A PROSPECTIVE STUDY OF NEUROLOGICAL ABNORMALITIES IN A COHORT OF NIGERIAN PATIENTS WITH SCHIZOPHRENIA

BY

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DECLARATION

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ABSTRACT

Background

The changes in cognition, brain structure, and neurological soft signs which are characteristic of schizophrenia appear to have been present before the onset of the phenotype. They therefore find relevance as potential vulnerability markers of the disease. Neurological soft signs are of particular interest because they can be elicited quickly, reliably and cheaply. They have also been touted as markers of certain characteristics of schizophrenia. The most convincing evidence for these assertions come from prospective longitudinal studies of first episode, medication naive patients with schizophrenia. Most of these studies have been based on wholly Caucasian or mixed samples of Caucasians and other races. The present study provides important reference data on the nature of neurological soft signs in indigenous African subjects and clarifies the trait or state marking signs in this population.

Method

A total of 84 patients with first episode, schizophrenia, schizo-affective disorder, or schizophreniform disorder meeting criteria in the fourth edition of the Diagnostic and Statistical Manual for Mental Disorders were consecutively recruited. Information on demographic characteristics, personal medical and psychiatric history, as well as family history was obtained at baseline. Neurological assessment was based on the 26 item Neurological Evaluation Scale. An exploratory factor analysis of the items in the scale was conducted using the baseline measurements. The derived sub-sets of neurological soft

signs were then followed up longitudinally and in parallel with the 'functional categories' of the signs. The study describes the profile of neurological soft signs across the one year course of schizophrenia, as well as their relationship with a wide range of clinical and outcome variables. The severity of the baseline psychopathology was evaluated by administering the Positive and Negative Syndrome Scale. The overall clinical status was assessed using Clinical Global Impression. Additional assessments included the Calvary Depression Scale for Schizophrenia, Birchwood Insight Scale, Social and Occupational Functioning Assessment Scale, and the World Health Organisation Quality of Life Scale (WHO QoL-BREF). Pre-morbid adjustment was assessed using the Pre morbid Adjustment Scale, while extra-pyramidal effect of antipsychotics was assessed using the Extra-pyramidal Symptoms Rating Scale. Assessments were repeated at three monthly intervals for the full 12 months.

Results

Neurological soft signs were present in 96.4% of the sample at baseline. The signs loaded into a four factor structure: perceptual and motor sequencing (audio-visual integration, fist-edge palm, rhythm tapping, extinction, and right-left confusion), eye movements (synkinesis, convergence, and gaze impersistence), motor co-ordination and graphaesthesia (tandem walk, adventitious flow, and graphaesthesia), as well as stegreognosis. The scores for the perceptual and motor sequencing factor, as well as those for the sequencing of complex motor acts 'functional category' were stable across three measurements over 12 months ($F=1.26$, $p=0.287$, and $F=1.87$, $p=0.158$ respectively). The sequencing of complex motor act signs was not significantly correlated with the clinical and outcome characteristics of schizophrenia. However, other signs, as well as the NES

total score were significantly correlated with more severe negative and disorganized psychopathology, as well as poorer outcome in terms of functioning and quality of life.

Conclusion

Neurological soft signs were present at a high frequency at baseline. A preponderance of the signs was associated with a more severe negative and disorganization psychopathology, as well as a poorer functional outcome and quality of life. Abnormal sequencing of complex motor act signs, and signs of abnormal cognitive processing of perceptual stimuli where resistant to changes in psychopathology, and thus may represent viable trait markers for schizophrenia in this cohort.

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CHAPTER ONE

INTRODUCTION

Schizophrenia is a disease found in all societies and geographical areas around the world. Its incidence has often been quoted as roughly equal worldwide. This notion was established by early influential large scaled epidemiological studies funded by the World Health Organization (WHO), and also documented in the Diagnostic and Statistical Manual (DSM IV) (American Psychiatric Association, 1994). More recent reports estimate the prevalence of schizophrenia as 4.6/1000 for point prevalence, 3.3 per 1000 for period prevalence and 4.0 per 1000 for life time prevalence. The prevalence of schizophrenia may be higher in immigrant groups and lower in developing countries (Saha et al, 2005).

Schizophrenia commonly presents with impairments in perception, structure of thought, concept of self, cognitive functions, volition, and emotions, and in many cases evolves into a chronic disorder with deterioration in personal functioning. Abnormalities of cognition, brain structure, as well as neurological signs appear to have been present before onset of schizophrenia and have been recognized as part of the expression of the disease (Chen et al,2005., Chan and Gottesman, 2008., Serene et al, 2007).

Neurological abnormalities have often been conceptualized as 'soft or hard'. Hard signs are gross signs elicited by the traditional neurological examination. They often indicate a demonstrable lesion in the nervous system. They include signs such as visual field defects or hypotonia which can often be traced to specific malfunctioning of the brain, whereas Neurological Soft Signs (NSS) feature in individuals with no obvious neuropathology. No observable compromise in neurological functioning is identifiable in such individuals. Most of the signs suggest a decrement of the individual's performance abilities in motor or sensory tests of a neurological examination and are thought to offer little usefulness in localising any gross lesion (Gureje, 1988., Compton et al, 2006., Sewell et al, 2010).

The relevance of NSS in schizophrenia has been a subject of repeated research in the past 40 years. The prevalence of these abnormalities has been a central issue in most of these studies, and have been estimated to be between 50% and 65% (Heinrich and Buchanan, 1988., Shibre et al, 2002., Bombin et al, 2005). This prevalence appears to be particularly high in first episode schizophrenia subjects, reaching up to 97.1% (Browne et al, 2000) and 100% (Scheffer et al, 2004), depending on the definition of NSS in the relevant studies. This high prevalence among first episode, treatment naïve patients provides evidence for the presence of underlying brain disorder in schizophrenia prior to the onset of frank psychosis (Zhao et al, 2013., Gay et al, 2012), and supports a neuro-developmental model for the disorder (Peralta et al, 2011) Studies have also consistently shown a higher frequency of NSS in patients with schizophrenia than in other psychiatric subjects, and normal comparison groups (Boks et al, 2004., Chan et al, 2009.,Ellison-Wright and Bullmore, 2010., Peng et al, 2012), with relatives of patients with

schizophrenia showing rates that are somewhere in between those of the patients and normal comparison subjects (Gourion et al, 2003., Neelam et al, 2011). This pattern of similarity between patients and their relatives may indicate genetic or shared environmental factors or both (Sanders et al, 2006).

Thus, NSS have been considered by many as an indicator of vulnerability to schizophrenia and as correlates of both clinical and functional outcome. This is because they are represented to a large extent in patients with schizophrenia, and may be enduring through remission (Prikryl et al, 2012., Piccioni and Dazzan, 2009., Boks et al, 2006., Emsley et al, 2005., Bachman et al, 2005., Chen et al, 2005., Scheffer, 2004). They also occur in first degree relatives of the patients with schizophrenia as well as some schizophrenia spectrum disorders (Mechri et al,2010., Chan and Gottesman, 2008., Shubert and McNeil., 2005., Prasad et al, 2009., Sanders et al, 2006., Keshavan et al, 2008., Kaczorowski et al, 2009, Chan et al, 2010a and b).

Despite this compelling level of evidence, the true nature and prevalence of NSS in schizophrenia are still not fully understood, owing in part to a number of methodological issues such as the wide variation in neurological assessment procedures across studies, the inconsistencies in the criteria for defining normality and abnormality, the unresolved and sometimes ambiguous concept of "soft" and "hard" neurological signs, as well as the unresolved issues of the possible lateralization of neurological abnormalities in schizophrenia (Ismail et al, 1998., Gay et al, 2012., Kong et al, 2012). Furthermore, the

nature of the underlying neuropathology, as well as the aetiology of neurological abnormalities in schizophrenia remains unclear, as basic sensory and motor mechanisms are not particularly disturbed in schizophrenia (Heinrich and Buchanan 1989).

Studies on NSS in schizophrenia from the African population are few and far between. Out of a total of five African studies reporting on the nature of NSS in Schizophrenia (Gureje et al, 1988., Mubarak et al, 1999., Shibre et al, 2002., Emsley et al, 2005, and Smit et al, 2012), only one was based on a first episode sample (Emsley et al, 2005). That study, which is also the only prospective longitudinal study of NSS in the African continent, was based on a predominantly mixed sample of Caucasians and other races. Yet, prospective longitudinal clinical studies of NSS in first episode schizophrenia subjects have provided useful information in the last two decades on the nature of this clinically complex and aetiologically heterogeneous condition that affects about 1% of the general population.

This study describes the profile of NSS across the one year course of schizophrenia, as well as their relationship with illness specific and outcome variables in a group of first episode, largely medication-naïve Yoruba Nigerians with the disease. This is in the background of some reports suggesting that race and ethnicity affects the profile of NSS in schizophrenia (Chen et al, 2003., Keshavan et al, 2003., Bombin et al, 2005., Mechri et al, 2009). The study is expected to provide important reference data on the nature of NSS in indigenous African subjects and energize the pursuit of candidate genes in the causal

pathway of schizophrenia. This is with the hope that such a discovery will make it possible to develop better diagnostic procedures, treatments and preventive interventions targeted at the underlying illness process.

CHAPTER TWO

LITERATURE REVIEW

A search of the literature for relevant articles on neurological soft signs (NSS) in schizophrenia was conducted using the libraries of Stellenbosch University, University of Ibadan, and the Institute of Psychiatry, Kings College London. An English language search of PUBMED, MEDLINE, PsychINFO, and the World Health Organization (WHO) HINARI databases for literatures published between 1969 and 2011 was carried out. This was later updated to 2013. Search terms used were in accordance with the Medical Subject Headings (MeSH). They include: Neurological AND Soft AND Signs AND Schizophrenia OR Psychosis. A narrower search included the following terms: First AND Episode AND Schizophrenia OR Psychosis. All abstracts were screened, and articles that might have contained relevant information were read in full. The references of key articles were also searched to retrieve linked articles. The searches identified a total of 1,828 articles from which a total of 47 full texts relevant to the objectives of this dissertation were critically reviewed. These materials were of considerable clinical, methodological and statistical heterogeneity. The investigator also constantly interacted with three experts in the field of NSS and schizophrenia to identify grey literature; Oye Gureje (University of Ibadan), Robin Emsley (Stellenbosch University), and Paola Dazzan (Institute of Psychiatry, London).

2.0. WHAT IS SCHIZOPHRENIA?

Schizophrenia is a severe psychotic syndrome with a common onset in early adolescence, but with evidence of difficulties with psycho-social adjustment in early or late childhood in many cases. It is characterized by delusions which may be bizarre, auditory hallucinations, thought disorders, strange behaviour and progressive deterioration of personal, social and occupational functioning. These features characteristically occur in clear consciousness. They represent abnormalities in multiple functional domains, creating a complex mixture of psychological and physical signs and symptoms. Thus, there have been several attempts to simplify this heterogeneous group of symptoms into clinically meaningful sub-divisions.

The concept of 'positive and negative' symptoms was first described by Hughling Jackson using his experience in the treatment of patients with epilepsy. The fundamentals of Jackson's description were adopted by Andreasen and Olson to sub-divide patients with schizophrenia into positive: representing those with an increase in normal function or the presence of abnormal function, and negative: representing patients with a reduction or absence of normal function (Andreasen and Olson, 1982). Positive symptoms of schizophrenia are now known to include hallucinations, delusions, bizarre behaviour, formal thought disorders and inappropriate affect while symptoms such as flattened affect, alogia, avolition, anhedonia and inattention are generally classified as negative symptoms. This subdivision has considerable clinical utility. Positive symptoms respond better to

available antipsychotic medications, whereas negative symptoms respond less to both conventional and second generation antipsychotics. This categorical approach to schizophrenia psychopathology has influenced several subsequent attempt to simplify these symptoms such as those of Crows types one (predominantly positive) and two (predominantly negative) (Crow, 1985), and the deficit/ non-deficit sub-typification (Carpenter, 1988). Dimensional approaches to schizophrenia psychopathology have employed factor analyses to group symptoms that aggregate together statistically as forming independent syndromes. The three dimensions solution which include reality distortion, psychomotor poverty, and disorganization syndromes was proposed in the reports of some early factor analyses (Andreasen and Grove, 1986., Kay et al, 1987), while more recent factor analyses of the Positive and Negative Syndrome Scale (PANSS) has generated up to five or more dimensions of schizophrenia psychopathology (Wolthaus et al, 2000., Emsley et al, 2003., Serreti and Olgiatti, 2004., van de Gaag et al, 2006).

2.1. EPIDEMIOLOGY OF SCHIZOPHRENIA

Schizophrenia is found in all societies and geographical areas around the world. Its incidence has often been quoted as roughly equal worldwide, a notion that is now a central tenet in the epidemiology of schizophrenia. This notion became very popular after the publication of the findings in 1986 of the World Health Organisation (WHO) determinant of outcome study (Sartorius et al, 1986), an influential transnational study covering 12 sites in 10 different countries. However, some recent data are now challenging the similar incidence notion. For instance a systematic review of the incidence rate of schizophrenia

from 33 countries found a five-/fold variation in the incidence of schizophrenia between sites (McGrath et al, 2004).

Individuals who are born or raised in an urban location are known to have at least a two-fold increase in the risk of developing schizophrenia compared with those born or raised in rural areas (Kirkbride et al, 2006). In fact, urban birth has been shown to account for about 30% of the population attributable risks of schizophrenia (Mortensen and Pedersen, 2001). The difference in incidence between urban and rural locations has previously been attributed to social drift, where affected or vulnerable individuals lose their means of livelihood and drift to poorer inner city areas. Other reports also suggest that an artefact during selective migration may be responsible for rural/urban differences (Mortensen, 2000). However, more recent evidence suggests that the increased incidence of schizophrenia in urban centres is related to the degree of urbanization (Pedersen and Mortensen, 2006). Fluctuations in schizophrenia incidence have also been reported over many decades. For instance, Boydell et al. (Boydell et al, 2003) reported a large increase in Camberwell between 1965 and 1997 using case record analysis. The changing structure of the population may however account for some of the changes seen in the incidence rates over time. There is also a 3-5 fold increase in the incidence of schizophrenia among some migrant populations compared to the general population (Cantor-Grae and Selten, 2005). The magnitude of this risk has been found to be significantly greater among the second generation of these migrant groups (Selten et al, 2007). Some authors have aggregated evidence for a 'country of origin' hypothesis, which suggest immigrants carry an excess risk of schizophrenia from their countries of origin. However, this has been

challenged by findings that the incidence rates of schizophrenia in Caribbean countries is similar to those found among indigenous United Kingdom population (Hickling and Rogers-Johnson, 1995). Similarly, there is no consistent evidence for selective immigration as part of a pre-psychotic segregation (Selten et al, 2001). Immigrant population certainly experience considerable social disadvantages, discrimination, and other difficulties related to the ongoing process of acculturation (Veling et al, 2007). This chronic process may find relevance within the stress- diathesis model of the aetiology of psychosis. A small relative risk of schizophrenia during winter or spring birth has often been reported since the 1920s (Davies et al, 2003). This risk remains even in the southern hemisphere where winter is between June and July, although most birth are also known to occur during these seasons (Boyd et al, 1986). The male to female incidence of schizophrenia is now estimated to be about 1.4:1, with more males being diagnosed with the disease (Mcgrath et al, 2004).

A systematic review of the prevalence of schizophrenia by Saha et al (Saha et al, 2005), based on 136 prevalence estimates derived from 85 studies found a four to seven fold variation in the prevalence of schizophrenia between sites. The median prevalence is estimated 4.6/1000 for point prevalence, 3.3 per 1000 for period prevalence and 4.0 per 1000 for lifetime prevalence (Saha et al 2005). This is slightly different from the 1.0% quoted in many influential studies, as well as the DSM IV diagnostic manual (American Psychiatric Association, 1994). Saha et al, (Saha et al, 2005) also reported that the prevalence of schizophrenia was significantly higher in developed nations compared to

developing nations. This finding appears to be a corollary of the 'favourable outcome hypothesis', which holds that the outcome of schizophrenia is more favourable in poorer, developing nations in contrast to richer, developed nations (Jablenski et al, 1992., WHO, 1972).

2.2.0. NEUROBIOLOGY OF SCHIZOPHRENIA

The biological processes that are causal in the pathway to the expression of schizophrenia are presently not known. However, evidence for the involvement of biological mechanisms in the onset and progression of the disease presently exists and are quite robust. Specifically, information from genetic studies and other evidence for pre-morbid abnormalities such as obstetric complications, minor physical anomalies, non-progressive structural brain defects, as well as measurable neurological and neuropsychological abnormalities have allowed for an understanding of schizophrenia as disorder of brain development and plasticity.

Genetic factors appear to be important in making an individual vulnerable to schizophrenia. Evidence for this is derived from family, twin and adoption studies. Genetic factors are now known to account for a majority of the liability to schizophrenia, and heritability estimates above 50% have been reported in many studies (Ross et al, 2006). Results from rigorous family studies that employ a narrow criterion in defining schizophrenia such as those of Kendler et al. (Kendler et al, 1993) have shown strong

evidence for familial aggregation of schizophrenia. This is especially so in early onset schizophrenia, which has been shown to have aetiological continuity with late onset schizophrenia (Strandburg et al, 1999). The evidence of familial aggregation of schizophrenia is further supported by twin studies which have shown that the risk of schizophrenia in the co-twins of a schizophrenia proband is much higher in monozygotic than dizygotic twins (Cannon et al, 1998). Twin studies are based on the assumption that monozygotic and dizygotic twins share approximately the same environment, but while monozygotic twins share similar genetic properties, dizygotic twins share only about half of their genetic materials. Furthermore, some adoption studies done to exclude the influence of environmental factors in the heritability of schizophrenia have also reported that about 10% of the off-springs of schizophrenia patients who are adopted by non schizophrenia parents develop the disease, whereas there is no increase in schizophrenia among the off-springs of the healthy individuals adopted by schizophrenia parents (Kety et al, 1994). However, the pattern of the risk for the transmission of schizophrenia in the different types of family studies suggests that the inheritance of schizophrenia cannot be explained exclusively by a single gene effect. Inheritance of the disease is more likely the result of the combined effect of several genes interacting with each other. Consistent with this view is the reports of several studies that have identified significant linkages of schizophrenia inheritance to different chromosomal regions, especially 6p24-22 (HLA locus), 8p12-21 (neuregulin gene), as well as the gene deletion on 22q responsible for the Velocardiofacial syndrome which is associated with schizophrenia in 30% of subjects (Waterwort et al, 2002., Ross et al, 2006). It is noteworthy that none of the identified chromosomal regions have been replicated consistently in the different studies and none

have also been able to completely explain the contribution of these linkage regions to the biology of schizophrenia. Similarly, a recent genome wide study investigating the role of genetic variation in schizophrenia through mega-analysis of 17 separate large scale studies found significant associations with 7 loci, only 2 of which represented replications of previously identified loci (Ripke et al, 2011). There are good reasons to believe that some rare de novo mutations with protein altering potentials may have important roles in the pathogenesis of schizophrenia. This is because a large percentage of schizophrenia patients have no family history of the disease (Lichtenstein et al, 2009). Moreover, de novo mutations in several genes including the mutation in the DGCR2 gene located on 22q region have been identified (Xu et al, 2011).

Biochemical systems are important in the normal physiology of the brain as they are for other organ systems in the human body. This has naturally led to the conceptualization of schizophrenia as a disorder resulting from disruptions in the biochemistry of the human brain. Many different biochemical theories have been proposed in the effort to unravel the aetiology and processes of schizophrenia. However, the most popular, and probably the most plausible of the biochemical theories is the dopamine theory. It suggests that schizophrenia is due to a functional increase of dopamine at the post-synaptic receptors in the meso-limbic and cortical brain regions. This theory emerges from the observation that drugs such as amphetamines, cocaine or levodopa which are known to increase activities in the dopamine systems are also able to induce schizophrenia-like symptoms, whereas drugs that are capable of blocking post synaptic dopamine receptors reduce many symptoms of the disease (Lierberman et al, 1987). Additional evidence for the dopamine

theory is derived from functional neuro-imaging findings of increased dopamine receptors and binding in antipsychotic naïve patients (Breier et al, 1997), as well as post-mortem evidence of increased concentration of dopamine receptors in the brain tissues of schizophrenia subjects (Mackey et al, 1982., Roberts et al, 1996). The body of evidence on which this theory relied on appeared compelling in the early days of its development. However, it only partly explains the schizophrenia process, especially the psychopathology and treatment of positive symptoms (Kirkpatric et al, 2001). The validity of the dopamine theory in its original form has been challenged by the presence of evidence from contemporary genetic, epigenetic and neuro-imaging studies. Some further revisions of the dopamine hypothesis propose that positive symptoms emerge as a result of sub-cortical hyper-dopaminergia, while negative symptoms occur as a result of hypo-dopaminergia in the frontal lobes (Davies et al, 1991). The most recent evidence on the involvement of dopamine in the process of schizophrenia suggests that dopamine dysregulation has an indirect relationship with the disease. In this proposition, dopamine dysregulation results in psychosis in general, and a diagnosis of schizophrenia emerges from a combination of the dysregulation and other biological and psycho-social factors (Howes and Kapur, 2009). Other neurotransmitters that are thought to be involved in the neurobiology of schizophrenia include serotonin, acetylcholine, and Gamma amino-butyric acid (GABA).

Some of the supportive arguments for the contribution of neural mechanisms in the process of schizophrenia come from evidence of structural abnormalities in several areas of the brain of patients with the disease. It has been argued that the structural abnormalities also affect the functioning of neuronal circuits and therefore the balance of the neurotransmitters associated with such systems. Patients with schizophrenia exhibit widespread volumetric reduction and underlying cyto-architectural abnormalities in the cortical grey matter, as well as several sub-cortical structures involved in cortico-limbic, cortico-basal and integrative functions of the brain (Flaun et al,1995., Sedval, 1990., Sun et al, 2009). A process sometimes referred to as 'cognitive dysmetria' (Andreasen et al, 1998., Shroder and Heuser, 2008). Schizophrenia patients also have an increased frequency of cranio-facial and dermatoglyphic minor physical anomalies (Mellor,1992., Gabalda and Compton, 2010)

These abnormalities are present pre-morbidly and appear to be stable and non-progressive (James et al, 2002., Serene et al, 2007). Subtle neuro-cognitive impairments are also known to be present in schizophrenia patients before the onset of florid psychotic symptoms (Frommann et al, 2011). Rates of similar cognitive changes have been demonstrated to be higher than expected in family members of patients than in the general population (Montag et al, 2012). Furthermore, non-specific neurological soft signs (NSS) have been demonstrated in over 50% of patients with schizophrenia (Heinrich and Buchanan, 1989., Browne et al, 2000., Shibre et al, 2002., Scheffer et al, 2005., Bombin et al, 2005). The fact of the presence of these abnormalities pre-morbidly (Chen et al, 2005., Serene et al, 2007., Chan and Gottessman, 2008), their relative stability over the course of

schizophrenia (Prikryl et al, 2012., Piccioni and Dazzan, 2009., Boks et al, 2006., Emsley et al, 2005., Bachman et al, 2005., Scheffer, 2004), as well as their presence in excess in non-affected but vulnerable individuals (such as family members of patients) (Gourion et al, 2003., Neelam et al, 2011) or other high risk groups (Keshavan et al, 2008., Kaczorowski et al, 2009, Chan et al, 2010), has led to the supposition that these abnormalities may represent an intermediate phenotypic marker for schizophrenia (Gottesman and Gould, 2003).

2.2.1. ENDOPHENOTYPES OF SCHIZOPHRENIA

The term endophenotypes was coined by Gottesman and Shields in 1973, to represent an unseen but measurable phenomenon that is present in the distal genotype to a disease pathway (Gottesman and Shields, 1973). They are now more clearly defined as trait-markers that are present independent of the manifestation of the relevant disease, or otherwise, represent a phenotype in the patient below the level of overt clinical symptoms. Endophenotypes may be in the form of biochemical, neuro-imaging, electrophysiological, pathological, neuro-psychological, or socio-functional markers. Gottesman and Goulds (Gottesman and Goulds, 2003) suggested that certain criteria are required to be satisfied by an identified disease marker to be described as an endophenotype. These criteria are: 1) Association with a candidate gene or region, 2) presence in relatives of patients with a high relative risk, thus co-segregating with actual illness, 3) the association with the disease should be biologically plausible, 4) expression of the parameter should be independent of the disease, and hence a trait marker rather than a state marker, 5)

inheritability of the parameter, and 6) the marker is present in relatives of patients more than the general population (Gottesman and Gould, 2003).

Endophenotypes have been shown to be more closely related to the underlying gene expression in mental disorders than is psychopathology (Meyer-Lindenberg and Weinberger, 2006).They therefore find relevance in the study of the genetics of schizophrenia. It is anticipated that the genetics of a heterogeneous and inherently complex condition like schizophrenia can be studied easily if it is broken down into its constituent endophenotypes. Working memory deficits, information processing defects such as pre-pulse inhibition, smooth pursuit eye movement defects, glial cell changes and other specific putative neuro-cognitive markers are recognized endophenotypes of schizophrenia.

