# A Comparative Neuropsychological Evaluation of Individuals Over 65 years of Age who Present with Either Very-Late-Onset Schizophrenia-Like-Psychosis, Chronic Schizophrenia or a Late Onset Psychotic Depression.

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# Abstract

Widespread cognitive deficits have been consistently associated with psychosis. However there still remains little research examining cognitive deficits in older individuals with psychosis. Moreover there has been little consideration of the potentially different cognitive profiles of elderly individuals with a chronic yet typical onset schizophrenia (Chronically Ill, Typical Onset Schizophrenia: TOS), those of a similar age who had presented with a first-episode of schizophrenia psychosis when 60 years or more (i.e. a Very-Late-Onset Schizophrenia-Like-Psychosis: VLOSLP), and older individuals who had presented with a first-episode of psychotic depression when 60 years or more (i.e. a Late-Onset Psychotic Depression: LOPD). Existing research has utilised either limited cognitive screening tools, or abbreviated neuropsychological batteries, thus limiting comprehensive cognitive profiling of these populations.

The primary research objective of this Doctoral thesis is to better characterize the cognitive profile of elderly individuals with VLOSLP. The second objective is to compare and contrast the cognitive profile of this VLOSLP group with that of both a similarly aged elderly TOS group and LOPD control group. The general clinical aim is to identify any specific cognitive challenges for elderly individuals with a schizophrenia psychosis.

Twenty-five individuals with VLOSLP, 27 individuals with TOS and 18 individuals with a LOPD completed a comprehensive neuropsychological battery assessing various domains including attention, working memory, motor speed and speed of information processing, learning and memory, and executive functioning. Demographic information and clinical and social functioning measures were also collected.

The results indicated that individuals with VLOSLP showed a wide range of performance across the domains from within the average range to within the impaired range. Analyses of group differences revealed that the LOPD group performed significantly better than the two

schizophrenia groups, and within the average range on the majority of cognitive domains assessed. The cognitive profiles of the two elderly schizophrenia groups were similar across the majority of domains, with the performance of the VLOSLP group being somewhat better overall than that of the elderly early-onset group, albeit not significantly so.

Given the wide range of performance noted in the VLOSLP group, exploratory cluster was conducted and identified two statistically distinct Clusters. Follow-up comparisons of these two Clusters and the TOS group revealed that one Cluster's neuropsychological performance was similar to that of the TOS group, demonstrating widespread cognitive impairments, and with subtle indications of slightly greater impairment. The other Cluster presented with largely intact cognitive performance.

These preliminary findings raise more questions than answers. The first is whether only some individuals with a VLOSLP present with a classic schizophrenia illness characterised by widespread cognitive impairment consistent with TOS. The second is why this illness appears to cause greater cognitive impairment in this subset than seen in TOS. Alternatively, does this subset show the signs of an early neurodegenerative dementing condition, distinct from schizophrenia? Future longitudinal studies will be needed to answer these questions.

# Declaration

I certify that the work in this thesis entitled "A comparative neuropsychological evaluation of individuals over 65 years of age who present with either very-late-onset schizophrenia-like-psychosis, chronic schizophrenia, or late onset psychotic depression" has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree to any other university or institution other than Macquarie University. I also certify that the thesis is an original piece of research and it has been written by me. In addition, I certify that all information sources and literature used are indicated in the thesis.

As the author, I was responsible for the study conception and design, ethics application, data collection, data analysis, interpretation of the results, and preparation of the manuscript for publication. Dr Alan Taylor provided guidance on the statistical approach. Associate Professor Robyn Langdon provided guidance throughout the initial study design, data collection and provided feedback on the manuscript.

All of the research was conducted while I was employed as a Clinical Neuropsychologist with Sydney West Area Health Service.

The research in this thesis was approved by the Macquarie University Human Ethics Committee, reference number: HE01MAY2009-D06486 and the Sydney West Area Health Service Ethics Committee: 2007/12/4.10(2704) AU RED HREC/07/WMEAD/86.

Signed:……. Date:…….

# Chapter 1. Symptomatology, Epidemiology, Cognitive and Neuroanatomical Changes in Schizophrenia

## 1.1 Introduction

Schizophrenia remains one of the most complex and puzzling psychiatric illnesses. In the more than a hundred years since Emil Kraepelin (1896) first identified the condition as a disease entity, and despite the expansive amount of research conducted into the illness, there is little consensus today about its underlying cause, progression or indeed whether it is a unitary disease entity. This Chapter will begin by providing a brief overview of schizophrenia including discussion of symptomatology, epidemiology, and the clinical course of the illness. The major focus of this Chapter however is the cognitive and neuroanatomical changes associated with the illness and how these cognitive changes impact on an individual's functional abilities. This Chapter also briefly examines whether or not these cognitive deficits are ameliorated by current treatment methods.

## 1.2 Schizophrenia – General Overview

Today, schizophrenia ranks among one of the top ten causes of lifelong disability in developed nations (Murray & Lopez, 1996). It is a multifaceted and heterogeneous condition that is characterised by a range of features including 'positive' and 'negative' symptoms, neurocognitive deficits, and social, personal and occupational dysfunction. Schizophrenia impacts on a person's perception of the world, their emotions, speech, movement and their cognitive functioning, thus detrimentally affecting nearly every aspect of their daily functioning.

To date, there is no biological test to diagnose schizophrenia. The diagnosis is formed on the basis of clinical interviews and observations. Positive and negative symptoms are the most important diagnostic criteria. Positive symptoms refer generally to those symptoms characterised

by an excess or distortion of normal behaviour, or to the more active manifestations of abnormal behaviour (Barlow & Durand, 1995). For example, positive symptoms include delusions, hallucinations, disorganised speech, thought disorder and grossly disorganised or catatonic behaviour. Negative symptoms involve deficiencies in normal behaviour, for example, flat affect, alogia (lack of speech), avolition, anhedonia (i.e., loss of pleasure) and asociality. For some individuals with schizophrenia these positive and negative symptoms develop slowly, though in others these symptoms can onset very suddenly. Individuals with schizophrenia also tend to have poor insight into both the fact that they have a mental illness and also their symptoms, as well as the impact of these on their level of daily functioning.

### 1.3 The Impact of Schizophrenia

The estimated economical and financial cost of schizophrenia is substantial. Carr, Neil, Halpin, Holmes and Lewin (2003) reported the annual cost of schizophrenia for the Australian urban population in the year 2000 to be $601 million in terms of mental health care costs and $1.44 million in total costs, which includes both direct costs related to illness treatment and the costs associated with time / productivity losses.

The financial and health care burden of schizophrenia is long term given it is a chronic illness. Despite advances in the medical and psychological management of the illness, the majority of individuals with the illness are likely to have continued difficulty with functioning independently in society. Importantly, these functional difficulties tend to continue even when the psychotic symptoms respond to medication. Most individuals with schizophrenia will fluctuate between moderate and severe levels of functional impairment throughout their lives (Barlow & Durand, 1995). Obviously the impact of this illness has a tremendous effect on an individual and their families and friends' emotional wellbeing.

## 1.4 Schizophrenia – Epidemiology

The long-term financial and health care burden of the illness is somewhat directly attributable to the age of onset of the illness, which typically occurs in late adolescence to early adulthood between the ages of 15 and 25 (Barlow & Durand, 1995). However, there is vast heterogeneity in regards to the age of onset and outcome of the illness. It is widely accepted that men tend to develop the illness earlier than women on average (Salokangas, Honkonen & Saarinen, 2003). The age of onset for men has been typically found to be between the ages of 16 and 25 (average 18), whereas women develop symptoms several years later (at approximately 25 years of age). One explanation for this gender-bound age difference in age of onset is thought to be the antidopaminergic effects of estrogen that may provide some protection for premenopausal women (Hafner, 2003). This estrogen protection hypothesis is supported by a second peak in the incidence of the illness shown in women after the age of 50 following menopause, when the possible protective estrogen levels are subject to further decline (Riecher-Rossler & Hafner, 2000; Hafner, 2003). There is also a generally higher incidence of women in the Very-Late-Onset Schizophrenia-Like-Psychosis (VLOSLP) populations (i.e., with onset over the age of 60 years) which will be discussed further in later Chapters.

The varying age of onset has also been associated with other factors regarding the illness. For example, research has also demonstrated that earlier onset of the illness corresponds linearly with a poorer illness prognosis in both the short and long term (Rabinowitz, Levine & Hafner, 2006). Specifically, earlier age of onset has been linked to poorer educational and vocational adjustment (Lay, Blanz, Hartmann & Schmidt, 2000), decreased likelihood of ever being married (Jeste et al., 1995), poorer response to antipsychotic medication (Hollis, 2000; Meltzer et al., 1997), and greater chance of readmission (Eaton et al., 1992). Those with an earlier age of onset are also more likely to have relatives with schizophrenia (Rabinowitz et al., 2006), adding to the

evidence for a stronger genetic contribution in the earlier-onset cohort.

Schizophrenia occurs in all societies regardless of one's class, culture, colour or religion. A review paper of 188 studies from over 46 countries, examining the prevalence of schizophrenia, by Saha, Ghant, Welham and McGrath (2005) found that the median point prevalence (i.e., the prevalence of those who had the illness at a particular time point) was in the order of 4.6 per 1,000. The point prevalence for this figure was determined by papers examining the incidence of the illness over a period of one month or less. The prevalence for one month to one year was found to be 3.3 per 1,000 and lifetime prevalence estimates were in the order of 4.0 per 1,000. This review paper also estimated the lifetime morbid risk for individuals with schizophrenia to be 7.2 per 1,000.

Incidence rates of schizophrenia have however varied across studies. Some of these variations in incidence rates have been attributed to differences in diagnostic classifications across the various studies. For example, a ten country study conducted by the World Health Organisation in 1992 (Jablensky et al., 1992) examined the incidence of schizophrenia across developing and developed nations. This study utilised a consistent diagnostic classification and interviews were conducted using joint assessments. Two diagnostic classifications were used based on a computerised program, one utilising a broad set of diagnostic criteria and the other more narrow. Utilising these two classification criteria, Jablensky et al. (1992) reported an annual incidence range from 14-40 per 100,000 people (.14-.4/1000) across the ten participating countries. Jablensky et al. (1992), utilising the more narrow definition of schizophrenia, also found little difference in the incidence rate between the ten countries. However, a more recent comprehensive review by McGrath et al. (2004) of over 150 studies from over 33 countries encompassing the years 1965 to 2001 identified a wider range of between 7.7 to 43.0 per 100,000, with a mean incidence rate of 15.2 per 100,000. Of more import, McGrath et al.'s

(2004) review challenged the belief that the incidence of schizophrenia is uniform around the world. The incidence rates in their 2004 review varied more than fivefold from the lowest to the highest.

## 1.5 The Clinical Course of Schizophrenia – Progressive Deterioration, Amelioration or Both?

As with the age of onset, there is also vast heterogeneity in regards to the clinical course of the illness. A great deal of debate has existed in the literature as to whether or not schizophrenia is a stable / remissible or progressive illness. The early writings of Kraepelin about the illness he termed "dementia praecox" described an illness characterised by a largely therapy resistant mental illness that starts early and tends to grow more severe with every episode of the illness and one that finally results in a dementia-like state (Hafner, 2010). This view of a progressively deteriorating illness however is one that has been more recently challenged.

Research from Denmark using population based psychiatric hospitalisation registries is among the more influential studies that have provided evidence to challenge the notion of schizophrenia as a degenerative / deteriorating illness (Olesen & Mortensen, 2002). Findings from this Denmark study indicated that deterioration was only observed in a small group of patients. In more detail, the results of previous studies which had utilised longitudinal national population-based data on readmission rates from the Israeli National Psychiatric Case Registry (collected between 1978 and 1996) have been reanalysed. This data had originally been interpreted and reported to identify what appeared to be a progressively deteriorating course of schizophrenia. However, the reanalysis showed that the original group result was directly attributable to only a smaller sub-group of patients (24.8%) who were characterised by a high level of readmission (Rabinowitz, Levine, Haim & Hafner, 2007). Rabinowitz and colleagues

concluded that the majority of patients with schizophrenia in their study (75.0%) demonstrated a course of progressive amelioration. In addition, Levine, Lurie, Kohn and Levavm (2011) conducted an expansive study over a 34 year period of follow up that further supported this latter pattern of amelioration. Their findings indicated that, up to the age of 23, the course of schizophrenia is one of progressive deterioration, whereas following this age, the illness tends to assume a course of progressive amelioration (on average).

## 1.6 Schizophrenia and Cognition

Research over the past twenty to thirty years has also begun to focus on the cognitive profile of individuals with schizophrenia and the course of these deficits. It has now been well established that cognitive impairments are a core feature of schizophrenia and schizophrenia is now being viewed as, not only a psychotic illness, but also a disorder of neurocognition (Green & Nuechterlein, 1999). The acknowledgement that cognitive deficits are a core feature of the illness has seen an explosion of research into cognition in schizophrenia over the past three decades. Approximately 85% of individuals with schizophrenia have been found to be impaired on comprehensive neuropsychological assessments (Mortimer, 2008). In studies comparing current functioning to premorbid estimates, nearly all individuals with schizophrenia are found to be cognitively compromised following onset of psychosis, with findings of as high as 98% of these individuals showing deterioration in at least one cognitive domain (Keefe, Easley & Poe, 2005). The following section will provide a background into the type, extent and impact of cognitive impairments in schizophrenia.

## 1.7 Premorbid Cognitive Functioning and Vulnerability to Schizophrenia

The early identification of premorbid factors related to vulnerability to schizophrenia is

part of the growing evidence for a neurodevelopmental model for schizophrenia. It has been hypothesised that the neurodevelopmental processes active during adolescence are somehow involved in the deterioration in cognitive and real-world functioning associated with the onset of schizophrenia (Cannon & Clarke, 2005). The areas of normal healthy brain development active during adolescence involve both an increase in neuronal efficiency in combination with a pruning of excess synapses. It also involves the myelination of axonal connections in the prefrontal / frontal brain regions which are critical for normal executive functioning (Cannon & Clarke, 2005).

One major line of research examining premorbid functioning and vulnerability to schizophrenia has focused on children who are at higher risk of developing schizophrenia in later life, specifically the genetically pre-disposed children of parents who have schizophrenia. One of the earliest studies was the Jerusalem Infant Development Study, which followed from birth individuals who were born to parents with schizophrenia and other children born to parents with other mental health disorders (as well as a group of control children born to parents without any diagnosed mental illness). They found that 44% of the children born to parents with schizophrenia demonstrated neuro-behavioural dysfunction (specifically, difficulties in the areas of perceptual, cognitive and motor functioning), in contrast with only 24% of the children whose parents had other mental health disorders, and 15% of the healthy control children (Marcus, Hans, Auerbach & Auerback, 1993).

Several studies have further indicated that individuals identified as being at high-risk of developing schizophrenia often have difficulties on tasks assessing higher level cognition, particularly executive function. Research by Mirsky, Ingraham and Kugelmas (1995), involving the Israel high-risk study, for example, found that high-risk adolescents performed worse than low-risk controls on the Wisconsin Card Sorting Test (WCST: Heaton, 1981), believed to assess

novel problem solving. High-risk children and adolescents were also found to perform poorly on the Trail Making Test-Part B (Trails B) (Reitan & Wolfson, 1985), a test of cognitive flexibility, compared to low-risk controls (Mirsky et al., 1992).

Another study, the Edinburgh High Risk Study, found that high risk subjects performed significantly worse than controls in the following cognitive and behavioural domains; general intellectual functioning, mental control, motor speed, learning and memory, and executive functioning (Byrne, Hodges, Grant, Owen & Johnstone, 1999). Specifically, they found that the high risk individuals had significantly lower mean verbal, performance and full scale IQ scores. They were also found to perform poorer than controls on the Hayling Sentence Completion Test (HSCT: Burgess & Shallice, 1997) which is a measure of response initiation and response suppression, making significantly more errors than the control group. The male high risk group were found to perform significantly worse than the male control group on the Arithmetic subscore from the Wechsler Adult Intelligence Scale-Revised (WAIS-R, Wechsler, 1981) (though this difference was not seen in females). The high risk group was also found to perform worse on all measures of learning and memory from the Rey Auditory Verbal Learning Test (RAVLT), Wechsler Memory Scale – Revised (WMS-R, 1987) and the Rivermead Behavioural Memory Test (Wilson et al., 2008). Trends towards significant group differences were noted on several other tasks including one that assess inhibition, and measures of semantic fluency (specifically animal naming fluency) and WAIS-R vocabulary scores. These findings could be taken as support that there exists a genetic predisposition, associated with a relative cognitive impairment, in individuals who will later develop schizophrenia.

However, it should also be noted that a large number of individuals who go onto develop schizophrenia have no positive family history of the disorder. Research therefore has also utilised longitudinal population based studies to investigate the potential early cognitive

difficulties in those who are not genetically at risk and yet who later develop schizophrenia. A recent meta-analysis of longitudinal population based studies by Khandaker, Barnett, White and Jones (2011), examining solely premorbid IQ, indicated the presence of an IQ deficit of 0.4 standard deviations (or 6 actual IQ points) below that of the controls among young people who later go onto develop schizophrenia. They also found a linear association between schizophrenia and IQ, in that there was a 3.7% increase in risk for developing schizophrenia for every 1-point decrease in premorbid IQ. Khandaker et al. (2011) also reported that greater premorbid IQ deficits were strongly associated with an earlier age of illness onset in those who went on to develop schizophrenia.

Another alternative line of research has been to study individuals at ultra-high risk of developing schizophrenia. Generally this research has involved studying individuals who are clinically deemed to possibly be in the prodromal stages of a psychotic illness. For example Brewer et al. (2005) conducted a comprehensive neuropsychological assessment of individuals who were deemed at ultra-high risk due to the presence of either a genetically high risk *plus* a recent decline in functioning, or attenuated symptoms, or brief intermittent psychotic symptoms, and who were aged between 14 and 29. They found that the ultra-high risk individuals who went on to develop psychosis performed worse than those who did not on the Logical Memory and Visual Reproduction subtests on the WMS-R. Similar results were observed by Lencz et al. (2006), who found that individuals at ultra-high risk of developing schizophrenia showed significant deficits relative to healthy controls in both premorbid IQ (Wide Range Achievement Test – 3rd Edition; WRAT-III: Wilkinson, 1993) and current IQ (WAIS-R or Wechsler Intelligence Scale for Children – 3rd Edition: Wechsler, 1991). They also found significant differences between the two groups on various domains of cognition including attention (Continuous Performance Test – Individual Pairs; CPT, Conners et al. 2000), Letter Number

Span, Digit Span; (WAIS-R), motor speed (Trail Making Test, Part A; Strauss et al., 2006, Finger Tapping and Grooved Pegboard Test), verbal memory (California Verbal Learning Test, WMS-R), language (Vocabulary and Information (WAIS-R), Boston Naming Test (BNT; Kaplan et al., 2001), WRAT-III) and executive / working memory (indexed by the WCST, Controlled Oral Word Association Test (COWAT: Lezak, 1995), Trails B, Ruff Figural Fluency Test (Ruff, 1988). No significant differences were found between the two groups on the domain of visuospatial functioning. Analysis conducted on the at-risk individuals who were later diagnosed with a psychotic illness versus those at risk individuals who remained nonpsychotic indicated that only verbal memory emerged as a significant predictor of conversion to psychosis in at-risk individuals.

Thus, as can be seen, there is evidence to suggest there is early cognitive abnormalities in individuals with or without a genetic vulnerability who later go on to develop schizophrenia. The following sections will focus more specifically on the different domains of intellectual and cognitive functioning that become impaired in those diagnosed with schizophrenia.

## 1.8 Current Intellectual and Cognitive Functioning in Schizophrenia

There exists ample research investigating cognitive deficits in individuals diagnosed with Schizophrenia. As detailed in the following sections, many studies provide evidence for general intellectual decline, in addition to more specific cognitive impairments in areas of attention, working memory, speed of processing, learning and memory, and higher level executive functions. Deficient social cognitive processes have also been routinely identified. A summary of research findings within each of these domains in Schizophrenia will be covered in the following sections.

### *1.8.1 Intelligence*

There is a general consensus in the literature that individuals with schizophrenia have a lower overall Intelligence (IQ) than their aged matched peers (van Winkel et al., 2006). For example, Johnson-Selfridge and Zalewski (2001) identified a group of individuals with schizophrenia whose mean IQ was within the average range; though nevertheless their IQ was approximately 12.5 points below the mean of the normal control group. Individuals with schizophrenia have also been shown to display lower full scale IQ scores than other psychiatric groups including those with unipolar depression and bipolar disorder (Goldberg et al., 1993; Salome et al., 1998). A further relevant finding is that performance (or nonverbal) IQ is typically lower than verbal IQ in individuals with schizophrenia (Heaton & Drexler, 1987).

As with lower IQ in other clinical and psychiatric conditions, a lower IQ in schizophrenia has also been found to be associated with poorer outcomes. For example, lower IQ in schizophrenia has been found to be associated with both a poorer overall level of functioning in addition to poorer overall outcomes (Kremen, Seidman, Faraone and Tsuang, 2001). More specifically, Kremen et al. (2001) demonstrated that individuals with schizophrenia and a lower IQ displayed greater relative cognitive deficits on tasks involving attention-vigilance than did individuals with schizophrenia in the average to high average IQ group. However, regardless of this relative protective element of a higher IQ in schizophrenia, individuals with schizophrenia with a higher overall level of cognitive functioning still display a relative neurocognitive decline in specific isolated cognitive domains.

### *1.8.2 Attention / Working Memory*

Declines in premorbid functioning in the area of attentional skills have also been found in schizophrenia, with impairments of attention now being regarded as both a core deficit of, and an

underlying mechanism of, other cognitive impairments (Bowie and Harvey, 2006). However, as with other cognitive functions, substantial variation exists across individuals with schizophrenia, and the precise nature of these attentional impairments is not yet clear. Evidence has been presented, however, to suggest that any impairment in attention cannot be considered as secondary to symptoms; for example, poor attention in schizophrenia is neither due to distraction from positive psychotic symptoms nor due to poor motivation related to negative symptoms (Chen et al., 1997; Nuechterlein, Edell, Norris & Dawson, 1986; Addington & Addington, 1998).

Studies of sustained attention in schizophrenia which test the participants' ability to maintain optimal concentration on a specific task over an extended period of time have also consistently reported impairments in individuals with schizophrenia (Nestor et al., 1991; Green & Walker, 1986; Cornblatt, Risch, Faris, Friedman and Erlenmeyer-Kimling, 1988). Research into visual sustained attention deficits utilising the CPT have consistently shown individuals with schizophrenia have a lower ability to discriminate targets from non-targets (Franke, Maier, Hardt, Hain and Cornblatt, 1994; Laurent et al., 1999), and also show a higher rate of random errors (Franke et al., 1994; Laurent et al., 1999) compared with controls. These results have been found irrespective of chronicity or illness severity (Cornblatt & Malhotra, 2001). Deficits in sustained attention have also been reported amongst biological relatives of individuals with schizophrenia and non-clinical adults with schizotypal personalities (Jones et al., 2001). These results have led researchers to suggest that deficits in sustained attention represent a trait deficit in individuals with schizophrenia and may possibly be used as a vulnerability marker for the illness. Deficits in sustained attention have also been found to be highly correlated with negative symptoms in schizophrenia (Addington & Addington, 1997; Niewenstein, Aleman & de Haan, 2001, O'Grada et al., 2009).

Similar impairments have been found on tasks of selective attention, where individuals

with schizophrenia have been found to be generally more distractible than controls (Carter et al., 2010; Oltmanns & Neale, 1975; Baruch, Hemsley & Gray, 1988). In accordance with this view, Asarnow, Granhom and Sherman (1991) used the Span of Apprehension Task (Asarnow & Nuechterlein, 1994) to show that individuals with schizophrenia have significantly greater difficulty attending / dividing attention across a number of different items at once, compared to normal controls.

Individuals with schizophrenia have also been shown to perform worse than normal controls on immediate serial recall tasks assessing verbal attention span (Oltmans & Neale, 1975; Frame & Oltmans, 1982). Further examination of the impaired performance on these particular memory tasks has, however, suggested that these individuals' impaired performance is more likely to be a result of their vulnerability to distraction, rather than an inability to retain information in a short term memory store (Weiss, Vrtunski & Simpson, 1988).

Verbal and visuospatial working memory deficits, which are not solely reducible to attentional deficits, have also been identified in individuals with schizophrenia (Glahn et al., 2003; Park & Holzman, 1992; Gold, Carpenter, Randolph, Goldberg & Weinberger, 1997; Perlstein, Carter, Noll & Cohen, 2001). Working memory, in comparison to long term memory (discussed below), refers to one's limited capacity store for retaining and manipulating information over a very short period of time (i.e., from seconds to 1-2 minutes). A commonly used verbal working memory task that reveals deficits of this type in individuals with schizophrenia is the Digit Span Backwards Task (WMS-III), while a commonly used visuospatial working memory task that likewise reveals deficits in individuals with schizophrenia is the Spatial Span Backwards Task (WMS-III). Meta analytic reviews have summed up the findings to report that working memory deficits in individuals with schizophrenia are present for all modalities, across a range of methodologies, and are not accounted for simply by the differences

in overall IQ between these individuals and control groups (Lee & Park, 2005; Forbes, Carrick, McIntosh & Lawrie, 2009).

Nuechterlein et al. (2004) published a paper as part of the initiative to encourage the development of new interventions for cognitive deficits in individuals with schizophrenia, with this initiative named the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). One of their aims was to develop both a valid and reliable cognitive battery for use in individuals with schizophrenia. In doing so, they identified eight core areas of cognitive impairment in schizophrenia; impairments in attention, vigilance and working memory were all included as areas showing core deficits in individuals with schizophrenia.

### *1.8.3 Psychomotor Speed and Speed of Information Processing*

Problems with psychomotor slowing have also long been recognised in individuals with schizophrenia and were identified in the early writings of both Kraepelin and Bleuler (Morrens, Hulstijn & Sabbe, 2007). Slower psychomotor speed and speed of information processing is observable in the majority of individuals with schizophrenia, notably in their verbal responses but also in their slowed motor functions, with both gross and fine motor movements affected. Processing speed was also included in the MATRICS study by Nuechterlein et al. (2004) as one of the eight cognitive domains independently compromised in schizophrenia. Consistent with these observations, research has consistently reported prolonged reaction times in experimental studies involving individuals with schizophrenia (Morrens et al., 2007; Nuechterlein, 1977; Zahn & Carpenter, 1978), as well as slow handwriting (Henkel et al., 2004; Van Hoof, Jogems-Kosterman, Sabbe, Zitman & Hultijn, 1998) and poorer performance on other neuropsychological tasks tapping both motor speed and speed of information processing, including the Symbol Digit Substitution Test (Brebion et al., 2000), Trails, Grooved Pegboard

Task, Token Motor Test (Keefe, 2004) and Finger Tapping tasks (see. e.g., Morrens et al., 2007).

### *1.8.4 Learning and Memory*

Deficits of verbal and visual learning and memory were also included among the core cognitive impairments observed in individuals with schizophrenia in the influential MATRICS study (Nuetcherlein et al., 2004). Impaired performances on various measures of learning and memory, including the Wechsler Memory Scales and list learning tasks, are well documented in individuals with schizophrenia. Impairments are noted across all stages of memory functioning including encoding, consolidation and later retrieval (and also delayed recognition skill) (Saykin et al., 1991; Nathaniel-James, Brown & Ron, 1996; Calev, 1984; Calev, Venables & Monk, 1983; Calev, Berlin & Lerer, 1987). Further, a meta-analysis conducted by Aleman, Hijman, de Haan and Kahn (1999), examining 70 studies, reported that individuals with schizophrenia presented with severe impairments on tests of both delayed and free recall of verbal information, but with only moderate impairments of recognition memory as compared to control groups. Compared to the findings for immediate and delayed declarative memory tests, tests of procedural, implicit and long term semantic memories have typically revealed relatively spared capacities in individuals with schizophrenia (Green, 1998). It has also been noted that the more severe impairments are found in verbal memory performance as compared to visual memory performance in schizophrenia (Stevens, Goldman-Rakic, Gore, Fullbright & Wexler, 1998). The deficits in verbal and, to a lesser extent, visual learning, and declarative memory that have been noted in schizophrenia are enduring features of the illness (Saykin et al., 1991; Paulsen et al, 1995; Paul, Elvevag, Bokat, Weinberger & Goldberg, 2005), disproportionate to the level of overall cognitive functioning (Saykin et al., 1991; McKenna et al., 1990), and not attributable to deficits in either attention (Saykin et al., 1991) or poor motivation (Duffy & O'Carroll, 1994;

McKenna et al., 1990; Gruzelier, Wilson, Liddiard, Peters & Pusavat, 1999).

Some inconsistent findings have been reported, however, for research examining the impact of serial order position in the recall of individuals with schizophrenia. In more detail, primacy and recency effects are typically seen when an individual is asked to free recall a list of words. People tend to recall those items at the end of the list more easily (recency effect), and also those words presented at the start of the list (primacy effect). Stirling, Hellewell and Hewitt (1997) demonstrated both reduced primacy and recency learning effects in 27 individuals with schizophrenia. However, in contrast to Stirling et al.'s (1997) findings, Elvevag, Weinstock, Akil, Kleinman and Goldberg (2001) found near normal recency effects in individuals with schizophrenia, though they did report findings to support impaired primacy effects.

While memory impairments are enduring in individuals with schizophrenia, some studies have also demonstrated that these impairments are modifiable, with individuals successfully being taught how to better utilise encoding strategies (Koh, Kayton & Peterson, 1976). This evidence has been used to suggest that acquisition and retrieval deficits in the memory performance of individuals with schizophrenia are at least partly due to poor use of organisational strategies (Medalia, Revheim & Casey, 2000). That is, executive dysfunction, which is another well documented feature of the illness, may result in an inability to spontaneously employ such organisational strategies that assist effective learning of information in these individuals (Paul et al., 2005). Support for this view is seen in research that has shown that individuals with schizophrenia, when presented with a word list to learn and recall, show a greater reliance on rote rehearsal as their sole strategy than controls (Brebion, David, Jones & Pilowsky, 2004; Gold, Randolp, Carpenter, Goldberg & Weinberger, 1992).

While much research supports the presence of learning and memory deficiencies, several studies have shown that, as with most features of the illness, there is considerable heterogeneity

in the memory profile of individuals with schizophrenia. Paulsen et al. (1995) found that 35% of these individuals had a normal memory profile, 50% had a profile where free recall was impaired but recognition memory was preserved, and 15% were found to have both impaired recall and impaired recognition. Similar results were found by Abi-Saab, Fiszdon, Bryson and Bell (2005).

A smaller number of studies have also investigated prospective memory (i.e., the ability to remember to do something at a particular moment in the future – or remembering to remember) in individuals with schizophrenia. Woods, Weinborn, Posada and O'Grady (2007) found prospective memory deficits in individuals with schizophrenia on both time-based (e.g., "In fifteen minutes tell me it is time to take a break") and event-based (e.g., "When I hand you a postcard self address it") prospective memory tasks. Similarly, Henry, Rendell, Kliegel and Altgassen (2007) found individuals with schizophrenia were impaired on prospective memory tasks, irrespective of the specific task demand. Specifically, they found individuals with schizophrenia performed poorly on all time- and event-based tasks, whether these were tasks that an individual undertakes regularly during their normal daily duties or tasks that occur only occasionally. Henry et al. (2007) also controlled for IQ, executive dysfunction and retrospective memory dysfunction and found that the prospective memory deficits in the schizophrenia group still remained significant. They concluded that this was indicative of primary impairments in prospective memory in schizophrenia. A study by Wang et al. (2008) replicated these latter findings and confirmed that patients with schizophrenia performed significantly worse than controls on prospective memory tasks.

Overall, whilst considerable heterogeneity exists regarding learning and memory profiles within schizophrenia, current research suggests that both verbal and visual learning and memory recall deficits are pervasive and enduring features of the illness. The following section addresses higher level executive dysfunction in schizophrenia, which as mentioned above can impact on an

individual's ability to both learn and recall new information effectively.

### *1.8.5 Executive Functions*

Clinical descriptions of individuals with schizophrenia having poor planning skills, impaired social judgment, poor insight and lack of initiative are extremely common. As a result, several researchers, including Kraeplin in 1919, have hypothesized that impaired executive functioning is a core aspect of schizophrenia. In support of this view, impairments in volition, abstraction, theory of mind, problem solving, planning and organisation, self-monitoring, inhibition, verbal fluency, sequencing and cognitive flexibility have all been well established in individuals with schizophrenia (Delahunty, Morice & Frost, 1993; Enticott, Ogloff & Bradshaw, 2008; Mazza, De Risio, Tozzini, Roncone & Casacchia, 2003; Seidman, 1983; Gold & Harvey, 1993; Yogev, Hadar, Gutman & Sirota, 2003). In general, Johnson-Selfridge and Zalewski (2001) found that individuals with schizophrenia performed approximately one and a half standard deviations below the performances of normal controls on measures of executive functioning. However, as is found with other areas of cognitive functioning in schizophrenia, each individual is not affected uniformly (Goldberg & Weinberger, 1988; Shallice, Burgess & Frith, 1991).

Researchers using the WCST to test executive function abilities, such as problem solving, cognitive flexibility, ability to maintain set and impulse control, have found that individuals with schizophrenia tend to have difficulty attaining correct concepts on these problem solving measures (Grant & Berg, 2003). This study noted that these individuals typically attain fewer categories of the WCST, and also demonstrate difficulties by perseverating on the incorrect response even after feedback regarding the correct response has been given (Stuss et al., 1983). Goldberg, Weinberger, Berman, Pliskin and Podd (1987) also demonstrated that the

performances of these individuals on the WCST could be improved with card by card prompting, however as soon as this structure was removed, their performance returned to baseline levels.

One of the most commonly reported cognitive deficits in schizophrenia are seen on tasks of verbal generativity under certain constraints, such as on phonetic and semantic fluency tasks (Kolb & Whishaw, 1983; Goldberg & Weinberger, 1988; Moore, Savla, Woods, Jeste & Palmer, 2006). On these tasks, subjects are asked to quickly generate words under restricted conditions (e.g., generate words that belong to a particular phonemic category, such as starting with the letters FAS, or belonging to a semantic category, such as animals). Green, Kern, Braff and Mintz (2000) also found that a reduced ability to generate words on a phonetic fluency task was correlated with reductions in the levels of functioning of individuals with schizophrenia. These fluency deficits, particularly when seen on semantic fluency tasks, are often interpreted to represent a dysfunctional or disorganised semantic system, which has also been postulated to contribute to "formal thought disorder" in schizophrenia (Goldberg et al., 1998), as discussed in more detail below.

The term, formal thought disorder, when used in psychiatry, narrowly refers to a disturbance of speech, communication, or the "form" of thought, including, for example, poverty of thought, flight of ideas, perseveration in language use and loosening of associations. As an example of the role of semantic anomalies in formal thought disorder, Allen, Liddle and Frith (1993) found that schizophrenia patients had no general loss of lexical knowledge as compared to healthy controls, however, those patients with incoherence of speech produced more intrusions on a semantic fluency task than the healthy controls. Patients with poverty of speech also tended to prematurely terminate their performance on the same semantic fluency task.

In other related work on impaired performance on fluency tasks and relations with symptoms, Moore et al. (2006) found that patients with more severe negative symptoms had a

reduced ability to strategically switch between clusters on a semantic, Animal Fluency Task. That is, compared to healthy controls, individuals with more severe negative symptoms had significantly more difficulty using a strategy of switching between, say, identifying as many small animals as possible, then switching to naming large animals.

In all, it is clear that much evidence supports the view that higher level executive dysfunction is a common and persisting feature of schizophrenia.

### *1.8.6 Social Cognition and Schizophrenia*

Individuals with schizophrenia have also been found to present with impairments in social cognition (van Hooren et al., 2008). Social cognition is a multifaceted construct that comprises the cognitive operations that underlie one's social interactions, including perceiving, interpreting, managing and generating responses to social stimuli, such as the intentions and behaviours of others. Researchers have hypothesised that understanding the social cognitive impairments present in schizophrenia might provide insights into both the development and the persistence of the functional impairments seen in the illness. It has also been hypothesised that social cognition may serve as a mediating link between levels of neurocognition and an individual's community functioning (van Hooren et al., 2008).

