up in different stages of this study is significant. It demonstrates the reality that unless we have a complete TBI rehabilitation program, it will be impossible to properly managed Omani patients with TBI.

This is exactly what happens in real clinical practice in Oman. TBI Patients with psychiatric complications are usually referred from the Neurosurgical centre to behavioural medicine department in the university hospital. Most of these patients will refuse the referral and even the few who agree to be referred will attend the psychiatric clinic once or twice then will be lost to follow up.

As a result, substantial numbers of TBI patients do not get the maximum benefit of medical treatment, resulting in poor health outcomes, lower quality of life and increased health care costs. If these patients were managed in a proper rehabilitation centre without having to refer them to a different hospital, this would help to decrease the number of patients who are lost to follow up.

The related aim of this study was to assess the effectiveness of Methylphenidate for the treatment of Apathy in Omani TBI patients.

The study was an open trial with ten male and one female subject who had TBI between one and one hundred and sixty eight months previously. Initial baseline assessments (BL1, BL2) were employed to identify any natural (spontaneous) recovery. The mean apathy score of the 26 patients in the second assessment got slightly better by one point. However, the change was not statistically significant ( $p > 0.05$ ). Therefore, significant spontaneous recovery is unlikely in these patients given the long time between injury and treatment.

Despite trying to complete a study that would overcome many of the problems with earlier clinical research in this area, the dropout rate severely limits any conclusions that can be drawn.

The ensuing discussion will focus on the local factors that could have contributed to the high dropout rate. These factors will be discussed in terms of (i) the model of prevailing health care in Oman, and (ii) the interface between socio-cultural teachings and health care seeking. Other related themes to explore in this context are the side effects of Methylphenidate and ethnicity variations in drug pharmacokinetics responses.

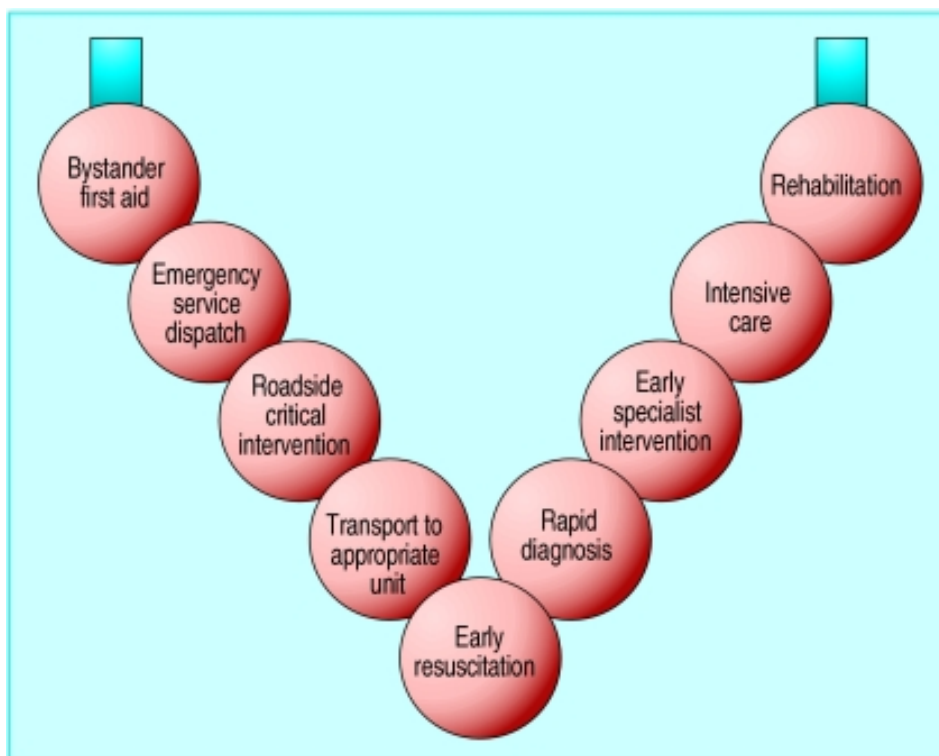
#### 4.5.1 Model of Health Care in Oman

There are likely to be several reasons for the poor adherence to the treatment regimen in this study. One of the main reasons is the lack of proper, well-structured, multidisciplinary rehabilitation centre for brain injury patients.

Oman has been instrumental in global strategy to reduce the growing menace on the road (Al-Kharusi, 2008). In the country itself, concerted effort has been made to improve post-crash care (Al-Kharusi, 2008). However, these efforts have been limited to acute care management. On the other hand, rehabilitation services for these patients have yet to mushroom in the country.

According to the World Health Guidelines (Peden et al., 2004). The following guideline constitutes the best stages of caring for individuals who have sustained road traffic accident.

**Figure 4.2: A Diagram Shows Stages of Helping Victims of Road Traffic Accidents.**



If one considers how the World Health Organization guideline fares in Oman, it appears that the country has adequate infrastructure for emergency services up to the rapid diagnosis. It is debatable whether “early specialist” interventions, neither intensive care do exist in Oman, except for limited urban hospital, Khoula Hospital.

In fact, despite the TBI and RTA are quite prevalent in developing countries such as Oman, rehabilitation for these patients has been limited to literally ‘patch up’ the survivors of RTA using orthopaedic and Neurosurgical procedures (Al-Azri, 2009; Al-Dulimi, Abdulaziz, Mohammed, & Bener, 2010; Al-Shaqsi, 2009; Neurology, 2010). Indeed, most of the discussions related to TBI in accident-prone countries have been limited to early resuscitation (Shahbaz, 2007). The emphasis has been on ‘cure’ rather than providing remedial and rehabilitative services for clinical population that are known to have pervasive and persistent chronic sequel of brain injury (Al-Kharusi, 2008).

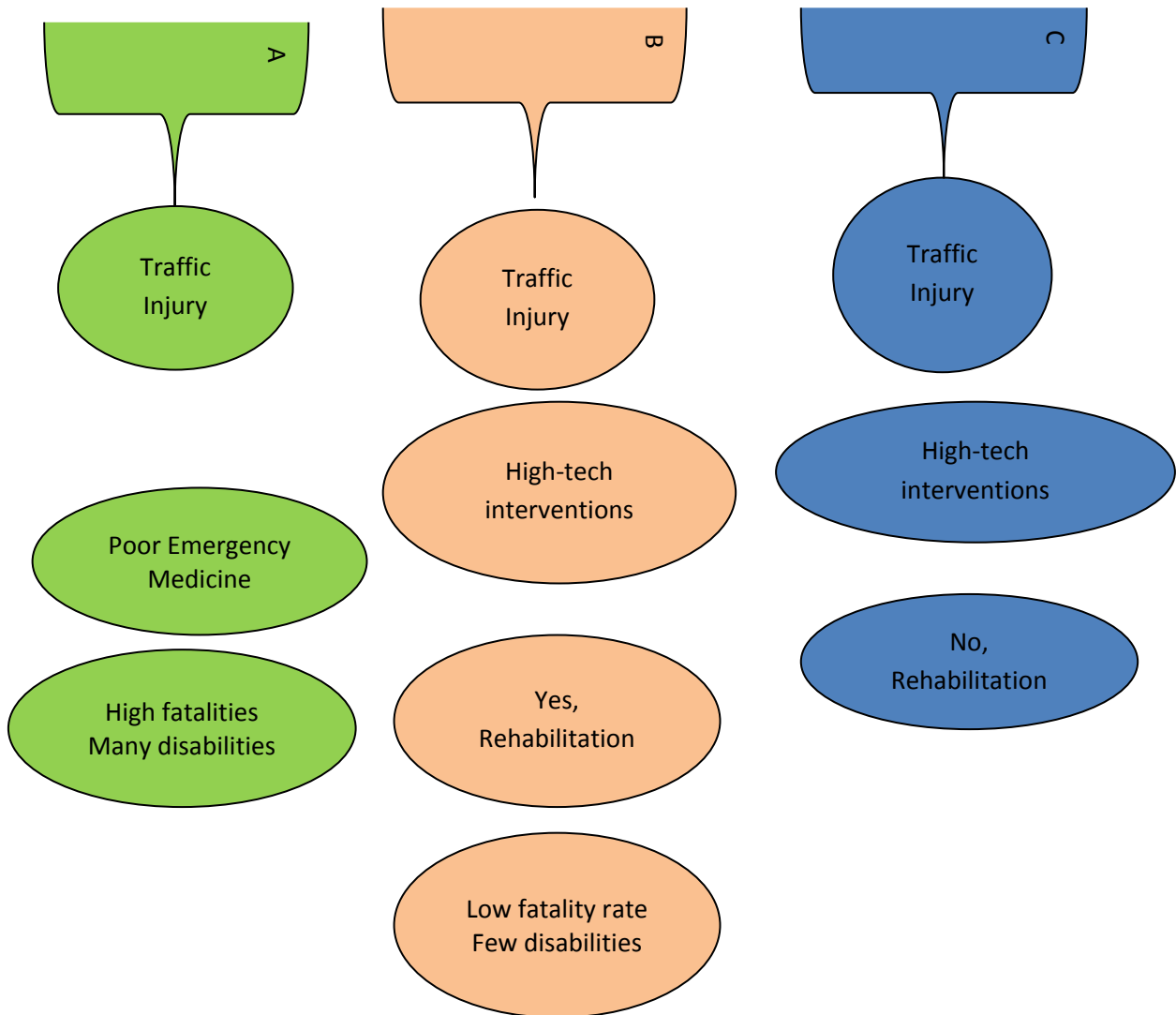
This resulted in the improvement of survival rate of RTA victims. However, because of a clear lack of rehabilitation services, most of these individuals are bound to be marked with intractable disabilities (Al-Naami, Arafah, & Al-Ibrahim, 2010; Bener, Omar, Ahmad, Al-Mulla, & Abdul Rahman, 2010)

However, the problem is not simply lack of rehabilitation services for these patients. The problem is rooted in the model of the health care system adopted in the country. This health care system is not geared toward taking care of patients with chronic disease such as brain injury patients.

This is clearly demonstrated in health care provided for victims of RTA. In comparison, of trends in medical care for RTA victims, Figure 4.3 illustrates three hypothetical models of care for these patients and their direct bearing on mortality and disability.



**Figure 4.3: A diagram showing three hypothetical models of health care and its direct bearing on mortality and disability**



The question, from the experience of the present thesis, is which among the three models is likely to describe the situation in Oman.

According to the WHO report, rehabilitation services for RTA patients do not exist in Oman (S. Al-Adawi, Al-Busaidi, & Burke, 2012; Group, 2012). This runs counter to what the country has achieved on its healthcare infrastructure.

Oman has been internationally lauded with its most efficient health care system in the world (Farsi & West, 2006). However, if one carefully considers the hypothetical model of health care and its impact on outcome (fatality and disability), Oman appears to fulfil the criteria for 'Model C', that is, health care system characterized by 'high tech medicine'.

What is often overlooked on such circumstances is the undeniable fact that rehabilitation does have a positive impact in attenuating some of the debilitating cognitive, emotional, and behavioural problems (M. K. Shah, S. Al-Adawi, A. S. S. Dorvlo, & D. T. Burke, 2004; Shah, Carayannopoulos, Burke, & Al-Adawi, 2007). This has the ultimate outcome of rendering one with more meaningful quality of life.

Therefore, one of the main reasons for the high dropout rate from this study is that the health care system in Oman is not properly designed for taking care of chronic disease patients such as TBI patients.

The lack of proper rehabilitation centre has made it difficult for patients to follow with the treatment regimen. The adherence to the program could have been improved if these patients were treated in a multidisciplinary rehabilitation centre, without having to refer them to another hospital.

#### **4.5.2 The Impact of Socio-Cultural Teaching on Care-Seeking**

The second factor that could have affected the adherence to treatment is the way Omani patients select the appropriate medical services.

Younger patients, such as those in this study, are likely to choose a modern medical intervention for their illnesses. However, patients in this study failed to appear for psychiatric assessment and intervention. This is because the health care seeking in this culture is not a patient but a family decision. This family decision is unlikely to select a psychiatric care for various reasons that will be analysed in the coming sections of this chapter.

There are numerous studies that have explored the health-seeking behaviours in different cultures (Olenja, 2004; Ruzek, Nguyen, & Herzog, 2011). It has been well established that the pathways to health care seeking is considerably modified by local, social, and psychological factors of patients, as well as factors related to the doctor-patient relationship.

Scant attention has been paid to the role of family advice on health care seeking in Oman. In this culture, interdependence and family values are the norm rather than the exception. Therefore, illness, such as brain injury, is a family rather than a personal matter.

In traditional communities such as those in Oman, the family members share the burden of the illnesses. In many rituals of healing, the whole family is called to witness and share the misfortune of the afflicted individual. This process is thought to help in increasing the patient's self-value and strengthen the patient's relationship with the community (S. Al-Adawi et al., 2012).

In support of such view, Al-Adawi et al have done a qualitative study among young Omanis who have sustained a brain injury (S. Al-Adawi et al., 2012). This study concluded, “Survivors of brain injury in Oman are often left without other support than that of family caregivers.” (S. Al-Adawi et al., 2012).

The family members in Oman society do not only share the burden of the illness, but also share the health care seeking decision. Consistent with this view, studies in Oman have suggested that individuals suffering from a chronic illness, such as brain injury, have a strong tendency to seek family member advice (A. Al-Mandhari, Al-Adawi, Al-Zakwani, Al-Shafae, & Eloul, 2009).

This health care advice from the family member is unlikely to be a psychiatric care for several interconnected reasons.

Firstly, as the families tend to ‘pull the string’, it is possible that many patients have dropped out because the family feel attending a psychiatric clinic indicate the presence of a mental disorder. This is not easily acceptable in Omani society. As discussed in chapter two, stigma toward mental illness is extremely high in this society. For many families in Oman, it is much easier to accept having a physical illness and attend a general hospital rather than a psychiatric illness. As a result, only a few patients were willing to come for the second assessment at a mental health clinic.

Secondly, psychiatric care in Oman is not a priority of patients and their families. According to Al-Sinawi and Al-Adawi: “As in many traditional communities, modern psychiatric services have yet to play a dominant role in the care of people with psychiatric disorders. Mental illness was largely the preserve of traditional healers, and many people with psychiatric illness are still unlikely to seek psychiatric help until they have reached an advanced stage of irreversible pathology or until ‘treatment shopping’ from complementary and alternative medicine has failed to provide any benefit” (Al-Sinawi & Al-Adawi, 2006).

These were also reported in other cultures. For example, the Chinese often consider western medicine to be quicker at removing the symptoms but does not cure a disease permanently. Therefore, they often use Western medicine for acute illness, but rely on the Chinese medicine for long-term treatments (Bishop, Lim, Leydon, & Lewith, 2009).

Thirdly, different cultures have alternative ideas of what constitutes illness, health, and the causes of illness. It has been suggested that depending on the level of education, emotional difficulties in Oman are usually attributed to the jinn and the evil eye (S. Al-Adawi et al., 2012). This is more pronounced in the illnesses that do not fit into the pattern of a familiar and easily manageable disease, such as the sequel of brain injury. Similarly, the neurobehavioral impairments in these patients are often seen as a “result of the action, vengeful intervention of anthropomorphic beings conjured up by a malicious and envious person” (S. Al-Adawi et al., 2012). The presence of “supernatural forces” in the cultural narrative would suggest that these people would not endorse modern medical treatment for such distress.

Fourthly, studies suggested that psychological distress in this culture is communicated in ‘somatic’ rather than ‘psychic’ ways (S. H. Al-Adawi, Martin, Al-Salmi, & Ghassani, 2001). On this ground, it could be speculated that such people are unlikely to find psychiatric services conducive to their need.

Even for those few who attended the second assessment (BL1), only eleven patients consented to participate in the drug trial.

A multidisciplinary rehabilitation centre might help to overcome such cultural obstacles. In such a centre, patients will attend not only for emotional and psychological difficulties but also for physical disabilities. This will make it easier for these patients to accept the treatment from such centres.

Furthermore, adequate interventions for victims of neurobehavioral impairment would not only reduce the impact of disability, but it would also provide a venue for caregivers to be informed about the available treatments, the sequel and the severity of acquired brain injury. This will also demonstrate the effectiveness of modern rehabilitation services by showing real examples of patients who improved because of the rehabilitation services. The overall results of this, is the improvement of adherence to treatment.

#### **4.5.3 Side Effects of the Medicine**

The road of the present chapter to its conclusion was also hampered by the side effects of the drug.

Although only three patients reported the side effects, it is possible that the other three patients, who did not come back for follow up, also had side effects.

In traditional cultures, such as Omani culture, patients usually tend to minimize or conceal side effects (Solomon, 2010). They might also just simply stop coming for follow up and stop the medicine without informing the healthcare provider. This is because the confrontation in general is considered to be rude, aggressive, and disrespectful (Solomon, 2010). Therefore, in order to avoid confrontation, patients find it easier just stop coming for follow up.

Several studies have shown that Methylphenidate tends to have a favourable side-effect profile. Even when the latter occur, they are usually of short duration and are dose dependent (Gruber et al., 2009). Indeed, children, who have been treated with Methylphenidate, usually have minimal side effects such as insomnia, decreased appetite, stomach aches, and headaches. The less common side effects include dizziness, motor tics, irritability, and anxiousness (Efron, Jarman, & Barker, 2000).

Previously, there was a suggestion that Methylphenidate may lower the seizure threshold. However, such opinion has not received strong support in the available literature (Prommer, 2012; Wroblewski, Leary, Phelan, & Whyte, 1992). Nevertheless, between one and four percent of patients stop using the drug because of the side effects (W. Morton & Stockton, 2000).

Few studies have compared the efficacy and the side effects of Methylphenidate to that of other medicines. For example, Lee et al. (Lee et al., 2005) reported that side effects of Sertraline were significantly more common than those of Methylphenidate among the brain-injured population. By contrast, in a recent study comparing Methylphenidate with Selegline in the treatment of apathy, Newburn et al. described four cases of apathy secondary to TBI who responded remarkably well with Selegline; in these patients, Selegline was well tolerated whereas Methylphenidate was not (Newburn & Newburn, 2005).

Considering the above studies carefully, there is no clear direction on the side effect of Methylphenidate on TBI population. Some authors have indicated that heterogeneity of the clinical populations, variations in time since injury, variable treatment periods, different dose regimens, age difference have been suggested to hamper the generalization of these studies (T. D. Challman & J. J. Lipsky, 2000).

#### **4.5.3 Ethnicity and Pharmacology**

As mentioned earlier, at least four patients (40 %), dropped out of the study because of the side effects. This is much higher than that reported in other ethnic groups (W. Morton & Stockton, 2000). In this regard, it is necessary to explore the relationship between ethnicity and pharmacology.

Inter-individual variability in drug pharmacokinetics had long been established in clinical medicine and more recently, the focus has been on the variability in different ethnicity (Tanii, Shitara et al. 2011). For example, studies have found that people response to alcohol tends to vary in different ethnicities (Cook et al., 2005).

Some studies suggested that certain ethnic groups have a higher propensity towards alcoholism. There is a plethora of studies suggesting that variant alleles of aldehyde dehydrogenase and alcohol dehydrogenase genes may play a critical role in response to alcohol. Differences in the prevalence of such genetic signature have been extrapolated to explain why some communities around the world are more prone to ill-effect of alcohol than others (Cook et al., 2005). Such interest has spurred interest into what is known as Pharmacogenetics. This explore the biological differences in metabolic pathways that can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects (Klotz, 2007).

In support of this view, different medications have been shown to have ethnic differences in the therapeutic range and the dosage required. For example, studies have shown that some ethnic groups required less anticoagulant, compared to others (Lam & Cheung, 2012).

In Psychopharmacology, studies have found that a protein that metabolizes several antidepressant medicines, is less active in Asians population, leading to higher rates of side effects (Brennan, 2012). Other studies have found that Asians have approximately 50% higher blood levels of Haloperidol compared to Caucasian counterparts when given the same dose of the medicine (Schraufnagel, Wagner, Miranda, & Roy-Byrne, 2006).

Within such background, the question remains whether the Methylphenidate was not tolerated because of Pharmacogenetics peculiar to Omanis. Therefore, among many factors that could help to circumvent the current stalemate, is to chart Pharmacogenetics response to Methylphenidate. This is not far-fetched idea that could require serious contemplation.

#### **4.5.4 Logistical Factors**

In addition to the above reasons, several organisational factors had also affected patient's compliance with treatment.

One of these factors is a lack of transport. Oman is a relatively large country and the transport system is not well developed. Therefore, patients find it difficult to commute from various parts of the country to the capital city where the psychiatric clinics are located. Even if they get the transport, these cars are not specially equipped for disabled patients.

Additionally, these two psychiatric centres are not properly equipped with staff and chairs in the waiting area for taking care of TBI patients with disabilities, especially that these patients will have to wait for long hours in the psychiatric clinics. The fact that they will have to come frequently, this also makes the matter worse, particularly that they will also need to attend other subspecialties clinics such as speech therapy, which also scattered in different hospitals in the country.

#### **4.6 CONCLUSION**

As in all process of education, learning leads one to shed light on prevailing 'ignorance'. This study sheds a light on the fact that the rehabilitation system in Oman is not properly organised in order to take care of these chronic patients.

The study has uncovered the fact that Oman's rehabilitation system has much to be desired. The country is urgently in need for a multidisciplinary rehabilitation centre for these patients. Unless the country establishes a proper TBI rehabilitation program, patients may find it difficult to adhere to the requirements of a sustained, regular follow-ups and reviews.

It will be appealing in the future to perform the complete study at a clinic other than the psychiatric clinic, such as the neurological / rehabilitation centre, and see if these would decrease the dropout rate. Similarly, follow up study of other psychiatric complications of TBI such as Depression and see if they will also have similar non-adherence rate.

Future studies with larger and randomised, double blind, placebo-controlled studies are needed in order to confirm the effectiveness of Methylphenidate in such patients.

Although these studies are usually expensive and require a team of researchers, the frequency of TBI and its effects on individuals and families require that such studies should be done.



## CHAPTER FIVE: INTEGRATION AND GENERAL DISCUSSION

### ABSTRACT

*This chapter will summarise the main findings of the four studies. However, the findings will be reviewed selectively rather than exhaustively. Then the key conceptual and methodological issues encountered in the studies will be addressed. Finally, trends in the data will be highlighted, and future directions of research into the psychiatric complications of traumatic Brain injury (TBI) in Oman will be suggested.*

### THEORETICAL BACKGROUND

The sequel of road traffic accident (RTA) (also known as ‘traffic accident’, ‘motor vehicle collision’, ‘motor vehicle accident’, ‘car accident’, ‘automobile accident’, ‘road traffic collision’) is one of the most challenging public health problems facing the Sultanate of Oman. Recent data indicated that the rate of crashes, injuries and fatalities in the country is one of the highest in the world (Al-Reesi et al., 2012).

In view of the fact that RTAs are the main cause of TBIs, the country has also one of the highest rates of TBI in the world. While the worldwide incidence of TBI is ranging from 200 to 316/ 100,000 populations, the incidence in Oman is ranging from 300-400/100,000 populations per year (Al-Reesi et al., 2012).

This number is expected to increase in the coming years due to the increasing incidence of RTAs and concurrent improvement in the acute care management (Al-Naamani & Al-Adawi, 2007). Therefore, more patients are surviving from TBI with various disabilities.

One of the most common and disabling complication of TBI is the disease that manifest as emotional, cognitive, and behavioural disturbance. These impairments fall under the umbrella of neuropsychiatric complications.

Studies have shown that more than 50% of patients with TBI have at least one neuropsychiatric complications and up to 44% of these patients suffer from more than one neuropsychiatric disorder (C. Corcoran et al., 2005).

In terms of specific psychiatric illness, studies have shown that 44% of TBI patients have depression, and 14% have anxiety disorders (van Reekum, Cohen, & Wong, 2000).

Another debilitating complication of TBI is neurobehavioral symptoms such as lack of initiation, poor motivation, and impaired goal directed behaviour. These symptoms are collectively operationalized here as Apathy. Studies have shown that 47% of TBI patients have apathy (R Van Reekum et al., 2000).

Given the similarities between Apathy and depression, many clinicians tend to consider the disease as a part of depression. However, studies have shown that these two diseases are distinct, and they are responding differently to a different medication (Bejjani & Kunik, 2011).

The disease was not only found to be common, but it is also associated with various negative outcomes such as chronicity, poor quality of life and reduced response to treatment (Hsieh, Chu, Cheng, Shen, & Lin, 2012). Therefore, more studies are needed to explore the prevalence, the best predictors, and the treatment of apathy in patients with TBI. This was one of the main aims of the present thesis.

Previous studies have suggested that the reduction in the dopaminergic transmission, particularly in the frontal lobe, is implicated in the pathogenesis of apathy. As a result, several drugs that increase dopamine transmission, often known as psychostimulants (e.g. Bromocriptine and Methylphenidate) have been tried as a possible treatment of apathy (Camargos & Quintas, 2011; Robert Van Reekum et al., 2005).

Despite the high prevalence of TBI in Oman, research on the neuropsychiatric complications of TBI is scant. Furthermore, the rehabilitation service for these victims is rudimentary, to say the least.

## **The Status of TBI Rehabilitation Program In Oman**

The National Institute of Health (NIH) consensus statement in 1998 indicated that “. Rehabilitation of person with traumatic brain injury (TBI) should include cognitive and behavioural assessment and intervention” (Khan, Amatya, & Hoffman, 2012).

However, many TBI rehabilitation programs do not routinely include psychological services in their programs. A study by the National Institute of Health found that 85% of brain injury patients did not receive any treatment or psychosocial intervention concerning the long-term difficulties caused by TBI (Brain Injury Resource Center, 2010).

This is unfortunate since studies have shown that the rehabilitation process is likely to fail if the psychological and vocational domains are not addressed (Gupta & Taly, 2012). Therefore, in order to be successful TBI rehabilitation programs should include psychiatric services.

Recently there have been significant improvements in the TBI rehabilitation programs. Several new intervention methods have come to the forefront. Complementing such a situation is the development of the pharmaco-rehabilitation field. Drugs, such as Methylphenidate, have been added to the rehabilitation programs and found to improve the outcome (Hartley et al., 2011; Walker et al., 2012).

Therefore, any successful TBI rehabilitation system should not only be able to provide a comprehensive bio-psychosocial rehabilitation program, but the system should also be able to test any novel treatment in this developing field of medicine.