There is an increasing interest in the status of Neurological Soft Signs (NSS) of schizophrenia as potential endophenotype of the disease. This is because NSS are more common in patients than in healthy controls and have been shown to occur independently of the overt clinical or psychopathological manifestation of schizophrenia (Chan and Gottesman, 2008). They also predate its onset (Chen et al, 2005). Furthermore, there is evidence to suggest that NSS are neuro-developmental in origin (Zabala et al, 2006., Peralta et al, 2011) and demonstrate significant heritability (Sanders et al, 2006). Neurological soft signs thus meet a minimum of two of the criteria spelt out by Gottesman and Shield for categorization as endophenotypes.

2.3.0. THE CONCEPT OF NEUROLOGICAL SOFT SIGNS (NSS)

Neurological Soft Signs (NSS) are subtle but observable neurological abnormalities that are not localized to specific areas of the brain or characteristic of any specific neurological condition. They include impairments in motor function, sensory integration, and persistence of primitive reflexes. These signs are documented to be in excess in schizophrenia patients at various stages of the disease (Heinrich and Buchanan, 1989., Browne et al, 2000., Shibre et al, 2002., Scheffer et al, 2005., Bombin et al, 2005), and especially among first episode antipsychotic naive schizophrenia patients (Browne et al, 2000., Shibre et al, 2002., Scheffer et al, 2004) and their unaffected first degree relatives (Gourion et al, 2003., Neelam et al, 2011).

The term ‘soft signs’ was first used by Bender in 1947 while describing physical examination findings which were thought to represent evidence for a non-specific neurological disease (Bender, 1947). It emerges from the inability of clinicians in those early days to locate the neuro-pathological underpinnings and the specific clinical relevance of such neurological examination abnormalities. Traditional neurological examination aims to elicit gross signs that often indicate a demonstrable lesion in the nervous system. Such signs as visual field defects or hypotonia can often be traced to specific malfunctioning of the brain. These signs are thus conceptualized as hard signs in view of their specificity in identifying neuropathology. Neurological soft signs on the other hand feature in individuals with no obvious neuropathology. No observable

compromise in neurological functioning is identifiable in such individuals. Most of the signs suggests a decrement of the individual's performance abilities in motor or sensory tests of a neurological examination and offer little usefulness in localising any gross lesion. They have been thought of by some researchers as indicators of diffuse brain damage (Gureje, 1988).

Categorisation of neurological signs as hard or soft may not always be straightforward because some of the so called ‘soft signs’ are also seen in specific brain pathology while some of the ‘hard signs’ do not always have localising value on their own. For example, signs such as fist-edge palm or the fist-ring require integration of the sensory and motor systems, and are therefore soft, but are also present in frontal lobe damage where it becomes a specific sign of this pathology. Similarly, tandem walk or finger to nose tests reflect impaired sensory and motor integration, but also represent specific signs of focal cerebellar damage.

Table 1. Some Hard and Soft Signs on Neurological Assessment Batteries

Hard Signs	**Soft Signs**
Gait deviation	Blink reflex
Whole body clumsiness	Gaze impersistence
Dysarthria	Ocular vergence
Unilateral reflex hyperactivity	Gaze nystagmus
Unilateral facial weakness	Suck reflex
Unilateral sensory loss	Snout reflex
Unilateral cogwheel rigidity	Oral apraxia
Spastic rigidity	Palmomental test
Hypotonia	Grasp reflex
Pes cavus	Stereognosis
Babinski reflex	Graphaesthesia
Involuntary movements	Diadochokinesia
Intention tremor	Tactile extinction
Postural tremor	Complex motor acts
Resting tremor	Rythm tapping
Choreiform movements	Motor perseveration
Athetotiform movements	

2.3.1. HISTORICAL PERSPECTIVES OF NSS

Historically, the 1896 re-conceptualization of Augustin Morel's demence preacose into what is now known as schizophrenia provided an understanding of the disorder as one with an early onset and a deteriorating course, which differentiated schizophrenia from the more episodic and better outcome characteristic of manic depressive disorder. This development also provided the earliest insight into the biological underpinnings of the disease. Emil Kraepelin described how partial damage or destruction of cells in the cerebral cortex may be compensated for, but "mostly led to a permanent impairment in the inner life of patients with dementia praecox" (Kraepelin, 1899). Thus his classic description of dementia praecox included such neurological examination findings as headaches, pupillary disorders, abnormal tendon reflexes, muscular movements, seizures, grimacing and aphasia. The exact relationship of these findings to dementia preacox was neither known to Kreapelin nor his contemporaries (Kraepelin, 1919). This may have contributed to the decline in interest in neurological examination abnormalities in psychiatric disorders witnessed in the better part of the 20th century. However, the concept of *woodteriness* (clumsiness) described in child and adolescent psychiatry reawakened interest into the phenomenon of neurological examination abnormalities in schizophrenia. Thus studies in adult psychiatry emerged (Rochford et al, 1970., Mosher et al 1971) and have increased in volume in the last 40 years.

2.3.2. EVOLUTION OF PSYCHIATRIC RESEARCH INTO NSS

In the 1980s, research interest in adult NSS grew significantly after associations were noted with both clinical outcome and neuropsychological correlates in schizophrenia (Liddle, 1987., Manshreck et al, 1982., Torey, 1980). Further research findings suggested that the prevalence of NSS in relatives of patients with schizophrenia was increased (Woods et al, 1986., Kinney et al, 1986). This discovery led to a surge in interest in NSS and it was hoped they would provide a trait marker for schizophrenia. As research into NSS flourished, the quality of these studies also improved greatly and more systematic and better validated means of assessment were introduced (Buchanan and Heinrichs, 1989., Chen et al, 1995).

The extensive studies of NSS also demonstrated the presence of these signs in numerous other conditions such as alcoholism, substance abuse, mood disorders, obscessive-compulsive disorder, neuroticism and personality disorders. Although this was to a lesser degree compared to schizophrenia. Also the body of research into the prevalence of NSS in these other neuropsychiatric conditions is much smaller, and limited by small sample sizes. It became apparent that a majority of the schizophrenia studies did not find a correlation between NSS and clinical outcome, and the specificity of the signs for schizophrenia thus appeared low. Therefore, the clinical usefulness of NSS seemed limited. This also led to some disappointment amongst many researchers who had hoped that NSS would provide the trait marker for schizophrenia. Interest in NSS research waned

as a result of this disappointment. In fact, some researchers held the subject in contempt for many years, doubting whether these signs can be defined with rigour, are reliable, reproducible or even have neurological meaning. Others have even described the use of the term soft signs as diagnostic of soft thinking (Ingram et al, 1973).

Research interest has re-emerged with the emergence of large scale fourth generation psychiatric epidemiological studies dealing with psychiatric genetics and a comprehensive set of biological markers including brain imaging, blood sampling and cerebrospinal fluid examinations. Advances in brain imaging have stimulated effort to characterize the neuropathology of schizophrenia, with an attendant interest in the neurology of schizophrenia. These studies have described the doubt on the meaning of NSS as "reflecting not the unreality of findings but the limitation in our knowledge" (Heinrich and Buchanan, 1989., Zhao et al, 2013).

2.3.3. NEUROBIOLOGY OF NSS

Although the origin of NSS is uncertain, these signs probably predate the onset of schizophrenia (Chen et al,2005., Chan and Gottesman, 2008., Serene et al, 2007),and are at least in part related to the pathogenetic process underlying the disease (Andreasen et al, 1998., Schroder and Heuser, 2008). Studies in children at genetic risk of schizophrenia (Walker and O'brien, 1999., Walker and Levine, 1990., Cannon et al, 1999., Prasad et al, 2009) and the general population (Schubert and McNeil, 2004., Crow et al, 1995., Jones

et al, 1994) have found evidence for an association of early disturbances in motor development and fine motor co-ordination with schizophrenia in adulthood. For instance, a review of the school records of 400 individuals with schizophrenia by Cannon et al. (Cannon et al, 1999) showed that these subjects performed significantly worse than a group of controls in activities requiring motor coordination. Also, from the observation of home videos recorded during the first 2 years of life of children who later developed schizophrenia, Walker and Levine (Walker and Levine, 1990) described the presence of neuro-motor abnormalities particularly localised to the left side of the body. Therefore, impairment of coordination, motor dysfunction and sensory integration has been observed in non-psychotic individuals at increased genetic risk of developing schizophrenia. This suggests that NSS could be part of a genetic vulnerability to the illness. Further support of this proposition come from studies documenting NSS among adults with high and ultra high risk of developing schizophrenia but who have not yet manifested the clinical symptoms of psychosis (Schubert and McNeil, 2005., Kaczorowski et al, 2009., Chan et al, 2010 a and b., Keshavan et al, 2008).

It has been confirmed by several systematic reviews and meta-analysis that NSS are distributed across people with schizophrenia and their first-degree relatives in a manner that is consistent with familial association (Gourion et al, 2003., Neelam et al, 2011). Neelam and others, (Neelam et al, 2011) in a systematic review of seven studies, with at least 1553 participants, carrying out a three way comparison of levels of NSS between people with schizophrenia or schizophrenia-like disorders, their first-degree relatives, and normal controls reported that NSS were significantly more common in first-degree

relatives of people with schizophrenia than in controls (pooled standardised mean difference (SMD) 1.24, 95% confidence interval (C.I) 0.59-1.89). The same review also showed that NSS were significantly more common in people with schizophrenia than in their first-degree relatives (SMD 0.92, 95% C.I 0.64- 1.20) (Neelam et al, 2011).

The prevalence of NSS in schizophrenia patients and their relatives is also known to be relatively stable across the course of schizophrenia (Prikryl et al, 2012., Piccioni and Dazzan, 2009., Boks et al, 2006., Emsley et al, 2005., Bachman et al, 2005., Chen et al, 2005., Scheffer, 2004., Mechri et al, 2009) . Emsley et al. (Emsley et al, 2005) conducted a study of temporal stability of NSS in a cohort of largely medication naïve South-African schizophrenia patients. In that study, the NES total score did not change significantly over a one year course of schizophrenia on treatment according to a fixed protocol. The most stable factor overtime was a factor for attention, as it was not influenced by changes in the symptom profile or the effect of antipsychotic medication. Significant changes were observed in the motor sequencing factor score at 3 months compared to baseline scores, but this factor remained stable at 6 through 12 months in the same study. Therefore, the authors argued that this characteristic may be specific to some individuals with schizophrenia. This argument was further supported by findings from a study by Keshavan et al. (Keshavan et al, 2003) that attentional factors correlated strongly with smaller volumes of the left heteromodal cortex. Another study by Mechri et al. (Mechri et al, 2009) using data from two independently replicated studies, also found that the prevalence of NSS in patients with schizophrenia and their relatives remained stable and was

independent of geographical origin, ethnicity, or socio-economic status. There is also evidence to suggest that NSS are more prevalent in schizophrenia spectrum disorders compared to other psychiatric disorders (Cuesta et al, 2002., Chan and Gottessman, 2008). This fact has also been demonstrated among subjects with schizotypal personality scores (Mechri et al, 2010., Chan et al, 2010a and b., Kaczorowski et al, 2009., Keshavan et al, 2008).

This body of evidence suggests that NSS are associated with genetic loading almost to a dose-response pattern, making it a trait feature of schizophrenia. Further evidence for the possible heritability of NSS comes from a study that examined 96 participants from eight extended families. In this study, Sanders and his colleagues, (Sanders et al, 2006) found that five of eleven NSS items were statistically significant in terms of hereditability h^2: rapid alternating movements (h^2=0.99 ± 0.19 for completion time), alternating fist-palm (h^2 =0.77 ± 0.19 for completion time and h^2=0.7 ± 0.32 for number of errors), fist-ring (h^2 =0.53 ± 0.23 for right-sided completion time;h^2=0.7 ± 0.21 for left-sided completion time), go-no go (h^2 =0.93 ± 0.33 for the number of correct responses), and audio-visual integration (h^2=0.79 ± 0.54 for the number of correct responses (Sanders et al, 2006). However, it is noteworthy that among all the studies investigating the relationship between NSS in schizophrenia patients, their relatives and healthy controls, at least 3 (i.e, Egan et al, 2001., Bollini et al, 2007., Compton et al, 2007) did not find any difference between relatives of patients with schizophrenia and healthy controls. Furthermore, Piccioni et al. (Piccioni et al, 2006) observed no difference in NSS between the non-schizophrenia co-twins from monozygotic and dizygotic discordant pairs.

Additional evidence for the neuro-developmental origin of NSS come from studies that showed that they tend to decrease in frequency as the brain matures. For instance, a study on a small sample of young healthy adolescents with first episode schizophrenia and a control group of non-schizophrenia patients, Zabala and his colleagues (Zabala et al, 2006) found an inverse correlation of NSS scores with age among the healthy adolescents, a trend for inverse correlation among non-schizophrenia patients and no correlation with age among the schizophrenia patients was observed. Specifically, it has been suggested that NSS represent abnormalities of neural integration (Chan et al, 2009., Zhao et al, 2013., Gay et al, 2012). It has been reported previously that neural integration and neuronal maturity are likely to be impaired among those at genetic risk for developing schizophrenia (Zabala et al., 2006., Andreasen et al, 1998., Schroder and Heuser, 2008). This may lead to an increase in the frequency of NSS in this population. Furthermore, some authors have linked NSS with a history of obstetric complications (Gureje, 1988., Madsen et al, 1999., Peralta et al, 2011). It is also possible that NSS and the pathophysiology of schizophrenia may share a common genetic background that affects the neuro-developmental process. However, no specific genetic variant has been associated with NSS (Prasad et al 2009). It is also possible that genetic risks only partly determine the presence or severity of NSS.

2.3.4. STRUCTURAL BRAIN CORELLATES OF NSS

Several structural brain abnormalities have long been described in psychotic disorders. Similarly, there is robust evidence to suggest that certain NSS correlate with region-specific structural brain deficits in people with schizophrenia. Rubin et al. (Rubin et al, 1994) in a study using computerised tomography (CT), and also measuring cerebral blood flow among patients with first hospitalisation on account schizophrenia or schizophreniform disorder compared with normal controls, had concluded that NSS correlated significantly with sulcal enlargement and reduced cerebral volume but not ventricular enlargement. This study was based on the manual, labour intensive Region of Interest (ROI) method which reduces the analyses to a few pre-selected brain regions. Almost a decade later, other authors investigating the structural brain correlates of NSS using advanced techniques such as the optimized Voxel Based Morphometry (VBM), an imaging techniques which allows for automated and unbiased image analysis, have suggested an association between some NSS factors, and volumetric reduction in areas of the basal ganglia (Hirjak et al, 2013., Ballmaier et al, 2008., Mamah et al, 2007., Keshavan et al, 2003., Jansen et al, 2009., Dazzan et al, 2004., Venkatasubramanian et al, 2008), areas that form part of the prefrontal (Gay et al, 2012., Chan et al, 2009), as well as the superior and inferior temporal cortices (Zhao et al, 2013)

The basal ganglia motor system comprises of the caudate nucleus, which receives cortical projections from motor areas in the frontal lobe, as well as the putamen, globus pallidus and substantia nigra, which receives the information from the caudate. A reduction in the right and left caudate nuclei volume have been associated with increased minor motor and cognitive neurological abnormalities, as measured by the NES, in adults with first-episode psychosis (Keshavan et al, 2003., Jansen et al, 2009., Thormann et al, 2009). However, enlarged caudate volumes have also been reported, albeit in people with chronic schizophrenia, this enlargement has been proposed to occur as a result of treatment with first-generation but not second generation antipsychotics (Corson et al, 1999). The pre-frontal cortex is an area involved in motor planning and working memory. It also has an important role in the control of sensory conflicts (Kelly et al, 2009, Chan et al, 2009). Specific neurological examination tasks based on sequencing of motor acts, or those requiring planning of motor acts, as well as its storage in working memory have been correlated with regional sulcation of the left dorso-lateral pre-frontal cortex in recent exploratory regional analyses of cortical morphology in patients with first episode schizophrenia (Gay et al, 2012).

Some studies using Magnetic Resonance Imaging (MRI) technique have also found association between volumetric changes in the cerebella cortex and some NSS dimensions (Thormann et al, 2009a and b., Bottmer et al, 2005). The cerebellum is closely involved in involuntary movements and motor co-ordination (Giuseppe et al, 2007). Smaller volume

of this structure have been reported to significantly correlate with both high total NSS scores, and motor sub-scores for tasks such as finger tapping, and right left extinction (Mouchet-Mages et al, 2011., Giuseppe et al, 2007). The study by Bottmer et al. (Bottmer et al, 2005) found that smaller cerebella volume in the right hemisphere is associated with NSS in remitted first-episode psychosis patients. Similar changes were also found in patients with chronic schizophrenia who had abnormalities in specific tests of rhythmic tapping and disruptions in motion while performing the finger-thumb opposition tests (Bersani et al, 2007).

Among the studies investigating the relationship between NSS and structural brain changes, Venkatasubramanian et al (2008) is one of the few reporting a negative correlation between at least some NSS dimensions (e.g, the motor sequencing signs) and total or regional grey matter volumes.

The specific neuro-anatomical correlates of severity of NSS have also been localized. Severity of sensory integration signs have been shown to be associated with reduction in the volume of the anterior part of the thalamus, after voxel-based morphometry, and reduction of total thalamic volume after segmentation of the thalamus (Jansen et al, 2009). In adults with first-episode psychosis, decreased volumes of the basal ganglia structures, especially the putamen, thalamus, and heteromodal cortex have been associated with increased severity of NSS (Dazzan et al, 2006, Thorman et al, 2009a and b., Venkatasubramanian et al, 2008). It is noteworthy that a decrease in thalamic volume has

been associated with both chronic schizophrenia and a genetic predisposition to schizophrenia (Konick et al, 2001, Lawrie et al, 2001).

These structural changes have led to the hypothesis that the presence of neurological abnormalities is associated with reduction in frontal and temporal association brain areas, and of sub-cortical brain structures such as the basal ganglia which are involved in the sequencing and integration of both motor and sensory processes, which are manifested in the symptoms of schizophrenia (Andreasen et al, 1998., Shroder and Heuser, 2008., Dazzan et al 2006). Furthermore, it appears that the assumption that NSS are abnormalities with non-focal neural representation now warrant a revision in the light of over-whelming evidence of identifiable structural correlate.

2.3.5. BRAIN MECHANISMS OF NSS

The dysfunctional networks involved in the pathogenesis of NSS are still not fully understood. Earlier studies had advocated that they emerge from deficits at sub-cortical levels, in such structures as the basal ganglia, the limbic systems, or the brain stem (Mosher et al, 1971). It has also been suggested that they reflect failure of integration between or within sensory and motor systems (Griffith et al, 1998). However, NSS may ultimately reflect the same impairment in inter-neuronal connectivity described in the pathophysiology of schizophrenia (Andreasen et al, 1998., Schroder and Heuser, 2008). This notion is supported by evidence from neuro-imaging studies suggesting that there is

an association between NSS and activation changes in the sensori-motor cortex and the supplementary motor area as well as their cerebella and sub-cortical afferents such as the basal ganglia and thalamus (Keshavan, 2003., Zhao et al, 2013., Mouchet-Mages et al, 2011., Hirjak et al, 2013). These structures are known to be involved in sensory integration and motor coordination (Giuseppe et al, 2007., Kelly et al, 2009., Chan et al, 2009., Dazzan et al 2006). Also, the presence of NSS has been associated with reduction in frontal and temporal association brain areas (Gay et al, 2012., Dazzan et al, 2004). Another support for the integrative hypothesis is found in the summation of Jansen and colleagues that since the thalamus functions as a central relay station of the brain, which filters and gates sensory inputs to the cerebral cortex, and since sensory integration functions, such as audiovisual integration and stereognosis, require transfer of sensory information from sub-cortical regions to multimodal cortical brain areas, structural impairment of the thalamus would appear to affect this transfer and consequently decrease performance in the sensory integration tasks (Jansen et al, 2009).

TABLE 2: MAJOR FUNCTIONAL AREAS OF THE CORTEX AND THEIR LOCATION

FUNCTIONAL DESIGNATION	LOBE	SPECIFIC LOCATION
Primary Sensory Cortex		
-Somatosensory	Parietal	Postcentral gyrus
-Visual	Occipital	Banks of calcarine fissure
-Auditory	Temporal	Heschl's gyrus
Unimodal Sensory Association Areas		
-Somatosensory	Parietal	Posterior parietal
-Visual	Occipito-temporal	Inferio-lateral surfaces of the occipital and temporal lobes
-Auditory	Temporal	Superior temporal gyrus
Multimodal Sensory Association Areas		
-Posterior multimodal sensory integration (including visuospatial localization, language, attention)	Parieto-temporal	Junction between lobes
-Anterior multimodal motor integration (including motor planning, language production, judgement)	Frontal	Prefrontal cortex, rostral to premotor areas on dorsal and lateral surfaces
-Limbic (emotion, memory)	Temporal, parietal, frontal	Cingulate gyrus, hippocampal formation, parahippocampal gyrus, amygdale
Motor association cortex		
-Premotor (motor preparation and programs)	Frontal	Rostral to primary motor cortex
Primary motor cortex		
-Motor cortex (Movement of a joint along a vector)	Frontal	Precentral gyrus

Adapted from; DAZZAN P and MURRAY R.M (2002)

Figure I. Structure of the Basal ganglia

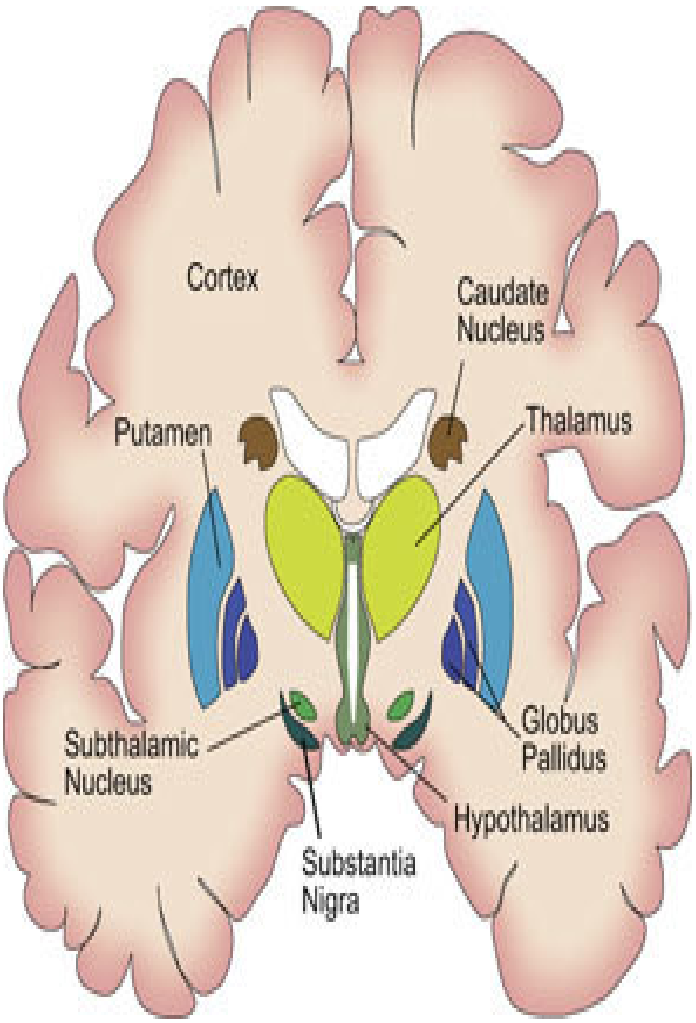

Image adapted from: Sukel Kayt. Basal Ganglia Contribute to Learning, but Also Certain Disorders. Dana. Org/ Brain work

Figure II. Connections of the Basal Ganglia

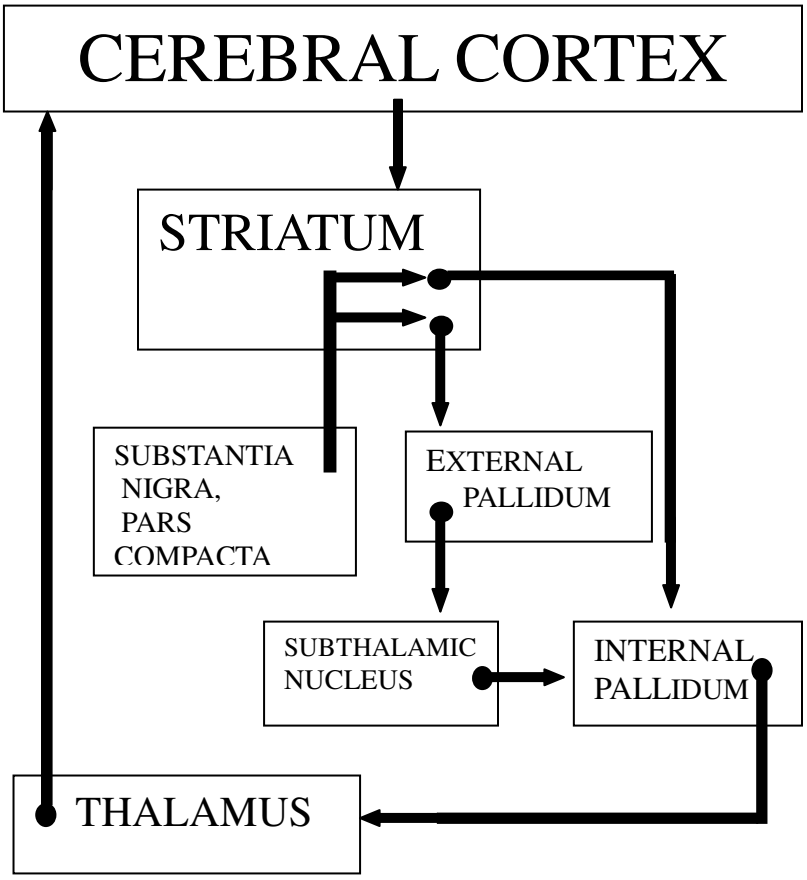

Image adapted from: Anatomy 530 lecture notes, The University of Western Ontario Department of Anatomy and Cell Biologyhttp://www.uwo.ca/anatomy/grad/531a/531a.html

2.4.0. NEUROLOGICAL SOFT SIGNS IN SCHIZOPHRENIA

2.4.1. PREVALENCE

The prevalence of Neurological Soft Signs (NSS) in schizophrenia, their unaffected relatives, and normal healthy controls has been a central issue in most of the studies on the subject in the last 40 years. A majority of studies report a prevalence of 50 -65% in all patients with schizophrenia, compared to about 5% in normal healthy controls (Heinrich and Buchanan, 1989., Shibre et al, 2002., Bombin et al, 2005., Chan and Chen, 2007). Among first episode patients,, at least one frontal sign out of a list consisting of the Ozereski test, tapping test, fist-ring test, fist-edge-palm test, piano test, and completion of two sequential drawings, has been described in 97.1%.(Cuesta et al,1996., Browne et al, 2000., Whitty et al, 2003). Other studies of first episode schizophrenia patients have also reported similarly high rates (Lawrie et al, 2001., Keshavan et al, 2003., Dazzan et al, 2004), even when a higher cut-off point for abnormality was used (Zabala et al, 2006., Ismail et al, 1998). Ismail and colleagues (Ismail et al, 1998) demonstrated that NSS had a better ability to differentiate between schizophrenia and healthy control. The authors used a standardized neurological assessment tool consisting of 44 items, the sum of which produced a score ranging from 0-24. They found that a score of at least 5 was present in at least 82% of patients with schizophrenia, while it was only found in 5% of healthy controls.

