COGNITIVE DYSFUNCTION IN PSYCHIATRIC PATIENTS: COMPARISON BETWEEN SCHIZOPHRENIC AND BIPOLAR DISORDER PATIENTS WITH HEALTHY SUBJECTS

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ABSTRACT

Background and Objective: The debate regarding the similarities and differences in cognitive functions in remitted schizophrenia and bipolar patients continues to be ongoing. This study was done to compare the level of cognitive functions as well as to determine associated factors influencing the cognitive functions of these patient populations with those of a healthy subject group.

Methodology: This was a cross sectional study on stable schizophrenic and euthymic bipolar patients and healthy subjects. Subjects were included after screening through stringent inclusion and exclusion criteria, along with healthy subjects. The cognitive assessment tools used were the perceived deficits questionnaire (PDQ) (subjective assessment), the trail making tests (TMT), and the digit span. TMT A was to measure attention, TMT B and reverse Digit Span task measured executive functions, whereas the forward Digit Span task measured working memory.

Results: Fifty-seven stable schizophrenic patients and forty euthymic bipolar patients as well as fifty-seven healthy subjects were included in the study. Stable schizophrenic patients did significantly poorly in all the objective tests ($p<0.01$) in comparison with the bipolar and healthy group. In the TMT A which measures attention, schizophrenic patients took 48.93 seconds on average, while on the TMT B, measuring executive function, they took 116.67 seconds. In comparison, the bipolar group spent 34.51 seconds on the TMT A, and 79.90 seconds on the TMT B. The healthy group used the least time to complete the tests, which was 23.98 seconds for the TMT A and 48.82 seconds in the TMT B. The bipolar group performed better than the schizophrenic

group but fared worse than the healthy group in all the tests except the digit span forward test, which measures working memory (p=0.857).

There were several demographic factors that were associated with poorer performance in the TMT and digit span tasks, namely more advanced age, Indian ethnicity, fewer years of education, being unemployed and longer duration of illness. After adjusting for those variables in multivariate analysis, the schizophrenia group performed significantly poorer than the healthy group in the TMT A and reverse digit span task (which measures executive function), and more advanced age and Indian ethnicity were independent risk factors for poorer performance in TMT A. The bipolar group performed significantly poorer than the healthy group in the TMT B and reverse digit span task. Indian ethnicity and less years of education were independent risk factors for poor performance in TMT A, and Chinese ethnicity performed better in the TMT B.

Conclusion: Cognitive dysfunction was found to be present in stable schizophrenic and bipolar patients. In the schizophrenia group, the cognitive dysfunctions found were those of poor attention and executive function in comparison with the healthy group; while in the bipolar group, executive function was the main cognitive impairment in comparison with the healthy group. Thus assessment for cognitive dysfunction and measures to alleviate these symptoms should be included in the management of these patient groups.

ABSTRAK

Latar Belakang dan Objektif: Pertentangan pendapat mengenai persamaan dan perbezaan fungsi kognitif pesakit skizofrenia dalam remisi dan bipolar masih berterusan. Kajian ini bertujuan untuk menilai dan membandingkan fungsi kognitif di antara pesakit dalam 2 kumpulan tersebut dengan subjek yang sihat tanpa penyakit.

Metodologi: Kajian jenis seksyen silang ini dilakukan untuk pesakit skizofrenia yang stabil dan pesakit bipolar eutimik. Mereka disertakan dalam kajian ini selepas penilaian menggunakan kriteria kemasukan dan pengecualian yang tegas, bersama-sama dengan kumpulan subjek yang sihat. Jenis ujian penilaian kognitif yang digunakan adalah PDQ (penilaian subjektif), TMT dan DS. Ujian TMT A menilai tumpuan perhatian, ujian TMT B dan DS terbalik menilai fungsi eksekutif, manakala ujian DS hadapan menilai daya ingatan sementara.

Keputusan: Lima puluh tujuh pesakit skizofrenia yang stabil dan empat puluh pesakit bipolar eutimik telah dimasukkan ke dalam kajian ini. Pencapaian pesakit skizofrenia yang stabil dalam semua ujian objektif kurang memuaskan berbanding dengan kumpulan pesakit bipolar dan kumpulan sihat ($p<0.01$). Untuk ujian TMT A (yang menilai tumpuan perhatian), kumpulan pesakit skizofrenia mengambil masa purata 48.93 saat dan 116.67 saat untuk TMT B (yang menilai fungsi eksekutif). Berbanding kumpulan pesakit bipolar, masa purata yang diambil untuk TMT A adalah 34.51 saat, dan 79.90 saat untuk TMT B. Kumpulan subjek sihat hanya mengambil masa purata 23.98 saat untuk TMT A dan 48.82 saat untuk TMT B. Pencapaian kumpulan bipolar lebih baik berbanding kumpulan skizofrenia, tetapi kurang baik apabila dibandingkan dengan kumpulan subjek sihat kecuali ujian DS hadapan (yang menilai daya ingatan

sementara) (p=0.857). Terdapat beberapa faktor demografi yang berkaitan dengan pencapaian yang kurang memuaskan untuk ujian TMT dan DS seperti umur yang lanjut, peserta kajian yang berbangsa India, tahap pendidikan yang rendah, menganggur dan tempoh masa penyakit yang lebih lama. Walau bagaimanapun, selepas analisa multivariat, pencapaian kumpulan skizofrenia kurang baik berbanding dengan kumpulan sihat untuk ujian TMT A dan DS terbalik (fungsi eksekutif). Umur yang lebih tinggi dan kumpulan etnik India adalah factor risiko bebas untuk prestasi buruk di TMT A. Pencapaian kumpulan bipolar juga kurang baik berbanding kumpulan sihat untuk ujian TMT B dan DS terbalik Etnik India dan kurang pendidikan adalah faktor risiko bebas untuk prestasi buruk di TMT A, dan kumpulan etnik Cina mendapat pencapaian yang lebih baik dalam TMT B.

Kesimpulan: Terdapat disfungsi kognitif dalam kumpulan pesakit skizofrenia dan juga pesakit bipolar yang stabil. Dalam kumpulan skizofrenia, disfungsi kognitif adalah dari segi tumpuan perhatian dan fungsi eksekutif apabila dibandingkan dengan kumpulan sihar; manakala untuk kumpulan bipolar, kekurangan kognitif adalah dari segi fungsi eksekutif. Penilaian untuk disfungsi kognitif dan langkah-langkah untuk merawat simptom tersebut patut dimasukkan dalam kaedah perawatan pesakit kedua-dua kumpulan tersebut.

*PDQ = Soal selidik defisit yang diperasan

*TMT = Ujian penjejakan

*DS = Digit span

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CHAPTER 1

INTRODUCTION

"My whole mental power has disappeared, I have
sunk intellectually below the level of a beast"
(a schizophrenic patient, quoted by Kraepelin in 1919, p. 25).

Emil Kraepelin was the first to be credited as the one who differentiated the types of psychoses into that of schizophrenia, and bipolar disorder; or dementia praecox and manic-depressive psychosis, as he called them (Decker, 2007). However he derived his insights from the Prussian psychiatrist Karl Halbaum (Jablensky, 2007) who had differentiated mental illnesses into two major groups, called *vecordia* and *vesadia* (Angst, 2002) according to their symptoms, course and outcome. *Vecordia* was a self-limiting disturbance of the mind, while *vesadia* was a complete disturbance (Angst, 2002). He also described *vecordia's* course to be continuous, with no dementia as its outcome; *vesadia's* course was progressive, and with dementia as a final outcome. Kraepelin based his nosology upon Kahlbaum's because he wanted to create a classifying system that would create a basis for accurate prognosis, as well as successful therapy and prevention (Roelcke, 1997).

According to the Kraepelinian dichotomy, those with schizophrenia differed from those with bipolar disorder on four accounts: their causes and symptoms, illness progression, as well as their outcomes (Angst, 2002). From his observations, those with schizophrenia were believed to have a continuously progressive illness, whereas those with bipolar disorder had periods of spontaneous recovery. He also categorized those with schizophrenia to ultimately develop dementia in their old age, but those with bipolar disorder would ultimately recover. This differed from Kahlbaum's concept as he

had described mania as a *vesadia,* which meant that the outcome for mania was also dementia.

Based on these observations, it can be seen that even from Kahlbaum's era in the 19th century, cognitive decline was a known consequence of severe mental illness, in the form of dementia. Dementia is a syndrome characterized by cognitive deficits, as well as emotional and behavioural decline, (*Management of Dementa (2nd Edition),* 2009). Probably it was due to Kraepelin's influence that it was traditionally believed that cognitive impairment was only apparent in elderly and deteriorated patients with schizophrenia (O'Carroll, 2000). However with recent research and findings, cognitive impairment is found to be the norm, and often pre-dates the illness, as it is found in drug-naïve patients (O'Carroll, 2000).

In a study done by Palmer et al in the United States, 161 schizophrenic patients were tested with a battery of neuropsychological tests, comparing them with 63 healthy subjects. They found that only 27% of patients with schizophrenia actually had comparable to norm functions (Palmer et al., 1997). This means that around 75% of patients with schizophrenia have significant cognitive impairment (O'Carroll, 2000). Palmer and his team found particularly that memory, attention, motor skills, executive function and intelligence were the areas of deficit. They also found that the 27% who performed as well as the normal controls had less negative symptoms, less extrapyramidal symptoms and were on less anticholinergic medications. Besides these, they also socialized more often, and did not have recent psychiatric hospitalization (Palmer et al., 1997).

Also differing from the Kraepelinian dichotomy is the current understanding that cognitive deficits are present in bipolar disorder as well (Caligiuri & Ellwanger, 2000). There has been a number of research that has provided evidence of persistent cognitive

deficits across the different phases of bipolar disorder, including in the euthymic state (Camelo et al., 2013). The following domains in particular were affected: sustained attention, memory, learning, visuospatial skills, and executive function (Caligiuri & Ellwanger, 2000; Latalova et al., 2011).

Despite these evidences, there are still conflicting data regarding the presence and extent of cognitive deficits in bipolar disorder. A review of 42 studies found that cognitive dysfunction is common in bipolar disorder, although mostly during episodes of depression and mania (Quraishi & Frangou, 2002). There was also some evidence for residual deficits in executive function and visual memory. The cognitive deficits during the acute phases of mania or depression were for verbal memory and sustained attention (Quraishi & Frangou, 2002).

However as can be seen from a study by Altshuler et al. done in the U.S. in which 40 subjects with bipolar disorder were compared with 20 subjects with schizophrenia as well as 22 healthy subjects, it was found that the subjects with bipolar disorder did not differ significantly from the healthy group in terms of visuoconstructive ability, language function, or procedural learning. Interestingly performance of bipolar subjects on the executive function tests was bimodal – suggesting that one group was relatively normal and the other group had impaired executive functioning (Altshuler et al., 2004).

Since as yet there has not been any conclusive evidence of differences in cognitive functions between the two groups, and thus far there has been a lack of studies in this topic in the local setting of Malaysia, the rationale of this study is to assess the cognitive functions in the local population, with the hopes of further contributing to the understanding of these complex illnesses.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview of cognitive functions and cognitive assessment tools

Broadly speaking, cognitive and brain functions in general can be divided into perception, attention, memory, motor skills, language, visual and spatial processing, and executive functions (Michelon, 2006). Executive functions are further divided into flexibility, theory of mind, anticipation, problem-solving, decision-making, working memory, emotional self-regulation, sequencing, and inhibition. Different authors appear to describe different components of cognitive functions. Another author described cognitive abilities as those of reasoning, memory and learning, visual perception and auditory reception, idea production, cognitive speed, knowledge and achievement, psychomotor abilities, and miscellaneous domains of personal characteristics and ability (Carroll, 1993).

The Woodcock-Johnson psychoeducational battery (Woodcock, 1977) divided the cognitive abilities into 12 cognitive tests based on 4 broad cognitive ability groups, discrimination-perception, memory learning, reasoning thinking and knowledge-comprehension. These have been ordered in ascending fashion in terms of lower mental processes, to higher mental processes, with the latter two being the highest on the scale of mental processes. Although the most current version of the Woodcock-Johnson (WJ) cognitive assessment battery is 39 years junior to its predecessor, the WJ IV® Cognitive Abilities Assessment (Schrank et al., 2016a) the basic cognitive abilities they described have not changed much for easier application, with more tools added for better assessment of higher mental processes.

Cognitive ability assessment tools are important as they help to translate the underlying cognitive processes into external neurocognitive research evidence (Schrank et al., 2016b). They are especially important in the field of psychiatry as most, if not all, mental illnesses such as schizophrenia, anxiety, and depression, are cognitive in nature (Robbins, 2011).

As can be seen from the fact that there is no consensus for the description of cognitive functions and abilities, there is also no one standardized battery of tests for cognitive functions for all mental illnesses. This can be understood as different mental illnesses differ in terms of their inherent cognitive dysfunction (J. K. Trivedi, 2006).

Although the range of cognitive dysfunction is diverse, three main aspects of cognitive function are more frequently at risk in most mental illnesses (J. K. Trivedi, 2006) and will be elucidated here. These aspects are working memory (WM), executive function (EF) and attention and information processing.

2.1.1 Working Memory

WM is understood to be in close relationship with short-term memory (STM), with their exact relationship being difficult to delineate (whether one is a component of the other, or whether they are separate) (Engle et al., 1999). WM plays an important role in many cognitive duties, such as learning, understanding, and reasoning. It is the ability to hold stimuli 'online' temporarily, and either use it directly, or after a short period, or process it mentally to solve cognitive and behavioural problems (J. K. Trivedi, 2006). WM is thought to be a function of the prefrontal cortex (Goldman-Rakic, 1987).

In a meta-analysis by Fiorovanti et al. that reviews cognitive dysfunction in schizophrenia, multiple tests for working memory were grouped according to what they

assessed, but the one outstanding test was the digit span, in which 31 other studies had used it as a test for memory function (Fioravanti et al., 2012). In another meta-analysis by Robinson et al that reviewed cognitive dysfunction in bipolar disorder, the Auditory/California Verbal Learning Test and Forward Digit Span were used to assess verbal learning and memory (Robinson et al., 2006).

2.1.2 Executive Function

EF is the capacity to take abstract concepts and use them in problem-solving and planning actions, for the achievement of future goals, all the while monitoring the self's mental and physical processes. These skills are most essential in handling new or complex situations (J. K. Trivedi, 2006). It is anatomically related to the cortical-subcortical circuits and frontal lobes (Cummings, 1993).

In the study done by Altshuler et al. that compares cognitive functions in schizophrenia and bipolar disorder and normal subjects, they noted that tests for EF used in other studies were as follows: the Wisconsin Card Sorting Test (WCST), Trail making test (TMT) A and B, and Stroop test (Altshuler et al., 2004). In the meta-analysis by Robinson et al. mentioned earlier, the tests for EF were verbal fluency, WCST, Stroop, TMT B, Reverse Digit Span, and Category Fluency (Robinson et al., 2006). For economical purposes, the author decided to use the TMT B as well as reverse digit span for measures of executive function in the study population.

2.1.3 Attention

Attention is the ability to recognize relevant stimuli, and focus on these stimuli instead of others (selective attention). It is also the ability to execute a task in the

presence of distractions (focused attention), and sustain the focus on the desired stimulus until it is processed (vigilance, or sustained attention), for the stimulus to be transferred to higher-level processes (information processing) (J. K. Trivedi, 2006).

In a U.S study by Medalia et al. which tested the effectiveness of testing attention in patients with schizophrenia, a review of previously used tests for attention included the continuous performance test (CPT), digit symbol substitution test, and TMT A (Medalia et al., 1998). The same tests were found to be used for attention testing in the meta-analysis by Robinson et al. (Robinson et al., 2006).

Based on this literature review, the researcher has chosen TMT A for the assessment of attention (besides visual scanning and psychomotor speed), TMT B and reverse digit span for executive functions, and forward digit span for the assessment of working memory in the patient as well as control populations. The details of the cognitive tools used will be described later in chapter 4.

2.2 Cognitive dysfunction in schizophrenia

As noted earlier, O' Carroll found that 75% of patients with schizophrenia had cognitive deficits (O'Carroll, 2000). In a more recent study by Keefe and colleagues done in North Carolina, 98% of patients with schizophrenia were found to perform more poorly than expected in neurocognitive tests when compared to their parents' educational level (Keefe et al., 2005). In addition, Goldberg et al. studied cognitive functions in discordant monozygotic twins in the U.S., and found that almost all the affected twins performed poorly when compared to their healthy twins (Goldberg et al., 1995).

The range of reported cognitive dysfunction varies. In a meta-analysis by Heinrichs and Zakzanis of 204 studies which compared patients with schizophrenia with controls, cognitive deficits were found in 22 different neurocognitive tests used in the diseased population (Heinrichs & Zakzanis, 1998). In the meta-analysis by Fiorovanti et al., studies were searched for in terms of deficits in the domains of memory, global cognitive functioning, language, executive function and attention (Fioravanti et al., 2012). Nuechterlein and colleagues thus attempted to develop a consensus battery of cognitive tests that is valid and reliable to be used in clinical trials (Nuechterlein et al., 2004). They did this by reviewing other studies and identifying what they believed to be the core deficits in cognition in schizophrenia, and selecting the tests that were replicable across studies. They concluded that there were 7 separable cognitive factors that could be assessed, including speed of processing, vigilance/attention, working memory, visual and verbal learning and memory, problem solving and reasoning, and social cognition.

Thus it can be seen that cognitive dysfunctions are a core feature of schizophrenia. It is important to understand this feature as cognitive deficits have been found to possibly precipitate positive and negative symptoms of schizophrenia (Crow et al., 1995). Friedman e. al. found these cognitive deficits to be relatively stable over time, in which progressive deterioration only tends to occur after the age of 65 (Friedman et al., 2001). Heaton found that cognitive deficits persist even after the remission of psychotic symptoms (Heaton, 1993). Indeed Keefe and Harvey asserted that cognitive deficits are not caused by symptoms of psychosis (Keefe & Harvey, 2012). Cognitive impairment has been thought to be related to negative symptoms but is a separate feature of schizophrenia on its own (Harvey et al., 1996). Cognitive deficits also determine the functional consequences or outcomes of patients with schizophrenia (Goldberg et al., 1990; Keefe et al., 2005; O'Carroll, 2000). Therefore another important

reason to study cognitive deficits in schizophrenia is to shift the focus from remission of symptoms, to cognitive rehabilitation.

2.3 Cognitive dysfunction in mood disorders

According to a recent meta-analysis by Rock et al., cognitive dysfunction is a core feature of depression that is not wholly secondary to the low mood (Rock et al., 2014). The deficits they found were in executive function, memory and attention. Cognitive impairment in depression can be severe besides being global, mimicking dementia (Rabins et al., 1984). Thus it was important to screen subjects for depression, to avoid this confounder.