As alluded above, despite the higher incidence of TBI in Oman, the rehabilitation services in the country are poorly developed. It consists of physiotherapy departments in different hospitals scattered throughout the country. These departments usually get involved with a TBI patient only after the patient has been discharged from a Neurosurgical ward. This program does not have any psychosocial or psychiatric input.

Some patients who are found to have a psychiatric illness such as depression are referred to a psychiatric hospital either to the behavioural medicine department at sultan Qaboos university hospital, where part of this study was conducted, or to another tertiary care mental health hospital, Ibn Sina Hospital. Both of these hospitals are in the capital city of Oman to where patients are referred from all over the country.

Most of these patients will refuse the referral because of stigma towards mental illness. Even the few who agreed to be referred will attend the psychiatric clinic once or twice, then will be lost to follow up.

This thesis paves a background towards better understanding of the prevailing situation of TBI patients in Oman, and therefore, rehabilitation system specific to this population could be contemplated.

## **THE AIMS**

In view of the above background, the specific aims of this thesis are:

1. To establish the prevalence of neuropsychiatric complications, including apathy, in the survivors of TBI in Oman
2. To investigate the prevalence and the predictors of Apathy in such population
3. To assess the prevailing condition of the rehabilitation system in Oman
4. To test the hypothesis that intervention with dopamine enhancers, will improve disorders characterized with poor initiation or apathy

## **THE HYPOTHESIS**

In view of the above theoretical background, it is hypothesized that:

1. Neuropsychiatric complications, including apathy, are common in Omani TBI patients.
2. Apathy is a distinct disease and not secondary to depression or cognitive impairment as often thought to be the case.
3. Apathy is associated with damage to the frontal-subcortical circuit, a brain region that is known to be innervated mainly with dopaminergic neurons.
4. The current rehabilitation system in Oman is not able to provide a comprehensive bio psychosocial rehabilitation services.
5. A multidisciplinary psychosocial rehabilitation centre is urgently needed in Oman and that the current system is not effective.
6. Dopamine enhancer, such as Methylphenidate, might be useful for treatment of Apathy in these patients.

## **THE STUDIES**

### **The first study**

This was the groundwork for the present thesis. The purpose of this chapter was to review the epidemiology of TBI from a global perspective as well as prevailing data in Oman.

Oman has one of the highest road traffic accidents in the world (Al-Reesi et al., 2012). According to Shahbaz and Naroo (Shahbaz, 2007), nearly five thousand patients sought medical intervention due to RTA in 1998. This data was collected from one hospital only, Khoula Hospital. Most patients in the study were younger, and had multiple injuries with a significant number of them showed signs and symptoms of acquired brain injury. Most dishearteningly, 96 percent of these patients were discharged with various cognitive, emotional, and behavioural impairments.

The impact of this is staggering. Although these impairments are often masked with subtle symptoms, they are likely to be disabling in terms of social and occupational functioning. Therefore, it is unfortunate that these patients were discharged back to their pre-morbid daily life with all consequences this may entail.

However, this is not surprising as the health care system in Oman is limited to 'cure oriented' services (Al-Sinawi et al., 2012). In addition to the modern facilities, the Oman health care system has all the essential and advanced medical equipments. However, the system does not have enough personnel who are equipped with skills for taking care of chronic disease patients (Al Riyami et al., 2012)..

A similar trend has been discussed at the global perspective (Gorman, 2008). It was argued that 'task oriented' practitioner, would be necessary in the situation marred with the rising tide of people living with chronic illness, ageing populations, escalating costs of health-related technology and increasing consumer expectations. This situation is obviously applicable to the prevailing conditions in Oman (Al Riyami et al., 2012).

The above-mentioned analysis was based on the alarming situation emerging from database kept at one hospital. The question remains whether such a situation could be generalized to the whole country.

Population based studies suggest that the dire situation is not limited to one hospital setting and it can be generalized to the whole of Oman. Al-Reesi and his colleagues (Al-Reesi et al., 2012) reported a population based study that reveals the extent of road traffic accidents in Oman. The trend from these studies appears to be stark: the number of crashes per year in Oman for the observed period, 1999-2009, ranging from 8,000 to 14,000 accidents (Al-Reesi et al., 2012).

Most disheartening for the present discussion is that the number of patients who survived with various disabilities appears to have doubled during the same period.

Such trends are likely to be a tip of the iceberg in brain injury statistics. There are empirical data suggesting that the milder forms of TBI, which are the most common types, are not adequately represented in these statistics (Feigin et al., 2012; McMillan, Teasdale, & Stewart, 2012). Various reasons for this under-representation were thoroughly reviewed in chapter two and three of this thesis.

On this ground, it would be relevant to backup this line of thinking with picture emerging from population-based studies that have been done in other countries (Feigin et al., 2012). On the whole, the magnitude of the problem is much larger in Oman compared, for example, with that in New Zealand and other parts of the world (Feigin et al., 2012; Hyder, Wunderlich, Puvanachandra, Gururaj, & Kobusingye, 2007).

In addition to the increasing number of patients with TBI, the sequels of these injuries are devastating and tend to follow a chronic course (A. W. Brown, Elovic, Kothari, Flanagan, & Kwasnica, 2008). Previous studies have shown that 66 % of moderate and 100 % of severe TBI patients will have permanent disabilities (King & Fogg, 2010).

Therefore, studies are urgently needed to assess the magnitude of various complications of TBI including psychiatric complications.

## **The second study**

The aim of this study was to determine the prevalence of psychiatric complications in Omani TBI patients.

The study was conducted in Khoula Hospital, located in the capital, Muscat. Until recently, this was the only hospital in Oman that provides Neurosurgical and rehabilitation services for TBI patients (Al-Naamani & Al-Adawi, 2007) . On this ground, the present cohort is likely to be perceived as a representative sample of patients with moderate to severe TBI in Oman. In addition, this has rendered the performance of this study relatively easier.

It is worthwhile to note that Khoula Hospital has 'high tech' facilities relevant for Neurosurgical services. However, it lacks services for patients with neuropsychiatric disorders.

Five hundred and forty patients were screened over a period of 6 months duration for inclusion and exclusion criteria. The inclusion criteria were any male or female TBI patient who is 15-70 years old. This patient should not have a past history of TBI, mental illness, or substance abuse.

Out of 540 patients, 103 patients met the inclusion and exclusion criteria and consented to the study. These patients were screened by the author using several psychological assessments relevant for emotional, cognitive, and behavioural impairment.

### **Results:**

Self-reporting questioner (SRQ) was used to measure the likelihood of these patients to have a psychiatric illness.

Sixty four percent of the 103 patients had a high probability of having a psychiatric illness. This was supported by the high score of patients who were found to have anxiety (39.8%), depression (41.7%) and apathy (41.7%), using tools for diagnosis of anxiety (HADS), depression (HADS), and apathy (Apathy evaluation scale) respectively.

Similarly, using Fatigue Assessment scale (FAS), 35% of these patients were found to have fatigue.



Cognitive assessments showed that these patients were grossly impaired in cognitive domains such as short-term memory, attention, and concentration compared to “normal” healthy control group. The differences were statistically significant in all cognitive assessments employed (p-values are less than 0.01).

### **Limitations**

Although the prevalence of psychiatric complications in these patients were similar to that found in other countries, this study had several limitations:

Firstly, although almost all patients with moderate to severe TBI in Oman were referred to this centre, it is still possible that some Omani TBI patients were missed. These missed patients could be those who are too severe cases of TBI or chronic patients who are no longer coming for follow up. Furthermore, acute TBI patients who were admitted in the Neurosurgical ward and not coming to the outpatient clinic might have been missed. Some patients were not included simply because they did not have an appointment during that six-month study period or mild TBI who were not referred to the Centre. Similar trends in brain injury statistics were also found elsewhere (Feigin et al., 2012). In New Zealand, for example, it was found that 95% of all TBI are milder cases; most of these patients usually are not included in brain injury statistics (Feigin et al., 2012).

Secondly, although most of the assessments used in this study have been validated in a similar culture, the suitability of some of the tests to be used in Omani culture is questionable (S Al-Adawi et al., 2007).

Thirdly, in the cognitive assessment section of this study, the main limitation was the small number of the subjects in the control group.

Unfortunately, there are no cognitive assessment tools that have been validated in the Omani population. To overcome this problem, a “healthy” control group was used in order to measure how impaired cognitively Omani TBI patients were in relation to the control group. For this purpose, patients who were attending an orthopaedic clinic were recruited as a “healthy” control group. Unfortunately, most patients in the orthopaedic clinic were also involved in a road traffic accident; therefore, they were excluded in this study for fear that they might also have some unnoticed brain injury. This was unfortunate, since only twenty patients were found to be suitable and willing to participate in the study.

However, these control group patients were well matched to the TBI patient group in terms of age and gender.

Recommendation for future studies is to perform the study in the community. This will help to estimate the prevalence of neuropsychiatric complications of TBI that is closer to the real situation. Although doing a good community study is expensive and time consuming the, prevalence and the impact of these disorders on the societies make these studies relevant.

One way is to do a population based study using the methodology of the BIONIC study as that done by Feigin et al (Feigin et al., 2012). This was drawn on the WHO Injury Surveillance Guidelines that uses multiple sources of information, including coroner or autopsy records, rest homes, community health services, schools, sports centres, ambulance services, and prison. The surveillance is a prospective and retrospective surveillance system that ensures registration of all TBI cases. These cases could then be registered, assessed, followed, and entered into studies if they wished.

Another way is that the community studies could be done by possibly announcing in the local media to all patients with TBI to come for an assessment and be screened for psychiatric complications. However, given the stigma towards mental illness, this system might not work. Furthermore, the sample would be biased.

Alternatively, the survey of neuropsychiatric complications of TBI could be done as a part of the national censuses.

Validity studies of cognitive assessments in Omani population are lacking, and therefore, there is an urgency to establish the validity of cognitive assessments in this population. These studies are usually time consuming and needs a team of neuropsychologist to perform the study. However, given the prevalence of psychiatric complications in TBI patients in Oman, the national research council could fund the project. Furthermore, the assessments could then be used not only in TBI population, but also in routinely clinical practice.

Despite the above limitations, this study gives an estimate of the magnitude of psychiatric complications in Omani patients with moderate to severe forms of TBI. It can be a starting point towards a comprehensive evaluation of psychiatric complications in Omani patients with TBI.

### **The third study.**

The main purpose of this study was to find out the best predictors of Apathy among various clinical and demographic variables in these patients.

This was part of the study described in chapter two of this thesis, where 103 patients were recruited for this study. These patients underwent various neuropsychiatric assessments, including the Apathy Evaluation scale (AES). The data were then analysed using factor analysis, correlation and multiple regression techniques.

### **Results**

Among the 103 patients, 43 patients were found to have apathy. Multiple regression analysis was used to determine the best predictors of apathy among various clinical and demographic factors of these patients. The results of the analysis showed that only Buschke Selective Reminding Test (BSRT) accounted for much of the variability in the AES.

Buschke Selective Reminding Test (BSRT) is a cognitive assessment that was found to be sensitive to frontal lobe system impairments (Lezak, 2004). Therefore, the finding of this study supports the main hypotheses of this study that apathy in TBI patients would be associated with cognitive impairments associated with frontal lobe system.

However, another cognitive assessment which is also associated with frontal lobe system, Wisconsin Card Sorting Task (WCST), failed to make any significant contribution to AES. This suggests a functional separation between cognitive functions concerned with learning new information (as assessed by BSRT) and those concerned with deductive reasoning and mental flexibility (WCST).

Another interesting finding of this study is that Apathy was not associated with a mood disorder particularly depression. However, this was also found in several other studies as cited in chapter three. This also confirms the prediction made in this study that Apathy will not be associated with depression. Even more interesting was the fact that there was a negative correlation between depression and fatigue on one hand, and apathy. However, this correlation was not statistically significant (P-value = 0.164).

The study also showed that Apathy is not related to the severity of the Brain injury and that the correlation was negative. This means that the more severe the Brain Injury is, the less apathetic the patient will be.

One possible explanation of this finding could be because the severity of head injury, according to The Glasgow Coma Scale (GCS), was done at the time of the injury while Apathy assessment was done over a long period. For some patients, the time between the two assessments reached 5 years.

However, although the GCS might change over time, the results in chapter four of this thesis showed that AES does not change with time since injury. Therefore, the time factor is unlikely to be the reason for the lack of association between Apathy and severity of the injury.

Another explanation would be that, in the case of severe brain injury, the patient's awareness of the level of disability might be grossly impaired, and this could be crucial in the pathogenesis of apathy.

In order to find out if this is the case, it will be interesting in the future studies to assess the relationship between disability awareness and apathy in Omani TBI patients.

## **Limitations**

The main limitation of this study was the fact that the multiple regression analysis was performed in a non-normal sample. Furthermore, a small number of the subjects and the missing data for many of the participants have limited the generalizability of the present study. Unfortunately, this is often the case when doing research with patients whose brain injury is diverse and with severe impairments (Felmingham, Baguley, & Crooks, 2001; L Turner-Stokes, Disler, Nair, & Wade, 2005)

Recommendation for future studies is to study the predictors of apathy in a larger number of TBI patients. Similarly, it will be interesting to study the predictors of Apathy in other patient populations, such as in orthopaedic patients.

Additionally, to study the best predictors of apathy using other mood assessment scales as some investigators have recently suggested that HADS may not be effective in the diagnosis of depression in Omani patients with TBI (S Al-Adawi et al., 2007).

It will also be interesting to analyse the sample using non-parametric regression and see if this would change the findings.

### **The Fourth study**

This study was planned to assess the effectiveness of methylphenidate to treat apathy in Omani TBI patients. The idea of using Methylphenidate in these patients was based on previous studies that have shown the drug to be helpful treating apathy in various neurological diseases.

However, during the study, it was obvious that the number of patients who could complete the study were extremely low. Therefore, it was unrealistic to report the result of this study. Instead, the study was used to assess the overall rehabilitation service.

On this ground, the initial employment of this study, to evaluate the effectiveness of Methylphenidate in the treatment of Apathy, became a tool to assess the overall status of TBI rehabilitation program in Oman.

Forty-three patients who were found to have apathy in study two of this thesis were recruited for this study. Various affective and cognitive assessments were employed for this study. Apathy Evaluation Scale (AES) was used for measuring apathy and Hospital Anxiety and Depression Scale (HADS) for assessing depression and Anxiety, in addition to several cognitive assessment tools.

A single-case methodology, (AABAA) design was used in this study in order to observe changes in AES before, during, and after the treatment.

The patients had two-repeated baseline, BL1 (A) and BL2 (A), before treatment in order to identify any possible spontaneous improvement. The period between BL1 and BL2 was variable were ranging from 13 to 773 days (mean = 281 days).

The initial plan was to start with 20 mg of Methylphenidate and then to increase the dose by 20 mg every two weeks until the patient improve or develop a side effect. Then the medicine will be stopped. However, in all, but one patient, methylphenidate could not be increased to more than 20 mg.

The patients were re-assessed at two weeks, then four weeks after stopping the medicine.

## **Results**

Among the forty-three, only three patients could complete the study. The remaining patients dropped out at different stages of the study.

This demonstrates the reality that the current TBI rehabilitation system in Oman cannot provide the comprehensive bio psychosocial program for TBI patients; and that the system cannot even accommodate a basic drug administration and follow up regimen.

These two factors significantly impinge on the effectiveness of the rehabilitation system in Oman. Without a proper rehabilitation centre, it will be difficult for these patients to comply with the required long-term regular follow-ups and reviews.

Various social, cultural, and organisational factors have been suggested to be the cause of the higher dropout rate. These factors were extensively reviewed in chapter four of this thesis. In the ensuing paragraphs, some of the findings that were not discussed in chapter four will be reviewed.

Although based on a small number of patients who could complete the study, there were several interesting observations from this study.

There were no spontaneous and natural improvements in apathy at assessment BL2 compared to BL1. Among the 43, only eleven patients consented to the study and agreed to take Methylphenidate. Thereafter, six more patients were excluded from the study. Three were lost to follow up, and three patients had to stop taking the drugs because of the side effects.

Two weeks after starting Methylphenidate, four of the five patients (67%) who could tolerate 20 mg Methylphenidate had less apathy. Similarly Depression, improved in four out of five patients; Anxiety improved in three out of five patients, and fatigue improved in all five patients. There were also improvements in all cognitive function assessments employed in this study except in one out of the five patients.

The medicine was stopped, and the patients were re-assessed after two weeks and then four weeks



One of the interesting findings of this study was that the improvement in Apathy did not happen in same patients who also improved in depression and fatigue. This finding suggests that Apathy is a distinct syndrome, and it is not related to depression or fatigue.

This observation is consistent with other work that suggests methylphenidate treatment of apathy has a direct effect on apathy rather than working through the improvement of depression, as was suggested in other studies (Powell et al., 1996; Weiss & Marsh, 2012).

Another interesting finding was that the improvement did not reverse in two out of four patients after stopping the medicine. This has also been found in other studies as reviewed in chapter four.

A possible explanation for this phenomenon is that Methylphenidate might stimulate neuroplasticity in these patients (Rabipour & Raz, 2012).

It will be interesting to follow up these patients for a longer period and see if these improvements continue.

## **Limitations**

This study is limited by various methodological problems:

Firstly, the main limitation of this study was the large number of patients who dropped out of the study. As reviewed in chapter four, it is suggested that a number of the patients (and their families) might have refused to be included in the study because of stigma of attending a mental health clinic. It was argued that having multidisciplinary rehabilitation centres for the treatment of TBI might decrease this problem.

Among the eleven patients who consented to the study, three dropped out because of the side effects. This could have been avoided if we started with a smaller dose of the medicine, instead of the 20 mg dose.

Secondarily, this study had no control group. However, the AABAA study design is often used to avoid such confounds since the patients are assessed several times before the treatment, during the treatment and after the treatment (S Al-Adawi et al., 2005). Therefore, the patients are functioning as their own control groups. Nevertheless, a full-randomised controlled trial (RCT) would be the ideal way to assess the effectiveness of methylphenidate in this group of patients.

Similarly, RCT can be done to assess the effectiveness of the current rehabilitation system in Oman. However, RCT is not usually done in TBI rehabilitation studies (L. Turner-Stokes, 2008). This is because rehabilitation is a complicated intervention, with many interrelated components. Additionally, as reviewed earlier, there is an expanding body of evidence for effectiveness of multidisciplinary rehabilitation in other condition such as stroke. This makes it ethically difficult to randomise patients to non-treatment group. However, the reality is that a multidisciplinary rehabilitation services are not available to many patients in Oman. Therefore, there is ethical urgency to undertake such studies in order to acquire evidence for use such services.

Nevertheless, the rehabilitation system in Oman has various practical and logistic barriers need to be overcome in order to be able to perform such studies.

Finally, the study was not long enough to ascertain whether the patients would develop tolerance for the treatment as previous studies suggested.

It was noted that, one patient in this study showed improvement in apathy scores after two weeks of taking the medicine. The improvement then reversed despite the patient continuing to take the medicine. It is possible that this patient had developed tolerance. However, the symptoms did not improve even after increasing the dose of Methylphenidate. Furthermore, the remaining patients did not show tolerance to the medicine. Possibly the period of taking the medicine was too short.

Similarly, after stopping the medicine, there were no patients in this group developed addiction as other studies suggested (T. Challman & J. Lipsky, 2000).

While recognizing the limitations of the present study, the observations are consistent with previous studies that showed Methylphenidate to be an effective treatment for apathy in TBI patients.

Future studies with larger and randomized, double blind, placebo-controlled studies are needed in order to confirm the effectiveness of Methylphenidate in such populations. Although these studies are usually expensive and require a team of researchers, the frequency of TBI and its effects on individuals and families require that such studies should be done.

It will be interesting to perform the complete study at the Neurosurgical / rehabilitation centre and see if these would decrease the dropout rate.

Future studies could employ dedicated staff to remind patients about the appointments, do home visits, and to provide transport with equipped vehicles. This will help retain more patients in the study.

Similarly, to involve the whole family in consenting to the study, provide an information sheet for the family would also help to recruit and retain more patients.

Additionally, following these patients for a longer period after stopping the medicine. This will help to confirm whether the non-reversal of the improvement will continue.

In addition to the limitations mentioned in the individual studies, there are several biases that were common on all three studies. These biases are:

1. Observer bias and not being blind ratter. All the assessments in this study were done by the author of the thesis. However, the advantage of this is that the author is a trained clinician. Additionally, all patients were assessed by one person and therefore they were no inter rater discrepancies.
2. Instruction bias. Although all assessments were done by one person, the instructions might change from time to time, and this would affect the results.
3. Interviewer or observer bias this is when one is able to elicit better response from a patient
4. Hawthorne effect. Since the patients knew that they were observed, it is possible that they response might have been influenced by this fact.
5. Repeat testing bias. This could happen in the fourth study, where some of the assessments have been repeated. Therefore, it is possible that some patients did better on psychological assessments not because of the effect of the medicine but because of repeating the assessments. Similarly, for some patients the assessment took a long time and this could cause fatigue and alter the response in these patients.
6. Bias due to non-response. Although statistically the non-responders in these studies were similar to the responded patients, the large number of drop out patients has reduced the sample size and therefore decreased the power of the studies.

## CONCEPTUAL AND METHODOLOGICAL ISSUES

Generally, the studies presented in this thesis are consistent with the model under tests here and consistent with other studies done elsewhere.

However, the absence of any relationship between Depression and Apathy is particularly puzzling because clinically, these two diseases usually present with similar signs and symptoms. Although this has been reported also by other studies (Weiss & Marsh, 2012), the conclusion that depression, as measured by the HADS, is different from Apathy may be premature.

There are several alternative explanations for this observation. One possible explanation is that the brain injury that these patients were suffering from might have caused impairment of their insight and disability awareness. Thus, patients may exaggerate their well-being, and this will show on HADS, a self-report measure, that the patient is less depressed than he actually is.

At the same time, the brain injury usually affects the frontal lobe, which has been shown, in this study, to be critically influential for the pathogenesis of Apathy (Helsinki & Tallinn, 2009). Therefore, these patients will be shown to be apathetic on AES. It will be interesting in future studies to use clinician-rating scale for depression and see if this will show similar results.

Furthermore, the contents of these two questionnaires are different. The questions in HADS are mainly to do with emotions and mood which patients in this culture are not forthcoming in revealing their negative emotions (Al-Busaidi, 2010). On the other hand, the questions in AES are more of physical and practical questions that are difficult for patients to conceal. This would lead to discrepancies in the findings.

As stated earlier, it will be interesting for future studies to use different assessment tools for depression and Apathy and see if this will lead to similar results.

After taking Methylphenidate, all patients improved in their cognitive function assessments, except one who had deteriorated performance in BSRT.

Interestingly, this patient also had a worsening of their Apathy score. This supports the link between BSRT and apathy as was suggested by Multiple Regression analysis in chapter three of this thesis.

Given the fact that BSRT is a specific test for frontal lobe function, this supports the hypothesis that the frontal lobe impairment is directly involved in the pathogenesis of Apathy as was found in this study and others (Helsinki & Tallinn, 2009).

However, the results of this study must be viewed as preliminary pending replication of these studies in a similar group with a larger number of patients.

Nevertheless, the results of these studies have generated additional questions of both clinical and theoretical interests. For example, the fact that these patients with apathy improved with an agent that increases dopamine activity, does this mean that Dopamine is the only neurotransmitter involved in the pathogenesis of apathy?. While the results of the current study do suggest this, the association it is by no means definite.

Although Methylphenidate is a dopamine enhancer, it is known to affect other transmitters as well such as Norepinephrine. Therefore, it is still possible that these neurotransmitters are also crucial in the pathogenesis of apathy. Particularly since not all patients responded positively with Methylphenidate. Indeed apathy in one patient got worse after taking the drug.

Further complicating this issue is the fact that improvement in apathy did not happen in the same patients who also improved in depression. This is puzzling since dopamine enhancers are also known to improve some patients with depression. This suggests that these two diseases are not a result of a single neurotransmitter such as dopamine dysfunction, rather a combination of several interacting neurotransmitters.

## **CONCLUSION**

In view of the present findings, it can be concluded that neuropsychiatric complications are common in Omani patients with moderate to severe TBI.

Although the prevalence of these diseases is similar to that cited internationally, the total number of patients with these complications is expected to increase in the coming years, given the fact that the number of TBIs is likely to raise.

This study had shown that the current health care system is not properly organized to take care of Omani TBI patients with psychiatric complications. The system does not enable these patients to adhere to the required regular follow-ups and reviews.

Therefore, a comprehensive brain injury rehabilitation centre is urgently needed. The centre must have all the subspecialties that have been found to be useful in these patients. This will help the patients so that they will only attend one centre and at one appointment day and see all the concern specialists. Additionally, in such centre patients can start therapy with a different therapist at different times. This will help to reduce the long waiting hours.

Additionally the centre must have dedicated staff to remind patients about the appointments. Particularly that memory impairment is one of the main psychiatric complications these patients have.

The dedicated staff to improve health education of these patients and their families and home visits for these patients will reduce the burden of the illness on these patients and their families.

The centre should also provide transport with specially equipped vehicles.

All these factors will help patients to be properly managed, keeps their appointments, improve adherence to treatment and therefore improve the outcome.

Unless the country establishes a proper TBI rehabilitation program, patients will continue to suffer from potentially treatable neuropsychiatric impairments resulting in poor quality of life for patients and their families.

## **APPENDICES:**

### **INDIVIDUAL CASE REPORTS**

#### **Patient Number One (A. A)**

A. A is a 19 years old Omani male. He was involved in RTA when he was 18 years old. At the time of the accident, A. A lost consciousness, his GCS was six, and his TBI was classified as severe TBI. His CT brain showed parietal and occipital fractures, multiple contusions mainly on the left side of the brain and diffuse axonal injury.

The pre morbid assessment showed that A. A had normal developmental milestone. He studied until 12<sup>th</sup> class and was a student at the time of injury. His pre-morbid IQ was estimated to be Average. He had no family history of psychiatric illness.

A. A was first seen by us about 14 months (400 days) after the accident. He had no retrograde amnesia, but had anterograde amnesia of about one month. A. A was complaining of multiple post-concussion symptoms such as memory impairment, forgetfulness, and irritability. The SPECT study showed perfusion defects in the frontal, parietal, occipital, and temporal region of the left hemisphere. Disability rating scale showed that A. A had no disability. However, his Self-Reporting Questionnaire showed that A. A had a higher probability of having a mental illness. FAS showed that A. A had a mild fatigue. HADS showed that A. A had a mild depression and moderate anxiety. The apathy evaluation scale showed that A. A had mild apathy.