A substantial amount of this social-cognitive research has focused on "theory of mind" (ToM) in individuals with schizophrenia. ToM refers to the capacity to attribute causal mental states, which are separate from reality, such as thoughts, beliefs, intentions and feelings to both oneself and others. Several tasks are used to assess ToM and include False-belief Tasks utilising either stories or pictures, which assess an individual's ability to understand that someone can act on the basis of a belief that in fact misrepresents reality (Frith & Corcoran, 1996; Brune & Bodenstein, 2005; Langdon et al., 1997). Another commonly used ToM task is the Hinting Task

(Corcoran, Mercer, & Frith, 1995), which is a measure of indirect speech comprehension. Frith (1992) originally hypothesised that impairments in ToM may underlie several symptoms of psychosis, including delusions of reference, persecution, and misidentification, and third person auditory hallucinations. Deficits in ToM have been identified in, not only adults with confirmed schizophrenia (Herold, Tenyi, Lenard & Trixler, 2002), but also children with schizophrenia (Pilowsky, Yirmiya, Arbelle & Mozes, 2000), as well as in ultra-high risk individuals (Chung, Kang, Shin, Yoo & Kwon, 2008), non-clinical individuals with high levels of schizotypal traits (Langdon & Coltheart, 1999), unaffected first degree relatives (Anselmetti et al., 2009; de Achaval et al., 2010; Janssen, Krabbendam, Jolles & van Os, 2003; Montag et al., 2012), and first episode patients (Bertrand, Sutton, Achim, Malla & Lepage, 2007). A meta-analysis highlighted that ToM deficits continue in individuals with remitted schizophrenia, that is, those no longer in the acute phase (Bora, Yucel & Pantelis, 2009). However, these authors also further reported that the ToM deficits were more severe during the acute phase of the illness. Further examination of the remitted patients in this meta-analysis showed that the impairments in ToM were correlated with general level of intelligence. Various hypotheses have been offered concerning the role of ToM impairment in schizophrenia. For example, Langdon and Coltheart (1999) have argued that the maintenance of delusions could occur in individuals with schizophrenia who are unable to reflect on beliefs as representations of reality, hence leading to the breakdown in the distinction between subjectivity and objectivity.

Other areas of social-cognitive research have focused on the capacity for empathy (i.e., the ability to understand and share the emotions and experiences of another individual/s) in individuals with schizophrenia. Empathy has been further broken down into two domains, emotional empathy (e.g., affective responsiveness) and, more pertinent to this review, cognitive empathy (or the cognitive understanding of other's emotional states). To date, research has

demonstrated impairments in both emotional and cognitive empathy in individuals with schizophrenia (Langdon, Coltheart & Ward, 2006; Achim, Ouellet, Roy & Jackson, 2011). Cognitive empathy can also involve engaging in and reasoning about and adapting to another individual's emotional point of view, whilst also maintaining a clear self - other distinction (Smith et al., 2012). Smith et al. (2012) reported deficits in self-reported empathy in individuals with schizophrenia. They also found that lower empathetic concern correlated with poorer episodic memory. Shamay-Tsoory, Shur, Harari and Levkovitz (2007) also identified impairments in cognitive empathy in individuals with schizophrenia compared to healthy controls. Furthermore, they found that the degree of impaired empathy was related to the severity of the individual's negative symptoms and to performance on tasks assessing executive function (such as flexibility and reversal).

Overall, such findings provide evidence for social cognitive impairments that accompany the multitude of other cognitive impairments in schizophrenia. Collectively, these findings highlight that the functional difficulties in schizophrenia are likely underlined by various differing cognitive, social and emotionally deficient processes, which, as described, can vary across individuals with this illness.

Underlying anatomical differences are next reviewed, in an effort to understand current knowledge of structural neural deficits underlying such functional deficits in schizophrenia.

## 1.9 Anatomy and Physiology of Schizophrenia and Related Neuropsychological Functioning at Different Stages of the Illness.

This review has thus far considered premorbid and current cognitive functioning in individuals with schizophrenia. The following section considers the underlying neuroanatomical basis for this illness and the associated cognitive deficits. Following sections also aim to address

the trajectory of cognitive impairment across the time-course of the illness (with a focus on current debate concerning whether schizophrenia is a neurodegenerative condition).

### *1.9.1 Structural and Functional Research Findings*

A large volume of anatomical research has demonstrated the presence of widespread neuroanatomical abnormalities in individuals with schizophrenia as compared to healthy controls. Studies have utilised a range of structural and functional imaging techniques as well as examining post-mortem tissue. Overall, these studies have identified abnormalities in regional grey matter volume and density throughout the brain (Shepherd, Laurens, Matheson, Carr & Green, 2012), enlarged ventricular volume (Davidson & Heinrichs, 2003; Glahn et al., 2008; Wright et al., 2000) and areas of white matter irregularities, particularly in the corpus callosum (Shepherd et al., 2012). More specifically, magnetic resonance imaging (MRI) studies have shown smaller volumes of overall global, frontal and temporal grey matter (Convit et al., 2001; Honea, Crow, Passingham & Mackay, 2005; Shenton, Dickey, Frumin & McCarley, 2001; Glahn et al., 2008; Rimol et al., 2010). Additionally, smaller volumes of the hippocampus (Rimol et al., 2010; Shenton et al, 2001), cerebellum, thalamus (Rimol et al., 2010), amygdala (Ellison-Wright, Glahn, Laird, Thelen & Bullmore, 2008; Rimol et al., 2010), insula, cingulate cortex, and post-central gyrus (Fornito, Yucel, Patti, Wood & Pantelis, 2009) have also been observed. Basal ganglia changes in schizophrenia have also been noted by several neuroimaging researchers, both when the brain is at rest and during the completion of various tasks (Manoach et al., 2000; Menon, Anagnoson, Glover & Pfefferbaum, 2001). Findings of structural basal ganglia changes have however been inconsistent, with reports of enlarged volume (Staal et al., 2000; Breier et al., 1992), normal volume (Gunduz et al., 2002) and also decreased volumes (Keshavan, Rosenberg, Sweeney & Pettegrew, 1998). Mamah et al. (2007) examined the various basal ganglia structures

individually in regards to the volume difference between individuals with schizophrenia and controls. Their results identified abnormally large volumes compared to total cerebral volumes in specific basal ganglia structures of the caudate nucleus, putamen and globus pallidus. This finding was supported by Rimol et al. (2010).

One of the most replicated findings in this general line of schizophrenia research to date is the evidence for enlarged volumes of the lateral ventricles among patients with schizophrenia compared to controls (Cobia, Csernansky & Wang, 2011; Honea et al., 2005; Rimol et al., 2010; Shenton et al., 2001; Shepherd et al., 2012; Wright et al., 2000; Weinberger, Torrey, Neuphytides & Wyatt, 1979). These changes have been noted in both first episode and chronic populations (Shepherd et al., 2012). Post mortem studies have also supported the imaging results with findings of lower brain weight (Harrison, Law & Eastwood, 2003) and smaller grey matter volume (Pakkenberg, 1987) in individuals with schizophrenia relative to controls. However, the exact cause(s) of the volume loss remains open for debate.

### *1.9.2 Associations with Cognitive Dysfunction*

Neuronal regional abnormalities, as discussed above, have also been directly linked to the various cognitive deficiencies, as previously reviewed in section 1.8. For example, in accord with the observation that impaired executive functioning is among one of the most commonly observed cognitive deficits seen in individuals with schizophrenia, various structural brain imaging studies have identified decreased frontal cortical volumes in schizophrenia (Andreasen et al., 1994; Harvey, Ron, DuBoulay, Wicks, & Lewis, 1993; Nopoulos, Flaum, Andreasen & Swayze, 1995). Functional brain imaging studies have also identified reduced frontal lobe activity, as well as decreased and inefficient functioning of the pre-frontal cortex during executive tasks which place demand on this brain region (Adreasen et al., 1992; Andreasen, et

al., 1996; McNeely, West, Christensen & Alain, 2003). Reductions in left orbito frontal cortex structures have also been noted and have been correlated with reductions in working memory and perceptual reasoning in schizophrenia (Schobel et al., 2009).

The superior temporal gyrus is another region of particular interest in schizophrenia because of its important network connections to critical temporal limbic brain regions, particularly in the left hemisphere, that play a major role in the production, interpretation and self-monitoring of language (Sun, Maller, Guo & Fitzgerald, 2009). Abnormalities in either the superior temporal gyrus, itself, or its elaborate networks is thought to be crucially involved in two of the hallmark symptoms of schizophrenia, that of auditory hallucinations and thought disorder (Shenton et al., 2001). In accord with this view, volume reductions have been noted in the superior temporal gyrus, (particularly in the left hemisphere), in several studies of individuals with both first episode and chronic stages of illness (Andreasen et al., 2002; Barta et al., 1990; Kasai et al., 2003; Rimol et al., 2010). A review conducted by Sun et al. (2009) identified 35 articles at that time that reported positive results regarding volume reductions in the superior temporal gyrus of people with schizophrenia. Memory dysfunction is another well described cognitive deficit in individuals with schizophrenia. To date, however, studies examining the specific relationship between structural brain volume loss and memory performance have produced inconsistent results. Research supporting such an association has found that volume reductions in the left dorsolateral prefrontal cortex in schizophrenia are associated with impairment of verbal recall (Seidman et al., 1994). Further, positive correlations have been found between hippocampal volume and word memory functioning in schizophrenia (Sanfilip et al., 2002). Baare et al., (1999) also found that reduced prefrontal cortex volumes were associated with verbal recall difficulties in individuals with schizophrenia but not in controls. However, other studies have demonstrated no significant relationship between brain volume and memory

performance in individuals with schizophrenia (Antonova et al., 2004).

Other findings have concerned the associations between cognitive dysfunction and abnormal hippocampal activity, which has also been well documented in individuals with schizophrenia (Weiss et al., 2004; Casanova & Rothberg, 2002; Shenton, Gerig, McCarley, Szekely & Kikinis, 2002; Schobel et al., 2009). Schobel et al. (2009) reported localized volume reductions in the left anterior hippocampus and these reductions were found to be strongly correlated with reductions in neuropsychological test performance on tasks involving verbal comprehension, perceptual reasoning and working memory. Similarly, anterior hippocampus structural and chemical abnormalities have previously been linked with executive task deficits in individuals with schizophrenia. Rusch and colleagues (2008) study found that altered hippocampal glutamatergic neurotransmission (and amygdala volume loss) was associated with executive dysfunction, indexed in this study by poor performance on the WCST.

The advent of diffusion tensor imaging (DTI) has now allowed for the investigation of white matter changes throughout the brain in individuals with schizophrenia and the associations with cognitive deficits. DTI studies have shown abnormalities in individuals with schizophrenia in the superior longitudinal fasciculi bilaterally (Shergill et al., 2007), a major white matter tract connecting large parts of the frontal lobe with parts of both the temporal and parietal lobes. A recent meta-analysis conducted by Ellison-Wright and Bullmore (2009), examining cross sectional diffusion tensor magnetic resonance imaging studies, further identified white matter changes in both deep frontal and temporal areas in schizophrenia. The relevance here is that these neuronal regions are particularly involved in the connection between Wernicke's and Broca's area, which raises the possibility that this abnormality is associated with the marked language dysfunction often seen in schizophrenia.

DTI studies have also identified disruption in the corpus callosum of individuals with

schizophrenia, which is the largest white matter tract in the human brain (Cheung et al., 2008; Patel et al., 2011; Walterfang et al., 2008). The corpus callosum is responsible for the large majority of communication between the various cortical regions in the right and left hemispheres. Abnormal white matter changes in schizophrenia have also been noted in the fornix (Fitzsimmons et al., 2009), which is an integral structure for connections between the hippocampus, septum, and anterior nucleus of the thalamus. Disruption to the fornix is believed to impact on functions such as spatial memory, memory retrieval and verbal memory, which are all affected in schizophrenia (Takei et al., 2008).

In sum, research to date has identified various cortical and subcortical structures as discussed that largely correlate with the corresponding cognitive deteriorations in attention, speed, learning and memory, language and executive functions.

### 1.10 Schizophrenia as a Neurodegenerative Condition

One enduring question surrounding the cognitive and neuroanatomical research into individuals with schizophrenia is whether or not these changes are static or progressive in nature. Historically, a dominant belief has been that individuals with schizophrenia present with a progressively worsening psychological and functional course of illness as they age. This belief has certainly been considered fundamentally important in the discussion considering whether or not schizophrenia is a neurodegenerative as well as a neurodevelopmental illness. In more detail, the belief that schizophrenia is a degenerative illness has been in existence from the initial writings of Kraeplin, who described the illness as ‘dementia praecox’ (Pantellis, Nelson & Barnes, 1996). Even Kraeplin though acknowledged, in later editions of his work, that the decline noted in functioning was not always irreversible or progressive (Palmer, McClure & Jeste, 2001).

Support for Kraepelin's later acknowledgment can be found in more recent neuro-imaging studies. Andreasen et al. (2011) utilised a longitudinal design to follow-up first episode patients for 18 years post their initial diagnosis. Her results certainly found support for the presence of progressive brain changes in individuals with schizophrenia but only in a subset of patients. The percentage of patients showing progressive brain changes at a rate faster than controls varied depending on the area of brain examined but overall involved only 34 to 47% of the patients studied. Nevertheless, a great deal of debate remains as to whether or not there is a post-morbid decline in intellectual and cognitive function in individuals suffering from schizophrenia. Heaton and Drexler (1987) conducted an analysis of 100 cross-sectional studies and 10 longitudinal studies examining the neuropsychological functioning of schizophrenia, with their analysis not providing support for the possibility of progressive neuropsychological impairment. A more recent literature review conducted by Shah, Qureshi, Jawaid and Schulz (2011) also presented mixed results. Of the twenty longitudinal studies they reviewed, only twelve showed significant evidence of intellectual post-morbid decline with eight showing no signs of such a decline. They did however identify several differences in both the study designs and the populations sampled between those studies that found significant versus null results. Specifically, the studies reporting null results were noted to have shorter follow up periods to assess degeneration and lower age ranges of their populations. Of relevance, a study by Harvey et al. (1999), which focused on older patients, demonstrated that a subset of institutionalised, chronically ill older patients exhibited a decline in their intellectual and cognitive functioning over a 30 month time period. Harvey, Reichenberg, Bowie, Patterson and Heaton (2010) and Reichenberg et al. (2014) also found that individuals who spent greater amounts of time in institutional care also demonstrated a decline in not only their cognitive abilities but also in their ability to perform the Instrumental Activities of Daily Living (IADL's) (Brodaty et al., 1999)

measure of function. Additional studies have further demonstrated that this decline in older individuals with schizophrenia may reflect, at least in part, the normal effects of aging on cognitive abilities (Goldberg et al., 1993; Harvey et al., 1995; Hyde et al., 1994).

Researchers have hypothesised several reasons as to why individuals with schizophrenia may be at risk of developing additional longitudinal cognitive impairments, including higher rates of dementia, later in the course of the illness, when compared to controls. These reasons generally include the effects of the presence of premorbid cognitive impairment, lower education levels and less cognitive reserve as people age. Individuals with schizophrenia, due to their lifestyle, may also increase their risk for cardiovascular disease and stroke due to metabolic syndromes related to their sedentary lifestyle, poor diet, smoking and chronic antipsychotic medication use. These factors, further compromise their cognitive functioning as they age (Jeste, Wolkowitz & Palmer, 2011).

Thus, as is evident, research remains somewhat mixed, with ongoing debate, as to whether cognitive and functional deteriorations persist over time in individuals with schizophrenia. What is not debated, however, is the impact of cognitive impairment in schizophrenia

## 1.11 The Impact of Cognitive Deficits in Schizophrenia

### *1.11.1. Cognitive Deficits and Outcomes*

Research by Green (1998), Heaton and Pendleton (1981) and Silverstein, Schenkel, Valone and Nuernberger (1998) suggests that the level of cognitive impairment is one of the best predictors of subsequent level of functioning in an individual with schizophrenia, even more so than that individual's symptomatology. In more detail, Harvey et al. (1998) and Velligan et al.

(1997) suggested that cognitive deficits predicted between 40 - 50% of the variance in community functioning in individuals with schizophrenia. More generally, cognitive deficits have also been found to be predictive of future hospitalisations (Lysaker, Bell & Beam-Goulet, 1995), length of hospitalisation (Wilder-Willis, Shear, Steffen & Borkin, 2002), future dependence upon mental health services (Wykes & van der Gaag, 2001), future level of social and vocational functioning (Addington & Addington, 1999), and quality of life / family burden (Belluci, Glaberman & Haslam, 2002). This is likely because cognitive disabilities contribute to ineffective learning and so compound the difficulties of patients attempting to return to education or training and avoid rehospitalisation.

A meta-analysis conducted by Green et al. (2000), and considering different cognitive domains, identified that verbal memory, sustained attention and executive functioning were the three basic cognitive skills that best predicted an individual's functional outcome. Specifically, verbal memory and vigilance deficits have been found to impact on an individual's ability to acquire social skills (Mueser, Bellack, Douglas & Wade, 1991), and exercise responsible social problem solving (Bellack, Sayers, Mueser & Bennett, 1994). Working memory deficits have consistently been found to be associated with poorer functional outcomes in schizophrenia (Green et al., 2000), while episodic memory impairments have been associated with more severe negative symptoms (Aleman et al., 1999).

Executive functioning (in particular, problem solving and conceptual reasoning) has also been found to be predictive of functional outcomes such as successful outpatient community functioning (Jaeger & Douglas, 1992), length of time until rehospitalisation (Lysaker et al., 1995), vocational performance (Bellack, Gold & Buchanan, 1999; Lysaker et al., 1995), impaired social functioning (Corrigan & Toomey, 1995; Spaulding et al., 1999), and independent living status and quality of life (Lysaker et al., 1995; Goldman et al., 1993). It has also been

hypothesised that executive impairments in people with schizophrenia may impact on these individuals' abilities to develop and / or access effective and flexible coping strategies (Wilder-Willis et al., 2002).

Recent research has argued that functional outcome in schizophrenia is more strongly related to impaired social cognition rather than the basic neurocognitive deficits discussed above (Smith et al., 2012; Fett, Viechtbauerb & Domingueza, 2011). In support of this view, deficits in ToM, emotional processing and social / relationship perception have been found to be related to real world functioning and symptoms in schizophrenia (Horan et al., 2012). Horan et al. (2012) also found that lower social cognition scores were significantly related to lower levels of work functioning, independent living, and social functioning. Fett et al. (2011) found similar correlations between impaired social cognition and poor community function; however their research further demonstrated that this association was stronger than that seen between neurocognitive deficits and poor community functioning. Similarly, a recent study by Smith et al. (2012) that examined self-reported empathy and functional outcome in individuals with schizophrenia found that poorer skills on tasks of perspective-taking were associated with both reduced functional capacity (indexed by ability to complete everyday tasks such as reading a bill, counting change or visiting a doctor), and reduced community functioning (indexed by overall score on the Specific Levels of Functioning Interview (Schneider & Struening, 1983) that assesses interpersonal relationships, social acceptability, activities of daily living and work skills). This latter correlation was found to occur even after accounting for neurocognitive and symptom variables.

Thus, it is apparent that both cognitive, but importantly also social cognitive deficits, contribute to poor functional and overall clinical outcomes in schizophrenia.

### *1.11.2. Cognitive Deficits and Symptoms*

As noted earlier, the large majority of research to date indicates that cognitive deficits share only a small common variance with symptoms (approximately 10% of the variance) (Cornblatt, Lenzenweger, Dworkin & Erlenmeyer-Kimling, 1985). Specifically, the major psychotic symptoms of delusions and hallucinations have shown almost no relationship to cognitive impairments, as measured by standardised neuropsychological tests (Nuechterlein et al., 1986; Frith, 1992). There is some evidence, however, that the degree of cognitive impairments is linked to the severity of negative symptoms in individuals with schizophrenia (Buchanan, Holstein & Breier, 1994; Cuesta & Peralta, 1995; Rund, 1998). Nevertheless, the amount of variance in negative symptom severity explained by cognitive deficits is often no more than 15% (Addington & Addington, 1993; Liddle, 1987). It has been proposed by Nuechterlein et al. (1986) that cognitive impairments might contribute more strongly to specific negative symptoms such as apathy and affective flattening. Studies that have found associations between negative symptoms and cognitive deficits have reported correlations with deficient performance on tasks of sustained attention (e.g. CPT, backward masking tasks and the Span of Apprehension Task) (Niewenstein, Aleman & de Haan, 2001), motor speed and dexterity (Green & Walker, 1985; Nuechterlien et al., 1986), and executive function (Nieuwenstein et al., 2001). Positive symptoms in contrast have been found to be associated (though much more weakly, as noted above) with tasks of verbal memory and auditory distractibility (Green & Walker, 1985; Cornblatt et al., 1985).

Beyond the general positive-negative dichotomy, cognitive impairments have also been found to be associated with more specific symptoms, as proposed by Nuechterlein et al. (1986). For example, severity of symptoms of disorganisation have been linked to cognitive impairments of planning and inhibition (Nuechterlein et al., 1986), attention and new learning (Liddle, 1987;

Baxter & Liddle, 1998, Niewenstein et al., 2001), verbal learning and recall, and cognitive flexibility (Lucas et al., 2004). In contrast, symptoms of psychomotor poverty have been linked to deficits in speed of information processing, but also memory, visuospatial abilities and executive functions (Bilder et al., 2000). However, attempts to replicate these findings have produced mixed results, with other researchers yielding contrary results (Williams, 1996; Norman et al., 1997; O'Leary et al., 2000).

In summary, research to date largely demonstrates correlations between cognitive deficits and negative symptoms of schizophrenia, with far less evidence to support any relationship between cognitive deficits and positive symptoms.

### 1.12 Effects of Medication on Cognitive Functioning in Schizophrenia

As research indicating that cognitive deficits are a core feature of schizophrenia has increased, so too has the interest of the pharmaceutical industry in examining the impact of anti-psychotic medication on these deficits. A meta-analysis conducted by Keefe, Silva, Perkins & Lieberman (1999) suggested that atypical antipsychotics are significantly more effective than the typical antipsychotics at improving cognitive functioning in schizophrenia. The main areas of cognition that these authors reported to improve with antipsychotic medication included verbal fluency, Digit-Symbol (indexing speed of information processing), fine-motor functions and executive functions.

A large multi-site study involving 817 individuals with TOS was conducted to specifically examine the neurocognitive effects of both typical and atypical antipsychotic medications (Keefe et al., 2007). This Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE Trial) study also had minimal exclusion criteria, allowing for comorbid conditions, concomitant medications and substance abuse, to examine more of a real world sample.

Individuals were randomly prescribed pre-set doses of either typical or atypical antipsychotic medication. The CATIE trial measured improvement in neurocognitive performance on both an overall composite scores, which used11 cognitive tests, and also across five composite domain scores. An improvement in the overall composite neurocognitive score was found in all groups over a two month time period. Further exploratory analysis involving 21% of the original cohort indicated that after 18 months of treatment the older antipsychotic perphenazine demonstrated the most neurocognitive improvement.

Research examining individual antipsychotic medications more closely reveals that typical anti-psychotics, such as haloperidol, have beneficial effects on the CPT, indexing sustained attention (Earle-Boyer, Serper, Davidson & Harvey, 1991), and the Span of Apprehension Task, which requires individuals to identify which target stimuli are flashed onto a screen and embedded into other non-target stimuli (Marder, Asarnow & van Putten, 1984). These results have been found using standard doses only, whereas higher doses were found to reduce performance (Spohn, Coyne, Lacoursiere, Mazur & Hayes, 1985).

In regards to atypical medications, several studies have been completed to date examining the effects of clozapine. The results suggest that clozapine leads to improvements on cognitive measures of attention, motor speed and verbal fluency (Goldberg et al., 1993; Buchanan et al. 1994). However, this atypical antipsychotic was also found to detrimentally affect performance on visual memory and verbal working memory tasks. Another atypical medication, olanzapine, has also been found to have beneficial effects on verbal learning and memory, verbal fluency and cognitive disinhibition (Meltzer & McGurk, 1999; Purdon, Labelle & Boulay, 2001).

Far fewer studies have been conducted examining the other two major atypical medications used in Australia, risperidone and olanzapine. However, the few studies to date examining Risperidone have found beneficial effects on attention, verbal and spatial working

memory, psychomotor speed and dexterity (Green, Marshall, Wirshing, 1997). A study by Kern et al. (1999) also suggested that patients taking risperidone had better verbal learning abilities than individuals taking haloperidol.

A caveat related to the above findings concerns the methodological problems that currently exist within this line of research. For example, individuals with schizophrenia differ greatly in regards to previous medications used before onset, current dosing amounts, clinical presentation prior to introduction of new medications in a trial, and effects of additional medications being taken.

### 1.13 Summary of Cognitive Functioning and Impact in Schizophrenia

A considerable amount of published research has extensively demonstrated the presence of cognitive deficits in individuals with schizophrenia. The range and severity of these deficits is extremely broad and affects the areas of general level of intelligence, as well as the cognitive domains of attention, working memory, motor speed, speed of information processing, learning and memory, perception, language functioning, motor functioning and executive functioning. (Seidman et al., 2002; Wykes & van der Gaag, 2001). While these deficits impact negatively on daily functioning, findings of associations with symptoms are more mixed, with negative symptoms appearing to be more closely related to the cognitive deficits. Research has also more recently focused on the poor social and occupational outcomes associated with social cognitive deficits in schizophrenia. Work addressing the underlying neuroanatomical and neurophysiological basis for these cognitive deficiencies has identified various brain abnormalities in individuals with schizophrenia including changes to frontal and temporal brain regions, as well as white matter changes throughout the brain and in particular the corpus callosum.

While much of the reviewed evidence on the impact of cognitive deficits in schizophrenia has focused on individuals with the typical onset age in late teens to early adulthood, there is comparatively little research in a similar vein conducted with individuals who develop a schizophrenia-like illness in later adulthood and even less research in those who develop the illness over the age of sixty years. The following Chapter will now focus on individuals who develop a schizophrenia-like illness after the age of 60 and, in particular, on the cognitive deficits observed in this population, which is a main focus of this thesis.

## Chapter 2. Psychosis in the Elderly

According to the Australian Bureau of Statistics (ABS) 2011 Census data individuals aged over 65 years currently account for approximately 14% (3.2 million) of the Australian population. The ABS (2011) data predicts that this percentage is expected to rise to between approximately 18.3% (5.7 million) to 19.4% (5.8 million) by the year 2031. The prevalence of psychotic symptoms in the elderly has been estimated to range from approximately 0.2% to 4.75% of community based populations (Broadway & Mintzer, 2007) while Champagne et al. (1996) reported that psychotic symptoms were present in as many as 26% of patients admitted to an inpatient aged care psychiatry ward. The reported prevalence rates of psychotic symptoms in individuals residing in aged care facilities have varied from 10% to as high as 63% (Zayas & Grossberg, 1998). With regard to more specific symptoms, Henderson and Kay (1997) reported rates of delusions of around 5% of elderly people with a Mini Mental State Examination (MMSE) score of 24 or above. Paranoid delusions have also been found in 6% of a general Australian population of elderly age of 70 years or older (Kay et al., 1985). A three year follow-up population study of elderly individuals aged 85 years and older in Sweden also found rates of 5.5% for delusions and 6.6% for paranoid ideation in these older individuals (Ostling & Skoog, 2002).

Multiple aetiologies exist that can cause late-life psychosis, for example, schizophrenia, schizoaffective disorders, delusional disorders, affective illnesses with psychotic symptoms, dementia, delirium, infections, endocrine conditions, nutritional deficiencies, autoimmune disorders and substance induced disorders (Webster & Grossber, 1998). Psychotic symptoms in the elderly, irrespective of aetiology, are also often associated with other behavioural disturbances, which are often reported as a source of distress for families and caregivers. Research by Steel, Rovner and Chase (1990) has reported that psychotic symptoms in elderly

patients can also result in neglect and abuse of those patients. The persistence of psychotic symptoms in the elderly has also been reported to result in high levels of institutionalisation (Stern et al., 1997).

The predicted increase in number of individuals aged over 65 years in the population in general will most certainly result in a concurrent increase in the number of elderly individuals who present with psychotic symptoms. In turn, there will be an exacerbation of the associated problems discussed above. As a result, research into late-life psychotic disorders is of increasing clinical importance.

The focus of this thesis is late-life schizophrenia. Individuals with late-life schizophrenia consist of two distinct groups, those individuals who have had the illness since early adulthood and have aged, and those who develop schizophrenia for the first time over the age of 60 years (and for whom all other medical / reversible causes have been ruled out). This thesis considers both these groups, in addition to a comparison group of older individuals with late-onset psychotic depression, all of which are the focus of both this Chapter and the following research. The following sections examine the history, epidemiology and clinical features of these late-life psychotic illnesses and review the current research into the relevant cognitive and neurological findings.

## 2.1 Late Onset Schizophrenia: A General Overview and History of Illness Concept

As previously discussed, schizophrenia has long been regarded as a neurodevelopmental disorder with onset of the illness occurring in late adolescence or early adult life. It is now well accepted though that schizophrenia and psychotic symptoms can first present at any time in the life cycle between childhood and old age. The debate continues in the literature as to whether or not “Late Onset Schizophrenia” (LOS) simply represents a delayed manifestation of the same

illness seen in "Chronically Ill, Typical Onset Schizophrenia" (TOS), or whether it in fact represents a clinically and etiologically distinct syndrome. Attempts to answer this question have focused on examining epidemiological and clinical differences between LOS and TOS samples. Arguments have been made in the literature that there is very little evidence to support an upper age limit for a diagnosis of schizophrenia. This had been the case in the Diagnostic and Statistical Manual of Mental Disorders – Third Edition) (DSM-III; American Psychiatric Association, 1980), where an upper age limit of 45 years for diagnosis had been suggested. This change in clinical opinion saw LOS included as part of the clinical definition of schizophrenia as per the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV; American Psychiatric Association, 1994), in which the diagnostic criteria for schizophrenia are now consistent across the life span. Similarly, "Late Paraphrenia", which had been included in the International Classification of Diseases-Ninth Edition (ICD-9; World Health Organisation, 1979) as a separate diagnostic category, was not included as a separate diagnosis in the more recent International Classification of Diseases – Tenth Edition (ICD-10, World Health Organisation, 1999).

Kraeplin, in his work with schizophrenia patients, noted that some of his later onset patients manifested with predominantly paranoid symptoms. He diagnosed these patients as having "Paraphrenia". Further research by Kraeplin (cited in Howard, 2008), and using a very restricted concept of "Dementia Praecox" which specifically excluded those individuals whom he diagnosed with Paraphrenia, showed that 5.6% of his 1054 patients had an onset after the age of 40 years and only 0.2% had an onset at older than 60 years. Kraepelin's description of individuals with Paraphrenia was of a course that was more benign than earlier onset Dementia Praecox, with better preservation of personality and less disturbance of volition. He also went on to describe that the delusions of these individuals with Paraphrenia were generally less fantastic

and that their reasoning was generally intact, apart from the content specifically relating to their delusional system (Castle, Wessely, Howard & Murray, 1997). In contrast, Eugene Bleuler did not believe that the age at onset of the illness or the clinical course characterised the disorder of schizophrenia (Jeste et al., 1997).

Systematic research into LOS began with Manfred Bleuler, who, in the 1940's, coined the term, 'Spatschizophrenie' (Late Schizophrenia) (Vahia et al., 2010). Manfred Bleuler examined 126 patients whose illness onset occurred after 40 years of age (Howard et al., 2000). These late onset cases constituted 15% of the patients with schizophrenia he examined, though another 4% were determined to have even later onset, occurring after the age of 60 years. Approximately 50% of these LOS patients were described as having symptoms that were indistinguishable from those seen in patients with the more typical, younger age of onset (cited in Howard et al., 2000).

Research into LOS continued in other European countries in the 1950's and 1960's. English researchers, using an age cut-off of 55 or 60 for onset, adopted the term "Late Paraphrenia" in order to both distinguish late onset schizophrenia from chronic schizophrenia but also to identify the similarities with the condition previously termed Paraphrenia by Kraeplin. Kraeplin had used the term Paraphrenia for a condition, in which delusions and hallucinations occurred at any age, and without deterioration or disturbance in affect or personality. Roth and Morrissey, in 1952 (cited in Harris & Jeste, 1988), presented 12 cases of individuals whose onset of psychotic symptoms occurred after the age of 60. They reported that these individuals' symptoms were characterised by prominent non-fantastic delusions within the context of what they described as well preserved personalities. Roth and colleagues were among the first to propose the term Late Paraphrenia. Roth (1955) defined Late Paraphrenia as involving a "well-organised system of paranoid delusions, with or without auditory hallucinations, in a setting of well preserved personality and affective response" (p.283). This was due to the fact that Roth

believed that the clinical presentation of this group was similar to that of the Paraphrenia group described by Kraeplin. Roth believed that this group of individuals was clinically distinct from both affective and organic psychoses. He believed that these individuals, with onset over the age of 60, were, in fact, presenting with a variant of schizophrenia that was unique to old age and that its aetiology was possibly different and multifactorial (Roth, 1955). Kay and Roth (1961) published research into a group of 43 individuals with a diagnosis of Late Paraphrenia. Their research suggested that these individuals were socially isolated, and had a considerably higher prevalence of hearing disturbance compared to a control group, but not a higher level of visual disturbance. As a result of this research, the ICD-9 implemented a category of 'Late Paraphrenia'. Any reference to Paraphrenia has, however, been excluded from both the ICD-10 and the DSM-IV.

Other researchers went on to classify subtypes of LOS. For example, Felix Post (1966, cited by Harris & Jeste, 1988) classified individuals whose symptoms first appeared over the age of 50 into three subgroups. The first was 'Paranoid Hallucinosis' which referred to individuals presenting with only auditory hallucinations against a background of delusions of persecution. The second he termed 'Schizophreniform Syndrome' which referred to individuals characterised by what he considered less fantastic paranoid experiences. The third was 'Schizophrenic Syndrome' which referred to individuals who would typically meet the criteria of Paranoid Schizophrenia or Paraphrenia. A three year follow up conducted by Post (cited by Harris & Jeste, 1988) reported that he was unable to identify any etiological differences between the three subgroups, suggesting that they simply represented different clusters of symptoms along a continuum.

Others have attempted to classify LOS into two groups depending on whether or not individuals present with a typical schizophrenia illness or a delusional disorder. However,

research by Riecher-Rossler, Hafner, Hafner-Ranabauer, Loffler & Reinhard (2003) indicated that individuals divided into these two groups did not, in fact, differ significantly from one another. Specifically, they examined individuals classified as either late onset schizophrenia or late onset delusional disorder (aged >40 years at time of diagnosis) and found that there was a higher overlap of symptoms between the two groups. Moreover, discriminant analysis based on symptomatology did not clearly differentiate between these two groups.

In regards to manuals for the formal diagnosis of schizophrenia, the Diagnostic and Statistical Manual of Mental Disorders – First Edition (DSM-I; American Psychiatric Association; 1952) did not have age of onset as a criterion for a diagnosis of schizophrenia, though it did include 'Involutional Psychotic Reaction' as a classification for individuals who present with psychotic reactions occurring for the first time in middle age. The involutional psychotic reaction was generally characterised by delusional guilt and self-loathing. Similarly, the DSM-II (American Psychiatric Association; 1968) made no reference to age of onset or an age cut-off for a diagnosis of schizophrenia. However they did include an 'Involutional Paranoid State (Involutional Paraphrenia)', which referred to a paranoid psychosis that was characterised by delusions with an onset in the involutional period. The ICD-9 (World Health Organisation, 1979) also did not have an age cut-off for a diagnosis of schizophrenia. However the DSM-III excluded both Paraphrenia and Involutional Paranoid Disorder as diagnosistic conditions and introduced the use of age 45 as the cut-off for a diagnosis of schizophrenia. As a result, anyone who presented with a psychotic illness for the first time after this age was given other diagnosis such as "Psychosis, Not Otherwise Specified". By the introduction of the Diagnostic and Statistical manual of mental Disorders – Third Edition –Revised (DSM-III-R, American Psychiatric Association; 1987), the upper age limit for diagnosis had been removed and the description for previously mentioned LOS diagnosis was included in the general introduction for

cases where the illness onset after age 45. The release of the DSM-IV (1994) and the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2004) and Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V; American Psychiatric Association, 2013) also made no reference to an upper age limit of onset for diagnosis of schizophrenia.

As can be clearly seen, there has been very little consistency in the terminology used for individuals presenting with schizophrenia for the first time after the age of 45. The inconsistent diagnostic classifications and nomenclature used to classify individuals who develop schizophrenia in middle to late ages has limited the ability to make comparisons of previous research into the area. To assist with future research, and bring greater consistency to the diagnosis and study of late onset cases, a conference was held in 1998, which was attended by experts in the area of late onset psychosis from around the world (Howard et al., 2000). This international consensus group agreed that the available evidence at the time regarding epidemiology, phenomenology and pathophysiology supported homogeneity within schizophrenia symptoms occurring in later years up until the age of 60. As a result the term LOS was adopted for individuals whose illness occurred after the age of 40 years and prior to 60 years. However the conference members also agreed, by contrast, that the occurrence of the illness, if after the age of 60 years, was distinct from that of typical schizophrenia. As a result, individuals whose psychosis onset occurred after 60 years of age came to be classified as having "Very-Late-Onset Schizophrenia-Like Psychosis" (VLOSLP). The phrase, Schizophrenia-Like-Psychosis, was adopted due to the fact that these individuals are at an age at which they are at greater risk of developing a primary dementia. Howard et al. (2000) suggested that these LOS and VLOSLP diagnostic categories have face validity and clinical utility in terms of epidemiology, symptom profile, and associated pathophysiologies.