The acute phase of bipolar disorder is also understood to have profound cognitive deficits, even possibly progressing to a stuporous state (J. K. Trivedi, 2006). Quraishi and Frangou in their review found that the cognitive deficits during acute mania and depression were global. During recovery, the areas of deficit that remained were those of sustained attention and verbal memory (Quraishi & Frangou, 2002).

In a meta-analysis for cognitive impairment in euthymic bipolar disorder, large effect sizes were noted for impairment in executive functioning and verbal learning, with medium effect sizes in immediate and delayed verbal memory, set-shifting and abstraction, psychomotor speed, sustained attention and response inhibition. They also reported small effect sizes for immediate memory, sustained attention and verbal fluency by letter (Robinson et al., 2006).

As cognitive deficits are present even in the remitted/euthymic states, it is suggested that certain cognitive impairments are fundamental trait characteristics. In a study by Lebowitz et al., done in the U.S, it was found that verbal fluency deficits were

correlated to the number of manic episodes (Lebowitz et al., 2001). In the U.K., El-Badri and colleagues found that the electroencephalogramme (EEG) changes of neurocognitive deficits in bipolar patients were related to the number of previous mood episodes (El-Badri et al., 2001). Also in the U.K., Cavanagh and colleagues conducted a study comparing euthymic bipolar patients with normal controls and found that performance on the California Verbal Learning Test (CVLT) was negatively correlated with number of manic episodes and overall duration of illness. They also found that it was not correlated with the number of depressive episodes or hospital admissions (Cavanagh et al., 2002). Therefore it can be concluded that cognitive impairments, especially those of memory and executive function, have been shown to correlate with the number of manic episodes and the total duration of illness.

Cognitive impairment has also been found to impair the daily functioning of the remitted bipolar patient in a Brazilian study (Lima et al., 2014). Therefore examining cognitive impairment during remission may encourage a better understanding of the illness course of bipolar disorder in the non-affective state, as well as aiming towards neuropsychological rehabilitation, in an attempt to minimize the impact of cognitive deficits in the patient's overall functioning.

2.4 Comparison of cognitive deficits in schizophrenia and bipolar disorder

There have been relatively few studies comparing cognitive performance in these two groups. In a meta-analysis by Krabbendam and colleagues, only 31 English studies were included from 1985 until 2004 that assessed cognitive functioning using reliable and standardized neuropsychological tests in adult patients (Krabbendam et al., 2005).

In the studies done, the general finding is that cognitive deficits are reported in both patient groups; however the severity of impairment seems to be greater in schizophrenia. Martínez-Arán A. et al. from Spain compared executive functions in 49 euthymic bipolar and 49 stable schizophrenia patients using the Wisconsin Card Sorting Test (WCST), FAS test (COWAT), and TMT. They found that there was a similar pattern of executive function impairment in both groups, but the schizophrenia group performed significantly worse in the number of categories in WCST (i.e., quantitatively). They also found that in the schizophrenia group, functional outcomes were predicted by negative symptoms as well as perseverative errors (WCST). However in the bipolar group, the best predictor of functional outcome was general psychopathology (Martínez-Arán et al., 2004).

Altshuler and team have also compared the cognitive performance in these two groups to assess the degree and pattern of impairment in comparison to a control group. The domains assessed were executive function, visual and verbal memory, visuoconstructive ability, procedural learning and language functions. They found that the stable schizophrenia group demonstrated a generalized impairment when compared with healthy subjects. The euthymic bipolar group was only significantly impaired in comparison to the healthy group in executive functioning and verbal memory. They also found that performance on EF tests was bimodal among the bipolar participants, suggesting 2 subgroups; one with impaired EF, and one that was relatively normal. They did not find significant differences between the control and bipolar groups in the other cognitive domains assessed (Altshuler et al., 2004).

In a study in India done by Trivedi and colleagues, 15 stable schizophrenic patients were matched with 15 euthymic bipolar patients and 15 healthy subjects, by age and education level. They found that the schizophrenia group performed poorly on all the neurocognitive parameters tested (WCST, Spatial Working Memory Test, and

Continuous Performance Test). The bipolar group also performed poorly in the EF test in comparison with the healthy group but quantitatively better than the stable schizophrenia group. They interpreted that these two disorders may be qualitatively distinguished in terms of the neuropsychological profiles of cognitive impairment (J. Trivedi et al., 2007).

Sánchez-Morla and colleagues from Spain compared the cognitive profiles of 73 euthymic bipolar patients with 89 stable schizophrenia patients and 67 healthy participants. They assessed domains of EF, verbal and visual memory, and sustained attention. They found that the bipolar group performed poorly in all domains when compared with the healthy group, which was qualitatively similar to the schizophrenia group. They also attributed persistent verbal memory impairment to poor psychosocial functioning in the former group (Sánchez-Morla et al., 2009).

More recently Vöhringer and colleagues did a systematic review that included studies with the following domains: EF, IQ, attention-concentration, memory and perceptuomotor function. They ensured that the studies included had operationally defined remitted and euthymic patient groups as well as healthy groups. They found that both groups had deficits on all cognitive measures when compared to the healthy subjects. However the schizophrenia group had more pervasive and severe cognitive dysfunctions while those with bipolar had milder and more confined impairment. Therefore the conclusion was that the cognitive impairment in bipolar disorder could be similar to schizophrenia in terms of profile (qualitative), however the latter group's deficits may be more severe and widespread (quantitative) (Vöhringer et al., 2013).

CHAPTER 3

RATIONALE AND OBJECTIVES OF STUDY

3.1 Rationale of the study

The aim of this study was to assess cognitive functions, and more specifically executive functions as well as verbal memory and attention in stable schizophrenic and bipolar patients, as well as to compare how they performed against healthy subjects.

Many studies of this kind have been done in other countries, but none have been done here in Malaysia before. According to Provenzano, A., et al., studies should reflect the reality of the local situation in order to produce results that are relevant to the population. This would provide long-term benefits to the local community as the study would then accurately reflect the locale's culture and history, political and judicial systems, as well as economic situations (Provenzano et al., 2010).

3.2 Objectives

1. To assess the performance on cognitive function tests in stable schizophrenic patients.
2. To assess the performance on cognitive function tests in euthymic bipolar disorder patients.
3. To compare the performance on cognitive function tests between the stable schizophrenic and bipolar disorder patients with a healthy group.
4. To assess the sensitivity and specificity of the cognitive tests used in the study populations.

5. To determine the associated factors of cognitive impairment in the study populations.

3.3 Study Null Hypotheses

1. There are no differences in the performance on cognitive function tests between patients with schizophrenia and bipolar disorder.

2. There are no differences in the performance on cognitive tests between stable schizophrenic and bipolar disorder patients, and the healthy population.

3. There are no significant association factors for cognitive impairment in patients with stable schizophrenia and bipolar disorder.

CHAPTER 4

METHODOLOGY

4.1 Study Setting

This study was conducted in the clinic of the Department of Psychological Medicine, Universiti Malaya Medical Centre (UMMC) in Kuala Lumpur. UMMC is one of the earliest university-affiliated hospitals in Malaysia, and was established in 1965. Since then it has been a national tertiary referral centre.

The Department of Psychological Medicine was founded in 1965, soon after the establishment of the Medical Faculty of the University Malaya in 1964. The department was spearheaded by Professor N.N. Wagner from America who was a clinical psychologist. Professor Tan Eng Seong was the first Malaysian psychiatrist to be the head of department. Its early function was to provide training in psychological medicine for undergraduate students. The department then expanded to provide postgraduate training in Psychological Medicine in 1973.

Apart from training, clinical work is very much ongoing with an in-patient facility, out-patient facility, day care centre, and community psychiatry services. It is also home to the department's research facility. UMMC is situated in the Petaling Jaya area of Selangor, which is one of the most developed areas of Malaysia. The population of this area consists of mostly Chinese, Malay and Indian ethnicities ("List of cities in Malaysia with large Malaysian Chinese populations."). It is one of the few government-affiliated hospital facilities around Selangor, thus it caters to a large population.

The in-patient wards have 22 beds for the male side and 22 beds for the female ward. The out-patient facility caters to new and old walk-in cases, as well as clinics run

by medical officers, specialists and consultants, as well as clinical psychologists and counsellors. The day care facility has rehabilitation and psychoeducation facilities, including a sheltered workshop. The community psychiatric services cater to a 15km radius around the hospital, with assertive and semi-acute care facilities.

Permission to conduct this study was obtained from the ethics committee of UMMC. Prior to that, a thesis proposal presentation was presented within the departmental level and improvements were made based on the feedback received during the proposal presentation.

4.2 Study Design and Sampling method

This was a cross-sectional study to assess cognitive functions in patients with stable schizophrenia and bipolar disorder, as well as to compare them with healthy subjects.

All patients in the outpatient clinic as well as the day care centre who were willing to participate and fulfilled the inclusion criteria, without having any of the exclusion criteria, were included in the study. Healthy subjects were selected from among the nursing and supporting staff.

4.2.1 Inclusion criteria for patients

1. Age – 18 – 45 years

2. Patients with established diagnoses of schizophrenia and bipolar disorder – according to the DSM V criteria

3. Patients who have had at least 8 years of formal education

4. Patients with the diagnoses of bipolar disorder and schizophrenia who are stable as per the following:

A. For schizophrenia – Brief Psychiatric Rating Scale (BPRS) score of 31 or less

B. For bipolar disorder – Young Mania Rating Scale (YMRS) less than 7

C. For both, Beck's Depression Inventory (BDI) of less than 11

4.2.2 Inclusion criteria for healthy subjects

1. Age – 18 – 45 years

2. Never been diagnosed with any mental illness

3. At least 8 years of formal education

4. Those who score less than 11 on the BDI

4.2.3 Exclusion criteria for patients

1. Patients with any co-morbid mental illnesses or disorders

2. History of head injury severe enough to cause concussion or memory loss

3. History of ECT in the past 6 months

4. History of chronic illicit substance use

5. History of epilepsy
6. History of chronic alcoholism
7. History of stroke

4.2.4 Exclusion criteria for healthy subjects

1. History of being diagnosed with any mental illness or disorder
2. History of head injury severe enough to cause concussion or memory loss
3. History of chronic illicit substance use
4. History of epilepsy
5. History of chronic alcoholism
6. History of stroke

4.3 Study duration

This study was conducted over a period of 5 months, from January 2017 until May 2017.

4.4 Sample Size Calculation

The sample size was calculated using the following formula, using β of 0.2, or power of 80, and α of 0.05, and Θ of 7.84.

$$n = 2\theta[\frac{\sigma^2}{(\mu_t - \mu_c)^2}]$$

In this formula, σ is the standard deviation of the population with the illness as referenced from previous studies. The study used was the one done by Sanchez-Morla et al. which compared cognitive functions in euthymic bipolar disorder patients, with patients with stable schizophrenia and healthy subjects (Sánchez-Morla et al., 2009). They used a comprehensive battery of neurocognitive tests, among which trail making test B (TMT B) and reverse digit span were used.

Based on this study, the standard deviation (SD) for patients with schizophrenia in the TMT B was 125.4, while the mean of the diseased population (μ_t), was 198.83; and the mean of the healthy population (μ_c) was 86.8. Given the numbers, the sample size required for patients with schizophrenia would be 19.6 (20). For bipolar disorder, the standard deviation was 111.5, with the mean of the bipolar population being 168.5. The sample size would thus be 29.

To calculate the sample size using the reverse digit span, the SD for schizophrenia patients was 1.9. The mean for the diseased population was 4.5, while the control group was 5.91. The sample size calculated was 28. The SD for bipolar patients was also 1.9, and the mean was 4.9. The sample size was thus 55. The researcher thus aimed to enrol 60 patients with bipolar disorder, as well as 60 with stable schizophrenia and 60 healthy subjects.

4.5 Study Procedure

A list of inclusion and exclusion criteria for subjects was placed in all the rooms of the outpatient clinic of the department of psychological medicine. Patients who consented to participate in the study were referred to the researcher. Healthy subjects were selected from hospital staff. The subjects who were included for the study according to the inclusion and exclusion criteria were given an information sheet

regarding the study. They were also assured of their anonymity and that confidentiality would be maintained for the data obtained. If the subject was not fit to give consent, consent was obtained from the subject's relatives. Data collection was through clinical patient interview and with the use of study instruments as noted below.

4.6 Study Instruments

This study employed the use of seven tools and questionnaires for data collection for the patient subjects, and six for control subjects. For both the control and patient subjects, the tools included were a demographic data questionnaire, Beck's depression inventory (BDI), the Perceived Deficits Questionnaire (PDQ), Trail Making Test Part A (TMT A), Trail Making Test Part B (TMT B) and Digit Span Test.

For patients with schizophrenia, an additional test of Brief Psychiatric Rating Scale (BPRS) was used to determine their illness stability state. For patients with bipolar disorder, an additional test of Young Mania Rating Scale (YMRS) was used to ascertain stability.

4.6.1 Demographic data questionnaire (Appendix E)

The researcher developed a demographic data questionnaire that would have questions to obtain demographic data, as well as questions that would filter out participants that had any of the exclusion factors. The demographic data obtained were details such as age, gender, ethnicity, marital status, years of formal education, and employment status. The age of more than 55 was used as an exclusion point to avoid silent strokes (Trivedi et al., 2007). Participants with a history of other mental illnesses,

including learning disabilities and other neurodevelopmental disorders were also excluded.

Other questions included were such as history of mental illness, duration of mental illness, history of electroconvulsive therapy in the last 6 months, history of head injury with loss of consciousness of more than half an hour, history of diagnosis of epilepsy, chronic alcohol and substance use, as well as history of stroke, were used to exclude participants with any of the exclusion criteria.

4.6.2 Beck's Depression Inventory (BDI) (Appendix F and G)

The BDI was included for both patients and healthy subjects as the researcher wanted to ensure that none of the subjects were clinically depressed, since it has been shown that depression causes cognitive deficits (Goodwin, 1997). The BDI is a widely used and well-accepted tool for the measurement of depressive symptoms (Beck et al., 1996). Although it is a self-administered scale, the benefit of using this scale is that it can be administered orally to those with reading or concentration difficulties by the examiner (Beck et al., 1996). Not only that, it has been translated to and validated in Malay (Muhktar & Oei, 2008).

4.6.3 Brief Psychiatric Rating Scale (BPRS) (Appendix H)

This psychometric test was used only in the schizophrenia group to ascertain stability status of the illness. It was developed by Overall and Gorham in the 1950's-60's as a tool for rapid evaluation of psychiatric patients with comprehensive coverage of the patient's current symptomology, thus providing a view of the patient's current mental status, and also aims to monitor changes with treatment. It consists of 18

separate items but 10 main constructs, the severity of which can be rated by the examiner according to a likert scale that ranges from absent (scored as 1) to extremely severe (scored as 7). The total score is summed for an overall view of the illness status. The authors recommend it for use when speed, economy and efficiency are the main considerations (Overall & Gorham, 1962). It has also been found to be a reliable, valid and sensitive tool, but with unclearly defined cut-off points (Leucht et al., 2005). Hence Leucht and colleagues have compared it to the Clinical Global Impression (CGI) scale and found that the cut-off point of 31 (for BPRS) corresponded to "mildly ill" on the CGI.

4.6.4 Young Mania Rating Scale (YMRS) (Appendix I)

The author chose the YMRS as it is one of the most widely-used for the assessment of manic symptoms and easily administered. It has also been found to be valid, reliable and sensitive (Young et al., 1978). The YMRS has 11 items to assess the patient's condition over the last 48 hours. Each item can also be rated for severity. The sum of the individual scores is the final score. A score of 12 or more indicates mania while a score of 7 and below indicates a stable state (Lukasiewicz et al., 2013).

4.6.5 Perceived Deficits Questionnaire (PDQ) (Appendix J)

The PDQ was developed as a component in the Multiple Sclerosis Quality of Life Inventory (MSQLI) (Ritvo et al., 1997). It is a subjective tool for the assessment of the patient's perception of his or her own cognitive ability. According to the user's manual (Ritvo et al., 1997), patient's perceptions of their own cognitive functions may not correspond with objectively–measured functions; hence scores on this scale need to

be interpreted cautiously. The manual also encourages the use of objective neuropsychological measures for the assessment of cognitive function. Administration of the PDQ is per the response format given and the items are answered based on the initial question of "**During the *past 4 weeks,* how often did you . . .",** with most of the items being self-explanatory. The possible responses are never, rarely, sometimes, often, and almost always. Only for item 19, whereby if the person doing the PDQ is not taking any medication, should the response be scored as 0 or never.

The PDQ was designed so that there would be 5 questions to measure four features of cognitive function. The cognitive functions assessed were *Attention/Concentration, Retrospective Memory, Prospective Memory,* and *Planning/Organization.* Items 1, 5, 9, 13, and 17 are for *Attention/Concentration;* items 2, 6, 10, 14, 18 are for *Retrospective Memory*; items 3, 7, 11, 15, 19 are for *Prospective Memory*; and items 4, 8, 12, 16, 20 are for *Planning/Organization*. The details of each item can be seen from the questionnaire in Appendix G.

Sullivan et.al. reported scoring procedures for the 4 subscales given (Sullivan et al., 1990), but the MSQLI advises caution on interpreting subscale scores as factorial analysis done by the MSQLI did not yield separate factors. Instead the total score should be added together, which would range from 0-80.

4.6.6 Trail-making Test (TMT) (Appendix K)

The TMT is one of the most widely-used neuropsychological tests, as it is simple to administer and is freely available (Tombaugh, 2004). It is used to assess scanning and visual search, mental flexibility, speed of processing, and executive functions (Tombaugh, 2004). It was originally designed as part of the United States' Army Individual Test Battery (Army, 1944) as an intelligence test. It consists of 2 parts,

A and B. TMT A requires lines to be drawn to sequentially connect 25 encircled numbers that are distributed on a single piece of paper. The task is similar for TMT B except that the individual must alternate between letters and numbers (e.g., 1 to A, 2 to B and 3 to C, etc.). They are both scored by measuring the amount of time taken to complete the task. Ultimately part A is used to assess attention (Medalia et al., 1998) and cognitive processing speed (Bhatia et al., 2007), while part B is used to examine executive functioning (Tombaugh, 2004). The TMT has been shown to be sensitive to detect cognitive impairment in Alzheimer's disease and other dementias (Cahn et al., 1995).