A. A was reassessed again after about five months (157 days) from the first assessment. Although his SRQ showed slight improvement, his fatigue and depression got worse. However, there were no changes in anxiety, apathy, BSRT and Digit span test as shown in table 6.1 and 6.2.



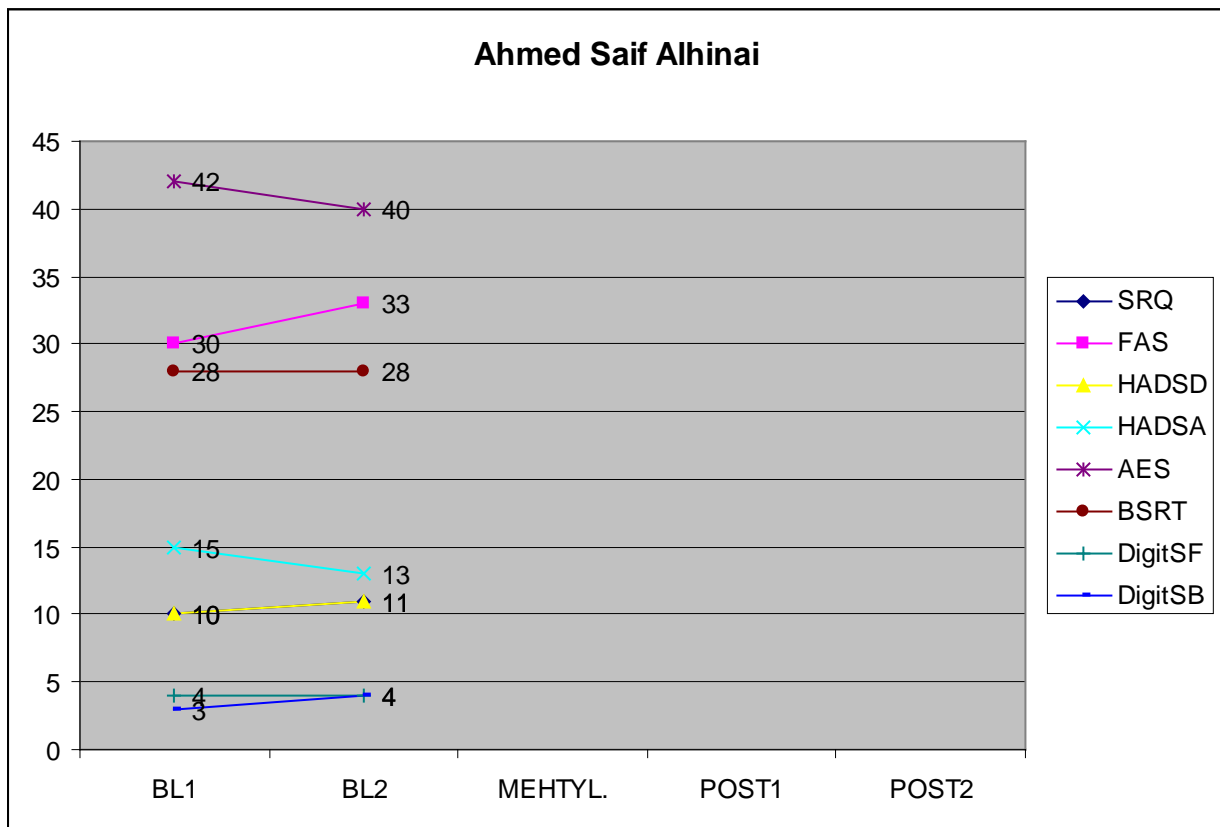
**Table 6.1: A table shows the results of Affective and Cognitive Assessments of A. A**

<b>ASSESSMENT</b>	<b>BL1</b>	<b>BL2</b>	<b>METHYL</b>	<b>POST1</b>	<b>POST2</b>
SRQ	High Range (10)	Middle Range (11)	Did not Come Back for a follow-up		
AES	Mild (42)	Mild (40)			
HADS (Depr.)	Mild (10)	Moderate (11)			
HADS (ANX.)	Moderate (15)	Moderate (13)			
FAS	Mild Fatigue (30)	Moderate Fatigue (33)			
IQ	Not Done				
BSRT	28	28			
Digit (FOW)	4	4			
Digit (BACK)	3	4			
Wisconsin Card Sorting Test	Not Done				

The patient consented to the study and he was prescribed Methylphenidate SR 20 mg.

Unfortunately, the patient did not come again for follow-up.

**Graph 4.8 A Graph shows Changes in Affective and Cognitive Symptoms of A. A**



### **Patient Number two (F.F)**

F.F is 31 years old Omani female. She had RTA when she was 30 years old. Following the accident, F.F lost consciousness. Her GCS was five and her TBI was classified as severe TBI. Her CT scan showed a left temporal and parietal contusion and generalized cerebral oedema.

F.F had normal developmental milestone, her pre-morbid IQ was estimated to be average, and she finished 11<sup>th</sup> class. She had no significant family history of mental or psychiatric illness.

F.F was seen after about seven months (210 days) after the injury. She claimed to have anterograde amnesia of about 4 weeks and retrograde amnesia about 4 weeks. She complained of multiple post-concussion symptoms such as forgetfulness, irritability, and headaches. Her DRS showed that she is having a moderately severe disability. SRQ showed that F.F was having a high probability of having a mental illness. HADS scores showed that F.F was not having depression or anxiety. Interestingly, AES showed that F.F was suffering from severe Apathy. FAS showed that F.F was suffering from mild fatigue.

F.F was assessed again after a period of about 11 months from the first assessment. Before the second assessment, F.F also had a SPECT scan which showed low perfusion on the posterior part of the left hemisphere. The second assessment showed that there were no changes in the HADS, Apathy, and Digit Span backward. Her scores on SRQ and BSRT got worse. However, her Digit span forward scores and her level of fatigue got better from moderate to mild (Table 4.18)

**Table 6.2: A table shows the results of Affective and Cognitive Assessments of F.F**

Assessment	BL1	BL2	METHYL	POST1	POST2
SRQ	High Range (15)	High Range (18)	Lower Range (5)	Middle Range (7)	High Range (10)
AES	Severe (66)	Severe (65)	Severe (69)	Severe (66)	Severe (66)
HADS (Depr.)	Normal (6)	Normal (4)	Normal (7)	Normal (6)	Normal (7)
HADS (ANX.)	Normal (5)	Normal (7)	Mild (8)	Normal (7)	Normal (7)
FAS	Moderate Fatigue (34)	Mild Fatigue (30)	None Fatigue (20)	Mild (25)	Mild (27)
IQ		80	80		
BSRT	10	9	11	13	11
Digit (FOW)	3	4	4	4	4
Digit (BACK)	2	2	3	3	3
Wisconsin Card Sorting Test		0.17	0.55		

F.F was started on Methylphenidate SR 20 mg once daily. F.F and her family felt much better after starting Methylphenidate. The family reported that F.F was much less forgetful, and less fatigue compared the way she was before starting the treatment. Psychological assessment, which was done two weeks after starting the Methylphenidate, revealed the following results. SRQ scores improved from severe to lower range. Her FAS score showed no fatigue. However, AES remains severe apathy, and HADS showed a slight increase in the anxiety subscale. Cognitive function tests revealed improvement on BSRT, and backward digit span.

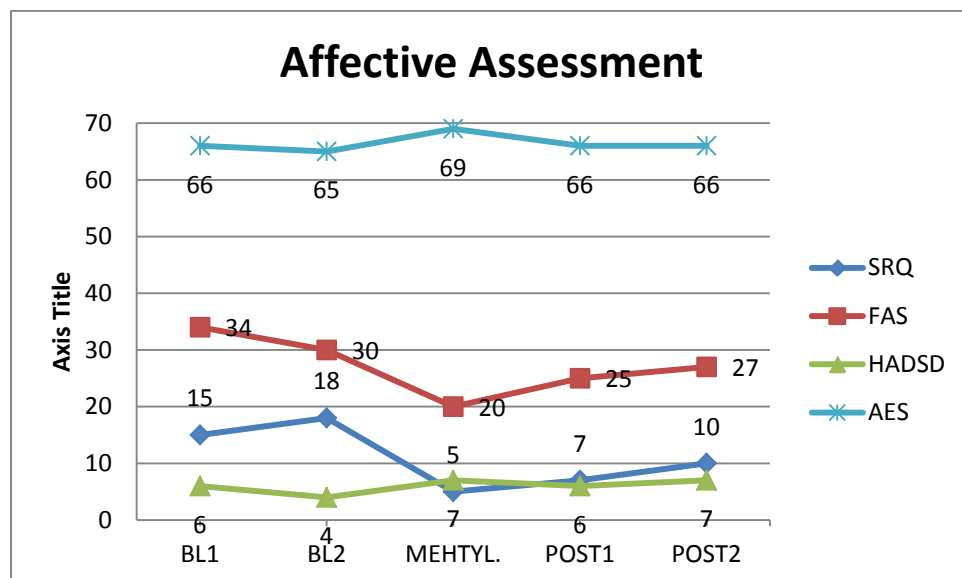
Unfortunately, the patient was reluctant to continue taking the medication and hence the drug was stopped.

However, the patient was reassessed again after two weeks of stopping the medicine. Her SRQ scores slightly increased.

Fatigue has increased to mild. Apathy remains severe. Depression remains normal, and anxiety improved from mild to normal. Surprising, her cognitive function test showed further improvement on BSRT, and there were no deteriorating of both forward and backward digit span.

After four weeks of stopping Methylphenidate, F.F was assessed again. SRQ further deteriorated to a higher probability. Fatigue slightly increased. Apathy, anxiety, and Digit Span remain same However, Depression and BSRT slightly deteriorated.

**Graph 5.9 A Graph shows Changes in Affective and Cognitive Symptoms of F.F**



### **Patient Number three (H.Z)**

H.Z is 26 years old Omani gentle man. He had RTA when he was 20 years old. At the time of the accident, H.Z had loss of consciousness. His GCS was 11 and his TBI was classified as moderate TBI. However, the patient had a normal CT scan of the brain.

H.Z had a normal developmental milestone. However, his pre-morbid IQ was estimated to be below average. He finished third secondary class and was unemployed before the accident.

H.Z was assessed about six years after the accident. He claimed to have retrograde amnesia of only about 30 minutes, but anterograde amnesia of one-month duration. The only complaint he had was blurred vision.

His DRS showed no disability. However, his SRQ showed a high probability of having a mental illness. FAS showed moderate fatigue and HADS showed severe anxiety and depression subscales. His AES scores showed mild apathy.

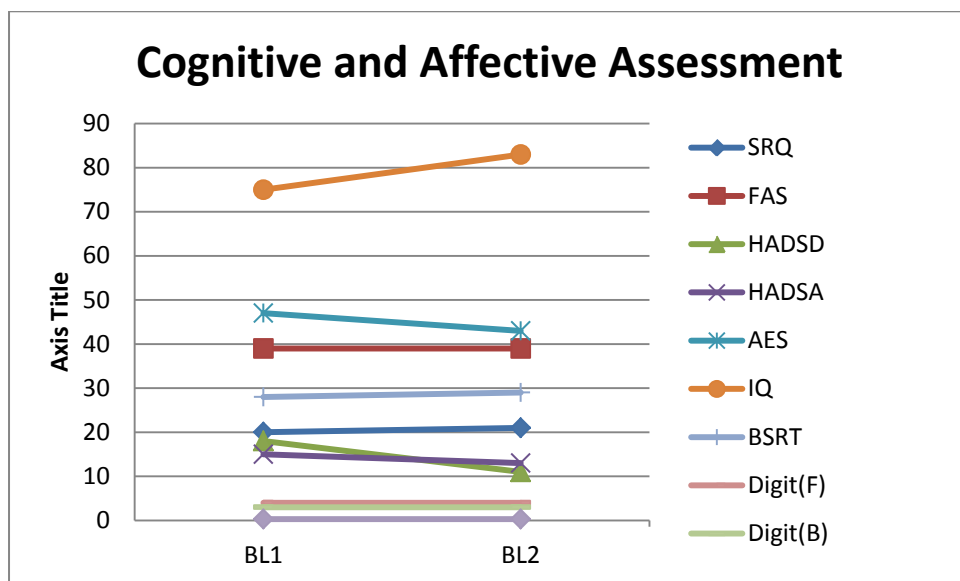
H.Z was reassessed again after about ten months from the first assessment. His SRQ remains high, FAS remains moderate fatigue, and HADS anxiety subscale remains severe. However, his HADS depression subscale improved from severe to moderate depression (Table 4.19 and figure 4.10).

H.Z was started on Methylphenidate SR 20 mg once daily but unfortunately, the patient was lost to follow up.

**Table 6.3: A table shows the results of Affective and Cognitive Assessments of H.Z**

Assessment	BL1	BL2	METHYL	POST1	POST2
SRQ	High Range (20)	High Range (21)	Did not Come Back For Follow-Up		
AES	Mild (47)	Mild (43)			
HADS (Depr.)	Severe (18)	Moderate (11)			
HADS (ANX.)	Severe (15)	Severe (13)			
FAS	Moderate Fatigue (39)	Moderate Fatigue (39)			
IQ	75	83			
BSRT	28	29			
Digit (FOW)	4	4			
Digit (BACK)	3	3			
Wisconsin Card Sorting Test	.30	.31			

**Graph 4.10 A Graph shows Changes in Affective and Cognitive Symptoms of H.Z.**



### **Patient Number four (H.R)**

H.R is 23 years old Omani male. He had RTA when he was 22 years old. At the time of accident H.R lost consciousness and his GCS was five. His Brain injury was classified as severe TBI. His CT brain showed right frontal extradural haemorrhage.

H.R had normal developmental milestone, he finished sixth class, and his pre-morbid IQ was classified as average. H.R had no significant family history of psychiatric or medical history.

H.R was seen after about six months post TBI. He claimed to have anterograde amnesia of about 2 months, but no retrograde amnesia. The only post-concussion symptom he was complaining of was a headache. There were no cognitive or emotional post-concussion symptoms.

His psychological assessment revealed that Mr H.R had no disability, according to DRS. SRQ showed lower range of probability of having a mental disorder. He had mild fatigue, according to FAS and HADS revealed moderate depression and mild anxiety. AES scores showed moderate Apathy.

Mr H.R was reassessed again after about ten months after the first assessment. He also had SPECT that showed perfusion defect on the right frontal parietal region. His psychological assessment showed no changes in SRQ, FAS, AES and HADS depression and anxiety subscale. (Table 4.20 and figure 4.11).

His cognitive function assessment showed improvement on BSRT and Digit span backward and forward scores.



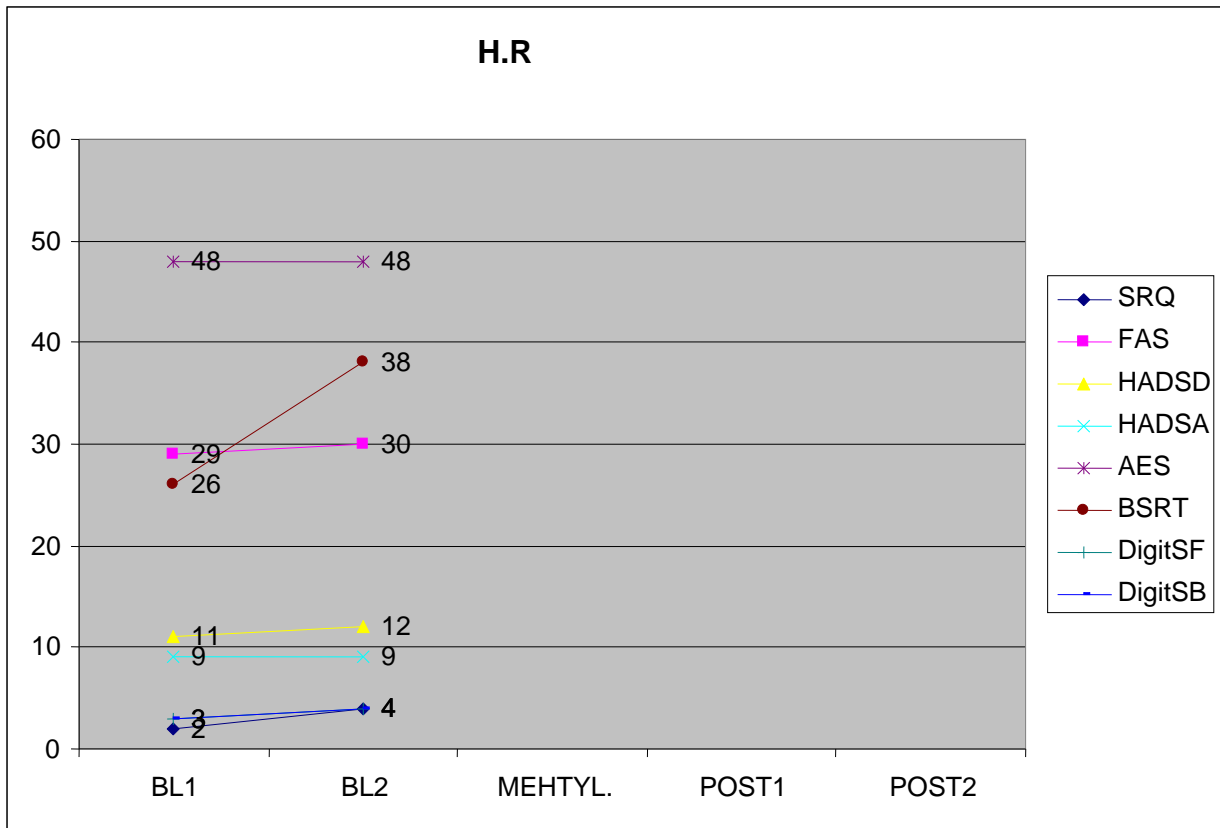
**Table 6.4: A table shows the results of Affective and Cognitive Assessments of H.R**

Assessment	BL1	BL2	METHYL	POST1	POST2
SRQ	Lower Range (2)	Lower Range (4)	Stopped the medicine because of the side effects		
AES	Moderate (48)	Moderate (48)			
HADS (Depr.)	Moderate (11)	Moderate (12)			
HADS (Anx.)	Mild (9)	Mild (9)			
FAS	Mild Fatigue (29)	Mild Fatigue (30)			
IQ					
BSRT	26	38			
Digit (FOW)	3	4			
Digit (BACK)	3	4			
Wisconsin Card Sorting Test	0.17	0.15			

H.R was started on Methylphenidate SR 20 mg once daily. Unfortunately, H.R could not tolerate the medicine. After taking only two tablets, he started to feel giddy, not able to walk properly. These symptoms disappear after stopping Methylphenidate. Two weeks after stopping Methylphenidate he started to have episodes of falling down, loss of consciousness, but denies the history of fits, and there were no urine or stool incontinence.

The patient denied history of epilepsy. However, he was given prophylactic antiepileptic that was stopped five months prior to our assessment. EEG was done and was reported to be normal. Because of this incident, the patient was withdrawn from the study.

**Graph 4.11 A Graph Shows Changes in Affective and Cognitive Symptoms of H.R.**



### **Patient Number five (H. A)**

H. A is 37 years old Omani male. He was involved in a road traffic accident and had TBI three months before our first assessment. H. A lost his consciousness at the time of injury, but unfortunately, his GCS was not recorded. His CT brain was normal.

H. A had a normal developmental milestone. He finished only sixth class, and his pre-morbid IQ was estimated to be below average. H. A was working as a driver before the accident.

When we assessed H. A, he claimed to have anterograde amnesia of about 10 days, but no retrograde amnesia. He complained of multiple post-concussion symptoms such as headache, memory impairment, irritability, and mood swings.

Psychological assessment revealed that H. A had no disability, according to DRS. However; SRQ showed that H. A has a high probability of having a mental illness. FAS showed severe fatigue. HADS showed moderate depression and mild anxiety. AES showed mild apathy.

H. A was reassessed again after about nine months. He also had a SPECT scan which showed normal results. The second psychological assessment showed no changes in SRQ, FAS, AES, and depression subscale of HADS. However, the Anxiety subscale of HADS showed improvement of anxiety from mild to normal. Cognitive function tests showed improvement on BSRT. However, both backward and forward digit span remains same as shown in table 6.5 and figure 4.12.

**Table 6.5: A table shows the results of Affective and Cognitive Assessments of H. A**

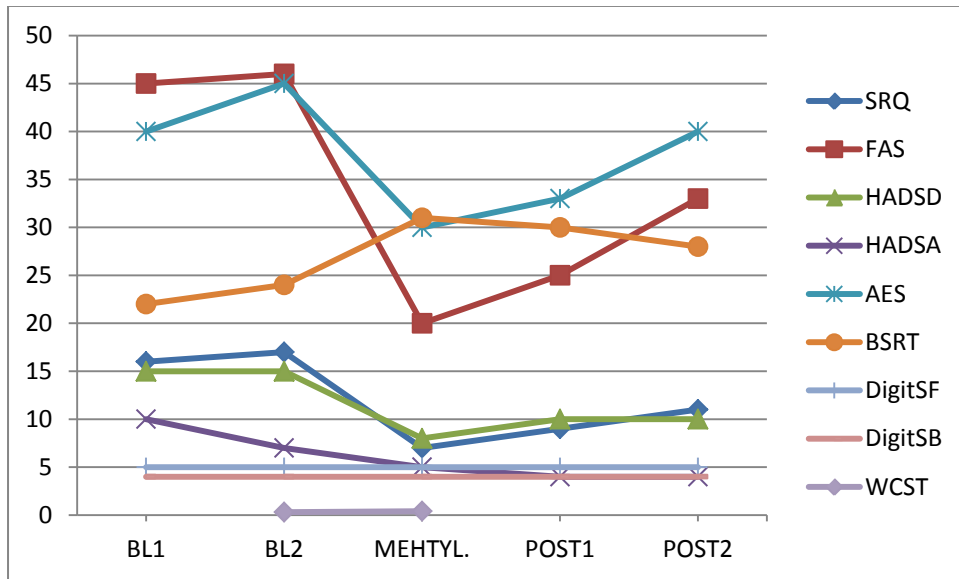
Assessment	BL1	BL2	METHYL	POST1	POST2
SRQ	High Range (16)	High Range (17)	Middle Range (7)	Middle Range (9)	High Range (11)
AES	Mild (40)	Mild (45)	Normal (30)	Normal (33)	Mild (40)
HADS (Depr.)	Moderate (15)	Moderate (15)	Mild (8)	Mild (10)	Mild (10)
HADS (ANX.)	Mild (10)	Normal (7)	Normal (5)	Normal (4)	Normal (4)
FAS	Severe Fatigue (45)	Severe Fatigue (46)	None Fatigue (20)	Mild (25)	Moderate (33)
IQ		83	90		
BSRT	22	24	31	30	28
Digit (FOW)	5	5	5	5	5
Digit (BACK)	4	4	4	4	4
Wisconsin Card Sorting Test		0.31	0.4		

H. A was started on Methylphenidate SR 20 mg once daily After two weeks has reported being much better, less headaches, sleeps well, improvement in fatigue. Psychological assessment showed improvement on SRQ, FAS, HADS, and BSRT and AES. The medicine was stopped and he was asked to be reviewed after two weeks.

After two weeks of stopping Methylphenidate, the patient was assessed again. His psychological assessment showed deteriorating of SRQ, fatigue, depression, BSRT, and apathy. However, there were no changes in the scores of anxiety and digit span.

After four weeks of stopping Methylphenidate, the patient was reassessed. The second assessment showed further deterioration of SRQ, fatigue, BSRT and apathy. However, there were no changes in anxiety and depression.

**Graph 4.12: A Graph Shows Changes in Affective and Cognitive Symptoms of H. A**



### **Patient Number 6 (I.H.).**

I.H. is 21 years old Omani male, he was involved in RTA 20 days prior to our first assessment. He lost his consciousness at the time of the injury, and his GCS was seven. His TBI was classified as severe. His CT brain was normal. However, his MRI showed findings suggestive of diffuse axonal injury.

I.H had a normal developmental milestone, he finished third secondary class, and he was self-employed. His pre-morbid IQ was classified as Average. I.H had no significant family history of medical or psychiatric illness.

I.H was assessed after 20 days of TBI. He was complaining of multiple post-concussion symptoms such as poor memory and concentration, low mood and stuttering.

His psychological assessment revealed higher probability of having a mental illness, according to SRQ, moderate fatigue, according to FAS, moderate anxiety and depression according to HADS, and mild apathy according to AES.

I.H was assessed again after two weeks from the first assessment. The second assessment showed improvement of SRQ and the anxiety subscale of HADS. There were no changes on the scores of FAS, the depression subscale of HADS, and the AES.

The cognitive assessment of I.H showed improvement of BSRT, and there were no changes in both backward and forward digit span test. (Table 4.22 and figure 4.13).