## 2.2 Late Onset Schizophrenia and Very-Late-Onset Schizophrenia-Like-Psychosis - Clinical Features

To date, the diagnostic criterion for LOS has been that of a symptom profile similar to that of individuals with a chronically ill, typical onset schizophrenia illness. Despite the similarities, however, research has also consistently shown several trends that differentiate individuals who develop psychosis in early or mid-life from those who develop a schizophrenia-like illness in late life. Phenomenologically, individuals with LOS and Very-Late-Onset Schizophrenia-Like-Psychosis (VLOSLP) have consistently been found to present more often with visual, tactile and olfactory hallucinations as compared to TOS individuals (Moore, et al., 2006; Sato, Bottlender, Schroter & Mooler, 2004; Tune & Salzman, 2003). For example, Almeida, Howard, Levy and David (1995a) conducted a study of individuals who presented with an ICD-10 diagnosis of late Paraphrenia and who were over the age of 55 years. Utilising the Present State Examination (PSE: Wing, Cooper & Sartorius, 1974) this research found that 46.8% of patients presented with auditory-verbal hallucinations (hearing voices), as compared to a prevalence rate of 75% in a general sample of hospitalised hallucinating schizophrenia patients (see, e.g., Baethge, Baldessarini, Freudenthal, Streeruwitz, Bauer, & Bschor, 2005). Visual hallucinations were also found in 12.7% of these LOS cases and olfactory hallucinations in 4.3%, as compared to prevalence rates of 14 and 18% respectively for visual and olfactory/gustatory hallucinations in a general sample of hospitalised hallucinating schizophrenia patients (Baethge et al, 2005). Other researchers have, however, reported running commentary auditory hallucinations and third person auditory hallucinations were more prevalent in VLOSLP individuals at 21% and 29% respectively, compared to TOS individuals (Grahame, 1984). Similarly Howard, Castle, Wessley & Murray (1993) found that third person hallucinations occurred in 42.8% of their VLOSLP group as compared to 28.9% in a TOS group. Similar

results were also found by Castle et al. (1997).

Several studies have also closely examined differences in delusional themes between individuals who develop the illness later in life compared to those with earlier ages of onset. For example, persecutory delusions have been found to be more common in individuals with a later age of onset, symptomatology which is characteristic of the previous nomenclature of Paraphrenia. Persecutory delusions were seen in 93.3% of VLOSLP versus 71.4% of TOS patients in the study by Howard et al. (1993). Similarly Pearlson et al. (1989) found the presence of persecutory delusion to be greater in LOS samples at 92.6% versus 77.3% in elderly TOS groups and only 44.4% of young TOS patients. Pearlson et al. (1989) also found more grandiose delusions, being present in 31.8% of their LOS group as compared to only 5.6% of TOS patients and 16.7% of elderly TOS patients. Another consistent finding in LOS populations has been the increased presence of "partition" delusions, that is, beliefs that people, animals, materials or radiation can pass through a structure that would normally constitute a barrier to such passage (e.g. a wall). Partition delusions have been reported in as many as two thirds of LOS patients (Brodaty, Sachdev, Rose, Rylands & Prenter, 1999), while Pearlson et al. (1989) found that this type of delusion was present in 48% of their LOS patients and Howard et al. (1993) reported it to be present in 68% of their VLOSLP group, compared with only 13% of the latter group's TOS group who have grown old and 20% of their sample of young people with schizophrenia. In contrast, "loss of boundary" delusions are less common in VLOSLP. For example, in the VLOSLP population reviewed by Grahame (1984), thought insertion and thought withdrawal did not occur, whereas he reported that it had been found in up to 47% of TOS individuals. Similarly, Howard et al. (1993) found that thought insertion occurred in only 7.5% of their VLOSLP patients and Castle et al. (1997) found it in only 1.4%. Howard et al. (1993) also identified that thought withdrawal was less common in VLOSLP individuals at 2.4% versus 12.5% in TOS

groups.

Two other notable differences consistently reported are the relative absence of formal thought disorder and fewer negative symptoms in VLOSLP individuals (Barak, Aizenberg, Mirecki, Mazeh & Achiron, 2002; Castle et al., 1997; R. Moore, et al., 2006). For example, Howard et al. (1993) found a relative absence of thought disorder in VLOSLP groups at 10.4%. Pearlson et al. (1989) found formal thought disorder in only 5.6% of their LOS individuals compared to 55% of elderly, early onset individuals. Howard et al. (1993) also found that the negative symptoms of inappropriate and lack of affect were more common in their TOS group. Castle et al. (1997) reported that only 4.3% of their VLOSLP group presented with inappropriate affect versus 21.6% of their TOS group. Similarly, Castle et al. (1997) identified that none of their VLOSLP group presented with restricted affect versus 17.9% of their TOS group. LOS individuals have also been found to be less impaired on the IADL (Brodaty et al., 1999) measure of function.

Other differences include that VLOSLP individuals often present with more medical comorbidity (e.g. developing dementia, vascular issues), given their age, with sensory and perceptual deficits also common, such as vision and hearing problems (R. Moore et al., 2006). Consistent with previous studies dating back as early as Bleuler in 1943, individuals with LOS are also reported to be more sensitive to medication side effects and have been found to be at greater risk of developing tardive dyskinesia (Tune & Salzman, 2003).

Contradictory research findings regarding some of these differences are, however, also evident in the literature (e.g., Girard & Simard, 2008 found no significant increase in the frequency of visual hallucinations between a VLOSLP group and a LOS group). Nevertheless, the overall pattern of findings leads to suggestions that it may be possible to differentiate late onset groups from early onset groups, not only on the epidemiological grounds discussed earlier,

but also on the basis of symptomatology itself.

## 2.3 Late Onset Schizophrenia and Very-Late-Onset Schizophrenia-Like-Psychosis - Epidemiology

Epidemiological data on LOS and VLOSLP populations is scarce, which is certainly in part due to the inconsistencies in classification systems discussed above. Difficulties have also arisen due to the longstanding debate as to whether or not LOS is a diagnosable illness in and of itself. Earlier research has also limited itself to hospital admissions only, excluding community samples. In regards to the incidence of LOS (i.e., onset of the illness after age 40), based on first admission rates, Copeland et al. (1998) using the DSM-III-R reported it to be at 12.3 per 100,000 population per year. Copeland et al. (1998) further reported the incidence rate of those aged 65 years and over to be much lower at 3.0 per 100,000 for schizophrenia, while incidence was 16.5 per 100,000 for delusional disorder. Castle et al. (1997) applying the same criteria reported a similar incidence rate of 12.6 per 100,000 per year. Based on DSM-IV criteria, Mitford, Reay, McCabe, Paxton and Turkington (2010) reported the incidence of psychosis of any sort in individuals who first present over the age of 65, to be 33.31 individuals per 100,000 population, with 14.28 per 100,000 presenting with a first episode schizophrenia spectrum disorder. Of importance to the current research study, and as will be further addressed later in this chapter, lower rates of 10.05 per 100,000 were found to present with a psychotic depression in research conducted by Mitford et al. (2010).

When only the older years of onset are examined, lower prevalence rates are seen, however. For example, the Epidemiologic Catchment Area study in the USA reported a prevalence rate of late life schizophrenia of 0.6% among individuals aged 45 to 64 years and down to 0.2% for individuals aged 65 years and older. Similarly, Howard et al. (2000) found the

prevalence rate for individuals with VLOSLP, that is onset over the age of 60 years, to range from 0.1% to 0.5%, while Moran and Lawler (2005) found the proportion of individuals whose illness first presents after the age of 60 to be 1.5% compared to 23.5% when first presenting after the age of 40. Similarly, a retrospective chart study of 420 patients hospitalised over a ten year period conducted by Alici-Evcimen, Ertan & Eker (2003) found that 1.9% had an onset of schizophrenia over the age of 40 years, with 1.4% diagnosed with VLOSLP.

Epidemiological differences have also been identified between those individuals who present with a schizophrenia illness for the first time in old age compared to those with TOS who have aged. For example, psychosocial differences have been identified in that VLOSLP have higher levels of education and are more likely to have been married (Barak et al., 2002; Jeste et al., 1997). Castle and Murray (1993) reported that only 5% of the LOS group were deemed to have had poor premorbid work adjustment compared to 50% of their TOS group. This research further found that 22% of their LOS group demonstrated poor premorbid social adjustment, compared to 43% of their TOS group. They also found a disparity between the two groups in regards to marriage, with 66% of the LOS group were or had been married, versus 33% of the TOS group. Researchers have hypothesised that this is due to the fact that the delayed or later onset of the symptoms enabled the LOS individuals to more likely succeed in such social and family roles earlier in their life. Further research has also found that relatives of individuals with LOS illness were less likely to have the illness themselves than compared to TOS groups, although they still had a greater risk than that of the general population (Harris & Jeste, 1988). In contrast, a study conducted by Howard et al. (1997) found the lifetime risk among first-degree relatives of the LOS patient group was 2.3% and 2.2% for the relatives of the control group. Of some interest however, the lifetime risk of depression was significantly higher in their LOS patient group than their control group.

Gender differences in terms of age of onset are also an extremely robust finding. Relative to TOS, LOS cases have consistently been found to have a higher proportion of women. Castle and Murray's (1993) population based epidemiological analysis found the male to female ratio for the 16-25 year age group was 1.56 to 1. The ratio reached unity around 30 years of age and then reversed to 0.38 to 1 in the 66 - 75 year old group. Further analysis of their results found that nearly half of all males first presented with schizophrenia before the age of 25, with 12% presenting between the ages of 46 and 65 and only 4% after the age of 65 years. In contrast, less than a third of females had presented prior to the age of 25, with 20% presenting between the ages of 46 and 65 years, and 18% presenting for the first time after the age of 65 years. Similar gender based results were found by Castle et al. (1997) whose research examined a population based first contact cohort: 76% of their VLOSLP group were females as compared to only 39% whose onset occurred prior to the age of 25.

Questions however remain as to the epidemiological findings in LOS, not only due to the previously mentioned difficulties with diagnosis and the population studied, but also given the possibility that such individuals may be less likely to present to psychiatric services at all.

## 2.4 Proposed Risk Factors / Causes of Schizophrenia-like Psychosis in Later Life

While the current clinical, epidemiological, brain imaging and neuropsychological research largely support the diagnostic concept of VLOSLP, the debate is ongoing as to whether or not it is simply a classic schizophrenia with delayed onset or some other form of neurological disorder. The argument for the latter view comes from the evidence of psychosis in other later-onset neurological disorders such as Alzheimer's disease, Lewy Body Dementia, Parkinson's Disease, Fronto-Temporal Dementia, and multi-infarct dementia (Cullum, Heaton, Harris & Jeste, 1994; Jones et al., 2005). Other important factors that suggest a distinct neurological basis

for VLOSLP include the roles of gender, genetics, premorbid personality, social isolation, and sensory impairment, and migration or other life events. Each of these factors will be considered in turn in the following section.

**2.4.1** ***Gender*** **–** As noted in the preceding chapter, the onset of schizophrenia tends to be generally later in females than males. Females also show two peaks. The first occurs in the early twenties and the second in the late forties to mid-fifties (Arora & Praharaj, 2006). The second peak has often been hypothesised to be related to the hormonal changes of menopause and the protective effects of estrogen prior to this. This finding of a second peak has contributed to the "estrogen protection hypothesis" of schizophrenia (Osterlund & Hurd, 2001). In general, this is the view that estrogen provides some protection for premenopausal women who are genetically predisposed to developing schizophrenia. One explanation for these protective effects is that estrogen has also been found to be involved with the dopaminergic, serotonergic and glutamatergic systems and so may have similar antidopaminergic effects of atypical antipsychotic medications (Hughes et al., 2009; Kulkarni et al., 2008). An argument against this hypothesis in VLOSLP, however, has been the time lag of several decades between menopause and the occurrence of late life psychosis in women in their 60's, 70's, 80's and sometimes 90's (Howard, Almeida & Levy, 1994). This led Howard et al. (1994) to propose other factors that could account for the increased risk in these VLOSLP women such as the increased vulnerability to cerebrovascular disease due to decline in oestrogen levels. The exact clinical significance of increased cerebrovascular brain changes present in VLOSLP however remains unclear.

In all, while it is clear that women are more likely to develop a later onset of schizophrenia than men, the neural mechanisms underlying such gender-related predispositions in VLOSLP are unclear.

**2.4.2 *Genetics* -** Studies of prevalence rates of schizophrenia in first degree relatives of VLOSLP patients suggest that genetics appear to play less of a role in the onset of a schizophrenia-like psychosis after the age of 50 or 60 years compared to TOS. As previously mentioned, a study involving data from 269 first degree relatives of individuals with VLOSLP and a comparison group of relatives of health elderly individuals, estimated the lifetime risk of schizophrenia was 2.3% for VLOSLP relatives and 2.2% for relatives of healthy controls (Howard et al., 1997). Further, a recent controlled family study of late onset non-affective psychosis, in which most cases fulfilled ICD-10 criteria for schizophrenia, found no differences in lifetime risk for relatives of individuals with schizophrenia compared to controls. However, it did find that a history of depression was significantly more common among relatives of VLOSLP cases than among controls (Howard, et al. 1997). This familial link with depression has led some to suggest that perhaps LOS has more in common aetiologically with an affective than non-affective psychosis.

Overall, available research does not suggest an increase in the prevalence rates of schizophrenia in VLOSLP first degree relatives as is found for TOS.

**2.4.3. *Premorbid Personality* -** Kay and Roth (as cited in Henderson and Kay, 1997) described individuals with Late Paraphrenia as having some similarities to TOS in being jealous, suspicious, sensitive, with few interests, cold or solitary; but also, unlike younger individuals with schizophrenia being more quarrelsome, dictatorial, domineering and determined. Research investigating the premorbid personality styles of individuals who develop LOS have also consistently reported a lifelong history of abnormal personality traits, most commonly schizoid or paranoid personality traits, which fall short of the current diagnostic criteria for personality disorders (Jeste et al., 1995; Quin, Clare, Ryan & Jackson 2009). In contrast, the premorbid

personality styles of individuals with TOS are far more variable. The literature has used these findings to suggest a greater role for abnormal premorbid personality traits in increasing an individual's vulnerability to psychological distress later in life (Fuchs, cited in Quinn, Clare, Ryan & Jackson, 2009). In support of this view, Giblin, Clare, Livingston and Howard (2004) examined individuals aged older than 60 years during their first presentation of schizophrenia-like psychosis using the Young Schema Questionnaire – Short Version (Young, 1998). They identified that this late onset psychotic group scored significantly higher, in comparison to a healthy control group, on the domains of rejection and disconnection, impaired autonomy and performance, other directedness and over vigilance and inhibition.

As well as these differences in personality traits and psychological distress in comparison with younger onset schizophrenia, occupational histories of LOS individuals indicate that the large majority have been in regular employment up until retirement age (Henderson & Kay, 1997).

**2.4.4** ***Social Isolation*** **-** Social isolation in elderly people with late onset psychosis is much more marked than that seen in TOS (Henderson & Kay, 1997). Research has suggested that this isolation is often longstanding and not of recent onset due to the onset of psychotic illness as is often the case in TOS (Almeida et al., 1995b). Almeida et al. (1995b) found that 78.7% of late paraphrenic patients in their research were socially isolated over the 6 months prior to the inclusion in the research versus 18.2% of the elderly controls. This greater isolation in LOS versus TOS has been hypothesised as being due to either a more marked absence of close relatives in the former, or more extreme personality traits that may alienate the individuals from other people. For example, Kay and Roth (as cited in Henderson and Kay, 1997) found that 40-60% of both males and females in their LOS population had never been married and a high

proportion of their female patients (51-77%) had no children. Similar results were reported by Howard et al. (1994) who found 36% of their population had never married and 50% had no children. Other studies have also reported that LOS patients have difficulties in establishing and maintaining relationships; are more likely to be divorced, live alone; and have few or no social contacts (Almeida et al., 1992; Howard & Levy, 1993). However it remains unclear as to how more extreme socially isolating predispositions and vulnerabilities may impact on an individual's experience to result in the later onset of a psychotic illness.

**2.4.5** ***Sensory Impairment*** **-** Several researchers have proposed certain sensory impairments, in particular hearing loss, as a possible aetiological factor in the emergence of VLOSLP versus TOS. Research by Almeida et al. (1995a) found that 42.6% of their late paraphrenic patients (ICD-10 / aged over 55 years) presented with hearing impairment, a four-fold increase as compared to appropriate age matched controls (15.2%). Similar results have previously been found by Herbert and Jacobson (1967), and Kay and Roth (as cited in Howard, 2008). Almeida, Howard, Forstl and David (1993) also reported improvement in psychotic symptoms in their LOS group following the fitting of hearing aids. Arguing against a pivotal role for hearing loss in VLOSLP is the evidence that approximately 50% or more of elderly people have some degree of hearing impairment, with the large majority not developing a psychotic illness (Hassett, 2002). Further, Brodaty et al. (1999) did not find a higher rate of hearing impairment in their LOS group (onset after 50 years) compared to an aged-matched control group. Prager and Jeste (1994) further failed to identify any significant differences in hearing loss between their LOS group and controls. Overall, whilst results are inconclusive, hearing difficulties may be one of several possible risk factors combining to trigger a LOS illness. This may be because deafness reinforces some pre-existing tendencies to social isolation, withdrawal and suspiciousness

(Howard, 2008).

In summary, while many risk factors for LOS are similar to those for TOS, including migration (Reeves, Sauer, Stewart, Granger and Howard (2001) and traumatic life events (Gilblin et al., 2004), evidence for differences between LOS and TOS with regard to the role of gender (Howard et al., 1994), lifelong premorbid abnormalities (Henderson & Kay, 1997), less genetic influence (Howard et al., 1997), increased incidence of social isolation (Almeida et al., 1995b) and sensory impairment (Almeida et al., 1995a) suggest a possible different neurological basis. As such, the next section focuses on the findings regarding the neuroanatomy and physiology of LOS.

## 2.5 Neuroanatomy and Physiology of Late Onset Schizophrenia and Very-Late-Onset Schizophrenia-Like-Psychosis

Research into the neuroanatomical changes present in VLOSLP is still largely in its infancy. Research to date largely focuses on LOS cases (i.e., first onset of symptoms after the age of 45 years) with some inconsistent findings. Focusing first on ventricular enlargement, which is a relatively consistent finding in brain imaging studies of younger populations of individuals with schizophrenia, some LOS studies have reported similar ventricular enlargement. For example, Rabins, Pearlson, Jayaram, Steele & Tune (1987), examining 29 patients whose LOS illness onset was after the age of 44 with Computed Tomography (CT), found that the mean ventricle-to-brain ratios (VBR's) in their LOS patients was 13.3% compared to 8.6% in aged matched controls. Naguib and Levy (1987) found very similar results in their CT study, with VLOSLP patients' VBR at 13.09% compared to 9.75% in controls. Expanding on this, a study by Forstl et al. (1994) examined the third and lateral ventricles in 14 patients with onset of symptoms after the age of 50 years, 14 patients with Alzheimer's disease and 14 normal controls.

They found that the VBR's for the LOS group were between that of the normal controls and the dementing group, that is, 1.83% for controls, 12.22% for LOS group and 16.9% for the Alzheimer's disease group. Of even more import, Jeste et al. (1997), utilising an MRI study, found significantly greater ventricular enlargement in their LOS group compared to TOS and normal control groups who were similar in age (>45 years), gender and education. Looking for more specific differences, Barak et al. (2002) identified significantly larger cerebral ratios of the fourth ventricle to the width of the cerebellum for their VLOSLP group as compared to the TOS group who had grown old and were matched on age. In contrast, however, Sachdev, Brodaty, Rose and Cathcart (1999), examining individuals who were diagnosed with schizophrenia over the age of 50, and also utilising an MRI brain study, found significantly larger lateral ventricles in this group than in an age matched control group but no significant difference between the LOS sample and an TOS age-matched sample.

In addition, some differences in cerebral structures have also been noted. Sachdev at al. (1999) reported significantly greater cortical atrophy in the anterior temporal and mid parietal regions in a LOS group compared to the TOS and normal control groups. They also reported that the LOS group had more signal hyperintensities than the TOS and control groups in the periventricular, centrum semiovale and subcortical regions, with statistically significant differences in the periventricular region. Finally, Jeste et al. (1997) found significantly larger thalamic volumes in their LOS group as compared to their TOS and normal control groups.

Grey / white matter differences have also been reported. A study by Casanova and Lindzen (2003) examined the average grey and white matter volumes at autopsy in individuals with VLOSLP, a geriatric schizophrenia group and an aged matched control group. Their results suggested that the average left sided grey / white matter ratio in the anterior parahippocampal gyrus of individuals with VLOSLP was 17% greater than that in the geriatric schizophrenia

patients and 27% greater than that in the normal control group. Similarly in the right hemisphere, the average grey / white matter ratio in the anterior hippocampal gyrus in VLOSLP patients was 23% greater than in the geriatric TOS group and 21% greater than in the control group, with no significant difference in this study between the geriatric TOS and control groups. Further the VLOSLP patients in this study were noted to present with neuritic changes in both the hippocampus and parahippocampal gyrus. However, unlike in Alzheimer's disease, where the neurofibrillary changes are linked to the destruction of the affected cells, these cells were preserved in VLOSLP patients. In contrast, Howard and Reeves (2003) demonstrated that abnormalities within the fronto-temporal white matter tracts were present in their TOS group (on the left side) but were not present in their VLOSLP group.

In earlier autopsy studies, Casanova et al. (2002) had also reported hippocampal tau-positive glial fibrilary tangles in 20/34 of their LOS group (first presentation after the age of 40 years) compared to 11/30 of their TOS group (first presentation before age 40) matched on age. Similar glial tangles are reportedly seen in other conditions such as fronto temporal dementia and progressive supranuclear palsy and are also reported as distinguishable from those seen in Alzheimer's disease. However, contrasting studies by Bozikas, Kovari, Bouras and Karavatos (2002), examining for the presence of neurofibrillary tangles in elderly individuals with LOS (disease onset after 40 years of age), found that neurofibrillary tangles were not increased in their elderly LOS individuals and were consistent with normal aging.

Overall, available evidence suggests that differences may exist between LOS and TOS control groups in ventricular and thalamic enlargement, in addition to atrophy in anterior temporal and mid parietal but not frontal areas. Research has also implicated differences in periventricular, centrum semiovale and subcortical regions, in addition to differential grey/white matter ratios between groups.

## 2.6 Neuropsychological Deficits and Late Onset Schizophrenia and Very-Late-Onset Schizophrenia-Like-Psychosis

Given the suggestions of differences in the neuroanatomy and physiology of LOS compared to TOS, one of the current areas of interest surrounding the cognitive functioning of individuals with LOS is whether or not there is any discernible difference in cognitive performance between these groups. To date, the bulk of the research on cognitive functioning in those with a latter age of onset of psychotic illness has focused on LOS samples, that is, those who present with psychotic illness for the first time after the age of 45 years, and general effects of age.

Focusing first on the general effects of age, a recent meta-analysis examining differences in general cognition as a function of age at onset in schizophrenia conducted by Rajji, Ismail and Mulsant (2009) reported that individuals with young onset schizophrenia (maximum age at onset of 19 years) were more impaired than those with a later age of onset (minimum age of onset at 40 years) on cognitive tasks (based on aged normative data) of Arithmetic, Digit Symbol Coding, Vocabulary and the WCST and similar tests. In contrast, they also reported that the young onset group were less impaired than the older onset group on attention, both auditory and visual.

Turning next to LOS, Jeste et al. (1995) compared groups of patients with LOS (aged over 45 years at time of diagnosis) with similarly aged TOS and normal comparison groups using a comprehensive neuropsychological assessment. Their results derived from normative data indicated that both the schizophrenia groups performed worse than the normal controls, but similarly on tasks of WAIS-R Verbal and Performance IQ, Category Test (Halstead Reiten Neuropsychological Test Battery, Reiten & Wolfson, 1993) of executive functioning (number of errors), story memory learning and delayed recall, figure memory learning and delayed recall, Grooved Pegboard test, Aphasia Screening Examination (verbal component) and on a Sensory-

Perceptual Examination task which assesses whether or not an individual is able to perceive stimulation on one side of the body when both sides are stimulated. Significant differences between the TOS and LOS groups were noted, however, on the California Verbal Learning Test (total learning), with the LOS group performing better than the TOS group. In contrast, the TOS group were found to perform significantly better than the LOS group in terms of the number of perseverative responses on the WCST of executive function, suggesting worse set shifting in the LOS compared to TOS group.

Extending on that earlier study, Jeste et al. (1997) assessed the cognitive performance of individuals with TOS who were still young (who were all under the age of 45 and with mean age of 30), an older age TOS group (who were all aged over 45 years and with a mean age of 57) and a LOS group (who presented with the illness for the first time over the age of 45 and with a mean age of 63). Utilising an expanded version of the Halstead Reitan Test Battery they found an overall similar pattern of neuropsychological impairments between the three schizophrenia groups. They did identify some differences between the older age chronic TOS group and the LOS group with the LOS group being found to be less impaired on tasks of learning and abstract reasoning / flexibility of thinking. Jeste et al. (1997) further examined the pattern of learning and memory in regards to age of onset and reported that age of onset of schizophrenia was positively associated with total recall across the learning trials and negatively associated with the presence of retrieval problems.

Similarly, a study by Sachdev et al. (1999), also utilising an expanded neuropsychological battery which included the National Adult Reading Test (Nelson, 1982), selected subtests from the WAIS-R and the WMS-R, the WCST, COWAT, Mazes subtest from the Wechsler Intelligence Scale for Children – Revised (WISC-R), and the Annett's Hand Preference Questionnaire, examined the cognitive performance of three groups: (1) a LOS (aged over 50

years at onset), (2) an TOS group (aged <30 years at onset) and (3) a normal control group (with a mean age of 72 years). Following correction for both age and education, non-significant group differences were found on the tests of Similarities, Mental Control, recall of paired associated words and Digit Backwards recall. Significant differences remained between the two schizophrenia groups and the control groups on Logical Memory, Figural Memory, Visual Reproduction, Verbal Fluency and WCST perseverative errors.

Vahia et al. (2010) also conducted a comprehensive neuropsychological examination of groups of patients with TOS (aged <40 years at onset of symptoms), LOS (aged > 40 years at age of onset) and a normal control group. The individuals examined in this study however had a younger mean age than the previously mentioned studies with the mean age of the three groups being 59.8 for the normal controls, 51.0 for the early onset and 57.6 for the late onset group. Significant differences were found between the TOS and LOS groups on tests of processing speed (WAIS-R/Wechsler Adult Intelligence Scale for Adults – 3rd Edition; WAIS-III Digit Symbol), verbal memory (long delay score on the California Verbal Learning Test adjusted for performance on the trial 5 of the learning trials), visuospatial functioning (WAIS-R/WAIS-III Block Design) and on the perseverative responses score on the WCST, with the TOS group performing significantly worse than the LOS group on all these measures. On all other measures assessed including the WAIS-R/WAIS-III Information, Vocabulary, Similarities, Picture Arrangement and Arithmetic scaled scores, both the TOS and LOS group were found to perform similarly and significantly worse than the normal control group.

A different study into LOS (Late Paraphrenia – aged over 55 years) was conducted by Almeida et al. (1995d) who found that individuals with LOS performed significantly poorer on most neuropsychological measures studied than an aged matched normal control group. Of more interest, Almeida et al. (1995c) used cluster analysis to suggest the presence of two groups of

patients with Late Paraphrenia. The first cluster experienced both generalised cognitive impairment as well as executive dysfunction, with the second group demonstrating more specific executive dysfunction. Specifically, the second group only demonstrated difficulty with extra dimensional set shifting on the Tower of London task. They also highlighted clinical differences between the two clusters with the first group demonstrating less complex psychiatric symptoms and no increased family history of psychiatric illnesses. The second cluster however was noted to show an increased severity of positive psychotic symptoms (a more traditional schizophrenia symptom profile) and a relatively higher frequency of family history of schizophrenia-like illnesses. Thus, this study suggested that there may in fact be two distinct clinical groups that make up late onset schizophrenia, each with cognitive, psychiatric and background differences.

Research into the characteristic neuropsychological profile of individuals with VLOSLP is very limited and began with Hopkins and Roth in 1953 (cited by Howard, 2001). They administered a general test of orientation, the Vocabulary subtest of the Wechsler-Bellevue Scale and a shortened form of the Ravens Progressive Matrices of IQ. They found that the group of 'late paraphrenics' performed as well as a group of elderly patients with depression and better than a group of patients with dementia on all of the three tests (Howard, 2001). Naguib and Levy (1987) also examined the cognitive performance of 43 individuals with VLOSLP (or late paraphrenia) on selected cognitive tests including the Mental Test Score, Digit Copying Test and the Digit Symbol Substitution Test. They found that the VLOSLP 'late paraphrehenia' patients performed worse than an age-matched control group on all cognitive domains examined, that is on the global dementia screening scale, on an attention task and on both a task of motor speed and speed of information processing. Another related study examined the memory functioning of 33 elderly individuals with a suspected late onset delusional disorder (Herlitz & Forsell, 1996). They reported that the delusional disorder group performed at lower levels than expected

according to age adjusted normative data on recall tasks but not on recognition tasks.

As can be seen, previous research has primarily compared the cognitive profile of individuals with TOS and LOS, but not VLOSLP. Differences in study design and neuropsychological tools used also make direct comparison between these studies difficult. Thus, much debate continues concerning whether VLOSLP has a distinct neuropsychological profile to TOS. This debate also relates to the questions concerning whether VLOSLP should be seen as more of a precursor to a dementing illness than a classic schizophrenia, as discussed further below.

## 2.7 Very-Late-Onset Schizophrenia-Like-Psychosis as a Neurodegenerative Condition

The debate as to whether or not VLOSLP is a precursor to a dementing illness is a longstanding one. This debate has most likely stemmed in part from the observation of high rates of psychotic symptoms in individuals with a dementing illness. Along these lines, a study by Holroyd and Laurie (1999) examined 140 geriatric outpatients that had previously been investigated for psychosis. Of this elderly sample they found that 36.7% had been diagnosed with dementia. Psychotic symptoms have also been found to be one of the prominent symptoms of Alzheimer's disease, with prevalence rates of psychotic symptoms ranging from 30 to 50% (Jeste & Finkel, 2000).

As previously discussed, cross sectional studies investigating cognitive functions in individuals with schizophrenia have generally found that they are relatively stable over the course of the illness. That is, research has largely shown that no overall decline in cognitive functioning is noted to occur after the early years of the illness (Harvey, Docherty, Serper & Rasmussen, 1990; Sweeney, Haas, Keilp & Long, 1991; Fucetola et al., 2000). Similar questions are now being asked about the stability of cognitive deficits seen in individuals with LOS. More

specifically, questions are now being asked as to whether or not late onset psychotic illness is indicative of a prodromal neurodegenerative dementing illness. As a result, the cognitive profile of individuals with VLOSLP is quickly gaining greater clinical importance, however to date the results of these longitudinal research studies have been mixed.

In investigating whether VLOSLP is a precursor to neurodegenerative illness, Palmer et al. (2003), utilising two dementia screening tools (MMSE and the Dementia Rating Scale; DRS), followed up four patient groups, including TOS, LOS, Alzheimer's disease with psychotic symptoms, and an Alzheimer's disease "cognitive" group (i.e., without psychotic symptoms). These groups were reviewed each year for two years. Their results found no significant decline in MMSE or DRS scores over the two year period in the individuals with both early and late onset schizophrenia. However significant declines were noted in both the Alzheimer's groups. However it is important to remember the follow-up period in this study was limited to only two years. Lengthier longitudinal studies by Rabins and Lavrisha (2003) followed up individuals with LOS, Major Depression and Dementia with Psychosis over a seven - ten year period. Utilising a decline in four points on the MMSE as a marker of dementia, they found that patients with LOS were no more likely to develop dementia than the group with Major Depression over their seven year follow up period. However they found that approximately 50% of individuals with LOS and Major Depression did go onto develop dementia at the ten year follow up (though it is important to note that this is based on a 4 point decline on gross MMSE scores).

Similarly, Holden (1987) using the Camberwell Register and the Maudsley Hospital Register, identified and examined all new cases of late onset psychosis in individuals aged over 60 who presented to the area over a five year period. Of this sample they identified 37 patients who fulfilled Roth's criteria (1955) for Late Paraphrenia. Holden (1987) followed up these patients over a ten year period, and found that of the original 37 patients, thirteen were noted to

progress to dementia over a three year period, based on a clinical interview and their results on a cognitive screener similar to the MMSE.

Zakzanis, Andrikopoulos, Young, Campbell and Sethian (2003) conducted a more comprehensive neuropsychological comparison between a group of patients with LOS (aged over 45 years at time of diagnosis) and a group of patients meeting diagnostic criteria for Alzheimer's disease. Surprisingly, their results found no significant difference in the performance between the two groups on most neuropsychological tasks. However significant differences were found on tests including Trails B, WMS-III Logical Memory delayed recall and the California Verbal Learning Test Long delay free recall, with the Alzheimer's disease group performing significantly worse than the LOS group.

Brodaty and colleagues (2003) conducted a five year follow up review of cognitive functioning in individuals with LOS over the age of 50 years (as a follow-up of the Sachdev et al., 1999 paper discussed in the previous section). They found that nine out of the 19 LOS patients met the DSM-IV criteria for dementia at the five year follow up mark. The breakdown included five who met the criteria for Alzheimer's disease, one for vascular dementia and three of unknown type. In comparison, none of the control group met the criteria for dementia. Further, the LOS group's MMSE score was noted to decline by 6.5 points on average over the 5 year period, whereas the healthy control group's score remained stable. There were no significant differences between the 2 groups in the levels of neurological abnormality at the five year follow up. These researchers have all proposed that LOS is in fact a prelude to dementia in a high proportion of cases. It is important to note however that, as with all the previously discussed research, not all individuals went on to develop a diagnosable dementia. This further adds to the view that LOS is a heterogeneous illness. As such better understanding of the cognitive profile of this population, and its possible subgroups, is important in order to improve our identification

of those who will in fact go on to develop a dementia later. Examining the LOS group on their own however revealed a disparity in outcome between those who went on to develop a diagnosable dementia compared to those who did not. Brodaty and colleagues highlighted that this was most notable in the mean Global Assessment of Functioning scale scores, with those diagnosed with dementia showing decline at five years compared to LOS patients without dementia whose global functioning scores were noted to rise from 41.6 to 61.6. This increase was deemed most likely due to the full or partial resolution of psychotic symptoms in these individuals.

A review of the clinical, anatomy and cerebral imaging studies by Lagodka and Robert (cited in Girard et al., 2011) suggested that the possibility of LOS and VLOSLP being solely a prodromal phase to Alzheimer's disease appeared very unlikely. They based this conclusion on several factors. Firstly, they noted that no greater family history of dementia disorders is evident in individuals with LOS / VLOSLP than in the general population. Secondly, they pointed out that neuropsychological test performance has been found to be different between those with LOS / VLOSLP and Alzheimer's disease. Thirdly, they summarised that anatomy studies have shown the LOS is not consistent with Alzheimer's disease and is in fact more related to restricted limbic tauopathy. Lastly, they summarised that very little differences have been found on neuroimaging studies between LOS and TOS. They did, however, point out that some studies have been confounded by the vast age ranges of inclusion in LOS and VLOSLP studies which make direct comparisons somewhat difficult.

Martin Roth (1955) also conducted a comprehensive review into the outcome of elderly psychotic and psychotically depressed individuals as far back as 1955. He reviewed the outcome of 450 patients six months after their admission to hospital. Roth's longitudinal research suggested that that 58% of individuals admitted with a late onset psychotic depression had been

eventually discharged, whereas 76% admitted with a 'late paraphrenia' remained an in-patient, and 58% of individuals with a more chronic schizophrenia were deceased. This distinctive pattern of outcome was noted to continue at two years after admission. Whilst substantial advancements have been made in the medical, pharmacological and psychological treatment of elderly mentally ill patients it does highlight the possibility that these illnesses are in fact three clinically distinct illnesses with three distinct causes, resulting in three very distinct clinical outcomes.