4.6.7 Digit Span (Appendix L)

The digit span is a neuropsychological tool used to measure working memory (in particular, its number storage capacity) (Turner & Engle, 1989). It consists of 2 parts – digit span forward and digit span backwards (or reverse). In digit span forwards, the subjects are made to listen to a sequence of numbers and are asked to recall the sequence exactly, with an additional digit added after every 2 tries. In digit span backwards, the subject listens to the sequence given and is made to recall the numbers in reverse order, also with increasingly longer sequences. The subject's span (ability) is the longest number of digits accurately recalled (either way). The forward digit span (DF) tests attention, auditory memory (short-term), sequencing and verbal expression (Hale et al., 2002), while the backwards digit span (DB) is more sensitive for working memory (Wilde & Strauss, 2002).

The digit span is one of the most commonly used tests for memory span, because performance on this test is not affected by factors such as complexity, frequency of appearance in daily life, and semantics (Turner & Engle, 1989). Verbal

working memory is also one of the factors underlying intelligence, thus it is a component of the Weschler Adult Intelligence Scale (WAIS) (Wilde & Strauss, 2002). Performance on the digit span is associated with learning languages; thus improving the verbal memory may therefore aid in mastering a new language (Schroeder et al., 2012).

4.7 Data Analysis

Data analysis was performed using the 23rd version of the Statistical Packages for Social Sciences (SPSS). The data was checked and cleaned prior to analysis.

Sociodemographic data was summarized using descriptive statistics. Continuous variables (e.g., years of education, duration of illness) were described using measures of central tendency (mean) and dispersion (standard deviation). Categorical variables were described in percentages and frequencies. The normality of the data was checked using the Shapiro-Wilk normality test. Non-normally distributed results were analysed using non-parametric tests. Thus comparison of performance on the cognitive tests was analysed using Mann-Whitney U tests, to detect differences in the performance on the tests between groups.

Prior to association analyses, Receiver Operating Characteristic (ROC) Curve was plotted to determine optimal cut off points. The cut off points were determined based on the optimal level of sensitivity and specificity of the cognitive assessment tools used in this study. The data for each tool were obtained from the patient group versus the healthy group (either the schizophrenic or bipolar group). Those tests that were found to be sensitive in detecting cognitive impairment were thereafter analysed using the chi-square test to determine associations between sociodemographic characteristics and cognitive impairment. When the expected count was less than 5, Fisher's exact test was used instead of the chi-square test.

In single factor (univariate) analysis, any sociodemographic characteristics that were found to be significantly associated with cognitive impairment in the patient group were later analysed using logistic (multivariate) regression to determine the factors that might affect the likelihood of cognitive impairment. The level of significance was set at 0.05 for all analyses.

4.8 Ethical considerations

This study's proposal was approved by the Medical Ethics Committee of Universiti Malaya Medical Centre (UMMC). The registration number was MREC 2016121-4656. Written informed consent was obtained from all the participants prior to recruitment. Confidentiality was assured as a coding system was used to identify the subjects.

CHAPTER 5

RESULTS

5.1 Socio-demographic data

Table 5.1 shows the demographic characteristics of the study participants. A total of 154 participants were included in this study – 57 patients with stable schizophrenia, 40 with euthymic bipolar disorder, and 57 healthy subjects. The mean age of the participants with schizophrenia was 38.44 with a standard deviation (SD) of 9.791. The mean age of those with bipolar disorder was 37.22 with SD of 9.547, and the mean age of the healthy group was 30.02 with SD of 7.465. In summary, patients with schizophrenia were older than patients with bipolar disorder by about one year, and older than the healthy group by about 8 years. The sex of the participants were roughly equally divided, with 56.1% of the schizophrenia group being male (n=32) and 43.9% female (n=25). 57.5% of the bipolar group was male (n=23), and 42.5% was female (n=17). For the healthy group there were slightly more females (56.1%, n=32) than males (43.9%, n=25).

The ethnicities of the participants are as follows: for the schizophrenia group, 21.1% (n=12) was Malay, 54.5% (n=31) was Chinese, and 24.6% (n=14) was Indian. For the bipolar group, 27.5% was Malay (n=11), 47.5% (n=19) was Chinese, 22.5% (n=9) was Indian and one (2.5%) was a foreign national. Of the healthy group, 42.1% (n=24) were of Malay and Chinese ethnicity (respectively), 10.5% (n=6) was Indian and 5.3% (n=3) was of other races. Thus the majority of participants was Chinese, followed by those of Malay and Indian ethnicity.

Of the schizophrenia group, 78.8% (n=45) was single, 15.8% (n=9) was married while 5.3% (n=3) was divorced. In the bipolar group, 47.5% (n=19) was married and the same amount were single; 5% (n=2) were divorced. 57.9% (n=33) of the healthy group was single, 23 were married (40.4%) and one was divorced (1.8%). With regards to years of education, the schizophrenia group's mean was 11.61, with SD of 2.420; the bipolar group's was 13.29 (SD=2.815), and the healthy group's was 16.75 with a SD of 2.286.

With regards to occupation, 52.6% (n=30) of the schizophrenia group was employed, while 72.5% (n=29) of the bipolar group and 100% (n=57) of the healthy group was employed. For the patient population, the mean duration of illness for the schizophrenia group was 13.32 years with a SD of 8.578 and 12.17 years for the bipolar group with a SD of 8.323.

TABLE 5.1

Sociodemographic data of the schizophrenia group (Sch), bipolar (Bi) patients and healthy (H) group.

Demographic	Schizophrenia (n = 57)	Bipolar (n = 40)	Healthy (n = 57)
Age, mean (sd)	38.44 (9.791)	37.22 (9.547)	30.02 (7.465)
Gender, n (%)			
Male	32 (56.1)	23 (57.5)	25 (43.9)
Female	25 (43.9)	17 (42.5)	32 (56.1)
Ethnicity, n (%)			
Malay	12 (21.1)	11 (27.5)	24 (42.1)
Chinese	31 (54.5)	19 (47.5)	24 (42.1)
Indian	14 (24.6)	9 (22.5)	6 (10.5)
Others	0	1 (2.5)	3 (5.3)
Marital status, n (%)			
Single	45 (78.9)	19 (47.5)	33 (57.9)
Married	9 (15.8)	19 (47.5)	23 (40.4)
Divorced	3 (5.3)	2 (5.0)	1 (1.8)
Years of education, mean (sd)	11.61 (2.420)	13.29 (2.815)	16.75 (2.286)
Occupation, n (%)			
Yes	30 (52.6)	29 (72.5)	57 (100.0)
No	27 (47.4)	11 (27.5)	0
Duration of illness (years) mean (sd)	13.32 (8.578)	12.17 (8.323)	0

5.2 Response of the participants in the PDQ

Table 5.2A is a comparison of the response of the schizophrenia group vs the healthy group in each item of the PDQ. The items are summarized in short for convenience. The items were all questions in the form of "During the past four weeks, how often did you……" Item 19 was regarding forgetting to take medication. The control group was scored as 0 as per the instructions of the PDQ (Ritvo et al., 1997). For items 4, 5, 7, 8, 17, 19 and 20, there were statistically different answers given by the schizophrenia group compared to the control group. Items 4, 8 and 20 are those from the domain of planning/organization. Items 5 and 17 are from the domain of attention and concentration, while items 7 and 19 are from the domain of prospective memory.

Table 5.2A: Perceived deficits questionnaire (PDQ) and its domains, mean (sd) of the Schizophrenia (Sch) group compared to the Healthy group (H)

PDQ items	Schizophrenia (Sch) (n = 57)	Healthy (H) (n = 57)	p value Sch vs H (2-tailed)
1 Lose train of thought while speaking	1.02 (1.329)	0.91 (0.786)	0.592
2 Have difficulty remembering names	1.19 (1.493)	0.96 (0.865)	0.878
3 Forget purpose of entering room	0.70 (1.034)	0.72 (0.750)	0.341
4 Have trouble organizing things	0.75 (1.272)	0.84 (0.774)	< 0.05
5 Have trouble concentrating during a conversation	0.86 (1.156)	1.18 (0.782)	< 0.05
6 Forget if already done something	0.95 (1.156)	1.00 (0.732)	0.300
7 Miss appointments and meetings	0.33 (0.764)	0.63 (0.723)	< 0.01
8 Difficulty planning daily activities	0.47 (1.120)	0.77 (0.780)	< 0.01
9 Have trouble concentrating on watching TV or reading a book	0.67 (1.107)	0.82 (0.869)	0.080
10 Forget deeds of the night before	0.98 (1.275)	0.63 (0.771)	0.375
11 Forget the date	1.46 (1.402)	1.12 (0.946)	0.334
12 Have trouble getting started on activities	1.14 (1.394)	1.23 (1.086)	0.315
13 Find mind drifting	1.04 (1.239)	1.35 (0.954)	0.072
14 Forget what was talked about after a phone conversation	0.72 (1.082)	0.54 (0.600)	0.800
15 Forget to do things like turn off stove or turn on alarm clock	0.68 (1.121)	0.51 (0.658)	0.828
16 Feel like mind went totally blank	0.91 (1.272)	0.65 (0.668)	0.911
17 Have trouble holding phone numbers in head	1.86 (1.529)	1.21 (1.048)	< 0.05
18 Forget what you did last weekend	1.23 (1.488)	0.89 (0.920)	0.625
19 Forget to take medication	0.40 (0.821)	0	< 0.01
20 Have trouble making decisions	0.67 (1.107)	1.21 (1.013)	< 0.01
Domain			
(Attention/Concentration): PDQ (1+5+9+13+17)	5.44 (4.110)	5.47 (3.163)	0.813
(Retrospective Memory): PDQ (2+6+10+14+18)	5.07 (4.371)	4.04 (2.884)	0.420
(Prospective Memory): PDQ (3+7+11+15+19)	3.58 (2.666)	2.98 (2.134)	0.360
(Planning/Organization): PDQ (4+8+12+16+20)	3.95 (4.228)	4.70 (3.229)	< 0.05
Total	18.04 (12.656)	17.19 (9.986)	0.955

Table 5.2B is a comparison of the response of the bipolar group vs the healthy group. Only items 11 and 19 were statistically different and they are both features of prospective memory.

Table 5.2B: Perceived deficits questionnaire (PDQ) and its domains, mean (sd) of Bipolar disorder patients (Bi) compared to the healthy group (H).

PDQ items	Bipolar (Bi) (n = 40)	Healthy (H) (n = 57)	p value Bi vs H (2-tailed)
1 Lose train of thought while speaking	0.72 (1.062)	0.91 (0.786)	0.104
2 Have difficulty remembering names	1.15 (1.331)	0.96 (0.865)	0.902
3 Forget purpose of entering room	0.98 (1.097)	0.72 (0.750)	0.450
4 Have trouble organizing things	0.98 (1.209)	0.84 (0.774)	0.864
5 Have trouble concentrating during a conversation	1.23 (1.291)	1.18 (0.782)	0.723
6 Forget if already done something	0.85 (0.864)	1.00 (0.732)	0.332
7 Miss appointments and meetings	0.43 (0.675)	0.63 (0.723)	0.110
8 Difficulty planning daily activities	0.63 (0.897)	0.77 (0.780)	0.205
9 Have trouble concentrating on watching TV or reading a book	0.88 (1.305)	0.82 (0.869)	0.451
10 Forget deeds of the night before	0.88 (1.137)	0.63 (0.771)	0.596
11 Forget the date	2.03 (1.330)	1.12 (0.946)	< 0.01
12 Have trouble getting started on activities	1.15 (1.189)	1.23 (1.086)	0.614
13 Find mind drifting	1.25 (1.171)	1.35 (0.954)	0.546
14 Forget what was talked about after a phone conversation	0.48 (0.784)	0.54 (0.600)	0.248
15 Forget to do things like turn off stove or turn on alarm clock	0.60 (0.928)	0.51 (0.658)	0.899
16 Feel like mind went totally blank	0.70 (0.939)	0.65 (0.668)	0.757
17 Have trouble holding phone numbers in head	1.35 (1.477)	1.21 (1.048)	0.997
18 Forget what you did last weekend	1.22 (1.209)	0.89 (0.920)	0.231
19 Forget to take medication	0.67 (0.859)	0	< 0.01
20 Have trouble making decisions	1.33 (1.269)	1.21 (1.013)	0.861
Domain			
(Attention/Concentration): PDQ (1+5+9+13+17)	5.43 (4.169)	5.47 (3.163)	0.675
(Retrospective Memory): PDQ (2+6+10+14+18)	4.58 (3.768)	4.04 (2.884)	0.655
(Prospective Memory): PDQ (3+7+11+15+19)	4.70 (2.848)	2.98 (2.134)	< 0.01
(Planning/Organization): PDQ (4+8+12+16+20)	4.77 (3.786)	4.70 (3.229)	0.938
Total	19.33 (12.556)	17.19 (9.986)	0.490

Table 5.2C is a comparison of the response of the Schizophrenia group vs the bipolar group. The difference in scores for items 11, 19 and 20 were statistically significant. Items 11 and 19 are from the prospective memory domain, while item 20 is from the domain of planning and organization.

Table 5.2C: Perceived deficits questionnaire (PDQ) and its domains, mean (sd) of Schizophrenia compared to Bipolar disorder patients

PDQ	Schizophrenia (Sch) (n = 57)	Bipolar (Bi) (n = 40)	p value Sch vs Bi (2-tailed)
1 Lose train of thought while speaking	1.02 (1.329)	0.72 (1.062)	0.356
2 Have difficulty remembering names	1.19 (1.493)	1.15 (1.331)	0.956
3 Forget purpose of entering room	0.70 (1.034)	0.98 (1.097)	0.158
4 Have trouble organizing things	0.75 (1.272)	0.98 (1.209)	0.212
5 Have trouble concentrating during a conversation	0.86 (1.156)	1.23 (1.291)	0.140
6 Forget if already done something	0.95 (1.156)	0.85 (0.864)	0.975
7 Miss appointments and meetings	0.33 (0.764)	0.43 (0.675)	0.179
8 Difficulty planning daily activities	0.47 (1.120)	0.63 (0.897)	0.076
9 Have trouble concentrating on watching TV or reading a book	0.67 (1.107)	0.88 (1.305)	0.472
10 Forget deeds of the night before	0.98 (1.275)	0.88 (1.137)	0.819
11 Forget the date	1.46 (1.402)	2.03 (1.330)	< 0.05
12 Have trouble getting started on activities	1.14 (1.394)	1.15 (1.189)	0.676
13 Find mind drifting	1.04 (1.239)	1.25 (1.171)	0.313
14 Forget what was talked about after a phone conversation	0.72 (1.082)	0.48 (0.784)	0.418
15 Forget to do things like turn off stove or turn on alarm clock	0.68 (1.121)	0.60 (0.928)	0.986
16 Feel like mind went totally blank	0.91 (1.272)	0.70 (0.939)	0.673
17 Have trouble holding phone numbers in head	1.86 (1.529)	1.35 (1.477)	0.106
18 Forget what you did last weekend	1.23 (1.488)	1.22 (1.209)	0.701
19 Forget to take medication	0.40 (0.821)	0.67 (0.859)	< 0.05
20 Have trouble making decisions	0.67 (1.107)	1.33 (1.269)	< 0.01
Domain			
(Attention/Concentration): PDQ (1+5+9+13+17)	5.44 (4.110)	5.43 (4.169)	0.982
(Retrospective Memory): PDQ (2+6+10+14+18)	5.07 (4.371)	4.58 (3.768)	0.712
(Prospective Memory): PDQ (3+7+11+15+19)	3.58 (2.666)	4.70 (2.848)	< 0.05
(Planning/Organization): PDQ (4+8+12+16+20)	3.95 (4.228)	4.77 (3.786)	0.154
Total	18.04 (12.656)	19.48 (12.426)	0.475

5.3 Performance on the TMT

Table 5.3 is a comparison of the performance of all the participants in the Trail making tests (TMT). The mean amount of time taken by the schizophrenic group for TMT A was 48.93 seconds, with SD of 32.51; for the bipolar group was 34.51 seconds (SD=12.73), and for the healthy group was 23.98 seconds (SD 5.73). There was statistical significance in the difference in performance when comparing the schizophrenic group with the healthy group, bipolar with the healthy group, and also when comparing the schizophrenic group with the bipolar group; i.e., the schizophrenic group did poorer compared to both the bipolar group as well as the healthy group, and the bipolar group did worse than the healthy group.

For TMT B, the mean amount of time taken by the schizophrenic group was 116.67, with SD of 69.33, while for the bipolar group, the mean was 79.90, with SD of 42.82. The mean of time taken by the healthy group was 48.82 with SD of 15.75. Similarly there was statistical significance in the performance of the schizophrenic group vs the healthy group, and the bipolar vs the healthy subjects, as well as the schizophrenic group vs the bipolar group; i.e., the schizophrenic group also performed more poorly than the bipolar group as well as the healthy group, and the bipolar group performed worse than the healthy group.

Table 5.3: Trail making test (TMT) A and B, mean (sd)

TMT	Schizophrenia (n = 57)	Bipolar (n = 40)	Healthy (n = 57)	p value Sch vs H	p value Bi vs H	p value Sch vs Bi
A	48.93 (32.51)	34.51 (12.73)	23.98 (5.73)	< 0.01	< 0.01	< 0.01
B	116.67 (69.33)	79.90 (42.82)	48.82 (15.75)	< 0.01	< 0.01	< 0.01

Sch: Schizophrenia
Bi: Bipolar disorder
H: Healthy participants

5.4 Performance on the digit span

Table 5.4 is a comparison of the performance of all the participants in the digit span task. The mean number of digits that participants from the schizophrenic group could recall in the digit span forward task was 5.84 (SD of 1.36), while for the bipolar group, the mean number of digits recalled was 6.43 (SD of 1.52) and for the healthy group, the mean number of digits recalled was 6.51 (SD=1.31). The p values were obtained using the Mann-Whitney U test. The difference in the schizophrenic group's performance was statistically significant when compared to the healthy group's, and also when compared to the bipolar group's performance; i.e., the schizophrenic group performed more poorly than the healthy group as well as the bipolar group, but the bipolar group performed similarly to the healthy group.

For the digit span reverse, the mean number of digits recalled by the schizophrenic group was 3.58 with SD of 1.05, 4.28 (sd=1.01) for the bipolar group, and 5.39 (SD=1.25) for the healthy group. There was statistical significance in the difference in performance in the schizophrenic vs healthy group, bipolar vs healthy subjects, as well as schizophrenic vs bipolar group; i.e., the schizophrenic group performed more poorly than the healthy group as well as the bipolar group, and the bipolar group performed worse than the healthy subjects.