**Table 6.6: A table shows the results of Affective and Cognitive Assessments of I.H**

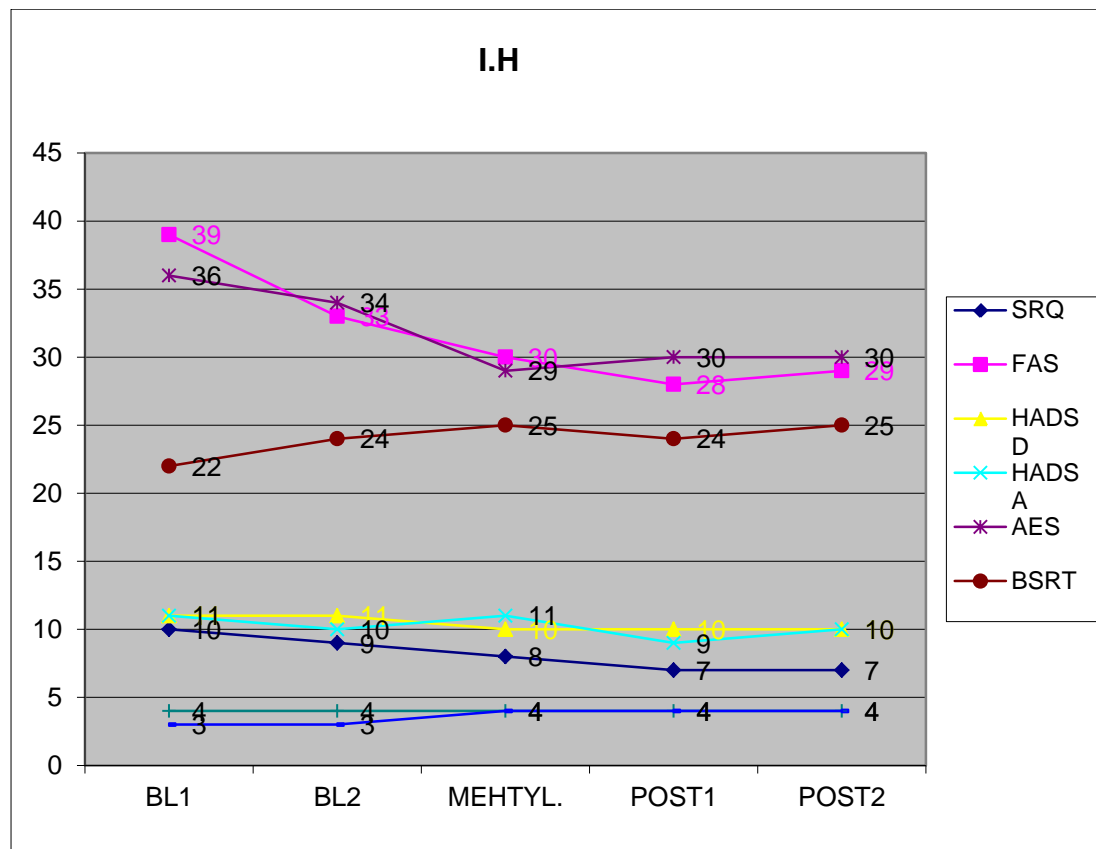
Assessment	BL1	BL2	METHYL	POST1	POST2
SRQ	High Range (10)	Middle Range (9)	Middle Range (8)	Middle Range (7)	Middle Range (7)
AES	Mild (36)	Mild (34)	Normal (29)	Normal (30)	Normal (30)
HADS (Depr.)	Moderate (11)	Moderate (11)	Mild (10)	Mild (10)	Mild (10)
HADS (ANX.)	Moderate (11)	Mild (10)	Moderate (11)	Mild (9)	Mild (10)
FAS	Moderate Fatigue (39)	Moderate Fatigue (33)	Mild Fatigue (30)	Mild (28)	Mild (29)
IQ		85	90		
BSRT	22	24	25	24	25
Digit (FOW)	4	4	4	4	4
Digit (BACK)	3	3	4	4	4
Wisconsin Card Sorting Test		0.40	0.40		

I.H was stated on Methylphenidate SR 20 mg once daily for two weeks. After two weeks he was assessed again, but there were no much improvement. As a result, Methylphenidate was increased to 20 mg two times daily for two weeks. Psychological assessment after 4 weeks of Methylphenidate showed no changes in SRQ, WCST, and digit span forward. However, there were improvement in AES, FAS; IQ ravens scores, BSRT, backward digit span, and improvement of Depression subscale of HADS from moderate to mild. However, his anxiety subscale of HADS got worse from mild to moderate. Methylphenidate was stopped.

After two weeks of stopping Methylphenidate, the patient was assessed again. He showed no deterioration in SRQ, FAS, Depression (HADS), AES, and Digit span. There was slightly deterioration on BSRT (from 25 to 24). However, his anxiety subscale of HADS got even better.

After 4 weeks of stopping Methylphenidate the patients was reassessed again. There was no deterioration on SRQ. His fatigue scale showed a slight increase from 28 to 29 although it was still classified as mild, his anxiety and depression subscale were still same mild categories. His cognitive function test showed no deterioration of the digit span test. However, his BSRT continues to improve.

**Graph 4.13 A Graph Shows Changes in Affective and Cognitive Symptoms of I.H.**





### **Patient Number 7 (M.J)**

M.J is 19 years old Omani male. He had a TBI when he was 6 years old after falling down from a camel. M.J lost consciousness at the time of the accident, his GCS was one and his injury was classified as a severe TBI.

M.J had normal developmental milestone and his pre-morbid IQ was estimated to be average. However, he could study only until second class. M.J had no significant family history of medical or psychiatric illness.

M.J was assessed for the first time by us after about 13 years of this accident. He had no post-concussion symptoms apart from poor concentration. Psychological assessment showed that M.J was mildly disabled according to DRS. He had a mild range probability of having a mental illness. FAS showed mild fatigue, and HADS showed moderate anxiety and depression. AES showed that M.J was suffering from mild Apathy.

M.J was reassessed again after about one year from the first assessment. His SRQ increase to high, his fatigue increased to moderate. However, there were no changes in Apathy, anxiety, and depression level.

Cognitive assessment showed deterioration of IQ ravens' and forward digit span. There was improvement in BSRT and backward digit span (table 4.23 and graph 4.14).

M.J also had a SPECT scan which showed low perfusion at the right temporal lobe.

**Table 6.7: A table shows the results of Affective and Cognitive Assessments of M.J.**

<b>Assessment</b>	<b>BL1</b>	<b>BL2</b>	<b>METHYL</b>	<b>POST1</b>	<b>POST2</b>
SRQ	Middle Range (9)	High Range (12)	Middle Range (6)	Middle Range (9)	High Range (10)
AES	Mild (34)	Mild (35)	Normal (25)	Normal (23)	Normal (25)
HADS (Depr.)	Moderate (14)	Moderate (14)	Normal (6)	Mild (9)	Mild (10)
HADS (ANX.)	Moderate (11)	Moderate (14)	Moderate (12)	Mild (10)	Mild (10)
FAS	Mild Fatigue (30)	Moderate Fatigue (33)	None Fatigue (15)	None (20)	Mild (30)
IQ	110	90	90		
BSRT	13	30	30	21	22
Digit (FOW)	5	4	5	5	5
Digit (BACK)	3	4	5	3	3
Wisconsin Card Sorting Test		0.00	0.23		

M.J was started on Methylphenidate 20 mg SR. After two weeks, he was assessed again. The patient felt much better. His psychological assessment showed improvement in SRQ. Fatigue and depression improved from moderate to none. Apathy also improved from mild to no Apathy. However, his anxiety level remains at moderate level.

Cognitive assessment showed no change in IQ ravens and BSRT. However, there were improvements in Digit span.

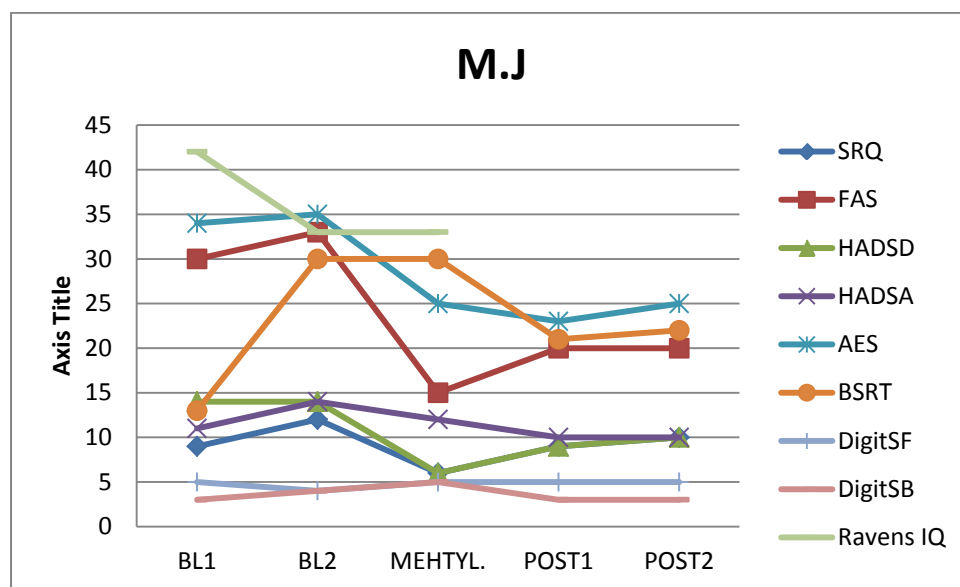
Because of the dramatic improvement, his medication was continued. After one week, he started to have on/off low mood again. He decided to stop the medication. After one week of stopping medication, he was reassessed again. His psychological assessment showed no change in SRQ, although his fatigue level remains no fatigue the actual scores increase from 15 to 20, depression increase to mild, however anxiety decrease to mild. Surprising his AES further improved from 25 to 23.

Cognitive function tests showed deterioration of BSRT and digit span backward. However, his forward scores remain same. The patient was still reluctant to take medication

After four weeks of stopping the medication, the patient came back again for follow up. He was complaining that his condition is getting worse feels more depressed. His psychological assessment showed an increased probability of having a mental illness, and increase fatigue. However, depression and anxiety remain same, according to HADS scores. Although apathy remains normal his actual scores increase from 23 to 25.

His cognitive assessment showed slight improvement in BSRT, and there were no changes on Digit span.

**Graph 4.13 A Graph Shows Changes in Affective and Cognitive Symptoms of M.J.**



NB: this patient was put back again on Methylphenidate. However, he did not show any improvement after one month of his treatment and hence Methylphenidate was stopped.

### **Patient Number eight N.H**

N.H is 29 years old Omani male. He was involved on RTA five months prior to assessment. The patient had no loss of consciousness, and his GCS was 15. His TBI was classified as mild TBI.

The patient was complaining of multiple post-concussion symptoms such as headache, dizziness, fatigue, and forgetfulness. However, the patient had no retrograde or anterograde amnesia.

The patient had normal developmental milestone. He finished 12<sup>th</sup> class and his pre-morbid IQ was estimated to be average. The patient was and still working as a technician. He had no significant medical or psychiatric illness in the family.

Psychological assessment of N.H revealed that the patient had no disability, according to DRS, his SRQ showed the lower probability of having a mental illness, had no fatigue, mild depression and anxiety, and moderate apathy.

The patient was reassessed again after eight months. Psychological assessment showed an increase in the probability of having a mental illness, increase fatigue, but improved depression and anxiety. His apathy remained at a moderate level.

Cognitive assessment showed no changes in BSRT and digit span scores. His SPECT showed normal findings (table 4.24 and graph 4.15).

**Table 6.8: A table shows the results of Affective and Cognitive Assessment of N.H.**

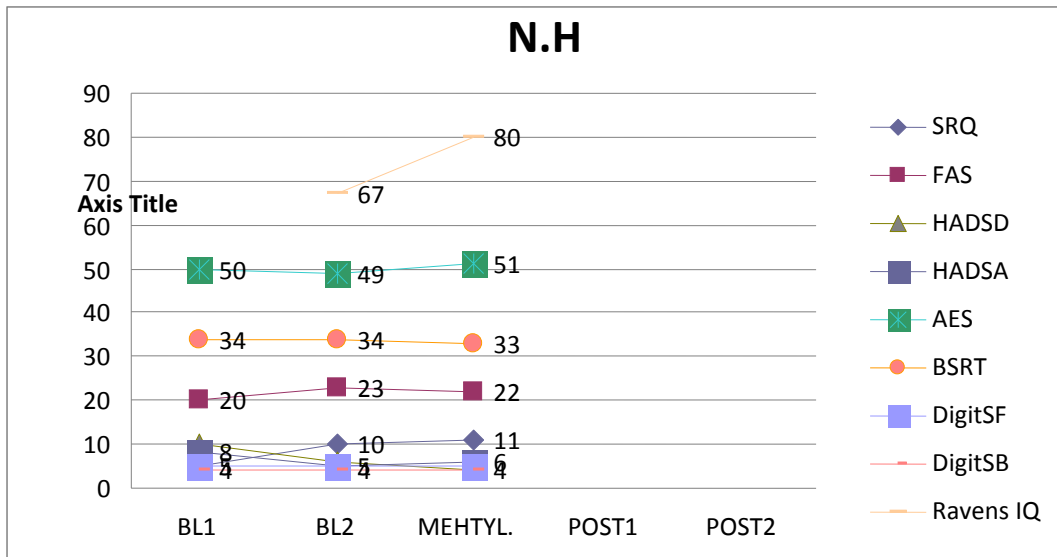
Assessment	BL1	BL2	METHYL	POST1	POST2
SRQ	Lower Range (5)	Middle Range (10)	High Range (11)	This patient took only four Tablets then could not tolerate due to the side effects	
AES	Moderate (50)	Moderate (49)	Severe (51)		
HADS (Depr.)	Mild (10)	Normal (6)	Normal (4)		
HADS (ANX.)	Mild (8)	Normal (5)	Normal (6)		
FAS	None Fatigue (20)	Mild Fatigue (23)	Mild Fatigue (22)		
IQ		67	80		
BSRT	34	34	33		
Digit (FOW)	5	5	5		
Digit (BACK)	4	4	4		
Wisconsin Card Sorting Test		0.32	0.36		

The patient was started on Methylphenidate SR 20 mg once daily. The patient felt better initially, less headache and less forgetfulness. Unfortunately, the patient stopped medication after 4 days because of loss of appetite and irritability.

The patient was reassessed again after 2 weeks his psychological assessment showed a higher SRQ, no change in fatigue, depression, and anxiety. However the patient had a worsen of AES.

His cognitive function tests showed improvement of Ravens IQ; worsen of BSRT but no changes in Digit span.

**Graph 4.14: A Graph Shows Changes in Affective and Cognitive Symptoms of N.H**



The patient was advised to restart Methylphenidate. This time there was no side effect, but also there was no rapid improvement the patient observed in the first time. The dose of Methylphenidate was increased to 40 mg once daily. After two weeks of 40 mg Methylphenidates, the patient did not show any improvement, and hence the drug was stopped.

### **Patient Number 9 (Q.H.)**

Q.H. is 22 years old Omani male. He was involved in a car accident 13 months prior to the assessment.

The patient had a loss of consciousness at the time of the accident, his GCS score was 10, and his TBI was classified as moderate. His CT brain showed right frontal, parietal haemorrhage a repeat CT brain after 10 days showed resolving of the haemorrhage. The patient had seizures post injury.

The patient had normal developmental milestones. He finished a technical school and was working as an electrical technician. His estimated pre-morbid IQ was average.

The patient was complaining of multiple post-concussion syndromes such as headache, dizziness, insomnia, and forgetfulness. However, he had no anterograde amnesia, but had retrograde amnesia of about two months. His psychological assessment showed mild disability, according to DRS, the mild probability of having a mental illness, mild fatigue, mild Apathy, normal depression, and anxiety.

The patient was reassessed again after 12 months from the first assessment. Psychological assessment revealed. Worsen of SRQ and depression. However, there were no changes in anxiety, digit span, and BSRT (table 4.25).

**Table 6.9: A table shows the results of Affective and Cognitive Assessment of QH.**

Assessment	BL1	BL2	METHYL	POST1	POST2
SRQ	Middle range (6)	High range (12)	The patient Stopped the medicine because of the side effect.		
AES	Mild (45)	Mild (42)			
HADS (Depr.)	Normal (6)	Moderate (11)			
HADS (ANX.)	Normal (3)	Normal (6)			
FAS	Mild fatigue (22)	Mild fatigue (24)			
IQ	80	92			
BSRT	28	30			
Digit (FOW)	4	4			
Digit (BACK)	3	3			
Wisconsin (WCST)		0.31			

The patient was started on Methylphenidate SR 20 mg once daily Unfortunately, he could take only one tablet then he started to feel giddy, tremor, and generalised body weakness after 1 hour of taking the tablet. The symptoms lasted for 5 hours.

The patient could not restart the medicine, and hence it was stopped.



### **Patient Number 10 (S.J)**

S.J. is 29 years old Omani male. He was involved in RTA 7 days prior to the assessment. The patient had a loss of consciousness, his GCS was 13, and his TBI was classified as mild.

S.J had normal developmental milestone, he finished ninth class, and his pre-morbid IQ was estimated to be Average. He was working as a soldier in the army.

He had anterograde amnesia of 3 days and retrograde amnesia of about 1 hour. The patient was complaining of multiple post-concussion symptoms such as headache, dizziness, blurred vision, poor memory, and poor concentration. His psychological assessment showed mild disability, high probability of having a mental illness, moderate fatigue, moderate depression and anxiety, and mild Apathy.

The patient was reassessed 10 months after the first assessment. The second assessment showed no change in SRQ, depression, anxiety, and depression. However, the patient fatigue got worse.

Cognitive function assessment of Mr S.J Showed, no change in the forward digit span, however backward digit span got better (table 4.26).

**Table 6.10: A table shows the results of Affective and Cognitive Assessments of S.J.**

Assessment	BL1	BL2	METHYL	POST1	POST2
SRQ	High Range (14)	High Range (16)	Did not come back		
AES	Mild (36)	Mild (34)			
HADS (Depr.)	Moderate (13)	Moderate (15)			
HADS (ANX.)	Moderate	Moderate			
FAS	Moderate Fatigue (36)	Severe Fatigue (46)			
IQ		100			
BSRT					
Digit (FOW)	4	4			
Digit (BACK)	3	4			
Wisconsin Card Sorting Test		0.34			

The patient was started on Methylphenidate SR 20 mg once daily. Unfortunately, the patient did not come back for follow up.

### **Patient Number 11 (S.H)**

This, 16 years old, Omani male had TBI four months prior to the assessment. He had a loss of consciousness at the time of injury, and this brain injury was categorised as severe TBI, based on GCS that was seven. A CT scan showed left frontal haemorrhage.

The patient had normal developmental milestone, his IQ was estimated to be Average, he was a student at secondary school, had no significant past medical or psychiatric history and had no family history of psychiatric illness.

At the time of assessment, he was complaining of multiple post-concussion symptoms such as headache, fatigue, insomnia, irritability, memory impairment, and dizziness.

The patient psychological assessment revealed a moderate disability, according to DRS. He has a high probability of having a mental illness, mild fatigue, normal anxiety and depression, and mild apathy.

The patient was reassessed again 11 months after the first assessment. The second assessment showed no change in SRQ, Fatigue, depression, anxiety, and apathy.

Cognitive assessment showed no change in the forward digit span, but the backward digit span got worse. Similarly, BSRT got slightly worse (table 4.27 and graph 4.16).

**Table 6.11: A table shows the results of Affective and Cognitive Assessments of S.H**

Assessment	BL1	BL2	METHYL	METHYL	METHYL
SRQ	High Range (20)	High Range (15)	Middle Range (8)	High (11)	High (12)
AES	Mild (44)	Mild (46)	Normal (30)	Normal (32)	Normal (30)
HADS (Depr.)	Normal (3)	Normal (2)	Normal (2)	Normal (2)	Normal (2)
HADS (ANX.)	Normal (3)	Normal (2)	Normal (2)	Normal (5)	Normal (4)
FAS	Mild Fatigue (22)	Mild Fatigue (25)	No Fatigue (20)	None (14)	None (15)
IQ		67	83		
BSRT	27	26	30	31	32
Digit (FOW)	4	4	5	5	4
Digit (BACK)	3	2	4	3	4
Wisconsin Card Sorting Test		0.58	0.67		

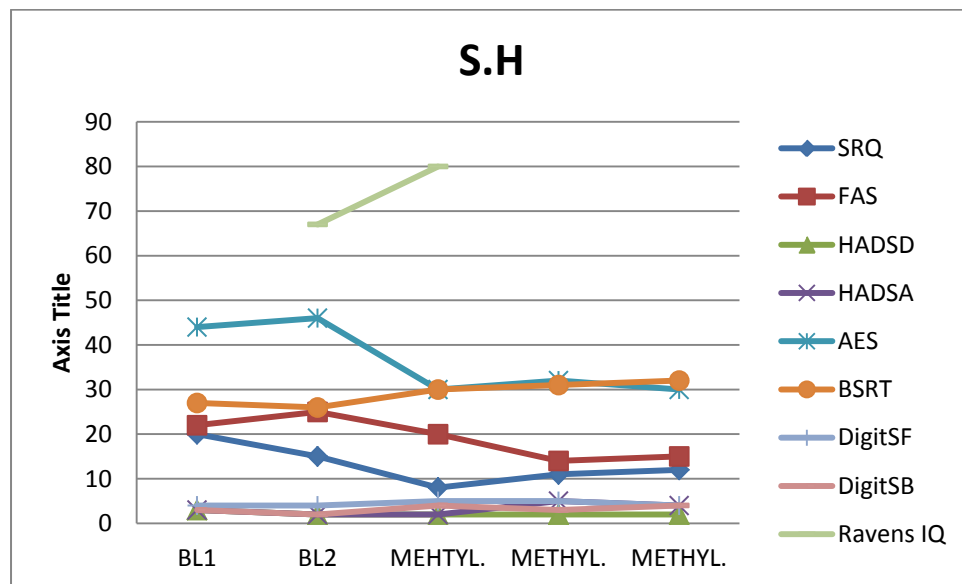
The patient was started on Methylphenidate SR 20 mg eleven months post TBI.

After two weeks of Methylphenidate, the patient felt much better with less fatigue and headache. Psychological assessment showed improvement in SRQ, fatigue, and Apathy. Cognitive assessment showed improvement on both backward and forward digit span, IQ raven's, BSRT, and WCST. Because of this dramatic improvement, the patient refused to stop the medicine.

The patient came again for follow-up after 4 weeks of starting Methylphenidate. The patients SRQ scores and Digit span backward are getting worse. However, Fatigue and BSRT are getting better. There were no changes in Depression, anxiety, Apathy, and digit span forward.

After 5 weeks of starting Methylphenidate, the psychological assessment showed slightly increased in SRQ, FAS, digit span forward. However, there was an improvement in Anxiety, Apathy, Digit span backward and BSRT. There were no changes in the depression subscale of HADS. The patient is still on Methylphenidate.

**Graph 4.15: A Graph Shows Changes in Affective and Cognitive Symptoms of S.H**



## ASSESSMENT MEASURES

### LEVEL OF DISABILITY

1. **Disability Rating Scale**
2. **Glasgow Coma Scale**
3. **Post-traumatic amnesia**

#### **1. The Disability Rating Scale (DRS).**

The Disability Rating Scale (DRS) was developed to assess the level of disability, in rehabilitation settings, of patients with moderate to severe brain injury. The assessment measures a wide range of functional ability and is able to track the level of disability of patient from a coma to community (Rosenbaum & Stewart, 2004).

The first three items of the DRS ("Eye Opening", "Communication Ability", and "Motor Response") are a slight modification of the GCS and reflect impairment ratings (Teasdale & Jennett, 1974). Cognitive ability for "Feeding", "Toileting", and "Grooming" reflect a level of disability. The "Level of Functioning" item is a modification of a measure used by Scranton et al. (Scranton, Fogel, & Erdman 2nd, 1970) and reflects handicap as does the last item, "Employability."

The maximum score a patient can obtain on the DRS is 29 (extreme vegetative state). A person without a disability would score zero. The DRS rating must be reliable, i.e., obtained while the individual is not under the influence of anaesthesia, other mind-altering drugs, recent seizure, or recovering from surgical anaesthesia.

The scale is intended to measure accurately general functional changes over the course of recovery. Rappaport et al. (Rappaport, Herrero-Backe, Rappaport, & Winterfield, 1989) obtained DRS scores on 63 TBI individuals at rehabilitation admission, discharge, and up to ten years post injury (median = nine years).

Results showed a proportional change in DRS scores based on the time elapsed between injury and admission to rehabilitation. A significantly greater improvement was seen in the early admission group. Others have also demonstrated the utility of the DRS to make comparisons across time (Novack, Bergquist, Bennett, & Gouvier, 1991).

The relative sensitivity of the DRS was addressed by Hall et al. (Hall, Cope, & Rappaport, 1985). In a comparison with the Glasgow Outcome Scale, 71% of TBI individuals showed improvement on DRS vs. 33% showed improvement on the GCS (Jennett, Snoek, Bond, & Brooks, 1981).

DRS is further categorized into the following categories:

<b>DRS SCORES.</b>	<b>DRS CATEGORY.</b>
0	No Disability
1	Mild Disability
2-3	Partial Disability
4-6	Moderate Disability
7-11	Moderately Severe Disability
12-16	Severe Disability
17-21	Extremely Severe Disability
22-24	Vegetative State
25-29	Extreme Vegetative State.

## **2. The Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974).**

The GCS is the most widely used scoring system used in quantifying the level of consciousness following a TBI (Chan, 2010). The scale based on an eye opening, verbal response, and the best motor response. The three values are considered both separately and as a sum. The lowest possible GCS (the sum) is three (deep coma or death) while the highest is 15 (a fully awake person) (Teasdale & Jennett, 1974). The GCS was initially developed to measure the depth of coma, but it has been commonly used to assess the severity of TBI (Anna Sundström, 2006). The assessment has been widely used because “it is simple, has a relatively high degree of inter-observer reliability, and because it correlates well with outcome following severe brain injury” (S. E. Starkstein & Leentjens, 2008).

Where available, the GCS was used for classifying the severity of the brain injury. The following classification was used (Bergman, Maltz, & Fletcher, 2010).

<b>GCS SCORE</b>	<b>SEVERITY OF TBI</b>
13 to 15	Mild
9 to 12	Moderate
< 8	Severe

## **3. Posttraumatic amnesia (PTA)**

PTA is a confusion state that occurs immediately after TBI where the injured patient is unable to remember events occurred after the incident. During this state, the patient will also be disoriented to time, place, and person and new events cannot be stored in the memory. Following a suggestion by Rees PM (Rees, 2003), PTA is usually classified as the following: No PTA, one day or less, more than one day and less than one week, one to two weeks, two to four weeks, more than four weeks.



## **NEUROBEHAVIORAL FUNCTIONING**

- 1. Post-concussion syndrome (Physical, Cognitive & Emotional symptoms)**
- 2. Neuropsychiatric inventory**
- 3. Apathy Evaluation Scale**
- 4. Fatigue Assessment Scale**
- 5. Competency Rating**

### **1. Post-concussion syndrome (Ryan & Warden, 2003)**

Post-concussion syndrome, also known as post concussive syndrome or PCS, is a set of symptoms that a person may experience for weeks, months, or occasionally years after a TBI. From the present data, three interrelated symptoms were classified (I) physical, such as headache, (ii) cognitive, such as difficulty concentrating, (iii) Emotional and behavioural, such as irritability. These were elicited over a period in all patients who could make a meaningful response.