## 2.8 Pharmacotherapy Use in Late Onset Schizophrenia and Very-Late-Onset Schizophrenia-Like-Psychosis

Like individuals with TOS, antipsychotic medications are the most commonly used pharmacological treatment for individuals with a late onset psychotic illness. However, elderly individuals have been shown to have both increased side-effects and sensitivity to the use of antipsychotic medication and medications in general (Karim & Byrne, 2005). The list of potential side effects of antipsychotic use in the elderly is long and includes an increase in extrapyramidal side effects (pseudoparkinsonism, akathesia, acute dystonia and tardive dyskinesia), anticholinergic effects (urinary hesitancy, constipation, blurred vision, dryness of the mouth, delirium), postural hypotension, sedation, hypersalivation, gastrointestinal effects, liver effects, cardiovascular effects, endocrine effects (weight gain, diabetes mellitus) and epilepsy (Karim & Byrne, 2005; Jeste, 2004; Essali & Ali, 2012). Adverse effects in the elderly are often increased or complicated by comorbid physical illness, polypharmacy, nutritional deficiencies and dehydration. Lindsey (2011) suggested that elderly individuals generally respond to dose amounts that are 33% to 50% of those given to TOS cases, with slow titration up.

A few controlled drug trials have assessed the clinical efficacy and safety of using

atypical and typical antipsychotics in elderly populations. Scott, Greenwald, Kramer and Shuwall (2011) followed VLOSLP patients treated with atypical antipsychotics and reported an overall treatment response rate of 62% in their sample. Previous LOS studies have reported that the response to typical antipsychotic medications is reduced and in the range of 40% to 50% (Brodaty et al., 1999; Howard et al., 2000; Jeste et al., 1999a & 1999b). Similarly, Barak et al. (2002) found that their VLOSLP patient group responded significantly better to treatment with atypical antipsychotic medication, reaching 71.4% as compared to their TOS group.

In summary, the available research to date supports the therapeutic use of atypical over typical antipsychotics in treating symptoms of LOS, with additional warning concerning possible increased side effects. General consensus also suggests that elderly individuals generally respond to dose amounts that are 25% to 50% of those given to TOS cases.

## 2.9 Late Onset Psychotic Depression

A substantial amount of research in recent years has been conducted into late-life (non-psychotic) depression. Research has identified that the development of late life (non-psychotic) depression often occurs in the context of multiple medical illnesses including vascular diseases, arthritis, asthma and diabetes and is associated with higher morbidity, mortality, disability and neuropsychological deficits than early onset (non-psychotic) depression (Alexopoulos & Kelley, 2009). Neuropsychological deficits in late life (non-psychotic) depression have been found in the areas of information processing speed (Lesser et al., 1996), memory (Salloway et al., 1996), visuospatial functioning (Krammer-Ginsberg et al., 1999) and more notably in the areas of executive functioning (Lockwood, Alexopoulos & Van Gorp, 2002). Late life (non-psychotic) depression also differs from early-life depression in that it is often accompanied by more frequent impairments in executive tasks of response inhibition and sustained effort (Alexopoulos & Kelly,

2009). Further, individuals with specifically comorbid late-life (non-psychotic) depression and vascular disease have been shown to demonstrate greater executive dysfunction, accompanied with also poorer insight, greater psychomotor retardation, less agitation and guilt, and more disability (Alexopoulos, 2005). At an anatomical level, individuals with a late-life (non-psychotic) depression have also been found to have a greater severity of hyperintensities on T2 weighted MRI studies than individuals with an early onset depression (Hickie et al., 1995; Salloway et al., 1996). This relationship between late-life depression and vascular disease has led to the development of the 'vascular depression hypothesis' (Alexopolous, 2005). In summary, individuals with a non-psychotic 'vascular depression' have been found to have both greater disability and cognitive impairment than those without vascular disease (Salloway et al., 1996).

However, given the findings of the Roth (1955) review, and that the second most common cause for psychosis in the elderly is depression, this section provides a brief overview of relevant findings on Late Onset Psychotic Depression (LOPD) before outlining the reasons for the current study. Individual's with a psychotic depression not only present with a severe depressed mood, they also present with a severe social impairment, severe psychomotor disturbance involving either agitation, retardation or cognitive processing problems, they also however present with psychotic features including delusions and / or hallucinations. Holroyd and Laurie's (1999) findings suggested that Psychotic Depression made up 20.4% of all cases of psychosis in the elderly. As per the DSM-IV-TR, Psychotic Depression is classified as Major Depression with psychotic features. Psychotic Depression typically includes more feelings of guilt, more pronounced psychomotor disturbance, more impaired cognitive functioning and the presence of somatic, nihilistic and / or paranoid delusions with increasing clinical evidence to suggest that Psychotic Depression is a distinct subtype of depression in the elderly (Broadway &

Mintzer, 2007). Similar to VLOSLP there is also a higher ratio of women to men who present with Psychotic Depression. Research on the cognitive profile of LOPD is very limited. With regard to studies investigating the cognitive functioning of individuals with Psychotic Depression (of any age onset) versus those with a nonpsychotic depression, it has been found that individuals with Psychotic Depression perform more poorly on measures of: visual memory and visual spatial perceptions (Hill, Keshavan, Thase & Sweeney, 2004); attention, psychomotor speed, motor functioning and learning (Jeste et al., 1996); and verbal memory and response inhibition (Schatzberg et al., 2000). However the most consistent findings appear to be in the areas of psychomotor speed, verbal memory and executive functioning which are all worse in Psychotic Depression (Fleming, Blasey & Schatzberg, 2004). Hill et al. (2004) also found that the profile of neuropsychological impairment seen in Psychotic Depression was also similar to that seen in a group of individuals with Schizophrenia, but less severe.

Research into the cognitive profile of older individuals with Psychotic Depression (> 45 years) has produced varied findings. Jeste et al. (1996) compared the neuropsychological performance of individuals age 45 years and over with Unipolar Depression, Psychotic Depression and chronically ill, typical onset schizophrenia. Their findings showed that the cognitive performance of individuals with Psychotic Depression was generally comparable to those with Schizophrenia, though both psychotic groups demonstrated more impairments than the nonpsychotic Unipolar Depression group on measures of attention, psychomotor speed, motor skills and learning. Another study by Schatzberg and Rothschild (1992) reported findings for reduced frontal and temporal lobe brain functioning in both younger and middle aged individuals with psychotic depression as compared to other individuals with non-psychotic depression. Finally, Simpson, Baldwin, Jackson and Burns (1999) researched a group of elderly individuals with late onset Psychotic and nonpsychotic Depression (i.e., average age of onset >

63) and identified significant differences between the two groups only on tasks of working memory and motor speed / speed of information processing. Alternative cognitive domains were reported to be within average ranges for both groups.

It is evident that research into the cognitive aspects of individuals with more specifically a late onset depression with psychosis (LOPD) as compared to TOS and LOS groups remains in its infancy. This gap in knowledge needs to be addressed in the context of research on late-life onset psychoses particularly since Psychotic Depression is the second most common form of late-onset psychosis after LOS.

## 2.10 Rationale for the Current Study

It has been estimated by several studies that approximately 1% of the elderly population has schizophrenia, similar to that seen in younger adults (Jeste, 1993; Cohen, 1990). The number of older adults in our community is expected to rise dramatically over the next few decades with the ABS estimating that by 2051 there will be approximately 6.4 million people (up from 2.2 million in 2007) living in Australia aged between 65-84 years and approximately 1.7 million (up from 344,000 in 2007) aged 85 years and older. As a result, the number of older adults in Australia living with schizophrenia will concurrently increase, with corresponding increases to be expected in the cost of public health care of this population. As mentioned previously, cognitive deficits in schizophrenia have been identified as one of the strongest predictors of functional outcome (Green et al., 2000). Given this, research into the cognitive deficits in individuals with chronically ill, typical onset schizophrenia has exploded over the past couple of decades. However, as is illustrated in this chapter, research remains quite sparse regarding the cognitive profile of individuals aged over 65 years either with chronically ill, typical onset schizophrenia, who have now grown old, or with psychotic symptoms presenting for the first

time in late life. Very little is also known about the clinical and cognitive evolution of individuals with VLOSLP.

Increasing the knowledge base surrounding VLOSLP is particularly important as it will assist health staff, such as general practitioners and psychiatrists, to better identify the illness and avoid simply attributing the symptoms to the behavioural psychological symptoms of prodromal dementia. There is general consensus that, at a global level, the overall cognitive decline seen in the majority of these VLOSLP patients is different to that seen in individuals with dementia. However, to help clinicians better distinguish individuals presenting with VLOSLP from those in a prodromal dementia phase, elucidation of the distinct neuropsychological profile of VLOSLP, which is the primary aim of this study, will assist in successfully delineating it from other conditions.

This study has also attempted to address some of the limitations of previous related research. Firstly, the current study utilises clear diagnostic definitions based on current literature and the International Late-Onset Schizophrenia Group (Howard et al., 2000). It also examines VLOSLP and older TOS cases matched on age, as well as another clinical control group for comparison, a LOPD group. This study has also utilised a comprehensive neuropsychological battery of normed tests to better specify the distinct profiles of the three groups, rather than using limited dementia screening tools, as used previously in related research.

## 2.11 Aims and Hypothesis of the Current Study

The primary aim of this study is to more definitively describe the specific pattern of neuropsychological functioning of individuals who present with VLOSLP. Associated with this primary aim, this study also aims to evaluate any differences in the neuropsychological presentation of individuals who present with VLOSLP over the age of 65 years, compared with

those who first developed schizophrenia prior to the age of 45 years and who have now grown old, and those who present with a psychotic depressive illness for the first time over the age of 65 years. All groups, including the LOPD control group, will also be similar in currently receiving antipsychotic medications. In addition to assessing the three groups' neuropsychological test performances, their levels of functioning will also be examined.

Based on the existing empirical research reviewed, we hypothesised that:

1) if VLOSLP is a schizophrenic illness, albeit with an atypical very late onset, the VLOSLP group's neuropsychological performance would be generally reduced, as is seen in schizophrenia samples across all stages of the illness, as compared to both the battery's normative healthy control data and the performance of the LOPD psychiatric control group;

2) if schizophrenia is a neurodegenerative condition, as well as a neurodevelopmental condition, the VLOSLP group will be less impaired than the TOS individuals, who have had the illness for 20+ years longer;

3) the VLOSLP and the TOS groups would perform at similar lower levels on some tasks, which, according to the literature, would be expected to include those of working memory, story learning and story recall, visual memory, abstract reasoning and cognitive flexibility, and which may associate more with vulnerability to schizophrenia and/or the brain changes that can associate with onset of a schizophrenia illness;

4) in contrast, the VLOSLP would present with less decline than the TOS group in the

areas of verbal list learning, visuospatial functioning and verbal fluency, and which may associate more with the neurodegenerative changes that can occur with schizophrenic illness; and

5) the LOPD control group would present with a generally similar profile of reduced neuropsychological functioning to that of the schizophrenia groups, but these individuals' impairments would be less pronounced.

# Chapter 3. Research Design

## 3.1 Ethical Considerations

The study was approved by Sydney West Area Health Service and Macquarie University's Research Ethic Committees. All individuals were provided with a complete written and oral description of the study and following this, written informed consent was obtained from all research participants. All data were coded and registered anonymously.

## 3.2 Sample

All individuals with psychotic illnesses who presented to the Sydney West Area Health Service between the years of 2008 and 2013 were considered as possible participants for the present study. Participants were recruited from both the local inpatient unit and local mental health outpatient services. All individuals were aged 65 years of over. The upper age limit aligned with the nature of the service from which the research population was obtained, given the above services only accepted individuals over the age of 65 years (which is retirement age in Australia). No age-matched healthy control group was recruited as the neuropsychological test results were converted to z scores utilising age corrected normative data. All participants were native English speakers and were in receipt of antipsychotic medications.

**3.2.1** ***Very-Late-Onset Schizophrenia-Like-Psychosis Sample*** **-** The VLOSLP group comprised of 25 individuals who met DSM-IV-TR criteria for schizophrenia or delusional disorder as assessed by independent psychiatrists. Each individual was aged 65 years or older at first manifestation of their prodromal symptoms, as confirmed by an informant. All the VLOSLP group were first admission and or first contact patients and as a result age of onset aligns with current age for this group.

**3.2.2** ***Chronic Chronically Ill, Typical Onset Schizophrenia Sample*** **-** The chronic schizophrenia sample comprised of 27 individuals who were currently aged 65 years or older. Each individual in this sample had presented with the first manifestation of their prodromal symptoms prior to 40 years of age. This was confirmed by an informant and / or medical record files. The diagnosis of schizophrenia was also confirmed by independent psychiatrists.

**3.2.3** ***Late Onset Psychotic Depression Sample*** **-** The very late onset psychotic depression sample comprised of 18 individuals who met DSM-IV-TR criteria of Major Depression with Psychotic Features as assessed by independent psychiatrists. Each individual was currently aged 65 years or older and were seen at the time of the first manifestation of their symptoms.

**3.2.4** ***Exclusion Criteria*** **-** The following exclusion criteria was also used for all groups -

a. Any history of drug / alcohol abuse
b. History of stroke, transient ischaemic attack, epilepsy, Parkinson's disease, other diagnosable brain disease or head injury resulting in a loss of consciousness.
c. Organic Mental Syndrome (e.g. delirium)
d. A score of 24 or less on the Mini Mental State Examination (MMSE)
e. Developmental Learning difficulties
f. IQ less than 75.
g. Worse than mild tardive dyskinesia
h. Previous history of mental illness
i. Lack of corroborative (e.g. from informant) history

### 3.3 Demographic and Clinical Measures

Detailed hospital and / or community medical record files were available in all cases and included information about prominent symptoms, disease course, family history, substance abuse and medications.

**3.3.1** ***Demographic Characteristics*** **-** Age, gender, years of education, employment history, self-identified ethnic background, migrant status, current / previous marital status, and current accommodation status were determined via both patient interview and review of available medical record files.

**3.3.2** ***Clinical Characteristics*** **-** Age at onset of prodromal symptoms, duration of current illness and current antipsychotic medication usage (type and dose converted to chlorpromazine equivalents) were determined through both patient interview and corroborative interview, as well as via review of available medical records. We also obtained information on level of premorbid functioning or family psychiatric history from the patient and from all other available sources, including family members / significant others and medical records.

**3.3.3** ***Clinical Evaluations*** **-** Appropriate laboratory evaluations (e.g. serum B12, thyroid function tests, serology test for syphilis) were done. CT Brain scans and MRI scans were not routinely available for all patients. Vascular risk factors such as presence of hypercholesterolemia, hypertension or diabetes were recorded.

**3.3.4** ***Psychopathology*** - The following rating scales were used:-

a. Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) - The current severity of positive, negative and general psychopathologic symptoms was measured using the BPRS. This is an 18-item scale that measures major psychotic and non-psychotic symptoms. Each symptom construct is rated on a seven point scale (where 1 = not present to 7 = extremely severe). The scale has been shown to be suitable for assessing baseline psychopathology, clinical course and treatment response and has excellent reliability in clinical trials (Overall & Gorham, 1988). This measure was selected in order to provide a relatively brief, though comprehensive overview of the psychopathology across the three geriatric groups.

b. Geriatric Depression Scale (GDS; Yesevage et al., 1982) - Self reported measure assessing depressive symptoms.

c. Hamilton Depression Rating Scale (HAM-D-17; Williams, 1988) - Observer rated 17-item measure assessing the presence / severity of an individual's depressive symptoms.

**3.3.5** ***Everyday Functioning*** - Measures of everyday functioning were assessed utilising the:

a. Global Assessment of Functioning (GAF: From DSM-IV-TR, pg. 34American Psychiatric Association, 2000).

b. Role Functioning Scale (RFS: Goodman, Sewell, Cooley & Leavitt, 1993)

Numerous measures exist to assess the functional capacity of individuals with schizophrenia, including the University of California Performance-based Skills Assessment (UPSA) (Heinrichs, Statucka, Goldberg & McDermid, 2006). However, this research utilised the above, commonly

used interviewer based rating scales which are brief and easy to administer.

## 3.4 Neuropsychological Measures

**3.4.1** ***Neuropsychological Assessment*** **-** Patients were assessed with a comprehensive neuropsychological assessment battery. This comprehensive battery comprises tasks that assess domains which are generally consistent with the previously mentioned MATRICS battery. Specific tests were chosen for this battery based upon the literature cited above. Selected measures from individuals tests were grouped into 10 broad domains (see below). The decision regarding grouping of individuals test measures into domains was based on a priori assessment of the content validity of individual tests (Strauss, Sherman & Spreen, 2006). The focus of this study was restricted largely to neurocognitive domains in order to enable the assessment to be completed in only one or two sessions in order to reduce the number of drop outs. It is our aim for future studies that we expand the area of interest to also include that of social cognitive domains. The assessment was generally conducted over one or two sessions. All tasks were administered using standardised instructions and scoring procedures. The neuropsychological test battery is detailed in the following sections.

### 3.4.2 *Dementia Screening Measures*

a. Mini-Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975) - This is a widely used screening test for dementia. A score of 24/30 or less has been used in clinical research to denote the presence of a possible dementia (Folstein et al., 1975). All participants were required to have a score of 25 or more.

### 3.4.3 *Premorbid Intellectual Functioning*

a. Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) - This task is designed to assess an individual's premorbid level of functioning. It involves the individual reading a list of fifty irregular words, presented in two columns on a single piece of paper. The dependent variable for this test was the total number of correctly read words. The raw score was converted to an age corrected predicted Full Scale IQ score following the manual instructions and utilising the UK norms.

### 3.4.4 *Immediate Auditory Span of Attention*

a. Digit Span Forward (Wechsler Adult Intelligence Scale - 3rd Edition, WAIS-III; Wechsler, 1997a) - Involves individuals repeating a number sequence in the same order as it is presented to them. The variable used on this task was the longest digit span forward, that is, the longest number of digits the individual was able to correctly repeat back to the examiner. Using the normative data in the WAIS-III manual, this raw score was converted to an age corrected z-score.

### 3.4.5 *Working Memory*

a. Digit Span Backwards (WAIS-III; Wechsler, 1997a) - This task involves the individual repeating a number sequence in the reverse order to which it was originally presented to them. The variable used on this task was the longest digit span backwards, that is, the longest number of digits the individual was able to correctly repeat back to the examiner. Using the normative data in the WAIS-III manual this raw score was converted to an age corrected z-score.

### 3.4.6 *Motor Speed and Speed of Information Processing*

a. Trails Part A (Trails A; Trail Making Test; Strauss et al., 2006) - This task requires the individuals to connect, by drawing pencil lines, 25 numbers randomly spread across a single A4 page, in numerical order as quickly as they can. The dependent variable used on this task is the time it takes (in seconds) for an individuals to complete the task, which was then converted to age and education corrected z scores using the Australian normative data from Hester, Kinsella, Ong and McGregor (2005). This normative data was used due to the relatively large number in the normative sample, 363 individuals aged 60 years and over, which is further classified by years of education and more pertinently based on an Australian sample.

b. Digit Symbol (WAIS-III; Wechsler, 1997a) - This task requires an individuals to copy abstract symbols associated with different numbers. Nine abstract symbols are paired with the numbers from one to nine and are presented in a key format at the top of the page. Rows of boxes are presented below this key, in which various numbers are placed above empty boxes. The individual is instructed to insert the correct symbol below each of the corresponding numbers. The dependent variable is the number of correct substitutions an individual is able to complete in a two minute period. The raw score on this task was changed to an age corrected scaled score using the WAIS-III manual normative data.

### 3.4.7 *Verbal Learning and Memory*

a. Rey Auditory Verbal Learning Test (RAVLT; Strauss et al., 2006) - This task is a serial word list learning task, which involves the presentation of five independent learning trials of the same list of fifteen words. This is followed by the presentation of an interference

trial, and a subsequent immediate recall trial of the initial target list. Twenty minutes later a delayed recall trial and a recognition trial is also completed. The dependent variables used from this task were the Total number of words recalled by individuals over the five learning trials (Learning Over the Trials - LOT) and the total number of words recalled on the delayed recall (Trial VII - delayed memory). The raw scores were converted to age corrected scaled scores utilising the normative data from the Mayo's Older Americans Normative Studies (Ivnik et al., 2007). This normative data was utilised due to the high number of individuals in each age range. Available Australian normative data by Senior (1999) were considered inappropriate due to the large age range of 55-80 year age bracket used for the older normative data. Other normative data were also considered, for example, Geffen et al. (cited in Strauss et al., 2006), but were also considered inappropriate due to the limited normative data for individuals over the age of 70.

b. Logical Memory (Wechsler Memory Scale – Third Edition, WMS-III; Wechsler, 1997b) - This task involves the individuals learning and retaining a verbally presented short story. Two stories are read verbatim to the individual. Story A has only one presentation, with story B presented twice. Individuals are scored 1 point for each correctly recalled story unit from both stories. The dependent variable for this task involves the Immediate Recall of both stories, which is calculated by summing the total number of correct units from the immediate recall of story A with the number of correctly recorded units from both presentations of story B. The other variable used was the Delayed Recall of both stories, which refers to the total number of story units recalled from the two stories

following a 25-35 minute delay. The Raw scores are converted to age corrected scaled scores using the WMS-III manual normative data.

### 3.4.8 *Visual Memory*

a. Rey-Osterrieth Complex Figure Test (RCFT; Rey 1941, Osterrieth, 1944 cited in Strauss et al., 2006) - This was assessed using the 30 minute delayed recall trial of the RCFT. The task was administered according to the criteria of Meyers and Meyers (1995), including the copy, 3 minute and 30 minute delayed recall trial. However for the purpose of this study only the copy and the 30 minute delayed recall trial data were examined. Participants were initially asked to copy this complex figure and then were required to independently recall as much of the figure as they could thirty minutes later. The scoring criteria used was that of Meyers and Meyers (1995) where the figure was broken down into 18 scorable units and a score of 0.5, 1 or 2 was given dependent upon accuracy and positioning of the element. The normative data used for the delayed recall trial was that of Meyers and Meyers (1995).

### 3.4.9 *Visuospatial Functioning*

a. Visuospatial Construction - This was assessed using the Block Design Subtest of the WAIS-III (Wechsler, 1997a). This test was administered and scored according to the WAIS-III manual. Participants were asked to replicate various models / pictures of two-coloured designs with either four or nine, 3 dimensional blocks. The participants raw scores were converted to age corrected normative data utilising the WAIS-III manual.

b. Rey-Osterrieth Complex Figure Test Copy (RCFT, Rey, 1941; Osterrieth, 1944; cited in Strauss et al., 2006):- The individuals copy of the RCFT was scored according to the 36 point scoring criteria of Meyers and Meyers (1995) as previously discussed (see section

3.4.8a). The total raw score was converted to age corrected scaled score utilising the Mayo's Older Americans Normative Studies (MOANS) normative data from Machulda et al. (2007). This normative data was chosen over that of Meyers and Meyers (1995) due to the large sample size of elderly participants included in the normative study.

### 3.4.10 *Language Functioning*

a. Confrontational Naming - This was assessed with the Boston Naming Test – 2nd Edition (BNT; Kaplan, Goodglass & Weintraub, 2001). This task involves the individuals being presented with 60 line drawings, which they need to spontaneously name. The dependent variable derived from the BNT is the number of correct responses, without cueing. These scores were converted to age corrected z-scores using the Australian Normative data published by Worrall, Yiu, Hickson & Barnett (1995).

### 3.4.11 *Executive Functioning*

a. Verbal Abstract Reasoning - This was assessed with the Similarities subtest from the WAIS-III (Wechsler, 1997a). This task requires the individual to describe the similarity between two objects (for example a piano and a drum). The dependent variable is the total score on this task. This raw score was converted to an age and education corrected Standard Score using the normative data in the WAIS-III manual.

b. Phonetic Fluency - This was assessed with a test of word list generation (FAS; Strauss et al., 2006). Participants were given sixty seconds to generate as many words as possible beginning with a specified letter excluding proper nouns or the same word with a different suffix (e.g. eat and eating). The dependent variable is the number of correct responses summed across each of the three letters. This raw score was

converted to an age and education corrected z-score using the normative data from Tombaugh, Kozac and Rees (1999). This normative data was employed over the MOANS normative data due to the ability to adjust for both age and education for the elderly sample.

c. Semantic Fluency - This was assessed with a test of word list generation involving Animals (Strauss et al., 2006). Participants were given sixty seconds to generate responses. The dependent variable used on this task was the total number of correct words recalled over the sixty seconds. This raw score was converted to an age and education corrected z-score using the normative data from Tombaugh, Kozac and Rees (1999). Similarly to phonetic fluency, this normative data was employed over the MOANS normative data due to the ability to adjust for both age and education for the elderly sample.

d. Visual Problem Solving (Tower Test, Delis-Kaplan Executive Function System; D-KEFS, Delis, Kaplan & Kramer, 2001) - This task requires individuals to move discs of varying sizes, from small to large, across three vertical pegs in order to construct a pictorially displayed tower. Individuals need to construct the tower using the fewest number of moves possible, whilst obeying two rules; the first in that they are only able to move one of the discs at a time, and the second is never placing a larger disc on top of a smaller one. The dependent variable used on this task is the total overall achievement score across all the trials, converted to Standard Scores utilising the age corrected D-KEFS manual normative data.

e. Cognitive Flexibility (Trails B, from the Trail Making Test, Strauss et al., 2006) - This task requires an individual to connect circles containing either numbers or letters

in alternating, sequential order, as quickly as possible. The dependent variable used on this task is the time it takes an individual in seconds to complete the task, which was converted to age and education corrected z scores using the Australian normative data from Hester et al. (2005).

f. Cognitive Inhibition (Inhibition Total Error Score, from the Colour Word Interference Test, D-KEFS, Delis et al., 2001) - The Colour Word Interference Test is comprised of four individual tasks and on each task the individual is instructed to respond as quickly as they can. The first task is a colour naming task, where the individual is presented with a page of coloured squares (red, green and blue) which they have to name. The second is a word reading task which requires the individual to read a page of randomised colour names (red, green and blue) written in black ink. The third task is the inhibition task, where the individual is presented with a page of randomised colour names (written in incongruent coloured ink, for example the word red might be written in green ink). The individual is required to name the colour of the ink and ignore what the word says. The inhibition task measures an individual's ability to supress an automatic response in favour of a novel / unusual one. The fourth task is an extension on this and requires the individual to switch between colour naming and word reading on a similarly designed inhibition task. The dependent variable used was the number of errors made on the inhibition task (the third task). This raw score was converted to Standard Scores utilising the age corrected D-KEFS manual normative data.

g. Wisconsin Card Sorting Test (WCST, Heaton, 1981) - the 64 card version was administered to all individuals. This task involves continuously matching new cards

to one of four target cards. After each response, the individual is informed as to whether or not that response was correct or incorrect. After ten consecutive correct responses, the correct concept for sorting the categories is changed. Several different scores can be drawn from this task, but the dependent variable examined for this research was the number of perseverative responses. On this task a perseverative response was defined as a response that matched a previous category.

### 3.5 Procedures

Diagnosis was independently established by the treating clinicians (Staff Specialist; Aged Care Psychiatrist) certified by the Australian Medical Association and using DSM-IV-TR criteria for schizophrenia. Diagnoses were made during routine clinical interviews. The neuropsychological assessment was carried out by a qualified Clinical Neuropsychologist. The neuropsychological assessment was completed in the same order with all participants. The battery of neuropsychological tests was usually completed over one session of 3 hours duration, with rest breaks taken as required. Neuropsychological testing was only conducted after each individual had been psychiatrically, medically and pharmacologically stable for at least one month. Of special note, the individuals in the LOPD group who received electrical convulsive therapy (ECT) as part of their treatment were assessed at least three months post their final ECT treatment session.

### 3.6 Data Analysis

The Statistical Package for the Social Sciences (SPSS) version 21 for Windows was used for all statistical analysis conducted in this research (SPPS, 2012).

### 3.6.1 *Data Analysis Involving all Three Clinical Groups*

Descriptive statistics (means, standard deviations and ratios) were examined initially for the demographic characteristics of the three clinical groups. In order to examine the degree to which the three groups were comparable on the core demographic and clinical variables, univariate analysis of variances (ANOVA's) were conducted (Bonferroni-adjusted for inflated Type 1 error rate), followed by Bonferroni-adjusted post-hoc comparisons when group differences were significant. Chi-square analyses were run to assess for between group differences on categorical demographic variables, for example, gender or marital status.

In regards to the neuropsychological test variables, we converted all participants' neuropsychological test scores on each measure to z-scores using age corrected (and education adjusted where available) normative data (see measures section for normative data used). To reduce the number of statistical comparisons, we limited the number of test scores explored by examining specific neuropsychological tests covering broad cognitive domains, highlighted previously in the measures section. The variables from tests designed to assess similar neurocognitive domains were grouped together and between group analyses were conducted within each of the various domains (e.g. attention / executive functioning). Initially, given this research is a preliminary, clinical exploratory study, individual test scores were analysed rather than creating composite domain scores. The reasoning for this is that, at a clinical level, understanding the individual's test profile is more important than the domain profile (for which it is not possible to understand performance on individual tests). Baseline comparisons of the three groups on domains that consisted of only one variable (e.g. language functioning) were performed with one way ANOVA's. For domains that involved more than one dependent variable (e.g. executive functioning), a multivariate approach to repeated measures analysis was used to investigate the pattern of performance across the tests. Stacked data sets were employed,

thus allowing for each observation rather than each participant to be viewed as a case in the SPSS data file. This approach was employed in order to avoid losing an entire participant's data, as would occur in a standard Multivariate Analysis of Variance (MANOVA) analysis, if data from any particular measure was missing. We felt the latter would potentially affect the representativeness of the sample. Further, we took the view that replacing missing values with either group means or age appropriate means could also misrepresent the data, as some missing data was due to the inability of an individual to complete the task. In this type of analysis, subject is treated as a factor. This is done in order to deal with the fact that there are multiple observations for each subject and avoid the analysis treating each observation as though they came from different subjects. On both these analyses, the clinical sample was used as the between-group factor and the neuropsychological test score as the dependent variable. The rationale underlying conducting separate analysis for each cognitive domain relates largely to the modest sample size in the current study. We acknowledge a single multivariate approach would provide protection against inflated Type 1 errors, whereas analysing the data on each domain would provide comparatively more power when the participant numbers are relatively small.

Since there were multiple comparisons and a greater danger of Type 1 error, a Bonferroni correction was applied to each of the domain alphas (see individual analysis in the results section for each of the adjusted alphas). Preliminary data analysis was conducted to assess normality of the sample's scores on the dependent variables in order to determine the appropriate selection of statistical techniques. Descriptive data regarding the skewness and kurtosis of the dependent variables were obtained, with an acceptable level of skew and kurtosis achieved on all dependent variables for the sample. Levine's test of equality of error variances was used throughout the ANOVA / MANOVA procedures to determine whether the statistical assumptions for ANOVA's / MANOVA's were fulfilled. Separate traditional MANOVA's were employed (not utilising

stacked data) to examine such assumptions. No analysis violated these assumptions.

We were specifically interested in the differences between the VLOSLP and chronic TOS group and between the VLOSLP and LOPD groups, therefore we used planned contrasts (for those analyses showing significant differences between samples) to compare the means for the VLOSLP group with those of the other two patient groups.

Pearson product-moment correlations were calculated to explore relationships between neuropsychological functioning, symptomatology (BPRS) and general real-world functioning. All of the correlational analyses were two-tailed, with alpha Bonferroni corrected for each of the comparisons. Any variables that demonstrated a significant association with functional outcome measures were then entered in a multiple regression model in order to examine the shared versus independent contributions of the neurocognitive and clinical variables to functional outcome.

### 3.6.2 *Exploratory Analysis Involving the Very-Late-Onset Schizophrenia-Like-Psychosis Group Only*

Descriptive statistics (means and standard deviations) were examined for both sociodemographic characteristics (presented in Table 1 below) and for all neuropsychological tests administered to the VLOSLP group (see Tables 4-9 below). Tables 4-9 include means and standard deviations for all the raw scores / scaled scores / z scores for all of the neuropsychological tests. For the purpose of these descriptive statistics, individuals were classified into three groups, those aged 65-74 years, 75 to 84 years and those 85 years and over. Tables 4-9 also include the means and standard deviations for all the normative corrected z scores, again presented into the three separate age ranges. The raw scores for each age group are also included to allow for more clinical examination of the data presented.

K-Means cluster analysis was also conducted to explore for the presence of possible

clusters which could explain the large range found in the neuropsychological test performance of individuals with VLOSLP. K-Means analysis was used as, given the very small sample size, we were looking at exploring the possibility of only two clusters. The initial neuropsychological measures chosen for the exploratory cluster analysis of the VLOSLP group were MMSE, Logical Memory II (indexing verbal memory) and Trails B (indexing cognitive flexibility). We focused on these three measures because the MMSE has traditionally been used as a global measure of cognition and previous studies have utilised this tool to identify ongoing cognitive decline. We also wanted to include a measure of memory functioning to further investigate the involvement of prodromal dementia. A test of cognitive flexibility was also chosen based on Almeida et al's (1995) existing cluster research into LOS samples. Having identified the clusters, further analysis was conducted to examine which of these three variables were significant in discriminating between the two VLOSLP Clusters. Additional exploratory analysis utilising Independent t-tests was then conducted to identify if other neuropsychological tests results were significantly different between the two identified Clusters.

Finally, Post Hoc analysis comparing the two VLOSLP Cluster groups and the TOS group were also conducted on the demographic and neuropsychological measures, utilising the same statistical analysis previously described for comparing the three overall clinical groups. The small sample sizes of the VLOSLP Clusters is certainly acknowledged, however, it has already been highlighted that this part of the analysis is exploratory in nature and conducted to inform possible future direction in this research. The limitations will be further discussed in detail in the Discussion chapter.

# Chapter 4. Results

## 4.1 Demographic and Clinical Variables

The frequencies, means and standard deviations of the demographic and clinical characteristics of all three psychiatric groups are presented in Table 1 below. After Bonferroni correction for inflated Type 1 error rate (alpha adjusted to 0.003), no significant differences were found among the three groups in terms of mean age, gender, or marital status, nor were significant differences found in terms of mean years of education or mean pre-morbid IQ or migrant status. However, significant differences were found among the three psychiatric groups in regards to whether the individuals currently lived alone. Bonferroni-adjusted post-hoc comparisons indicated that these differences were between the VLOSLP and the LOPD group, with increased numbers of the VLOSLP living alone than the LOPD group.

*Also,* no significant differences were found among the three groups in terms of a positive family psychiatric history, with all groups reporting prevalence rates of 20-61.1 % for family history of various diagnoses for example including depression, schizophrenia, 'nervous breakdown', bipolar and psychosis. It is noted, however, that the prevalence was higher in the LOPD group (61.1%) with the suggestion of a trend towards group difference ($p = .014$: see Table 1). There was also a weaker trend regarding group difference in migrant status ($p = .064$), with all groups reporting rates of 16-40% of participants having been born overseas. However the prevalence rate was higher for the VLOSLP group with 40% of individuals being born overseas. No significant differences were also noted among the three groups in terms of the presence of vascular related issues or daily medication dosages. However, a significant difference was found among the three groups in regards to their MMSE score. Follow-up Bonferonni-adjusted (alpha = 0.016) post-hoc comparisons indicated that the significant contrasts were between the LOPD group and both the VLOSLP group and the TOS group, with the LOPD

group showing higher levels of general cognitive function.