Table 5.4: Digit span task (DST) forward (F) and reverse (R), mean (sd)

DST	Schizophrenia (n = 57)	Bipolar (n = 40)	Healthy (n = 57)	p value Sch vs H	p value Bi vs H	p value Sch vs Bi
F	5.84 (1.36)	6.43 (1.52)	6.51 (1.31)	< 0.05	0.857	≤ 0.05
R	3.58 (1.05)	4.28 (1.01)	5.39 (1.25)	< 0.01	< 0.01	< 0.01

Sch: Schizophrenia
Bi: Bipolar disorder
H: Healthy subjects

5.5 Correlation between PDQ (Domains 1-4), TMT(A), TMT(B), DST(F) and DST(R)

Table 5.5 is a comparison of the performance of all the participants on all the cognitive tests. The PDQ was not correlated with any of the other cognitive tests. However the TMT and the Digit span tests, both forward and reverse, were strongly correlated to each other, at the significance level of <0.01. Both the trail making tests were positively correlated with each other and negatively correlated with the digit span tests, and vice versa.

Table 5.5: Correlation between PDQ (Domains 1-4), TMT(A), TMT(B), DST(F) and DST(R)

	PDQ	Domain 1	Domain 2	Domain 3	Domain 4	TMT(A)	TMT(B)	DST(F)	DST(R)
PDQ	1.000	0.884**	0.828**	0.780**	0.828**	0.011	-0.068	-0.068	-0.022
Domain 1	0.884**	1.000	0.641**	0.613**	0.682**	0.051	-0.072	-0.059	0.020
Domain 2	0.828**	0.641**	1.000	0.584**	0.549**	0.028	-0.041	-0.075	-0.067
Domain 3	0.780**	0.613**	0.584**	1.000	0.550**	0.046	0.027	-0.070	-0.105
Domain 4	0.828**	0.682**	0.549**	0.550**	1.000	-0.116	-0.150	0.012	0.082
TMT(A)	0.011	0.051	0.028	0.046	-0.116	1.000	0.795**	-0.289**	-0.622**
TMT(B)	-0.068	-0.072	-0.041	0.027	-0.150	0.795**	1.000	-0.370**	-0.626**
DST(F)	-0.068	-0.059	-0.075	-0.070	0.012	-0.289**	-0.370**	1.000	0.351**
DST(R)	-0.022	0.020	-0.067	-0.105	0.082	-0.622**	-0.626**	0.351**	1.000

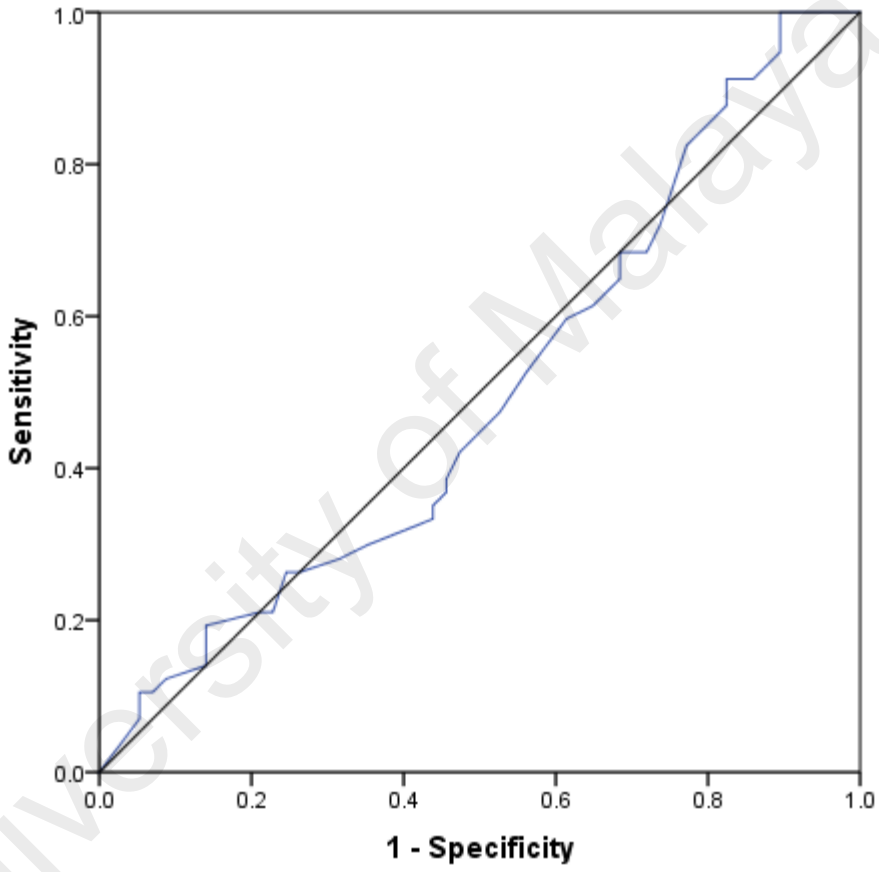
** Correlation is significant at the 0.01 level (2-tailed)

5.6 Sensitivity, specificity, ROC and AUC of the assessment tools

ROC curves were plotted to determine the optimal cut off points used in this study.

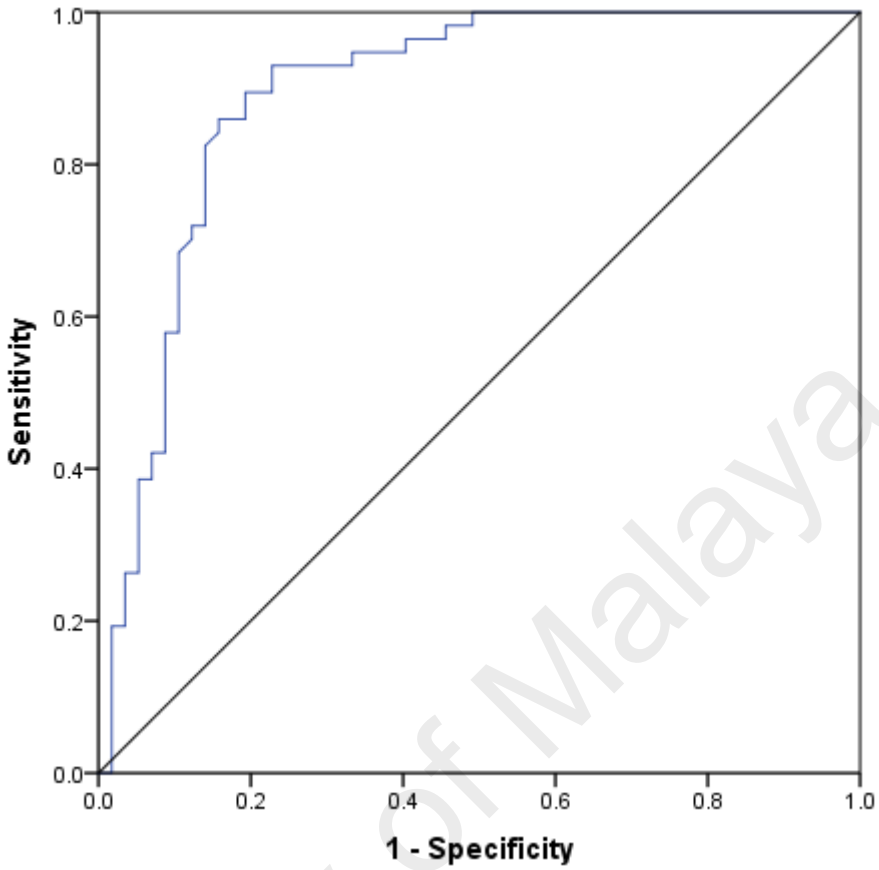
5.6.1 Schizophrenia group vs healthy subjects

Figure 5.6.1A Receiver operating characteristics (ROC) curve for the PDQ.



The area under the curve (AUC) is 0.497 (around 0.5), thus it is impossible to assess the sensitivity or specificity of the PDQ, and no cut-off points were obtained.

Figure 5.6.1B Receiver operating characteristics (ROC) curve for the TMT A.



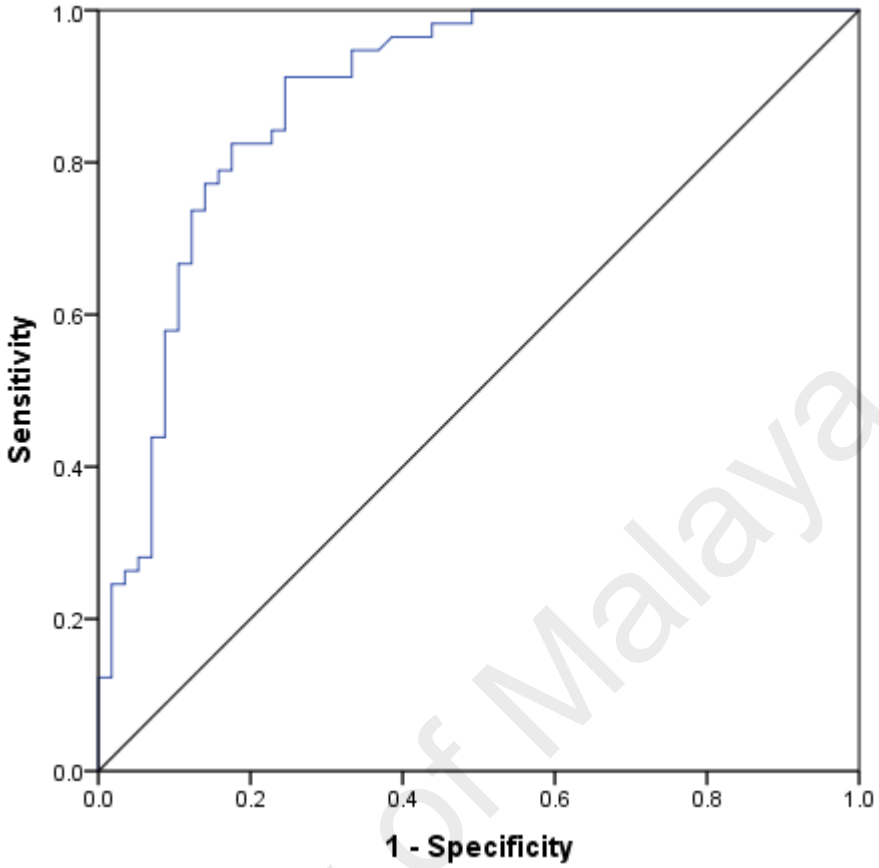
The AUC is 0.892. Table 5.6 shows the coordinates of sensitivity and specificity of the performance on the TMT A. The cut-off point is 29.05 which has a sensitiviy of 84.2% and specificity of 86%.

Table 5.6: The coordinates of sensitivity and specificity of the performance on TMT A.

Coordinates of the Curve

Test Result Variable(s):	TMT_A	
Positive if Greater Than or Equal To[a]	Sensitivity	Specificity
28.7150	.860	0.825
28.9000	.842	0.842
29.0500	**.842**	**0.860**
29.1450	.825	0.860
29.5950	.807	0.860

Figure 5.6.1C Receiver operating characteristics (ROC) curve for the TMT B.



The AUC is 0.885. Table 5.7 shows the coordinates of sensitivity and specificity of the performance on the TMT B. The cut-off point is 58.425 which has a sensitiviy of 82.5% and specificity of 82.5%.

Table 5.7: The coordinates of sensitivity and specificity of the performance on TMT B

Coordinates of the Curve

Positive if Less Than or Equal To[a]	Sensitivity	specificity
57.8600	0.789	0.825
58.1750	0.807	0.825
58.4250	**0.825**	**0.825**
59.3350	0.825	0.807
60.0150	0.825	0.789

Figure 5.6.1D Receiver operating characteristics (ROC) curve for the Digit Span Forward.

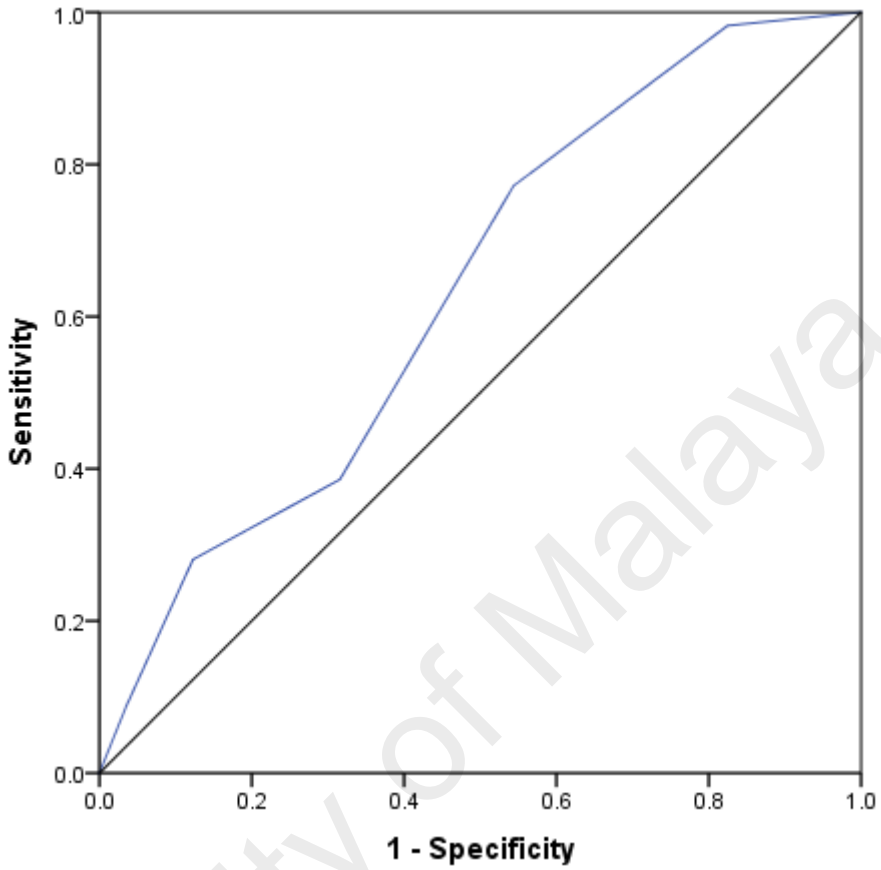


Table 5.8: The coordinates of sensitivity and specificity of the performance on the Digit Span Forward.

Coordinates of the Curve
Test Result Variable(s):

Positive if Less Than or Equal To[a]	Sensitivity	Specificity
3.000	0.000	1.000
4.500	.175	0.982
5.500	**.456**	**0.772**
6.500	.684	0.386
7.500	.877	0.281
8.500	.965	0.088
10.000	1.000	0.000

Table 5.8 shows the coordinates of sensitivity and specificity of the performance on the Digit Span Forward Task. The cut-off point is 5.5 at the sensitivity of 45.6% and specificity of 77.2%. The area under the ROC curve of Figure 5.6.1D is 0.634.

Figure 5.6.1E Receiver operating characteristics (ROC) curve for the Digit Span Reverse.

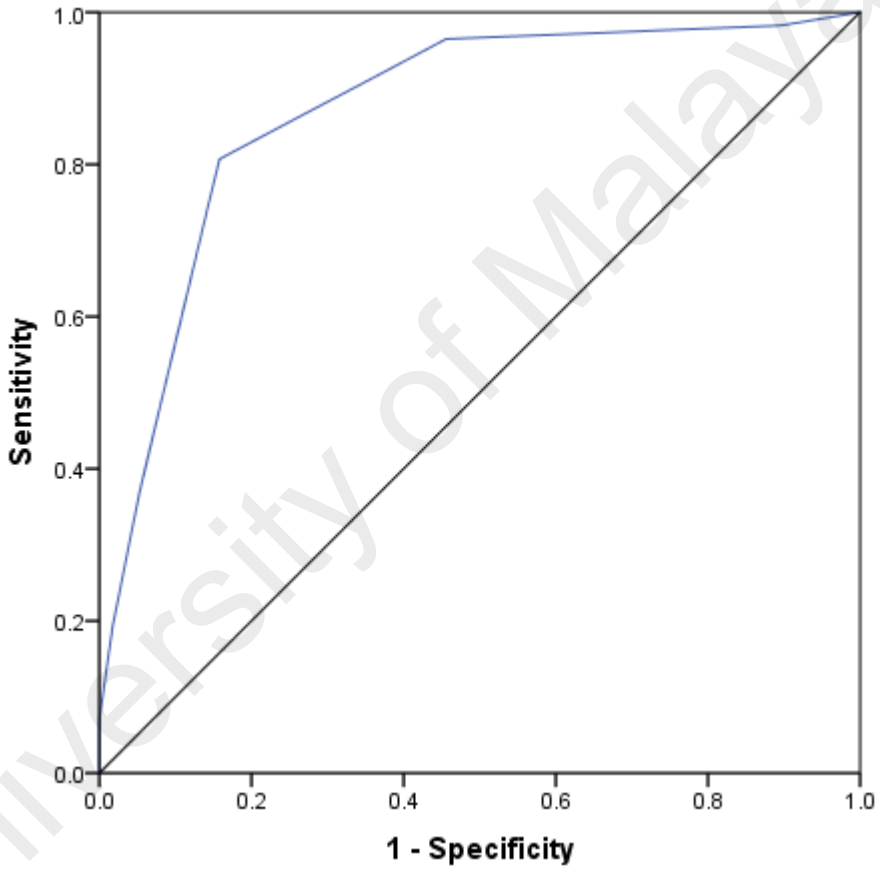


Table 5.9: The coordinates of sensitivity and specificity of the performance on the Digit Span Reverse.