### **2. Neuropsychiatric inventory (NPI) (Cummings et al., 1994)**

The Neuropsychiatric Inventory (NPI) was employed to assess 12 behavioural disturbances occurring after neurological events: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, Apathy/Indifference, disinhibition, irritability / lability, aberrant motor activity, Night-time behaviours, and Appetite/Eating. The NPI is based on a structured interview with a caregiver who is familiar with the patient. For each domain, a screening question is asked to determine if the behavioural change is present or absent. If the answer is positive, then the domain is explored in greater depth with the sub-questions. For the present purpose, the severity of these non-cognitive symptoms were elicited and scored as the following: 0= absent, 1=Mild (noticeable, but not a significant change), 2 = Moderate (significant, but not a dramatic change), 3 = Severe (very marked, prominent, or a dramatic change).

### **3. The Apathy Evaluation Scale (AES) (Marin et al., 1991)**

Apathy Evaluation Scale (AES) has been designed to indicate that a particular patient probably is apathetic. It consists of 18 items covering interest, initiation of activity, motivation, insight, and emotionality. Each item is rated on a scale of 1 to 4. A composite score for a patient therefore ranges between 18 and 72. Higher scores indicate heightened apathetic state.

The Apathy Evaluation Scale can be administered in three different forms; self-report informant report and clinical interview. For the present purpose, apathy was quantified using the Self-Report Version of the AES (Marin et al., 1991).

To make the AES dialectically adaptive to an Omani sample, experienced staff members produced another Arabic-language version of the scale, using the method of back-translation (S. Al-Adawi et al., 2001).

Following preliminary trials, it was felt necessary for the interviewer to read all items to patients in order to accommodate various sensory and motor impairments as well as to allow the inclusion of those subjects who were not literate. Therefore, interviewers were trained to read out the items of the AES in the local dialect of spoken Arabic and to rate the responses accordingly. Using this method we noted an adequate inter-rater agreement on the various items of the scale ( $r=0.86$ ,  $p$  value  $<0.001$ )” (S Al-Adawi et al., 2004).

Studies have shown that AES is able to differentiate depression (discriminant validity;  $p <0.01$ ) and anxiety (discriminant validity  $p = 0.03$ ) from apathy (Marin et al., 1991).

For this study, a cutoff score of 34 or greater was used to define the presence of apathy (S Al-Adawi, Powell, & Greenwood, 1998; Glenn et al., 2002; Isella et al., 2002) and the AES was further categorized the scale into mild (34-47), moderate (48-61), severe (62-72).

#### **4. The Fatigue Assessment Scale (FAS) (Michielsen et al., 2003)**

The Fatigue Assessment Scale (FAS) consists of 10 items to elicit severity of fatigue. The response scale is a 5-point scale with scores ranging from 10 to 50 with higher scores indicating heightened fatigue state. The present study used a score of 21 or greater as an indication of clinical fatigue.

To make the FAS dialectically adaptive to an Omani sample, experienced staff members produced an Arabic-language version of the scale using the method of back-translation (S. Al-Adawi et al., 2001). For the present study, we have further classified fatigue into 21-31 mild, 32-42 moderate, 43-50 severe

#### **5. The Patient Competency Rating Scale (PCRS) (Hart, 2000)**

The primary purpose of the PCRS is to evaluate self-awareness “the ability to appraise one's current strengths and weaknesses following traumatic brain injury” (Prigatano, 1986). PCRS is a 30-item self-report instrument that asks the subject to use a 5-point Likert scale to rate their degree of difficulty on a variety of tasks and functions. Total scores range from 30 to 150, with higher scores indicating greater competency. The subject's responses are compared to those of a significant-other (e.g. a relative or therapist) who rates the subject on the identical items. Impaired self-awareness may be inferred from discrepancies between the two ratings, such that the subject overestimates their abilities compared to the other informant.

Awareness of deficit may also be examined separately for the various domains sampled by PCRS items. These include activities of daily living, behavioural and emotional function, cognitive abilities, and physical function.

## **THE COGNITIVE FUNCTION TESTS**

### **1. GENERAL IQ.**

**1.1. Pre-morbid IQ.**

**1.2. Present IQ. Raven's Standard Progressive Matrices (Raven, 2000).**

### **2. TESTS OF FRONTAL-SUBCORTICAL FUNCTIONS**

**2.1. Test Of Deductive Reasoning And Mental Flexibility: Modified Wisconsin Card-Sorting Test (WCST) (Nelson, 1976).**

**2.2. Verbal Fluency Controlled Oral Word Association Test (Benton, 1968).**

**2.3. Tower Of London (Shallice, 1982).**

### **3. Tests of attention and memory functions**

**3.1. Digit Span Wechsler Adult Intelligence Scale sub-test (Wechsler, 1981).**

**3.2. Buschke Selective Reminding Test (Buschke & Fuld, 1974).**

## **1. GENERAL IQ**

### **1.1. Pre-morbid IQ**

We decided to estimate pre-morbid functioning by asking the school performance. This is because in Oman, there is no study on established pre-morbid indices of intellectual capacity.

Oman has a central education system and therefore there is a uniform school curriculum. School entry starts at the age of 6 years. The education classes in Oman are grouped into primary (1-6 classes), preparatory (7-9 classes) and secondary (9-12 classes) and then the college education.

In the present context, for those who were in classes that corresponded to their expected age, the academic performance was used to classify them as below, average, or above average. Similarly, those who were older than expected age at that class, or were attending handicapped school; their pre-morbid intellectual functioning was classified as 'below the average. This information was further verified with information sought from the accompanying family members.

### **1.2. Present IQ. Raven's Standard Progressive Matrices (Raven, 2000).**

This was used to assess current reasoning ability. The test requires neither language nor academic skills (Raven, 2000). It consists of 60 items grouped into five sets. Each item contains a pattern problem with one part removed and between six and eight pictured inserts of which one contains the correct pattern. The subject points to the pattern he/she selects as correct (Lezak, 2004). This test is normally used for children aged 5-11 years or adults 65 years and older; it was employed in the present context because administering it is easy and quick, and because its level of complexity is appropriate to the cognitive level at which most of these patients are functioning.

## **2. TESTS OF FRONTAL-SUBCORTICAL FUNCTIONS**

Several tests sensitive to frontal and subcortical cognitive function were included as follows:

### **2.1. The Modified Wisconsin Card-Sorting Test (WCST) (Nelson, 1976).**

This test was used here to assess deductive reasoning and mental flexibility. The test assesses the ability to discover the principles according to which a deck of cards must be sorted (Grant & Berg, 1948; Milner, 1963).

The cards have geometric figures that vary simultaneously in shape (triangle, star, cross or circle), colour (green, red, blue, or yellow) and number (1, 2, 3 or 4 figures). Four reference cards are permanently placed in front of the subject. The subject has another deck of cards called 'reference' or 'response' cards. She or he is asked to match each response card successively with one of the four reference cards.

The experimenter selects one of the dimensions (e.g. Colour) as the 'sorting rule'. The first rule reflects the first card placement made by the subject. After each response, she or he is told only whether it was correct or not. If the response was incorrect, she or he is not permitted to move it, but is given the next card to try to place appropriately. Normal subjects use a hypothesis-testing or deductive reasoning approach to identify which sorting rules is in operation. When she or he has correctly placed 6 consecutive cards, she or he is told simply that the rule has changed. The second rule is selected according to the subjects' next card placement that uses a different rule.

After this has been correctly employed, six times in succession, the rule changes again. The third rule is the remaining dimension (shape, colour, or number). The three rules are then cycled through again in the same order. This procedure is continued until six categories are achieved or the pack of 48 cards is used up.

The scoring system of Nelson was adopted (Nelson, 1976). Accordingly, two indices were recorded: the number of categories achieved and number of perseverative errors. A perseverative error is defined as an incorrect card placement made based on the same dimension as used in the preceding placement. Although not all studies agree (Anderson et al., 1991; Mountain & Snow, 1993), the majority (e.g. Berman et al., 1996) have found that patients with frontal lobe damage are more impaired on this task than patients with lesions in non-frontal areas (Berman et al., 1995).

Milner suggested that patients with excisions of the dorsolateral prefrontal cortex (DLPFC) had worse performance on the WCST than those with orbitomedial or other lesions (Milner, 1963). Recently, it has been shown that performance on the WCST is associated with an increase in metabolic activity in (DLPFC) (Ohrmann et al., 2008).

**a. Verbal Fluency (Controlled Oral Word Association Test) (Benton, 1968).**

This examines initiation and speed of verbal responses. Subjects are asked to produce as many different words as possible that begin with each of three specific letters, with one minute per letter. Subjects are told explicitly not to repeat the same word twice, and not to say the same word with a different ending (for example, fish, fishing, and fisherman).

Following instruction, examples, and a demonstration that the subject understands the task requirements, she or he is given each letter in turn. The total score for Verbal Fluency thus is the total number of different acceptable words produced across the three 60-second periods. In this study, the letters used were F, A, and S.

It has been well substantiated that frontal lobe patients are often significantly impaired on this test (Milner, 1963). Using PET, Friston et al. (1991) has shown that verbal fluency is associated with increased blood flow in the Dorsolateral Prefrontal Cortex (DLPFC) (Friston, Frith, Liddle, & Frackowiak, 1991).

**b. The Tower Of London (Shallice, 1982).**

The Tower of London is widely regarded as a standard test for assessing prefrontal function (Owen, Doyon, Petrides, & Evans, 1996). Subjects are asked to formulate a plan to move coloured beads that are stacked on one pole to achieve a predetermined realignment on three adjacent poles, in the minimum possible number of moves.

The task has a range of difficulties, requiring only two moves to achieve the predetermined goal position at the simplest level, whilst more difficult levels of the task require as many as five moves. The starting position of the coloured beads is varied so that in any particular trial the solution can only be reached after a minimum of two, three, four, or five moves.

Subjects are instructed to examine the position of the coloured beads at the beginning of each problem and attempt to solve it in the minimum possible number of moves. They are encouraged not to make the first move until they are confident that they can execute the entire sequence needed to solve the problem.

Three indices were recorded: number of correctly solved problems (Number Solved), planning time/latency to first move (Planning Time) and execution time/time to complete moves once a response has been initiated (Execution Time) were coded such that a high score reflects speedy responses. Planning Times and Execution Time were coded as follows:

1 = 30-60 seconds

2 = 15-30 seconds

3 = < 15 seconds



### **3. Tests of Attention and Memory Functions**

Attention and memory abilities are likely to be related to motivation. These abilities are prerequisites of goal planning, and they require a certain amount of effort. These two assessments were chosen as they have been shown to be associated with the motivation.

#### **3.1 Digit Span (Wechsler Adult Intelligence Scale Subtest) (Wechsler, 1981).**

This measures verbal / auditory attention and short-term memory. The scale has two components: Digits Forward and Digits Backward.

In Digits Forward, the examiner reads out a list of digits at the rate of one digit per second and the subject is required to repeat back the sequence in the same order.

The first sequence comprises three digits, and if the subject succeeds with this, sequences of increasing length are presented. Two sequences of each length are given, and the test is stopped when the subject fails both sequences of a particular length.

The same procedure was followed for Digits Backward, with the difference that, in this case, subjects were requested to reproduce the sequences of digits in reverse order.

In the present context, in the longest number of digits the patients succeeded in repeating. For example, if the subject corrected repeated 1-8-5-2-4, his score will be labelled as 5.

Brain-injured patients have been reported to show impaired Digits Backward performance (Black, 1986), but this observation has not always been supported (Warschusky, Kewman, & Selim, 1996).

It has been argued that a poor score on Digit Span may reflect deficits of attention, motivation, or working memory (Lezak, 2004). Cantor Graae et al. (1993) have indicated an increased regional cerebral blood flow (RCBF) activation of the Dorsolateral Prefrontal Cortex (DLPFC) during the word fluency test (Cantor-Graae, Warkentin, Franzen, & Risberg, 1993).

### **3.2 The Buschke Selective Reminding Test (BSRT) (Buschke & Fuld, 1974).**

This test examines the rate of learning new information. Participants are read a list of 12 common words and are immediately asked to recall as many of these words as possible.

Participants are given a minute for recall, which is immediately followed by the next trial. Each subsequent learning trial involves the selective presentation of only those items that were not recalled on the immediately preceding trial.

After the selective presentation (or "reminding") of the missed words, the subject is asked to recall as many words as possible from the whole list. There are 12 trials in all. There are multiple forms of the word list.

The BSRT is included as a measure of immediate recall and learning and allows for a fine-grained analysis of encoding, storage, and retrieval mechanisms. This technique has been argued to provide a means of assessing encoding, retention, and retrieval (Lezak, 2004).

It is an effortful task, in that learning and recall can be enhanced by application of encoding and/or retrieval strategies, and/or rehearsal.

For the present purposes, the score were a summation of first three trials (out of 36 possible maximum scores).

## **PSYCHIATRIC STATUS**

- 1. Self-Reporting Questionnaire**
- 2. Hospital Anxiety and Depression Scale**

Psychiatric functioning was screened using semi-structured interviews, CIDI based on the International Classification of Disease (ICD-10) (WHO, 1993). In addition, the Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) were used to screen for the presence of affective dysfunction. These particular assessment measures have been chosen because their psychometric properties have been established in the Arabic speaking population (Malasi, Mirza, & El-Islam, 1991).

- 3. The Self-Reporting Questionnaire (SRQ) (Beusenberg & Orley, 1994).**

To find out the psychological morbidity, Self-Reporting Questionnaire (SRQ) (Beusenberg & Orley, 1994) was used. This test consists of 24 short questions related to main symptoms of mental disorders.

Most of these questions had been selected from existing psychiatric questionnaires such as the Symptom Sign Inventory (Foulds & Hope, 1968), the General Health Questionnaire (Goldberg, Cooper, Eastwood, Kedward, & Shepherd, 1970) and the Present State Examination (Wing, Cooper, & Sartorius, 1974). The patient has to respond either 'yes' or 'no' to each question.

Designed by the World Health Organization, SRQ has been validated in various developing countries to determine the prevalence of 'conspicuous psychiatric morbidity' (CPM), without specific diagnoses (Al-Subaie et al., 1998; Beusenberg & Orley, 1994; Kortmann, 1988) (Beusenberg & Orley, 1994). For the present analysis, the scores were categorized as follows: 'high' range = 10 – 20, 'middle' range = 6 – 9, 'lower' range = 0 - 5.

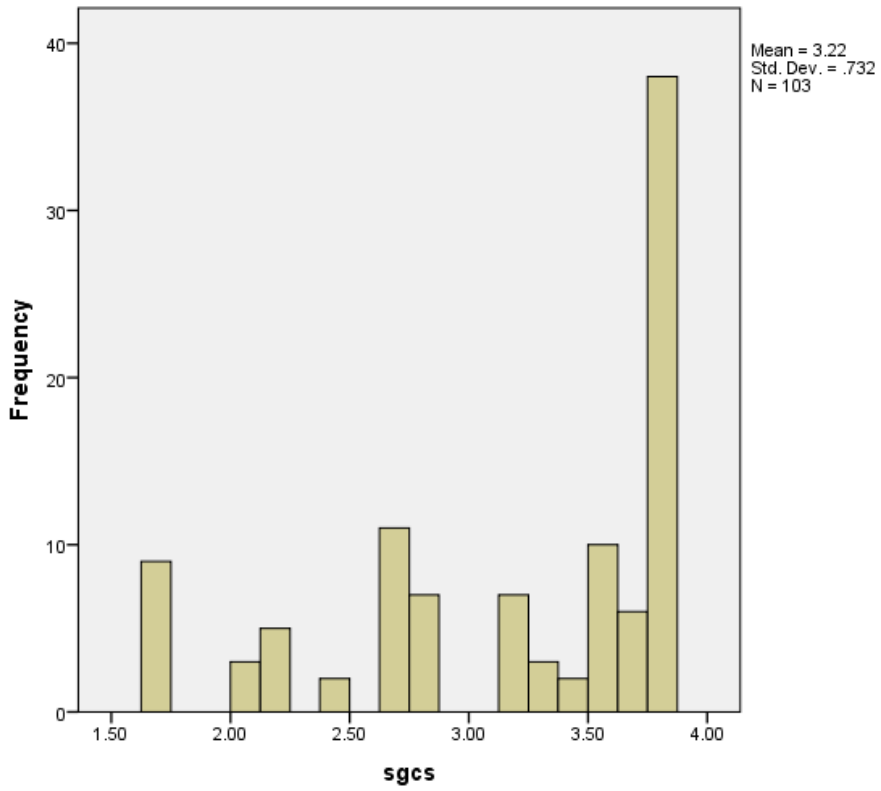
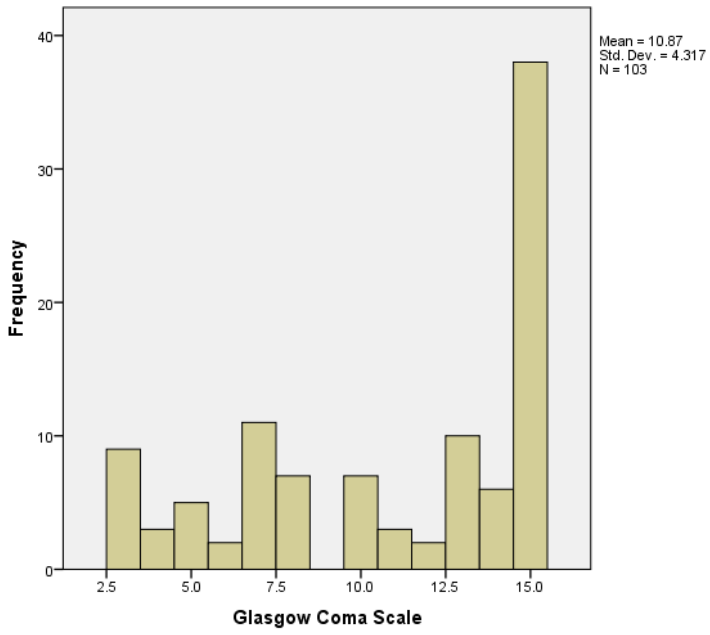
#### **4. Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983).**

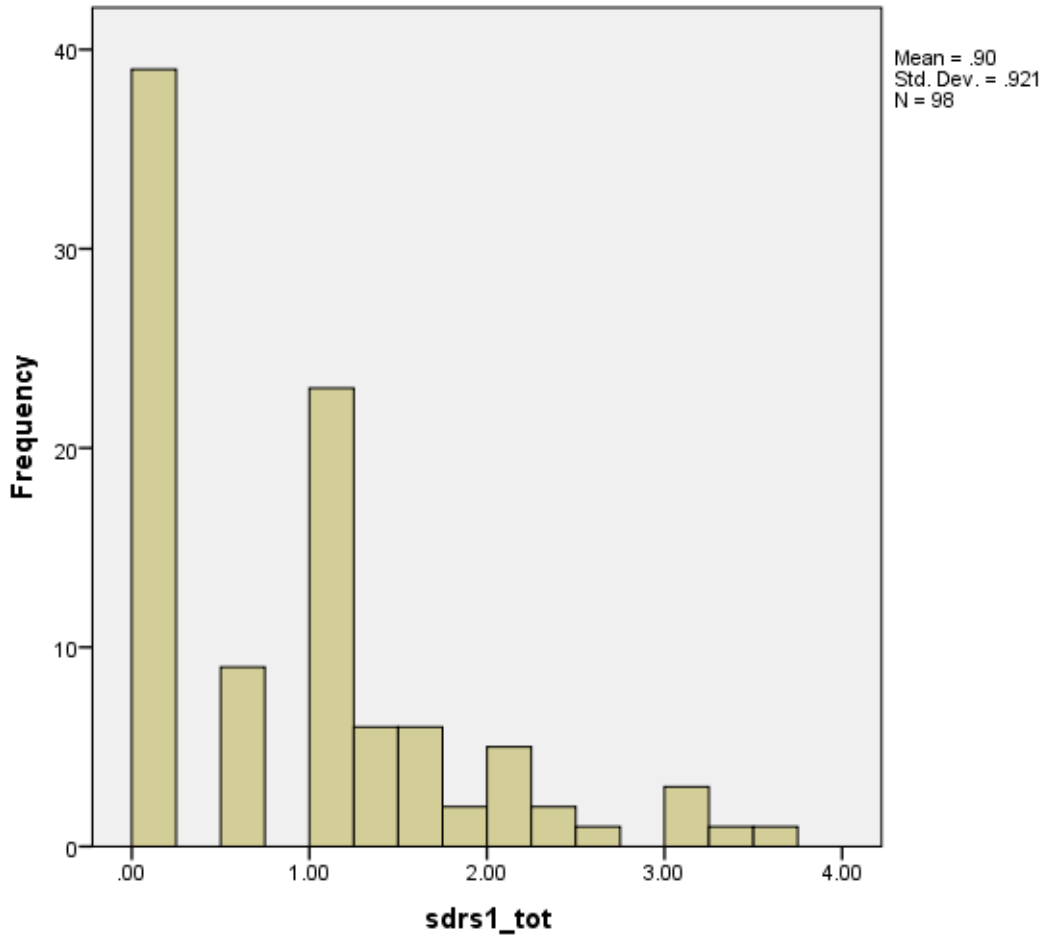
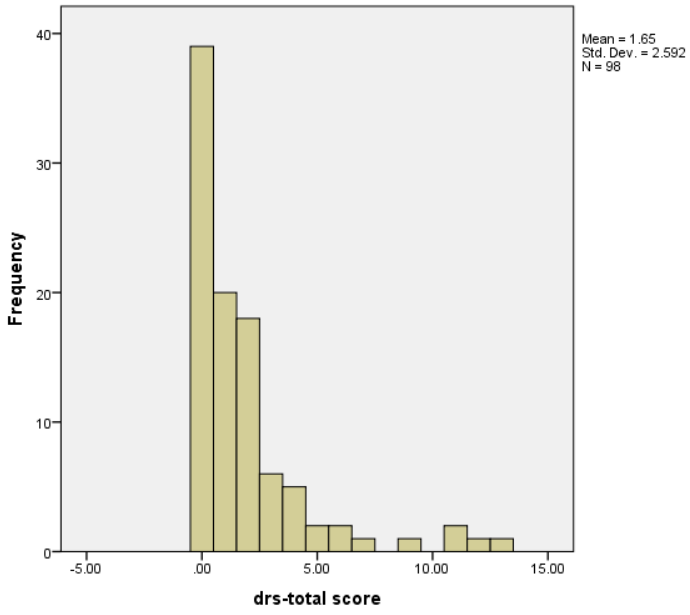
The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) is a 14-item questionnaire with two 7-item sub-scales, one for depression and one for anxiety. Symptoms are listed, and subjects rate their frequency or severity during the previous week on a 4-point scale (0-3), making a maximum possible score of 21 on each sub-scale.

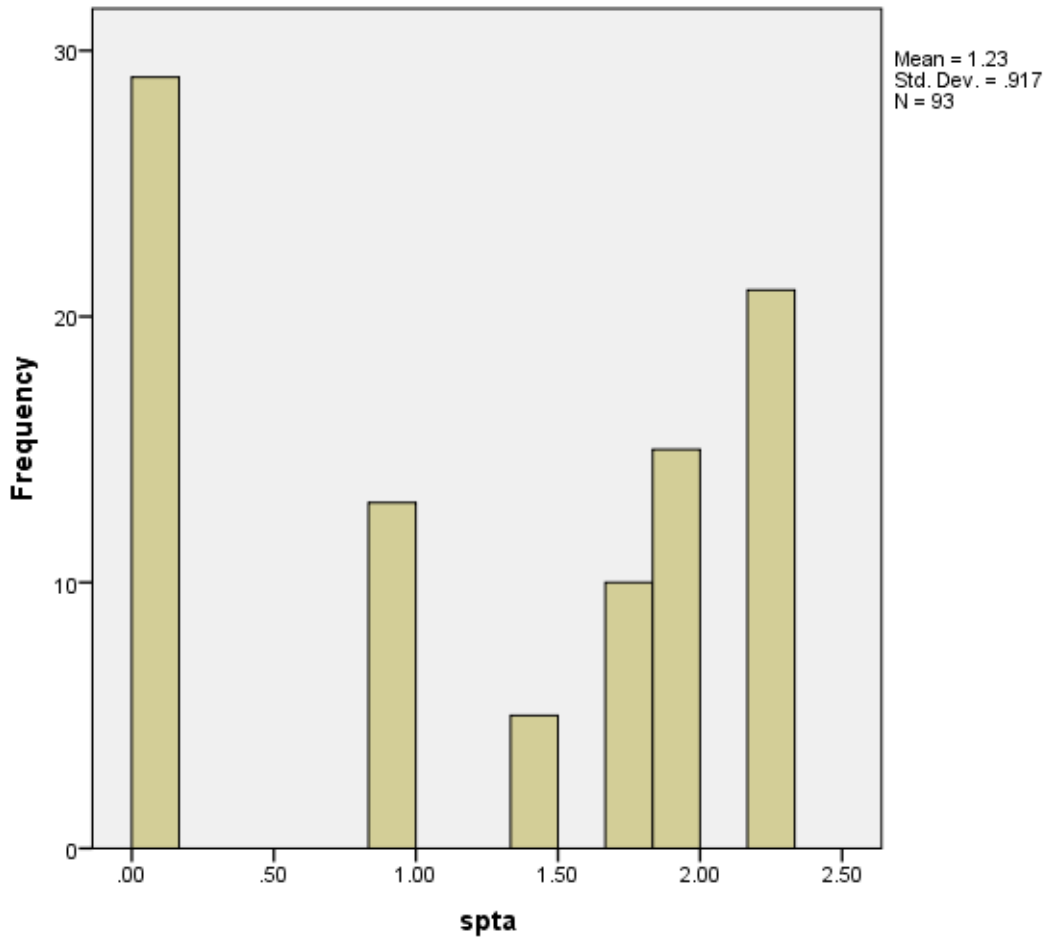
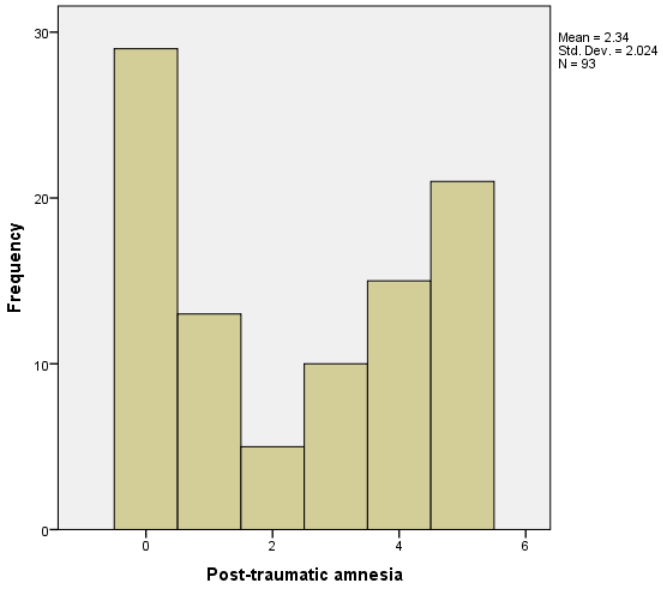
The original validation study for the HADS suggested that on either sub-scale, non-cases scored seven or less, doubtful cases 8-10, and definite cases 11 or more. Separate indices of Anxiety and Depression were recorded.