Neurological soft signs have also been reported in other psychiatric disorders especially bipolar mood disorders (Boks et al, 2000., 2004., Dazzan et al, 2008., Goswani et al, 2006., Negash et al, 2004.,Whitty et al, 2006), obsessive –compulsive disorders (Peng et al, 2012., Stein et al, 1994), and impulsive personality disorders (Stein et al, 1993). A review of relevant studies of NSS in schizophrenia and mood disorders published between 1966 and 1998 was conducted by Boks and colleagues (Boks et al, 2000). The review focused on three diagnostic groups of schizophrenia spectrum disorders, including schizophrenia, schizophreniform disorder and schizoaffective disorder, mood disorders such as depression and bipolar disorders, as well as healthy control subjects. Only those neurological signs assessed in at least two different studies were included. A total of 258 studies met their eligibility criteria, of these, 17 studies presented data on the prevalence of specified neurological signs in one or more diagnostic groups. In the schizophrenia group the weighted mean prevalence of all 30 signs averaged 19.2%. The weighted mean prevalence of the 17 signs in the mood disorder group averaged 16.4%, but they encompassed a smaller selection. The weighted mean prevalence of 30 neurological signs in the control group was 8.9%. The result suggested the mean prevalence of most neurological signs is significantly different between schizophrenia patients and normal controls, but there were fewer differences between schizophrenia and mood disorders. The authors however noted that the number of patients in the mood disorder group was comparatively smaller than those in the other groups, as such the difference in the mood disorder group and the other groups may not have reached significance due to limited statistical power (Boks et al, 2000). Whitty et al, (Whitty et al, 2006) also did not report

any difference between schizophrenia, bipolar disorder and other psychotic disorders, neither did the recent meta-analysis of both functional and structural Magnetic Resonance Imaging studies of NSS in schizophrenia or mood disorders (Zhao et al, 2013).

In Africa, Mubarak et al. (Mubarak et al, 1999) measured NSS in 30 Egyptian patients with schizophrenia and 15 healthy controls. This study found a significant higher NSS scores in all patients compared with the control group. This applied to both total Neurological Evaluation Scale (NES) scores and scores for its three main components, sensory integrative functions, motor in-coordination, and impaired sequencing of complex motor acts. Also, Shibre et al. (Shibre et al, 2002) reported on the pattern of NSS among 200 treatment naïve schizophrenia patients and 78 healthy subjects in Butajira, a traditional society in Ethiopia. The impairment rate of NSS in the schizophrenia patients in that study was significantly higher than in controls. The authors found that 65% of schizophrenia patients had a score of 2 or more versus 50% of the healthy controls. They further noted that NSS in the treatment naïve schizophrenia cohort was as common as those reported in studies of subjects on neuroleptic medication. However, a controlled study done among a cohort of Nigerian, chronic, admitted and medicated, patients with schizophrenia, affective disorders, and normal control subjects over a decade earlier than those of Mubarak et al (1999) and Shibre et al (2002) found that the two patient groups did not differ from one another in prevalence of four neurological signs, but both showed significant differences from normal control in the occurrence of right-left confusion (Gureje et al 1988).

It is important to highlight the several methodological issues in studies reporting no difference between schizophrenia and other neuro-psychiatric disorders. These include inadequate control for common confounders such as age, educational levels and intelligent quotient, use of different assessment tools for measuring NSS, as well as the combination of bipolar and major depression as a single mood disorder group in many studies. The consensus of opinion from most studies in the literature is that NSS are associated strongly with schizophrenia across cultures and occur at low rates in the general population. Studies done among first episode patients such as Boks et al, (Boks et al, 2004) have shown that some specific NSS items such as mirror movements and smooth saccadic eye movements could differentiate schizophrenia from bipolar disorders or major depressive disorders. Other reports suggest that patients with schizophrenia have more sensory integration and cognitively demanding signs than patients with other psychotic disorders (Keshavan et al, 2003).

Some studies on NSS in patients with schizophrenia that have employed a comprehensive assessment technique have found that motor abnormalities were more discriminative in differentiating patients with schizophrenia and their relatives from healthy subjects (Bombin et al, 2005., Mechri et al, 2009). Specifically, the description of the meaning of NSS by Heinrich and Buchanan (Heinrich and Buchanan, 1989) suggests that such motor sequencing signs better differentiate patients with schizophrenia from those of other psychosis. While Krebs and colleagues concluded that integrative motor functions differentiated patients with schizophrenia from those with mood disorders (Krebs et al,

2000). These assertions reinforce the idea that motor abnormalities are especially genetically mediated (Sanders et al, 2006) and may therefore constitute reliable markers of vulnerability. In factor analyses conducted on the NES, motor sequencing items such as fist-ring test, fist-edge-palm test, and Ozereski test, have been known to load together (Keshavan et al, 2003., Sanders et al, 2000). Factor analysis of the NES conducted by Emsley et al. (Emsley et al, 2005) as part of a study of the temporal stability of NSS in a cohort consisting of 66 mostly medication naïve South-African schizophrenia subjects also found a factor for abnormal motor sequencing. The items of this factor have important overlap with those of Keshavan and her colleagues. In the report by Keshavan et al. (Keshavan et al, 2003) motor sequencing and attention abnormalities were more specific to schizophrenia. This was consistent with those of other contemporary reports on the specificity of NSS in schizophrenia (Delevoye-Turrell et al, 2003., Sullivan et al, 2001). The sequencing of complex motor act NSS have also been reported to be stable across the course of schizophrenia (Mayoral et al, 2012, Bachman et al, 2005), or in individuals with high schizotypy scores (Theleritis et al, 2012) regardless of symptom improvement or reduction in the other clusters of NSS. Impairment of motor sequencing tasks is indicative of problems with initiation and organization of action, activities which requires integration of sensory and motor functions (Piccioni and Dazzan, 2009), and an intact frontal lobe executive function (Bersani et al, 2004., Rao et al, 2008), as well as its basal ganglia connections (Heinrich and Buchanan, 1988., Dazzan and Murray, 2002., Jansen et al, 2009., Bersani et al, 2011) to execute.

2.4.2. NSS AND DEMOGRAPHIC CHARACTERISTICS IN SCHIZOPHRENIA

Available data on the relationship between NSS in patients at various stages of schizophrenia and demographic variables such as age, gender, educational level and ethnicity show conflicting results. For instance, there is no current support for a significant relationship between gender and the presence or severity of NSS among 10 studies reviewed by Hui et al. (Hui et al, 2009). However, there are isolated reports suggesting that NSS is especially increased among male patients with schizophrenia (Heinrich and Buchanan, 1989). Male patients with schizophrenia were also described as having a significant increase in the number of neurological abnormalities 5 years after onset in a follow-up study by Madsen et al. (Madsen et al, 1999). In that sample, males were also more likely to have had obstetric complications and a non-remitting course of illness. It is possible that the excess of obstetric complications and neurological abnormalities in male patients as well as an increased risk of other neurodevelopmental abnormalities are part of a greater vulnerability of the developing male brain to insults.

Some studies have reported a higher prevalence of NSS among African- American subjects when compared to Caucasians, but with very few differences between the prevalence of NSS among Caucasians and Asians (Chen et al, 2003, Mechri et al, 2009). Similarly, another study found that non-Caucasian patients, including African–Americans and other ethnic groups, had more cognitive/perceptual neurological abnormalities (Keshavan et al, 2003). Gureje et al. (Gureje et al, 1988) in a study described earlier also

reported the presence of NSS among a population of Nigerians with a history of obstetric complications.

There are some reports on the relationship between older age and the prevalence of NSS. Chen et al. (Chen et al, 1996) reported that the frequency of NSS increased with age in their sample of patients with schizophrenia. While Emsley et al. (Emsley et al, 2005) found only the motor sequencing factor of the NES correlated with age in a sample of schizophrenia patients with a mean age of 28.1 (SD 8.5) years, and mean duration of illness 371 (SD 787) days ($r=0.333$, $p=0.04$). A systematic review and meta-analysis of 57 eligible studies of NSS in schizophrenia and healthy controls found that effect sizes based on summary measures of NSS decreased in magnitude with increasing age of the samples. The controls were generally older in the studies reviewed. The authors argued that since NSS is known to increase in rates with increasing age in the general population, higher rates in the older control samples may have attenuated the effect found in the younger patient samples (Chan et al, 2009). The same meta-analysis found an inverse relationship between NSS and age in healthy control samples. This clearly contradicts the argument for a relationship between age and NSS. This kind of contradictions in the literature has made the relationship between age and NSS unclear. In fact a majority of the studies that have investigated the relationship between the presence of more NSS and age reports no association (Keshavan et al, 2003., Mohr et al, 2003., Whitty et al, 2003). Furthermore, many of the studies reporting this association appear limited by methodological issues of design, and data analyses. These studies hardly corrected for some of the obvious confounding factors such as duration of illness and doses of medications (Chen et al,

2003., Heinrich and Buchanan, 1989).

Similarly, there is inconclusive evidence for the influence of socio-economic status on the prevalence of NSS. While Griffiths et al. (Griffith et al,1989) reported an inverse correlation between social class and NSS, Gupta et al. (Gupta et al, 1995) found that NSS are not related to socioeconomic status of patients. This finding was later confirmed by Mechri et al. (Mecri et al, 2009) when using data from two independently replicated studies from two different geographical and ethnic population of French Caucasians and Tunisian Arabs. The authors also found no ethnic or geographical differences in the prevalence of NSS, but an inverse correlation between NSS and school levels in both groups was reported (Mechri et al, 2009). The South-African study by Emsley and colleagues (Emsley et al, 2005) described earlier, also found a corellation between educational level and NSS, but this was specific to factors of attention ($r=0.457$, $p=0.005$), and rythmicity ($r=0.337$, $p=0.04$).

2.4.3 NSS AND SCHIZOPHRENIA SYMPTOM DIMENSIONS

An association between Neurological Soft Signs (NSS), or abnormalities in specific neurological domains and some symptom dimensions of schizophrenia may explain which neurological dysfunction is an intrinsic characteristic of the illness. However, studies investigating the relationship between symptom dimensions of schizophrenia and NSS have often yielded inconsistent results. Some studies have suggested that NSS could be

secondary to some psychiatric symptoms, such as impaired attention (Lawrie et al, 2001., Browne et al, 2000), or could characterize more severe psychopathological processes of schizophrenia (Mechri et al, 2009). Others, such as Whitty et al, (Whitty et al, 2006) suggested that NSS was not specific to any of the diagnoses that shares the presence of psychotic symptoms. This is similar to reports from an Ethiopian cohort by Shibre et al. (Shibre et al, 2002) where there were no relationship between NSS and the clinical profile of schizophrenia, such as duration of illness, remission status, positive symptoms, negative symptoms and disorganisation.

However, Malla and his colleagues in a 1997 study that relied on Liddle's three dimensions of schizophrenia found a modest relationship between extrapyramidal factors and psychomotor poverty dimensions in males. They also found a significant relationship between psychomotor poverty in their female subjects and neurological factors reflecting attention and initiative (Malla et al 1997). In more recent studies of this relationship, categorical ratings of Parkinsonisms, motor sequencing, release signs, and indeed total NSS scores have been independently related to deficit syndrome (Peralta et al, 2012) or severe negative symptoms of schizophrenia (Prikryl et al, 2012., Chan et al, 2010a., Chan et al, 2010b., Ruiz-veguella et al, 2008., Bombin et al, 2005., Smit et al, 2012). Other similarly designed studies have also reported that deficit syndrome was significantly related only to sensory integration abnormalities, while hallucination and delusions were not related to any neurological abnormalities (Arango et al, 2000). Moreover, that study (Arango et al, 2000), and many others (Schroder et al, 1996., Mechri et al, 2009., Compton et al, 2007) have found a significant relationship between the disorganization

domain of schizophrenia and global neurological abnormalities, sensory integration deficits, as well as abnormal sequencing of complex motor acts NSS.

However, Bombin et al. (Bombin et al, 2005) suggested that negative symptoms and, less often disorganization, could be correlated to NSS, especially signs of frontal function (motor) and those of parietal function (sensory integration), whereas positive symptoms consistently appear unrelated to NSS. On the other hand, Browne et al. (Browne et al, 2000) described an association between NSS and total symptom severity and positive symptoms. These different results could reflect the complex interrelationship between the NSS and the clinical and therapeutic features of schizophrenia and the possible effect of potential confounding factors.Another possible reason for the inconsistency of these results may be as a result of the different scales used in measuring NSS in the various studies reviewed. For example, some of the studies did not use a scale that included measures for attention and initiative (Flykt et al, 1999). Furthermore, studies reporting an association between more NSS and positive symptoms have also argued that such association reflects attentional deficits created by the presence of florid psychotic symptoms especially in untreated cases (Browne et al, 2000).

2.4.4. NSS AND COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

Cognitive deficits were already described as part of the neurological examination findings in dementia praecox in the classic description of the construct by Emil Krepelin (Kraepelin, 1919). They have been consistently reported in neuropsychological studies of schizophrenia since then (Heinrichs and Zakzanis,1998, Heinrichs, 2005), and therefore recognized as an important feature of the disease. The pattern of cognitive deficits in schizophrenia has been a source of much controversy in the schizophrenia literature. It may involve a broad range of neuropsychological functions, such as attention, abstraction, flexibility, learning and memory (Braff et al, 1991., Blanchard and Neale, 1994). However, some researchers describe a more circumscribed deficit in verbal learning as well as semantic and visual memory in schizophrenia (Saykin et al, 1991., 1994). Yet, other groups describe impairment in specific cognitive functions that are super-imposed on a generalized impairment in both first episode and chronic patients (Albus et al, 1996., 1997).

Neurological soft signs (NSS) have been associated with greater cognitive impairment in schizophrenia, as well as in children at high risk of developing the disease (Chen et al, 2003). Similar to the controversy in the pattern of cognitive deficits in schizophrenia, the pattern of the relationship between NSS and cognitive impairment has also been wiewed differently in the literature. Some studies have demonstrated a positive correlation between NSS and specific impairments in the Raven progressive matrice test or other

measures specifically eliciting impairments in executive functions (Mohr et al, 1996., Wong et al, 1997., Chen et al, 2001). Other authors however report a relationship between NSS and impairments in measure of generalised cognitive deficits such as Intelligent Quotient (I.Q) (Kennard et al, 1960., Mosher et al, 1971), or the Mini-Mental State Examination (Quitkin et al, 1976., Manschrek and Ames, 1984).

Recently, the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) group (Dazzan et al, 2008) investigated the relationship between NSS and generalized as well as specific cognitive deficits in schizophrenia and normal controls. The study reports that while NSS in general was associated with worse general cognitive impairments, more sensory integration signs were associated with poorer specific impairment in memory, verbal abilities, executive function and visual perceptual skills (Mellacqua et al, 2012). The study also reported that primary signs such as primitive reflexes, abnormal eye movements, were not associated with any specific cognitive function in either the patients with schizophrenia or healthy individuals. A finding which replicated aspects of the results of the meta-analysis by Chen et al. (Chen et al, 2009) described previously, in which sensory integration signs were particularly related to Intelligent Quotient (IQ) scores.

Motor NSS have also been specifically associated with cognitive disturbances in schizophrenia. For instance, it has been reported that timed motor speed correlated with cognitive impairments in schizophrenia patients with NSS, even after controlling for the effects of lifetime medication, extrapyramidal symptoms and abnormal involuntary

movements (Flashman et al, 1996). Also, Neurological Evaluation Scale (NES) motor sub-scale has been related to verbal pairs subscale of the Wechsler's memory scale, while NES sequencing of complex motor acts was associated with Stroop test and figural memory subscale of the Wechsler's memory Scale in the same study (Arango et al, 1999). Similarly, repetitive motor tasks were observed to be related to a number of cognitive functions except executive function, while cognitive/perceptual tasks were associated with memory and executive function (Sanders et al, 2006). Yet, other investigators believe that the pattern of cognitive impairment in schizophrenia, where specific deficit in verbal memory and visuo-motor processing super-imposed on a generalised cognitive deficit (Albus et al, 1996., 1997), is stable and not affected by the presence of NSS. In this argument, NSS would appear not to have any influence on the relative performance in cognitive functions and therefore, they may not be related to specific brain functions (Mohr et al, 2003). This notion has received support from other studies comparing schizophrenia patients and normal controls. For instance, reporting from the AESOP study, Dazzan and Colleagues (Dazzan et al, 2008) suggested that after controlling for differences in general cognitive ability, some NSS such as sensory integration deficits are no longer more prevalent in patients with schizophrenia when compared with controls. In the same vein, deficits in sensory and motor sequencing functions have also been associated with worse cognitive ability in healthy individuals (Keshavan et al, 2003., Bombin et al, 2005).

It would therefore appear that general intellectual functioning affects the integration of sensory information irrespective of the presence of schizophrenia.One area of consensus in the literature is related to the observation that in every instance of the relationship between NSS and cognitive impairments, NSS are reflective of a more severe dysfunction (Chan et al, 2009).

Findings of a relationship between NSS and impairment in general cognitive functioning are important because they may suggest that NSS are a reflection of a pre-existing global dysfunction in the brain, such as those emanating from neuro-developmental deficits. The fact of this association may also suggest that both NSS and cognitive impairment are a reflection of the same patho-physiological process that underlies schizophrenia (Wong et al, 1997, .Arango et al, 1999., Chan and Toulopoulou, 2006). Both constructs have also been suggested as complimentary, viable endophenotypes of schizophrenia (Bombin et al, 2005, Chan and Gttesman, 2008).

It is important to point out that many of the studies reporting a positive relationship between cognitive impairment and NSS are limited by methodological issues relating to assessment of only a limited number of items of cognition, as well as failure to control for several confounding variables. For instance age and IQ may influence these associations. While IQ may also be influenced by illness, NSS may be associated with age (Chen and Chan, 2003). As such the specific relationship between cognitive impairment and NSS remain poorly understood.

2.4.5. NSS AND ANTIPSYCHOTIC MEDICATIONS IN SCHIZOPHRENIA

The relationship between NSS and antipsychotic treatments in schizophrenia has been examined either in the form of current antispychotic doses (Chen et al, 1995., Lane et al 1996., Morh et al, 1996., Flashman et al, 1996., Gureje et al, 1988), lifetime antipsychotic exposure (Flyckt et al, 1999., Flashman et al, 1996) or in the form of longitudinal studies that have assessed symptom response to antipsychotic medications (Madsen et al, 1999., Chen et al, 2000., Scheffer et al, 2004., Bachman et al, 2005., Whitty et al, 2006., Mayoral et al, 2008). These studies have attempted to control for the possible contribution of antipsychotic medication to NSS. Many of the studies have combined scales for NSS with scales for extra-pyramidal symptoms, akathisia, and tardive dyskinesia. The vast majority of studies comparing medicated and un-medicated patients, or patients with and without extrapyramidal symptoms (EPS) report no association between neurological abnormalities and antipsychotic medication or extrapyramidal symptoms (Sheffer et al, 2004., Browne et al, 2000., Arango et al, 2000). This issue was more clearly addressed by Sheffer and colleagues when they administered the NES to 26 drug naïve and 3 drug free patients prior to treatment administration and after 6 week antipsychotic treatment, and found no significant changes in the NES scores at 6 weeks (Sheffer et al 2004). Similarly, the community study by Shibre et al (Shibre et al, 2002) in rural Ethiopia, which included 200 treatment naïve patients with schizophrenia, found that NSS in the treatment naïve schizophrenia cohort was as common as those reported in studies of subjects on neuroleptic medication. Schizophrenia patients in this sample had more total, motor sequencing, motor co-ordination, and sensory integration signs than a group of healthy controls (Shibre et al, 2002).

Studies in first-episode schizophrenia patients have often reported more NSS in the first episode antipsychotic naïve patients, when compared to healthy controls (Keshavan et al, 2003, Sheffer et al, 2004). However, similar to studies in other patient groups, significant differences have not been consistently reported between anti-psychotic naive and treated patients. For instance, the first episode Irish study (Browne et al, 2000, Whitty et al, 2003) reported that the rate of NSS did not differ significantly between antipsychotic naïve and antipsychotic treated patients, with 97.1% of antipsychotic naïve psychotic patients showing at least one neurological sign.

Some authors have argued for a hypothetical protective effect of antipsychotics on neurological dysfunction (Madsen et al, 1999), or indeed a decrease in NSS seriousness during treatment (Bachman et al, 2005, Whitty et al, 2006., Mayoral et al, 2008). For instance, in the follow up study by Madsen et al. (Madsen et al 1999), there was an increase in NSS in patients with schizophrenia 5 years after their first presentation. This increase was however more marked in those who had not received antipsychotic medication over the same period. Signs related to the cortico-spinal tracts were over represented. The authors reported how the antipsychotic load in non responding patients was inversely related to changes in total neurological abnormalities. It is however possible that the positive effect observed is related to the efficacy of antipsychotics on the clinical presentation. This improvement of neurological function following antipsychotic treatment may not be present in a sub-set of patient with a more chronic illness. Thus,

some studies have also reported worsening of neurological functions after antipsychotic treatments in chronic patients (Chen et al, 2000, Dazzan and Murray, 2002). The weight of evidence from empirical factor analysis suggests that antipsychotic treatment has some effect on the distribution of NSS in schizophrenia. A study by Goldstein and colleagues, (Goldstein et al, 2005) investigating the factor structure of the Neurological Evaluation Scale (NES) administered to 78 medicated patients with the illness, showed that the factor structure dramatically changed between when patients were un-medicated and when they became medicated. The un-medicated group had three clear factors and one factor that were not easy to characterize. However, after medication, the NES factors increased to five unclear factors. The subjects were part of 108 un-medicated patients reported by an earlier factor analysis by Sanders et al. (Sanders et al, 2000), and the same 12 items of the NES used in the earlier study were entered into the Goldstein's factor analysis.

Rates of NSS are reported to be similar among first episode schizophrenia patients exposed to conventional antipsychotics when compare to those exposed to atypical antipsychotics (Schroder et al, 1998., Boks et al, 2003., Jahn et al, 2006). In the study by Boks and colleagues, (Boks et al, 2003), tardive dyskinesia signs were an exception. They occurred more frequently among patients exposed to conventional antipsychotics. This would suggest that the type of antipsychotic treatment may have an influence on the appearance of tardive dyskinesia, but not on NSS in general.