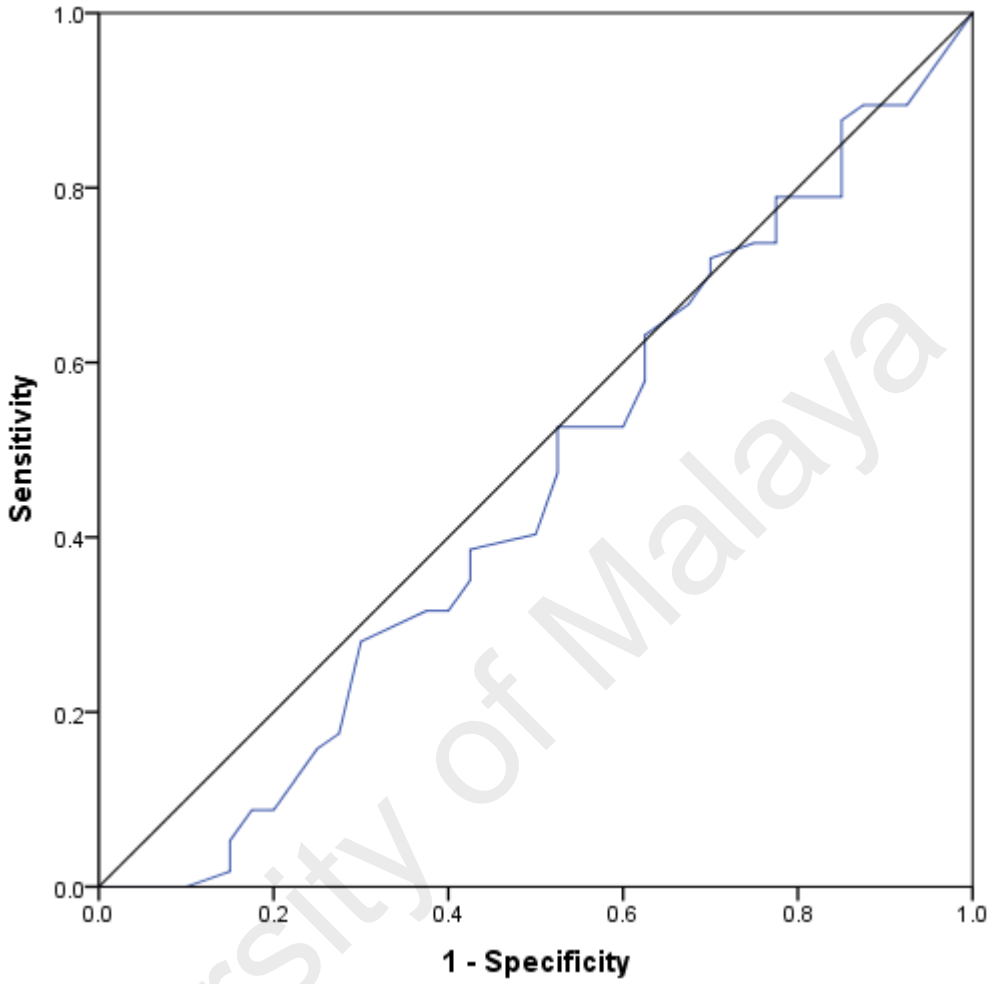
Coordinates of the Curve

Test Result Variable(s):		
Positive if Less Than or Equal To[a]	Sensitivity	Specificity
1.000	0.000	1.000
2.500	.105	0.982
3.500	.544	0.965
4.500	**.842**	**0.807**
5.500	.947	0.368
6.500	.982	0.193
7.500	1.000	0.070
9.000	1.000	0.000

Table 5.9 shows the coordinates of sensitivity and specificity of the performance on the Digit Span Reverse Task. The cut-off point is 4.5 at the sensitivity of 84.2% and specificity of 80.7%. The area under the ROC curve of Figure 5.6.1E is 0.87.

5.6.2 Bipolar group vs Healthy Subjects

Figure 5.6.2A Receiver operating characteristics (ROC) curve for the PDQ.



The AUC is 0.454 (around 0.5), thus it is impossible to assess the sensitivity or specificity of the PDQ, and no cut-off points were obtained.

Figure 5.6.2B Receiver operating characteristics (ROC) curve for the TMT A.

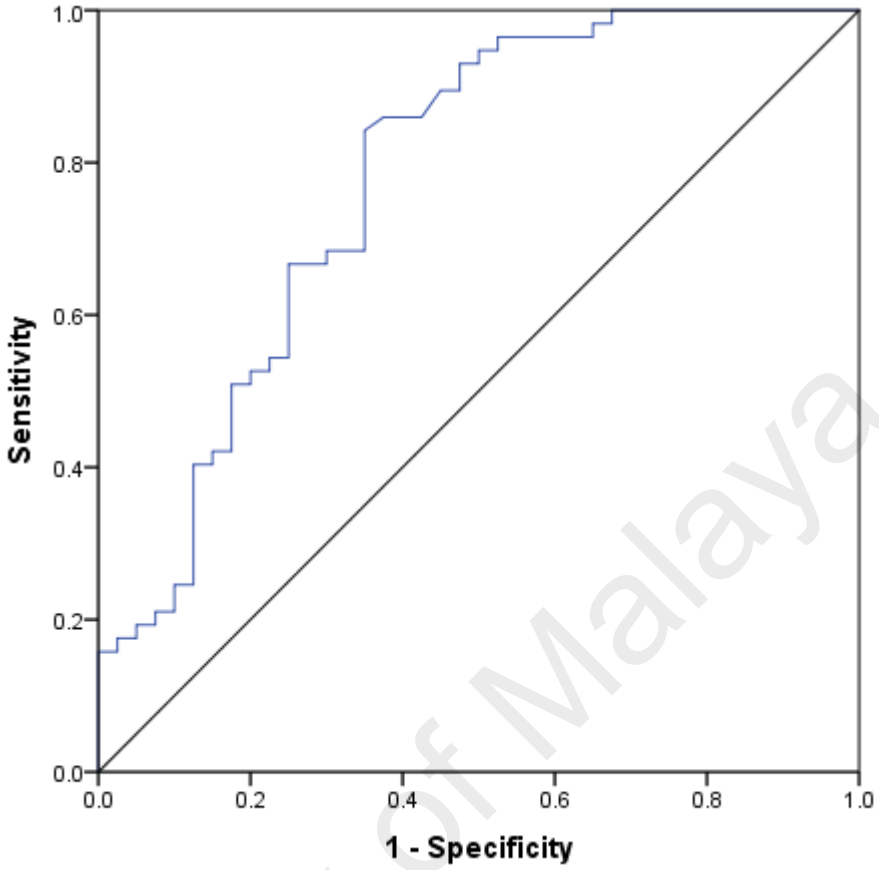


Table 5.10: The coordinates of sensitivity and specificity of the performance on TMT A

Coordinates of the Curve

Positive if Less Than or Equal To[a]	Sensitivity	Specificity
26.0850	0.667	0.725
26.2900	0.667	0.700
26.4500	**0.684**	**0.700**
26.7350	0.684	0.675
26.9750	0.684	0.650

Table 5.10 shows the coordinates of sensitivity and specificity of the performance on the TMT A. The cut-off point is 26.45 at the sensitivity of 68.4% and specificity of 70%. The area under the ROC curve of Figure 5.6.2C is 0.778.

Figure 5.6.2C Receiver operating characteristics (ROC) curve for the TMT B.

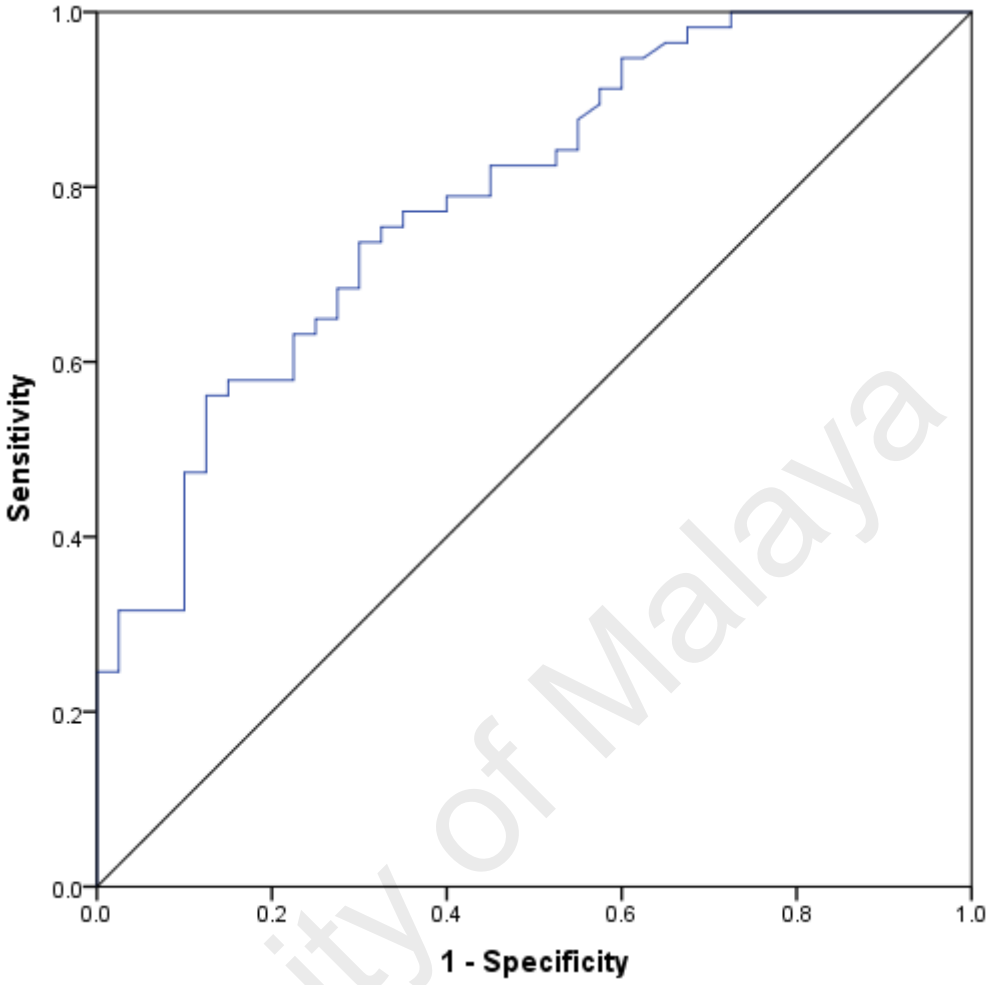


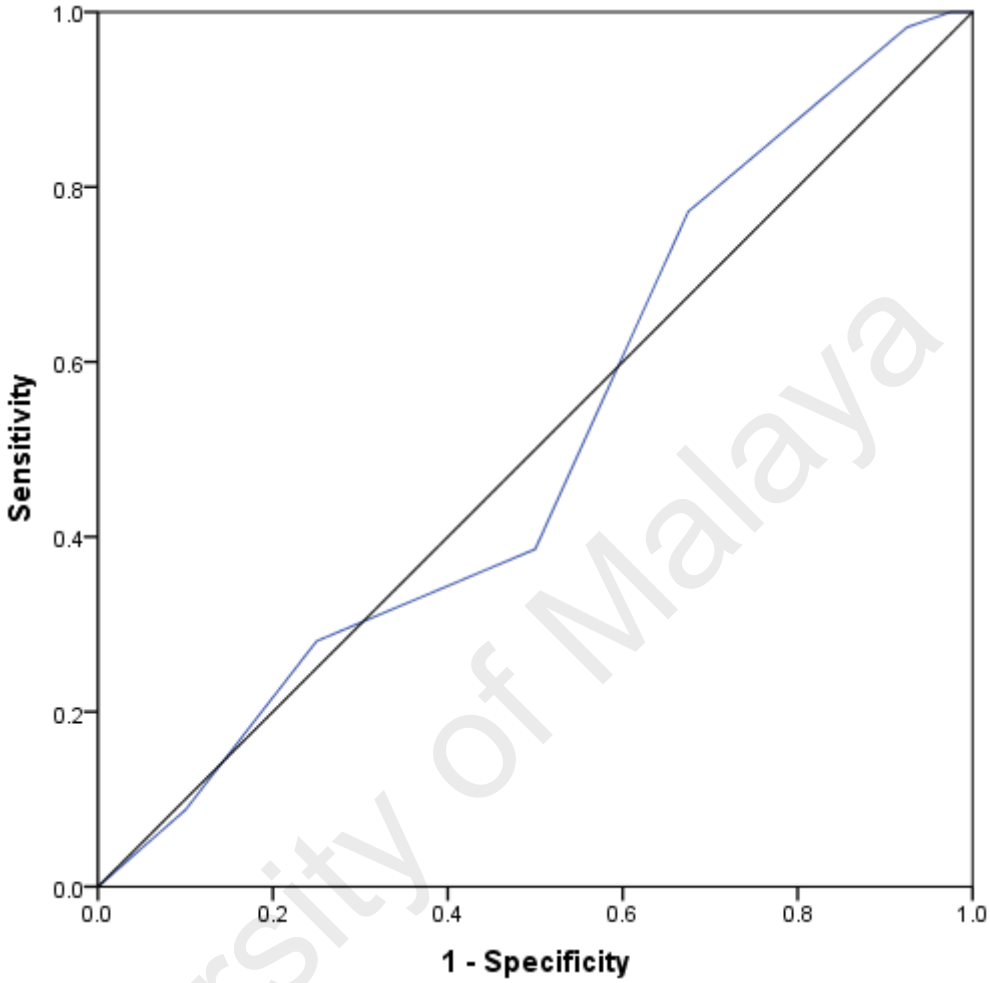
Table 5.11: The coordinates of sensitivity and specificity of the performance on TMT B

Coordinates of the Curve

Positive if Less Than or Equal To[a]	Sensitivity	Specificity
54.7850	0.702	0.700
54.9250	0.719	0.700
55.0750	**0.737**	**0.700**
55.5850	0.737	0.675
56.0600	0.754	0.675

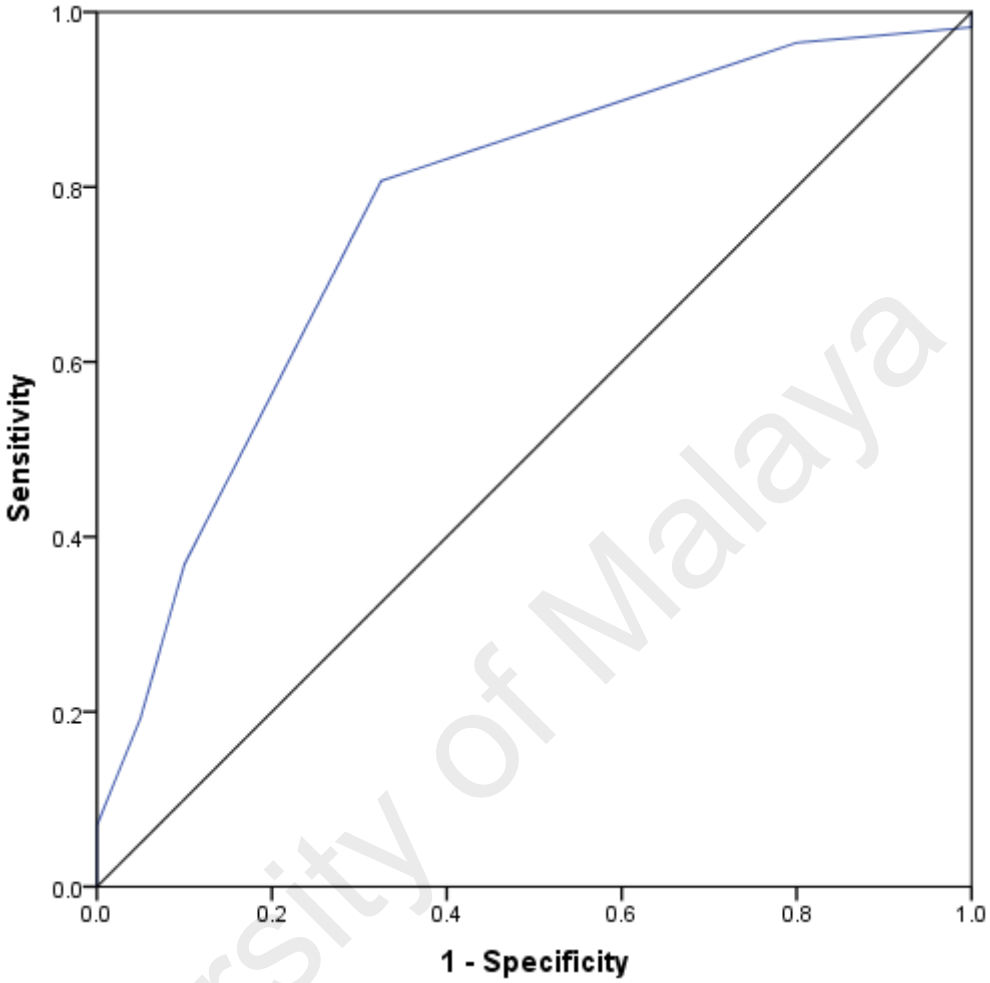
Table 5.11 shows the coordinates of sensitivity and specificity of the performance on the TMT B. The cut-off point is 55.0755 at the sensitivity of 73.7% and specificity of 70%. The area under the ROC curve of Figure 5.6.2C is 0.787.

Figure 5.6.2D Receiver operating characteristics (ROC) curve for the Digit Span Forward.



The area under the curve is 0.511, thus it is impossible to assess the sensitivity or specificity of the Digit span forward, and no cut-off points were obtained.

Figure 5.6.2E Receiver operating characteristics (ROC) curve for the Digit Span Reverse.



The area under the ROC curve in Figure 5.6.2E is 0.768. Table 5.12 shows the coordinates of sensitivity and specificity of the performance on the digit span reverse test. The optimal cut off point is 4.5 as it has the highest sensitivity of 80.7% and specificity of 67.5%.

Table 5.12: The coordinates of sensitivity and specificity of the performance on the Digit Span Reverse.

Coordinates of the Curve

Test Result Variable(s):		
Positive if Greater Than or Equal To[a]	Sensitivity	Specificity
1.000	1.000	0.000
2.500	0.982	0.000
3.500	0.965	0.200
4.500	**0.807**	**0.675**
5.500	0.368	0.900
6.500	0.193	0.950
7.500	0.070	1.000
9.000	0.000	1.000

5.7 Association of sociodemographic factors with performance on the cognitive tests.

All the variables were categorized into 2 groups based on the cut-off points determined from the ROC analysis for univariate analysis and subsequent analyses if necessary.

Univariate analysis of the association of the sociodemographic factors with the performance on the cognitive tests was done using the chi-square test, or Fisher's exact test when the number of subjects was less than 5.

5.7.1 Association analysis for cognitive function in schizophrenic patients

Table 5.13 shows the association analysis results between sociodemographic factors and cognitive performance based on the TMT A test. Poorer performance on the TMT A (> 29.05 seconds) was significantly associated with age (≥ 34) (p=<0.01, OR=9.583). Poorer performance on the TMT A (> 29.05 seconds) was associated with Indian ethnicity (p=<0.01, OR=5.4). Less years of education (≤ 14) was associated with poorer performance on the TMT A (p=<0.01, OR= 0.069). Those who were employed also performed better on the TMT A (p=<0.01, OR= 0.073). Duration of illness was also associated with the performance on the TMT (p=<0.01,0R=24.267).