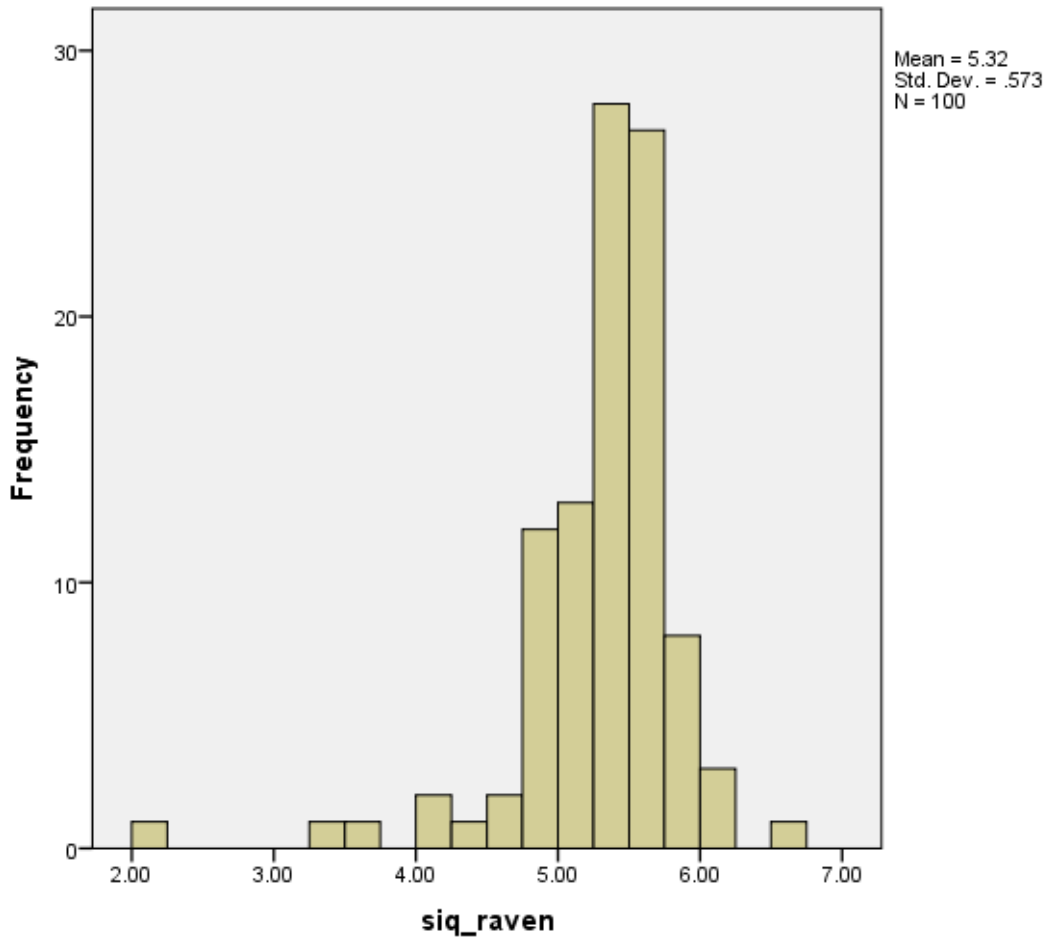
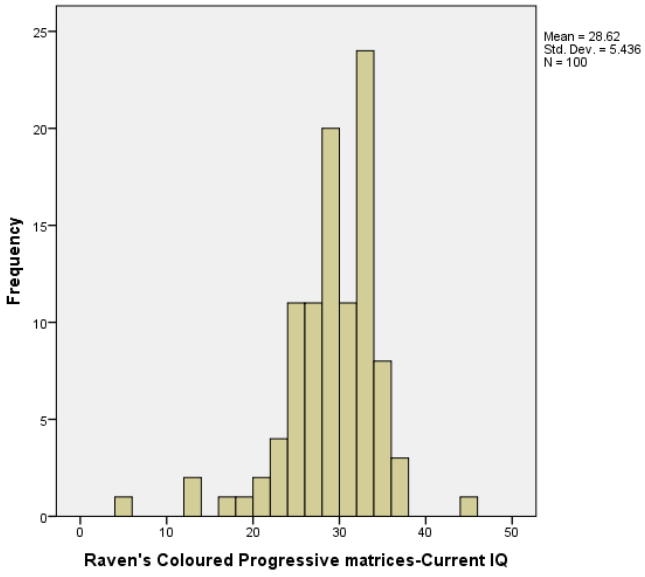
The two subscales, anxiety and depression, have been found to be independent measures. In its current form the HADS is now divided into four ranges: normal (0-7), mild (8-10), moderate (11-15) and severe (16-21).

**GRAPHS SHOW DISTRIBUTION OF THE VARIABLES BEFORE AND AFTER TRANSFORMATION.**

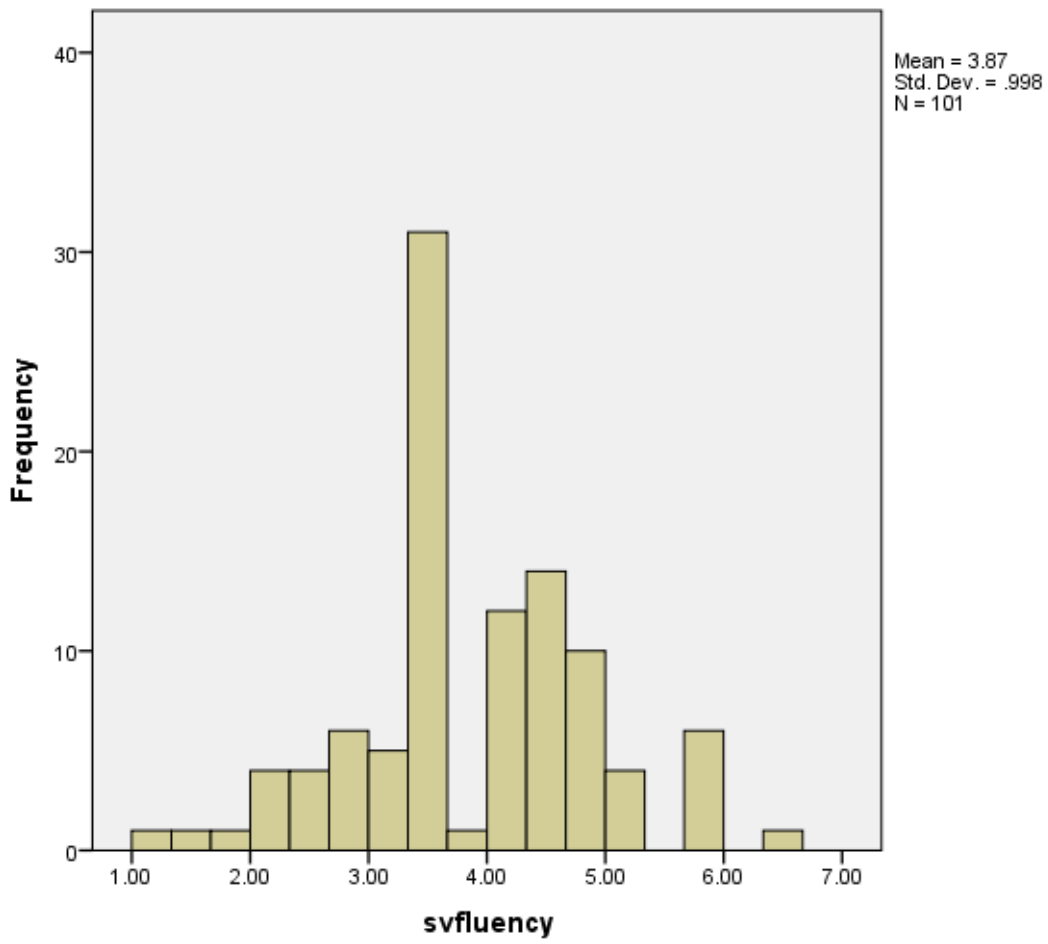
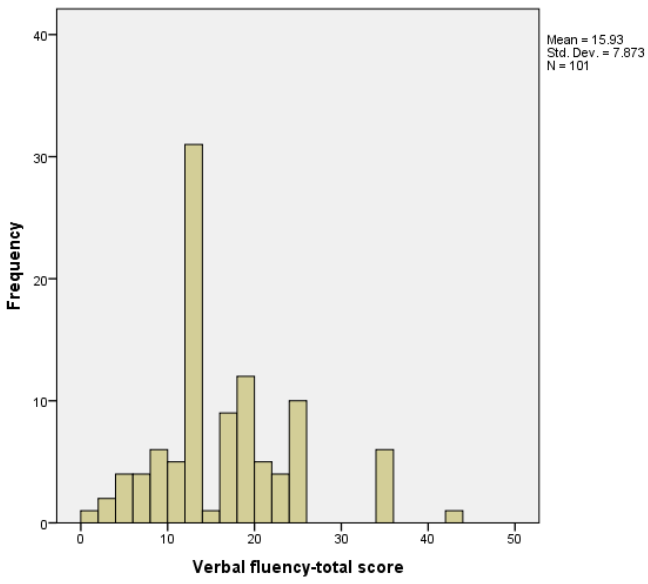


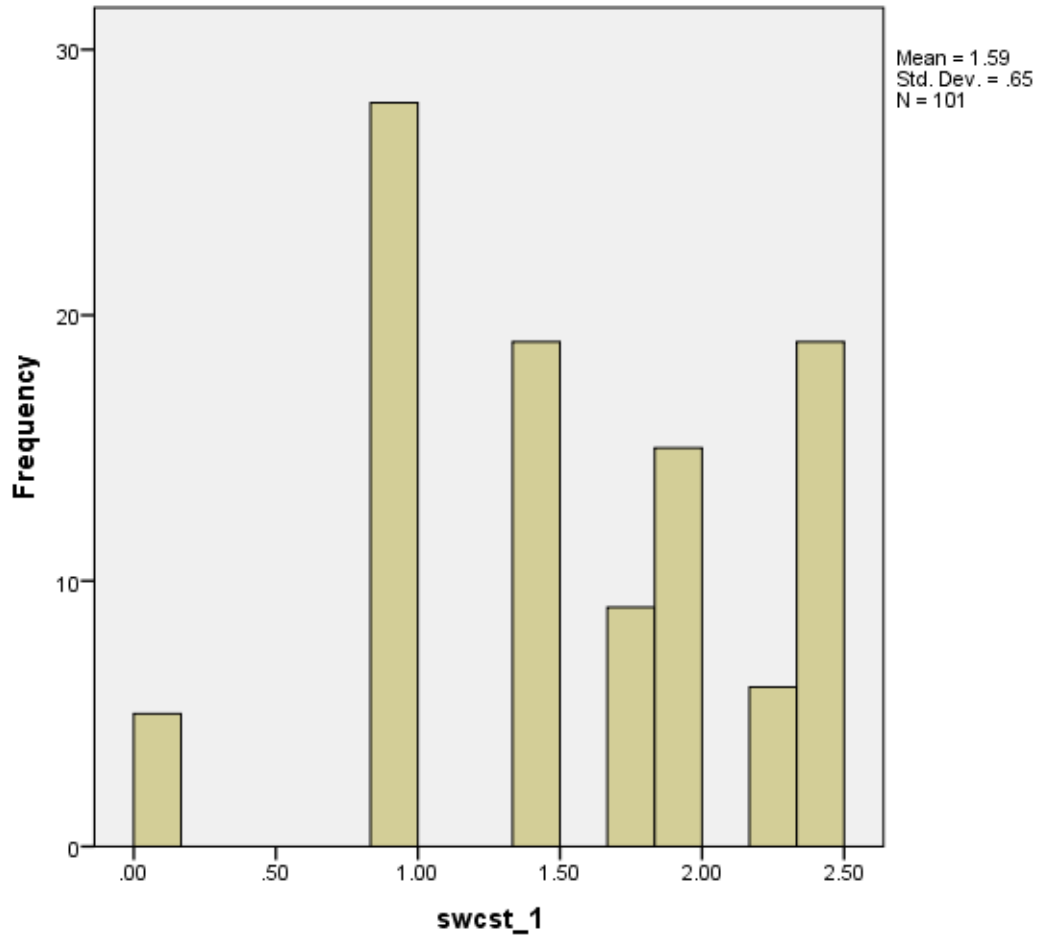
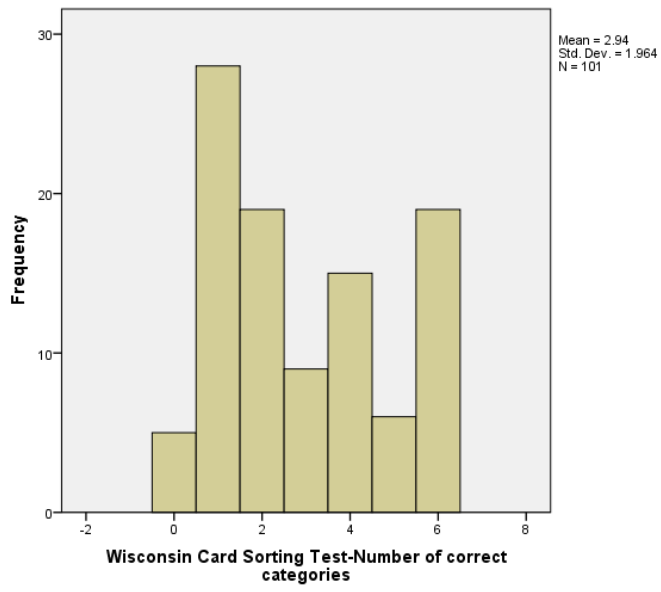


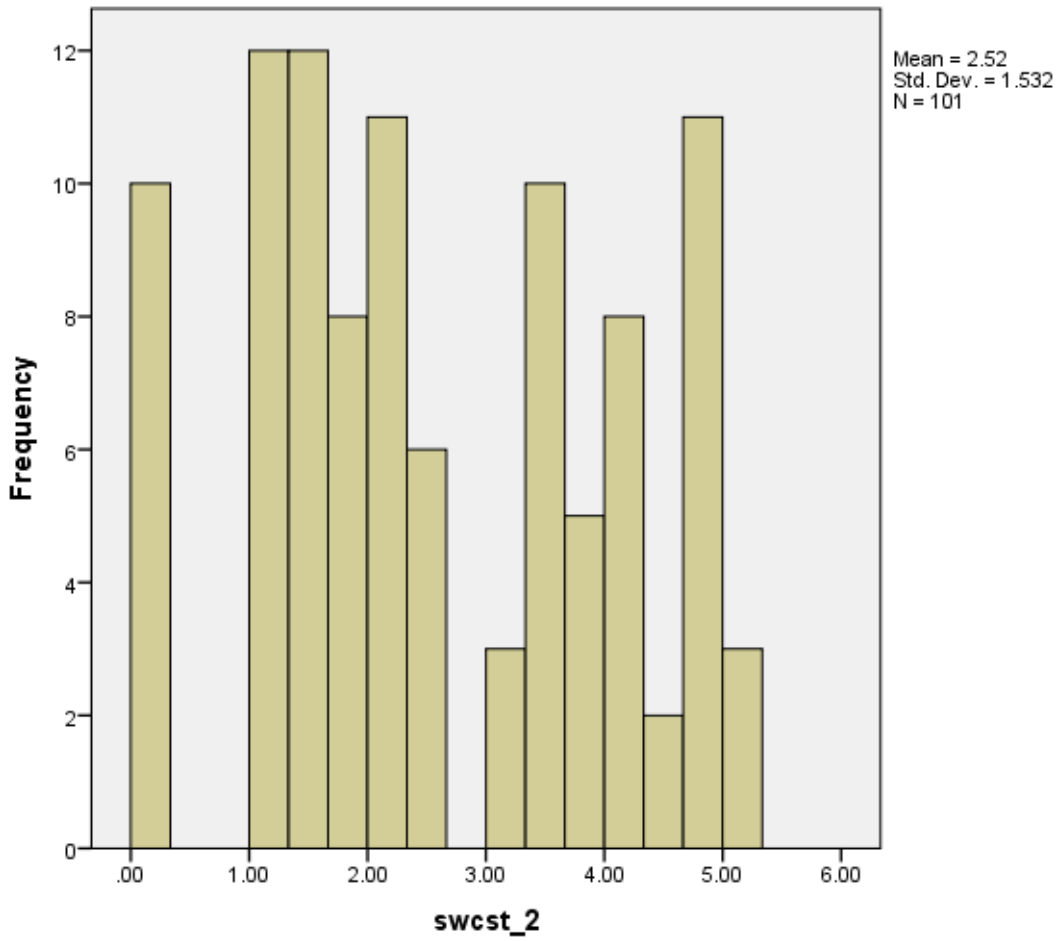
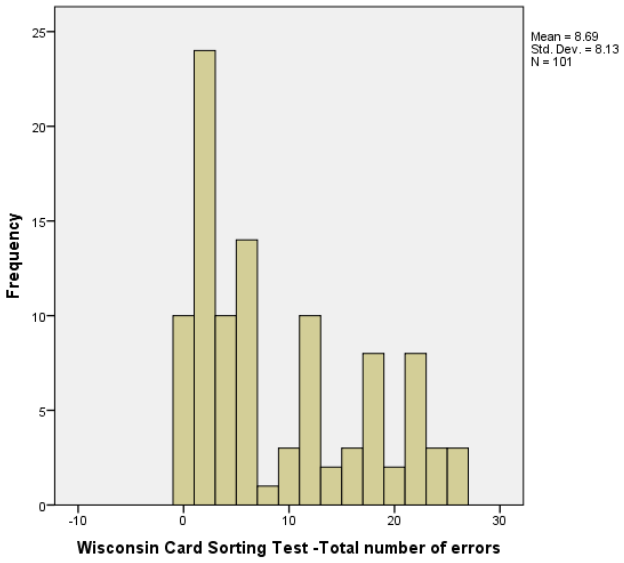


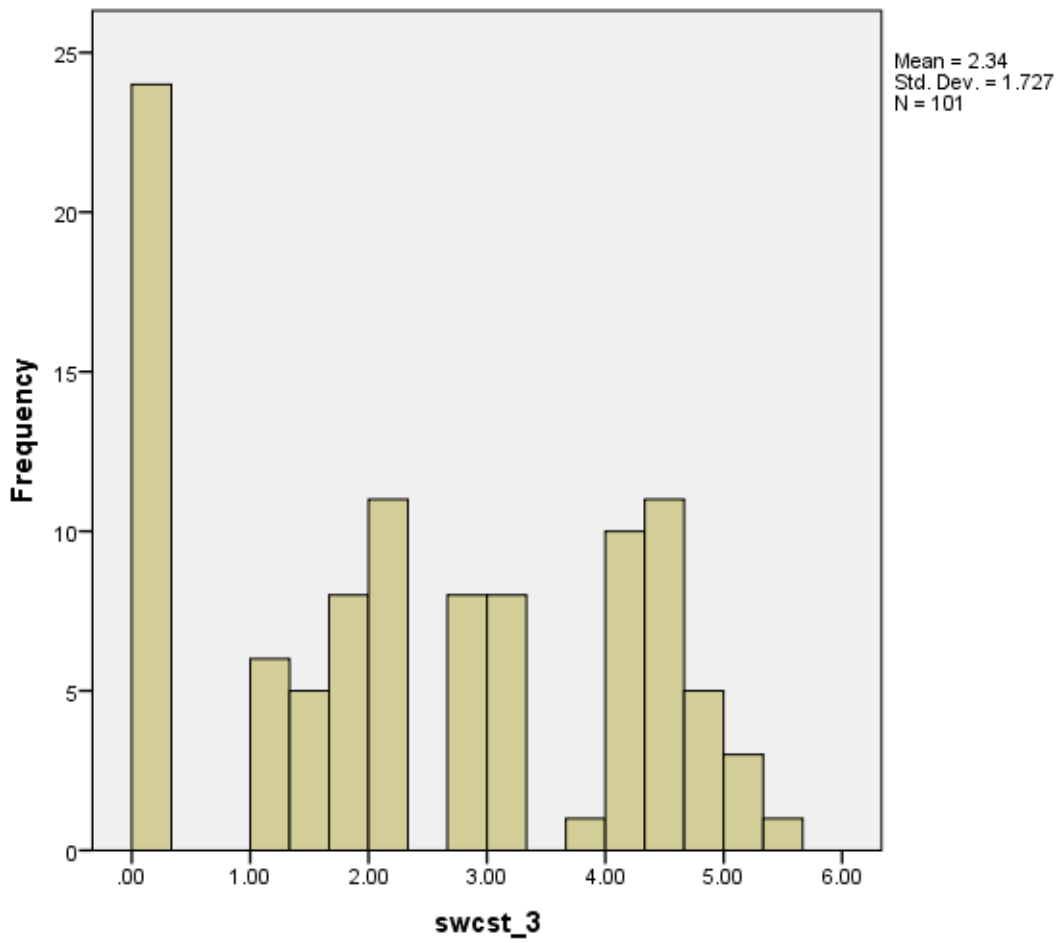
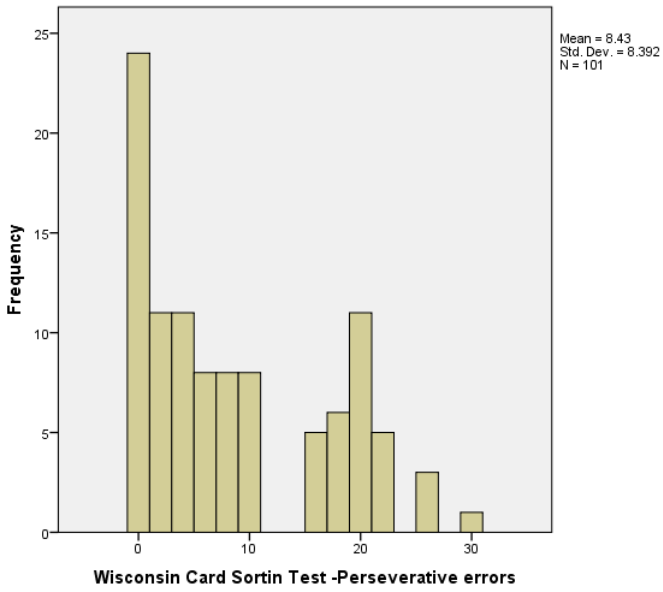


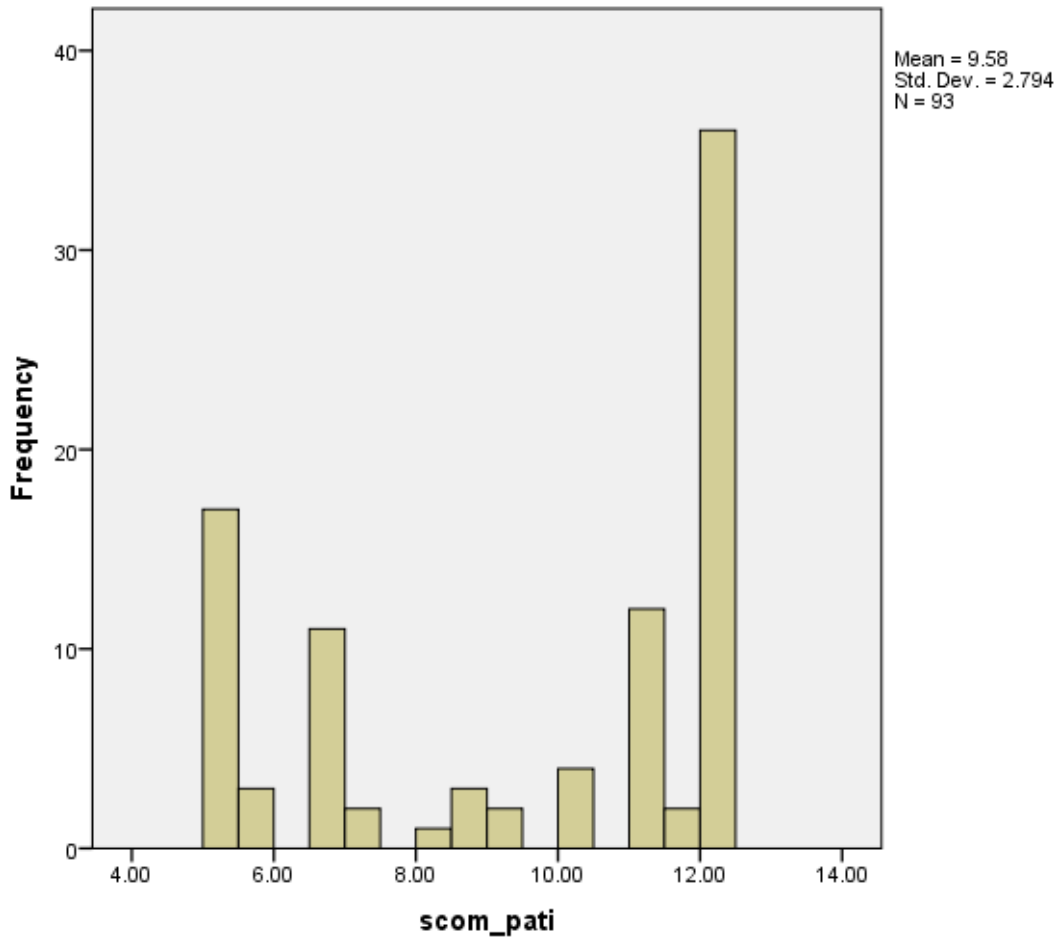
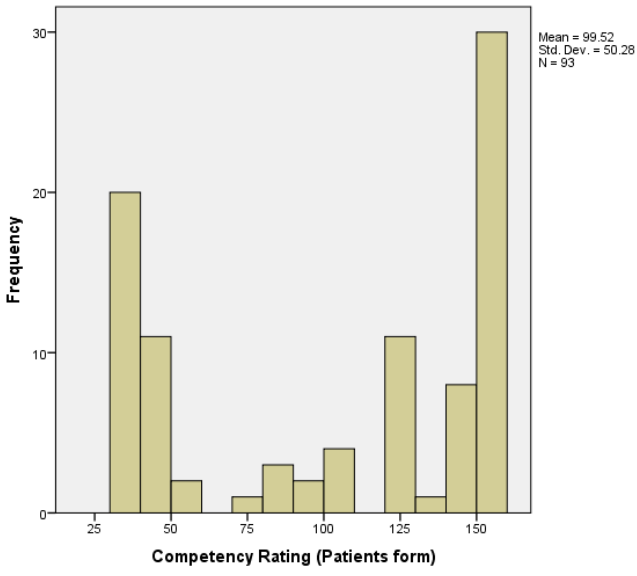