**Table 1.** Demographic and Clinical Characteristics of Patients with VLOSLP, TOS and LOPD.

| Variable | VLOSLP | | Chronic Sz | | LOPD | | Analysis | | | Sig Pairwise Comparison |
|---|---|---|---|---|---|---|---|---|---|---|
| | N= 25 | | N=27 | | N=18 | | Value | df | p | |
| | Mean | SD | Mean | SD | Mean | SD | | | | |
| **Age (yrs)** | 75.76 | 7.34 | 74.04 | 6.69 | 77.44 | 4.82 | 1.515 | 2,68 | 0.227 | |
| **Education yrs** | 9.84 | 2.53 | 8.64 | 2.68 | 9.00 | 3.29 | 1.247 | 2,68 | 0.294 | |
| **WTAR** | 98.76 | 8.38 | 95.43 | 7.97 | 100.6 | 10.63 | 2.021 | 2,68 | 0.140 | |
| **Female Gend.** | 21 | 84.0 | 22 | 81.5 | 10 | 55.6 | 4.85 | 2 | 0.088 | |
| | No. | % | No. | % | No. | % | | | | |
| **Marital Status** | | | | | | | | | | |
| **Currently** | 4 | 16.0 | 5 | 18.5 | 11 | 61.1 | | | | |
| **Widowed** | 9 | 36.0 | 7 | 25.9 | 5 | 27.7 | | | | |
| **Divorced** | 10 | 40.0 | 6 | 22.2 | 1 | 5.6 | | | | |
| **Never** | 2 | 8.0 | 9 | 33.3 | 1 | 5.6 | | | | |
| **Ever Married** | 23 | 92.0 | 18 | 66.7 | 17 | 94.4 | 7.691 | 2 | 0.021 | |
| **Children** | 22 | 88.0 | 19 | 70.4 | 16 | 88.9 | 4.514 | 2 | 0.105 | |
| **Lives Alone** | 19 | 76.0 | 10 | 37.0 | 3 | 16.7 | 16.52 | 2 | **0.000** | VLOSLP>LOPD p<.0005 |
| **Migrant** | 10 | 40.0 | 4 | 16.0 | 3 | 16.7 | 5.497 | 2 | 0.064 | |
| | Mean | SD | Mean | SD | Mean | SD | | | | |
| **MMSE** | 27.56 | 2.45 | 27.86 | 2.01 | 29.56 | 0.78 | 7.126 | 2,68 | **0.002** | LOPD>VLOSLP p<.0005 LOPD>TOS<0.010 |
| **Medication** | 109.2 | 71.5 | 154.3 | 121.1 | 115.3 | 61.9 | 3.864 | 2,68 | 0.026 | |
| | No. | % | No. | % | No. | % | | | | |
| **Positive Family Ψ Hx** | 5 | 20.0 | 8 | 29.6 | 11 | 61.1 | 8.47 | 2 | 0.014 | |
| **Evidence of Comorbid Vascular Disease** | 16 | 64.0 | 18 | 66.7 | 12 | 66.7 | 0.038 | 2 | 0.981 | |
| | Mean | SD | Mean | SD | Mean | SD | | | | |
| **Symptom Profile** | | | | | | | | | | |
| **BPRS** | 36.0 | 6.00 | 37.50 | 6.10 | 27.56 | 4.38 | 18.23 | 2, 68 | **0.000** | VLOSLP>LOPD (p<.0005) TOS>LOPD(p<.0005) |
| **GDS** | 6.88 | 6.62 | 4.43 | 5.11 | 5.72 | 8.27 | 0.931 | 2, 68 | 0.399 | |
| **HAM-D** | 4.08 | 4.71 | 3.07 | 4.36 | 4.72 | 7.64 | 0.534 | 2,68 | 0.589 | |
| **GAF** | 61.01 | 15.07 | 56.07 | 12.57 | 78.50 | 5.83 | 30.62 | 2,68 | **0.000** | LOPD>VLOSLP p<.0005 LOPD>TOS p<.0005 |
| **RFS** | 19.44 | 3.62 | 18.07 | 4.39 | 25.44 | 1.65 | 24.41 | 2,68 | **0.000** | LOPD>VLOSLP p<.0005 LOPD>TOS p<.0005 |

VLOSLP,Very Late Onset Schizophrenia Like Psychosis; LOPD, Late Onset Psychotic Depression; TOS, Chronic Schizophrenia; WTAR, Wechsler Test of Adult Reading; MMSE, Mini mental State Examination; BPRS, Brief Psychiatric Rating Scale; GDS, Geriatric Depression Scale; HAM-D, Hamilton Depression Rating Scale; GAF, Global Assessment of Functioning; RFS, Role Functioning Scale. Gend., Gender; Hx, History;

In regards to other clinical measures, no significant differences were found among the three groups at assessment on both measures of depression, the GDS and the HAM-D, despite the different diagnoses, although the assessment was completed when individuals were psychiatrically well / stable. Significant differences among the three psychiatric groups were however found on the BPRS. Bonferroni-adjusted post-hoc comparisons indicated that the significant contrasts were between each of the two schizophrenia groups and the LOPD group, with the LOPD group demonstrating significantly lower severity of psychiatric symptoms, as assessed using the BPRS, than either the VLOSLP group or the TOS group. Significant differences were also found on the two functional outcome measures, GAF and RFS. Bonferroni-adjusted post-hoc comparisons for both measures indicated that the LOPD group scored significantly higher on the functional measures than either the VLOSLP group or the TOS group.

### 4.2 Pattern of Performance on the Various Neuropsychological Domains Across the Three Main Clinical Groups

The mean z score and standard deviation for each of the three groups, including the VLOSLP group as a whole, on all of the neuropsychological measures is presented in Table 2 below, along with the results of the multivariate approach to repeated measures analysis presented in Table 3 below. These results will be discussed in detail in the following sections.

**Table 2.** Neuropsychological Performance Across the VLOSLP, TOS and LOPD Groups.

| Variable | VLOSLP n(25) | | TOS n(27) | | LOPD n(18) | |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD |
| **Attention and Working Memory** | | | | | | |
| **Longest DSF** | -0.21 | 1.14 | -0.49 | 0.86 | -0.04 | 1.24 |
| **Longest DSB** | -0.53 | 1.18 | -0.89 | 0.62 | -0.32 | 0.96 |
| **Motor Speed and Speed of Information Processing** | | | | | | |
| **Trails A** | -1.41 | 1.50 | -1.46 | 0.94 | -0.38 | 1.11 |
| **Digit Symbol** | -1.07 | 0.92 | -1.65 | 0.68 | -0.41 | 0.84 |
| **Learning and Memory** | | | | | | |
| **RAVLT(LOT)** | -0.18 | 0.82 | -0.24 | 0.19 | 0.20 | 1.06 |
| **RAVLT VII** | -0.56 | 0.98 | -0.64 | 0.19 | 0.08 | 1.14 |
| **LM I** | -1.01 | 1.00 | -1.29 | 0.92 | -0.24 | 0.75 |
| **LM II** | -0.92 | 1.01 | -0.94 | 0.87 | -0.12 | 0.70 |
| **RCFT Delayed** | -1.06 | 1.17 | -1.18 | 1.48 | -0.31 | 1.08 |
| **Visuospatial Functioning** | | | | | | |
| **RCFT Copy** | -0.34 | 1.13 | -0.79 | 1.24 | -0.08 | 1.07 |
| **Block Design** | -0.95 | 0.90 | -0.94 | 0.70 | -0.48 | 0.79 |
| **Language Functioning** | | | | | | |
| **BNT** | -1.22 | 1.10 | -1.45 | 1.28 | -0.43 | 0.97 |
| **Executive Functioning** | | | | | | |
| **Similarities** | -0.64 | 0.89 | -1.29 | 0.94 | -0.68 | 0.88 |
| **Trails B** | -2.18 | 1.86 | -2.75 | 1.44 | -1.33 | 1.95 |
| **FAS** | -0.33 | 1.10 | -0.89 | 0.81 | 0.34 | 0.79 |
| **Animals** | -0.96 | 1.14 | -1.07 | 1.28 | 0.04 | 1.21 |
| **Errors Inhib** | -0.99 | 1.18 | -1.19 | 1.19 | -0.51 | 1.33 |
| **Tower TAS** | -1.18 | 0.88 | -1.28 | 0.98 | -0.66 | 0.73 |

*DSF, Digit Span Forward; DSB, Digit Span Backwards; RAVLT, Rey Auditory Verbal Learning Test; RAVLT (I-V), Total recall on trial one to five; RAVLT VII, Delayed recall score; RCFT, Rey Complex Figure Test; BNT, Boston Naming Test; FAS, Verbal Fluency - letters FAS; Errors Inhib, Colour Word Interference Test -Total Errors on inhibition task; Tower TAS, Tower Total Achievement Score.*

**Table 3.** Repeated Measures MANOVA Results Comparing the VLOSLP, TOS and LOPD Groups on the Above Performances.

| Variable | Analysis F | Df | P | Significant Pairwise Comparison |
|---|---|---|---|---|
| **Attention and Working Memory** | | | | |
| **Neuropsychological Test Performance** | 7.497 | 1,65.84 | **0.008*** | DSF>DSB (p<.008) |
| **Patient Group** | 1.957 | 2,66.39 | 0.149 | |
| **Patient Group * Neuropsychological Test** | 0.097 | 2,65.86 | 0.907 | |
| **BPRS as covariate** | 0.288 | 1, 65.08 | 0.594 | |
| **Motor Speed and Speed of Information Processing** | | | | |
| **Neuropsychological Test Performance** | 0.053 | 1,67 | 0.819 | |
| **Patient Group** | 9.644 | 2,67 | **<0.0005*** | LOPD>VLOSLP (p=.003)<br>LOPD>TOS (p< .0005) |
| **Patient Group * Neuropsychological Test** | 1.671 | 2,67 | 0.196 | |
| **BPRS as covariate** | 2.417 | 1,66 | 0.125 | |
| **Learning and Memory** | | | | |
| **Neuropsychological Test** | 11.967 | 4,248.1 | **<0.0005*** | RAVLTTOT>LMI (p<.0005)<br>RAVLTVII>LMI (p<.0005)<br>RAVLTTOT>LMII (p<.0005)<br>RAVLTVII>LMII (p<.0005)<br>RAVLTOT>RCFTDel (p<.0005)<br>RAVLTVII>RCFTDel (p=.001) |
| **Patient Group** | 7.563 | 2,65.76 | **0.001*** | LOPD>VLOSLP (p=.002)<br>LOPD>TOS (p=.001) |
| **Patient Group * Neuropsychological Test** | 0.560 | 8,248.12 | 0.810 | |
| **BPRS as covariate** | 9.80 | 1, 65.80 | **0.002*** | |
| **Visuospatial Functioning** | | | | |
| **Neuropsychological Test** | 7.204 | 1,61.734 | **0.009*** | RCFTCopy>BD (p<.009) |
| **Patient Group** | 3.048 | 2,64.261 | 0.054 | |
| **Patient Group * Neuropsychological Test** | 1.484 | 2,61.845 | 0.235 | |
| **BPRS as covariate** | 0.971 | 1,65.188 | 0.328 | |
| *** Language Functioning** | | | | |
| **Patient Group** | 4.362 | 2, 62 | **0.017*** | LOPD>TOS (p=.006) |
| **BPRS as covariate** | 1.183 | 1,65 | 0.281 | |
| **Executive Functioning** | | | | |
| **Neuropsychological Test** | 27.580 | 5,292.58 | **<0.0005*** | SIM>TrailsB (p=.0005)<br>FAS>SIM (p=.0005)<br>FAS>TrailsB (p=.0005)<br>Animals>TrailsB (p=.0005)<br>ErrorsInhib>TrailsB (p=.0005)<br>TowerTA>TrailsB (p=.0005)<br>FAS>ErrorsInhib (p=.0005)<br>FAS>TowerTA (p=.0005) |
| **Patient Group** | 6.690 | 2,68.04 | **0.002*** | LOPD>TOS (p=.0005) |
| **Patient Group * Neuropsychological Test** | 1.479 | 10,292.48 | 0.146 | |
| **BPRS as covariate** | 2.125 | 1,67.61 | 0.150 | |

* An ANOVA was conducted for this analysis

### 4.2.1 *Overall Group Effects for Attention / Working Memory*

As can be seen in Table 3, a repeated measures MANOVA with diagnosis (VLOSLP, TOS and LOPD) as the between subject factor, and performance on the two attention and working memory tasks (Longest Digit Span Forward and Longest Digit Span Backwards) as the within-subject factor (with a bonferonni corrected alpha = .025) revealed no significant difference between the three groups. The MANOVA however did reveal a significant main effect for test performance, with all participants finding Digit Span Backward task more difficult (see Figure 1 below). A non-significant result for Patient Group * Cognitive Test interaction was also found indicating no difference between the profile shapes for the three clinical patient groups. See Figure 1 below. At a clinical level it is important to note that, compared to the normative samples, the mean z score on the Digit Span Forward task was within the average range for all three clinical groups. On the working memory task the mean z score for both the VLOSLP and LOPD group were also within the average range, with the mean z score for the TOS group falling within the low average range.

When current symptom profile (BPRS score) was entered as a covariate, the results also revealed the covariate was non-significant, demonstrating that an individual's current symptom profile (that is the severity of psychotic symptoms) had no impact on their attention or working memory performance.

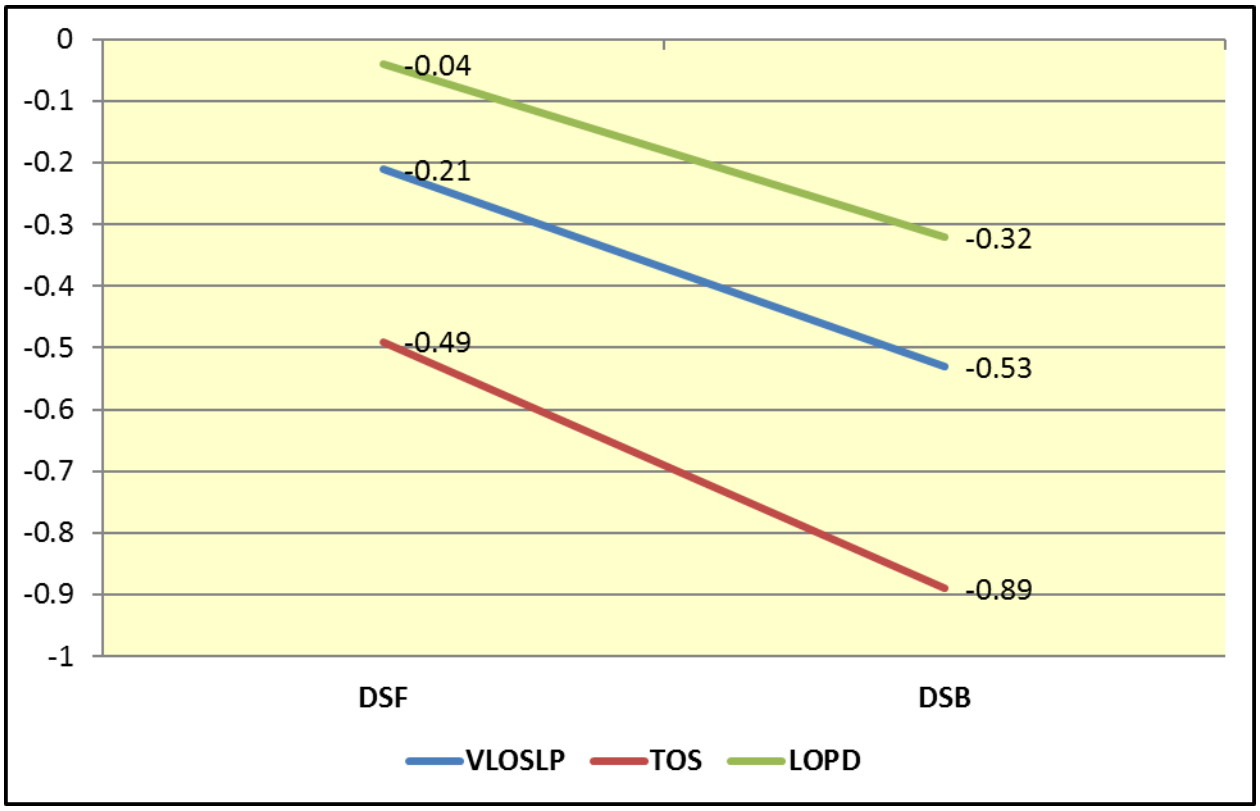


**Figure 1.** Immediate Auditory Attention Span and Working Memory Span for the VLOSLP, TOS and LOPD Groups.

### 4.2.2 *Overall Group Effects for Motor Speed and Speed of Information Processing*

A repeated measures MANOVA with diagnosis (VLOSLP, TOS and LOPD) as the between subject factor and performance on the motor speed and speed of information processing tasks (Trails A and Digit Symbol from WAIS-III) as the within-subject factor revealed a significant overall difference between the three groups (See Table 3). The MANOVA did not reveal a significant main effect for test performance. A non-significant result was also evident for the Patient Group * Cognitive Test interaction indicating no statistically significant difference between the z-score profile shapes for the three clinical patient groups.

Visual examination of the neuropsychological profiles of the three groups (see Figure 2 below) suggests that clinically, the LOPD group performed within the average range on both the speeded tasks, while the VLOSLP group performed within the low average to borderline-

impaired range and the TOS group performed within the borderline-impaired range. In regards to the significant differences between the three groups, post-hoc pairwise analyses (bonferroni adjusted alpha = .016) comparing the three groups revealed that these differences were significant between the LOPD group and both the VLOSLP group and TOS group (see Table 3 for p-values), such that the LOPD group performed significantly better on both tasks compared to the two schizophrenia groups.

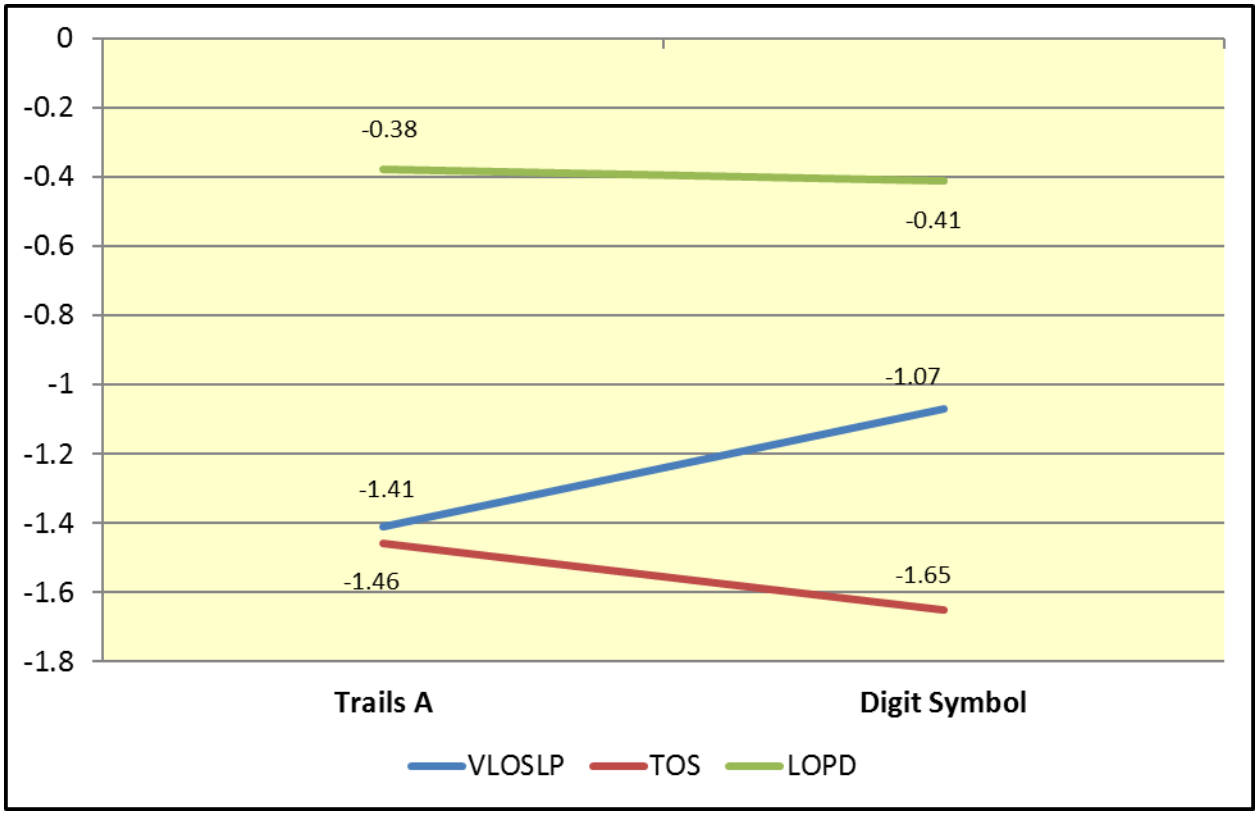


**Figure 2.** Motor Speed and Speed of Information Processing for the VLOSLP, TOS and LOPD Groups.

When current symptom profile (BPRS score) was entered as a covariate, it was found that this covariate was non-significant, which again suggests that an individual's current symptomatology (that is the severity of psychotic symptoms) has no significant impact on their motor speed or speed of information processing.

### 4.2.3 *Overall Group Effects for Verbal and Visual Learning and Memory*

A repeated measures MANOVA was conducted with diagnosis (VLOSLP, TOS and LOPD) as the between subject factor, and performance on the learning and memory tasks (RAVLT LOT; RAVLT-VII; LMI; LMII; RCFT Delayed) as the within-subject factors. After bonferonni correction for Type 1 error (alpha = .01), this analysis revealed a significant difference between the three groups and a significant main effect for memory test performance. A non-significant interaction of Patient Group * Memory Test interaction was found indicating no difference between the profile shapes for the three clinical patient groups on the memory tests (see Figure 3 below).

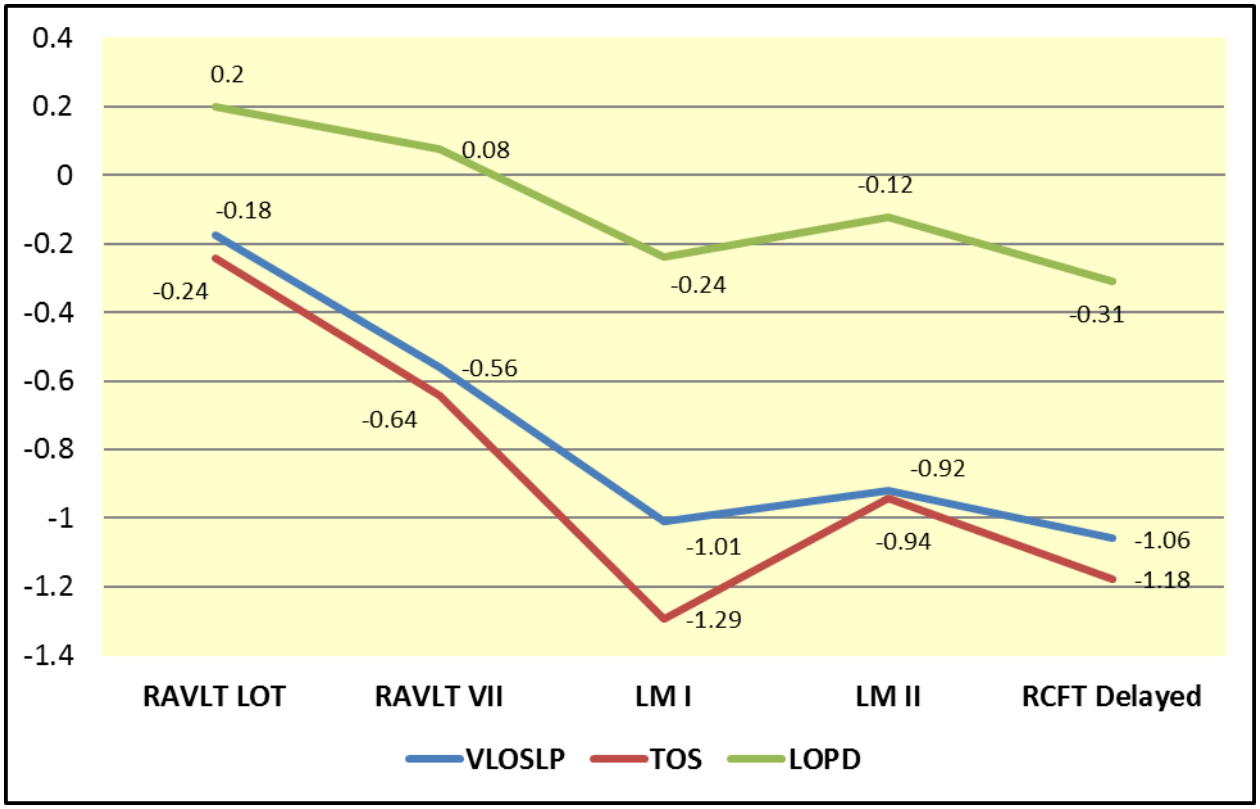


**Figure 3.** Verbal and Visual Learning and Memory Performance for the VLOSLP, TOS and LOPD Groups.

Visual examination of the neuropsychological profiles of the three groups (Figure 3. above) suggests that compared to the normative sample, the LOPD groups mean z score

performance was within the average range on all verbal and visual learning and memory tasks. Visual examination also indicates that the mean z score performance on all tests for both schizophrenia groups was very similar, with their mean z score performance clinically ranging from within the average to low average ranges compared to the normative sample across all tasks. Consistent with this visual examination, post-hoc pairwise analyses (bonferroni adjusted alpha = .016) comparing the three groups, revealed that these differences seen in Figure 3 above were significant between the LOPD group and both the VLOSLP group and TOS group (see Table 3 for p-values). This demonstrates that the LOPD group performed significantly better on learning and memory tasks than did the two schizophrenia groups.

In regards to the neuropsychological tests, post-hoc pairwise analysis (bonferonni adjusted alpha =.005) comparing the different neuropsychological tests indicated a significant difference in performance of the three groups between the list learning task (RAVLT Learning Over Trials) and both the story learning task (LM I) and Visual memory Task (RCFT delayed) with all three groups performing better on the list learning task. Significant differences were also noted between the learning over trials and delayed recall on the list learning task, with all three groups performing better on the learning over trials than on the delayed recall component. Significant differences were also found between list learning delayed and story learning (LM I) and between performances on story delayed (LMII) and story learning (LMI) with performances on story learning (LMI) significantly poorer than on both list learning delayed and story learning delayed (see Table 3 for p-values).

When current symptom profile (BPRS score) was entered as a covariate, this covariate was found to be a significant predictor of task performance (see Table 3) indicating that an individual's current symptomatology (that is the severity of psychotic symptoms) does have an impact on their performance on learning and memory tasks. However, follow-up correlational

analysis found at best mild correlations with any of the learning/memory task performances, indicating that the levels of symptomatology had only a mild impact on the memory performance across the three groups. Moreover, it is important to recall that there was no difference between groups in levels of symptomatology, as indexed by the BPRS.

### 4.2.4 *Overall Group Effects for Visuospatial Functioning*

A repeated measures MANOVA was conducted with diagnosis (VLOSLP, TOS and LOPD) as the between subject factor and including performance on both the two visuospatial tasks (Block Design and RCFT Copy) as the within-subject factors. After bonferonni correction for Type 1 error (alpha =.025), this analysis revealed no significant difference between the three groups. It did reveal a significant main effect for test performance, with all groups performing significantly better on the RCFT Copy than on the Block Design task. A non-significant interaction of Patient Group * Visuospatial Test was also found indicating no difference between the profile shapes for the three clinical patient groups on the visuospatial tests (See Figure 4 below).

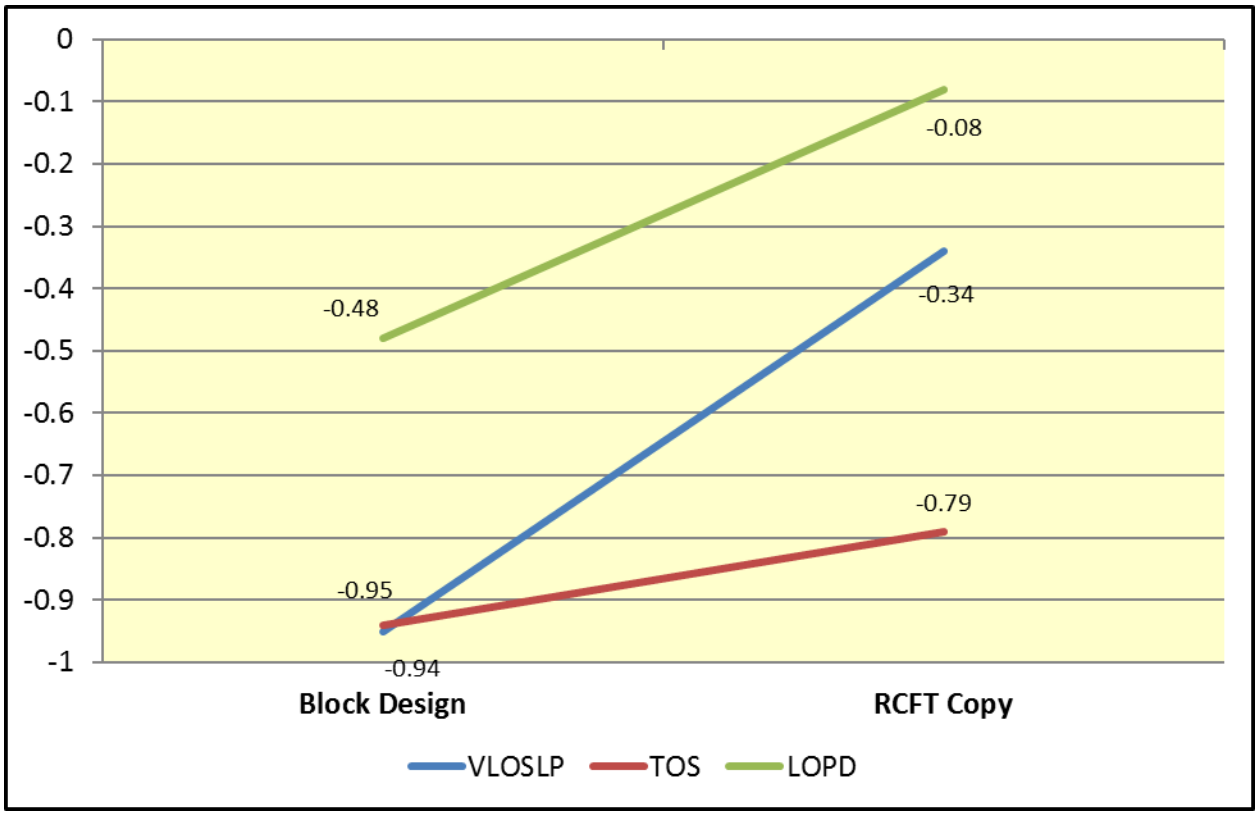


**Figure 4.** Visuospatial Functioning Performance for the VLOSLP, TOS and LOPD Groups.

From a clinical perspective, visual examination of the above graph indicates that the LOPD group is consistently performing within the average range across both visuospatial tasks. In comparison, some variability exists between the two schizophrenia groups. The TOS and VLOSLP groups perform similarly within the low average range on the task of visuospatial construction (BD). Differences however appear between these two groups on the Copy task (RCFT Copy) with the VLOSLP group performing within the average range and the TOS group performing within the low average range. It is acknowledged, however, that the interaction of Patient Group * Visuospatial Test was non-significant and so the above observations of different patterns across tasks should be treated with some caution.

Post-hoc pairwise analyses (bonferroni adjusted alpha = <.025) comparing the neuropsychological tests indicated a significant difference in performance of the three groups between the RCFT Copy task and the Block Design task, with all three groups performing better

on the RCFT Copy task. (see Table 3).

When current symptom profile (BPRS score) was entered as a covariate, the covariate, was found to be non-significant. This demonstrates that symptom profile across all three groups had no significant impact on an individual's level of visuospatial functioning.

### 4.2.5 *Overall Group Effects for Language Functioning*

A one way ANOVA was conducted with group (VLOSLP, TOS and LOPD) as the between subject factor, and performance on the language functioning task, BNT, as the dependent variable. This analysis revealed a significant overall difference between the three groups on the language task (see Figure 5 below).

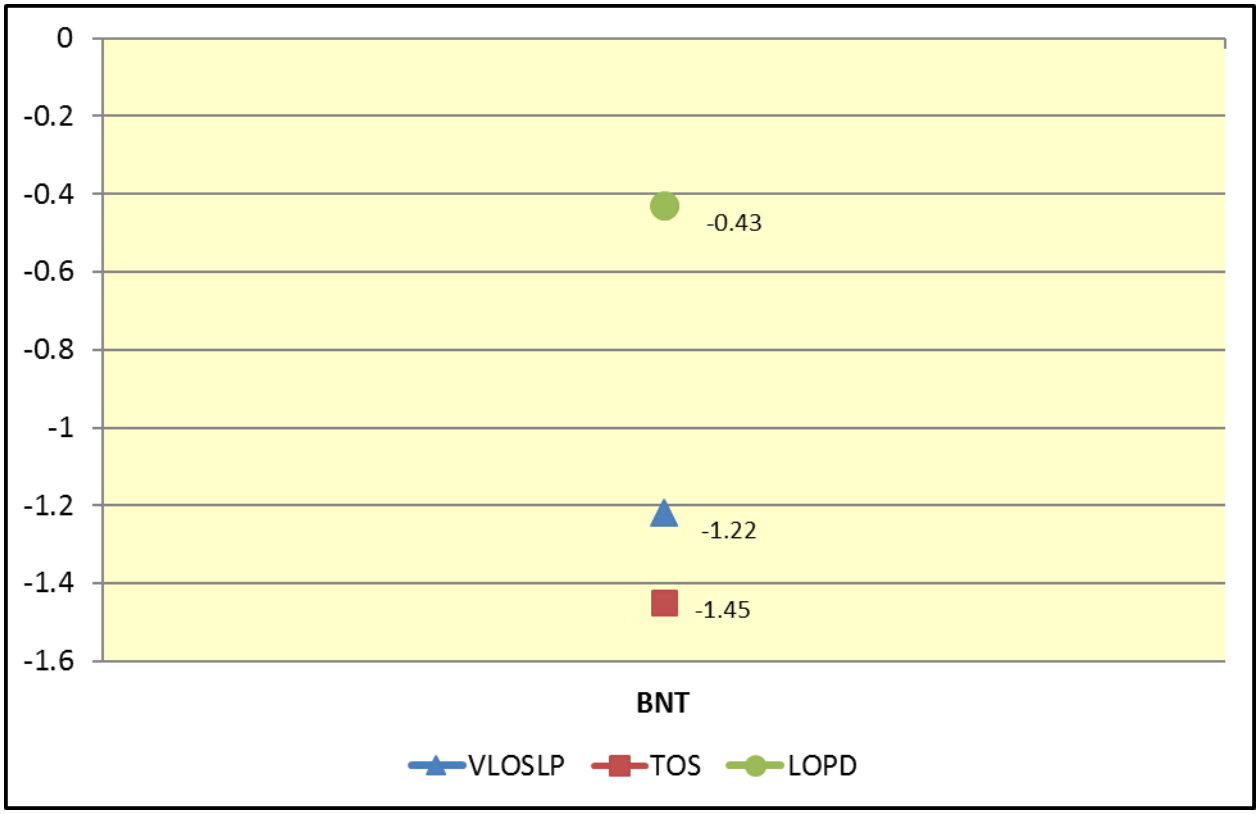


**Figure 5.** Language Functioning Performance for the VLOSLP, TOS and LOPD Groups.

Visual examination of the data indicate that the LOPD group performed within the

average range on this task, with the VLOSLP group performing within the low average range and the TOS group within the borderline-impaired range.

Post-hoc pairwise comparisons (alpha =.016) revealed a significant difference between the LOPD group and the TOS group, while no other simple contrasts were significant. This indicates that overall, the LOPD group performed better on the language functioning task than the TOS group.

### 4.2.6 *Overall Group Effects for Executive Functioning*

A repeated measures MANOVA was conducted with group (VLOSLP, TOS and LOPD) as the between subject factor, and performance on the executive functioning tasks (Similarities, Trails B, FAS, Animals, Errors Inhibition (D-KEFS stroop) and Tower Scores) as the within-subject factors. After bonferonni correction for Type 1 error (alpha = 0.008), this analysis revealed a significant overall difference between the three groups and a significant main effect for executive test performance. A non-significant interaction for Patient Group * Executive Test interaction was found indicating no difference between the profile shapes for the three clinical patient groups on the executive tests (See Figure 6 below).