Table 5.13: Associated factors for performance of Schizophrenia patients in TMT(A)

Factors	TMT(A)		χ^2	Odds Ratio	P value
	≤ 29.05 n (%)	> 29.05 n (%)			
Age					
*< 34	46 (74.2)	16 (25.8)	29.567	9.583	< 0.01
≥ 34	12 (23.1)	40 (76.9)			
Gender					
Male	25 (43.9)	32 (56.1)	2.246	0.568	0.134
Female	33 (57.9)	24 (42.1)			
Ethnicity					
Non-Chinese	28 (47.5)	31 (52.5)	0.572	0.753	0.449
Chinese	30 (54.5)	25 (45.5)			
Non-Malay	37 (47.4)	41 (52.6)	1.170	0.645	0.279
Malay	21 (58.3)	15 (41.7)			
Non-Indian	54 (57.4)	40 (42.6)	9.253	5.400	< 0.01
Indian	4 (20.0)	16 (80.0)			
Marital status					
Non-Married	41 (50.0)	41 (50.0)	0.090	0.882	0.764
married	17 (53.1)	15 (46.9)			
Years of Education					
*≤ 14	14 (23.3)	46 (76.7)	38.451	0.069	< 0.01
> 14	44 (81.5)	10 (18.5)			
Occupation					
Unemployed	3 (11.1)	24 (88.9)	22.386	0.073	< 0.01
Employed	55 (63.2)	32 (36.8)			
Duration of illness in years					
*≤ 13.32	56 (65.1)	30 (34.9)	28.406	24.267	< 0.01
> 13.32	2 (7.1)	26 (92.9)			

*New means for were calculated to account for both the schizophrenic and healthy groups

Table 5.14 shows the association analysis results between sociodemographic factors and cognitive performance based on the TMT B test. Age (<34) was associated with better performance (≤ 58.43 seconds) (p=<0.01, OR=7.333). Non-Indian ethnicity was also associated with better performance (p=<0.05, OR=3.714). Less years of education (≤ 14) was associated with poorer performance on the TMT B (>58.43 seconds) (p=<0.01, OR=0.063). Being employed was significantly associated with better performance (p=<0.01, OR=0.076). Lastly, shorter duration of illness (≤ 13.32) was associated with better performance on the TMT B (p=<0.01, OR=14.063).

Table 5.14: Associated factors for performance of Schizophrenic patients in TMT(B)

Factors	**TMT(B)**		χ^2	**Odds Ratio**	**P value**
	≤ 58.43	> 58.43			
	n (%)	n (%)			
Age					
*< 34	44 (71.0)	18 (29.0)	23.903	7.333	< 0.01
≥ 34	13 (25.0)	39 (75.0)			
Gender					
Male	27 (47.4)	30 (52.6)	0.316	0.810	0.574
Female	30 (52.6)	27 (47.4)			
Ethnicity					
Non-Chinese	26 (44.1)	33 (55.9)	1.721	0.610	0.190
Chinese	31 (56.4)	24 (43.6)			
Non-Malay	39 (50.0)	39 (50.0)	0.000	1.000	1.000
Malay	18 (50.0)	18 (50.0)			
Non-Indian	52 (55.3)	42 (44.7)	6.064	3.714	< 0.05
Indian	5 (25.0)	15 (75.0)			
Marital status					
Non-Married	39 (47.6)	43 (52.4)	0.695	0.705	0.404
married	18 (56.3)	14 (43.8)			
Years of Education					
*≤ 14	13 (21.7)	47 (78.3)	40.674	0.063	< 0.01
> 14	44 (81.5)	10 (18.5)			
Occupation					
Unemployed	3 (11.1)	24 (88.9)	21.402	0.076	< 0.01
Employed	54 (62.1)	33 (37.9)			
Duration of illness in years					
*≤ 13.32	54 (62.8)	32 (37.2)	22.914	14.063	< 0.01
> 13.32	3 (10.7)	25 (89.3)			

*New means were calculated illness to account for both the schizophrenic and healthy groups

Table 5.15 shows the association analysis results between sociodemographic factors and cognitive performance based on the Digit Span Test Forward (DSTF). Being of non-Indian ethnicity was associated with better performance on the DSTF (able to recall >5.5 digits) (p=<0.05, OR=0.347). The higher the number of education years (>14), the better the performance on the DSTF (p=≤0.01, OR=2.864). Shorter duration of illness was also associated with better performance on the DSTF (p=<0.01, OR=0.274).

Table 5.15: Associated factors affecting performance of Schizophrenia patients in DST(F)

Factors	DST(F)		χ^2	Odds Ratio	P value
	≤ 5.5	> 5.5			
	n (%)	n (%)			
Age					
*< 34	18 (29.0)	44 (71.0)	1.619	0.604	0.203
≥ 34	21 (40.4)	31 (59.6)			
Gender					
Male	22 (38.6)	35 (61.4)	0.974	1.479	0.324
Female	17 (29.8)	40 (70.2)			
Ethnicity					
Non-Chinese	25 (42.4)	34 (57.6)	3.620	2.153	0.057
Chinese	14 (25.5)	41 (74.5)			
Non-Malay	26 (33.3)	52 (66.7)	0.084	0.885	0.771
Malay	13 (36.1)	23 (63.9)			
Non-Indian	28 (29.8)	66 (70.2)	4.658	0.347	< 0.05
Indian	11 (55.0)	9 (45.0)			
Marital status					
Non-Married	29 (35.4)	53 (64.6)	0.173	1.204	0.677
married	10 (31.3)	22 (68.8)			
Years of Education					
*≤ 14	27 (45.0)	33 (55.0)	6.552	2.864	≤ 0.01
> 14	12 (22.2)	42 (77.8)			
Occupation					
Unemployed	12 (44.4)	15 (55.6)	1.646	1.778	0.199
Employed	27 (31.0)	60 (69.0)			
Duration of illness in years					
*≤ 13.32	23 (26.7)	63 (73.3)	8.673	0.274	< 0.01
> 13.32	16 (57.1)	12 (42.9)			

*New means for years of education and duration of illness were calculated to account for both the schizophrenic and healthy groups

Table 5.16 shows the association analysis results between sociodemographic factors and cognitive performance based on the digit span test reverse (DSTR). Here, younger age (<34) is also associated with better performance on the DSTR (>4.5 digits recalled) with a p value of <0.01, and OR of 0.159. Less years of education (≤ 14) is also associated with poorer performance on the DSTR (<4.5 digits recalled) (p=< 0.01, OR=12.654). Being employed was also associated with better performance (p=< 0.01, OR=11.886), whereas less years of illness (≤ 13.32) was associated with better performance (p=< 0.01, OR=0.022).

Table 5.16: Associated factors affecting performance of Schizophrenic patients in DST(R)

Factors	DST(R)		χ^2	Odds Ratio	P value
	≤ 4.5	> 4.5			
	n (%)	n (%)			
Age					
*< 34	20 (32.3)	42 (67.7)	20.692	0.159	< 0.01
≥ 34	39 (75.0)	13 (25.0)			
Gender					
Male	31 (54.4)	26 (45.6)	0.316	1.235	0.574
Female	28 (49.1)	29 (50.9)			
Ethnicity					
Non-Chinese	33 (55.9)	26 (44.1)	0.855	1.416	0.355
Chinese	26 (47.3)	29 (52.7)			
Non-Malay	40 (51.3)	38 (48.7)	0.022	0.942	0.882
Malay	19 (52.8)	17 (47.2)			
Non-Indian	45 (47.9)	49 (52.1)	3.234	0.394	0.072
Indian	14 (70.0)	6 (30.0)			
Marital status					
Non-Married	46 (56.1)	36 (43.9)	2.207	1.868	0.137
married	13 (40.6)	19 (59.4)			
Years of Education					
*≤ 14	47 (78.3)	13 (21.7)	35.837	12.654	< 0.01
> 14	12 (22.2)	42 (77.8)			
Occupation					
Unemployed	24 (88.9)	3 (11.1)	19.539	11.886	< 0.01
Employed	35 (40.2)	52 (59.8)			
Duration of illness in years					
*≤ 13.32	32 (37.2)	54 (62.8)	29.667	0.022	< 0.01
> 13.32	27 (96.4)	1 (3.6)			

*New means were calculated to account for both the schizophrenic and healthy groups

5.7.2 Association analysis for cognitive function in bipolar patients

Performance on the TMT A was associated with several factors: Younger age (<33 years) was associated with better performance (≤ 26.45 seconds), with a P value of <0.01, and OR of 4.618. Non-Indian ethnicity was also associated with better performance (p=<0.01, OR=9.652). Being unmarried was also associated with better performance (p=<0.05, OR=2.381). More years of education was associated with better performance (p=<0.01, OR=0.143) as well as being employed (p=<0.01, OR=0.072). Less illness years was also associated with better performance (p=<0.01, OR=11.855).

Table 5.17: Association analysis for factors affecting performance of Bipolar disorder patients in TMT (A)

Factors	**TMT(A)**		χ^2	**Odds Ratio**	**P value**
	≤ 26.45	> 26.45			
	n (%)	n (%)			
Age					
*< 33	39 (67.2)	19 (32.8)	12.441	4.618	< 0.01
≥ 33	12 (30.8)	27 (69.2)			
Gender					
Male	21 (43.8)	27 (56.3)	2.970	0.493	0.085
Female	30 (61.2)	19 (38.8)			
Ethnicity					
Non-Chinese	25 (46.3)	29 (53.7)	1.927	0.564	0.165
Chinese	26 (60.5)	17 (39.6)			
Non-Malay	31 (50.0)	31 (50.0)	0.458	0.750	0.499
Malay	20 (57.1)	15 (42.9)			
Non-Indian	49 (59.8)	33 (40.2)	10.960	9.652	< 0.01
Indian	2 (13.3)	13 (86.7)			
Marital status					
Non-Married	34 (61.8)	21 (38.2)	4.350	2.381	< 0.05
married	17 (40.5)	25 (59.5)			
Years of Education					
*≤ 15	10 (25.6)	29 (74.4)	18.980	0.143	< 0.01
> 15	41 (70.7)	17 (29.3)			
Occupation					
Unemployed	1 (9.1)	10 (90.9)	9.410	0.072	< 0.01
Employed	50 (58.1)	36 (41.9)			
Duration of illness in years					
*≤ 12.17	49 (61.3)	31 (38.8)	13.770	11.855	< 0.01
> 12.17	2 (11.8)	15 (88.2)			

*New means were calculated to account for both the bipolar and healthy groups

Table 5.18 shows the association analysis results between sociodemographic factors and cognitive performance based on the TMT B. Younger age (<33) was associated with better performance (≤ 55.08 seconds), with P value of <0.01, and OR of 3.968. Being of Chinese, or non-Indian ethnicity was also associated with better performance on the TMT B respectively, with P value of <0.05 for both, and OR of 0.416 for the former group, and OR of 4.297 for the latter group. More years of education (>15) was associated with better performance as well, with P value of <0.01, and OR of 0.252. And finally, shorter duration of illness (≤ 12.17 years) was also associated with better performance (P=<0.01, OR=8.207).

Table 5.18: Associated factors affecting performance of Bipolar disorder patients in TMT(B)

Factors	TMT(B)		χ^2	Odds Ratio	P value
	≤ 55.08	> 55.08			
	n (%)	n (%)			
Age					
*< 33	40 (69.0)	18 (31.0)	10.333	3.968	< 0.01
≥ 33	14 (35.9)	25 (64.1)			
Gender					
Male	25 (52.1)	23 (47.9)	0.495	0.750	0.482
Female	29 (59.2)	20 (40.8)			
Ethnicity					
Non-Chinese	25 (46.3)	29 (53.7)	4.337	0.416	< 0.05
Chinese	29 (67.4)	14 (32.6)			
Non-Malay	35 (56.5)	27 (43.5)	0.043	1.092	0.837
Malay	19 (54.3)	16 (45.7)			
Non-Indian	50 (61.0)	32 (39.0)	6.048	4.297	< 0.05
Indian	4 (26.7)	11 (73.3)			
Marital status					
Non-Married	31 (56.4)	24 (43.6)	0.025	1.067	0.875
married	23 (54.8)	19 (45.2)			
Years of Education					
*≤ 15	14 (35.9)	25 (64.1)	10.333	0.252	< 0.01
> 15	40 (69.0)	18 (31.0)			
Occupation					
Unemployed	3 (27.3)	8 (72.7)	4.054	0.257	0.057[a]
Employed	51 (59.3)	35 (40.7)			
Duration of illness in years					
*≤ 12.17	51 (63.7)	29 (36.3)	12.076	8.207	< 0.01
> 12.17	3 (17.6)	14 (82.4)			

a = Fisher's Exact p value

*New means were calculated to account for both the bipolar and healthy groups

DSTF univariate analysis was not done as there was no significant difference in the performance between the bipolar and healthy group.

Table 5.19 shows the association analysis results between sociodemographic factors and cognitive performance based on the DSTR. Younger age (<33) was associated with better performance (>4.5 digits recalled), with a P value of <0.05 and OR of 0.355. More years of education (>15) was also associated with better performance (p=<0.05, OR=2.339). Shorter duration of illness (≤ 12.17 years) was associated with better performance (p=<0.05, OR=0.278)

Table 5.19: Association analysis for factors affecting performance of Bipolar disorder patients in DST(R)

Factors	DST(R)		χ^2	Odds Ratio	P value
	≤ 4.5	> 4.5			
	n (%)	n (%)			
Age					
*< 33	17 (29.3)	41 (70.7)	5.892	0.355	< 0.05
≥ 33	21 (53.8)	18 (46.2)			
Gender					
Male	19 (39.6)	29 (60.4)	0.007	1.034	0.935
Female	19 (38.8)	30 (61.2)			
Ethnicity					
Non-Chinese	25 (46.3)	29 (53.7)	2.592	1.989	0.107
Chinese	13 (30.2)	30 (69.8)			
Non-Malay	21 (33.9)	41 (66.1)	2.029	0.542	0.154
Malay	17 (48.6)	18 (51.4)			
Non-Indian	31 (37.8)	51 (62.2)	0.418	0.695	0.518
Indian	7 (46.7)	8 (53.3)			
Marital status					
Non-Married	19 (34.5)	36 (65.5)	1.143	0.639	0.285
married	19 (45.2)	23 (54.8)			
Years of Education					
*≤ 15	20 (51.3)	19 (48.7)	4.012	2.339	< 0.05
> 15	18 (31.0)	40 (69.0)			
Occupation					
Unemployed	6 (54.5)	5 (45.5)	1.230	2.025	0.331[a]
Employed	32 (37.2)	54 (62.8)			
Duration of illness in years					
*≤ 12.17	27 (33.8)	53 (66.3)	5.638	0.278	< 0.05
> 12.17	11 (64.7)	6 (35.3)			

a = Fisher's Exact p value

*New means were calculated to account for both the bipolar and healthy groups

5.8 Multivariate analysis of associated factors for cognitive performance.

Multivariate analysis of the variables significantly associated with poorer performance on the cognitive tests was done. Significant associated factors from univariate analysis were included into the multivariate logistic regression analysis. Table 5.20 shows the multivariate analysis done for the schizophrenia group vs the healthy group. After adjusting with multivariate logistic regression analysis, having schizophrenia (p value of <0.01, adjusted odds ratio of 9.224, CI 1.763-48.246), age ≥ 34 (p value <0.05, adjusted OR of 3.708, CI 1.015-13.544) and Indian ethnicity (p value <0.05, adjusted OR 6.053, CI 1.291-28.378) were significantly associated with poorer performance on TMT A. Performance in the TMT B and DSTF were no longer significantly different from the healthy group. However, performance of the schizophrenic group in the DSTR was still significantly poorer than the healthy group, with a p value of <0.05, adjusted OR of 0.228, and CI of 0.053-0.982).

Table 5.21 shows the multivariate analysis done for the bipolar vs healthy subjects. After adjusting for confounding factors, performance of the bipolar group on the TMT A was no longer significantly different from that of the healthy subjects, but Indian ethnicity (p<0.01, adjusted OR 15.894, CI 2.742-92.113) and less years of education(<15 years) (p<0.01, adjusted OR 0.187, CI 1.291-28.378) were significantly associated with poorer performance. Performance on the TMT B and DSTR however, were still significantly different from the healthy group after adjusting for confounding factors. For the TMT B, the p value was <0.05, with adjusted OR of 3.680, and CI of 1.089-12.434. Chinese subjects had significantly better performance in TMT B as well after multivariate analysis with p value of <0.05, and adjusted OR of 0.286and CI of 0.091-0.899. For the DSTR, the p value was <0.01, with adjusted OR of 0.288, and CI of 0.150-0.551.