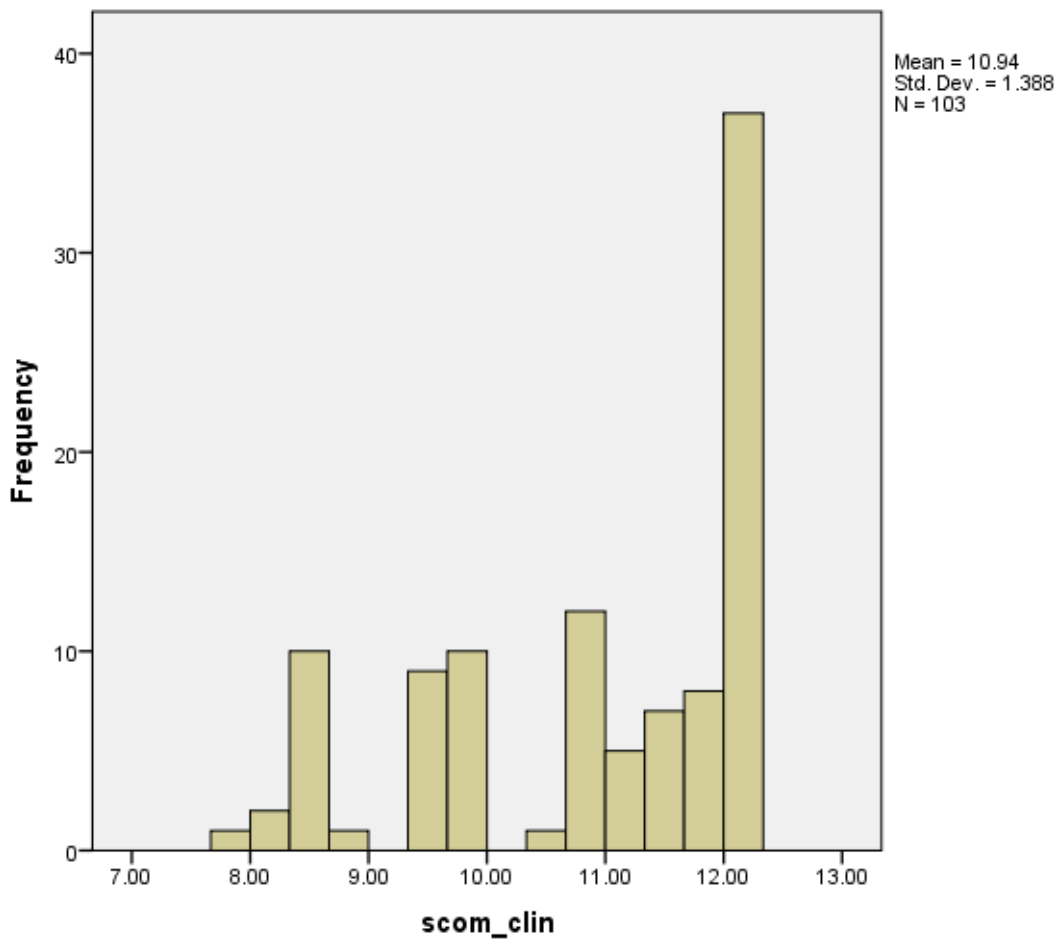
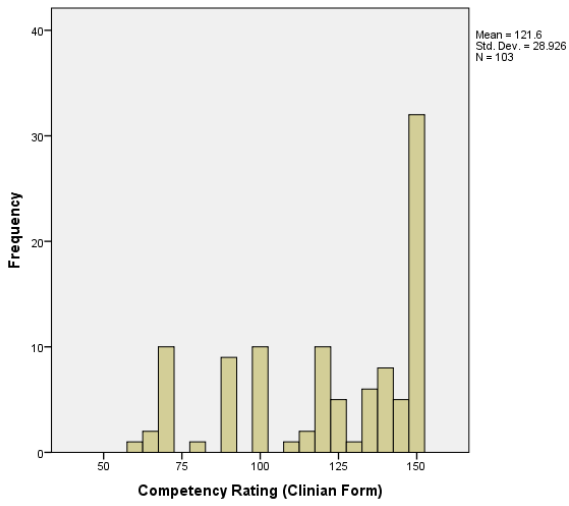


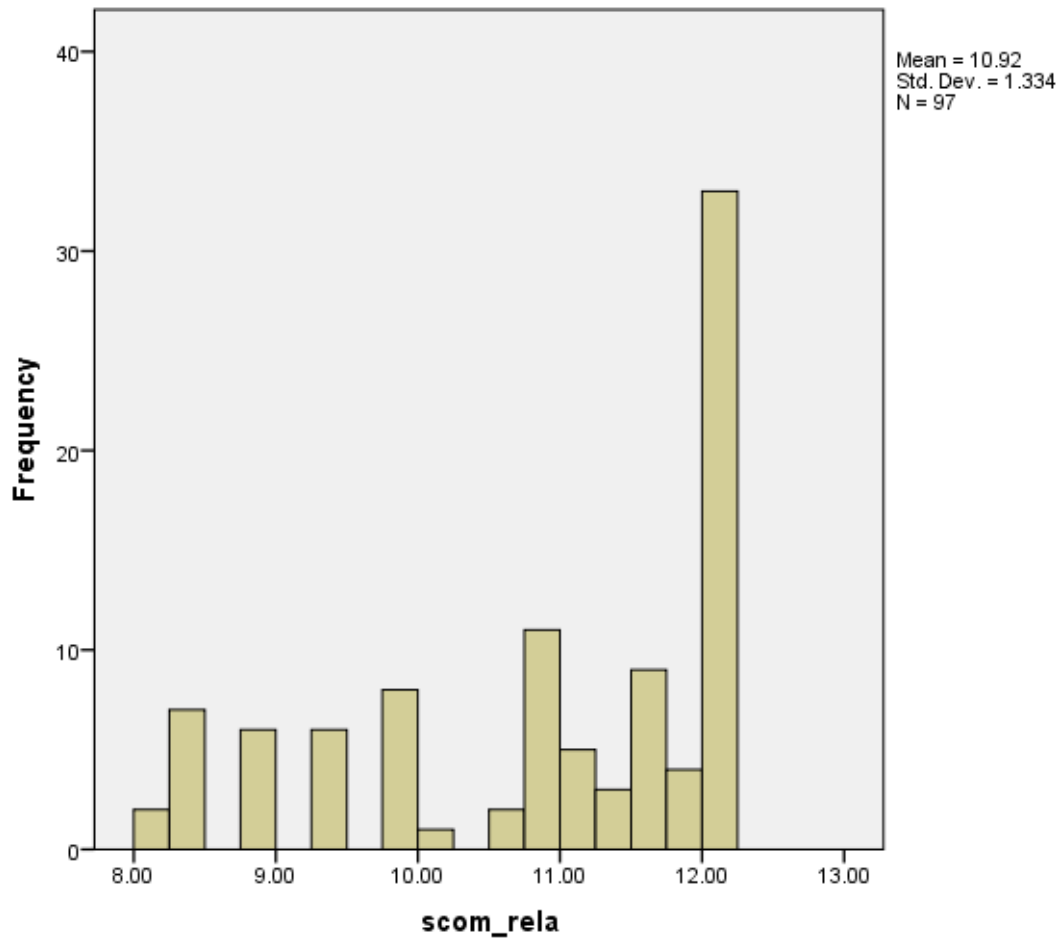
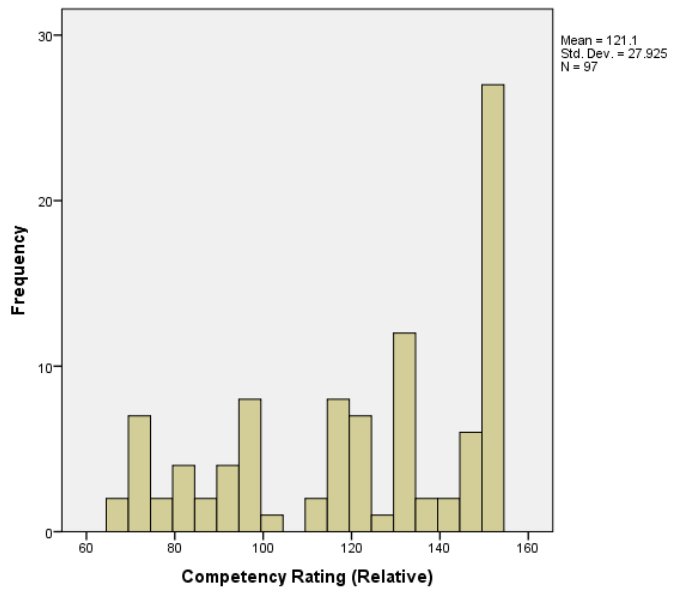


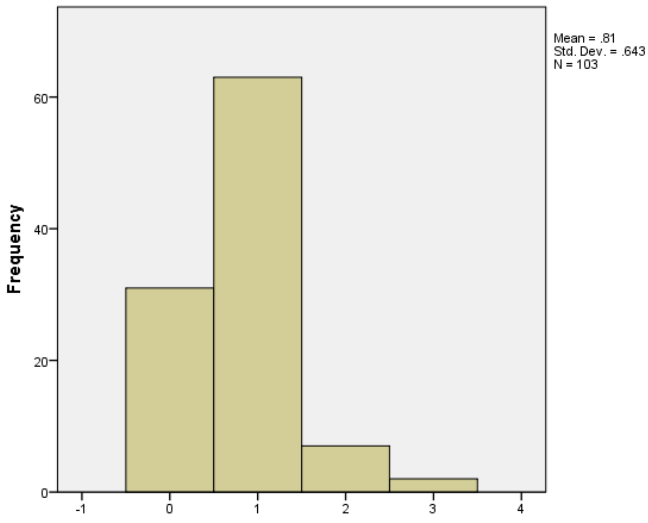




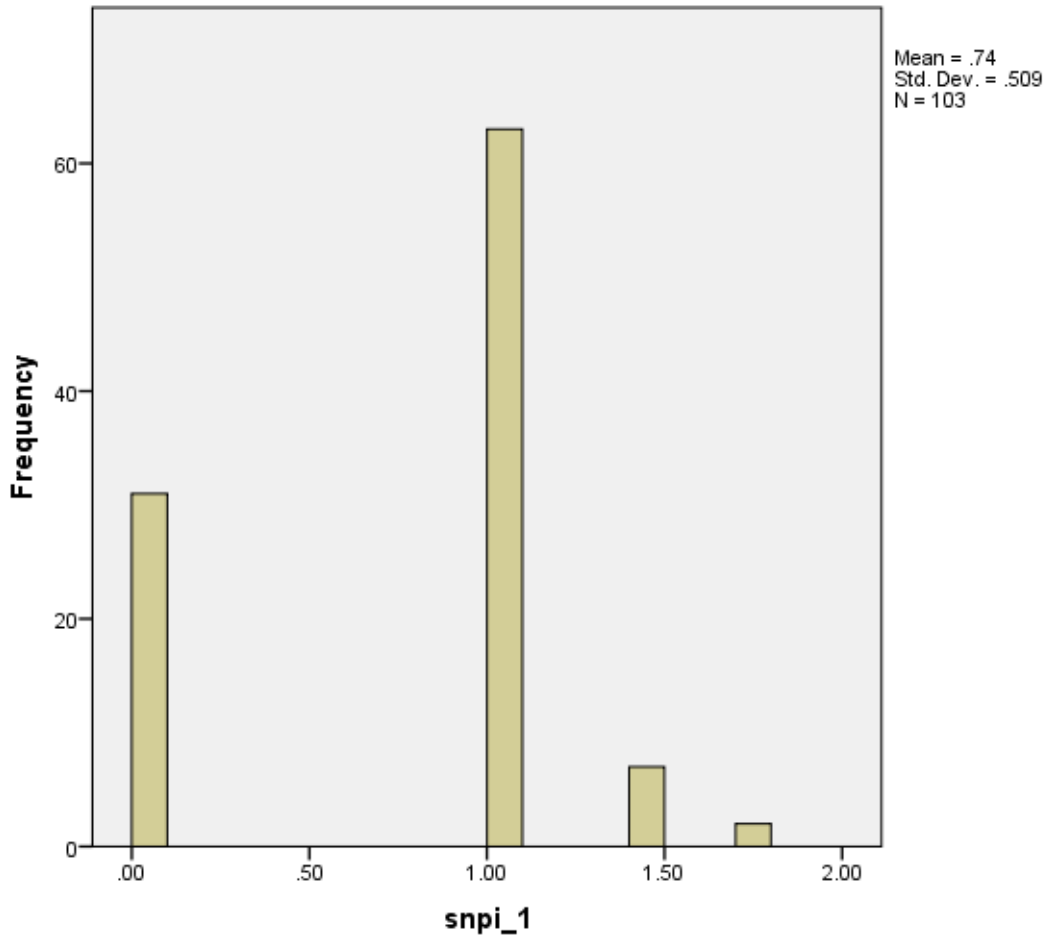




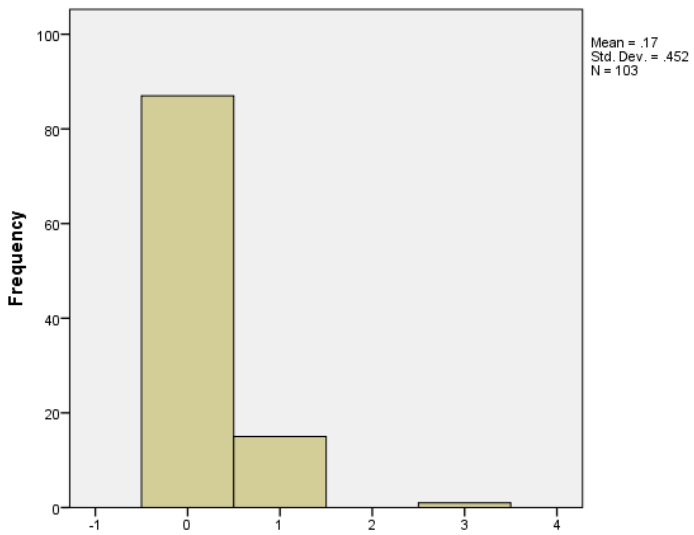




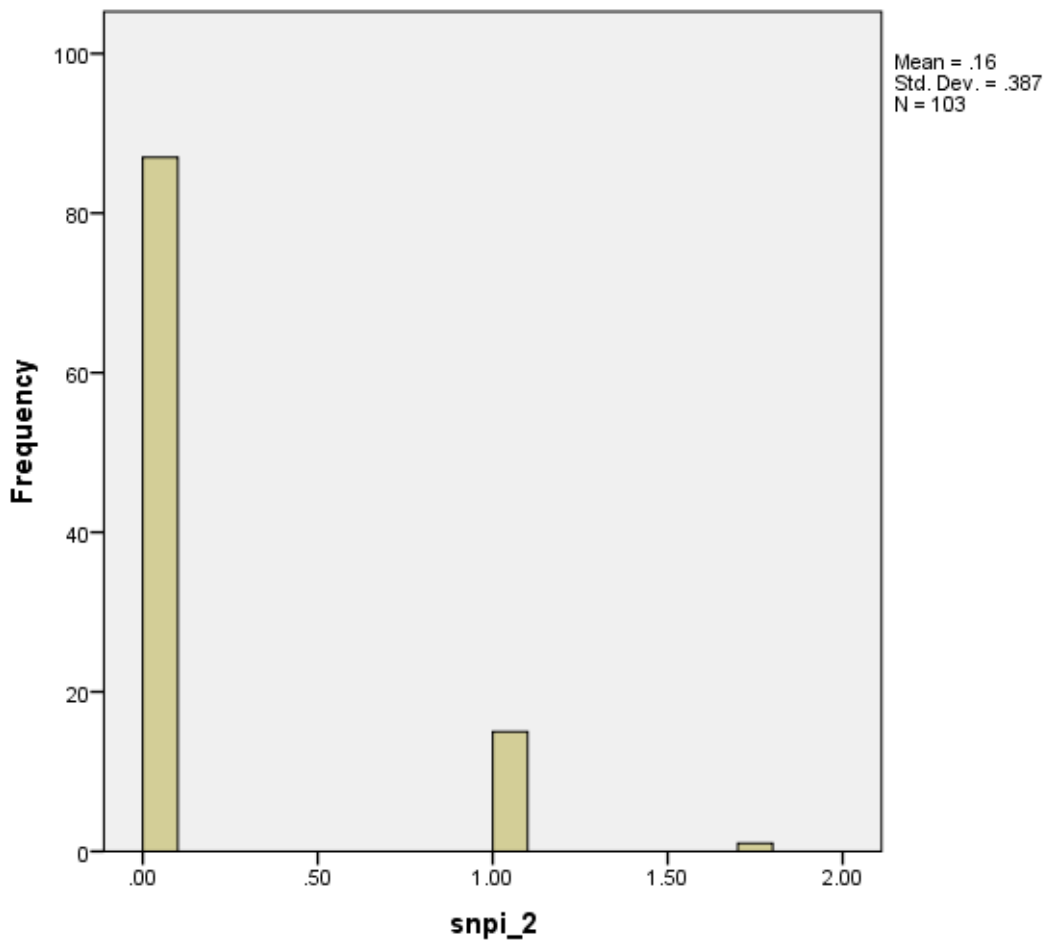
**NPI: Delusions: Does the patient have false beliefs, such as thinking that others are stealing from him/her or planning to harm him/her in some way?**

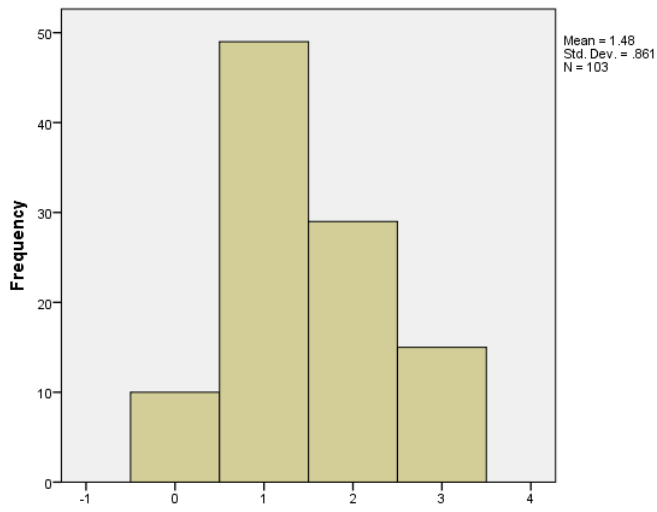




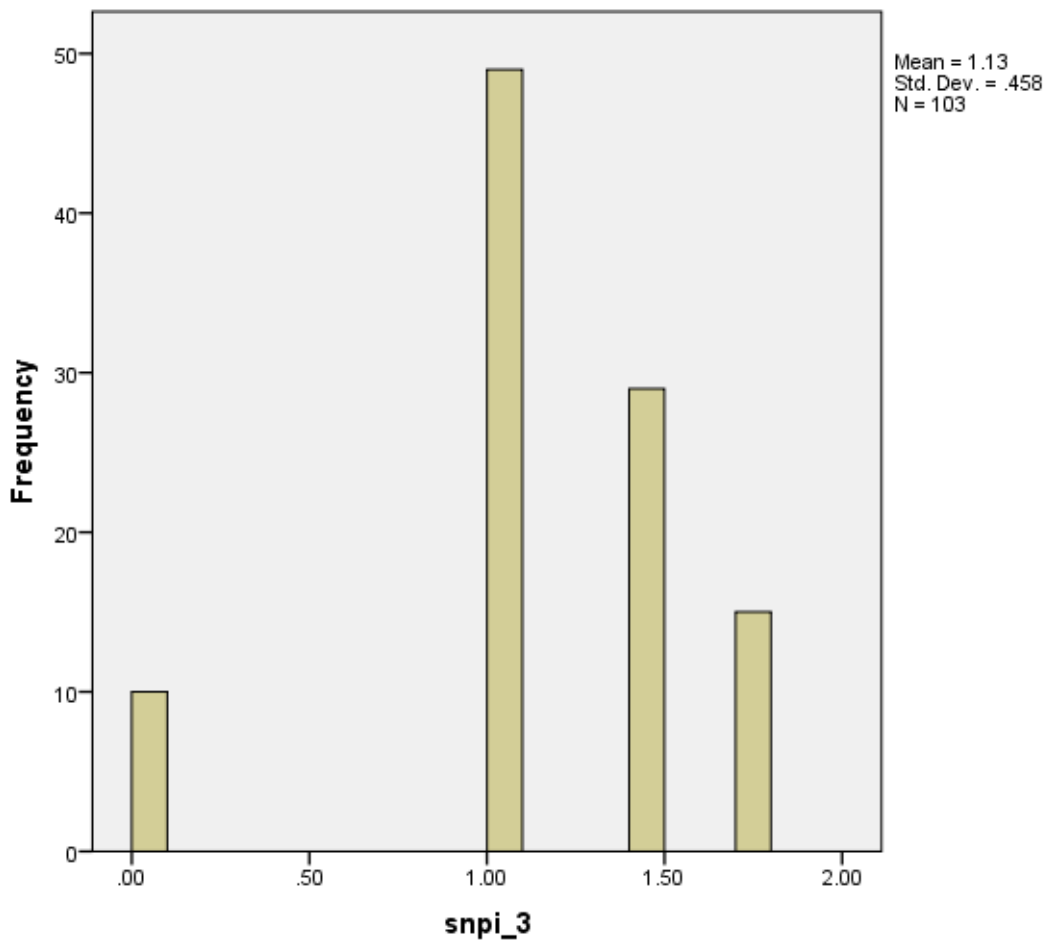


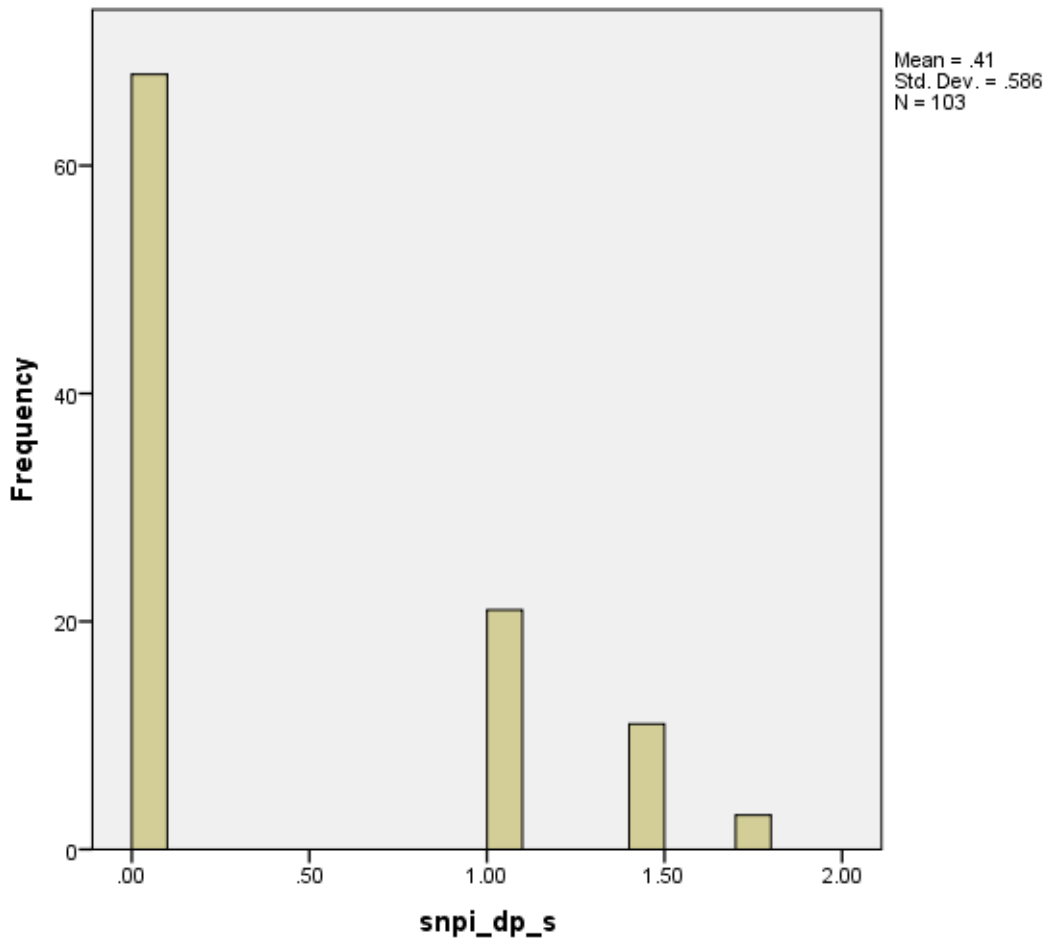
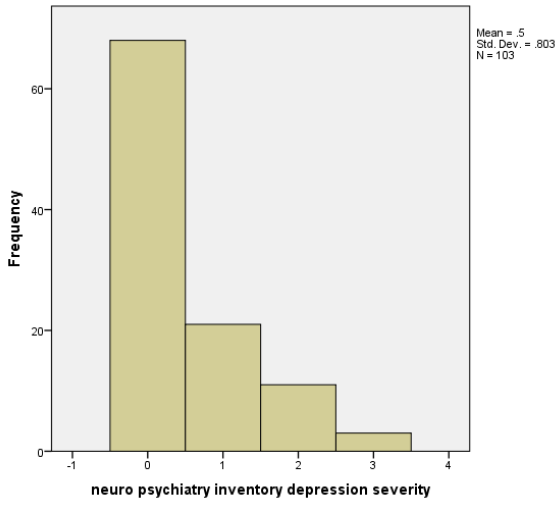
**NPI: Hallucinations: Does the patient have hallucinations such as false visions or voices? Does he or she seem to hear or see things that are not present?**