2.4.6. NSS AND THE COURSE OF SCHIZOPHRENIA

The evidence for a relationship between NSS and cognitive impairment in schizophrenia as well as those suggesting that NSS could characterise a more severe schizophrenia psychopathological process such as thought disorders, negative symptoms and deficit states, as argued by Mechri et al (Mechri et al, 2009), suggest a state-like quality of at least some NSS factors. Such NSS factors may be associated with a chronic course of illness (Smith and Kadewari, 1996, Madsen et al, 1999., Prikryl et al, 2012). Some researchers also believe that NSS represent a trait characteristic of chronically ill schizophrenia patients (Buchanan et al. 1994, Smith et al, 1999., Chen et al, 2005). In the study by Smith et al. (Smith et al, 1999) comparison of 25 non-responders and 20 relative responders to conventional antipsychotic medications was conducted on the bases of an NSS battery and neuropsychological tests which evaluated deficits influenced by functioning of frontal and non-frontal brain areas. The data indicated that differences in the number and severity of NSS strongly differentiated between chronic schizophrenia patients who were persistently symptomatic after treatment with conventional antipsychotics and those whose positive symptoms resolved after several weeks or months of treatment with these medications. The authors suggested therefore that high NSS scores may predict individuals who will fall into the category of schizophrenia patients who are chronic non-responders to conventional antipsychotics (Smith et al, 1999). Smith and Kadewari (1996) had reported that severity of NSS correlated inversely with the degree of reduction in positive symptoms in chronically hospitalized non-responding schizophrenia patients who were given a trial of risperidone for several months (Smith and Kadewari, 1996). Another 5

year prospective study has also reported an increase in the number of neurological abnormalities in patients who had a genetic predisposition, as well as those with a non-remitting course (Madsen et al, 1999). In support of this finding are studies showing that Schizophrenia patients with few or no NSS at baseline have greater improvements on verbal fluency, memory and psychomotor speed following atypical antipsychotic treatments for 6 months when compared with those with many NSS (Das et al, 2004). Similarly, some studies have demonstrated that improvement in psychopathology also correlates positively with reduction in the rates of NSS, including those assessing the temporal stability of the signs over the course of schizophrenia (Emsley et al, 2005, Sheffer et al, 2004, Whitty et al, 2003, Prikryl et al, 2012). For instance, a study of the temporal stability of NSS over a one year course in antipsychotic naïve patients reported significant improvement in the motor sequencing factor as psychopathology improved over time (Emsley et al 2005). However, the same study reported that rapid alternative movements worsen overtime with treatment at 3 months. Similarly, Whitty et al. (Whitty et al, 2003) reported improvements in motor related cortical NSS at 6 months in a prospective study of first episode schizophrenia patients. This improvement was associated with improvement of psychopathology. Interestingly, rates of NSS at follow up may be positively related to negative symptoms. This is in consonant with the believe that there exist a link between NSS and a chronic course of schizophrenia (Buchanan et al. 1994., Smith et al, 1999., Smith and Kadewari, 1996., Madsen et al, 1999., Sheffer et al,2004., Chen et al, 2005., Prikryl et al, 2012).

A majority of studies report no association between NSS and age at onset of schizophrenia (Madsen et al, 1995., Gupta et al, 1995), duration of untreated psychosis (Emsley et al, 2005., Browne et al, 2000), relapse rates (Emsley et al, 2005), and global assessment of functioning (Sanders et al, 1995). It is possible that factors such as global assessment of functioning and occupational outcome are worse in advance phases of the illness, and are therefore not associated with neurological dysfunction in the early stages of the illness. However, Browne et al. (Browne et al, 2000) and Peralta et al, (Peralta etal, 2011) described an association between NSS and poor pre-morbid social functioning. This association can be related to the fact that higher rates of the signs are part of a more severe clinical picture. Furthermore, higher rate of NSS at baseline has been associated with the likelihood of developing side effects to antipsychotic medications during the course of schizophrenia. This was especially highlighted for tardive dyskinesia in the study by Emsley et al. (Emsley et al, 2005) described earlier, where it was reported that although the profile of NSS did not change much over a 12 month course, high scores on the motor sequencing factor predicted the emergence of persistent dyskinesia at 24 months in a pre-treatment antipsychotic naïve sample. A similar finding was also reported for other antipsychotic related effects in a French Caucasian sample of patients with schizophrenia by Mechri et al. (Mechri et al, 2009).

2.4.7. THE RELEVANCE OF NSS IN SCHIZOPHRENIA

The importance of NSS in schizophrenia as a vulnerability marker has been emphasized by various studies in the literature showing that young offspring of patients with schizophrenia have more neurological abnormalities compared to matched controls, especially among male offspring, who have been noted to have increased problem with co-ordination, right-left orientation and sensory integration (Prasad et al, 2009). These findings have also been replicated among other relatives of patients with schizophrenia, with the nature of the abnormalities clearly resembling those commonly seen in early and adult onset schizophrenia (Sanders et al, 2006., Neelan et al, 2011). Moreover, other categories of patients with elevated risk of schizophrenia such as healthy individuals with schizotypy (Chan et al, 2010a and b., Kaczorowski et al, 2009., Keshavan et al, 2008), have been shown to demonstrate increased numbers of NSS. Furthermore, a review of studies in children and adolescents has also shown that these abnormalities were already present at the first overt psychotic episode (Serene et al, 2007). Thus, there is a linear reduction of the risk across individuals of various genetic identities, from schizophrenia and normal controls. They therefore appear to be associated with genetic loading almost to a dose-response pattern. This pattern of distribution of NSS across schizophrenia patients and their relatives, or other high risk groups, is consistent with familial association, and appears to fit more into a mathematical model of familiar risk. Furthermore, the pattern of distribution of NSS across schizophrenia patients and their relatives has been found to be stable and resistant to external ethno-demographic influences.

Further evidence for NSS as a trait marker of schizophrenia comes from several longitudinal studies confirming the stability of NSS across the course of schizophrenia (Scheffer et al, 2004., Chen et al, 2005., Emsley et al, 2005., Boks et al, 2006., Mechri et al, 2009., Dazzan and Piccioni, 2009., Prikryl et al, 2012). This characteristic of NSS differentiates it from phenotypic measures of schizophrenia which are more maleable in the presence of multi-factorial and polygenic influences. They are thus attractive in the quest to isolate culprit genes for schizophrenia.

Contemporary genetic science aims to identify genes conferring vulnerability to psychiatric disorders including schizophrenia, and the brain proteins they code for. This is with the hope that such a discovery will make it possible to develop better diagnostic procedures, treatments and preventive interventions targeted at the underlying illness process. To date however, there has only been limited progress in this quest especially for schizophrenia. This is because of the polygenic and quantitative nature of the disorder. The attention in contemporary genetic research has shifted towards endophenotypes such as the NSS to facilitate gene discovery (Egan et al, 2001). Endophenotypes are characteristics that may represent more accessible readout of gene functions such as for example neuro-imaging findings. Thus classifying patients based on endophenotypes may accelerate the process of gene discovery. It is anticipated that the genetics of a complex construct like schizophrenia can be studied easily in more or less Mendelian fashion if the construct is broken down into its constituent endophenotypes. It is natural to think that the more simple a construct under study, the less number of genes will be on the causal pathway.

Neurological soft signs can be elicited quickly, reliably and cheaply, and could therefore be used in ordinary clinical settings to establish that an individual had progressed along the neuro-developmental pathway to schizophrenia (Bombin et al, 2003). If viewed from this perspective, the presence of higher rates of NSS has the potential to augment the predictive power of psychopathological tests for the prodrome of schizophrenia.

2.5. NSS IN OTHER MENTAL DISORDERS

Neurological Soft Signs (NSS) have been reported in other neuropsychiatric conditions such as mood disorders, Obsessive Compulsive Disorders (OCD), personality disorders and substance abuse. The body of research into NSS in these other neuropsychiatric conditions is much smaller than in schizophrenia and sample sizes are often small. Also only few studies have investigated more than one neurological domain in these other psychiatric disorders, often focussing only on motor signs.

Apart from the issue of relatively small sample sizes, these studies addressing NSS disorder also differed greatly in methodology. Patients were often recruited from treatment settings. Moreover, these studies were primarily meant to explore the magnitude of NSS in cases of schizophrenia using different sets of controls as references. For instance, in a review of 258 literatures on NSS in schizophrenia and mood disorders, Boks et al (2000) found only 17 studies with useful data on one or more diagnostic groups addressing this

issue. The numbers of patients in their mood disorder group were so small that they were unable to reach a firm conclusion. The review found a weighted mean prevalence of the 17 signs in their mood disorder group averaging 16.4%, but encompassing a smaller selection. This was almost 2 times the weighted mean prevalence of 30 neurological signs in the control group, which was 8.9%. Therefore suggesting that the mean prevalence of most neurological signs is significantly different between mood disorder patients and normal controls, but there were fewer differences between schizophrenia and mood disorders. The schizophrenia group had a mean prevalence for 30 neurological signs of 19.2%. However, because of the comparatively small sample of subjects in the mood disorder group, the difference between this group and the schizophrenia group may not have reached significance due to limited statistical power (Boks et al, 2000). Only stereognosis and rhythm tapping were more frequent in mood disorder patients than in schizophrenia patients, where as tactile extinction, dysdiadochokinesia, tandem walk, finger thumb opposition and articulation were significantly more prevalent in schizophrenia than in mood disorders. Nevertheless, schizophrenia patients have previously been found to perform similarly to patients with psychotic depression on motor and pursuit eye movement tasks (Jeste et al, 1996., Sweeney et al, 1999).

In Africa, Negash et al, (2004) examined the extent to which NSS are associated with bipolar I disorder cases compared to healthy controls in a relatively large epidemiological sample in rural Butajira, Ethiopia. Their analysis was based on 224 treatment naïve bipolar I disorder patients and 78 healthy controls. This study also showed that cases of

bipolar I disorder were significantly impaired in the performance of NES items compared to healthy controls. The authors further noted the paucity of literature to compare their results with, and therefore relied on the review by Boks et al (2000) in discussing their results (Negash et al, 2004).

While interpreting findings on studies on mood disorder patients, it should be considered that motor dysfunction shows variability related to mood (Guenther et al, 1986). The phase of the illness and the diurnal variation may therefore influence the result of the assessment. The diagnostic specificity of NSS in mood disorders remains unclear, often because authors fail to present the different diagnostic sub-categories. It seems that patients with affective psychosis shows evidence of frontal and parietal dysfunction (Nasralla et al, 1983), and in general an impaired motor performance (Negash et al, 2004), similar to those of schizophrenia patients. The occurrence of NSS in mood disorders points to a shared genetic vulnerability for schizophrenia and mood disorders rather than contradict the idea of increased NSS as a reflection of vulnerability to schizophrenia. In support of this view are the findings from studies demonstrating similar genetic expression in bipolar mood disorders and schizophrenia of homeobox genes (Kromkamp et al, 2003), lipid and myelin related genes (Tkachev et al, 2003), as well as numerous other similarities in genetic architecture (Purcell et al, 2009). Furthermore, there is evidence of an overlap in chromosomal regions with susceptibility genes for both bipolar disorders and schizophrenia (Berretini, 2000). Studies of the neurobiology of schizophrenia and mood disorders have also shown that both patient groups exhibit similar reduction in

reelin (Fatemi et al, 2000), a glycoprotein involved in neuronal migration and synaptogenesis, as well as down regulation of inhibitory neurotransmitters -e.g, Glutamic acid decarboxylase 67- (Guidotti et al, 2000). Moreover, schizophrenia and mood disorders also present some common structural brain abnormalities (MacDonald et al, 2004). There is also an overlap between the symptomatology of schizophrenia and mood disorders (Wassink et al, 1999). These similarities suggest that schizophrenia and mood disorders lie on a continuum of vulnerability and may help to understand the underlying aetiological process. Some have proposed a model that positions both disorders on a similar genetic background, attributing their differences in clinical manifestation to environmental factors (Murray et al, 2004), while others present a 'schizophrenia- bipolar boundary' perspective (Ivleva et al, 2010), where even though both disorders are similar in origin, schizophrenia results from more severe affectation of the brain by the various brain structural and functional abnormalities, including NSS.

Among anxiety disorders, patients (particularly men) suffering with obsessive compulsive disorders show an excess of NSS especially those related to poor motor control (Stein et al, 1994., Bihari et al, 1991., Peng et al, 2012). In a neuro-imaging study, NSS in this group were associated with reduced volume of the caudate, a structure that could also be mediating obsessive compulsive symptoms (Stein et al, 1994). An excess of neurological abnormalities has also be described in adolescents with anxiety disorders (Shaffer et al, 1985). One study on patients with post traumatic stress disorder described abnormalities in motor sequencing and palmo-mental reflex in these patients (Gurvits et al, 1992), although these findings have not been replicated by subsequent study by the same authors (Gurvits

1993). Furthermore, NSS rates similar to those observed in schizophrenia have been observed in patients with personality disorders (Lindberg et al, 2004., Stein et al, 1993). Therefore, NSS including signs of motor dysfunction may not be specific to patients with schzophrenia. This can be clarified by investigating several neurological domains in groups of patients with different psychiatric diagnoses.

2.5.1. NSS IN HEALTHY INDIVIDUALS

Neurological soft signs are also present in healthy individuals. They have been reported to occur in this group at rates ranging from between 0 and 50% (Kennard, 1960; Hertzig and Birch, 1968; Rochford et al., 1970; Cox and Ludwig, 1979). However, the literature on NSS in healthy individuals is sparse. Most studies have extrapolated from findings when using healthy individuals as control in the investigation of NSS in schizophrenia. Such studies have consistently found a graded pattern of NSS prevalence and severity, with healthy relatives having an intermediate number between patients and healthy controls (Egan et al, 2001., Schubert and McNeil, 2004., Compton et al,2007).

In one study were NSS has been investigated in an epidemiological sample of healthy individuals using the Neurological Evaluation Scale (NES). NSS scores were almost entirely reflective of abnormalities in sensory integration functions (Dazzan et al, 2006). The majority of subjects did not show abnormalities in tests of motor co-ordination and motor sequencing. The investigators further reported that higher rates of sensory

integration NSS was associated with volumetric reduction in several temporal and frontal grey matter structures. Structural imaging in the study was achieved using high resolution Voxel Based Morphometry procedure. In contrast, an earlier study by Keshavan and Colleagues (Keshavan et al, 2003) did not find associations between NSS and structural brain changes while using the Region of Interest analysis.

In disparity with findings in schizophrenia patients, where higher rates of NSS were associated with a reduction of both cortical and subcortical areas (Dazzan et al.,2004), NSS in healthy individuals appear not to have any association with changes in sub-cortical structures (Dazzan et al, 2006). On the other hand, the same study reports that NSS in healthy individuals was associated with reduction in several white matter structures including the internal capsule. This finding is also in contrast with the report that NSS in schizophrenia is associated with increase in the white matter structures such as the internal capsule.

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2.6.0. MEASURING NSS

The distinction of some neurological signs as hard (reflecting impairment in basic motor, sensory, and reflex behaviour) or soft (reflecting impairments in coordination, sequencing or integration of complex sensory or motor functions) may appear ambiguous. This ambiguity has led to differences in categorization of neurological signs in the several instruments developed for their measurement.

Among the available instruments for assessing NSS, the most fully described and widely employed in adult psychiatry is the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs,1989). Other scales that have been developed for this purpose for use in adult psychiatry include the Quantified Neurological Scale, a composite examination developed by Convit et al, (Convit et al, 1994), the Heidelberg scale (Schroder et al,1992), and the Cambridge Neurological Inventory (CNI), a heterogeneous inventory of neurological abnormalities and behavioural observations with administration guidelines and reliability data for use in adult psychiatry (Chen et al, 1995). Measures have also been developed to target specific aspects of NSS such as the Brief Motor Scale (Jahn et al, 2006), for motor soft signs.

Although the batteries used in measuring NSS have varied, neurological abnormalities in adult patients with schizophrenia have been theoretically organized into three main neurological domains as follows (Heinrichs and Buchanan, 1989);

1. Integrative sensory dysfunction (possibly resulting from a parietal lobe dysfunction), reflected in items such as bilateral extinction, agraphesthesia, astereognosis, right/left confusion and impaired audiovisual integration.

2. Motor in-coordination, reflected in items such as tandem walk, finger to nose, finger to thumb opposition and dysdiadochokinesis.

3. Impaired sequencing of complex motor acts (possibly resulting from a fronto-basal ganglia circuitry), reflected in items such as the fist ring, fist edge palm and Ozerestski tests.

Abnormalities in frontal release signs, eye movements, and short term memory have also been frequently observed in schizophrenia cohorts.

TABLE 3. FUNCTIONAL CATEGORIES OF NEUROLOGICAL SOFT SIGNS IN SCHIZOPHRENIA, AND SOME OF THE TEST THAT ELICITS DISTURBANCES IN THESE AREAS

Primitive Reflexes	**Sensory Integration**	**Motor Coordination**	**Motor Sequencing**
Gaze	Audio-visual integration	Tandem Walk	Fist-Ring test
Palmomental	Stereognosis	Rapid alternating movements	Fist-Edge-Palm test
Snout	Graphaesthesia	Finger Thumb opposition	Ozereski
Grasp	Extinction	Finger nose test	
	Right-Left confusion	Rhythm tapping	

2.6.1.0. THE NEUROLOGICAL EVALUATION SCALE

The Neurological Evaluation Scale (NES) is based on an extensive review of NSS in schizophrenia by Heinrichs and Buchanan, (1988). The authors selected specific signs representing areas of frequent impairment noted across multiple studies focused on systematic reviews and controlled clinical evaluations.

From these considerations a battery of 26 items was designed. Fourteen of these items are tested and scored separately for the right and left sides of the body. The instrument includes representative items from each of the three functional areas of interest, plus the assessment of cerebral dominance, short term memory, frontal release signs and eye movement abnormalities. All items are judged to be easily administered by a clinician at the bedside or in the consulting room with minimal equipment required. Each item is scored on a three point scale of 0=No abnormality, 1=mild but definite impairment, and 2=marked impairment, except the snout and suck reflexes which are scored either as 0 or 2. Descriptive anchors are provided for each score to facilitate standardized judgement. In addition to item scores and total scores, subsets of items are totalled to yield scores for the three functional areas of interest described earlier.

Inter-rater reliability data were derived from 39 subjects with schizophrenia and 7 controls. The Intra-class correlation for total scores was 0.95, and 0.99 for the sensory integration sub-scale, 0,71 for the motor co-ordination sub-scale, and 0.89 for the sequencing of complex motor act subscale. The inter-rater reliability for 14 individual items was 0.90. The NES has been shown to predict cognitive dysfunction, severity of psychopathology, and response to antipsychotics (Buchanan and Heinrichs, 1989, Bombin et al, 2003). Apart from these important psychometric properties, the NES appear superior to other instruments of its kind as it assesses a moderate number of soft signs. This characteristic allows for minimization of administration time and maximization the number of relevant items of the NES. It has also been extensively used in studies of neurological abnormalities in schizophrenia.

Table IV. Items in the Neurological Evaluation scale.

Sensory integration scale
Audiovisual integration
Stereognosis
Graphaesthesia
Extinction
Right/left confusion
Motor coordination subscale
Tandem walk
Rapid alternative movements
Finger-thumb opposition
Finger-nose test
Sequencing of complex motor acts subscales
Fist-ring test
Fist-edge palm
Ozereski test
Rythm tapping test, B
'Others' subscale
Adventitious flow
Rhomberg test
Tremor
Memory, 5 minutes
Memory, 10 minutes
Rhythm tapping test, A
Mirror movements
Synkinesis
Convergence
Glabellar reflex
Snout reflex
Grasp reflex
Suck reflex

Adapted from: Arango et al, 1999

2.6.1.1. FACTOR ANALYSES OF THE NES

The original sub-scales of the NES were derived according to the brain functions or regions they were thought to represent (Henirichs and Buchanan, 1989). It contained factors for sensory integration, sequencing of complex motor acts, as well as motor co-ordination. Other such conceptually derived sub-scales of the NES include those of Egan et al. (Egan et al, 2001) which contained sub-sets for cerebellar, frontal and parietal functions. Although such conceptualization of soft signs appear to have hypothetical significance, they have never been confirmed by empirical methods such as exploratory factor analysis (Sewell et al, 2010., Compton et al, 2006., Emsley et al, 2005., Goldstein et al, 2005., Sanders et al, 2000., Keshavan et al, 2003., Krebs et al, 2000 and Malla et al, 1997), or confirmatory methods (Sanders et al, 2005). However, this tentative classification has been used in many previous studies of NSS in schizophrenia (Arango et al, 1999., Shibre et al, 2002., Mohr 1996, 2003., Scheffer et al, 2003., and Dazzan et al, 2004)

Factor analysis is a standard technique for reducing data sets to underlying consistent sub-set that can be used to find principal variables among many observed variables in a data set through the grouping together of items with similar characteristics. Previous studies have shown that the NES is made up of different factors which can be subjected to factor analysis (Malla et al, 1997, Sanders et al, 2000, 2005). These factors are also known to reflect different aspects of brain functions in schizophrenia and as such, they are

associated with the various clinical and outcome characteristics of the disease (Sewell et al, 2010., Compton et al, 2006., Emsley et al, 2005).

2.6.2. THE HEIDELBERG SCALE

The Heidelberg scale is a 17-item instrument along 5 domains of motor coordination, integrative functions, complex motor tasks, right/left and spatial orientation, as well as hard signs. Ratings are given on a 0–3-point scale (no/slight/moderate/marked abnormality, respectively). All items except for gait, tandem walk, Ozeretzki's test, articulation, and right/left orientation are assessed separately for both the right and the left side. Scores in the Heldeberg scale has been shown to be associated with disorganisation symptom dimensions, working memory impairment, increased third ventricular volume, as well as increased ventricular brain ratio. Cronbach's alpha derived from an assessment of 42 schizophrenia patients and healthy controls by two independent raters was 0.85 for the schizophrenia sample and 0.89 for the healthy controls. Inter-rater reliability was 0.88 ($p<0.005$) (Bombin et al, 2003).

Table V. Items in the Helderberg scale

Motor Coordination
Ozeretzki test
Diadochokinesis
Pronation/supination
Finger/thumb opposition
Articulation
Sensory Integration
Gait
Tandem gait
2-point discrimination
Complex Motor Tasks
Finger- to- nose test
Fist-edge-palm test
Right /Left and Spatial Orientation
Right/left orientation
Graphaesthesia
Face/hand sensory test
Stereognosis
Hard Signs
Arm-holding test
Mirror movements

Adapted from: Bachman et al, 2005

2.6.3. THE CAMBRIDGE NEUROLOGICAL INVENTORY (CNI)

The CNI is a standardised comprehensive neurological examination. It includes most neurological signs from the Neurological Evaluation Scale (NES) along with items that assess extrapyramidal symptoms, tardive dyskinesia, and catatonia. It covers 3 soft signs domains, including motor coordination, sensory integration, and disinhibition. A rating of 0 indicates no abnormalities; 0.5, 1 and 2 indicate equivocal, abnormal and grossly abnormal responses, respectively. Inter-rater reliability assessed with Kendall's *w* on 14 items which were not part of an already validated scale ranged from 0.82 to 1.0 ($p<0.04$) (Chen et al, 1995)

Table VI. Items in the Cambridge Neurological Inventory (CNI).

Stereognosis
Graphaesthesia
Extinction
Right-left confusion
Tandem walk
Dysdiadochokinesia
Finger-thumb opposition
Finger-nosetest
Fist-edge-palm
Ozeretski test
Rhomberg test
Tremor
Rythm tapping test
Mirror movements
Gaze impersistence
Glabellar reflex
Snout reflex
Grasp reflex
Gait
Palmomental reflex

Adapted from; Bombin et al, 2003.

2.6.4. MODIFIED QUANTIFIED NEUROLOGICAL SCALE

This scale was designed to differentiate between violent and non-violent schizophrenia patients. It consists of 96 items, of which 48 assesses NSS. These items are scored as normal or abnormal. The scale also groups the items according to the probable localisation of the NSS. Kappa values for individual items ranged from 0.69 to 1.60 (Convit et al,1994). The modified quantified neurological scale scores correlates with symptom severity, poor psychosocial performance, and cognitive impairment (Bombin et al, 2003)

Table VII. Items in the Modified Quantified Neurological scale.

Stereognosis
Graphaesthesia
Extinction
Right-left confusion
Tandem walk
Finger-thumb opposition
Finger-nosetest
Fist-ring test
Fist-edge palm
Rhomberg test
Hopping
Pronation and supination
Foot tap
Face-hand
Babinski

Adapted from; Bombin et al, 2003.

2.6.5. OTHER SCALES FOR MEASURING NSS

Wood Scale

This scale contains 79 items that assesses both soft and hard signs. It is rated on a 4 point scale, where 0=absent, 1=mild, 2=moderate, and 3=severe. The scale also provides a classification of the probable aetiology of the neurological impairment (Bombin et al, 2003).

Rossi Scale

This is a 26 item scale in which 7 items are rated bilaterally. While some of the items are rated as present or absent, other items are rated from 0-6. Inter-rater reliability for the total score as evaluated by the Spearman correlation was 0.76 (Bombin et al, 2003).