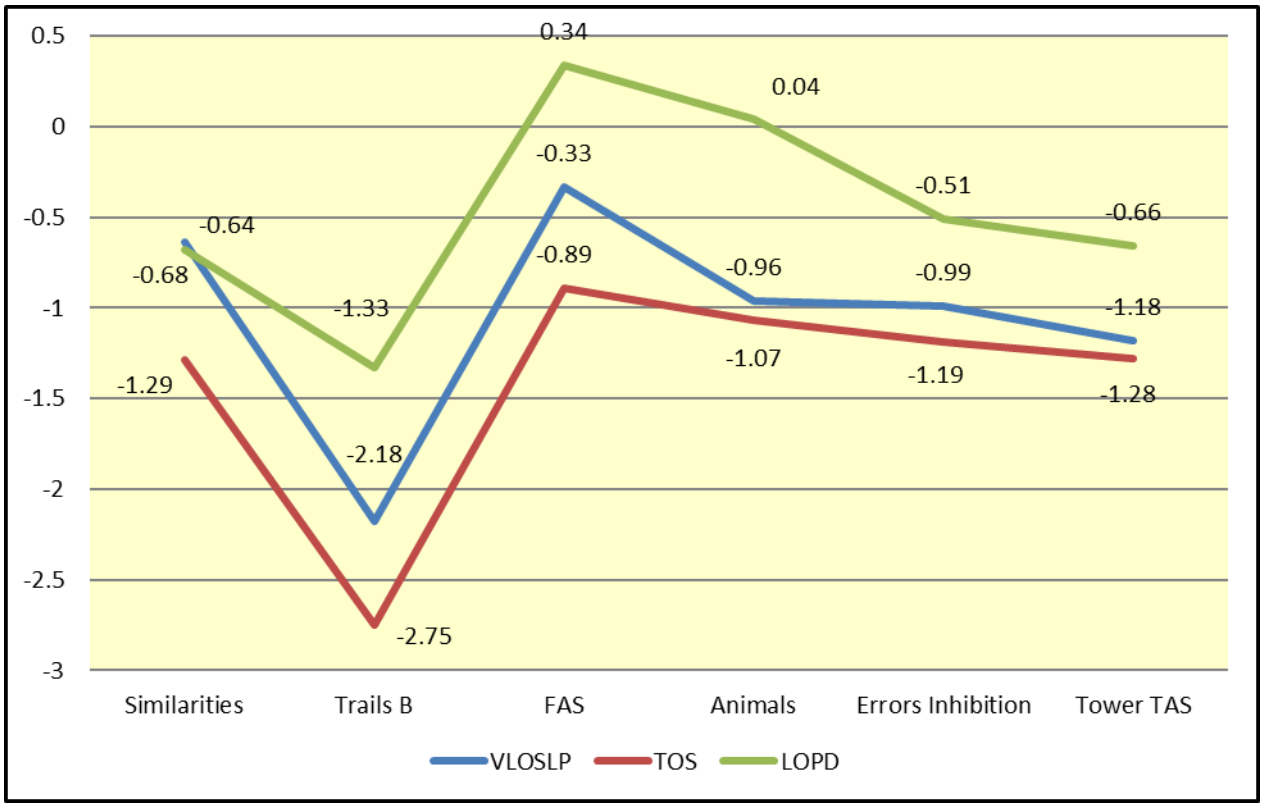


**Figure 6.** Executive Functioning Performance for the VLOSLP, TOS and LOPD Groups.

Visual examination of the data from a clinical perspective indicates quite a varied performance between the three groups on the individual's executive functioning tasks. The LOPD group are again performing within the average range on the majority of tasks, with the exception of Trails B for which their performance was within the low average to borderline-impaired ranges. Comparatively, the TOS and VLOSLP groups perform similarly within the low average range on the majority of executive tasks, with the exception of Trails B in which both groups are noted to be performing within the impaired ranges. Also, somewhat better performances were also noted in average level Similarities and FAS (verbal generativity task) for VLOSLP group, relative to low average performances of the TOS group.

Post-hoc pairwise comparisons (bonferroni adjusted alpha =.016) of the three groups examining the main effect of group revealed a significant difference between the LOPD and the TOS groups. This indicates that overall, the LOPD group performed significantly better on

executive functioning tasks than the TOS group. No other simple contrasts were significant.

In regards to the neuropsychological tests, post-hoc pairwise analysis (bonferonni adjusted alpha = .003) comparing the different neuropsychological tests indicated a significant difference in performance on several of the executive functioning tasks. Performance of the three groups, as a whole, was significantly different between FAS and similarities; Trails B; Errors Inhibition and Tower TAS, with all three groups performing significantly better on the FAS task (see Table 3 for p-values). Similarly, albeit in the reverse, all three groups performed significantly worse on the Trails B task than on Similarities, Animals, Errors Inhibition and Tower TAS (see Table 3 for p-values).

When current symptom profile (BPRS score) was entered as a covariate, the covariate, was found to be non-significant predictor of test performance, indicating that an individual's symptom profile has no significant impact on their performance on executive tasks.

#### 4.2.7 *Summary of Overall Differences Between the Very-Late-Onset Schizophrenia-Like-Psychosis, Chronically Ill, Typical Onset Schizophrenia and Late Onset Psychotic Depression Groups.*

In sum, the three groups differed on all cognitive domains with the exception of attention and working memory and visuospatial functioning. For the domains of motor speed and speed of information processing, learning and memory, language functioning and executive functioning, the VLOSLP group generally fell between the TOS group and the LOPD psychiatric control group; however, no differences between the TOS group and the overall VLOSLP group were significant, with both of these groups performing more poorly than the LOPD group.

## 4.3 Raw and Scaled Score Profiles of the Very-Late-Onset Schizophrenia-Like-Psychosis Group on all Neuropsychological Tests

The raw score (or scaled score where appropriate) for each of the neuropsychological test scores for the VLOSLP group are presented below. The neuropsychological data for the group is presented for three age groups, 65-74 years, 75-84 years and 85+ years, as well as for the VLOSLP group as a whole. Each of the raw scores / scaled scores was also converted to age-corrected (and education-adjusted where available) z scores which are also presented in the tables below (see Tables 4-9).

### 4.3.1 *Attention and Working Memory Profile in the Very-Late-Onset Schizophrenia-Like-Psychosis Group*

The raw Longest Digits Forwards and Backwards scores from the Digit Span Subtests in the WAIS-III, as well as the z scores, are presented in Table 4 below.

**Table 4.** VLOSLP – Mean Raw and Mean Z-Scores for Longest Digit Span Forwards and Backwards

| Test | Age Groups | Raw Mean Score | SD | Range | | Z-Score Mean | SD |
|---|---|---|---|---|---|---|---|
| | | | | Lower | Upper | | |
| **Digit Span Forwards (Longest Digit Span Forwards)** | | | | | | | |
| **n=13** | 65-74 years | 5.77 | 1.59 | 4 | 9 | -0.37 | 1.20 |
| **n=8** | 75-84 years | 6.50 | 1.31 | 5 | 8 | -0.08 | 0.97 |
| **n=4** | 85 + years | 5.75 | 1.50 | 5 | 8 | 0.06 | 1.49 |
| **n=25** | Total | 6.00 | 1.47 | 4 | 9 | -0.21 | 1.14 |
| **Digit Span Backwards (Longest Digit Span Backwards)** | | | | | | | |
| **n=13** | 65-74 years | 4.00 | 1.48 | 3 | 8 | -0.39 | 1.33 |
| **n=8** | 75-84 years | 3.63 | 1.30 | 2 | 6 | -0.74 | 0.73 |
| **n=4** | 85 + years | 3.50 | 1.73 | 2 | 6 | -0.57 | 1.65 |
| **n=25** | Total | 3.79 | 1.41 | 2 | 8 | -0.53 | 1.18 |

As can be seen the mean z score performance on both Longest Digits Forward and Backwards scores across the age ranges is largely within the average range, with the exception of

the Longest Digit Span Backwards performance in the 75-84 year group whose mean performance was within the average to low average ranges. Clinically, this data demonstrates quite a range in raw score results across some of the age ranges on simple attention / working memory tasks (given the reasonably large standard deviations noted within groups).

### 4.3.2 *Motor Speed / Speed of Information Processing Profile in the Very-Late-Onset Schizophrenia-Like-Psychosis Group*

Table 5 below summarises the performance of the VLOSLP group, and across the same age ranges, on the tasks of motor speed (i.e., Trails A) and speed of information processing (i.e., Digit Symbol).

**Table 5.** VLOSLP - Mean Total Time Taken on Trails A and Mean Scaled Score on the Digit Symbol Subtest (WAIS-III)

| Test | Age Groups | Raw Mean Score | SD | Range | | Z-Score SD Mean | |
|---|---|---|---|---|---|---|---|
| | | | | Lower | Upper | | |
| **Trails A - Total Time Taken** | | | | | | | |
| **n=13** | 65-74 years | 71.25 | 27.68 | 23 | 122 | -1.47 | 1.58 |
| **n=7** | 75-84 years | 81.29 | 40.85 | 47 | 161 | -1.16 | 1.42 |
| **n=4** | 85 + years | 127.25 | 80.93 | 52 | 205 | -1.61 | 1.72 |
| **n=24** | Total | 84.04 | 46.5 | 23 | 205 | -1.41 | 1.50 |
| **Digit Symbol Age Scaled Score** | | | | | | | |
| **n=13** | 65-74 years | 6.50 | 2.94 | 4 | 15 | -1.08 | 0.97 |
| **n=8** | 75-84 years | 7.43 | 2.23 | 4 | 10 | -0.84 | 0.74 |
| **n=4** | 85 + years | 5.50 | 3.79 | 3 | 11 | -1.43 | 1.18 |
| **n=25** | Total | 6.61 | 2.84 | 3 | 15 | -1.07 | 0.92 |

In regards to Trails A performance, the 75-84 year old group performed in the low average range, while the remaining age groups performed within the borderline-impaired range.

In regards to performance on the Digit Symbol Subtest, the two younger age groups were found to perform within the low average range, while the older VLOSLP subjects (>85 years) performed to within borderline-impaired ranges.

These findings indicate that, on tasks assessing motor speed / speed of information processing, the VLOSLP group were performing on average 1 to 1.5 standard deviations below age matched control subjects (relative to appropriate normative data). Evidently however, and as indicated by the large standard deviations, a quite substantial range in individual performances is again noted on both of these tasks.

### 4.3.3 *Verbal and Visual Learning and Memory Profile in the Very-Late-Onset Schizophrenia-Like-Psychosis Group*

The learning profile of individuals with VLOSLP is summarised in Table 6 below.

**Table 6.** VLOSLP – Mean Raw and Z Scores From the Learning and Memory Tests

| Test | Age Groups | Raw Mean Score | SD | Range | | Z-Score Mean | SD |
|---|---|---|---|---|---|---|---|
| | | | | Lower | Upper | | |
| **LM I Total Immediate Recall (Age Scaled Score)** | | | | | | | |
| **n=12** | 65-74 years | 6.46 | 3.69 | 1 | 14 | -1.13 | 1.16 |
| **n=8** | 75-84 years | 8.13 | 2.48 | 5 | 11 | -0.61 | 0.80 |
| **n=4** | 85 + years | 5.75 | 2.06 | 4 | 8 | -1.43 | 0.68 |
| **n=24** | Total | 6.88 | 3.15 | 1 | 14 | -1.01 | 1.00 |
| **LM II Total Delayed Recall (Age Scaled Score)** | | | | | | | |
| **n=13** | 65-74 years | 7.31 | 3.35 | 3 | 15 | -0.88 | 1.09 |
| **n=8** | 75-84 years | 7.00 | 3.89 | 1 | 11 | -0.93 | 1.16 |
| **n=4** | 85 + years | 7.00 | 1.83 | 5 | 9 | -1.00 | 0.61 |
| **n=25** | Total | 7.16 | 3.24 | 1 | 15 | -0.92 | 1.01 |
| **RAVLT (Learning Over Trials)** | | | | | | | |
| **n=13** | 65-74 years | 31.17 | 11.00 | 15 | 53 | -0.07 | 0.78 |
| **n=8** | 75-84 years | 29.0 | 7.64 | 20 | 43 | -0.39 | 0.92 |
| **n=4** | 85 + years | 26.75 | 5.12 | 21 | 32 | -0.08 | 0.83 |
| **n=25** | Total | 29.71 | 9.04 | 15 | 53 | -0.18 | 0.81 |
| **RAVLT VII Delayed Recall (Raw Total Number)** | | | | | | | |
| **n=12** | 65-74 years | 4.83 | 4.13 | 0 | 13 | -0.68 | 1.08 |
| **n=8** | 75-84 years | 4.13 | 3.52 | 0 | 9 | -0.48 | 0.94 |
| **n=4** | 85 + years | 3.75 | 2.87 | 0 | 7 | -0.33 | 0.86 |
| **n=24** | Total | 4.42 | 3.64 | 0 | 13 | -0.56 | 0.98 |
| **RCFT Delayed Recall (Raw Score)** | | | | | | | |
| **n=10** | 65-74 years | 10.85 | 7.13 | 0 | 28.0 | -0.89 | 1.34 |
| **n=7** | 75-84 years | 6.07 | 5.13 | 0 | 10.5 | -1.31 | 1.17 |
| **n=3** | 85 + years | 4.83 | 1.76 | 3.0 | 6.5 | -1.10 | 0.50 |
| **n=20** | Total | 8.28 | 6.32 | 0 | 28.0 | -1.06 | 1.17 |

In regards to the Story Learning Task, the performance of all three age groups on immediate learning was largely between the low average to borderline-impaired range on immediate recall trials (LM I), with the exception of the 75-84 year old group who performed within the average range. Performance on delayed recall trials (LM II) across groups' consistently revealed low average performances (though across groups the range of performance in all three age ranges is again quite large).

As can be seen in Table 6, in regards to the list learning task (RAVLT – Learning over trials), all three age groups performed within the average range for the number of words learnt over the five trials. Similarly, all three age groups continued to perform within the average range in regards to the number of words recalled following a delay period (RAVLT – Delayed Recall). These findings indicates that all three VLOSLP age groups performed slightly better on the list learning task than on the story learning task discussed above.

Lastly, on a visual memory task assessing recall of a complex design following a delay period (RCFT – Delayed Recall), all three age groups were found to perform within the low-average range (75-84 years low average to borderline-impaired range). However, it is noted that numbers in these groups completing this task were slightly lower than on other tasks due to the somewhat imposing task requirement in the initial learning or copy phase, in which some clients refused to continue. The refusal in these small numbers of patients to complete the initial copy and hence learning of the figure would serve to confound subsequent testing on delayed recall trials, and hence these patients were not administered the memory recall component of this measure (explaining the lower numbers).

### 4.3.4 *Visuospatial Functioning Profile in the Very-Late-Onset Schizophrenia-Like-Psychosis Group*

Table 7 below summarises the raw and z-score performances of the three VLOSLP age groups on the visuospatial functioning tasks.

As previously discussed, due to the somewhat imposing nature of the Rey Complex Figure Test, several individuals refused to attempt the task, reducing the numbers overall. Those that did (as seen in Table 7) largely performed within the average to low average range across the age groups. As with all other results documented to date, there was also quite a large range in results for all the age ranges. Similar ranges in results were found on another visuospatial task, Block Design (WAIS-III) with mean results falling within the low average range across the age groups.

**Table 7.** VLOSLP- Mean Raw Score / Scaled Scores on Visuospatial Tests.

| Test | Age Groups | Raw Mean Score | SD | Range | | Z-Score Mean | SD |
|---|---|---|---|---|---|---|---|
| | | | | Lower | Upper | | |
| **RCFT Raw Copy Score** | | | | | | | |
| **n=10** | 65-74 years | 28.80 | 4.93 | 21.5 | 35.0 | -0.34 | 1.13 |
| **n=6** | 75-84 years | 23.17 | 7.87 | 9.5 | 33.0 | -0.71 | 0.99 |
| **n=3** | 85 + years | 26.33 | 4.75 | 21.5 | 31.0 | -0.33 | 0.74 |
| **n=19** | Total | 26.63 | 6.20 | 9.5 | 35.0 | -0.46 | 1.01 |
| | | | | | | | |
| **Block Design (Age Scaled Score)** | | | | | | | |
| **n=13** | 65-74 years | 6.15 | 2.58 | 1 | 12 | -1.11 | 0.31 |
| **n=8** | 75-84 years | 7.88 | 2.23 | 5 | 11 | -0.72 | 0.25 |
| **n=4** | 85 + years | 6.25 | 0.50 | 6 | 7 | -1.30 | 0.10 |
| **n=25** | Total | 6.72 | 2.34 | 1 | 12 | -0.95 | 0.90 |

### 4.3.5 *Language Functioning Profile in the Very-Late-Onset Schizophrenia-Like-Psychosis Group*

Table 8 below summarises the raw and z-score performances of the three VLOSLP age groups on the language functioning task.

Results on the task of confrontational naming (Boston Naming Test) demonstrated performances largely within the borderline-impaired range with the exception of an average performance for the 75-84 year age range.

**Table 8.** VLOSLP- Mean Raw Score / Scaled Scores on the Language Test.

| Test | Age Groups | Raw Mean Score | SD | Range | | Z-Score Mean | SD |
|---|---|---|---|---|---|---|---|
| | | | | Lower | Upper | | |
| **Boston Naming Test (Total Raw Score)** | | | | | | | |
| **n=13** | 65-74 years | 45.08 | 6.16 | 33 | 53 | -1.49 | 1.21 |
| **n=8** | 75-84 years | 44.25 | 8.17 | 31 | 55 | -0.61 | 0.95 |
| **n=4** | 85 + years | 37.50 | 2.38 | 35 | 40 | -1.57 | 0.39 |
| **n=25** | Total | 43.60 | 6.83 | 31 | 55 | -1.22 | 1.10 |

### 4.3.6 *Executive Functioning Profile in the Very-Late-Onset Schizophrenia-Like-Psychosis Group*

Table 9 below presents the mean raw scores and mean z scores for each age range on measures of executive functions. It is important to note that when clinically interpreting the Trails B test that a large number (9 individuals) were extremely impaired on this task and were not able to complete this measure. These are not reflected in age breakdown of the statistical numbers presented below, as it was felt for reasons of accuracy for this section that it would be best to qualitatively note these findings and not include these individuals, so as to not skew the accurate representation of those that could complete the test. Of those that could complete the Trails B test, performances were within borderline-impaired to impaired ranges across the age groups. However, for all other statistical analysis discussed below in future sections, those individuals who could not complete the task due to extreme impairment were allocated the total maximum allowed time of 300 seconds as their score.

Similarly the WCST was also initially included in the research design, but was ultimately

discontinued due to the fact that the majority of the individuals were unable to complete this task and would refuse to continue the task to completion, invalidating any results from that task.

As can be seen in Table 9 below, results varied across the other different executive functioning tasks. Individuals with VLOSLP generally performed within the average range on tasks of phonetic fluency, and within the average to low average range on verbal abstract reasoning tasks. Findings on these tasks were similar across the age ranges. In comparison, low average performances were noted on a task of semantic fluency and low average to borderline-impaired performances were noted on tasks of inhibition and novel problem solving. Impaired performances were also noted on the task of cognitive flexibility, across all age ranges. However, as with all other cognitive areas discussed previously, large ranges were again noted in performance on all tasks, across all age ranges.

**Table 9.** VLOSLP - Mean Raw / Scaled Scores and Mean Z-Scores on Tests of Executive Functioning

| Test | Age Groups | Raw Mean Score | SD | Range | | Z-Score Mean | |
|---|---|---|---|---|---|---|---|
| | | | | Lower | Upper | | |
| **Similarities (Age Scaled Score)** | | | | | | | |
| **n=13** | 65-74 years | 8.38 | 2.60 | 5 | 14 | -0.55 | 0.89 |
| **n=8** | 75-84 years | 8.00 | 2.62 | 5 | 11 | -0.66 | 0.83 |
| **n=4** | 85 + years | 7.25 | 3.59 | 4 | 12 | -0.90 | 1.20 |
| **n=25** | Total | 8.08 | 2.68 | 4 | 14 | -0.64 | 0.89 |
| **Trails B Raw Total Time Taken** | | | | | | | |
| **n=11** | 65-74 years | 188.45 | 79.98 | 48 | 290 | -1.85 | 1.84 |
| **n=4** | 75-84 years | 154.33 | 41.89 | 105 | 300 | -2.21 | 2.07 |
| **n=1** | 85 + years | 203.00 | | | | -0.82 | |
| **n=25** | Total (inc. +9) | 214.13 | 95.70 | 48 | 300 | -2.18 | 1.86 |
| **Phonetic Fluency – FAS (Total Number of Words)** | | | | | | | |
| **n=13** | 65-74 years | 28.3 | 13.47 | 7 | 56 | -0.56 | 0.89 |
| **n=8** | 75-84 years | 29.14 | 10.12 | 18 | 45 | -0.19 | 1.13 |
| **n=4** | 85 + years | 31.0 | 11.14 | 21 | 43 | +0.09 | 1.69 |
| **n=25** | Total | 29.0 | 11.5 | 7 | 56 | -0.33 | 1.10 |
| **Semantic Fluency – Animals (Total Number of Words)** | | | | | | | |
| **n=12** | 65-74 years | 12.73 | 4.17 | 6 | 21 | -0.81 | 0.90 |
| **n=8** | 75-84 years | 11.86 | 4.49 | 5 | 17 | -1.07 | 1.51 |
| **n=4** | 85 + years | 10.00 | 4.58 | 5 | 14 | -1.17 | 1.19 |
| **n=24** | Total | 12.05 | 4.21 | 5 | 21 | -0.96 | 1.14 |
| **D-KEFS Colour Word Interference Test (Error / Inhibition Age Scaled Score)** | | | | | | | |
| **n=13** | 65-74 years | 6.92 | 4.80 | 1 | 12 | -0.82 | 1.31 |
| **n=8** | 75-84 years | 6.29 | 3.90 | 1 | 11 | -1.09 | 1.15 |
| **n=4** | 85 + years | 6.50 | 0.71 | 6 | 7 | -1.33 | 0.96 |
| **n=25** | Total | 6.67 | 4.16 | 1 | 12 | -0.99 | 1.18 |
| **D-KEFS Tower Test – Total Achievement (Age Scaled Score)** | | | | | | | |
| **n=10** | 65-74 years | 5.78 | 3.49 | 1 | 12 | -1.18 | 1.06 |
| **n=8** | 75-84 years | 7.00 | 2.92 | 3 | 10 | -1.09 | 0.77 |
| **n=4** | 85 + years | 5.75 | 2.5 | 3 | 9 | -1.38 | 0.79 |
| **n=22** | Total | 6.09 | 3.12 | 1 | 12 | -1.18 | 0.88 |

### 4.3.7 *Summary of the Neuropsychological Performance of the Very-Late-Onset Schizophrenia-Like-Psychosis Group*

In sum, for the VLOSLP group as a whole, average performances were seen for the tasks of immediate auditory attention span, working memory, list learning and recall, visuospatial copy, abstract reasoning and phonetic fluency, while the performances as a whole for the other

tasks showed quite a wide range.

### 4.3.8 *Exploratory Cluster Analysis of the Very-Late-Onset Schizophrenia-Like-Psychosis Group on Selected Neuropsychological Tests*

Due to the noted large range in individual results across all neuropsychological domains and across all age ranges, further exploratory K-Means cluster analysis was conducted. A K-Means cluster analysis was conducted on the 25 VLOSLP cases' results for the MMSE, Logical Memory II and Trails B. As noted in Chapter 2, we focused on these three measures because the MMSE has traditionally been used clinically as a global measure of cognition and previous studies have utilised this tool to demonstrate ongoing cognitive decline. We also wanted to include a measure of memory functioning to further investigate the possibility of dementia. The Trails B test of cognitive flexibility was chosen based on Almeida et al's (1995) existing cluster research into LOS samples. Results revealed two Clusters, between which all three variables were identified as significantly different, as seen in Figure 7 below. Cluster Two's mean performance was in the upper range of average (bordering on high average) and Cluster One's mean performance was in the lower range of average (bordering on low average). There are obvious limitations of this analysis due to the sample size, which will be discussed in detail in Chapter 5.

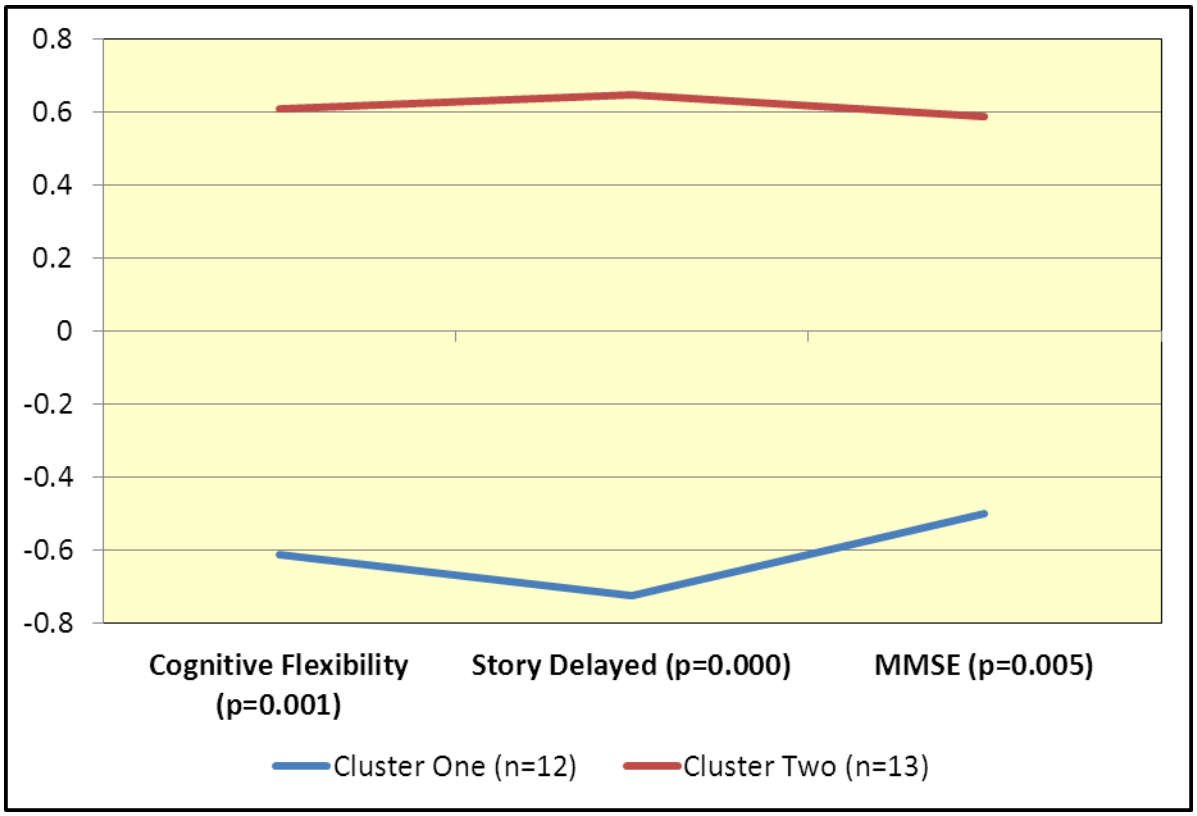


**Figure 7.** Exploratory Cluster Analysis Results for the VLOSLP Group

### 4.3.9 *Further Statistical Analysis Involving the Two Clusters*

As seen in Table 10 below, using a bonferonni corrected alpha of p<.005, no significant difference was found between the two statistically derived Cluster groups on other demographic or clinical symptoms.

**Table 10.** Demographic and Clinical Characteristics of the two VLOSLP Cluster Groups.

| Variable | Cluster-One | | Cluster-Two | | T (df) | P | Difference |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | | | |
| Age | 77.25 | 7.98 | 73.67 | 6.58 | 1.20 (22) | 0.243 | |
| Education | 10.00 | 2.73 | 9.83 | 2.48 | .157 (22) | 0.877 | |
| WTAR | 98.42 | 7.50 | 99.83 | 9.42 | -.373 (22) | 0.688 | |
| GDS | 5.25 | 6.82 | 8.75 | 6.54 | -1.291 (22) | .210 | |
| HAM-D | 5.08 | 5.82 | 3.08 | 3.50 | 1.020 (22) | .319 | |
| BPRS | 36.83 | 7.64 | 35.92 | 3.48 | 0.378 (22) | .709 | |
| GAF | 51.17 | 11.99 | 55.42 | 12.33 | -0.856 (22) | .401 | |
| RFS | 18.92 | 4.52 | 19.58 | 2.43 | -0.450 (22) | .657 | |

In regards to the differences between the two statistically derived VLOSLP Clusters on neuropsychological variables, several significant differences were identified within each domain, using Bonferroni-adjusted alpha levels as reported in Table 11 below. For all of these significant differences, Cluster Two was found to be performing significantly better than the Cluster-One group. These significant differences were identified on the Digit Span Backwards task, Trails A, Digit Symbol, Block Design and the Boston Naming Task. Significant differences were also noted on three of the five learning and memory tasks including, RAVLT Delayed, and LM I, as well as LM II, which had been used in the initial VLOSLP cluster analysis. Performances of the two Clusters were also noted to approach significance on the RCFT Delayed recall task (p=.027) with Cluster Two performing better than Cluster One. Three out of the six executive functioning variables were also noted to be significantly different between the two Cluster groups, the FAS test of phonemic fluency and Animals test of semantic fluency, as well as the Trails B test used in the initial VLOSLP cluster analysis. It is interesting to note however that whilst the FAS performance between the two Clusters was noted to be significantly different, Cluster Two's mean performance was noted to be within the average range, with Cluster One's mean performance within the low average range, representing minimal clinical significance. Further, group differences on the D-KEFS Colour Word Interference Test (Error / Inhibition Age Scaled Score, p=.014) and the D-KEFS Tower Test (Total Achievement Score, p=.020) were found to approach significance, with Cluster Two performing better than Cluster One.

**Table 11.** Individual ANOVA Results Comparing Neuropsychological Variables Between the Two Cluster VLOSLP Groups.

| Variable | Cluster-One Mean | SD | Cluster-Two Mean | SD | T (df) | P | Difference |
|---|---|---|---|---|---|---|---|
| **Attention and Working Memory – (alpha = 0.025)** | | | | | | | |
| **Longest DSF** | -0.52 | 0.91 | 0.14 | 1.33 | -1.43 (22) | 0.167 | |
| **Longest DSB** | -1.26 | 0.69 | 0.26 | 1.13 | -3.97 (22) | **0.001*** | Cluster 2 >1 |
| **Motor Speed and Speed of Information Processing – (alpha = 0.025)** | | | | | | | |
| **Trails A** | -2.12 | 1.38 | -0.70 | 1.29 | -2.60 (22) | **0.016*** | Cluster 2 > 1 |
| **Digit Symbol** | -1.68 | 0.41 | -0.46 | 0.89 | -4.31 (22) | **<0.0005*** | Cluster 2 >1 |
| **Learning and Memory - (alpha = .01)** | | | | | | | |
| **RAVLT(LOT)** | -0.43 | 0.75 | -0.01 | 0.81 | -1.31 (22) | 0.203 | |
| **RAVLT VII** | -1.26 | 0.67 | 0.12 | 0.77 | -4.68 (22) | **<0.0005*** | Cluster 2 >1 |
| **LM I** | -1.70 | 0.59 | -0.38 | 0.93 | -4.15 (22) | **<0.0005*** | Cluster 2 >1 |
| **LM II** | -1.65 | 0.56 | -0.26 | 0.89 | -4.57 (22) | **<0.0005*** | Cluster 2 >1 |
| **RCFT Delayed** | -1.64 | 0.93 | -0.54 | 1.16 | -2.39 (19) | 0.027 | |
| **Visuospatial Functioning - (alpha = .025)** | | | | | | | |
| **RCFT Copy** | -0.65 | 0.99 | -0.22 | 1.07 | -1.03 (22) | 0.313 | |
| **Block Design** | -1.46 | 0.43 | -0.38 | 0.95 | -3.56 (22) | **0.002*** | Cluster 2 >1 |
| **Language Functioning - (alpha = .05)** | | | | | | | |
| **BNT** | -1.71 | 1.09 | -0.65 | 0.86 | -2.64 (22) | **0.015*** | Cluster 2 >1 |
| **Executive Functioning - (alpha = .008)** | | | | | | | |
| **Similarities** | -0.91 | 1.01 | -0.35 | 0.73 | -1.55 (22) | 0.135 | |
| **Trails B** | -3.32 | 1.50 | -1.04 | 1.47 | -3.74 (22) | **0.001*** | Cluster 2 >1 |
| **FAS** | -0.91 | 0.71 | 0.32 | 1.16 | -3.10 (21) | **0.005*** | Cluster 2 >1 |
| **Animals** | -1.58 | 0.91 | -0.18 | 0.88 | -3.72 (21) | **0.001*** | Cluster 2 >1 |
| **Errors Inhib** | -1.60 | 1.02 | -0.43 | 1.11 | -2.68 (22) | 0.014 | |
| **Tower TAS** | -1.58 | 0.65 | -0.70 | 0.93 | -2.53 (19) | 0.020 | |

*DSF, Digit Span Forward; DSB, Digit Span Backwards; RAVLT, Rey Auditory Verbal Learning Test; RAVLT (I-V), Learning over Trials on trial one to five; RAVLT VII, Delayed recall score; RCFT, Rey Complex Figure Test; BNT, Boston Naming Test; FAS, Verbal Fluency - letters FAS, CFS, Colour Form Sort; Errors Inhib, Colour Word Interference Test -Total Errors on inhibition task; Tower TAS, Tower Total Achievement Score.*

## 4.4 Post-hoc Comparison of the Two Very-Late-Onset Schizophrenia-Like-Psychosis Clusters and the Chronically Ill, Typical Onset Schizophrenia Group

Given the variability noted earlier in the VLOSLP group, it was possible that this variability might have been obscuring differences within the individuals with schizophrenia. So, we followed up the above overall analyses and focused solely on the schizophrenia individuals to specifically compare the two VLOSLP Clusters and the TOS group. These results will be discussed in detail in the following sections.

### *4.4.1 Demographic and Clinical Variables Comparing the Two Very-Late-Onset Schizophrenia-Like-Psychosis Clusters and the Chronically Ill, Typical Onset Schizophrenia Group*

The means and standard deviations of some of the demographic and clinical characteristics of the two VLOSLP groups (Cluster-One and Cluster-Two) and the TOS group are presented again in Table 12 below for ease of comparison. After Bonferroni correction for inflated Type 1 error rate (alpha adjusted to 0.013), no significant differences were found between the three schizophrenia groups in terms of mean age or mean years of education or mean pre-morbid IQ. However, significant differences were found between the three groups in regards to their MMSE score, consistent with the initial VLOSLP cluster analysis. Follow-up Bonferonni-adjusted (alpha = 0.016) post-hoc comparisons indicated that the significant contrasts were between the VLOSLP Cluster-One group and both the VLOSLP Cluster-Two group and the TOS group, with the VLOSLP Cluster-One group showing lower levels of general cognitive function.

In regards to other clinical measures, no significant differences were found on both measures of depression, the GDS and the HAM-D. No significant differences were also found

between the three schizophrenia groups on the BPRS. Nor were any significant differences found on the two functional outcome measures, GAF and RFS. Thus, the three schizophrenia groups did not differ in their symptoms and level of functioning.

**Table 12.** Demographic and Clinical Characteristics Analysis of the two VLOSLP Cluster Groups and the TOS Group.

| Variable | Cluster-One | | Cluster-Two | | TOS | | F (df) | P | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | | | |
| Age | 77.25 | 7.98 | 73.67 | 6.58 | 74.04 | 6.69 | 1.060 (2,49) | .354 | |
| Education | 10.00 | 2.73 | 9.83 | 2.48 | 8.64 | 2.68 | 1.505 (2,49) | .232 | |
| WTAR | 98.42 | 7.50 | 99.83 | 9.42 | 95.43 | 7.97 | 1.396 (2,49) | .257 | |
| MMSE | 26.0 | 2.66 | 29.0 | 1.54 | 27.86 | 2.01 | 8.60 (2,49) | **.001** | **CL1<TOS .001 CL1<CL2 .008** |
| GDS | 5.25 | 6.82 | 8.75 | 6.54 | 4.43 | 5.11 | 2.324 (2,49) | .109 | |
| HAM-D | 5.08 | 5.82 | 3.08 | 3.50 | 3.07 | 4.36 | 0.893 (2,49) | .496 | |
| BPRS | 36.83 | 7.64 | 35.92 | 3.48 | 37.5 | 6.1 | 0.295 (2,49) | .746 | |
| GAF | 51.17 | 11.99 | 55.42 | 12.33 | 56.07 | 12.57 | 0.674 (2,49) | .514 | |
| RFS | 18.92 | 4.52 | 19.58 | 2.43 | 18.07 | 4.39 | 0.615 (2,49) | .545 | |

*CL1 – VLOSLP Cluster-One; CL2 – VLOSLP Cluster-Two*

### 4.4.2 *Overall Very-Late-Onset Schizophrenia-Like-Psychosis Clusters and Chronically Ill, Typical Onset Schizophrenia Group Effects for Attention / Working Memory*

As can be seen in Table 13 below, a repeated measures MANOVA with schizophrenia group (VLOSLP Cluster-One, VLOSLP Cluster-Two and TOS) as the between subject factor, and performance on the two attention and working memory tasks (Longest Digit Span Forward and Longest Digit Span Backwards) as the within-subject factor (with a bonferonni corrected alpha = .025) revealed a significant overall difference between the three groups. The MANOVA however did not reveal a significant main effect for test performance. A non-significant result for Patient Group * Cognitive Test interaction was also found indicating no difference between the profile shapes for the three clinical patient groups. See Figure 8 below.