Table 5.20: Multivariate analysis of variables associated for performance of Schizophrenia (Sch) vs Healthy Subject (HS) groups in TMT(A), TMT (B), DST(F) and DST(R)

Group	Sub-group	TMT(A)		Odd ratio (OR)	Adjusted Odd ratio (AOR)	95% confidence interval	p value
		n (%) *≤ 29.05	n (%) > 29.05				
HS vs Sch	HS	49 (86.0)	8 (14.0)	32.667	9.224	1.763-48.246	< 0.01
	Schizo	9 (15.8)	48 (84.2)				
Age	#< 34	46 (74.2)	16 (25.8)	9.583	3.708	1.015-13.544	< 0.05
	≥ 34	12 (23.1)	40 (76.9)				
Ethnicity	Non-Indian	54 (57.4)	40 (42.6)	5.400	6.053	1.291-28.378	< 0.05
	Indian	4 (20.0)	16 (80.0)				
YoE	#≤ 14	14 (23.3)	46 (76.7)	0.069	0.614	0.139-2.711	0.520
	> 14	44 (81.5)	10 (18.5)				
Occupation	Unemployed	3 (11.1)	24 (88.9)	0.073	0.388	0.076-1.978	0.255
	Employed	55 (63.2)	32 (36.8)				
DoI (year)	#≤ 13.32	56 (65.1)	30 (34.9)	24.267	2.065	0.303-14.075	0.459
	> 13.32	2 (7.1)	26 (92.9)				

		TMT(B)					
		n (%) *≤ 58.43	n (%) > 58.43				
HS vs Sch	HS Schizo	47 (82.5) 10 (17.5)	10 (17.5) 47 (82.5)	22.090	4.119	0.927-18.299	0.063
Age group	#< 34 ≥ 34	44 (71.0) 13 (25.0)	18 (29.0) 39 (75.0)	7.333	2.341	0.703-7.789	0.166
Ethnicity	Non-Indian Indian	52 (55.3) 5 (25.0)	42 (44.7) 15 (75.0)	3.714	3.196	0.792-12.903	0.103
YoE	#≤ 14 > 14	13 (21.7) 44 (81.5)	47 (78.3) 10 (18.5)	0.063	0.307	0.084-1.125	0.075
Occupation	Unemployed Employed	3 (11.1) 54 (62.1)	24 (88.9) 33 (37.9)	0.076	0.364	0.076-1.732	0.204
DoI (year)	#≤ 13.32 > 13.32	54 (62.8) 3 (10.7)	32 (37.2) 25 (89.3)	14.063	1.642	0.295-9.145	0.571
		DST(F)					
		n (%) †≤ 5.5	n (%) > 5.5				
HS vs Sch	HS Schizo	13 (22.8) 26 (45.6)	44 (77.2) 31 (54.4)	0.352	0.975	0.261-3.649	0.970
Ethnicity	Non-Indian Indian	28 (29.8) 11 (55.0)	66 (70.2) 9 (45.0)	0.347	0.394	0.139-1.117	0.080

YoE	#≤ 14 > 14	27 (45.0) 12 (22.2)	33 (55.0) 42 (77.8)	2.864	1.847	0.548-6.221	0.322
DoI (year)	#≤ 13.32 > 13.32	23 (26.7) 16 (57.1)	63 (73.3) 12 (42.9)	0.274	0.397	0.133-1.188	0.099
		DST(R)					
		n (%) †≤ 4.5	n (%) > 4.5				
HS vs Sch	HS Schizo	11 (19.3) 48 (84.2)	46 (80.7) 9 (15.8)	0.045	0.228	0.053-0.982	< 0.05
Age group	#< 34 ≥ 34	20 (32.3) 39 (75.0)	42 (67.7) 13 (25.0)	0.159	0.703	0.222-2.227	0.550
YoE	#≤ 14 > 14	47 (78.3) 12 (22.2)	13 (21.7) 42 (77.8)	12.654	2.295	0.632-8.331	0.207
Occupation	Unemployed Employed	24 (88.9) 35 (40.2)	3 (11.1) 52 (59.8)	11.886	2.171	0.435-10.821	0.344
DoI (year)	#≤ 13.32 > 13.32	32 (37.2) 27 (96.4)	54 (62.8) 1 (3.6)	0.022	0.116	0.012-1.157	0.066

YoE = Years of education

DoI = Duration of illness (in years)

*Mean performance on the TMT A/B measured in seconds

†Mean performance on the Digit Span (Forward or Reverse) in number of digits

#Mean age, duration of education or illness in years

Table 5.21: Multivariate analysis of variables associated with performance in TMT(A), TMT(B) and DST(R) of Bipolar (Bi) vs Healthy (HS) Subjects

Group	Sub-group	TMT(A)		Odd ratio (OR)	Adjusted Odd ratio (AOR)	95% confidence interval	p value
		n (%) *≤ 26.45	n (%) > 26.45				
HS vs Bi	HS	39 (68.4)	18 (31.6)	5.056	0.850	0.429-1.683	0.641
	Bipolar	12 (30.0)	28 (70.0)				
Age	#< 33	39 (67.2)	19 (32.8)	4.618	1.297	0.365-4.605	0.688
	≥ 33	12 (30.8)	27 (69.2)				
Ethnicity	Non-Indian	49 (59.8)	33 (40.2)	9.652	15.894	2.742-92.113	< 0.01
	Indian	2 (13.3)	13 (86.7)				
Marital status	Non-Married	34 (61.8)	21 (38.2)	2.381	1.836	0.584-5.777	0.299
	married	17 (40.5)	25 (59.5)				
YoE	#≤ 15	10 (25.6)	29 (74.4)	0.143	0.187	0.056-0.631	< 0.01
	> 15	41 (70.7)	17 (29.3)				
Occupation	Unemployed	1 (9.1)	10 (90.9)	0.072	0.107	0.008-1.431	0.091
	Employed	50 (58.1)	36 (41.9)				
DoI (year)	#≤ 12.17	49 (61.3)	31 (38.8)	11.855	8.265	0.935-73.045	0.057
	> 12.17	2 (11.8)	15 (88.2)				

		TMT(B)					
		n (%) *≤ 55.08	n (%) > 55.08				
C vs Bi	Control	42 (73.7)	15 (26.3)	6.533	3.680	1.089-12.434	< 0.05
	Bipolar	12 (30.0)	28 (70.0)				
Age	#< 33	40 (69.0)	18 (31.0)	3.968	1.933	0.632-5.911	0.248
	≥ 33	14 (35.9)	25 (64.1)				
Ethnicity	Non-Chinese	25 (46.3)	29 (53.7)	0.416	0.286	0.091-0.899	< 0.05
	Chinese	29 (67.4)	14 (32.6)				
Ethnicity	Non-Indian	50 (61.0)	32 (39.0)	4.297	2.087	0.471-9.238	0.332
	Indian	4 (26.7)	11 (73.3)				
YoE	#≤ 15	14 (35.9)	25 (64.1)	0.252	0.618	0.207-1.839	0.387
	> 15	40 (69.0)	18 (31.0)				
DoI (year)	#≤ 12.17	51 (63.7)	29 (36.3)	8.207	3.029	0.527-17.409	0.214
	> 12.17	3 (17.6)	14 (82.4)				
		DST(R)					
		n (%) †≤ 4.5	n (%) > 4.5				
HS vs Bi	HS	11 (19.3)	46 (80.7)	0.115	0.288	0.150-0.551	< 0.01
	Bipolar	27 (67.5)	13 (32.5)				
Age group	#< 33	17 (29.3)	41 (70.7)	0.355	0.447	0.142-1.411	0.170
	≥ 33	21 (53.8)	18 (46.2)				

YoE	#≤ 15	20 (51.3)	19 (48.7)	2.339	0.620	0.190-2.016	0.426
	> 15	18 (31.0)	40 (69.0)				
DoI (year)	#≤ 12.17	27 (33.8)	53 (66.3)	0.278	1.986	0.422-9.349	0.385
	> 12.17	11 (64.7)	6 (35.3)				

YoE = Years of education

DoI = Duration of illness (in years)

*Mean performance on the TMT A/B measured in seconds

†Mean performance on the Digit Span (Forward or Reverse) in number of digits

#Mean age, duration of education or illness in years

CHAPTER 6

DISCUSSION

The aim of this study was to assess the cognitive functions of patients with stable schizophrenia and euthymic bipolar disorder and to compare them with those of a healthy group as well as each other.

The study yielded several main findings: Firstly, that the participants' response to the Perceived Deficits Questionnaire (PDQ), a subjective measure of cognitive function, did not correlate with the findings on objective tests. Secondly, in direct comparison of performance on the trail making and digit span tests, the schizophrenia group performed worse than the bipolar and healthy group in all the tests; and the bipolar group performed worse than the healthy group in all the tests except the forward digit span test.

Thirdly, after multivariate analysis of the performance on the cognitive tests, the schizophrenic group did more poorly than the healthy group in the TMT A as well as the DSTR. Fourthly, that more advanced age and being of Indian ethnicity were independent risk factors in poor performance in TMT A. Fifth, after multivariate analysis, the bipolar group performed poorer than the healthy group in the TMT B and DSTR, with Chinese ethnicity being an independent factor for better performance. Finally, although the bipolar group's performance in the TMT A was not significantly different from the healthy group's after adjusting for confounders, Indian ethnicity and years of education were independent risk factors for poor performance.

To understand these findings, there is a need for the researcher to describe the methodological process. First, participants were selected based on stringent inclusion

and exclusion criteria, so as to minimize the presence of confounding factors. These confounders were such as extremes of age, significant physical disorders (e.g., head trauma, epilepsy or stroke), co-morbid psychiatric disorders, significant substance (either alcohol or illicit drugs) use. Extremes of age were defined as those being younger than 18 and older than 55. For those younger than 18, the reason for them to be excluded is based on the understanding that the maturation processes of the younger populations' brains are not complete, particularly with respect to the arrangements of the grey matter and myelination (Sowell et al., 2001). As for the older population, it was found that cognitive decline, particularly in terms of reasoning, memory, vocabulary and speech fluency, started from as early as middle age (Singh-Manoux et al., 2012). Hence the age of more than 55 was selected as a cut-off point.

Physical disorders such as head trauma, a long-term history of epilepsy and stroke can also affect cognitive function. It is a well-known scientific fact that the sequelae of traumatic brain injury (TBI) include disturbances in cognitive functioning, besides changes/disturbances in the mood and personality of the affected individual. The most common neurocognitive disturbances in TBI are problems in attention, executive functioning and memory (Arciniegas et al., 2002). Current studies have shown that even one episode of mild TBI, or concussions, can have lasting neurocognitive effects, manifesting as dementia in older age (Daneshvar et al., 2011).

Epilepsy has been linked to a spectrum of psychiatric, behavioural and cognitive dysfunctions (Berg, 2011). The theories for these associations include: 1) Structural brain lesions which are involved in epilepsy that also impair the other functions of the area. 2) Effects of seizure activity that arise before and persist after the observed fit, including effects of epilepsy in early childhood/during critical periods of brain development which may be potentially irreversible and are usually severe. 3) Similar

mechanisms of seizures with other disorders, in the absence of other diseases or structural lesions of the CNS (Berg, 2011). To put it in perspective, about a quarter of children with epilepsy have impaired overall intellectual function consistent with the designation of "mental retardation" (Berg et al., 2004).

As for stroke, cerebrovascular diseases are the second most common cause of decline in cognitive functions and dementia in the elderly (Kalaria & Ballard, 2001). Kalaria and Ballard also found that the predominant deficit in early stages was in executive functioning. Co-morbid psychiatric conditions were also an exclusion point because most psychiatric disorders are "cognitive disorders" in that there are biological underpinnings, which can explain the psychopathologies of the individual psychiatric disorders, and are related to the course, treatment strategies as well as the outcome of these illnesses (Trivedi, 2006). For example, in major depressive disorder, cognitive dysfunction can be global and rather severe, mimicking dementia (Rabins et al., 1984). The deficits are usually in executive function, as well as visual and verbal memory (Elliott et al., 1997).

In obsessive-compulsive disorder (OCD), deficits have been found in executive functioning (Aronowitz et al., 1994) and visual working memory (Dirson et al., 1995). It has also been suggested that people with OCD are unable to disregard unimportant stimuli and thus become overwhelmed by the excess information (Okasha et al., 2000). Somatic symptom and related disorders have psychopathological and neuropsychological symptoms besides somatic ones. The cognitive complaints frequently reported by patients include poor concentration, word-finding abilities and recent memory (Barrows, 1995). Even in borderline personality disorder, research has found evidence for poor decision-making skills (O'Leary et al., 1991), as well as

associations between attention and memory impairment with self-injury (Burgess, 1991).

In chronic substance users, cognitive impairments due to withdrawal effects when abstinent are present but often temporary; however long-term use can also cause lasting cognitive decline (Gould, 2010). The nature of impairment varies with the type of substance abused, the user's genetic makeup, and the environment (Gould, 2010). For example, chronic heroin and amphetamine users have deficits in verbal fluency, planning, and attention (Ornstein et al., 2000) as importantly, decision making (Rogers et al., 1999).

Thus from all this evidence, the reason for excluding patients with co-morbid mental disorders (including substance use disorders) is clear, as the presence of inherent cognitive dysfunction of those psychiatric conditions could become confounders for poor performance on cognitive testing in this study.

Apart from this, a minimal level of cognitive capabilities was ascertained by ensuring that the participants had a minimum of 8 years of formal education, following the study by Trivedi and colleagues (Trivedi et al., 2007). The patients also had to be free from electro-convulsive therapy (ECT) for at least 6 months. This was in accordance with Calev et. al's findings that anterograde and retrograde memory had returned to pre-ECT levels after one month, but was even better after 6 months (Calev et al., 1991). Mohn and Rund also found that cognitive functions improve to pre-ECT levels before 6 weeks, and are maintained, as well as extended, at 6 months after ECT (Mohn & Rund, 2016).

Besides all these criteria for all the study's participants, subjects with schizophrenia and bipolar were further screened to ensure the stability of their mental states. The subjects from the bipolar group were screened for manic and hypomanic

symptoms using the Young Mania Rating Scale. The Brief Psychiatric Rating Scale (BPRS) was chosen as a tool to assess stability of patients with schizophrenia due to its brevity and simplicity of use, as well as being efficient. However the limitation of its use may have been the relatively low cut-off point of 31, as the BPRS has 18 separate items, each of which is scored on a Likert scale of 0-7. There are 10 main constructs in the BPRS comprising both positive and negative symptoms. There are at least 4 items for negative symptoms, such as emotional withdrawal, conceptual disorganization, motor retardation and blunted affect. If a participant scores 7 (extremely severe) in just these 4 domains, and has residual hallucinatory or other symptoms, they would have to be excluded from the study as their overall score would be more than 31, even if their overall condition is generally considered stable in that they do not deteriorate. Therefore the schizophrenia subjects in this study are those who likely had more positive symptoms that had resolved, and thus, patients with prominent negative symptoms could have been excluded from the study.

6.1 Socio-demographic Characteristics

A total number of 154 subjects were enrolled in this study. This study was conducted in the University of Malaya Medical Centre, which caters as a tertiary referral centre to patients in Malaysia. However because of its location in Petaling Jaya, most of the clientele is from an urban area. This may be a reason as to why the majority of the participants were of Chinese ethnicity (List of cities in Malaysia with large Malaysian Chinese populations), with 54.5% (n=31) of the schizophrenia group, 47.5% (n=19) of the bipolar group, and 42.1% (n=24) of the healthy group being of Chinese ethnicity. The number of Indian respondents was relatively much lower, with only 24.6% (n= 14) of the schizophrenia group, 22.5% (n=9) of the bipolar group, and 10.5%

(n=6) of the healthy control group being of Indian ethnicity. Their small number may also influence the statistical analysis as it will add more variance to the difference.

The urban location may also explain the relatively high levels of education across the participant groups. In the schizophrenia group, the mean years of education was 11.61; in the bipolar group it was 13.29, and in the control group it was 16.75 years. The higher number of years in the healthy group is explained by the fact that they consisted mainly of hospital staff. Most of the participants were also employed – 52.6% of the schizophrenia group, 72.5% of the bipolar group, and 100% of the healthy group. Any participant who was a full-time student was classified as being employed.

Interestingly the mean duration of illness for both schizophrenia and bipolar disorder was rather long – 13.32 years for schizophrenia and 12.17 for bipolar. This may be due to the fact that UMMC is the only government hospital that caters to several locations including Puchong, Damansara, Subang Jaya and Petaling Jaya. Psychiatric follow-up is much more affordable in the government compared to the private sector, hence there are many patients that have their long-term follow up here.

6.2 Response of the participants in the PDQ

Scores from the PDQ are meant to be summed up according to their cognitive domains, and in total, according to the Multiple Sclerosis Quality of Life Inventory (MSQLI) (Ritvo et al., 1997). The answers on the PDQ were in the form of a Likert scale, such as never, rarely, sometimes, often, and almost always. The author scored these answers as 0, 1, 2, 3, and 4 respectively. Therefore higher scores indicate poorer perceived cognitive function in the respondent.

In the comparison between the schizophrenic group and the healthy subjects, there were 7 domains that had significantly different responses between the groups. Based on the means calculated, it would appear that the schizophrenia group felt they had less deficits in items 4, 5, 7, 8, and 20. For item 4 (trouble organizing things) – the schizophrenia group's mean was 0.75, while the healthy group's mean was 0.84. For item 5 (difficulty concentrating during conversations), the mean for the schizophrenia group was 0.86, and 1.18 for the healthy group. For item 7 (miss appointments and meetings) – the mean for the schizophrenia group was 0.33, and 0.63 for the healthy group. For item 8 (difficulty planning daily activities) – the mean for the first group was 0.47, and the mean for the healthy group was 1.18. For item 20 (difficulty making decisions), the mean for the former group was 0.67, and 1.21 for the latter group.

Only in items 17 (trouble holding phone numbers in head) and 19 (forget to take medication) did the ill group score higher than the healthy group. Based on cognitive domains, the schizophrenia group's total score was less than the healthy group's score in the domain of planning and organization, with a p value of <0.05. Thus it would seem to imply that the healthy group felt they had more difficulties with planning and organization than the schizophrenia group. These findings are likely explained by the finding in several studies that subjective assessments of cognitive dysfunction do not correlate with objective examinations (Chan et al., 2008; Johnson et al., 2011). Apart from that, patients with schizophrenia tend to have poor insight into their illness and cognitive abilities (Joseph et al., 2015; Morgan & David, 2004).

For the bipolar vs healthy group, only items 11 (forget the date) and 19 (forget to take medication) were statistically significant. These were both in the domains of prospective memory, and the p value was <0.05. In other words, the bipolar group performed similarly to the healthy group, in which there were a few cognitive

impairments in certain areas, but the bipolar group felt that their memory was poorer. This is similar with the findings of Demant and colleagues that there was a correlation between global objective and subjective measures of cognitive impairment but not within separate cognitive domains. However the correlation found was weak, suggesting that complaints about cognition are not a suitable assessment of cognition (Demant et al., 2015). It is important to note however that working memory deficits have been found to be present in euthymic bipolar patients (Thompson et al., 2007).

Comparison of the perceived deficits between the schizophrenia and bipolar groups yielded significantly different answers in items 11, 19 and 20. The schizophrenia group scored lower than the bipolar group in items 11 (mean for schizophrenia - 1.46, for bipolar 2.03) and 19 (mean for schizophrenia 0.40, bipolar – 0.67). Overall Mann-Whitney analysis of the cognitive domains only showed statistical significance ($p=<0.05$) in the domain of prospective memory. This might imply that the schizophrenia group felt they had not much difficulty with memory or trouble making decisions.

In conclusion, the subjective response of the schizophrenic group of their perceived deficits was more favourable compared to the responses of the healthy and bipolar group. This is likely because patients with schizophrenia have poor insight into their cognitive abilities, besides their illness condition (Joseph et al., 2015; Morgan & David, 2004). It must also be reiterated that the scoring of the PDQ should be interpreted with caution as the participants' perceptions of their cognitive abilities may not correspond with their objectively measured abilities (Ritvo et al., 1997). Haring et al. also found that there was no correlation between objective and subjective measures of cognitive function in schizophrenic patients (Haring et al., 2017), and several authors

have also found little correlation between subjective and objective measures of cognitive function in bipolar patients (Jensen et al., 2015; Martinez-Aran et al., 2005).

6.3 Direct comparisons between schizophrenia and bipolar disorder patients with healthy subjects

The result of the direct comparisons is that the schizophrenia group performed poorly compared to both the bipolar and healthy group on both the TMT as well as digit span tests, and the differences were statistically significant ($p = <0.01$ for all) For the bipolar group, performance was better than the schizophrenia group in both the trail making tests and the reverse digit span with p values of <0.01, and also the forward digit span with a p value of ≤ 0.05. Performance of the bipolar group was not as good as the healthy group in trail making and digit span reverse tests (with p value of <0.01 for all), but was not significantly different from the healthy group's in the forward digit span test (DSTF).