The Brief Motor Scale

The BMS specifically assesses movements and motor skills in patients with schizophrenia and other psychiatric disorders (Jahn et al, 2006)

2.7. LIMITATIONS OF PREVIOUS RESEARCH ON NSS

Psychiatric research into NSS has employed a collection of neurological examination items obtained from the clinical traditions of previous studies. Some batteries were partly or entirely drawn from general neurology text, while others were selected from familiar neuropsychological batteries (e.g, Cox and Ludwig, 1979., Schultz et al, 1995., Gupta et al, 1995). Several scales were developed for use with children during extensive research into neurological aspects of paediatric psychiatry in the 1930s and 1940s (e.g, Rutter et al, 1970., Nichols et al, 1981., Tupper, 1987), and were later modified for application in the adult population. The various scales applied by researchers over the years differed in their definition of neurological impairments. These differences have resulted in pronounced variability in the reported prevalence rates of NSS in schizophrenia subjects. Studies in which neurological impairment is defined more broadly to include 'at least one neurological sign present' tended to give a higher prevalence rate (e.g, Bartko et al, 1988., Browne et al, 2000., Ismail et al, 1998) whereas studies using a more restrictive definition of neurological impairment gave a lower prevalence rate (King et al, 1991). The prevalence rates also depended on the scope of coverage of the neurological assessment scale. This has ranged from 4 signs (e.g, Gureje, 1988) to up to 108 signs in some studies (Braun et al, 1995). This fact on its own may explain differences in prevalence rates. Scales with a smaller number of signs are likely to have low sensitivity, and may omit signs that are relevant to schizophrenia, creating a type II error of concluding that certain neurological abnormalities are not specific to schizophrenia. On the other hand, very comprehensive scales are likely to have low specificity and may include signs that have no

direct bearing on primary neurological abnormalities, and therefore classify subjects as neurologically impaired when in fact their signs are secondary to other variables. Furthermore, most of the neurological examination scales do not provide cut off scores or set thresholds that define the neurological impairment range. Reports that include a matched healthy control group are able to establish what constitute a neurological normal or abnormal state and hence allow for comparison with the patients with schizophrenia. This approach of looking for statistically significant differences among groups is less ambiguous than the use of subjective definitions of neurological impairment. Studies of these kinds that compare the prevalence of NSS in schizophrenia patients and healthy controls have consistently found significant differences.

2.8. RATIONALE FOR THE PRESENT STUDY

Globally, the existing evidence for the nature of Neurological Soft Signs (NSS) in schizophrenia has been based on wholly Caucasian population or mixed population of Caucasians and other races. Many more of the studies from which this evidence is derived have been conducted outside the African continent. Out of a total of five African studies reporting on the nature of NSS in Schizophrenia (Gureje et al, 1988., Mubarak et al, 1999., Shibre et al, 2002., Emsley et al, 2005, and Smit et al, 2012), only one was based on a first episode sample (Emsley et al, 2005). That study, which is also the only prospective longitudinal study of NSS on the African continent, was composed of a sample drawn from 21% white, 71% mixed, and 8% black Africans with first episode schizophrenia. Another important study reported on the nature of NSS in a sample comprising of 90%

African-Americans and 10% other races, but with considerable clinical heterogeneity (Compton et al, 2006). Therefore, a knowledge gap still exists on the nature of NSS in indigenous African subjects

Recent systematic re-examination of the epoch making World Health Organisation (WHO) epidemiological studies in schizophrenia, as well as larger scale replications of these studies have revealed important ethnic and geographical variations in many aspects of the disease (Mcgrath et al, 2006., Saha et al, 2005., Cohen et al, 2008). This body of evidence challenges the previously held axiom that schizophrenia is an egalitarian disease, with similar incidence and expression across all regions and cultures. Moreover, some previous studies have demonstrated that race or ethnicity influences the prevalence of NSS in schizophrenia (Chen et al, 2003., Keshavan et al, 2003., Bombin et al, 2005., Mechri et al, 2009). It is therefore becoming more difficult to generalize findings from one geographical area or indeed any one sample or population. This is especially so in the science of population genetics and epi-genetics of mental disorders, and the immediately congruent concept of NSS or indeed other intermediate phenotypes. Furthermore, there are other evidence to suggest that there are important peculiarities among indigenous Africans in the genetics and clinical aspects of many other neuropsychiatric disorders, including major depression and dementia (Gureje, 2007). In the light of this body of evidence, prospective longitudinal studies of neurological abnormalities in first episode schizophrenia in a clinically and racially homogenous cohort of indigenous African subjects become pertinent, and indeed long overdue.

This study describes the profile of NSS across the one year course of schizophrenia, as well as their relationship with illness specific and outcome variables in a group of first episode, largely medication-naïve Yoruba Nigerians with the disease. It is expected that this study will provide important reference data on the nature of neurological soft signs in indigenous African subjects and energize the pursuit of candidate genes in the causal pathway of schizophrenia. This is with the hope that such a discovery will make it possible to develop better diagnostic procedures, treatments and preventive interventions targeted at the underlying illness process.

CHAPTER THREE

AIM AND OBJECTIVES

3.1 AIM:

The overall aim was to conduct a longitudinal study to investigate the frequency, stability and demographic and clinical correlates of neurological soft signs over a 12 month course of schizophrenia among a clinically and racially homogenous cohort of Nigerian Africans.

3.2. OBJECTIVES:

1) To investigate the frequency and the one year longitudinal profile of neurological soft signs in a cohort of Nigerian patients with schizophrenia

2) To determine the relationship between neurological soft signs and pre-morbid adjustment.
3) To determine the relationship between neurological soft signs and the clinical characteristics of schizophrenia. The clinical characteristics of interest will include; age at onset of schizophrenia, duration of untreated psychosis, symptom dimensions of schizophrenia, presence of depressive symptoms overtime, and insight overtime.

4) To determine the relationship between baseline neurological soft signs and the emergence of extrapyramidal symptoms over time.

3) To determine the relationship between neurological soft signs and the outcome of illness over 12 months. Outcome will be determined in terms of symptom reduction, functionality, and quality of life.

3.3. HYPOTHESES:

1). There will be no significant difference in the scores of NSS dimensions in patients with schizophrenia after three repeated measurement over a 12 month period.

2). Higher NSS scores at baseline will be associated with a poorer premorbid adjustment, a younger age at onset of schizophrenia, and predominant negative or disorganization symptoms of schizophrenia.

30. Higher NSS scores at baseline will be associated with treatment emergent extrapyramidal symptom over a 12 month course.

4). Higher NSS scores will be associated with a poorer outcome over a 12 month course, but will have no significant relationship with insight or the presence of depression symptoms over this period

CHAPTER FOUR

METHODOLOGY

4.1. STUDY LOCATION AND SETTING

The study was conducted in Ibadan, Nigeria. Ibadan is located in south-western Nigeria, about 80 Kilometres from Lagos, and the population is mostly Yoruba speaking. There are two main hospitals in Ibadan with functioning psychiatric units. The University College hospital (UCH), which is a tertiary referral general hospital, and the Oyo state general hospital (Adeoyo) a secondary health-care facility.

4.2. STUDY DESIGN

This was a cohort study with a longitudinal (repeated measures) design. The cohort comprised of Nigerian patients with first episode, largely medication naive, schizophrenia, schizo-affective disorders, and schizophreniform disorder. It was racially homogenous. Patients were from the Yoruba ethnic group and were resident within and around Ibadan.

4.3. SUBJECTS

The study was carried out among patients aged between 16 years and 45 years with first presentation to the psychiatric units of the UCH and Adeoyo hospitals, Ibadan. A total of 84 patients, 47 males and 37 females, were consecutively recruited over a period of 26months, between April, 2009 and June, 2011 from the outpatient clinics of the two hospitals. Patients were approached after they had been seen by the clinician, usually a consultant psychiatrist or a trainee psychiatrist, who was responsible for their routine clinical assessment at presentation. Only those who were assessed by the clinician to have a psychotic illness were approached for possible participation in the study. Written informed consent was obtained from all participants, and/ or their guardians after the procedure of the study was explained to them in either English or Yoruba language. On the basis of these criteria, 84 patients were consecutively recruited into the study. Following recruitment into the study, subsequent evaluations and treatment were conducted in the research office for the study at the University College Hospital, Ibadan. In all, 65 patients completed 12 months follow- up assessment, while 19 patients dropped out of the study for various reasons, giving a follow-up rate of 77.4%. Of these, 12 subjects were lost to follow-up or relocated from study location, 2 withdrew their consent during the study, and another 2 withdrew from the study because of poor efficacy of the prescribed anti-psychotic medication. All the attritions occurred before the second assessment for neurological soft signs, which was at 6 months. They were mostly males (57.9%), and had a mean age of 28.7 (±5.8) years. Fourteen of them had received a diagnosis of schizophrenia, while the remaining 4 had a diagnosis of schizophreniform disorder. There

were no significant differences in the baseline characteristics of patients who dropped out of the study and those who completed the 12 month assessments. Only patients who fulfilled the research inclusion and exclusion criteria were enrolled into the study.

4.3.1. INCLUSION CRITERIA

1. Male or female, in- or outpatients

2. Aged between 16 and 45 years.

3. DSM IV diagnosis of schizophreniform disorder, schizophrenia or schizo-affective disorder

4. Lifetime exposure to antipsychotics of not more than 12 weeks.

4.3.2. EXCLUSION CRITERIA

1. Previous treatment with long acting depot antipsychotics.

2. Physical illness of significance. This was assessed using clinical history, a full physical examination including neurological examination. Appropriate special investigations were also requested where necessary.

3. Mental retardation. This was determined from clinical history and general clinical impression. Formal testing of cognitive capacity was not done.

4. Current substance abuse meeting DSM IV criteria. This was determined from clinical history.

4.3.3. SAMPLE SIZE DETERMINATION

The sample size was calculated based on the formula for repeated measures data. The minimum number of participants followed up for three repeated measures assuming a type 1 error rate of 5% and a power of 90% of detecting a difference in pattern of neurological soft signs is given by the formula (Diggle et al, 2002)

$$m = \frac{2(Z_\alpha + Z_\beta)^2 \sigma^2 (1 - \rho)}{n s_x^2 d^2}$$

Where;

m =the minimum sample size studied.

Z_α = the standard normal deviate corresponding to a type 1 error rate (2 sided level of significance of 5% = 1.9)

Z_β = the standard normal deviate corresponding to a one sided beta error of 10% (90% power) = 1.28

σ = the standard deviation of the neurological symptom score obtained from a preliminary study = 9.9

ρ = the correlation between successive measurements = 0.44

s_x^2 = the within subject variance of the measurements = 3.25

d = the meaningful difference in neurological symptom score between those with soft sign and those without. A difference of 1 unit was assumed

n = the number of repeated observations = 3

This gave a minimum of 64 participants. Assuming 5% loss to follow up rates, about 67 participants was required to be followed up.

4.4. STUDY INSTRUMENTS

The following instrument was employed in the diagnostic assessments of patients:

Structured Clinical Interview for DSM-IV (SCID) (First et al, 1996).

This instrument was developed to provide for a standardized assessment that generates DSM-IV diagnoses. It is a semi-structured diagnostic interview beginning with a section on demographic information and clinical background. There are seven diagnostic modules focused on different diagnostic groups: mood, psychotic, substance abuse, eating, somatoform and adjustment disorders. All available information, including those from hospital records, informants and patients' observations are used to rate the SCID. It is considered a standard interview to verify diagnoses in clinical trials and is extensively used in other forms of clinical research.

The following instruments were employed in the assessment of patients with schizophrenia (and related disorders):

1. The Positive and Negative Syndrome Scale (PANSS) (Kay et al, 1987).

The PANSS include 30 items on three sub scales; seven items covering positive symptoms, seven covering negative symptoms and 16 covering general psychopathology. The PANSS requires a clinician rater because considerable probing and clinical judgment is required. Reliability for each scale was shown to be fairly high with excellent internal consistency and inter-rater reliability (Kay et al, 1987). The PANSS has become the standard tool for assessing clinical outcome in treatment studies of schizophrenia and other psychotic disorders and has been shown to be sensitive to change with treatment. Factor analyses by several groups over the years now overwhelmingly favour a five factor solution (Lancon et al, 1998., 2000., Wolthaus et al, 2000), instead of the original three categories. These factors include those of positive (P1= Delusion, P3= Hallucination ,P5= Grandiosity ,and P6= Suspiciousness), negative (N1= Blunted affect, N2= Emotional withdrawal, N3= Poor rapport, N4= Passive social withdrawal, N6= Lack of flow of conversation, and G7= Motor retardation), disorganised/cognitive (P2= conceptual disorganization, N5= Poor abstraction, G9= Unusual thought content, G10= Disorientation, G11=Poor attention, G13=Disturbance of volition, and G15=Preoccupation), excitement/hostility (P4= Excitement, P7= Hostility, G8= Unco-operativeness, G12= Lack of insight, and G14= Impulsivity), and depression/anxiety (G2= Anxiety, G3= Guilt, G4= Tension, and G6= Depression) dimensions of schizophrenia.

They are generally described as stable and unaffected by age, disease severity or medication use. Therefore they have found wide acceptance in several studies of the outcome of schizophrenia and other psychotic disorders (Monteiro et al, 2008., Llorca et al, 2011).

The PANSS was administered to all subjects by the investigator at baseline and at three monthly intervals throughout the duration of this study.

2. Clinical Global Impression (CGI) (Guy, 1976).

The CGI was developed to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning prior to and after initiating treatment. The assessment takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behaviour, and the impact of the symptoms on the patient's ability to function. The CGI comprises two companion one-item measures evaluating the severity of psychopathology on a 7-point scale and change from the initiation of treatment on a similar seven-point scale. Subsequent to a clinical evaluation, the CGI form can be completed in less than a minute by an experienced rater. The CGI can track clinical progress across time and has been shown to correlate with longer, more tedious and time consuming rating instruments across a wide range of psychiatric diagnoses. The investigator rated patients on the CGI at baseline and at 3 monthly intervals.

3). Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al, 1993).

The CDSS is a nine-item scale specifically developed for assessment of depression in patients with schizophrenia. It is presented as a semi-structured interview. The first question for each section is asked as stated, although the rater is encouraged to ask additional questions as he or she feels appropriate. All items are rated on a four-point scale. Anchor point descriptions are provided to aid differentiation between each item score. The first eight items are rated on the basis of the patient's responses to questions; the ninth item is based on the clinician's assessment of the patient over the course of the interview. The CDSS was administered to all subjects at baseline and 3 monthly intervals.

4. Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard and Margolese, 2005).

The ESRS was designed to rate three types of extrapyramidal symptoms: Parkinsonism, dystonia and dyskinetic symptoms. The scale includes subjective questions covering the above three categories of extrapyramidal symptoms. These subjective questions help to differentiate subjective akinesia from depressive symptoms related to the anti-adrenaline effects of some antipsychotic drugs (e.g chlorpromazine). But they also help to differentiate akathisia from anxiety and psychotic agitation. Also included in the ESRS are sections for physical examination covering Parkinsonism, dystonia, and dyskinetic movements as well as sections for clinical global impression items. The ESRS was administered to all subjects by the investigator at baseline and 3 monthly intervals.

5. Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association).

The SOFAS is a scale that focuses on the individual's level of social and occupational functioning and is not directly influenced by the overall severity of the individual's psychological symptoms. Also any impairment in social and occupational functioning that is due to general medical conditions is considered in making the SOFAS rating. This is in contrast to the older Global Assessment of Functioning (GAF) scale which seems to tie functioning to psychopathology. The SOFAS is usually used to rate the level of functioning at the time of the evaluation. However, the SOFAS may also be used to rate functioning for other time periods. For example, the highest level of functioning for at least a few months during the past year. The SOFAS was administered to all subjects by the investigator at baseline and 6 monthly intervals.

6. The World Health Organisation WHOQOL-BREF Quality of Life Scale (WHO, 1998).

The WHOQOL-BREF is an abridged version of the WHOQOL-100 quality of life assessment scale, an instrument that allows a detailed assessment of the individual facets of quality of life. The WHOQOL-BREF contains a total of 26 questions arranged in a four domain structure of physical health, psychological health, social relationships and environment. To provide a broad and comprehensive assessment, one item from each of the 24 facets contained in the WHOQOL-100 was included in this abridged version. Two

items from the overall quality of Life and general health facet of the parent instrument were also included. The domain scores are indicative of an individual's subjective perception of quality of life in the corresponding domain. Higher scores denote higher quality of life. The mean score of items within each domain is used to calculate the total domain score. The WHOQOL-BREF could be self-administered if respondents have sufficient ability. Otherwise, interviewer-assisted or interview-administered forms are used. A research nurse who received training in the use of the WHOQOL-BREF rated patients with schizophrenia using this instrument.

7. Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al, 1982).

The PAS is a rating scale designed to evaluate the degree of achievement of developmental goals in the major areas at each of several periods of a subject's life before the onset of schizophrenia. It assesses premorbid functioning during childhood (up to 11 years), early adolescence (12 to 15 years), late adolescence (16 to 18 years), and adulthood (19 years and above). The premorbid period referred to by this measure is the period ending 6 months before the first episode of the psychotic disorder. The domains include sociability and withdrawal, peer relationships, scholastic performance, adaptation to school, and social-sexual functioning. Social-sexual functioning is not assessed during childhood. Ratings are made on a 0 to 6 point scale, with 0 indicating normal adjustment and 6 indicating severe impairment. Ratings are averaged across each of the domains, to obtain individuals scores for the childhood, early adolescence, and late adolescence periods.

In accordance with the procedure used in previous studies, separate scores were calculated for Social and Academic functioning at each age period. These composite domains had been derived by factor analytic studies of the PAS (Allen et al, 2001). The average scores for the sociability and withdrawal, peer relationships and social-sexual functioning items were calculated to generate a score for the social domain. The same method was used to generate an academic domain from the scholastic performance and adaptation to school items. The PAS was completed according to standardized procedures. A semi-structured interview of the patients and their family members was conducted with the requirement that the interviewed family member had substantial contact with the participant during childhood, adolescence, and early adulthood

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8. Birchwood Insight Scale (BIS) (Birchwood et al 1994)

The BIS is a self-report Insight Scale which measures three dimensions of insight: awareness of illness (2 items), awareness of symptoms (2 items) and awareness of the need for treatment (4 items). Each item is scored: 0 – no insight (yes to 2, 3, 6, and 8; no to the others), 1 – unsure (all items), 2 – insight (no to 2, 3, 6 and 8; yes to the others). Each sub-scale is given equal weight when calculating the total score. Higher score indicate better insight. A research nurse who had received training in the use of the BIS supervised the rating of insight by patients with schizophrenia. In the final analysis, lack of insight was regarded as no insight or being unsure about the answers to all 8 questions.

9. The Neurological Evaluation Scale (NES) (Heinrichs & Buchanan, 1989).

The NSS were evaluated using the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989), which is the most widely used instrument for assessing neurological deficits in schizophrenia. It is a battery of 26 discrete measures of neurological soft signs, of which 14 items are tested and scored separately for the right and left sides of the body. The instrument includes representative items from the three functional areas of interest (functional categories).This include a sub-scale that reflect signs of motor in-coordination such as tandem walk, rapid alternation movements, finger to thumb opposition, and the finger-to-nose test. There is also sensory integration sub-scale which reflects a dysfunction in integration of sensory information. This sub-scale includes such signs as audiovisual integration, stereognosis, graphesthesia, extinction, and right to left confusion. A third category called sequencing of complex motor acts sub-scale reflects the ability to perform complex motor acts such as the first-ring test, the first-edge-palm test, the Ozeretski test, and rhythmic tapping test. The NES also assesses cerebral dominance, short-term memory, frontal release signs and eye movement abnormalities. The items are scored with reference to the descriptive anchors provided, on a three-point scale (no abnormality=0; mild, but definite impairment=1; marked impairment=2) with the exception of “suck” and “snout” reflexes which are scored 0 or 2. A neurological abnormality was defined as a score of 2 in at least one item of the NES. This is similar to the definition of an abnormality that have been used in previous studies of NSS in first episode schizophrenia (Browne et al, 2000., Zabala et al, 2006).

The research psychiatrist underwent training for the NES from experienced researchers in the standard manner and according to the instructions of the developers of the instrument. Each item was tested according to a fixed order. The NES assessments were conducted at baseline, 6 and 12 months. To reflect the diversity of neurological abnormalities in schizophrenia, the total NES scores and scores for the subscales were analysed separately. Factor analysis of the NES was also conducted and the factor scores were analysed separately.

4.5.1 PROCEDURE

The diagnosis of schizophrenia, schizo-affective disorder or schizophreniform disorder was arrived at using criteria from the Diagnostic and Statistical Manual for Mental Disorders-Fourth edition (DSM-IV) (American Psychiatric Association, 1994), based on the assessment of the research psychiatrist conducted with the use of the Structured Clinical Interview for the DSM-IV Axis I Disorders, Patients edition (SCID-P) (First et al, 1994).

Baseline evaluations were performed as far as possible before antipsychotic medications were prescribed. In the few cases where severity of psychopathology prevented immediate assessment, the evaluations were conducted as soon as patients were deemed well enough to co-operate for the examinations. The following information was obtained from all study participants at baseline: demographic data, personal history, psychiatric history, medical history, family history. All study participants underwent full physical examination at baseline. This was repeated at 6 months and at 12 months.

Psychiatric Assessment

The severity of the baseline psychopathology was evaluated by administering the Positive and Negative Syndrome Scale (PANSS) (Kay et al, 1987). The overall clinical status was assessed using Clinical Global Impression (CGI and CGI-Severity) (Guy et al, 1976). Additional assessments included the Calvary Depression Scale for Schizophrenia (CDSS) (Addington et al, 1993), Birchwood Insight Scale (BIS) (Birchwood et al 1994), Social and Occupational Functioning Assessment Scale (SOFAS), and the World Health Organisation Quality of Life Scale (WHOQOL-BREF) (WHO, 1998).

Pre-morbid adjustment was assessed using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al, 1982), while extrapyramidal effect of antipsychotics was assessed using the Extrapyramidal Symptoms Rating Scale (ESRS) (Chouinard and Margolese, 2005). These assessments were repeated at three monthly intervals for the full 12 months.

4.5.2 TREATMENT

For patients who were on medication at the time of recruitment, there was a washout period of 7 days during which all psychotropic medications were discontinued. The standard treatment for all patients was long acting flupenthixol injection. Treatment with oral flupenthixol 0.5mg to 4mg per day was commenced for one week before the first long-acting flupenthixol dose to rule out hypersensitivity to flupenthixol. The starting dose

of the long-acting flupenthixol was 10mg fortnightly, with 6-weekly increments of 10mg allowed, to a maximum of 30mg fortnightly. However, for patients aged 16 – 18 years, the starting dose was 5mg fortnightly. The dose interval of long-acting flupenthixol was increased to 4-weekly in one subject because of the development of significant extrapyramidal symptoms. Additional oral flupenthixol tablets were given when required, at the discretion of the investigator. Furthermore, lorazepam was prescribed for sedation at the discretion of the investigator up to a maximum dose of 12mg per day during the acute phase of illness. Thereafter, doses not exceeding 4mg per day were prescribed for a few days for some patients who required sedation. Patients also received benzhexol, and propranolol for treatment of emergent extrapyramidal symptoms and akathisia. However, patients did not receive any additional medications for at least 12 hours before each assessment.

Concomitant medications were allowed if they were for treatment of physical conditions that were present before entry into the study, or developed during the course of the investigation. This was also at the discretion of the investigator.

To ensure adherence to the treatment protocol, additional assertive monitoring was built into the study. The investigator, a mental health nurse, and a social worker were responsible for this. A good relationship was established with the patients and carers. They were provided psycho-education emphasising the need for continuous treatment. A register was kept for patients' appointment dates. Reminders were sent out by mobile

phone text messaging. In the event of a missed appointment patients or their carers were contacted telephonically by the nurse and social worker, and encouraged to come in for their scheduled treatment. Where necessary, the nurse and the social worker were requested to conduct home visits.

4.5.3. DURATION OF UNTREATED PSYCHOSIS

Data relating to date of onset of psychosis was obtained during interviews with the patient and a close relative. Duration of untreated psychosis was defined as the period in months from the onset of psychotic phenomena to first presentation to the psychiatric unit. In line with previous studies, onset of psychosis was defined as the presence for one week or more of one of the following psychotic symptoms; delusions, hallucinations, marked thought disorder, marked psychomotor disorder, and bizarre, grossly inappropriate and/or disorganised behaviour, with a marked deterioration of functioning.

4.5.4. TRAINING

The investigator received training on the use of the above instruments at the Tygerberg Hospital, Cape-Town, South-Africa. Moreover, the acceptability and reliability of the instruments were assessed prior to commencement of the study.

4.6. ETHICAL APPROVAL.

Ethical approval for the study of this cohort of patients with schizophrenia was obtained from the University of Ibadan/University College Hospital Joint Ethics Committee. All study procedures were approved by the ethical committee, in agreement with the Nigerian national regulation, and followed the ethical principles of the Declaration of Helsinki. The ethical approval covered the study of several other aspects of schizophrenia in this cohort.

4.7. STATISTICAL ANALYSIS

All data were recorded in a case record format. Statistical analysis was conducted with the assistance of a bio-statistician. Data analysis was performed using the Statistical Package for the Social sciences (SPSS) version 16.0.

Descriptive statistics such as mean and standard deviation were used to summarize quantitative variables including the NES scores while frequencies and proportions were used for discrete variables. The differences between mean scores were tested using the student t-test, while the chi^2 test was used to examine the difference between groups. The Fisher's exact test was invoked appropriately. Factor analysis was conducted on NES items that were abnormal in more than 10% of the entire sample. Items testing for cerebral dominance were excluded from the factor analysis. Factors obtained following initial

maximum likelihood exploration were further rotated using the varimax procedure. Factors are reported when they have eigenvalues greater than unity (Andreasen et al, 1995), and when they contribute at least 10% to the cumulative variance (Sewell et al, 2010). In subsequent analyses, two neurological abnormality scores are used: NES total scores, as well as the factor derived scores. The pattern of factor derived, and total NES scores from repeated measurements were explored. The repeated measures Analysis of variance was used to compare differences in the observed NES scores. The Mauchly's sphericity assumption was tested to ensure the equality of variance of the between pairs values, and in cases where the assumption was violated, the Greenhouse-Geisser correction was invoked. The patterns of scores of the functional NES categories obtained from repeated measurements were also investigated using the same method.