**Table 13.** Repeated Measures MANOVA Results Comparing the VLOSLP Cluster-One, VLOSLP Cluster-Two and the TOS Groups on the Below Performance Measures.

| Variable | Analysis F | Df | P | Significant Pairwise Comparison Focusing Solely on Group Contrasts |
|---|---|---|---|---|
| **Attention and Working Memory** | | | | |
| **Neuropsychological Test** | 4.965 | 1,47.39 | 0.031 | |
| **Patient Group** | 7.716 | 2,47.82 | **0.001*** | CL2>CL1 (p<.001) CL2>TOS (p<..001) |
| **Patient Group * Neuropsychological Test** | 2.960 | 2,47.33 | 0.061 | |
| **Motor Speed and Speed of Information Processing** | | | | |
| **Neuropsychological Test** | 0.723 | 1,49 | 0.399 | |
| **Patient Group** | 9.708 | 2,49 | **<0.0005*** | CL2>CL1 (p=.0005) CL2>TOS (p< .001) |
| **Patient Group * Neuropsychological Test** | 1.564 | 2,49 | 0.220 | |
| **Learning and Memory** | | | | |
| **Neuropsychological Test** | 11.032 | 4,173.61 | **<0.0005*** | |
| **Patient Group** | 8.323 | 2,46.13 | **0.01*** | CL2>CL1 (p=.0005) CL2>TOS (p=.012) |
| **Patient Group * Neuropsychological Test** | 0.753 | 8,176.67 | 0.644 | |
| **Visuospatial Functioning** | | | | |
| **Neuropsychological Test** | 2.266 | 1,42.561 | 0.027 | |
| **Patient Group** | 2.682 | 2,44.406 | 0.079 | |
| **Patient Group * Neuropsychological Test** | 1.566 | 2,42.714 | 0.221 | |
| **** Language Functioning** | | | | |
| **Patient Group** | 2.918 | 2, 45 | 0.065 | |
| **Executive Functioning** | | | | |
| **Neuropsychological Test** | 20.729 | 5,205.42 | **<0.0005*** | |
| **Patient Group** | 10.348 | 2,45.730 | **0.0005*** | CL2>CL1 (p=.0005) CL2>TOS (p<.0005) |
| **Patient Group * Neuropsychological Test** | 1.481 | 10,205.6 | 0.148 | |

** An ANOVA was conducted for this analysis

Interpreting the results at a clinical level, compared to the normative samples, the mean z score on the Digit Span Forward task was within the average range for all three clinical groups. On the working memory task, the mean z score for the VLOSLP Cluster-Two group was also within the average range, with the mean z score for the VLOSLP Cluster-One group and TOS group falling within the low average range.

In regards to the significant differences between the three groups, post-hoc pairwise analyses (bonferroni adjusted alpha =.025) comparing the three groups revealed that these differences were significant between the VLOSLP Cluster-Two group and both the VLOSLP Cluster-One group and TOS group (see Table 13 for p-values), such that the VLOSLP Cluster-Two group performed significantly better on both the attention and working memory tasks compared to the VLOSLP Cluster-One group and the TOS group.

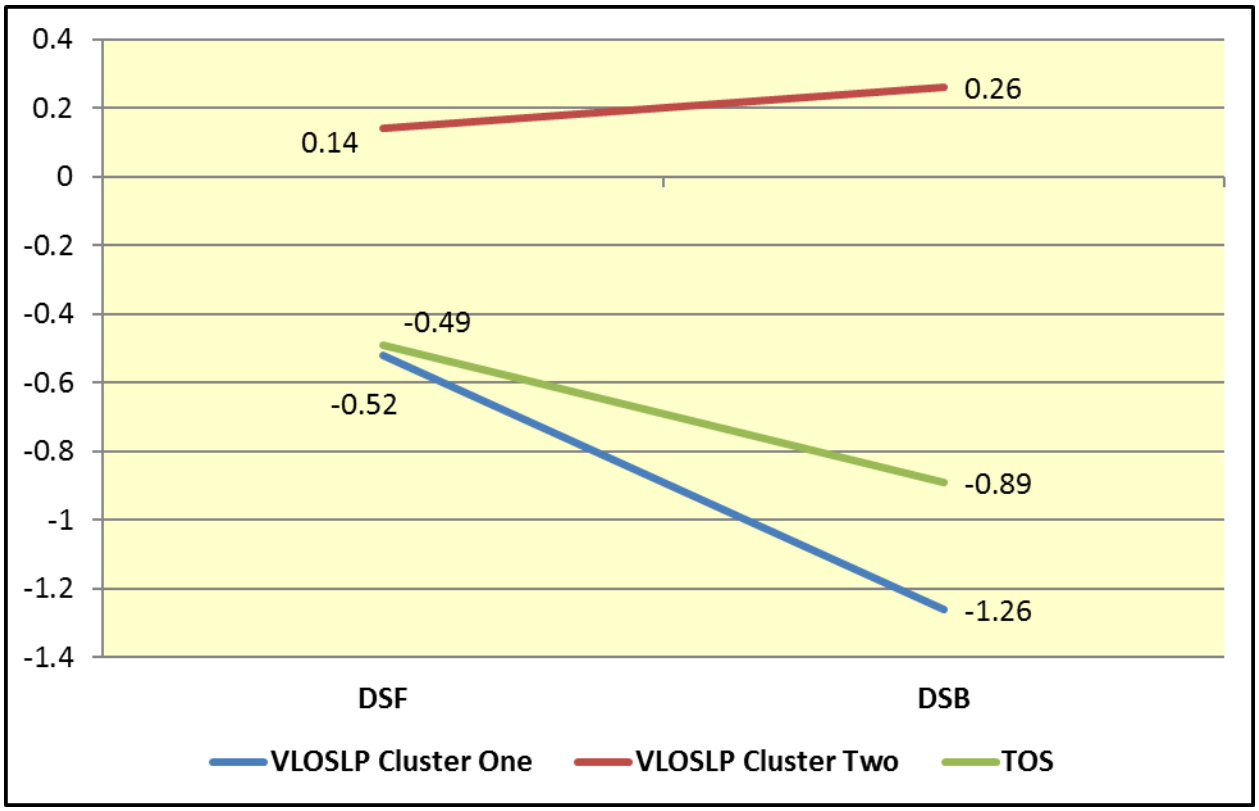


**Figure 8.** Immediate Auditory Attention Span and Working Memory Span for the VLOSLP Cluster-One, VLOSLP Cluster-Two and the TOS Groups.

### 4.4.3 *Overall Very-Late-Onset Schizophrenia-Like-Psychosis Cluster and Chronically Ill, Typical Onset Schizophrenia Group Effects for Motor Speed and Speed of Information Processing*

As above, a repeated measures MANOVA with schizophrenia group as the between subject factor and performance on the motor speed and speed of information processing Tasks (Trails A and Digit Symbol from WAIS-III) as the within-subject factor revealed a significant overall difference between the three groups (See Table 13). The MANOVA did not reveal a significant main effect for test performance. A non-significant result was also evident for the Patient Group * Cognitive Test interaction indicating no statistically significant difference between the z-score profile shapes for the three clinical patient groups.

Visual examination of the neuropsychological profiles of the three groups (see Figure 9 below) suggests that, from a clinical perspective, the VLOSLP Cluster-Two group performed within the average range on both the speeded tasks, while the TOS group performed within the borderline-impaired range and the VLOSLP Cluster-One group performed within the borderline-impaired to impaired ranges. In regards to the significant differences between the three groups, post-hoc pairwise analyses (bonferroni adjusted alpha = .016) comparing the three groups revealed that these differences were significant between the VLOSLP Cluster-Two group and both the VLOSLP Cluster-One group and TOS group (see Table 13 for p-values), such that the VLOSLP Cluster-Two group performed significantly better on both tasks compared to the VLOSLP Cluster-One group and the TOS group.

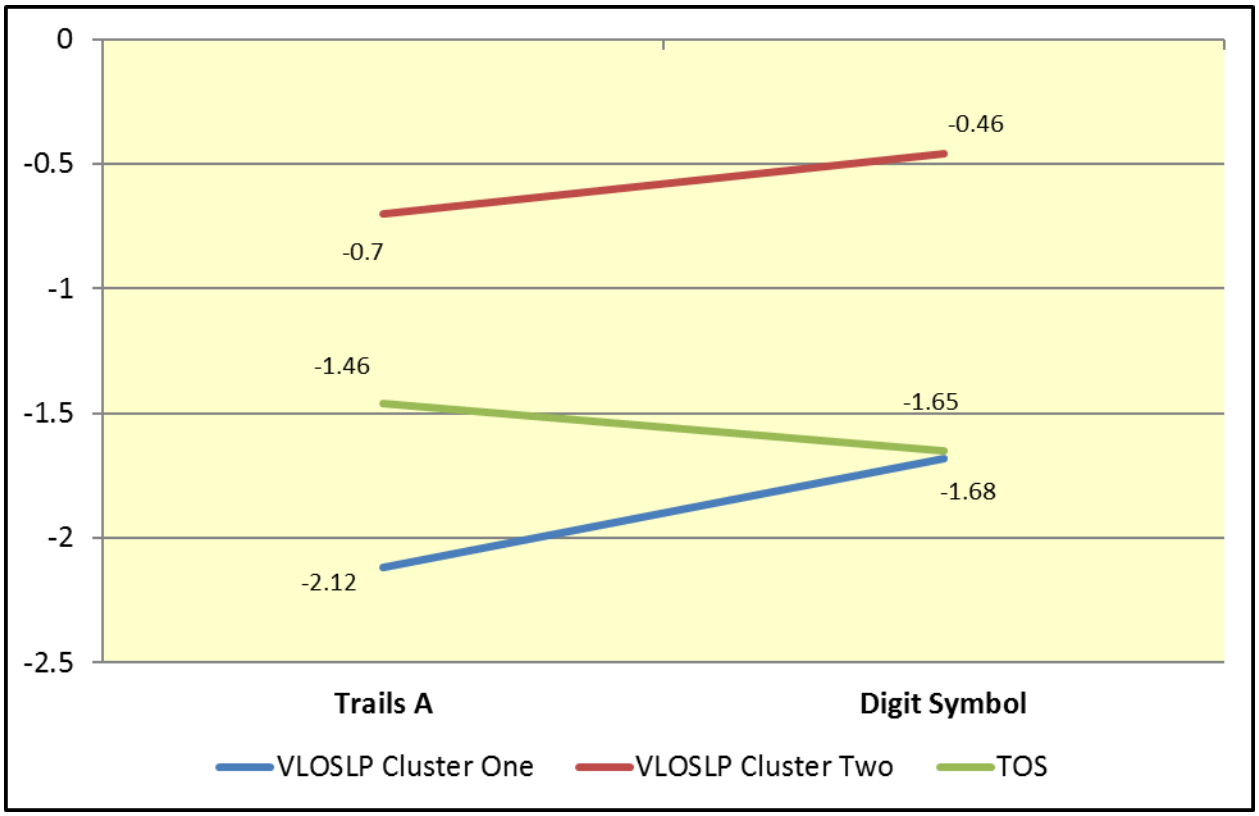


**Figure 9.** Motor Speed and Speed of Information Processing for the VLOSLP Cluster-One, VLOSLP Cluster-Two and TOS Groups.

### 4.4.4 *Overall Very-Late-Onset Schizophrenia-Like-Psychosis Cluster and Chronically Ill, Typical Onset Schizophrenia Group Effects for Verbal and Visual Learning and Memory*

A similar repeated measures MANOVA for performance on the learning and memory tasks (RAVLT LOT; RAVLT-VII; LMI; LMII; RCFT Delayed) and bonferonni correction for Type 1 error (alpha = .01) revealed a significant difference between the three groups and a significant main effect for memory test performance. A non-significant interaction of Patient Group * Memory Test interaction was found indicating no difference between the profile shapes for the three clinical patient groups on the memory tests (see Figure 10 below).

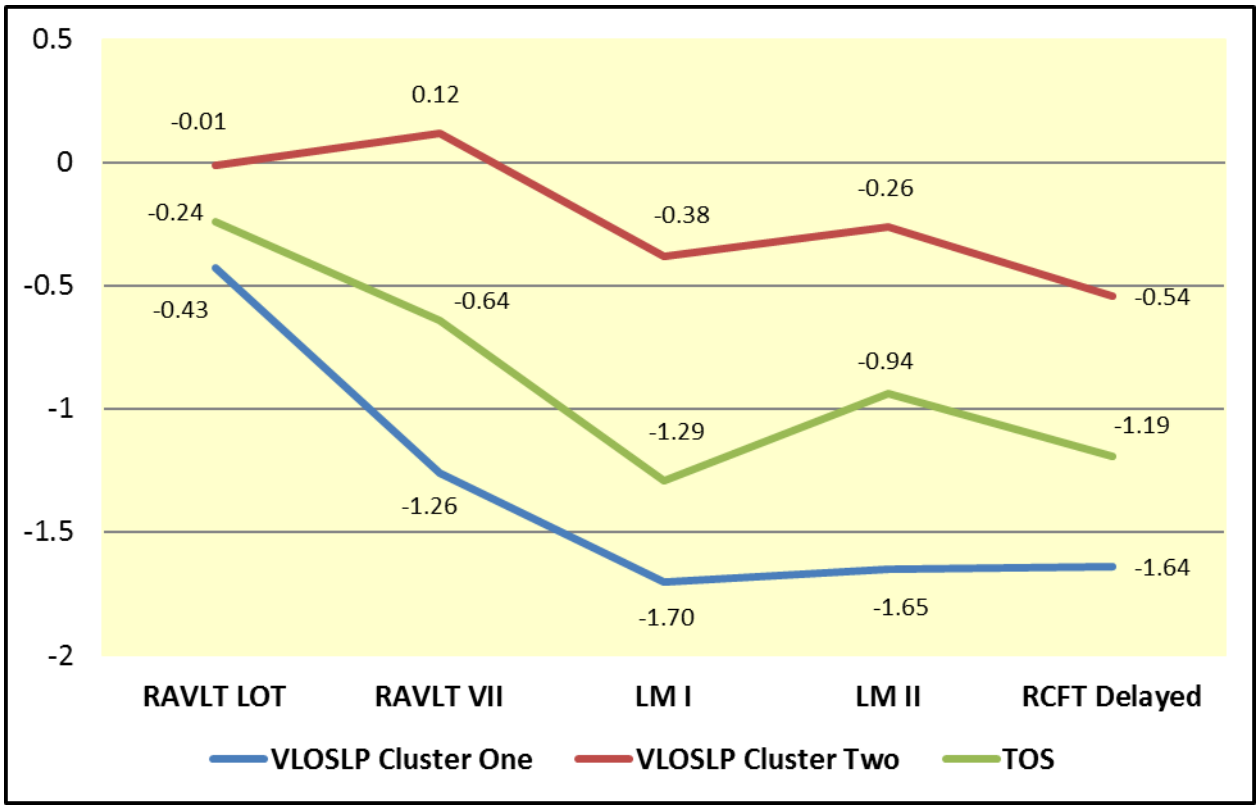


**Figure 10.** Verbal and Visual Learning and Memory Performance for the VLOSLP Cluster-One, VLOSLP Cluster-Two and TOS Groups.

In regards to the main effect of neuropsychological test, post-hoc pairwise comparisons of task performances were generally similar to that seen for the earlier comparison of the overall VLOSLP, TOS and LOPD groups and so will not be commented on further.

Visual examination of the neuropsychological profiles of the three groups (Figure 10 above) suggests that compared to the normative sample, the VLOSLP Cluster-Two group's mean z score performance was within the average range on all verbal and visual learning and memory tasks. Visual examination also indicates that the mean z score performance on all tests for the TOS group ranged from within the average to low average ranges, whereas the VLOSLP Cluster-One group's performance ranged from within the average to borderline-impaired ranges compared to the normative sample across all tasks. Consistent with this visual examination, post-hoc pairwise analyses (bonferroni adjusted alpha = .016) comparing the three groups,

revealed that these differences seen in Figure 10 above were significant between the VLOSLP Cluster-Two group and both the VLOSLP Cluster-One group and TOS group (see Table 13 for p-values). This demonstrates that the VLOSLP Cluster-Two group performed significantly better on learning and memory tasks than did the VLOSLP Cluster-One group and the TOS group.

### 4.4.5 *Overall Very-Late-Onset Schizophrenia-Like-Psychosis Cluster and Chronically Ill, Typical Onset Schizophrenia Group Effects for Visuospatial Functioning*

A repeated measures MANOVA on both the two visuospatial tasks (Block Design and RCFT Copy), with bonferonni correction for Type 1 error (alpha =.025), revealed no significant difference between the three groups, however the effect of group was noted to approach significance at p=.079. All other effects were non-significant (See Figure 11 below).

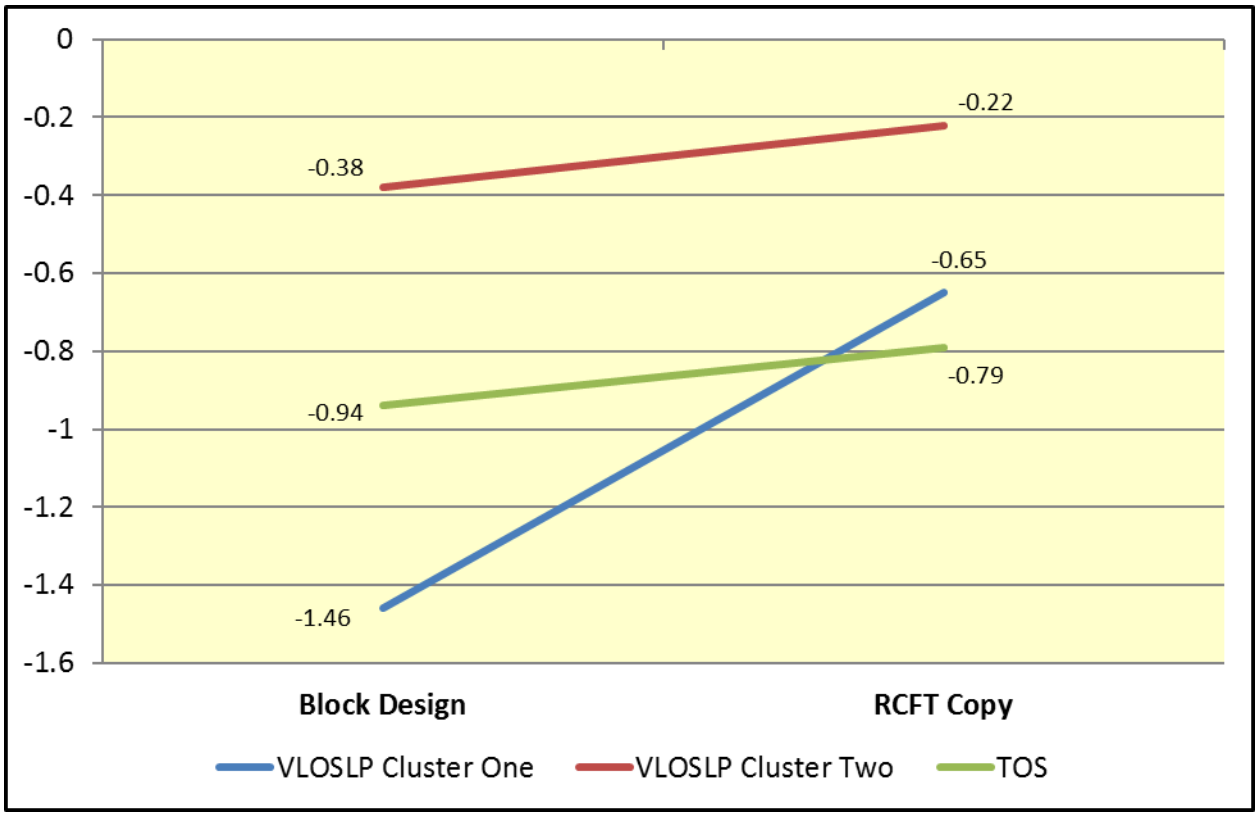


**Figure 11.** Visuospatial Functioning Performance for the VLOSLP Cluster-One, VLOSLP Cluster-Two and TOS Groups.

From a clinical perspective, visual examination of the above graph again indicates that the VLOSLP Cluster-Two group is consistently performing within the average range across both visuospatial tasks. In comparison, some variability exists between the other two schizophrenia groups. The VLOSLP Cluster-One group performance varies from within the borderline-impaired range to within the average to low average range across the two tasks, whereas the TOS group is performing within the low average range on both tasks.

### 4.4.6 *Overall Very-Late-Onset Schizophrenia-Like-Psychosis Clusters and Chronically Ill, Typical Onset Schizophrenia Group Effects for Language Functioning*

A one way ANOVA was conducted to compare schizophrenia groups (VLOSLP Cluster-One, VLOSLP Cluster-Two and TOS) with performance on the language functioning task, BNT, as the single dependent variable. This analysis revealed a non-significant overall difference between the three groups on the language task. However, this difference was noted to approach significance at p=.065.

Visual examination of the graph below (see Figure 12) indicates that the VLOSLP Cluster-Two group again performed within the average to low average range on the confrontational naming task, whereas the VLOSLP Cluster-One and TOS group's performance was within the borderline-impaired range.

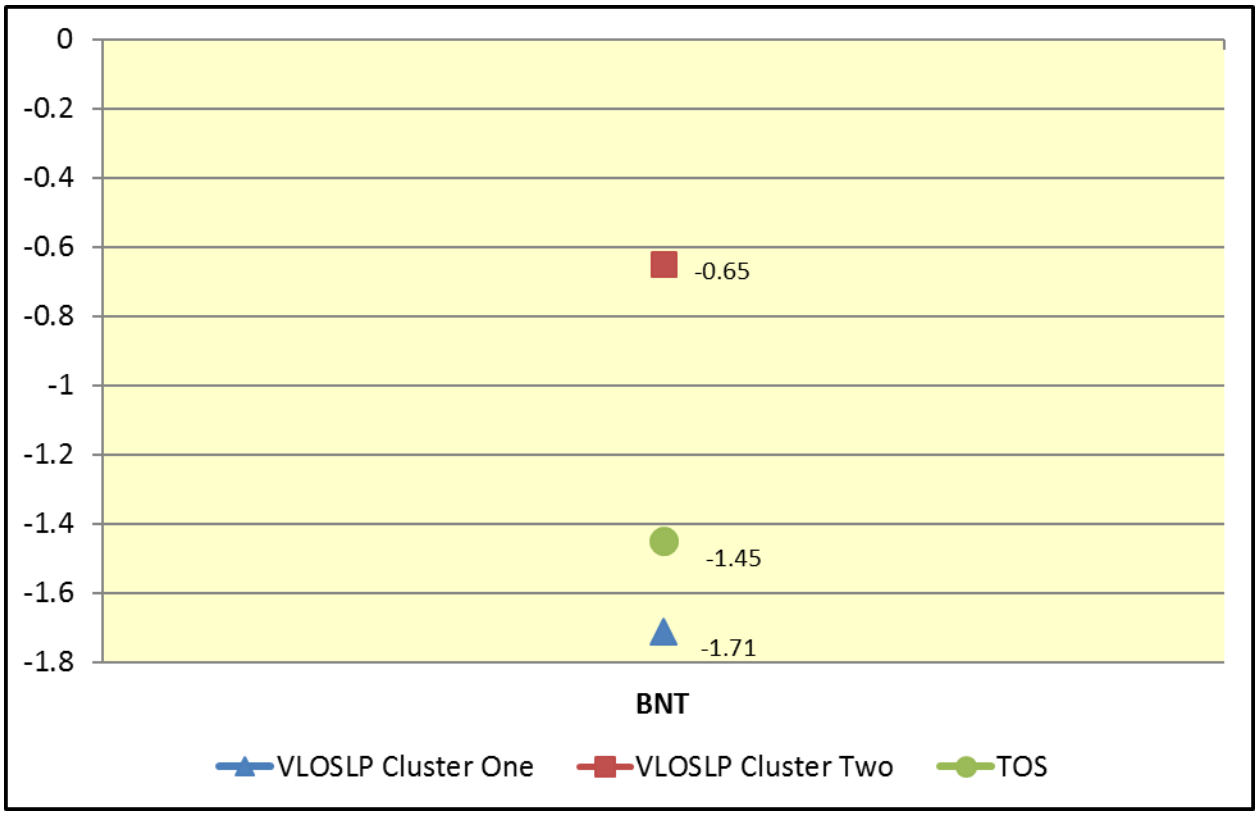


**Figure 12.** Language Functioning Performance for the VLOSLP Cluster-One, VLOSLP Cluster-Two and TOS Groups.

### 4.4.7 *Overall Very-Late-Onset Schizophrenia-Like-Psychosis Clusters and Chronically Ill, Typical Onset Schizophrenia Group Effects for Executive Functioning*

A repeated measures MANOVA was conducted with group (VLOSLP Cluster-One, VLOSLP Cluster-Two and TOS) as the between subject factor, and performance on the executive functioning tasks (Similarities, Trails B, FAS, Animals, Errors Inhibition (D-KEFS Colour Word Interference Task) and Tower Total Achievement Scores (D-KEFS Tower Test) as the within-subject factors. After bonferonni correction for Type 1 error (alpha = 0.008), this analysis revealed a significant overall difference between the three groups and a significant main effect for executive test performance. A non-significant interaction for Patient Group * Executive Test interaction was also found indicating no difference between the profile shapes for the three clinical patient groups on the executive tests (See Figure 13 below).

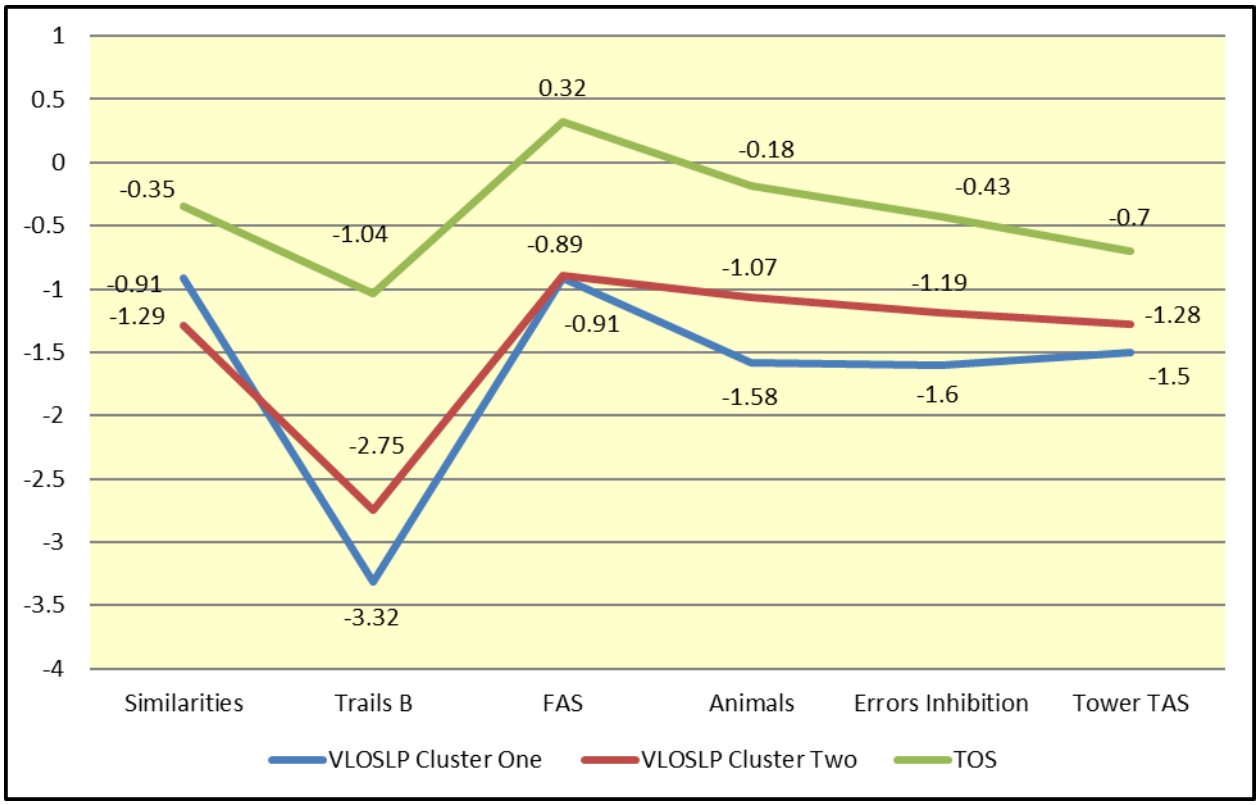


**Figure 13.** Executive Functioning Performance for the VLOSLP Cluster-One, VLOSLP Cluster-Two and TOS Groups.

In regards to the significant differences between the three groups, post-hoc pairwise analyses (bonferroni adjusted alpha = .016) comparing the three groups revealed that these differences were significant between the VLOSLP Cluster-Two group and both the VLOSLP Cluster-One group and TOS group (see Table 13 for p-values), such that the VLOSLP Cluster-Two group performed significantly better on executive tasks compared to the VLOSLP Cluster-One group and the TOS group.

Visual examination of the data from a clinical perspective indicate that the VLOSLP Cluster-Two group are again performing largely within the average range, with the exception of their performance on Trails B and D-KEFS Tower (Total Achievement Score) which were both within the low average range. Whereas the VLOSLP Cluster-One and the TOS groups performances range from within the low average to impaired ranges across the executive tasks.

It is acknowledged, however, that the interaction of Patient Group * Visuospatial Test was non-significant and so the above observations of different patterns across tasks should be treated with some caution.

### 4.4.8 *Summary of Performance of the Two Very-Late-Onset Schizophrenia-Like-Psychosis Clusters and the Chronically Ill, Typical Onset Schizophrenia Groups.*

In sum, the VLOSLP Cluster-Two group performed generally better than the VLOSLP Cluster-One group and the TOS group, with no significant differences between the latter two groups. The only domains for which the VLOSLP Cluster-Two group did not perform significantly better than the other two schizophrenia groups included visuospatial functioning and language functioning.

# Chapter 5. Discussion

The prevalence of psychotic symptoms amongst older adults has been estimated to range from approximately 0.2% to 4.75% of community based samples (Broadway & Mintzer, 2007) and from 10% to as high as 63% of individuals residing in aged care facilities (Zyass & Grossberg, 1998). Given that the The Australian Bureau of Statistics (2011) predicts the percentage of individuals aged over 65 years to be approximately between 19.5% to 20.8% by the year 2030, it is important that we aim to increase our understanding of the impact of psychotic symptoms on elderly populations. More specifically, research has also indicated that neuro-cognitive deficits are the strongest predictors of an individual's functional outcome in individuals who develop psychotic symptoms at a young age, therefore it is becoming increasingly important to better understand how these critical domains are influenced in elderly populations who develop psychotic symptoms both for the first time in old age and also in those who continue to present with psychotic symptoms in older age.

Very few studies have examined the cognitive functioning of individuals who develop psychosis for the first time in older life, and more specifically those who develop it for the first time over the age of 65 years. In this study we examined and compared the demographic, clinical and neuropsychological functioning of individuals with VLOSLP with that of individuals with TOS who have grown old and also a LOPD psychiatric control group. Each of the three clinical group's neuropsychological performance was assessed using a battery that allowed us to compare performance to published age related normative data for each of the specific neuropsychological tests.

Based on the existing research reviewed, it was hypothesised that, if VLOSLP is a schizophrenic illness, albeit with an atypical very late onset, the VLOSLP group's

neuropsychological performance would be generally reduced, as seen in schizophrenia samples across all stages of the illness, as compared to both the battery's normative healthy control data and the performance of the LOPD psychiatric control group. It was also hypothesised that, if schizophrenia is a neurodegenerative condition, as well as a neurodevelopmental condition, the VLOSLP group will be less impaired than the TOS individuals, who have had the illness for 20+ years longer. Based on existing empirical research we expected the VLOSLP group to present with less decline than the TOS group in the areas of verbal list learning, visuospatial functioning and verbal fluency – tasks which may be affected more by neurodegenerative changes. In contrast, the VLOSLP and TOS groups were expected to perform at similar lower levels on other tasks, including those of working memory, story learning and story recall, visual memory, abstract reasoning and cognitive flexibility – tasks which may associate more with vulnerability to schizophrenia and/or the brain changes that can occur during the prodrome and at onset of a schizophrenia illness. Finally, the LOPD control group was expected to present with a generally similar profile of reduced neuropsychological functioning to that of the schizophrenia groups, but these individuals' impairments would be less pronounced.

The current results were more complex than expected with noted heterogeneity in the VLOSLP group and indications that only a subset of VLOSLP individuals showed the hypothesised widespread cognitive impairments. The current findings will be examined in detail below, focusing first on the overall comparisons between the three clinical groups (VLOSLP, TOS and LOPD), before considering the exploratory results concerning the possibility of distinct clusters of VLOSLP individuals.

### 5.1. Demographic and Clinical Findings For the Three Clinical Groups.

Individuals in all three clinical groups were well matched for age and education with no

differences being found between the groups in regards to their age or years of education. Consistent with previous research identifying gender bias in LOS and VLOSLP, 84% of the individuals in the VLOSLP group were women. Surprisingly, a similar proportion (81.5%) of the elderly TOS group were also women, though this finding was consistent with the previous comparison research by Girard et al. (2011). Also surprisingly, a more even balance of gender was seen in the LOPD group with only 55.6% of this group being women. No significant differences were identified between the doses of prescribed antipsychotic medication between the three groups. This non-significant finding regarding antipsychotic medication enables us to assume that current antipsychotic medication usage is not responsible for any differences identified in the cognitive performances between the three groups. However it is important to remember that this study did not look at the length of antipsychotic medication use, which is of particular importance in regards to the TOS group. Nevertheless while such differences in length of medication usage might contribute to differences found between the cognitive performances of the LOPD and TOS groups, they would not explain any differences found between the LOPD and VLOSLP group.

Cognitively, all three clinical groups were found to be performing within the average range for premorbid intelligence, as estimated using the WTAR, with no significant difference found between the three groups. A cognitive screener, the MMSE, however was noted to be significantly different across the three clinical groups with the LOPD group performing better than both the VLOSLP and TOS groups. As per the exclusion criteria no individual in any of the three clinical groups however performed below 24/30 on the MMSE which is the clinically accepted cut-off for a diagnosis of possible dementia (O'Bryant et al., 2008; Anstey et al., 2010). A consistent finding of previous research into older individuals with a late onset psychotic illness (and a hypothesised risk factor) has been that of social isolation (Henderson & Kay, 1997). In

this study the percentage of individuals living alone was found to be significantly different between the VLOSLP group at 76% versus the LOPD group at 16.7%. Only 37.0% of the TOS group were also found to be currently living alone, however the differences between the VLOSLP and TOS groups were not found to be statistically significant, although they are suggestive. These results are similar to those previously reported by Almeida et al. (1995b) in their research with late paraphrenic patients. They found that 78.7% of their patients had been socially isolated in the six months prior to their onset of illness. Several hypotheses have been raised for this increase in social isolation seen in individuals who go on to develop VLOSLP. One theory is that LOS patients, including VLOSLP individuals, have long term difficulties in both establishing and maintaining relationships. They are often divorced, live alone and have few or no social contacts (Almeida et al., 1992; Howard & Levy, 1993) with others suggesting that they possess long term personality traits that may alienate themselves from other people (Kay & Roth, 1961). However, it is unclear how such predispositions and vulnerabilities may impact on an individual's current experience such that it results in the onset of a psychotic illness late in life versus those elderly individuals with similar isolation / background who do not. It may be that those who develop schizophrenic-like illness later in life have lived with vulnerability towards the illness that remains below threshold until the added stress of social isolation later in life.

Further on the topic of isolation, unlike previous research into late onset psychosis (Henderson & Kay, 1997; Howard et al., 1994), 92.0% of individuals in this study with VLOSLP had been married or in a defacto relationship previously, although only 16% currently remained married or in a defacto relationship at the time of this study. Specifically, 40% of the VLOSLP reported that they had been divorced and 36% were widowed. A similar percentage was seen in the LOPD group with 94.4% having previously been married, and 61.1% of this previously married group remaining married at the time of the study (with a divorce rate of only 5.6%). As

expected a lower percentage of individuals with TOS had previously been married at 66.7%, with only 18.5% currently remaining in a marriage, 25.9% widowed and 22.2% divorced. These differences between the three clinical groups were noted to approach significance. Similar percentages between the three clinical groups were found in regards to whether they had had children, with 88.0% of the VLOSLP group, 70.4% of the TOS and 88.9% of the LOPD group having had one of more children. No significant differences between the three groups were noted on this, however. Given the higher rate of current marriages and reduced percentage of social isolation in the LOPD group, this suggests that, at least for this group, continued socialisation is not a protective factor against the development of a psychotic illness.