The findings of the schizophrenic group's performance are not surprising as they are very much in line with the current literature that there are cognitive deficits across various domains in patients with schizophrenia, even in their remitted states, as found in chapter 2. As for the performance of the bipolar group, the findings of direct comparison, apart from performance on the DSTF, are also in line with the literature review studies. Most notably in the study done by Altshuler and colleagues that compared cognitive functions in remitted schizophrenic and bipolar patients, there was a generalized impairment across all the domains when compared with the healthy group. The bipolar group in their study only performed poorly in the areas of verbal memory and executive function (in comparison with their control group) (Altshuler et al., 2004).

Trivedi and colleagues also found poorer cognitive functions in the schizophrenia group compared with the bipolar group (Trivedi et al., 2007).

With the findings of the direct comparisons, further analyses were done to rule out the effects of confounding factors, which will be explained subsequently. With regards to the bipolar group's performance on the DSTF, attempts at finding a cut-off point with the ROC curve were unsuccessful, and no further analyses were done. This finding suggests that in the euthymic state, bipolar patients do not have deficits in the form of short-term, verbal working memory.

The results of euthymic bipolar patients having poorer cognitive functions than healthy subjects is in line with the findings of several studies, including those earlier mentioned in the literature review by Althsuler, Robinson and Trivedi (Altshuler et al., 2004; Robinson et al., 2006; Trivedi et al., 2007). According to Zubieta and colleagues, deficits in motor coordination, executive function and verbal learning were present in euthymic bipolar patients (Zubieta et al., 2001).

However the finding of this study of similar performance in the DSTF with the healthy group, suggests that in euthymic bipolar patients, there is no problem with working memory. This is in contrast with most existing evidence. As mentioned earlier, Thompson and colleagues found evidence for working memory deficits in the euthymic state (Thompson et al., 2007). Bourne and colleagues reiterated that the cognitive deficits in bipolar with the largest effects sizes were in verbal learning and memory tasks (Bourne et al., 2015).

The findings of this study suggest that DSTF may not be a suitable test for verbal working memory testing. Similarly, Thompson and colleagues who examined working memory with many different tests also found no difference between their bipolar patients' performance on the Forward Digit Span and their controls (Thompson

et al., 2007). This study was also limited in terms of lacking a measure of verbal working memory. Other tests, such as the California Verbal Learning Test, Rey Auditory Verbal Learning Test, Wechsler Memory Scale (WMS), etc., should also ideally be used for a more comprehensive assessment. Another potential confounding factor was that the sample size was not large enough. The targeted sample size for bipolar patients was 60, but the researcher was only able to get 40 subjects.

6.4 Performance on the TMT and Digit Span for schizophrenia vs healthy subjects.

After multivariate analysis was done comparing the schizophrenia group with controls, only performance on TMT A was significantly different between the groups after adjusting for confounding factors, with higher age and Indian ethnicity being independent risk factors for poorer performance. This finding indicates that there is a deficit in attention and processing speed in patients with schizophrenia.

With regards to higher age and Indian ethnicity, a descriptive sub-analysis was done. It was found that the mean age of all the Indian participants was 36. Tombaugh who described normative data for performance on the trail making tests found that more advanced age was significantly related to poorer performance (Tombaugh, 2004). Not only that, it was noted earlier in the discussion of sociodemographic backgrounds that the small number of Indian participants may add variance to the statistical analysis.

After multivariate analysis for performance on TMT B, there was no longer a significant difference between that of the schizophrenic group in comparison with the control group. This finding appears to be in contrast with the findings in the studies noted earlier during the introduction and literature reviews. However, in a study done by

Perianez et. al. that compared the performance on the TMT between controls, a schizophrenia cohort and a traumatic brain injury (TBI) cohort, it was found that education was the factor that was most correlated with TMT scores, along with age and gender. They therefore stratified education into 2 groups – with low education from 0-11 years, and higher education being 12 years or more. Their ANOVA analysis revealed that there were significant effects for education on the performance on the TMT B, but not on the TMT A (Perianez et al., 2007). Tombaugh stratified the years of education into less than 12 years, and 12 years and more (Tombaugh, 2004). In the researcher's study, the mean years of education for the schizophrenia vs healthy group (in univariate and multivariate analyses) was 14 years, which is considered a higher education level. This may thus affect the results of the analysis.

During univariate analysis for the DSTF, no associated factors were found. Multivariate analysis also revealed that performance on the DSTF was not significantly different in comparison with the control group. DSTF is a test of verbal learning working memory. This finding is also in contrast with the other studies as working memory has found to be impaired in schizophrenic patients in all the studies noted in the literature review. Specifically Conklin and colleagues assessed the performance of patients with chronic schizophrenia as well as their first degree relatives without the illness in the Digit Span Task as well. They found that patients with schizophrenia performed poorly on both the Digit Span forward and reverse task. Interestingly their relatives also had poorer performance on the Digit Span reverse task (Conklin et al., 2000).

After adjusting for confounding factors in multivariate analysis, performance on DSTR of the schizophrenia group was still significantly poorer than the control group,

with p value of <0.05. DSTR is a measure of both verbal working memory as well as executive function.

Based on these results, there is evidence for poor attention and executive function in patients with schizophrenia, even in the stable state, based on the TMT A and the reverse digit span. This is in line with the findings of those evidences noted in the literature review and most other studies. TMT A is a measure of both executive function and attention. In a local study by Normala and colleagues, performance of the schizophrenia group was poorer on the TMT A and several other neurocognitive tests (Normala et al., 2009). In a more comprehensive study of attention by Galaverna and colleagues, 32 patients with chronic schizophrenia performed poorly in all the tests in comparison with a healthy control group (Galaverna et al., 2012).

As noted from the literature review, poor executive functioning is an expected finding in the schizophrenia group. It has been found to precede the onset of psychosis and remains stable throughout the course of illness (Bowie & Harvey, 2006). Reed and colleagues found that executive dysfunction was present in patients with moderate to severe overall functioning impairment, but the deficits were greater in patients with very poor overall functioning. They also postulated that executive dysfunction is a core component of the illness rather than a disorganization caused by acute psychosis, with long-term outcome implications (Reed et al., 2002).

In contrast, there appears to be no difference in the performance of TMT B, another measure of executive function, as well as the DSTF, a measure of verbal working memory. A possible explanation might be that during the screening process for selecting the schizophrenia study subjects, those who scored very highly on more than any 4 items on the BPRS would be excluded from the study, even if their residual symptoms were stable (unchanged). Thus many patients with prominent negative

symptoms that had high scores on items related to that were excluded. A number of patients that were nursing home residents with prominent negative symptoms also were not willing to participate in the study. Presence of negative symptoms has been found to correspond with poorer performance on cognitive testing (Krishnadas et al., 2014). This may be due to the fact that negative symptoms are so closely related to cognitive deficits (Harvey et al., 2005). In this review, Harvey and colleagues also found in particular that negative symptoms were strongly associated with poorer set-shifting (type of executive function) skills in TMT B. Thus the exclusion of this group of patients has likely confounded this study's findings.

In the study done by Altshuler and colleagues, stability for schizophrenia patients was defined by no or little change (by 3 points) in the BPRS over 3 consecutive months (Altshuler et al., 2004). Given the time constraints of the researcher, screening of the schizophrenia population was only done once using the BPRS. Other studies used the Positive and Negative Symptom Scale for schizophrenia (PANSS) (Sánchez-Morla et al., 2009; Trivedi et al., 2007) which is more comprehensive however very time-consuming.

Another possible reason for the contrast in this study's findings with others is that there may not have been enough tests for executive function, or rather the specific components of executive function. Many of the studies reviewed used the Wisconsin Cart Sorting Test (WCST) (Altshuler et al., 2004; Trivedi et al., 2007), and its specific tests for assessment of individual measures of executive function, such as categories and perseverative errors. In a meta-analysis by Krabbendam and colleagues comparing cognitive functions in schizophrenia with bipolar, the WCST was found to be homogenous in effect size, suggesting its greater generalizability and usability (Krabbendam et al., 2005). However the limitation to its use is the cost. The stroop test,

particularly the colour-word test, and the verbal fluency test are also measures of executive function used in other studies (Barrett et al., 2009; Brissos et al., 2008).

Besides this, in the meta-analysis by Robinson which reviewed studies regarding the cognitive function in euthymic bipolar disorder, effect sizes for both the TMT B and reverse digit span were greatly heterogenous across the studies (Robinson et al., 2006). This may indicate a need to interpret the results on these tests with caution. Fiorovanti and colleagues did a meta-analysis on the cognitive deficits in schizophrenia. Although the overall finding was of widespread cognitive deficits, they also cautioned that a publication bias could not be excluded as they could only find studies with positive results; thus their results could potentially be biased by the underrepresentation of negative results (Fioravanti et al., 2012).

6.5 Performance on the TMT and Digit Span tests for bipolar vs healthy subjects.

After multivariate analysis was done, performance on the TMT A was no longer significant after adjusting for confounding factors, but being of Indian race and lesser years of education were still independent risk factors for poorer performance, with both p values being <0.01. This finding may imply that there is no deficit in attention and processing speed in patients with euthymic bipolar disorder, which is in contrast with the literature review, as most studies have found residual deficits in attention even in the euthymic state. For example, Clark and colleagues also found that sustained attention deficits were still present after controlling for mild affective symptoms (Clark et al., 2002). Quraishi and Frangou also found that sustained attention were impaired even in the euthymic state (Quraishi & Frangou, 2002).

The explanation for the contrast may be similar to how the schizophrenic group performed on the TMT B test. In the bipolar vs healthy group, the cut-off number of years of education was 15 or less. This number exceeds the stratified norm given by Tombaugh and Perianez of 12 years or less (Tombaugh 2004; Perianez et al., 2007), which may thus affect the results of the analysis. Not only that, lesser years of education were also identified as factors that would lead to poorer performance in the TMT, especially for TMT B (Tombaugh, 2004).

With regards to ethnicity, the explanation for the Indian ethnicity's performance is likely linked to the small number of participants – 15 out of the total 97 healthy subjects and those with bipolar disorder. There is also an interesting observation from a study in India which attempted to compare the performance of native, non-English speaking Indians with the given norms. They found that their subjects did indeed perform much worse than English-speaking subjects from other cultural groups. They also found that years of education and age were related to the performance, and proposed other factors that might have influenced these results, such as lack of familiarity with cognitive testing, and differences in styles of cognition (Bhatia et al., 2007). In a review by Fernandez et al which compared performance on the Trail Making Tests across several countries (including Argentina, Belgium, Canada, China, Denmark, Italy, New Zealand, Switzerland, the U.K, and the U.S.A), there were some differences in normative data, which they concluded were likely due to differences in administration of the test (Fernandez & Marcopulos, 2008).

Performance of the bipolar group on the TMT B was still significantly poorer after adjusting for confounding factors ($p=<0.05$), which is in line with the findings outlined in the direct comparisons and literature review. Interestingly, being of Chinese ethnicity was a protective factor, for better performance on the TMT B. The researcher

was unable to find studies linking these factors, but there have been several sources that found that Chinese and other Asian cultures with similar linguistic influence are better at numerical and mathematical tasks (Miller et al., 2005; Sarama & Clements, 2009). They attributed this to the regular sequence of number words in the Chinese language as well as the simplicity of the words.

For the DSTR, after multivariate analysis the performance of the bipolar group was still significantly poorer after adjusting for confounding factors, which indicates a deficit in executive functioning which is in line with the previous studies.

Thus given the results of impaired TMT B and DSTR performance, it can be concluded that executive function is impaired in bipolar patients, even in the euthymic state. This is in line with the findings from several studies, including the meta-analysis by Robinson et. al. which studied cognitive functions in euthymic bipolar patients (Altshuler et al., 2004; Robinson et al., 2006; Trivedi et al., 2007). Moderate to large effect sizes were found particularly in the domain of executive functioning (Robinson et al., 2006). Quraishi and Frangou found smaller effects sizes on impaired executive function in the euthymic state (Quraishi & Frangou, 2002). Robinson and colleagues gave possible explanations for the poor performance, such as presence of low-level residual symptoms and possible effects of medication (Robinson et al., 2006). However Goswami and colleagues still found evidence for cognitive dysfunction in euthymic patients who were free from mood stabilizers (Goswami et al., 2002), which suggests that the use of medication is not entirely responsible for these deficits.

6.6 Implications in clinical practice.

As a general conclusion of this study, patients with schizophrenia appear to have impaired attention and executive function, while bipolar patients have impaired executive function.

Impairment of attention and/or recent memory has deep impacts on many aspects of life, such as mathematical skills, deficits in social abilities, and forgetting to take medications (Trivedi et al., 2007). Zubieta and colleagues found that these impairments were correlated with a more severe disease course and worse occupational functioning (Zubieta et al., 2001). Malla et al. found that working memory and psychomotor retardation contributed to poor social relations, and thus community functioning (Malla et al., 2002). .

For executive dysfunction, most studies showed that both disease groups had a similar pattern of impairment, but with more diffuse deficits seen in the schizophrenia group. In the study by Martinez-Aran and colleagues, the schizophrenia group achieved significantly less number of categories in the WCST. They were also able to conclude that executive function (EF) and negative symptoms were good indicators of functional outcome in schizophrenia, while clinical variables were more indicative of functional outcome in bipolar (Martinez-Aran et al., 2002). Functional outcome was defined by Green et al. as including 3 aspects: 1) assessment of social problem solving, 2) success in rehabilitation, and 3) behavior in society (Green et al., 2000). They also found that vigilance (sustained attention), secondary verbal memory, EF and working memory were significantly related to functional outcome.

Apart from this, Gold et al. found that cognitive impairment, in particular visual spatial memory and EF were significant predictors of job tenure, i.e., the worse the performance, the shorter the duration to hold the job (Gold et al., 2002). Several other studies also found that WM and EF were predictors for work performance and

successful work rehabilitation in patients with severe mental illness (Bryson & Bell, 2003; Zaytseva et al., 2013). These authors also found improvement in work performance and tenure with cognitive or vocational rehabilitation.

Friedman and colleagues studied correlates of functional status of geriatric, chronically institutionalized schizophrenic patients and found that cognitive impairment was a major predictor of generalized functional deficits. The specific cognitive deficits were in verbal and visual spatial working memory, and EF, and they were correlated with deterioration of self-care (Friedman et al., 2002).

Fujii et al explored deficits in working memory and executive function independently and found the same results as the studies previously mentioned. When these deficits are considered collectively, they were associated with an overall poorer quality of life (QOL) (Fujii et al., 2004). Brissos and colleagues also explored the associations between psychopathology and neurocognitive deficits with QOL in patients with schizophrenia and bipolar. They found that QOL was more correlated with psychopathology in patients with schizophrenia, but both were more associated with lower QOL in bipolar patients (Brissos et al., 2008).

Thus it can be seen that the impacts of cognitive dysfunction in the lives of our patients with these illnesses are severe. It is therefore necessary for the healthcare providers to manage these patients as a whole and focus on cognitive rehabilitation as part of the overall management.

CHAPTER 7

STRENGTHS AND LIMITATIONS

7.1 Limitations

There were several limitations in this study:

1) The expected sample size for patients with bipolar disorder was 55. However the achieved sample size was 40. This may have been because many of the patients with bipolar disorder who were of the inclusion age group were often unwell and often recently warded, or had recently undergone ECT. The majority of patients with stable bipolar disorder who were approached in the clinic were of advanced age (more than 55 years).
2) The patient groups were only screened once for the assessment of clinical state. A series of screens over a period of time may have been more helpful.
3) Completion of the questionnaires and cognitive assessment was time consuming, ranging from 30 minutes to an hour, especially for those who had difficulty understanding the concepts of the questions and tasks. This caused a number of participants to become demotivated.
4) The neurocognitive assessment was not comprehensive enough and many aspects of cognitive function could not be assessed.
5) Most of the scales and tools used were in English, which was not the primary language of the participants.
6) This study was a cross-sectional study, in which data was collected at a point of time, thereby limiting further observations.

7) The sociodemographic variables were not comparable between the patient groups and healthy subjects. There were also many confounders that were not measured such as the types of medication used, and whether the patient had used benzodiazepines prior to doing the cognitive assessments.

7.2 Strengths

Despite the limitations noted above, this study has a few strengths:

1) This study is the first in Malaysia that attempts to compare cognitive functions in these illness populations with that of a healthy group.
2) Having a healthy control group for comparison also allows the observation of the extent of the cognitive deficits in the two patient groups.
3) All participants were chosen according to strict selection criteria to minimize confounding factors.
4) There were well-defined criteria for stability in schizophrenia and bipolar disorder patients.
5) Although the sample size for the bipolar group was not enough, an adequate number of schizophrenia patients and controls was enrolled.
6) The interviews were all conducted personally by the researcher and in separate rooms to ensure privacy. All the questionnaires were answered completely with no missing data. This study provides baseline data as a reference point for future studies.

CHAPTER 8

CONCLUSION AND RECOMMENDATIONS

8.1 Conclusions

The conclusions that can be drawn from this study are that patients with schizophrenia and bipolar disorder do have cognitive deficits, even in the remitted states, when compared to a healthy control group. Specifically for the schizophrenia group, the deficits were in attention and executive function. For the bipolar group, the deficit was in executive functions. In the TMT A, age and Indian ethnicity were independent risk factors for poorer performance. For the TMT B, Chinese ethnicity was a protective factor. DSTF was not a sensitive test for verbal working memory in both the illness populations. DSTR however was a sensitive test for detecting executive dysfunction in both the patient populations.

8.2 Recommendations

Based on the findings from this study and the literature review, it is now understood that cognitive dysfunction is present in both illnesses even in the stable state, and thus there is a need for measures to be taken to screen for or detect these deficits, from much earlier in the course of illness, and also worthwhile to assess the neuropsychological changes over time. Haring and colleagues found evidence for cognitive dysfunction even in the first episode of psychosis, albeit with variabilities in the type, direction and changes in size of the affected cognitive functions over time (Haring et al., 2017).

Although the outlook appears bleak for this group of patients, there has been evidence for the potential of improving the functional outcomes of cognitive dysfunction via cognitive interventions (Kurtz et al., 2001; Penades et al., 2002). Other studies have found that second generation antipsychotics may also improve cognition in schizophrenia and schizoaffective disorder (Bilder et al., 2002; Fujii et al., 1997). Thus by these interventions, we help to modify the individual's disease course and improve their quality of life.

Recommendations for similar studies in future include:

1) Use of more cognitive assessment tools for a broader range of cognitive functions, that have been proven to be more sensitive and specific to the local population.
2) Screening of patients over a period of time, and not just at one point of time, to ensure stability state.
3) Larger sample sizes for more accurate statistical analysis.

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