The correlations between indices of clinical profile, and those of clinical outcome and NES scores were tested using Pearson's Correlation coefficient. The data of subjects who fell out of the study were included in the analysis. A significant level of <0.05 was used throughout the study. Corrections for multiple testing were not carried out due to the exploratory nature of this component of the study.

CHAPTER FIVE

RESULTS

A total of 84 subjects were recruited into the study after an extensive clinical history and assessment conducted by the research psychiatrist, including the administration of the Structured Clinical Interview for the DSM-IV Axis I Disorders, Patients edition (SCID-P). The flow chart for the study is as shown in figure III.

5.1. DEMOGRAPHIC CHARACTERISTICS OF SUBJECTS

Details of the demographic characteristics of the subjects recruited are shown on Table 8.

Age and Gender

The sample is composed of 38 (45.24 %) women and 46 (54.76 %) men. Their mean age was 28.67 (±6.41) years. Female subjects were older than males at presentation (29.47 ± 6.64 versus 28 ±6.20 years) but the difference was not statistically significant (p=0.297). Similarly, female subjects were older than males at onset of the illness (26.42 ± 7.00 versus 23.15 ±8.90 years). The difference was also not statistically significant (p=0.069).

Education, Marital and Employment status

Most of the subjects, 78 (92.86%) were unemployed, and most 62 (73.81%) were single. A majority of them (73.81%) had at least secondary education with the rest (26.19%) having less than six years of formal education.

5.2. CLINICAL CHARACTERISTICS OF SUBJECTS

Tables 9 and 10 show the clinical characteristics of the subjects at baseline.

The sample included 68 (80.95%) subjects with a diagnosis of schizophrenia and 15 (17.86) with a diagnosis of schizophreniform disorder (17.86 %). Only 1 (1.19%) subject met DSM IV diagnosis of schizo-affective disorder (table 9).

The overall mean age at onset of illness was 24.63 (± 8.22) years. The mean duration of untreated psychosis was 38.89 (± 47.69) months, with a median of 26 months. In all, 52 (61.90%) subjects had illness duration longer than 12 months, while the remaining 32 (38.09%) subjects were ill for less than 12 months before recruitment into the study (table 9). The table also shows that 73 (86.90%) subjects were right handed while the remaining 11 (13.10) were mixed handed. Only 8 (9.52%) subjects had a family history of a serious mental illness. A majority of the subjects 79 (94.04%) had poor insight. Lack of insight

was computed as the total numbers of no insight and unsure responses to all questions about insight (table 9). The distributions of the mean scores for pre-morbid adjustment of the entire sample from childhood through late adolescents are also shown on table 9.

Table 10 shows that the overall mean baseline Positive and Negative Syndrome Scale (PANSS) score of the subjects was 73.38 (± 15.88). The mean score on the Social and Occupational Functioning Assessment Scale (SOFAS) was 44.17 (± 12.73). The mean score on the Clinical Global Impression (CGI) at recruitment was 5.13 (SD 0.85). In addition, the mean scores for the Calgary Depression Scale for Schizophrenia (CDSS), as well as those of the various aspects of the Extra-pyramidal Syndrome Rating Scale (ESRS) are shown on table 10.

Table 11 compares the baseline characteristics of patients who dropped out of the study and those who completed the 12 month assessments.

Figure III: Flow chart of the study

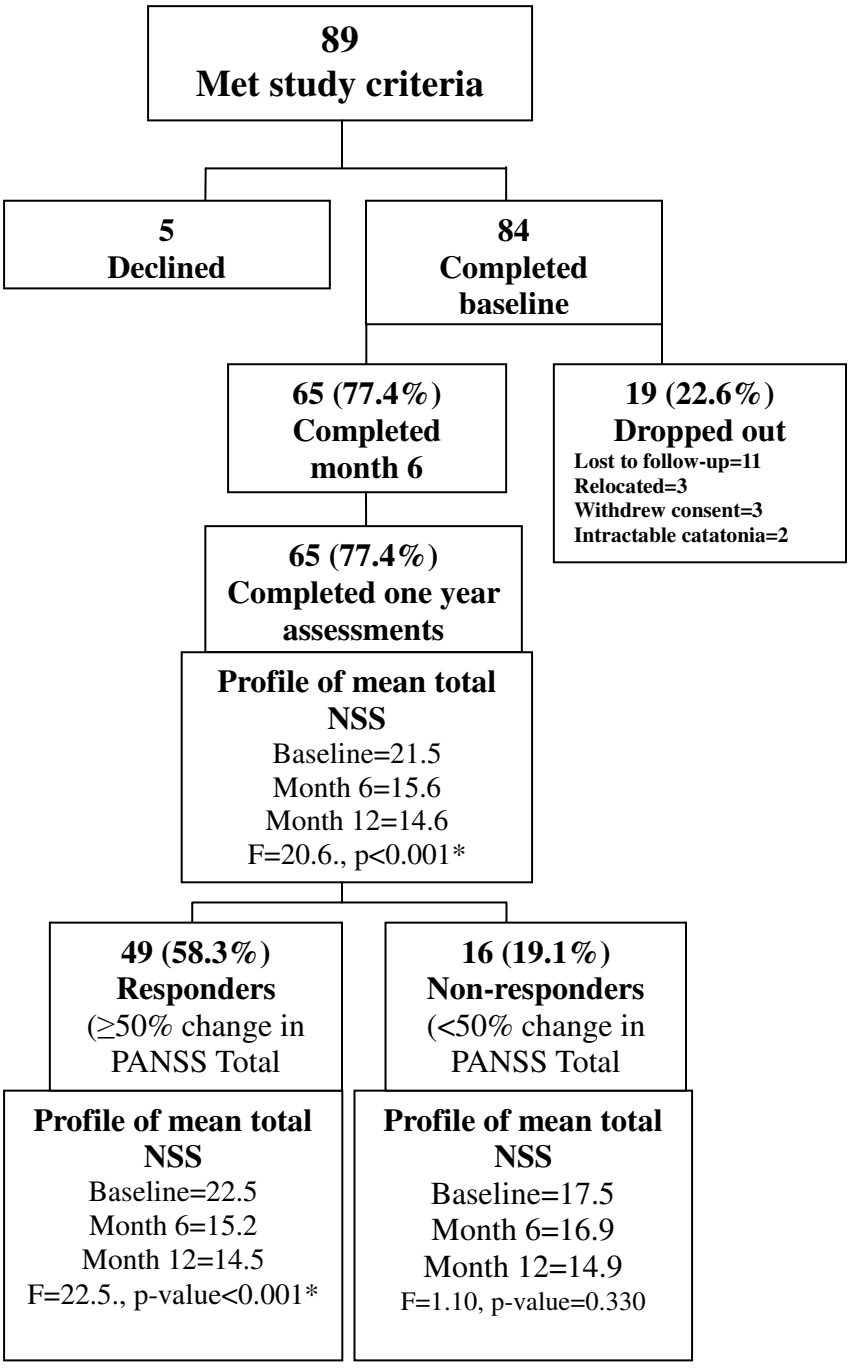


Table 8: Baseline Demographic Characteristics of Subjects

Characteristics	Mean (SD)
Age (years)	
Male	28.0 (6.20)
Female	29.47 (6.64)
Total	28.67 (6.41)

Characteristics	Number	Percent
Gender		
Male	46	54.76
Female	38	45.24
Total	84	100.00
Education		
Elementary	22	26.19
Secondary	31	36.90
Tertiary	31	36.90
Total	84	100.00
Marital Status		
Never Married	62	73.81
Married	22	26.19
Total	84	100.00
Employment Status		
Unemployed	78	92.86
Employed	6	7.14
Total	84	100.00

Table 9. Clinical Characteristics of Subjects at Baseline

Characteristics	Mean (SD)	Median
Age at Onset (years)		
Male	23.15 (8.90)	
Female	26.42 (7.00)	
All	24.63 (8.22)	
Duration of Untreated Psychosis (Months)	38.89 (47.67)	26.00

Characteristics	Number	Percent
Family History of Mental Illness		
Yes	8	9.52
No	76	90.48
Handedness		
Right	73	86.90
Mixed	11	13.10
DSM IV Diagnosis		
Schizophrenia	**68**	**80.95**
Paranoid type	30	35.71
Undifferentiated	20	23.89
Disorganized type	15	17.86
Catatonic type	2	2.38
Simple	1	1.19
Schizophreniform Disorder	15	17.86
Schizo-affective Disorder	1	1.19
Insight		
Yes	5	5.95
No	10	11.90
Unsure	69	82.14

Table 10. Baseline Clinical Assessment Scores

Scales	Mean	Standard Deviation	Range
Positive and Negative Syndrome Scale (PANSS)	11.79	4.86	4 - 23
Positive	19.92	9.98	7 - 42
Negative	19.68	7.00	7 - 34
Disorganized/cognitive	12.43	4.85	5 – 25
Excited	5.82	3.02	4-15
Depression/anxiety	73.32	15.89	37-108
Total			
Pre-morbid Adjustment Scale (PAS)			
Childhood			
Social/ Academic[a]	1.79/ 3.24	2.85/2.73	0-11/0-12
Early Adolescent			
Social/ Academic[b]	3.77/ 3.34	4.13/2.67	0-15/0-12
Late Adolescent			
Social/ Academic[b]	3.77/3.34	4.13/2.67	0-15/0-12
Clinical Global Impression-severity (CGI-S)	5.13	0.85	3 – 7
Social and Occupational Functioning (SOFAS)	44.17	12.73	
Calgary Depression Scale of Schizophrenia (CDSS)[a]	1.69	3.37	0 – 15
Neurological Evaluation Scale (NES)			
Sensory Integration	2.99	1.87	0 – 6
Motor Co-ordination	5.71	3.95	0 – 13
Motor Sequencing	4.63	2.00	0 – 6
Total NES	21.48	11.11	2 – 44

a = One observation missing
b = Four observations missing

Table 11. Comparison of the baseline characteristics of completers and drop-out subjects

Characteristics	Drop-out N=19	Completers N=65	$\chi 2$	p-value
Gender (%)				
Male	57.89	53.85	0.097	0.755
Female	42.11	46.15		
Marital status (%)				
Never married	78.95	72.31	0.335	0.768 [a]
Married	21.05	27.69		
Education (%)				
Elementary	26.32	26.15	0.0002	1.000
Secondary or higher	73.68	73.84		
DSM IV diagnosis (%)				
Schizophrenia	73.68	84.62	7.155	0.069
Other psychosis	26.32	15.38		
Insight (%)				
Present	15.79	3.08	4.244	0.074 [a]
Absent	84.21	96.92		

Characteristics. Mean (SD)			t-test	p-values
Age at presentation.	28.74 (5.77)	28.65 (6.63)	0.054	0.957
Duration of Untreated Psychosis	27.32 (35.5)	39.35 (56.0)	0.885	0.379
Positive and Negative Syndrome Scale (PANSS)	69.95 (2.94)	74.35(2.06)	1.072	0.287
Clinical Global Impression (CGI)	4.95 (0.21)	5.19 (0.10)	1.075	0.286
Social and Occupational Functioning (SOFAS)	44.63 (2.97)	44.03 (1.58)	0.180	0.858
Neurological Evaluation Scale (NES)	22.21(10.4)	22.26 (11.4)	0.356	0.745

a = Fisher's exact test

5.3. PROFILE OF NEUROLOGICAL SOFT SIGNS (NSS)

The mean Neurological Evaluation scale (NES) score for a total of 26 items in the entire sample was 21.48 (± 11.11), with the scores ranging from 2 to 44. A higher mean score was recorded for items conceptually regarded as representing motor co-ordination (5.71 ± 3.95, range 0-13) and motor sequencing abnormalities (4.63 ± 2.0, range 0-6) as described in the study methodology (Table 9). There was a mean score of 2.99 (± 1.87; range of 0-6) for items that represent sensory integration functions. These three functional areas of interest are subsequently referred to in this dissertation as the 'functional categories', as distinct from the empirically derived categories of NSS.

Neurological abnormality, defined as the rating of at least 2 on any 1 item on the NES, was elicited in 81 (96.43%) subjects in the sample. This definition is based on that of Browne et al. (Browne et al, 2000). It has been used in subsequent studies of NSS in first episode schizophrenia (Zabala et al, 2006., Dazzan et al, 2008).

5.4. FACTOR ANALYSIS OF THE NEUROLOGICAL EVALUATION SCALE (NES)

Exploratory factor analysis of the baseline Neurological Examination Scale (NES) scores was conducted using the methods of previously reported works dealing on Neurological Soft Signs (NSS) in schizophrenia (Malla et al, 1997., Sanders et al, 2000, Keshavan et al,

2003., Emsley et al, 2005., Compton et al, 2006., Sewell et al, 2010). Items that were present in less than 10% of the entire sample were eliminated. These included NES items 2, 4, 5, 9, 11, 23, 24, and 26. Items that test for cerebral dominance (NES 5 a, b, and c) were also eliminated from the factor analysis. This was necessary as cerebral dominance is not regarded as an abnormal NSS. It is included in the NES for the purpose of determining the dominant side of subjects, information that is useful in the examination of bilaterally occurring signs where the dominant side is required to be tested first. The following 18 NES items were included in the analysis after the eliminations as described; 1, 3, 6, 7, 8, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, and 25 (table 12). The maximum likelihood factors were rotated using the varimax procedure. The factors were derived according to the following criteria;

1). Eigenvalue greater than unity (Andreasen et al, 1995), and

2). A total of 10% variance contributed by each factor (Sewell et al, 2010)

The first five NES factors had eigenvalues greater than unity and accounted for 61.9 % of the total variance. However, only the first 4 factors contributed up to 10% variance individually. These four factors accounted for 54.1% of the total variance (table 13). The table also shows the results of the principal component matrix with the factor loadings of the analysis after orthogonal varimax rotation.

The first factor which contributed 18% to the cumulative variance is comprised of audio-visual integration, fist-edge-palm, rhythm tapping, extinction, and right-left confusion. The fist-edge palm test for functions associated with sequencing of complex motor acts. The rhythm tapping test has also been associated with such functions by some other authors (e.g, Bombin et al, 2005). The remaining components of factor 1 are items that test for perceptual functions. Factor 2 comprised of items testing synkinesis, convergence, and gaze impersistence. This factor is unique as it represents eye movement abnormalities in schizophrenia. Factor 3 includes tandem walk, adventitious flow and graphaesthesia. Whereas tandem walk and adventitious flow are items that test for primary motor functions, graphaesthesia is recognizable as a sensory integration function. Factor 4 comprises of stereognosis, another sensory integration function.

Table 12. Prevalence and mean baseline Severity scores of NES Items

NES Items	Number	Percent	Mean	Standard deviation
Audiovisual integration	45	53.6	1.21	0.91
Fist-edge-palm	60	71.4	1.56	0.77
Rythm tapping	47	56.0	1.29	0.87
Extinction	32	38.1	0.91	0.93
Right/left confusion	41	48.1	1.19	0.87
Synkinesis	22	26.2	0.70	0.86
Convergence	22	26.2	0.75	0.85
Gaze impersistence	30	35.7	0.93	0.89
Tandem Walk	14	16.7	0.50	0.77
Adventitious flow	5	6.0	0.24	0.55
Graphaesthesia	44	52.4	1.26	0.85
Stereognosis	15	17.9	0.51	0.78
Memory	63	75.0	1.30	0.82
Rapid alternating movements	25	29.8	0.77	0.88
Finger/thumb opposition	30	35.7	0.87	0.92
Mirror movement	16	19.0	0.51	0.80
Finger to nose test	15	17.9	0.57	0.78
Grasp reflex	21	25.0	0.50	0.87
Total NES score	84	100	21.5	11.1

Table 13. Factor structure of the NES Items

	Factors			
NES Items	**1**	**2**	**3**	**4**
Audiovisual integration	**0.6179**	0.3813	0.1862	0.0691
Fist-edge-palm	**0.8403**	-0.0635	-0.0507	0.0175
Rythm tapping	**0.6279**	0.4463	0.3077	0.0460
Extinction	**0.6112**	0.2675	0.2758	0.2573
Right/left confusion	**0.5355**	0.1595	0.3305	0.0876
Synkinesis	-0.0250	**0.7128**	0.2598	0.2451
Convergence	0.1743	**0.7300**	-0.0335	-0.0300
Gaze impersistence	0.2665	**0.6417**	-0.1330	-0.1574
Tandem Walk	0.1647	-0.0166	**0.6718**	0.0700
Adventitious flow	0.1534	0.0558	**0.7188**	-0.0706
Graphaesthesia	0.0702	0.3899	**0.5443**	0.2191
Stereognosis	0.2321	0.1389	0.0706	**0.8562**
Memory	0.4459	0.1318	0.3792	0.3235
Rapid alternating movements	0.3139	0.4897	0.1705	0.3702
Finger/thumb opposition	0.4290	0.4148	0.2145	0.3418
Mirror movement	0.3394	0.3911	0.1305	0.3925
Finger to nose test	0.0312	0.1174	0.1409	0.0929
Grasp reflex	0.3895	0.2048	0.1155	-0.6424
Explained variance (%)	18.1	15.5	10.4	10.1
Severity. Mean (SD)	6.44 (3.3)	2.38 (2.0)	2.00 (1.6)	0.51 (0.8)

5.5. TEMPORAL STABILITY OF NEUROLOGICAL SOFT SIGNS

To examine the longitudinal profile of the Neurological Soft Signs (NSS) across the one year course of schizophrenia, the mean total and sub-scale scores on the Neurological Evaluation Scale (NES) at baseline, month 6, and month 12 were compared. A repeated measures analysis of variance (ANOVA) of the NES scores across these three time periods was conducted for both the empirically derived factors of the NES and the functional categories of the NSS. The NES total score was also included in this analysis.

Table 14 shows the results of the repeated measures ANOVA for the total NES score, the derived NSS factors as well as the 'functional' categories of NSS. The mean scores for factor 1 of this study (Perceptual and motor sequencing) was not significantly different across the three time periods of baseline, month 6 and month 12 ($F= 1.262$, $p=0.287$). The sphericity assumption was also not violated (sig. 0.130) (Table 14). However, the mean scores of the other derived NES factors changed significantly between the three time periods. The sphericity assumption was violated for factor 4 (sig <0.0001) (table 14). When the functional categories of the NSS were considered, the mean scores for sequencing of complex motor acts category did not change significantly from baseline through month 6 to month 12 ($F=1.870$, $p=0.158$). The sphericity assumption was also not violated (sig = 0.372) (table 14). The mean scores for the remaining two functional categories changed considerably across the same time frame. The sphericity assumption was violated for the motor co-ordination category (sig <0.0001) (table 14). The mean total

NES scores also changed considerably over time ($F=20.56$, $p<0.0001$). The sphericity assumption for equal variance was also violated (sig=0.006) (table 14).

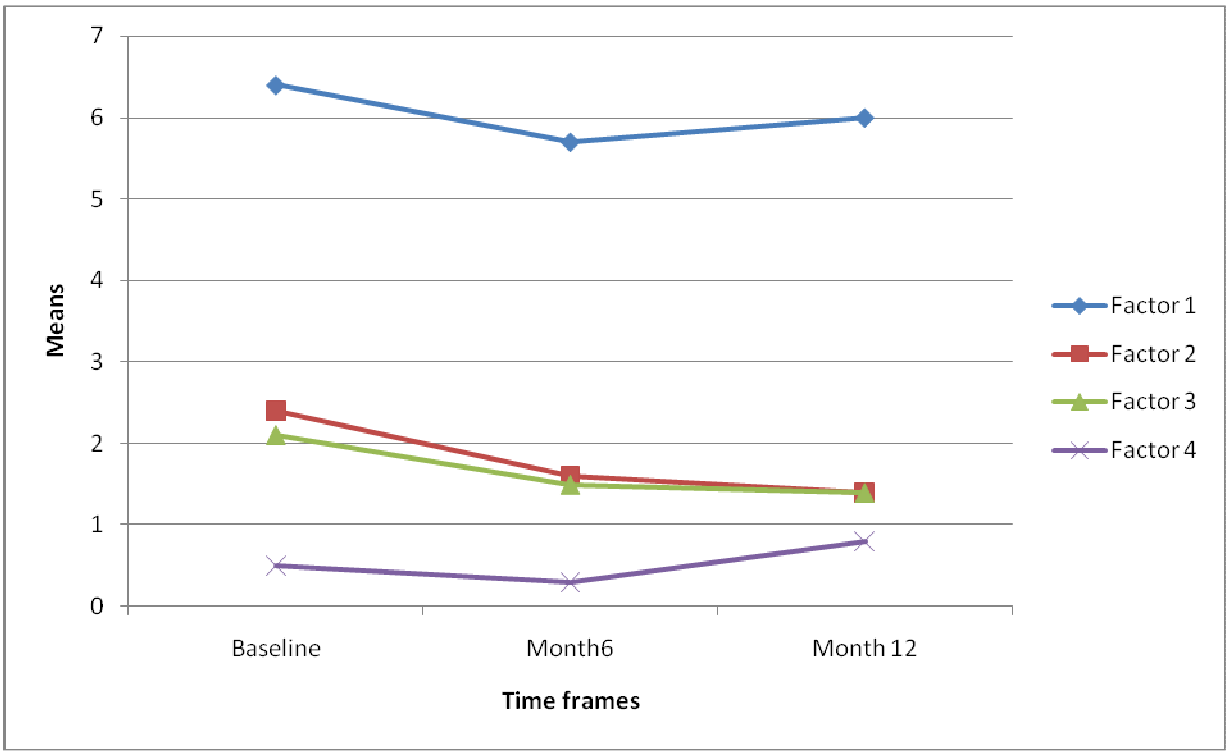
Table 14. Repeated Measures ANOVA of the mean scores for total NES, derived factors, and functional categories across three time periods (Baseline, month 6, and month 12)

	Baseline		Month 6		Month 12		Sphericity test significance	F-test	P-value
	Mean	S.D	Mean	S.D	Mean	S.D			
Factor 1	6.400	3.436	5.723	3.731	6.000	3.640	0.130	1.262	0.287*
Factor 2	2.400	1.983	1.615	1.608	1.369	1.626	0.120	11.32	<0.001
Factor 3	2.062	1.590	1.508	1.214	1.415	1.158	0.054	7.286	0.001
Factor 4	0.539	0.792	0.292	0.631	0.769	0.322	0.000	10.98	<0.001
Sensory integration	3.108	1.905	2.123	1.526	2.062	1.519	0.291	14.64	<0.001
Motor co-ordination	5.723	4.049	3.631	3.476	3.508	3.317	0.001	15.14	<0.001
Motor Sequencing	4.539	2.092	4.000	2.264	4.139	2.297	0.372	1.870	0.158*
NES total	21.48	11.11	15.62	9.661	14.62	8.732	0.006	20.56	<0.001

Asterisks *= Non-significant repeated Measures ANOVA

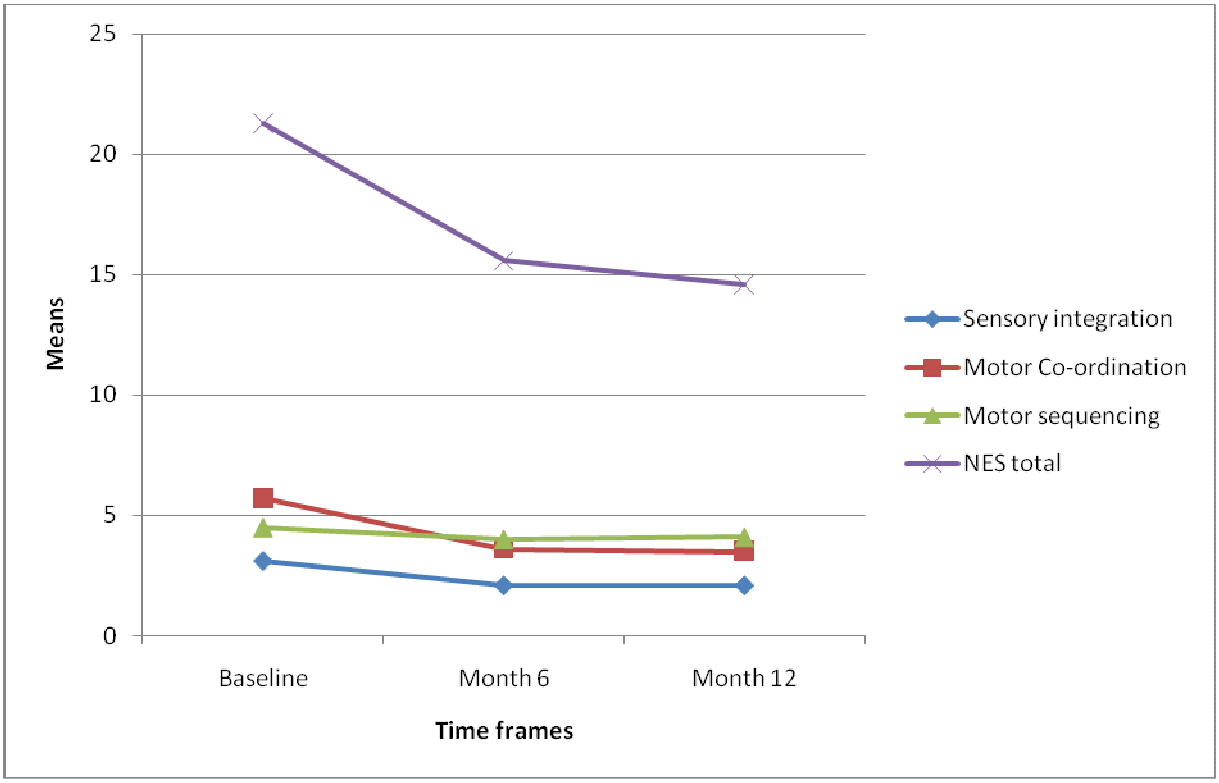
NES= Neurological Evaluation Scale

Figure IV: Repeated Measures ANOVA of the mean scores for the derived factors across three time periods (Baseline, month 6, and month 12)



Note: The derived factor 1 is relatively stable across the three time periods regardless of the clinical profile of the schizophrenia

Figure V: Repeated Measures ANOVA of the mean scores for total NES, and the functional categories across three time periods (Baseline, month 6, and month 12)



Note: The motor sequencing NSS appear stable across the three time periods regardless of the clinical profile of schizophrenia

5.6. RELATIONSHIP BETWEEN NEUROLOGICAL SOFT SIGNS AND THE CLINICAL CHARACTERISTICS OF SCHIZOPHRENIA

Tables 15 a and b summarise the relationship between the empirically derived factors as well as the 'functional' categories of neurological soft signs (NSS) and the clinical characteristics of schizophrenia. There were no significant correlations between the empirically derived factors and the age at onset, duration of untreated psychosis (DUP), or the pre-morbid adjustment of patients in the sample (Table 15 a). Similarly there were no significant differences between the age at onset, duration of untreated psychosis (DUP), or the pre-morbid adjustments (Social or academic) of patients with a higher mean number of (NSS), defined here and after by a score above the mean Neurological Evaluation Scale (NES) total score, and those with a lower number, defined here and after by a score below the mean total NES score. The mean total NES score was 21.5 (Table 15 b). This categorization of the NES total score by a split at the mean score was done in accordance with the method described in some previous studies of neurological soft signs in first episode psychosis in which the NES had been used (e.g, Ruiz-Veguilla et al, 2009).