This study also looked at the presence of a positive family history of any psychiatric illness. The decision to include 'any' history rather than just that of a history of schizophrenia / psychosis was largely due to the ever evolving diagnostic distinctions over the past century, and secondly, given the ages of the individuals involved in this research. We also did not want any confounds regarding individuals confusing specific details of previous family members' diagnosis / personal interpretations of symptoms. As a result the percentages of positive family history in this study are noted to be greater than that reported previously in the literature, which largely reports a positive family history of schizophrenia only. Interestingly a trend towards difference was identified between the three groups regarding the presence of a positive family history of psychiatric illness which was found to approach significance, with the LOPD group interestingly having the highest percentage of individuals with a family history at 61.1%. Both the schizophrenia groups in contrast demonstrated only 20% in the VLOSLP group and 29.6% in the TOS group.

Another proposed risk factor for the development of psychosis has been that of an individual's migrant status. No significant difference was found in this research between the

three groups in regards to their migrant status. However, a trend towards a larger number of migrants were noted in the VLOSLP group at 40.0% versus 16.0% in the TOS group and 16.7% in the LOPD group. However, these results need to be interpreted with caution as individuals from a non-English speaking background were excluded from this study due to the validity of completing current English based neuropsychological tests. This suggestion of a difference in proportion of migrants in VLOSLP individuals, which may hint at another exacerbating risk factor, will need to be further examined with larger sample sizes.

In terms of additional risk factors, no differences were found between the three groups in regards to the presence of vascular risk factors such as hypercholesterolemia, hypertension or diabetes, with 64.0% of the VLOSLP group, 66.7% of the TOS group and 66.7% of the LOPD group all having a history of vascular risk factors. This analysis was included to simply explore the possibility that differences in proportion of patients showing vascular risk factors amongst the three groups could potentially indicate increased vascular related brain changes in one group more than another. Any such differences may have been responsible for the presence of differences with regard to both the psychotic symptoms and the cognitive capacities in the late onset psychotic group compared to the TOS group, if the latter psychotic / cognitive differences were indeed found.

In regards to the symptom profiles of the three clinical groups, significantly more psychotic symptoms, as assessed using the BPRS, were reported in both the VLOSLP group and the TOS group compared to the LOPD group. However, no differences were noted between the three groups in regards to the presence of depression at assessment, with all three groups within the normal ranges on these self-reported (GDS) and observer rated (HAM-D) instruments. In contrast, in regards to their level of social / occupational functioning, the LOPD group presented with significantly better functional outcomes than that of both of the schizophrenia groups, with

no significant differences between the two schizophrenia groups.

## 5.2 Profile of Cognitive Functioning Across the Three Clinical Groups.

It had been hypothesised that, if schizophrenia is a neurodegenerative condition, as well as a neurodevelopmental disorder, and if VLOSLP is a variant of a schizophrenia illness, albeit with an atypical later age of onset, the VLOSLP group would be less impaired than the TOS group, with both schizophrenia groups performing poorly relative to the LOPD control group. The results were more complex than expected, as discussed above, but nevertheless provide evidence that some individuals who develop psychotic symptoms consistent with a schizophrenia type illness in later life, aged over 65 years, exhibit a decline in several areas of cognitive functioning early on in their illness process similar in profile to that seen in previous research with younger individuals with TOS and as compared to a LOPD control group. The pattern of these deficits in the VLOSLP group, although these individuals demonstrated slightly better performances as a whole than the elderly TOS group, was also shown to be consistent with the pattern of deficits seen in the individuals with TOS who have now grown old. Further, our findings also demonstrate that whilst the pattern of deficits is similar across the two overall clinical groups with schizophrenia illness, the extent of the deficits differentiate the schizophrenia groups from those with a late onset psychotic affective illness. These varying levels of cognitive functioning identified between the three clinical groups will be discussed in detail below with the caveat that most impairment with the VLOSLP sample was only seen in Cluster One.

### 5.2.1 *Attention / Working Memory Performance Across the Three Overall Clinical Groups*

No significant differences were found between these three groups on a task of immediate

attention span, with all three groups performing within the average range as compared to normative control data. Further, no significant differences were found between the three clinical groups on a task of working memory, with the mean performance of both the VLOSLP and LOPD group within the average range compared with the TOS group who performed within the low average ranges. A significant overall difference was however found across the attention and working memory tasks, with the three groups as a whole demonstrating better immediate verbal attention span than verbal working memory (relative to age-based norms). This result suggests a possible subtle decline in working memory functioning, possibility attributable to a psychotic illness in general (whether schizophrenia-like or not), as compared to that of immediate auditory attention span. This is reflected in the similarity of the profile (seen in Figure 2) between the three clinical groups. A great deal of the cognitive research into TOS has found evidence of both attention and working memory deficits in individuals with schizophrenia (Fitzgerald et al., 2004; Oltmans & Neale, 1975; Frame & Oltmans, 1982; Glahn et al., 2003). Thus, it is somewhat surprising that both schizophrenia groups' mean performance, as well as that of the LOPD group, is within the average to low average range on both tasks within our study. It is noted however, that previous research by Almeida et al. (1995d) also reported an average level performance on a task of immediate auditory attention span in their VLOSLP sample, consistent with current findings.

### 5.2.2 *Motor Speed and Speed of Information Processing Performance Across the Three Overall Clinical Groups*

In regards to performance of the three groups on speeded tasks, the two schizophrenia groups were noted to perform very similarly on a task of motor speed. Our findings demonstrated performances suggestive of cognitive deficiencies greater than 1.4 standard

deviations below the control normative sample (borderline-impaired range), while the LOPD group, however, were noted to be performing within the average range on this task. Differences between the three groups were also noted on tasks of speed of information processing. Specifically, while the LOPD Group performed within the average range, the VLOSLP group, as a whole, were within the low average range and the TOS group remained at borderline-impaired ranges.

Overall, the differences observed between the two schizophrenia groups and the LOPD group in both motor speed and speed of information processing were noted to be significant with the LOPD group showing better and average performance.

### 5.2.3 *Verbal and Visual Learning and Memory Performance Across the Three Overall Clinical Groups*

Previous research has reported no difference in the memory functioning between LOS and TOS groups on both verbal tasks of story learning and memory functioning, and also visual memory tasks (Jeste et al., 1995), while differences have been found on unstructured list learning and memory tasks (Jeste et al., 1995; Vahia et al., 2010). Overall, unlike previous studies, memory performance within schizophrenia groups in this present study was found to be very similar between the two groups (as seen in Figure 4). Interestingly, the profile of the LOPD group was also very similar, though showing less decline than the two schizophrenia groups and consistently performing within the average range on all tasks. Of further interest, though, in contrast to our original hypotheses, both the TOS and VLOSLP groups performed within the average range on both the verbal list learning and verbal list recall memory tasks. Subtle reductions in performance compared to the normative control data were however noted on both tasks of story learning / recall, and also visual memory, with both schizophrenia groups

performing within the low average range (0.9 to 1.3 standard deviations below the mean) on all three tasks. In contrast, and as hypothesised, the LOPD group fell within the average range on all learning and memory tasks. Significant differences were also found across the learning and memory tests themselves, with all three groups as a whole performing better on the unstructured list learning and memory recall tasks compared to the structured, more complex (i.e. lengthier and more detailed) story learning task and the visual memory task. This profile is depicted in Figure 4, which demonstrates that declines in learning and memory were more likely to be identified on the more complex story learning / recall task and also on the visual memory task. Whether or not these differential declines across the different learning/memory tasks, and noted across all three psychotic groups, are due to greater attentional difficulties or due to memory difficulty with the limited repetition of the information on the complex tasks of LM I and II and RCFT delayed recall, this is certainly of clinical interest and a possible area for future research into memory and later onset psychosis.

### 5.2.4 *Visuospatial Functioning and Language Functioning Performance Across the Three Overall Clinical Groups*

Consistent with expectation, a significant difference was found in the performances of the LOPD group on all three tasks compared to the performances of both the schizophrenia groups (see Figure 5 and Figure 6). However, in contrast to one of our specific hypotheses, which stated that the VLOSLP group would perform better than the TOS group on visuospatial tasks, no significant differences were found between the two schizophrenia groups on this task. In fact, very similar performances were noted between the two schizophrenia groups, as a whole, with a decline noted to be within the low average range for both groups on the task of visuospatial construction. Similarly, there were no significant differences noted between the VLOSLP group,

as a whole, and the TOS group on tasks of language functioning, with low average and borderline-impaired performance noted, respectively.

### 5.2.5 *Executive Functioning Performance Across the Three Overall Clinical Groups*

Qualitatively, a very similar cognitive profile across the three psychotic groups was also found for tasks of higher level executive functioning, with overall significant differences found only between the LOPD Group and the TOS group. As with all other cognitive domains, the LOPD group continued to perform within the average range compared to normative samples on tasks of higher level functioning with one exception. That is, interestingly, similar to the more marked decline in executive function seen within the two schizophrenia groups, the LOPD group was also noted to similarly demonstrate deficient performances to within the low average to borderline-impaired levels (1.33 standard deviation below normal) on an executive task of cognitive flexibility (Trails B). This more noted decline in Trails B performance, relative to norms, in the LOPD group is somewhat consistent with previous research by Alexopoulos and colleagues regarding noted executive dysfunction in individuals with a late-life depression (Alexopoulos & Kelly, 2009). Both schizophrenia groups were noted to present with more marked declines on this task, performing within the impaired range (>2 standard deviations below the mean).

Similar performances were found between the two overall schizophrenia groups on tasks of problem solving, inhibition and animal fluency with both schizophrenia groups performing within the low average range on all three tasks, which is again between 0.9 and 1.28 standard deviations below the mean. Mild clinically relevant (though statistically non-significant) differences were observed on a task of phonetic fluency, with the VLOSLP group as a whole performing within the average range, and the TOS group performing within the low average

range. Similarly on a task of abstract verbal reasoning the VLOSLP group as a whole also performed within the average to low average range while the TOS group performed within the low average range, with such observed differences possibly clinically relevant despite only 0.5 standard deviations difference (on average). A large number of significant differences were however identified between the neuropsychological test themselves for all psychotic patients as a whole, with significantly worse performance found on Trails B compared to all other executive tasks. Significantly better performances across all psychotic patients were also noted on a test of phonetic fluency than on tasks of abstract reasoning, inhibition or problem solving. These findings highlight the importance of neuropsychological studies examining the various different areas that comprise the 'executive functions', in order to gain better clinical understanding of which specific aspects of executive functions are compromised within these psychotic populations

### 5.3 Very-Late-Onset Schizophrenia-Like-Psychosis and the Profile of Cognitive Functioning.

As hypothesised if VLOSLP is a schizophrenic illness, our results show that, as a group, individuals who develop VLOSLP (above age 65) exhibit a general reduction in cognitive functioning across a broad range of cognitive domains early on in the illness process (when compared to healthy normative control data). This overall finding is certainly strongly consistent with that reported in the literature in individuals with both an chronically ill, typical onset schizophrenia illness (Mortimer, 2008; Keefe et al., 2005), as well as that reported in LOS studies (Jeste et al., 1995; Jeste et al., 1997; Sachdev et al., 1999; Vahia et al., 2010;Almeida et al., 1995d).

In this present study, however, the cognitive performance of individuals with VLOSLP on

the cognitive domains examined ranged notably from performances within the average range to performances within the impaired range. In more detail, average range performances for the VLOSLP group as a whole (relative to aged based normative data) were identified in some cognitive areas, including immediate auditory attention span, working memory, verbal list learning, verbal list delayed recall, visuospatial copy task, verbal abstract reasoning and phonetic fluency.

In contrast, subtle reductions in performance (that is, performance within the low average range defined as 0.7 to 1.4 standard deviations below the appropriate age related normative mean data) were noted on other tasks indexing speed of information processing, story learning and story delayed recall, confrontational naming, visuospatial construction, semantic fluency, inhibition and problem solving. The pattern on these cognitive tasks certainly suggests a decline in performance, based on normative age based healthy data, but does not necessarily represent a clinically substantial decline in actual overall functioning. However, individuals with VLOSLP were found to significantly underperform relative to healthy control data by 1.4 or more standard deviations (equating to the borderline-impaired range) on a task assessing motor speed, and by more than 2.0 standard deviations (equating to impaired ranges) on a task of cognitive flexibility.

As previously discussed very few studies have examined in detail the profile of cognitive functioning of individuals with VLOSLP. As a result these findings for the VLOSLP group as a whole are novel results that add to the small number of studies addressing these questions. Of perhaps greater import, the results for the VLOSLP group were further broken down into the various age ranges noted previously. This enabled more detailed clinical examination of the pattern of neuropsychological data itself. However, even after the breakdown of the VLOSLP group data into age ranges (which is recommended in future related research) a great deal of

variability was seen with performances from within the average to impaired ranges. In order to examine this variability in performance further, we conducted additional post hoc exploratory cluster analysis, the findings of which will be discussed in detail below.

## 5.4 Exploratory Cluster Analysis Within the Very-Late-Onset Schizophrenia-Like-Psychosis Group.

The evidence of a heterogeneity within the cognitive profile of individuals with VLOSLP is generally consistent with that previously found by Almeida et al. (1995c) in their LOS study and raises further questions regarding whether or not VLOSLP is, in some cases, an illness like TOS, which also shows a great deal of heterogeneity or, possibly in other cases, a precursor to dementia. Consistent with findings from Almeida et al. (1995c) who also performed cluster analysis, the current exploratory cluster analysis from this research using the cognitive results from the VLOSLP group (in particular, MMSE, Logical Memory II and Trails B) also produced two separate and evenly numbered subgroups with Cluster One generally performing worse than Cluster Two. These two VLOSLP Clusters did not differ from each other or from the TOS group, however, in their medication levels or their symptom profiles. In contrast, these two separate Clusters were found to be significantly different on a large number of the other neuropsychological tasks investigated in this study (refer again to Table 9), as detailed below.

Interestingly, in regards to attention, no significant or clinically noteworthy difference was found between the two VLOSLP Clusters on a task of immediate auditory attention span, with both groups' mean performance within the average range. Differences on a working memory task were however evident, with Cluster One found to be significantly more impaired (mean performance within the low average range) as compared to Cluster Two (whose mean performance remained within the average range). Significant differences were also found on a

task of motor speed (visual scanning and sequencing) with Cluster One found to be significantly more impaired (mean performance within the impaired range) as compared to Cluster Two (whose mean performance was within the low average range). Interestingly, in terms of cognitive speed, Cluster One similarly performed significantly worse on a task of speed of information processing (performing within the borderline-impaired range), compared to Cluster Two's performance within the average range.

In regards to learning and memory performance, no significant difference were found between the two Clusters in regards to the word list learning with both groups performing within the average range. A significant difference was however found between the two Clusters on the word list delayed recall task, with Cluster One performing more poorly within the low average range and Cluster Two within the average range. A similar difference of clinical significance between the two Clusters was present on both story learning and story delayed recall tasks, with significant differences found between the two Clusters on both tasks (Cluster Two performing significantly better than Cluster One). The visual memory task, the Rey Complex Figure Test, also produced a similar difference between the two Clusters, however the differences only approached significance on this task. These current results suggest that Cluster Two is adequately able to learn and retain new information both verbal and visual. However, Cluster One is able to learn new information when presented in a list format with multiple repetitions however they had difficulty on the verbal story learning task, with marked differences lying in the two Clusters' ability to spontaneously recall both verbal and visual information. It will be important for future research, utilizing larger VLOSLP sample sizes to further examine the different profiles of memory performance in different VLOSLP subgroups to determine whether or not this impaired recall in some VLOSLP individuals is attributable to a loss of information or due to a difficulty generating and implementing the strategies necessary to assist in their recall.

This detailed information regarding impaired delayed memory performance may be very important to further assist in possibly clarifying both diagnosis and outcomes for this population.

In terms of the visuospatial copy task, VLOSLP Clusters Two performed within the average range and VLOSLP Cluster One performed within the average to low average range, with no significant or clinical noteworthy differences noted. The copy task chosen for this study was both novel with regard to this population and quite complex, and results are suggestive, at least at a gross level, of no constructional apraxia on copying tasks in VLOSLP. Significant differences were however found between the two Clusters on a task of visuospatial construction (as opposed to copy), with Cluster One again falling within the borderline-impaired range and Cluster Two within the average range. Language functioning, specifically performance on a task of confrontational naming, was also significantly different between the two Clusters, with the same profile of clinically significant borderline-impaired performance for Cluster One compared to within the average to low average range performance for Cluster Two.

Clinically noteworthy and statistically significant discrepancies (or approaching significance) were also found on all tasks of higher level function, except for that of abstract verbal reasoning. On this task, Cluster One's mean performance was within the low average range while Cluster Two performed to within the average range. In contrast, significant differences were found between the two Clusters on a task of cognitive flexibility (Trails B) with Cluster One performing within the extremely impaired range and Cluster Two performing within the low average range (with this being one of the variables used to create the two Clusters). On tasks of verbal fluency, while a statistically significant difference was found between the two clusters in phonetic fluency (on the FAS task), Cluster One performed within the low average range and Cluster Two within the average range, which does not represent much of a difference of clinical significance between the two groups. Whereas on a task of semantic fluency

(Animals), Cluster One's mean performance was in the borderline-impaired range and Cluster Two's within the average range, representing both a statistically significant and clinically meaningful difference between the VLOSLP subgroups. Further, group differences on two additional executive tasks involving inhibitory control and reasoning were found to approach significance with Cluster One performing within the borderline-impaired range on both versus Cluster Two who performed within the average range on the inhibition task and within the low average range on the reasoning task.

Summing up the above, these results from the exploratory cluster analysis suggest that there is a subset of individuals with VLOSLP who continue to perform largely within the average to low average range across the majority of cognitive functions. Of note though, this 'cognitively intact' subgroup of individuals with VLOSLP nevertheless demonstrated reduced performances on a task of cognitive flexibility. In contrast, the second Cluster or subgroup of individuals with VLOSLP were found to perform within the borderline-impaired to impaired range on most areas of cognitive functioning. As previously mentioned the exception to this was on tasks of immediate auditory span of attention, verbal list learning and visuospatial copy tasks, where both Clusters showed average performances, and interestingly on tasks of abstract verbal reasoning, where Cluster One performed within the low average and Cluster Two within the average range.

In regards to comparison with previous similar research by Almeida et al. (1995d), it remains difficult to directly compare the current findings given the differences in neuropsychological tests used across the two studies and the ages at onset of psychosis in each study (LOS versus VLOSLP). What is of interest though, is that the results from both the current research and the Almeida et al. (1995c) study produced two evenly numbered clusters based on neuropsychological test performance. Almeida et al.'s (1995c) examination of the performance of the two clusters on the various tasks they used found that individuals in one of the clusters

were less accurate at problem solving and needed significantly more time to execute the various moves on one of the tasks. Such findings could be taken to reflect differences in executive functions between their two cluster groups, which is consistent with the findings from the current study. Of further interest, Almeida et al. (1995c) found no significant differences between their two identified clusters on any of the demographic variables or clinical measures used, with the exception of the MMSE. That is, the levels of psychotic symptoms were equivalent in both their clusters, as was the clusters' current levels of overall functioning. Similar results were also found between the two VLOSLP Clusters in this study. In regards to the MMSE, individuals in Cluster One from this study were found to have a mean MMSE score of 26.0 which falls in the 'grey' area on the MMSE where 24-27 indicates possible diagnosis of an emerging dementia, with Cluster Two presenting with a mean score of 29.

Overall, Almeida et al. (1995c) had thus concluded that one of their clusters was associated with impairment limited to executive dysfunction and thus had more specific involvement of localised frontal lobe deterioration. In comparison, they found the impairments in their second cluster were more pervasive, possibly indicating a more widespread brain disorder. The current findings however were not consistent with this pattern of localised frontal impairment in one Cluster, with one of the Clusters (Cluster Two) performing within the average to low average range on the majority of tasks, including all tasks of higher level executive functioning, with the exception of a borderline-impaired performance for cognitive flexibility. This does not fit with the presence of an isolated impairment in frontal lobe functioning in Cluster Two.

Further support for the possibility of two distinct patient subgroups in VLOSLP, including the possibility of VLOSLP as a precursor to dementia in some VLOSLP individuals, is found in the previous follow up research conducted with LOS populations. Several researchers

have conducted two to five year follow up studies of individuals with LOS, that is, those aged over 45 years at time of diagnosis. Utilising a cognitive battery in contrast to cognitive screeners (e.g. MMSE), Brodaty and colleagues (2003) found that nearly 50% of their patients met the DSM-IV criteria for dementia at the five year follow-up assessment. This decline identified in 50% of these LOS patients in previous research could potentially explain the discrepancies noted between Cluster One and Cluster Two in the current VLOSLP individuals. Specifically, the more impaired Cluster One may be manifesting signs of prodromal dementia (more on the later). Obviously, this is an area that requires further clarification through future longitudinal research with VLOSLP. This is especially so given this current study involves individuals who are all of greater age at initial onset than in the previous longitudinal work with LOS.

The suggestion of two distinct VLOSLP Clusters in the current study helps to account for the variability in the performances of the VLOSLP group as a whole across the age spans, as discussed previously, but it also further raises questions regarding possible different causes of schizophrenia-like illness in this elderly VLOSLP sample, as intimated above. Further post hoc analysis with a specific focus on comparing the three schizophrenia groups – the two VLOSLP Clusters and the TOS group - were therefore also conducted to further consider some of these questions, as discussed below.

Significantly different performances were found between the TOS and the Cluster-Two group on tasks involving attention and working memory, motor speed and speed of information processing, learning and memory and on tasks of executive performance. Differences between these two schizophrenia groups also approached significance on the language functioning task. Overall, the VLOSLP Cluster-Two group performed better than the similarly aged TOS group. However, it is important to remember the numbers are small to be conducting this type of analysis but the preliminary data does suggest that the neuropsychological performance of the

individuals in the VLOSLP Cluster-Two group are statistically different to that of the TOS group.

Further examination of the current findings from a clinical perspective, that is visual examination of the mean standardised scores on the various cognitive variables with regards level of performance, indicated another interesting observation which could be explored in future similar research. Specifically, the mean results for the VLOSLP Cluster-One group were reduced on the majority of cognitive domains when compared to that of the TOS group, albeit not significantly so. The mean performance of individuals in VLOSLP Cluster One fell within the borderline-impaired range on tasks of story learning and memory, visual memory, visuospatial construction, semantic fluency, inhibition and problem solving, as compared to the mean low average performance seen on these tasks by the TOS group.

The subtle difference noted in the poorer learning and memory performance in the VLOSLP Cluster-One group versus the TOS group at the very least continues to raise the question as to whether or not this subset of VLOSLP individuals is in the early stages of a dementing process. This is another issue that would be of extreme interest to further explore with both larger VLOSLP sample sizes so as to identify more statistically robust clusters and follow-up longitudinal assessment of the current study's Cluster-One and Cluster-Two VLOSLP groups.

Further implications will be discussed after providing an overview of the other findings concerning comparison of the three overall clinical groups – VLOSLP, TOS and LOPD, with more of a focus on the findings with regard to the LOPD group.

## 5.5 Overall Summary

In summary, consistent with Almeida et al's (1995c) research into the neuropsychological

functioning of a LOS sample, the current research suggests that individuals who present with VLOSLP may comprise two distinct subgroups, at least at a cognitive level (that is, the VLOSLP Clusters did not differ in symptoms or functioning). Our cluster analysis identified one subgroup which performed largely within the average to low average range across all cognitive domains, while the other subgroup's cognitive performance was more reflective of the widespread cognitive impairments seen in TOS individuals. The similarities in cognitive performances between our more impaired VLOSLP Cluster-One group and the age-matched elderly TOS group does suggest a similar underlying aetiology between these two schizophrenia groups, in keeping with a schizophrenia illness, albeit onsetting at different ages. However, on the other hand, the subtle differences of clinically relevant greater impairment noted in the VLOSLP Cluster-One group compared to the TOS group also raises the question of whether or not this VLOSLP subgroup is in fact in the precursor phase of a dementing illness. It needs to be acknowledged, however, that our cluster analysis may simply have split the VLOSLP group into a less impaired group and a more impaired group of individuals with the same underlying schizophrenia pathology. After all there is also variability in TOS. For example, perhaps the more intact Cluster-Two group simply had a less severe neurodevelopmental schizophrenia condition which only manifested later in life with additional stressors of aging, while the Cluster-One group had a more severe variant of the same condition. However, if that were the case, it is difficult to understand why the more severely affected Cluster-One group did not develop schizophrenia earlier in their life. Future longitudinal studies into the cognitive performance of the two VLOSLP Clusters identified in this study could better enable clinicians to determine the relevant diagnostic condition (dementia or schizophrenia illness) at apparent VLOSLP onset and the future progression of the illness. Of further note, the inclusion of the LOPD psychotic control group suggests that the cognitive findings of these three groups are not confounded by

medication effects. This is evidenced by the lack of significant difference between the antipsychotic medication dosages prescribed for the three groups. However, one other possible confound that could not be addressed is the possible effects of the length of time individuals have been prescribed antipsychotics. Clearly, the TOS group would be subjected to significantly longer medication periods than the other groups with later diagnosis. However, we do not believe that any such confound had marked effects since the TOS group who have been on the antipsychotic medication for a much longer period of time were not performing significantly differently to the VLOSLP Cluster-One group who have been on the medication for only a short period.

The current cognitive differences also do not appear to be confounded by the levels of symptomatology within the groups. When BPRS was entered as a covariate, it yielded non-significant results on all cognitive domains apart from memory functioning. Further correlational analysis of the BPRS results on memory functioning across the three groups found at best mild correlations with any of the learning/memory tasks, indicating that the levels of symptomatology had only a mild impact on the memory performance across the three groups. Existing research has also suggested that cognitive deficits present in schizophrenia share only a small common variance with symptom severity, explaining approximately only 10% of the variance (Cornblatt et al., 1985). More specifically the major psychotic symptoms of delusions and hallucinations have been found to have no relationship with an individual's neuropsychological test performance (Nuechterlein et al., 1986; Frith, 1992). However, Almeida et al. (1995c) in their research into VLOSLP had identified two distinct Clusters of patients, with differing profiles of not only cognitive functioning but also symptom severity. Their findings suggested the opposite pattern in regards to a link between cognitive functioning and symptomatology. That is, the Cluster of individuals with cognitive deficits restricted to that of executive functions was found

to present with more severe psychotic symptoms, while the second Cluster was found to have less complex psychotic symptoms but more generalized cognitive impairments. In contrast, the two Clusters identified in the current research did not differ at all in symptomatology.

## 5.6 Limitations of this Study

The results from this present study should certainly be interpreted with several limitations in mind. Firstly, the small sizes of patient groups limit the statistical power of the analysis in detecting between-group differences. It is important to note however, that our overall group numbers are similar to those of other neuropsychological studies of psychosis in the elderly and that the three clinical groups that were recruited, and without comorbid factors, are very rare in geriatric populations making the collection of larger numbers difficult. Our relatively small sample size in the VLOSLP group also urges caution about the results from the exploratory cluster analysis. Although the cluster analysis results were strongly significant, this methodology will need to be replicated in future with larger samples in order to increase the robustness of the results.

Further, in regards to the allocation of neuropsychological tests to neurocognitive domains, it is important to interpret the cognitive processes underlying the various neuropsychological test performances with caution, given that many of the individual neuropsychological tests used in this study require more than one cognitive process. That is, whilst this study has interpreted task performances as related to different neurocognitive domains, it is important to remember that individual tasks should not be interpreted as simply pure indicators of each domain. Further we were limited in using tasks that had age-relevant norms. This is why we were unable to consider other domains, such as social cognition, which is attracting increasing interest as a predictor of functioning.

## 5.7 Future Directions

Elucidating the profile and severity of cognitive deficits in individuals with VLOSLP may be central to better establishing definitive diagnosis (distinguishing between schizophrenia and emerging dementia) and determining the prognosis / outcome in each patient. Therefore it is imperative that future research continues to examine and explore this clinically important and relatively under-researched area.

As previously discussed, future research needs to obtain larger sample sizes of individuals with VLOSLP / TOS and LOPD to better specify the cognitive profiles of these three groups and to allow for more robust cluster analysis within VLOSLP individuals so as to more thoroughly understand the bases of the apparent heterogeneity within VLOSLP. Future research also needs to conduct long term follow up studies of these three groups, including any identified VLOSLP Clusters, in order to further examine possible decline in functioning and presence / absence of dementia. Future research should also utilise these preliminary neurocognitive findings to assist with test selection in future studies in order to maximise the sensitivity of the batteries of tasks chosen to index the various neurocognitive domains. Given the time constraints of conducting studies with an elderly population and the need for tasks with appropriate norms, it is also hoped that this study's findings will help to guide task selection to be better targeted at relevant neurocognitive domains. Similarly it would be important to include more comprehensive assessments of psychopathology related more specifically to schizophrenia in order to more specifically capture the differences / similarities in VLOSLP versus TOS symptomatology.

As is currently occurring in research in schizophrenia in younger populations, future neuropsychological research into VLOSLP groups should also expand to include social cognition measures, especially in light of the noted correlations with functional outcome. Further, it would

be important for future research to use other more comprehensive schizophrenia symptom measures such as the Scales for Assessing Positive and Negative Symptoms of Schizophrenia for more detailed consideration of correlation with / impact on cognition from distinct symptoms (e.g., positive versus negative).

## 5.8 Conclusion

These current preliminary findings represent an advance in research into VLOSLP. In contrast to much previous research, a comprehensive neuropsychological battery with age appropriate norms was used. This allowed us to take account of normal effects of ageing. The elderly VLOSLP and TOS samples were also compared to a similarly aged LOPD psychotic control group with similar levels of symptoms and medication. Overall, however, more questions were raised than answered, particularly with regard to heterogeneity within VLOSLP. These questions provide important direction for future research, however. One potential avenue for further research is the issue of whether or not individuals who present with VLOSLP (with or without marked cognitive impairments) are simply presenting with a more classic / true schizophrenia illness consistent with that of TOS samples. A related potential research question could address why this illness, which, whilst perhaps similar in symptomatology to TOS, appears to have a far greater cognitive impact in a subset of individuals. In contrast, the preliminary cluster analysis raises the question of whether or not the poorer performing Cluster-One group in the VLOSLP sample could in fact represent those with the onset of an early neurodegenerative dementing condition, distinct from schizophrenia. Allied to which is the question of whether the presence of a psychotic illness simply makes an elderly individual more at risk of developing a neurodegenerative illness? – a question that might be answered by follow-up longitudinal research comparing VLOSLP and LOPD groups. These questions need to be addressed through

longer term follow up studies of different VLOSLP Clusters, TOS and LOPD samples, using larger sample sizes, and including neuroimaging investigation which may detect changes not noticeable on cognitive functioning measures.

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# Abbreviations

| | |
|---|---|
| ABS | Australian Bureau of Statistics |
| ADL | Activities of Daily Living |
| ANOVA | Univariate analysis of variances |
| BD | Block Design |
| BNT | Boston Naming Test |
| BPRS | Brief Psychiatric Rating Scale |
| BPSD | Behavioural and Psychological Symptoms of Dementia |
| CAMCOG | Cambridge Cognitive Examination |
| CATIE | This Clinical Antipsychotic Trials of Intervention Effectiveness |
| CL1 | Very-Late-Onset Schizophrenia-Like-Psychosis Cluster One |
| CL2 | Very-Late-Onset Schizophrenia-Like-Psychosis Cluster Two |
| COWAT | Controlled Oral Word Association Test |
| CPT | Continuous Performance Test |
| CSM | American Committee on Safety of Medicines |
| CT | Computed Tomography |
| D-KEFS | Delis-Kaplan Executive Function System |
| DRS | Dementia Rating Scale |
| DSB | Digit Span Backwards |
| DSF | Digit Span Forwards |
| DSM-I | Diagnostic and Statistical Manual of Mental Disorders – First Edition |
| DSM-II | Diagnostic and Statistical Manual of Mental Disorders – Second Edition |
| DSM-III | Diagnostic and Statistical Manual of Mental Disorders – Third Edition |
| DSM-III-R | Diagnostic and Statistical Manual of Mental Disorders – Third Edition – Revised |

| | |
|---|---|
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition |
| DSM-IV-TR | Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition – Text Revision |
| DSM-V | Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition |
| DTI | Diffusion Tensor Imaging |
| ECT | Electrical Convulsive Therapy |
| GAF | Global Assessment of Functioning |
| GDS | Geriatric Depression Scale |
| HAM-D | Hamilton Depression Rating Scale |
| HSCT | Hayling Sentence Completion Test |
| Hx | History |
| IADL's | Instrumental Activities of Daily Living |
| ICD-9 | International Classification of Diseases - Ninth Edition |
| ICD-10 | International Classification of Diseases – Tenth Edition |
| IQ | Intelligence Quotient |
| LM | Logical Memory |
| LMI | Logical Memory Story 1 |
| LMII | Logical Memory Story 2 |
| LOPD | Late Onset Psychotic Depression |
| LOS | Late Onset Schizophrenia |
| LOT | Learning Over Trials |
| MANCOVA | Multivariate Analysis of Covariance |
| MANOVA | Multivariate Analysis of Variance |
| MATRICS | Measurement and Treatment Research to Improve Cognition in Schizophrenia |

| | |
|---|---|
| MMSE | Mini Mental Scale Examination |
| MOANS | Mayo's Older Americans Normative Studies |
| MRI | Magnetic Resonance Imaging |
| PSE | Present State Examination |
| RAVLT | Rey Auditory Verbal Learning Test |
| RCFT | Rey-Osterrieth Complex Figure Test |
| RFS | Role Functioning Scale |
| SS | Scaled Score |
| SPSS | Statistical Package for the Social Sciences |
| TAS | Total Achievement Score |
| ToM | Theory of Mind |
| TOS | Chronic, Typical Onset Schizophrenia who have grown old |
| Trails | Trail Making Test |
| VBR | Ventricle-to-brain ratios |
| VLOSLP | Very-Late-Onset Schizophrenia-Like-Psychosis |
| WAIS-R | Wechsler Adult Intelligence Scale – Revised |
| WAIS-III | Wechsler Adult Intelligence Scale – 3rd Edition |
| WCST | Wisconsin Card Sorting Test |
| WISC-R | Wechsler Intelligence Scale for Children – Revised |
| WMS-R | Wechsler Memory Scale – Revised |
| WMS-III | Wechsler Memory Scale – 3rd Edition |
| WRAT-III | Wide Range Achievement Test – 3rd Edition |
| WTAR | Wechsler Test of Adult Reading |

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13 May 2009

Ms Shelly Simpson
PO Box 694
Westmead
NSW 2145

**Reference: HE01MAY2009-D06486**

Dear Ms Simpson,

**FINAL APPROVAL**

**Title of project: A comprehensive neuropsychological evaluation on individuals aged 65 years and over who present with chronic schizophrenia, very late onset schizophrenia-like psychosis or late onset psychotic depression**

The above application was granted Interim Approval by the Executive of the Ethics Review Committee (Human Research) on 08 April 2009. This Interim Approval was considered by the Committee at its meeting on 01 May 2009 and was ratified.

Please note the following standard requirements of approval:

1. Approval will be for a period of twelve (12) months. At the end of this period, if the project has been completed, abandoned, discontinued or not commenced for any reason, you are required to submit a Final Report on the project. If you complete the work earlier than you had planned you must submit a Final Report as soon as the work is completed. The Final Report is available at: http://www.research.mq.edu.au/researchers/ethics/human_ethics/forms

2. However, at the end of the 12 month period if the project is still current you should instead submit an application for renewal of the approval if the project has run for less than five (5) years. This form is available at http://www.research.mq.edu.au/researchers/ethics/human_ethics/forms. If the project has run for more than five (5) years you cannot renew approval for the project. You will need to complete and submit a Final Report (see Point 1 above) and submit a new application for the project. (The five year limit on renewal of approvals allows the Committee to fully re-review research in an environment where legislation, guidelines and requirements are continually changing, for example, new child protection and privacy laws).

3. Please remember the Committee must be notified of any alteration to the project.

4. You must notify the Committee immediately in the event of any adverse effects on participants or of any unforeseen events that might affect continued ethical acceptability of the project.

5. At all times you are responsible for the ethical conduct of your research in accordance with the guidelines established by the University http://www.research.mq.edu.au/researchers/ethics/human_ethics/policy

If you will be applying for or have applied for internal or external funding for the above project it is your responsibility to provide Macquarie University's Research Grants Officer with a copy of this letter as soon as possible. The Research Grants Officer will not inform external funding agencies that you have final approval for your project and funds will not be released until the Research Grants Officer has received a copy of this final approval letter.

Yours sincerely

P.P.

Ms Karolyn White
Director of Research Ethics
Chair, Ethics Review Committee (Human Research)

**Cc: Dr Robyn Langdon, Macquarie Centre for Cognitive Science**