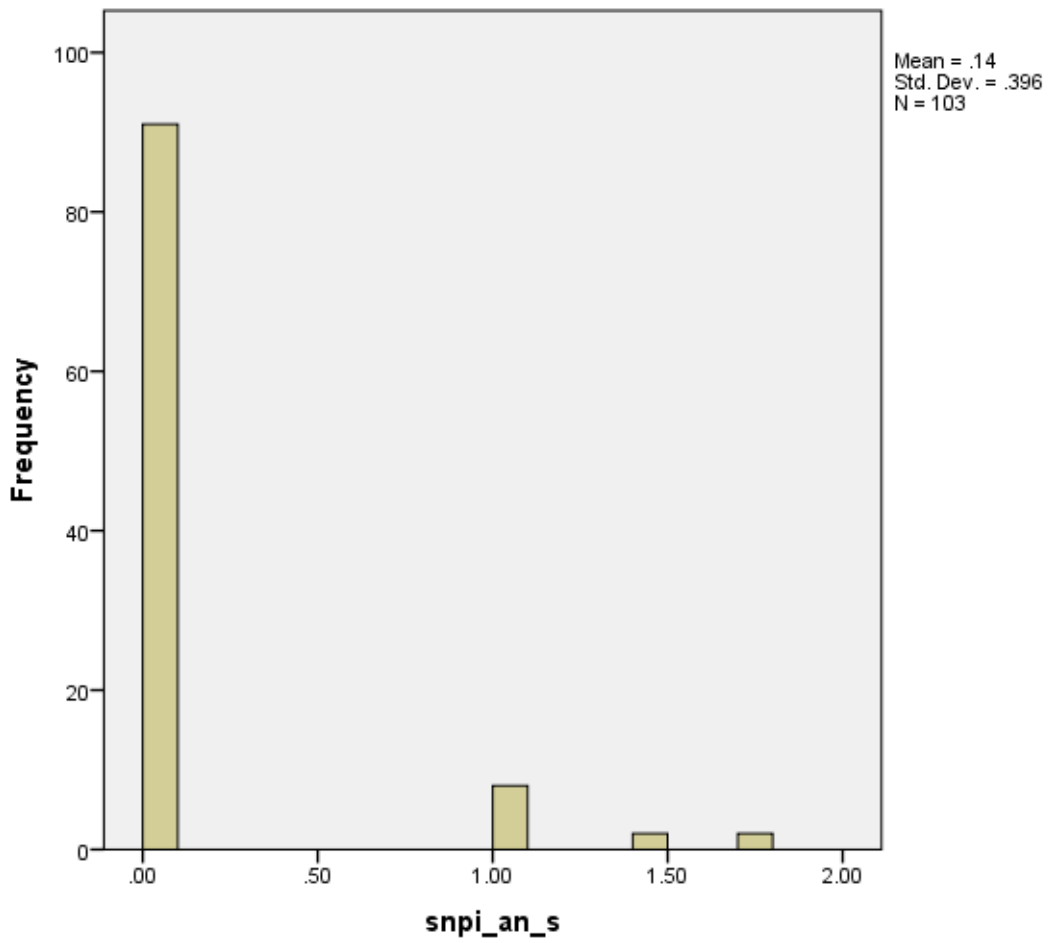
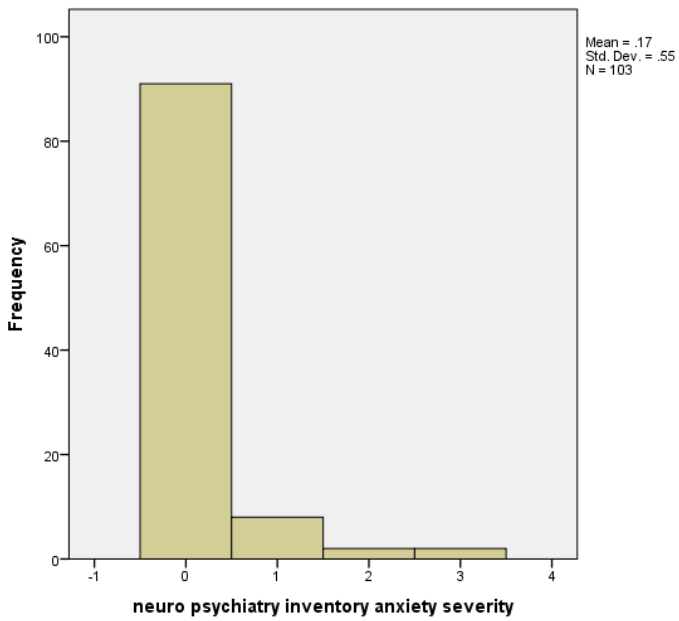


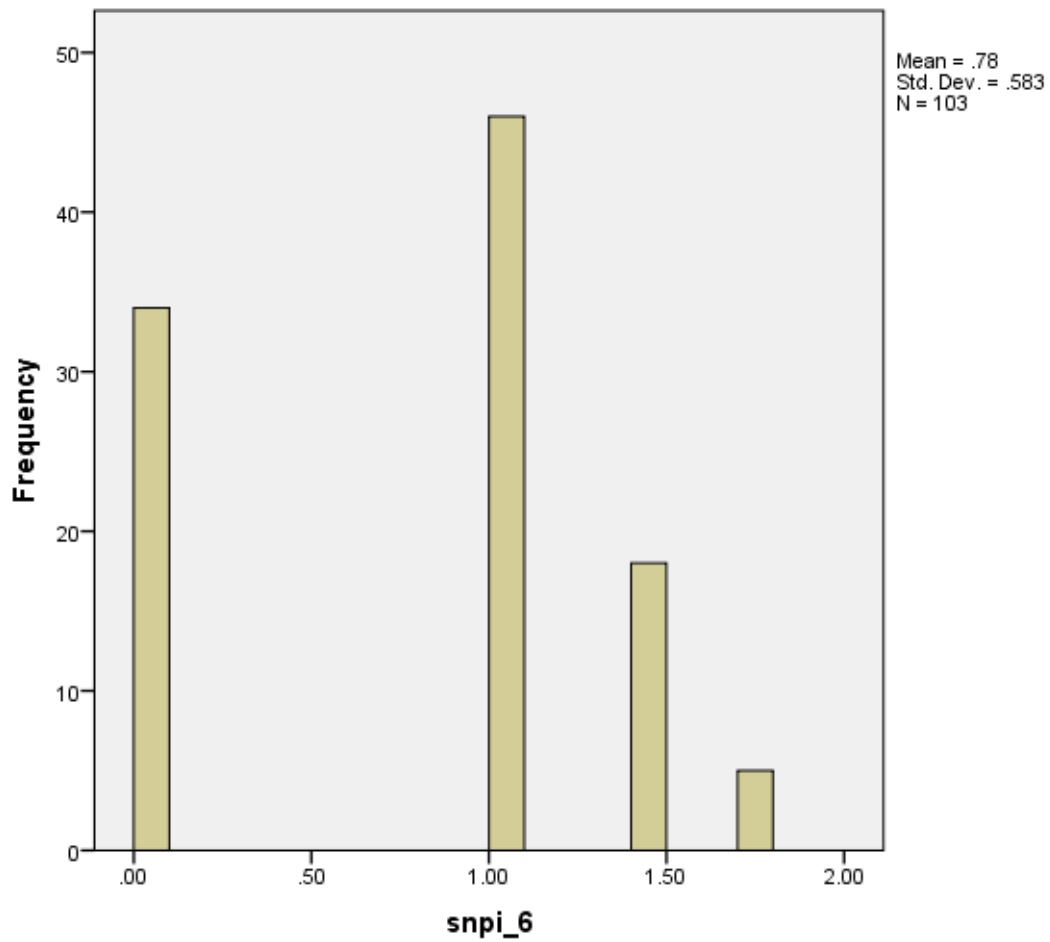
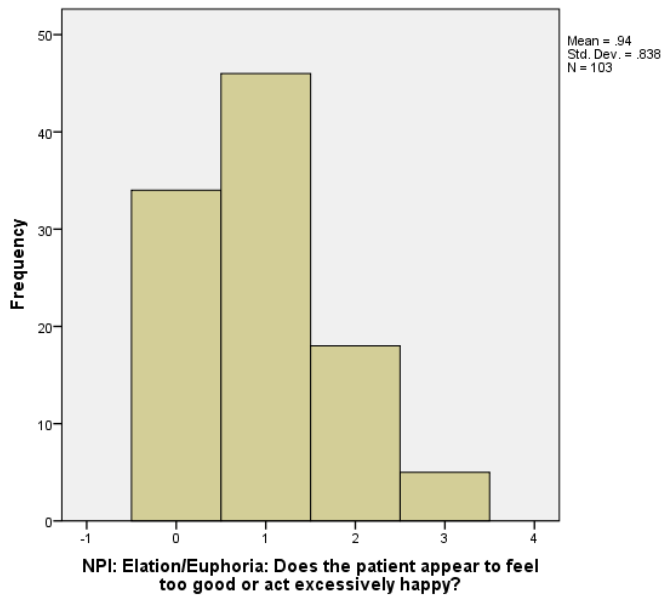


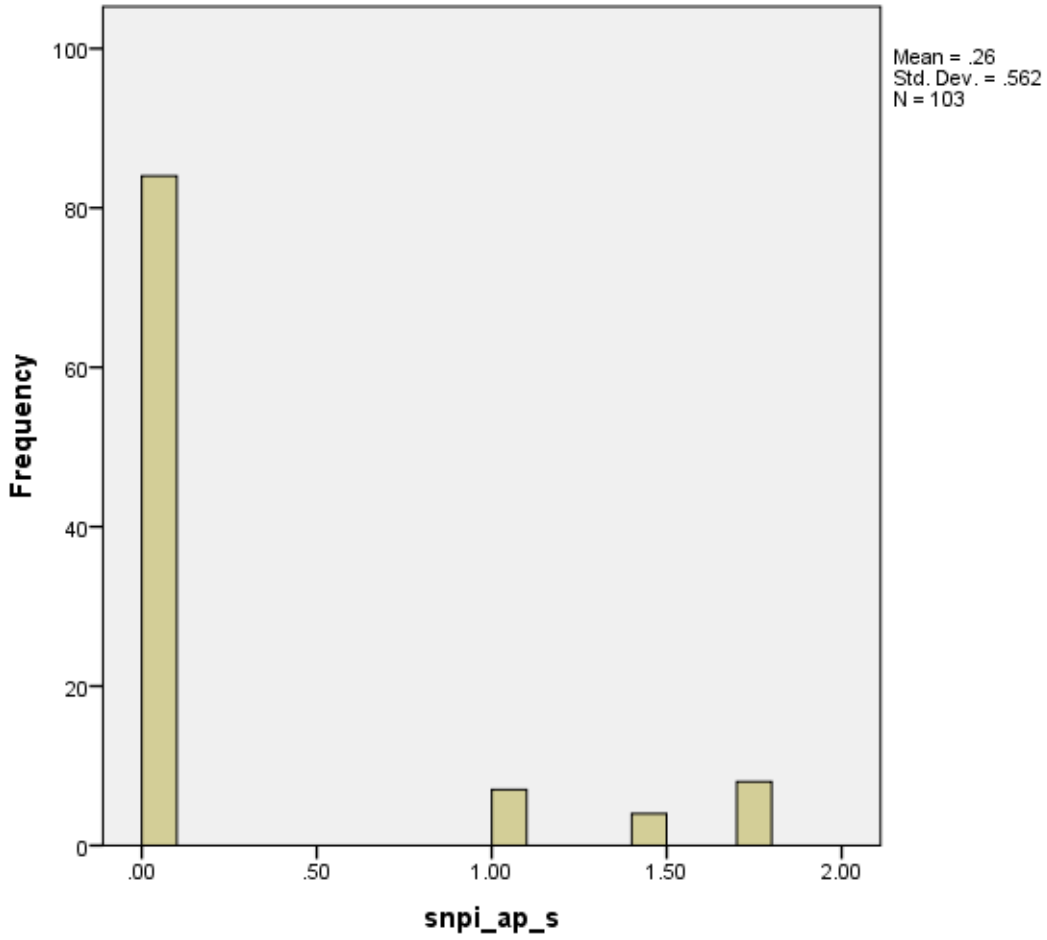
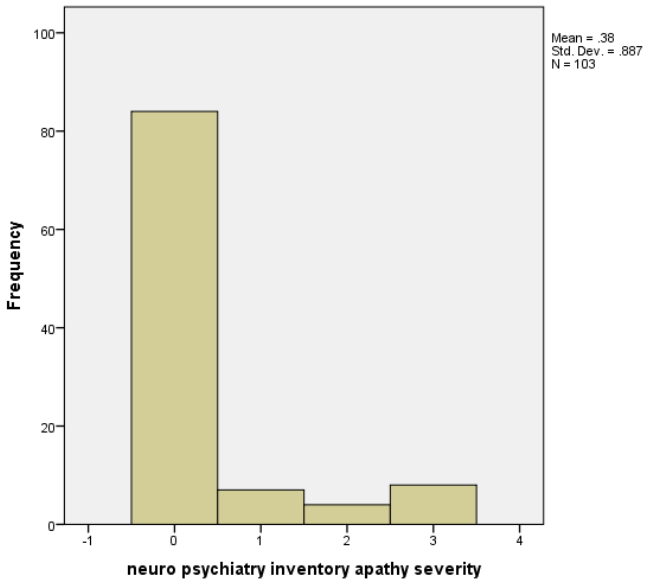
**NPI: Agitation.aggression: Does the patient have hallucinations such as false visions or voices? Does he or she seem to hear or see things that are not present?**

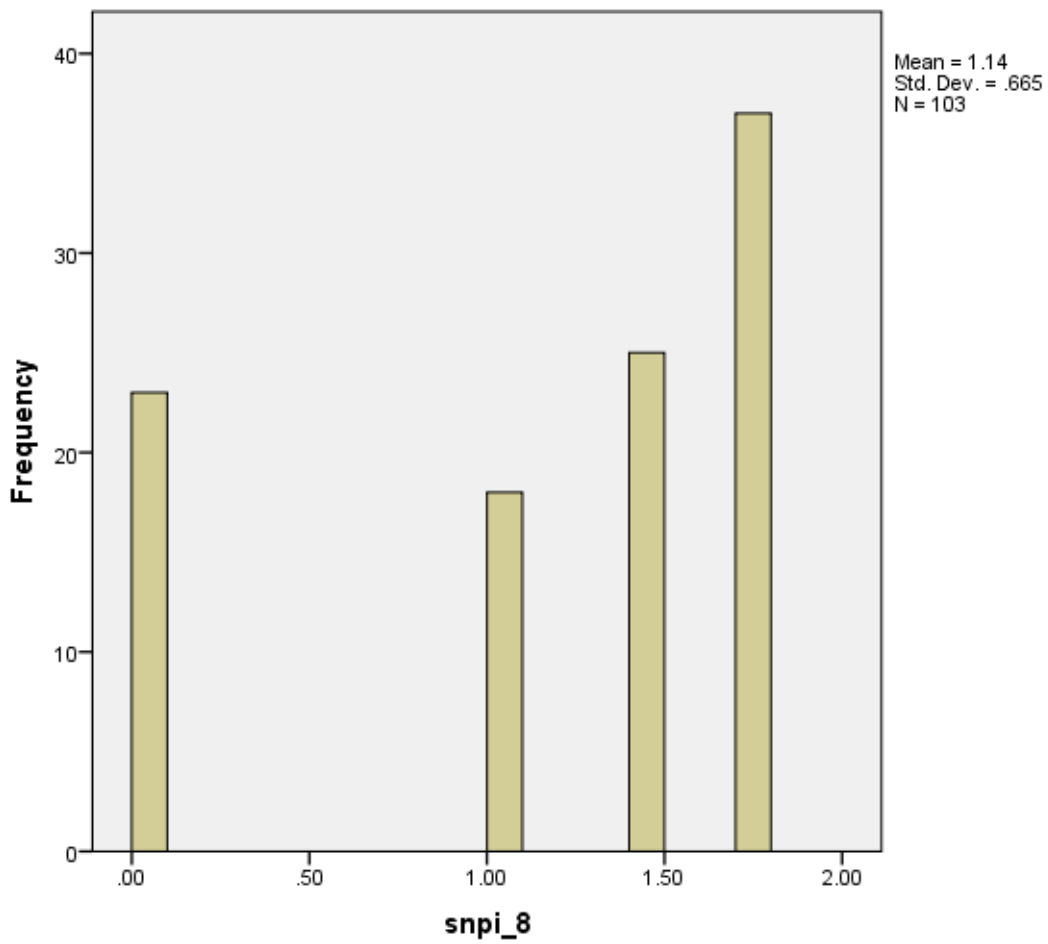
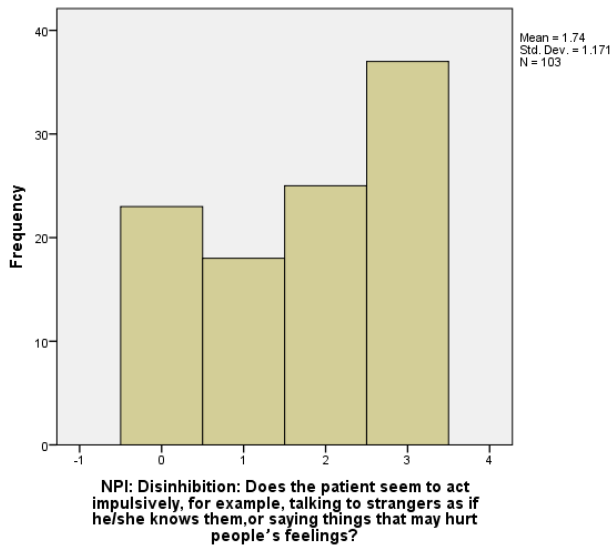


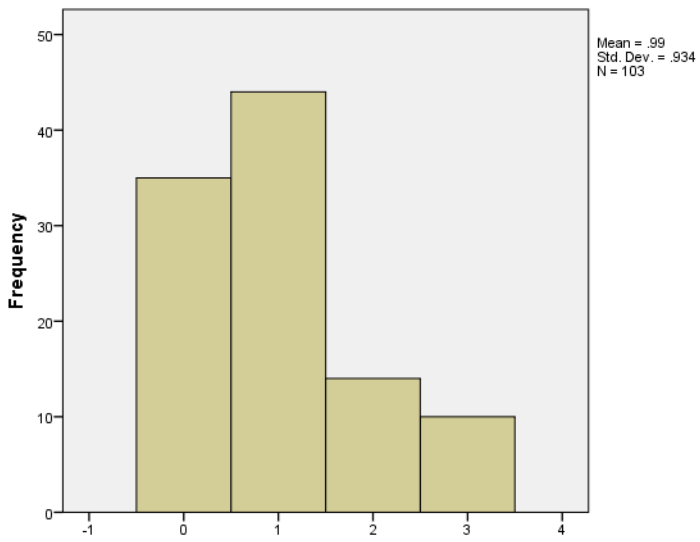




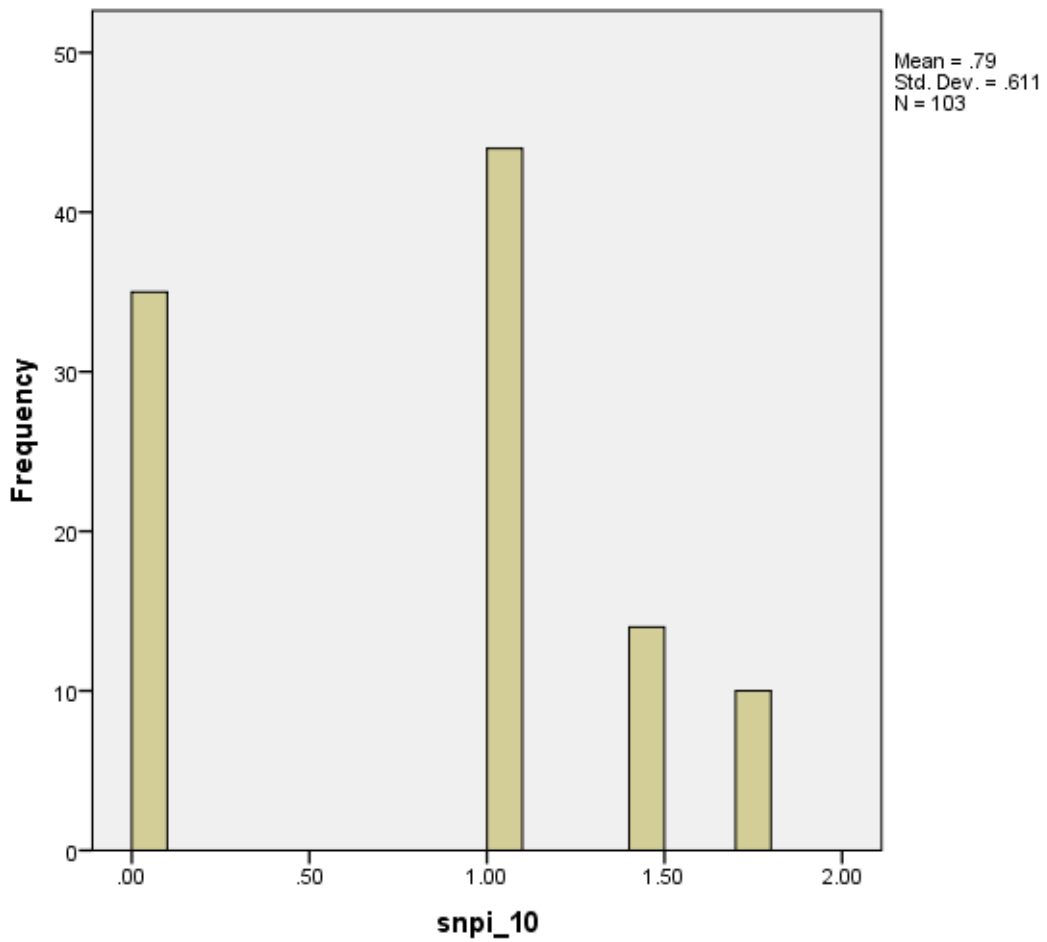




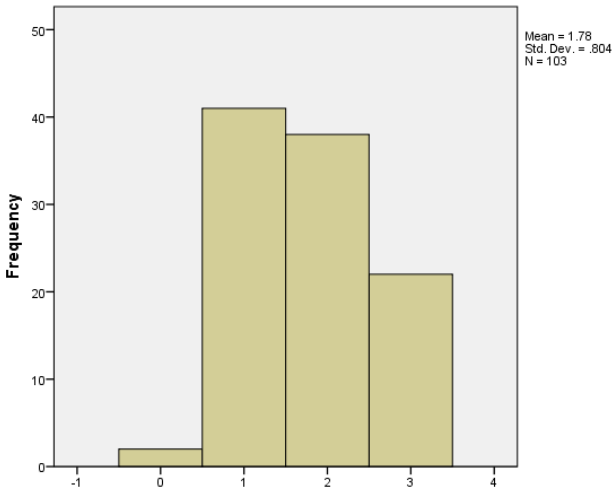




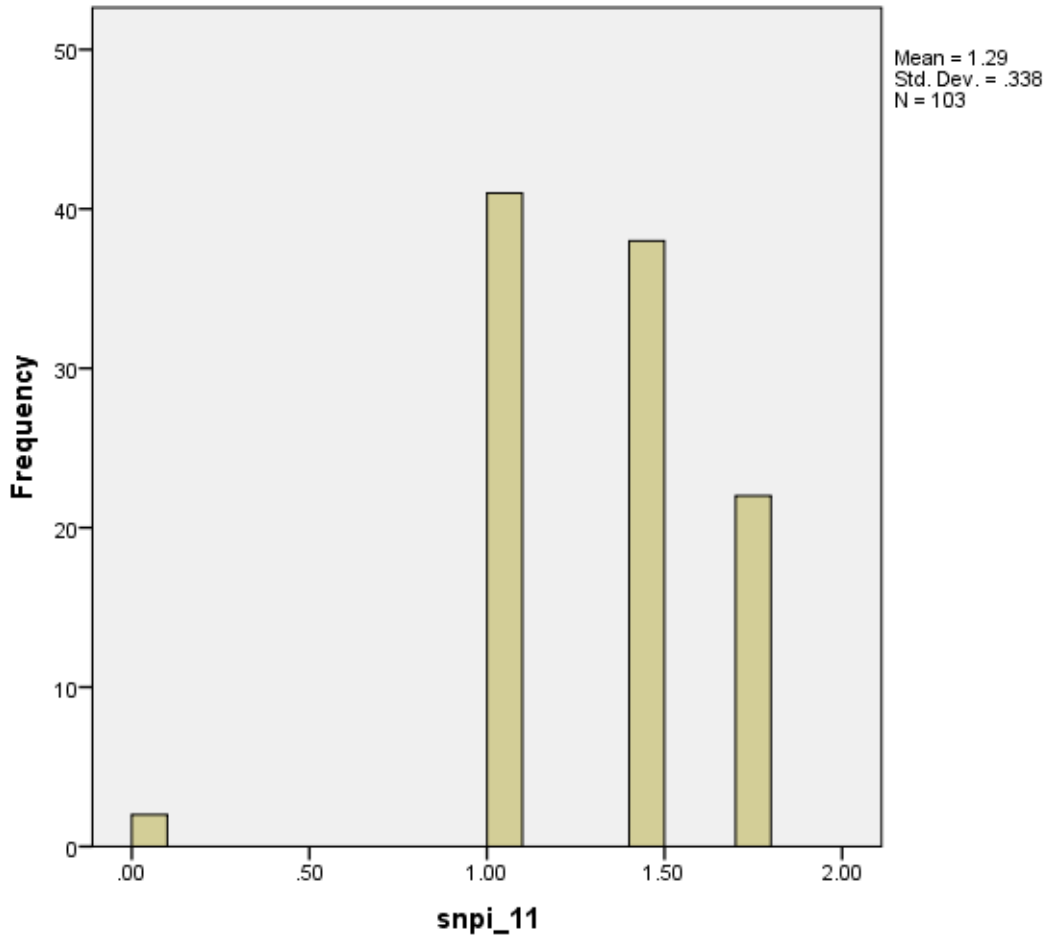
**NPI: Motor disturbance: Does the patient engage in repetitive activities such as pacing around the house, handling buttons, wrapping string, or doing other things repeatedly?**







NPI: Nighttime behaviors: Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?



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