Sensory integration abnormalities as a 'functional' category correlated significantly and inversely with the age at onset of schizophrenia ($r= -0.22$, $p=0.040$) (table 15 a). Other than the motor sequencing 'functional' category which correlated significantly with the depression/anxiety factor of the Positive and Negative Syndrome Scale (PANSS) ($r=0.29$, $p=0.007$), the other 'functional' categories, the empirically derived factors, as well as the

NES total score correlated significantly with the negative as well as with the cognitive/disorganised factors of the PANSS (table 15 a). Similarly, the derived factors 1 and 2, the NES total score, as well as the motor co-ordination 'functional' category correlated significantly with the excitement/hostility factor of the PANSS (table 15a). In all, the total baseline NES score, the functional categories, as well as the derived factors correlated significantly and positively with the severity of the disease as rated by the Clinical Global Impression scale (CGI-severity) (table 15a). Similarly, there was a significant difference in symptom severity of schizophrenia between patients with a higher mean number of NSS and those with a lower number of NSS, with the former tending to have a higher mean severity score compared to the latter ($t=5.21$, $p<0.001$) (table 15b). In summary, while the baseline motor sequencing scores had no association with the clinical characteristics of schizophrenia, the total NES scores, as well as the scores for the other major sub-categories correlated with a more severe psychopathology especially in terms of negative and cognitive/disorganization symptoms. The NES total score, the motor co-ordination functional category as well as the derived factors 1 and 2 also correlated with the excitement/hostility factors of the PANSS.

Baseline NSS did not correlate significantly with the development of depression over time ($r=0.031$, $p=0.803$., $r=-0.008$, $p=0.953$, for Months 6 and 12 total NES respectively) (table 15a). However, there was a significant inverse correlation between baseline motor sequencing 'functional' category signs and treatment emergent extra-pyramidal symptoms at 6 months and at 12 months ($r= -0.27$, $p=0.033$., $r= -0.27$, $p=0.033$, respectively) (tables 15a).

Table 15a. Pearson correlation of baseline NSS and the clinical characteristics of schizophrenia

	DERIVED NES FACTORS				NES FUNCTIONAL CATEGORIES			
	1 Perceptual/ motor sequencing	**2 Eye signs**	**3 Motor coordination /graphaesthesia**	**4 Stereognosis**	**Sensory Integration**	**Motor coordination**	**Motor Sequencing**	**NES Total**
Age at onset	-0.079	0.023	-0.050	-0.180	-0.224*	-0.034	0.202	-0.004
D.U.P	0.037	-0.021	0.116	-0.042	-0.006	-0.005	0.016	-0.005
Pre-morbid adjustment								
CHILDHOOD (Social/academic)	0.019/0.123	0.075/0.120	0.003/-0.051	0.074/0.078	0.029/0.010	0.051/0.136	0.031/0.158	0.034/0.101
ADOLESCENT (Social/academic)	0.067/-0.011	0.045/-0.132	-0.006/-0.055	0.059/0.052	0.031/0.069	0.116/-0.082	0.088/0.061	0.039/-0.081
PANSS								
Positive	-0.058	0.010	-0.072	-0.080	-0.020	-0.102	0.211	-0.075
Negative	0.472**	0.328**	0.239*	0.302**	0.412**	0.493**	0.069	0.456**
Disorganized	0.525**	0.384**	0.305**	0.349**	0.463**	0.567**	0.173	0.559**
Excited	0.238*	0.224*	0.204	-0.036	0.030	0.272*	0.145	0.228*
Depression	0.157	0.090	0.113	0.009	0.128	0.107	0.293**	0.169
CGI-severity	0.558**	0.506**	0.228*	0.297**	0.388**	0.555*	0.420**	0.566**
CDSS								
Baseline	0.065	0.020	0.134	0.076	0.155	-0.0004	0.137	0.095
Month 6	0.051	-0.027	0.138	-0.059	0.040	0.038	-0.021	0.031
Month 12	-0.009	-0.101	0.240	-0.060	-0.031	-0.021	-0.017	-0.008
ESRS								
Month 6	-0.138	-0.100	-0.004	-0.138	-0.135	-0.099	-0.269*	-0.154
Month 12	0.032	-0.045	0.049	-0.070	0.077	-0.038	-0.265*	-0.056

Significant Pearson Correlation Coefficient; *<0.05, **<0.01

PANSS= Positive and Negative Syndrome Scale, CGI= Clinical Global Impression, CDSS= Calgary Depression Scale of Schizophrenia, ESRS= Extra-pyramidal Symptoms Rating Scale

Table 15b. Relationship between baseline NES total score and clinical characteristics

Characteristics	NES score <21.5 (n=43)	NES score ≥21.5 (n=41)	Statistics	p-value
Age at onset	24.93	24.32	0.340	0.735
D.U.P (In months)	35.02	38.32	0.288	0.774
Pre-morbid Adjustments				
CHILDHOOD (Social/academic)	1.81/2.98	1.78/3.51	0.053/0.895	0.957/0.374
ADOLESCENT (Social/academic)	3.61/3.40	3.95/3.27	0.382/0.208	0.703/0.836
CGI-severity	4.72	5.56	5.210	<0.001*
CDSS				
Baseline	1.42	1.98	0.750	0.455
Month 6	1.58	1.94	0.458	0.648
Month 12	1.29	2.49	1.356	0.180

Asterisk * = Significant p-value of an unpaired t-test

CGI= Clinical Global Impression
CDSS= Calgary Depression Scale of Schizophrenia
D.U.P= Duration of Untreated Psychosis

5.7. NEUROLOGICAL SOFT SIGNS AND OUTCOME OF SCHIZOPHRENIA

Outcome was assessed in terms of symptom reduction and percentage change in the Positive and Negative Syndrome Scale (PANSS) scores between baseline and month 12. Additional measurements of outcome such as functioning, quality of life and the development of insight overtime were also employed. Table 16 shows the response rate measured on the PANSS from baseline to month 12. Response rate was defined as at least 50% or more reduction in the PANSS scores from baseline to month 12. In all, 75.8% of the subjects who completed month 12 assessments met the criteria for response using this definition. Apart from the PANSS depression scores on which a response rate of 18.1% as defined was observed, the other PANSS subscales scores had a response rate of over 60% at one year follow-up. Up to 78.8% of the subjects had at least 50% reduction in the scores for cognitive/ disorganization factor of the PANSS from baseline to month 12 (table 16).

There were significant differences in the percentage change in PANSS negative, disorganization, and total scores between patients with higher mean number of Neurological Soft Signs (NSS) and those with a lower number of NSS at baseline (Table 17 a). Baseline scores for the derived NES factors 1, 2 and 3 correlated significantly and positively with the percentage change in the PANSS negative symptoms scores from baseline to month 12. Also, baseline scores for factors 1 and 4 correlated significantly and positively with the percentage change in the PANSS cognitive/disorganized scores

from baseline to month 12 (table 17b). In all, baseline scores for the derived NES factors 1, 2 and 4 correlated significantly and positively with the percentage change in the PANSS total scores from baseline to month 12 (table 17 b). In the case of the functional categories of the NES, table 17b reveals a similar pattern for the PANSS negative and cognitive/disorganization sub-scale. The baseline scores for the sensory integration, motor coordination and the NES total scores correlated significantly and positively with the percentage change in the PANSS negative and cognitive/disorganization scores from baseline to month 12 (table 17 b). Interestingly, there were no correlation between the baseline motor sequencing category scores and the percentage change in the PANSS total or sub-scale scores from baseline to month 12 (table 17 b).

Table 17a also shows that subjects with a higher number of baseline NSS tended to have a significantly lower rating of functioning, as measured with the SOFAS, at month 6 and month 12 ($p=0.02$ and $p=0.04$ respectively) (table 17a). However, while baseline scores for the derived factors 1 and 3 correlated significantly and inversely to the ratings of the functioning at month 6, only the baseline scores for the derived factor 3 correlated with the functioning at month 12 (table 17 b). In the case of the functional categories, it was observed that while the baseline scores for sensory integration, motor co-ordination and the NES total scores correlated significantly with a lower rating for functioning at month 6, only the baseline sensory integration scores correlated significantly with a poorer level of functioning at month 12. (table 17b). As it was with the PANSS rating for psychopathology, the motor sequencing scores at baseline did not show significant correlation with functioning at any stage of the disease as measured in this study.

Similar to what was found for functioning, the baseline score of the derived factor 3 correlated significantly with a poorer rating on both the total quality of life domain of the WHO-QoL and the month 12 rating for the psychological health domain (table 17b). The derived factor 3 represents motor coordination/graphaestheia. Interestingly, when considering the functional categories, only the baseline score for motor coordination correlated with a poorer rating of quality of life at month 12. Specifically, this correlation was significant for the psychological health domain of the WHO-QoL (table 17 b). Also similar to what was observed for functioning, the baseline motor sequencing scores did it show correlations with the quality of life ratings. Therefore, while the motor sequencing signs had no bearing on the outcome of schizophrenia, the motor co-ordination scores at baseline is associated with a poorer quality of life at one year (table 17 a). Also, a preponderance of NSS at baseline is associated with poorer ratings of functioning at month 6 and month 12 (tables 17a and b). Functioning was rated by means of the Social and Occupational Functioning Scale (SOFAS), while quality of life was rated using the brief version of the World Health Organization Quality of Life rating measure (WHO-QOL-BREF).

Table 16. Twelve month clinical Response of subjects as measured on the PANSS

PANSS category	<50% reduction		≥50% reduction	
	N	%	N	%
Positive	20	30.3	45	69.7
Negative	24	36.4	41	63.6
Cognitive /disorganized	14	21.2	51	78.8
Excitement/hostility	22	33.3	44	66.7
Depression/anxiety	53	81.8	12	18.2
Total	**16**	**24.2**	**49**	**75.8**

Table 17a. Relationship between baseline NES total score and the 12 month outcome of schizophrenia

	NES<21.5	NES≥21.5	t-test	p-value
PANSS (Percentage change)				
Positive	160.4	159.3	0.035	0.973
Negative	68.16	168.6	3.237	0.002**
Disorganized	106.6	154.2	2.108	0.039*
Hostility	91.90	125.2	1.144	0.154
Depression	25.16	26.40	0.084	0.933
Total	87.25	125.1	2.487	0.016*
SOFAS (means)				
Month 6	76.14	67.72	2.14	0.019*
Month 12	80.18	72.72	2.07	0.043*
	NES <21.5	**NES≥21.5**	χ^2	**p-value**
BIS. %				
Month 6	6.25	0.00	3.000	0.223
Month 12	3.13	9.09	1.002	0.606
WHO-QOL. %				
Physical Health	22.90	23.33	0.545	0.588
Psychological Health	20.77	19.55	1.967	0.054*
Social relationships	9.07	7.93	1.587	0.118
Environment	27.26	26.90	0.420	0.676
Total	80.24	77.25	1.201	0.235

Asterisks *= p ≤0.05., **=p<0.01

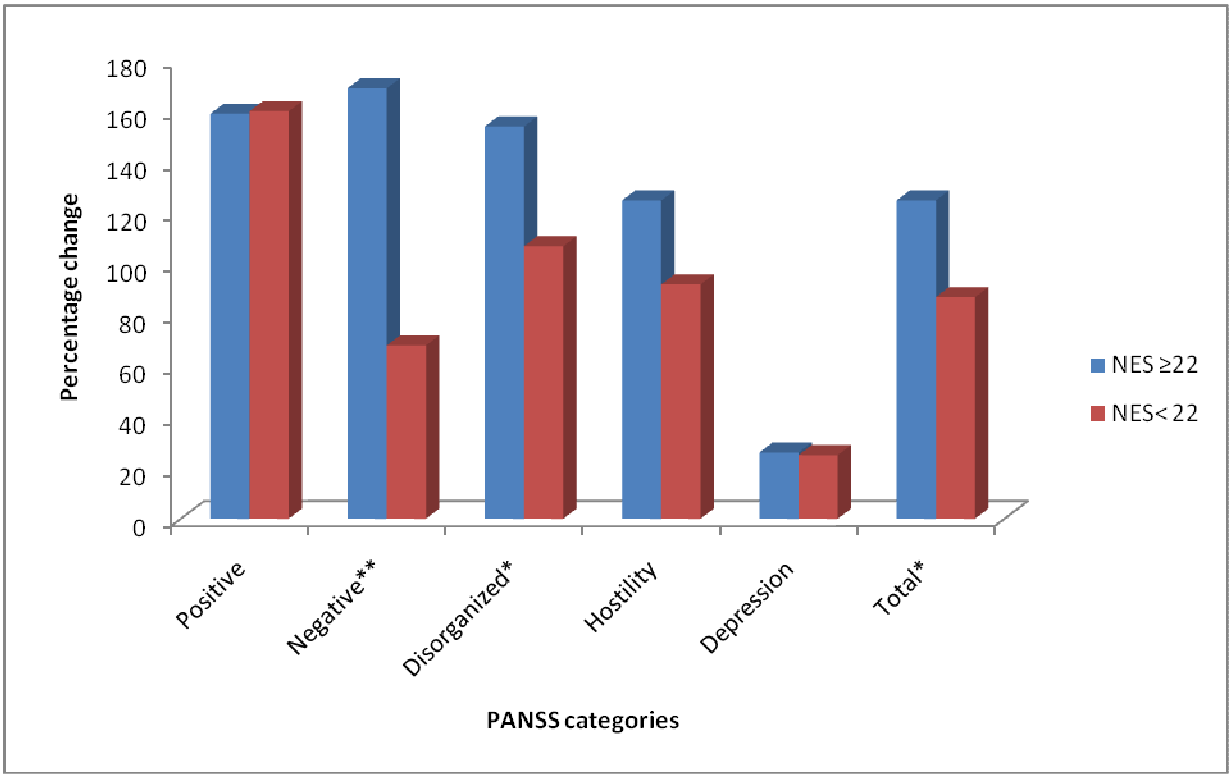
PANSS= Positive and Negative Syndrome Scale
BIS= Birchwood Insight Scale
SOFAS= Social and Occupational Functioning Scale
WHO-QOL= World Health Organization- Quality of Life

Table 17 b. Pearson correlation of baseline NSS and the outcome of schizophrenia

	DERIVED NES FACTORS				NES FUNCTIONAL CATEGORIES			
Characteristics	**1** Percptual/ motor sequencing	**2** Eye signs	**3** Motor coordination/ graphaesthesi	**4** Stereognosis	**Sensory Integration**	**Motor coordination**	**Motor Sequencing**	**NES Total**
PANSS (percentage change)								
Positive	-0.065	0.094	-0.056	0.093	0.004	-0.055	0.117	-0.008
Negative	0.327**	0.249*	0.261*	0.229	0.251*	0.448**	0.186	0.401**
Disorganized	0.318**	0.149	0.147	0.341**	0.276*	0.372**	0.145	0.345*
Excited	0.125	0.141	0.069	0.013	0.007	0.178	0.076	0.134
Depression	0.142	0.135	-0.021	0.036	0.049	0.140	0.239	0.157
Total	0.311*	0.264*	0.178	0.251*	0.226	0.407**	0.198	0.374**
SOFAS								
Month 6	-0.352**	-0.232	-0.466**	-0.148	-0.431**	-0.335*	-0.141	-0.349**
Month 12	-0.207	-0.124	-0.268*	-0.138	-0.270*	-0.161	0.015	-0.171
WHO-QOL-BREF %								
Physical Health	0.098	-0.009	-0.207	0.036	-0.068	0.070	0.163	0.072
Psychological Health	-0.175	-0.168	-0.318*	-0.009	-0.091	-0.258*	-0.134	-0.234
Social relationships	-0.223	-0.014	-0.250	0.026	-0.214	-0.187	0.054	-0.175
Environment	0.100	0.129	-0.192	0.137	0.025	0.054	0.225	0.071
Total	-0.124	-0.005	-0.360**	0.123	-0.156	-0.096	0.078	-0.109

Significance of Pearson correlation coefficient= * p<0.05., ** p<0.01
PANSS= Positive and Negative Syndrome ScaleSOFAS= Social and Occupational Functioning Scale
WHO-QOL-BREF= Brief version of the World Health Organization- Quality of Life

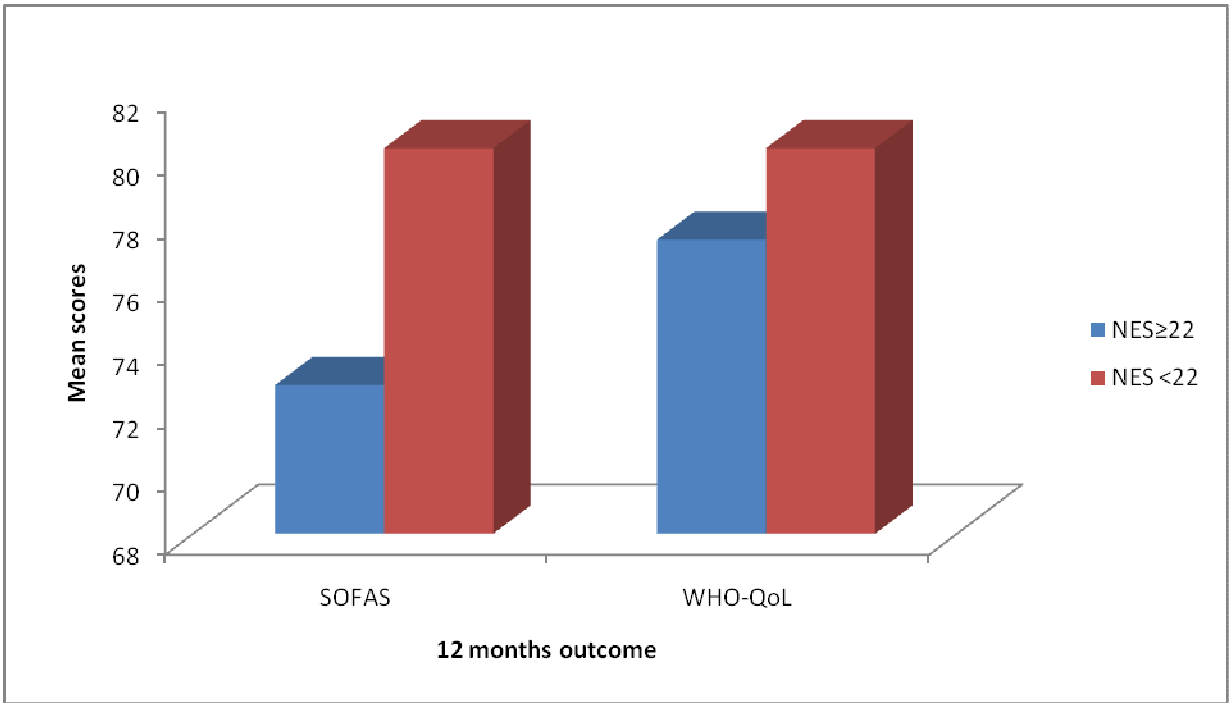
Figure VI: NES and the percentage change in the PANSS ratings from baseline to month 12



***= p<0.05., **= p<0.01., NES = Neurological evaluation scale., PANSS= Positive and negative syndrome scale**

Note: Baseline NSS were unrelated to change in positive or depression symptoms

Figure VII: Baseline NES total score and the 12 month outcome of schizophrenia



SOFAS= Social and occupational functioning scale
WHO-QoL= Brief version of the World Health Organization quality of life scale

Note: Baseline NSS was related to a poorer rating of functioning and quality of life at month 12

CHAPTER SIX

DISCUSSION

Neurological abnormalities are an important subset in the heterogeneous manifestation of schizophrenia. Their importance is derived from their potential as easy-to-measure vulnerability indicators of schizophrenia. They have also been suggested as correlates of both clinical and functional outcome. The most convincing evidence for these assertion comes from prospective longitudinal studies of first episode patients with the disease, or from studies of those without prior exposure to antipsychotic treatments (Dazzan et al, 2004., Emsley et al, 2005). Other evidence come from studies of first degree relatives of schizophrenia patients (Neelam et al, 2011., Mechri et al, 2009) or those investigating patients with schizophrenia spectrum disorders (Cuesta et al, 2002., Chan and Gottessman, 2008). Such studies are few and far between in the African continent. There is at least one longitudinal study of NSS in a cohort of predominantly mixed South-African first episode schizophrenia patient (Emsley et al, 2005), and another among a cohort predominated by African-Americans (Compton et al, 2006). Globally, the existing evidence has been based on wholly Caucasian populations or mixed population of Caucasians and other races. The present study describes the profile of NSS across the one year course of schizophrenia, as well as their relationship with a wide range of illness and outcome variables in a group of first episode, largely medication-naïve Yoruba Nigerians

with the disease. Neurological assessment in this study was based on the 26 item Neurological Evaluation Scale (NES). The items on this scale have been previously reduced to three main sub-scales of 'meaningful' theoretical and functional significance.

6.1. SUMMARY OF MAIN FINDINGS

The following findings were demonstrated in chapter five;

1. Neurological soft signs (NSS) were already present at a high rate in this cohort of patients with first episode schizophrenia or schizophreniform disorder, even before the introduction of antipsychotic drugs.

2. Neurological soft signs (NSS) demonstrated in this cohort, using the Neurological Evaluation Scale (NES), comprised of four empirical factors derived by the method of factor analysis: perceptual and motor sequencing, eye movements, motor co-ordination and graphaesthesia, as well as stegreognosis.

3. Some NSS categories exhibited a relative stability across the 12-month course of schizophrenia, and across three measurements. This was true for signs in the derived perceptual and motor sequencing category, as well as those in the motor sequencing functional category.

4. The motor sequencing signs were not associated with the clinical characteristics of schizophrenia. Other signs were associated with a predominant negative, and disorganization psychopathology. A preponderance of NSS was also associated with more severe schizophrenia psychopathology.

5. Baseline motor sequencing signs were also not associated with the outcome of schizophrenia. This was true when outcome was considered in terms of percentage change in psychopathology ratings from baseline through month 12, functioning, or quality of life. However, a higher cumulative number of NSS was associated with poorer outcome in terms of functioning and quality of life. Motor co-ordination NSS (functional or empirical) at baseline were especially associated with poor quality of life at one year.

These findings will be discussed within the context of the strengths and limitations of this study. The findings were made from the study of a sample comprising of men and women with first episode of mental illness diagnosed as mostly schizophrenia, or schizophreniform disorder using a structured interview according to the criteria codified in the Diagnostic and Statistical Manual for mental disorders (DSM IV) (American Psychiatric Association, 1994). The sample is derived from a homogenous population of black Africans native to the continent, and to the best of the knowledge of the investigator, it is the first to generate data on a comprehensive range of neurological

abnormalities in schizophrenia as it presents in this population. To achieve clinical homogeneity, only patients aged 16years to 45 years were included. Efforts were made to exclude patients with major medical or psychiatric co-morbidities. Patients were also mostly anti-psychotic naive, with only 5 (6.0%) subjects in the entire sample having a lifetime exposure to oral antipsychotic medication of one month or less before recruitment. Also, patients were treated with a uniform dose of flupenthixol depot according to a fixed protocol. Using a depot antipsychotic removed the important potential confounder of covert non-adherence. The study is designed as a prospective longitudinal investigation with repeated cross-sectional assessments at several critical time periods in the one year course of schizophrenia. These assessments were done using an array of validated measures targeting several aspects of a multi-dimensional disorder like schizophrenia. This report describes the profile of NSS across the one year course of the disease without relying on a single method of classifying the signs. In this way, empirically derived sub-sets of NSS were followed up longitudinally and in parallel with the functional categories of these signs classified in theory by Buchanan and Heinrichs (Buchanan and Heinrichs, 1989), as well as the total NES score. This was so as to separate NSS with trait-like characteristics for schizophrenia from those that have state defining features for a certain profile of the disease.

6.2. BASELINE CHARACTERISTICS OF SUBJECTS

6.2.1. BASELINE DEMOGRAPHIC CHARACTERISTICS

There were slightly more males than females meeting the inclusion criteria and hence recruited into this study. The male to female ratio was 1.2 to 1. Earlier studies of the epidemiology of schizophrenia as well as the information documented in Diagnostic and Statistical Manuals (DSM) (American Psychiatric Association, 1994) suggest equal rates of the disorder among male and female subjects. However, more recent findings with improved methodology as well as systematic reviews of the older studies have shown that men are more likely to receive a diagnosis of the disorder than women (McGrath et al, 2004., McGrath, 2007., Aleman et al, 2003). These reviews suggest that for every 3 male diagnosed with the disease, there are 2 females. However, rates of schizophrenia diagnosis in females may increase to catch up with the rate in male subjects as the mean age of the relevant sample increases. In this study, only subjects aged between 16 and 45 years were recruited. The mean age of the sample was 28.7 (SD 6.4) years and female subjects were older at onset and at presentation with the disease. Schizophrenia is known to have a later onset in females compared to males (Mcgrath et al, 2004). Female patients with the disease are also known to present or seek treatment later than males especially in low and middle income countries, as a lower priority is often given to paying for treatment for females with health problems compared to males (Large and Nielsen, 2008). There may also be some apprehension that a diagnosis of a psychotic disorder may affect a woman's prospect of getting married. All the participants in this study had at

least elementary education. Basic education is free and compulsory in most part of Nigeria, and this may have influenced the high rate o literacv in this sample. At a mean age of onset of 29 years, a majority of subjects in the sample (73.8%) had completed secondary or higher education. However, schizophrenia often leads to a deterioration of personal functioning. This is reflected in the finding in the present study that 92.9% of the subjects were unemployed, while 73.8% were un-married at recruitment into the study despite their pre-morbid educational attainment.

6.2.2. BASELINE CLINICAL CHARACTERISTICS

6.2.2.1. DURATION OF UNTREATED PSYCHOSIS

The mean duration of untreated psychosis was 38.9 months and a median of 26 months, with 61.9% of the subjects having illness duration longer than 12 months. Such a long duration of untreated psychoses is a common feature in low and middle income countries (Gureje, 1991., Murphy et al, 1998., Tang et al, 2007). In fact, some studies have suggested a causal relationship between low income and treatment delays in low and middle income countries (Large et al, 2008). In the absence of insurance, the cost of health-care may prevent many patients from seeking treatment. Qualitative mental health care may also be absent altogether in many areas (Mcready and Ohaeri, 1994). However, it is pertinent to note that this study relied on subjects presenting at the psychiatric unit for the first time with schizophrenia, having never received any orthodox treatment. A large proportion of psychotic patients in low income countries may present initially to traditional or faith healers because of socio-cultural beliefs about psychosis (Naqvi et al, 2009).

In the present study, onset of psychosis was defined as the presence, for one week or more, of one of the following psychotic symptoms; delusions, hallucinations, marked thought disorder, marked psychomotor disorder, and bizarre grossly inappropriate and/or disorganised behaviour, with a marked deterioration of functioning. The investigator relied on information provided by the patients and a close relation. Therefore, it was difficult to estimate the influence of factors such as recall bias or cultural differences in the conceptualisation of illness, on the exactness of the reported date at onset. Inclusion into the study was also limited to those who were between 16years and 45 years. The upper limit of 45years was used to ensure the generalisability of the results, while also avoiding the inclusion of late onset cases. Late onset of illness is a common characteristic of female subjects, and those with paranoid schizophrenia.

This strategy is by no means full proof, and the possibility of bias in recruitment of subjects with certain illness profile remains. Therefore, while the average age at onset of illness of 24.6 years reported in this study may fall within the usual expected range, factors inherent in the methodology of this study may also have influenced this value. Epidemiologic studies from developing countries report a wide variation in the age at onset of schizophrenia (Eranti et al, 2012). This observation has previously led to speculations that differences exist between developed and developing countries in the age at onset of schizophrenia (Gangadhar et al. 2002). The variation in the age at onset of schizophrenia across studies may be related to differences in definition, settings, age limit for inclusion, and diagnostic criteria employed in the different studies.

6.2.2.2. SYMPTOM DIMENSIONS OF SCHIZOPHRENIA

In this study, the Positive and Negative Syndrome Scale (PANSS) five factor solution was used to generate a parsimonious reduction of the multi-dimensional psychopathology of schizophrenia. This is in view of the stability and widespread acceptance of the five factor model, at least in more recent studies of the outcome of schizophrenia (Llorca et al, 2011). The schizophrenia psychopathology in this sample was well distributed along the lines of the five empirical factors, with a mean total PANSS score of 73.3 and a mean Clinical Global Impression of severity (CGI-S) score of 5.1, suggesting a sample populated by markedly ill schizophrenia patients at baseline. It would be expected that such a degree of illness severity would be associated with serious social, occupational and school functioning as well as poor insight. The mean Social and Occupational Functioning Assessment Scale (SOFAS) at baseline was 44.6, and about 94% of the subjects had poor insight. There was no attempt to selectively include patients with a certain distribution of psychopathology, or indeed a certain degree of severity of illness in this study so as to recruit a sample that is as close to the real life situation as possible.

6.2.2.3. PREMORBID ADJUSTMENT

The mean scores for pre-morbid academic and social functioning in this study were higher than those reported in the original work on the Pre-morbid Adjustment Scale (PAS) by Cannon-Spoor et al. (Cannon-Spoor et al, 1982). Patterns similar to those reported in the original report on the scale as well as in subsequent studies of

schizophrenia patients were however found in this study. The most prominent finding in this cohort was that of a poorer pre-morbid academic functioning from childhood through adolescence, whereas, the childhood social functioning was comparatively better. However, social functioning deteriorated through early to late adolescence. This may suggest that a rapid deterioration in pre-morbid social functioning in the individual may herald the onset of schizophrenia. Some have argued that pre-morbid deterioration either represents the onset of schizophrenia, or is an 'ultra at risk-factor' for the disorder (Buchanan et al, 1990., Peralta et al, 2012). Later onset deterioration of social functioning has always been seen as a clear sign of pre-morbid mal-adjustment, especially when they involve activities in interpersonal relationship occurring in settings outside the home (Strauss et al, 2012). Such activities occur in the pathway to the establishment of close emotional and sexual contacts in these circumstances. A certain level of social-sexual functioning is expected in the adolescent before the attainment of adult level functioning. Indeed some investigators have suggested that such rapid deterioration in social functioning in early adolescence may be a harbinger of certain types of poor prognostic psychotic disorders such as deficit schizophrenia (Buchanan et al, 1990., Strauss et al, 2012., Peralta et al, 2012). These studies also reported patterns of deterioration in academic functioning in relation to social functioning as is seen in the present study. This pattern is such that whereas social deterioration was observed during the early adolescent years, poor pre-morbid academic functioning was observed from childhood, and remained poor through the adolescent years. It is pertinent to note that childhood pre-morbid functioning measured using the PAS are those occurring from the age of 6years and 11 years. As such it may be difficult to determine if the onset of the deterioration

observed for academic functioning occurred earlier than the assessed period. A plausible conclusion would be that deterioration in academic functioning exists before social dysfunction is observed in the prodrome to schizophrenia.

6.3. PREVALENCE OF NSS

This study replicates many previous studies showing an increased prevalence of Neurological Soft Sign (NSS) in patients with first episode schizophrenia (Browne et al, 2000., Lawrie et al, 2001., Keshavan et al, 2003., Whitty et al, 2003., Scheffer et al, 2004). However, the direct comparison of the prevalence of NSS in first episode schizophrenia in this study with those reported across the different studies in the literature is complicated by the fact that many previous studies evaluated NSS using a variety of measures. The mean total NES score in this study was 21.5. When a neurological abnormality was defined as an abnormality in 1 item on the Neurological Evaluation Scale (NES), represented by a score of 2 on the corresponding item on the scale in this study, 96.4% of the subjects in the sample had NSS. Similar to this finding, at least one NSS, among a list that included the Ozereski test, tapping test, fist-ring test, fist-edge-palm test, piano test, and completion of two sequential drawings was described in 97.1% of a sample of 35 treatment naïve patients with first episode schizophrenia at a mean age of 26.4 years in the Irish first episode sample (Browne et al, 2000., Whitty et al, 2003). The Irish sample also used a cut-off of 2 in an item of the NES in defining the presence of (NSS). When the same criterion was used for the definition of abnormality among 24 adolescents with first episode psychosis, Zabala et al, (Zabala et al, 2006) reported that

100% of their sample had NSS. The same study reported that 89% of the subjects had greater than one NSS abnormality. Studies that have deployed a higher cut-off point for NSS have also reported similarly high prevalence. For instance, Ismail and colleagues (Ismail et al, 1998) demonstrated that at least 82% of their subjects had NSS even when the cut-off was raised to a score of 5 on items of the scale. However, in a community study in rural Ethiopia, Shibre et al. (Shibre et al, 2002) reported 65% of medication naive schizophrenia patients had a score of 2 or more on a neurological evaluation scale. Expectedly, community studies would include subjects with a wider spectrum of the stages and the severity of illness, including neurological abnormalities. The present study is based on a sample selected on the basis of contact with psychiatric services.

The mean total NES scores in this study also mirror those found in many previous studies of NSS in first episode schizophrenia (Buchanan and Heinrichs, 1989., Arango et al., 1999., Yacizi et al, 2002., Morh et al, 2003). However, some studies have recorded lower values when a conservative method of scoring the NSS abnormalities was used (Griffith et al, 1998., Dazzan et al, 2006). Such conservative estimation results from the recording of the lower values for NES items that are measured for both sides of the body.

6.4. FACTOR ANALYSIS OF THE NEUROLOGICAL EVALUATION SCALE

The factor analysis reported in this study was based on 18 items from the Neurological Evaluation Scale (NES) which were abnormal in more than 10% of the sample of 84 schizophrenia patients. Similar to previous factor analyses, it was difficult to identify the neuro-anatomical and conceptual meanings of the statistically derived sub-set of NSS. The first factor comprised of audio-visual integration, fist-edge palm, rhythm tapping, extinction, and right-left confusion. All the signs in this factor require a certain degree of sustained attention for successful performance. The fist-edge palm tests for functions associated with sequencing of complex motor acts (Buchanan and Heinrichs, 1989., Dazzan and Murray, 2002., Piccioni and Dazzan, 2009). The rhythm tapping test has also been suggested as an integrative complex motor act function (Bombin et al, 2005). The remaining components of factor 1 are items that test for cognitive processing of perceptual stimuli. As such, this factor may be conceptualized as representing perceptual and motor sequencing signs. Perceptual functions in this case are somato-sensory, visual or auditory. Sensory functions are generally understood as originating from the connections in the primary sensory cortex or the sensory association cortices in the parietal (somato-sensory), occipito-temporal (visual), and temporal lobes in the case of auditory sensations (Gay et al, 2012). In line with this hypothesis is the evidence from some structural correlation studies that have confirmed the association of NSS representing perceptual abnormalities with volumetric reduction in the pre-frontal (Zhao et al, 2013., Heuser et al, 2011), as well as the temporal cortices (Keshavan et al, 2003., Dazzan et al, 2004) in patients with schizophrenia. The motor sequencing signs such as

the fist-edge palm which also loaded in this factor is suggestive of difficulties with initiation and organization of complex actions. This is a well known frontal executive function (Ovsiew, 1994., Bersani et al, 2004., Emsley et al, 2005., Rao et al, 2008). However, sequencing of complex motor acts abnormalities are thought of as originating from defects in fronto-basal ganglia circuitry (Heinrich and Buchanan, 1989, Dazzan and Murray, 2002., Tosato and Dazzan, 2005). Learning and performance of complex motor sequencing tasks has also been shown to involve the superior temporal lobe and the cerebellum (Keshavan et al, 2003., Strangman et al, 2005). In sum, factor one of this study is a combination of the motor and sensory abnormalities that have been described as intrinsic to schizophrenia. These abnormalities are derived from dysfunctions in several cortical, sub-cortical and cerebellar brain regions. Schizophrenia is known to be associated with such widespread disturbances in the brain (Andreasen et al, 1998., Schroder and Heuser, 2008).

Factor 2 comprised of items testing synkinesis, convergence, and gaze impersistence. This factor is unique as it represents eye movement abnormalities that have been consistently described to be associated with schizophrenia even before the onset of the behavioural phenotype (Ross et al, 2000). Such eye movements are possible in the presence of intact sensory integration functions that require visuo-spatial localization. This function requires multi-modal sensory association and integration; as such it is a parieto-temporal function (Tosato and Dazzan, 2005., Jansen et al, 2009., Gay et al, 2012). However, volumetric reduction in the heteromodal cortex has not been specifically related to sensory integration abnormalities in the published structural correlation

analyses of NSS in schizophrenia (Dazzan et al, 2006., Thormann et al, 2009). The evidence from Thormann et al, (Thormann et al, 2009) suggests that such volumetric reduction in the heteromodal cortex may be non-specific in terms of its relationship to functional categories of NSS, rather, such brain changes are seen in schizophrenia patients with increasing NSS in general. However, Jansen et al. (Jansen et al, 2009) has argued that the severity of sensory integration abnormalities in schizophrenia has a significant correlation with total and anterior thalamic volume reduction. The thalamus is known to function as a central relay station of the brain, which filters and gates sensory inputs to the cerebral cortex. As such, structural impairment of the thalamus would appear to affect this transfer and consequently decrease performance on the sensory integration subscale (Jansen et al, 2009).

Factor 3 includes tandem walk, adventitious flow and graphaesthesia. Whereas tandem walk and adventitious flow are items that test for balance, a motor function conceptually localised to the cerebellar cortex (Sanders et al, 2000., Guiseppe et al, 2007), graphaesthesia is recognizable as a sensory integration function localised to the parieto-occipital areas of the brain (Bombin et al, 2005., Gay et al, 2012). Most of the structural correlation analyses of NSS in schizophrenia have shown that abnormalities of motor functions are associated with volumetric changes in the basal ganglia and its connections (Keshavan et al, 2003., Dazzan et al, 2004., Jansen et al, 2009., Thormann et al, 2009., Mouchet mages et al, 2011., Hirjak et al, 2013). Factor 4 comprised of stereognosis, another sensory integration function.

The factors derived from this study have not exactly replicated any of the previous published works on NSS in schizophrenia. This has also been the case in previous exploratory factor analyses (Sewell et al, 2010., Compton et al, 2006), and suggests considerable variablility in the expression of NSS in schizophrenia. Studies that appear to have replicated previous works have either relied on the same items or number of items in the study they attempt to replicate. For instance, Goldstein et al (Goldstein et al, 2005) and Keshavan et al, (Keshavan et al, 2003) included the same 13 items previously used by Sanders et al, (Sanders et al, 2000) in their exploratory factor analysis. Similarly, Emsley et al. (Emsley et al, 2005) used 13 items that bore similarities with those of Keshavan et al. (Keshavan et al, 2003). Apart from the work by Emsley and colleagues (Emsley et al, 2005), many of the attempts at replication have also relied on very similar, if not the same sample for their analysis (Goldstein et al, 2005., Keshavan et al, 2003., Sanders et al, 2000., 2006), making the findings of such replications difficult to generalize. The difficulty in replicating the NES factors empirically had led Compton and his colleagues, (Compton et al, 2006) to recommend that a one factor model be used in research until a consistently replicable factor model is found for the NES. The authors reached this conclusion when they derived three factors which could not replicate those of Sanders, Keshavan or Goldstein despite using the same 13 NES items relied on by these studies. This recommendation re-echoed an earlier suggestion by Sanders and his colleague that only the total NES is useful, having found one factor (fist-ring test, fist-edge palm test, Ozeretski test, and rapid alternating movements), out of a total of four with eigenvalue greater than unity, accounting for 20% of the total variance, out of a total

of 58% contributed by the four factors (Sanders et al, 2000). Similarly, it has always been difficult to replicate the functional categories of Buchanan and Heinrich, (Buchanan and Heinrich, 1989) using statistical derivations.

Nevertheless, the factor analysis reported in this study has considerable overlap with those of several other attempts at empirical classification of the neurological abnormalities in schizophrenia using the NES. An important similarity between this report and previous efforts at exploratory factor analysis of the NES is derived from the extent to which motor and sensory abnormalities have been separated. The result of the factor analysis in this study includes a factor for the important eye movement abnormalities known to be associated with the vulnerability to schizophrenia and the disease process itself, as a distinct factor.

The factor analysis reported here is most similar to those of Malla et al. (Malla et al, 1997) to the extent that 18 NES items were included in the analysis. But also because a strong factor that was very similar to the strongest factor in that study was generated. The second factor in this study which may be best described as an eye movement factor is very similar to the factor 1 of the study by Malla and colleagues, (Malla et al, 1997) in so far as all 3 items testing for eye movements loaded in the derived factors of both studies. Whereas factor 2 of this study distinctly grouped eye movement together, the factor 1 of

Malla et al, (Malla et al, 1997) included right-left orientation difficulties. Although this did not change the functional relevance of this factor in as much as all the items included tests for sensory integration function, it made the factor less characterizable as an eye movement factor. Interestingly, factor 1 of this study which may be described as a perceptual and motor sequencing factor bore resemblance to the second factor of the much repeated and seldom replicated exploratory factor analysis by Sanders et al. (Sanders et al, 2000., Keshavan et al, 2003., Prasad et al, 2009). In this study factor 1 contains the same factors testing for perceptual functions as those derived by Sanders and colleagues, (Sanders et al, 2000). Whereas factor 1 of this study included a factor for motor sequencing (fist-edge-palm), factor 2 of Sanders included a factor for cognition (memory). Furthermore, the first factor in this study also shows considerable overlap with sensory integration functional category conceptualised by Buchanan and Heinrich, (Buchanan and Heinrich, 1989). Similarly, the second factor, which is a factor for eye movement has been reported in a separate work by the same group while describing the usefulness of the signs and includes the same eye movement abnormalities present in the factor 2 of this study (Heinrichs and Buchanan, 1989., Sewell et al, 2010). Three out of a total of five items theoretically grouped together as representing sensory integraton functions by these authors also loaded together in the perceptual functioning factor of this study. Factor 3 of this study is best described as a motor and graphaesthesia factor. Factor 4 comprised of stereognosis, a function similar to graphaesthesia in so far as both test for complex somatosensory functions. Graphaesthesia has previously been reported to load with motor functions as seen in the factor 4 of Goldstein et al, (Goldstein et al, 2005) and in the exploratory factor analysis by Compton and colleagues, (Compton et al, 2006).

Whereas in this study graphaesthesia loaded with a primary motor function, it was grouped with a motor integration function in the analysis of Goldstein who used medicated subjects from the sample described by Sanders. Graphaesthesia in the African-American sample of Compton (Compton et al, 2006) loaded with a combination of primary motor functions of balance, and motor integration function.

6.5. TEMPORAL STABILITY OF NEUROLOGICAL SOFT SIGNS

An important reason for the surge in interest in the subject of Neurological Soft Sign (NSS) in schizophrenia is because of their potential as trait markers for the disease. They predate the onset of the disease (Chan and Gottessman, 2008., Chen et al, 2005., Serene et al, 2007). In addition to patients with schizophrenia, they also occur in vulnerable but well individuals relative to normal controls in a fairly stable continuum of severity (Mechri et al,2010., Chan and Gottesman, 2008., Shubert and McNeil., 2005.,Prasad et al, 2009., Sanders et al, 2006., Keshavan et al, 2008., Kaczorowski et al, 2009, Chan et al, 2010a and b., Neelam et al, 2011). An ideal trait marker would also be expected to exhibit a degree of stability across the course of the relevant disease. In this study, the mean scores for factor 1(Perceptual and motor sequencing) were not significantly different from baseline, month 6 and month 12. This is despite a general improvement in the symptoms profile of subjects. About 75% of subjects who completed the 12 months assessments had more than 50% reduction of their symptoms. Evidence exists in the literature to suggest that performance in perceptually demanding tasks is more impaired in schizophrenia compared to other psychoses or indeed normal controls, and as such

may be more specific to schizophrenia (Keshavan et al, 2003., Prasad et al, 2009). If this is true, then it is not surprising to find the factor for perceptual functions exhibiting considerable stability across the course of schizophrenia, showing clearly they are probably intrinsic to the disease. Keshavan and her group (Keshavan et al, 2003) relied on an empirically derived factor of the NES while working with a heterogenous group of medication naive schizophrenia patients. Using the same factor derived categories, they also confirmed that a cognitive/perceptual factor differentiated high risk siblings of patients with schizophrenia from normal controls after controlling for age and gender influences (Keshavan et al, 2003., Prasad et al, 2009). The memory item on the NES loaded with the items for perceptual functions to produce a factor for cognitive/perceptual functions in that study. The items in that factor have some similarities with the items loading for perceptual function in this study. In terms of clinical relevance of the correlation between the perceptual/cognitive factor and a diagnosis of schizophrenia, it is difficult to determine the differential influence of the perceptual or memory disturbances on this relationship. While the same study found a strong correlation between the derived cognitive/perceptual factor and neuropsychological tests for executive function, it is difficult to discountenance the influence of abnormal synthesis of perceptual stimuli in the process of schizophrenia. Similarly, it is difficult to determine the differential influence of the perceptual, or indeed the motor sequencing components of the factor 1 of this study in its relative stability across the course of schizophrenia. This is especially so in light of the strong evidence in the literature that supports sequencing of complex motor acts as a vulnerability marker of schizophrenia (Heinrich and Buchanan, 1988., Krebs et al, 2000., Sulivan et al, 2001., Delevoye-Turell et al, 2003., Keshavan et al, 2003.,

Bombin et al, 2005., Bachman et al, 2005., Sanders et al, 2006., Peralta et al, 2011., Mayoral et al, 2012). It is noteworthy that that the rhythm tapping test which also loaded on factor 1 has also been classified as a complex motor act task by some authors (Bombin et al, 2005). Therefore, factor 1 of this study is a combination of the motor and sensory abnormalities that have been described as intrinsic to schizophrenia. Emperically derived factors often show this kind of heterogeneity and difficulties with interpretation in terms of functional and neuro-anatomical relevance. This may be related to the multi-dimensional nature of schizophrenia. It is the view of several authors that schizophrenia is associated with structural changes in widely distributed network of cortical and subcortical structures (Andreasen et al, 1998., Schroder and Heuser et al, 2008) especially the heteromodal association cortices (Cannon et al, 2002., Keshavan et al, 2003., Bachman, 2005). Similarly, NSS that are specific to schizophrenia may reflect abnormalities in cortico-cortical and cortico-subcortical inter-neuronal connections (Dazzan and Murray, 2002., Dazzan et al, 2004., Piccioni and Dazzan, 2009). Therefore, the same widespread abnormalities that characterise NSS also characterise schizophrenia. In line with this heterogenous nature, Keshavan and colleagues (Keshavan et al, 2003) have also demonstrated that the perceptual/cognitive factor were strongly correlated with smaller volumes in the left heteromodal association cortex and the cerebellum. This finding reflects the importance of perceptual factors in the process of schizophrenia, and indirectly gives strength to the finding of temporal stability of the perceptual and motor sequencing factor of this study. Interestingly, perceptual /cognitive factors were also reported to be more prevalent among African-Americans when compared to Caucasians with schizophrenia (Keshavan et al, 2003., Mechri et al, 2009). This may be relevant to

the findings of the present study, which was conducted in a population of Nigerian Africans.

The NES total score and the mean scores for the other derived factors showed considerable differences from baseline, month 6 and month 12 with a trend towards reduction in the mean scores as the patients improved. Of particular interest was the eye movement abnormalities that loaded on factor 2. The evidence reviewed by Ross et al (Ross et al, 2000) suggests that eye movement abnormalities are intrinsic to schizophrenia since they also occur in unaffected relatives, and as such are expected to be stable across the course of the disease. This study could not replicate this expected stability. In an earlier study, Ross and colleagues (Ross et al, 1997) have argued that eye movements correlated strongly with sensory integration function. This is supported by evidence suggesting that sensory integration signs are not specific to schizophrenia as they occur with equal frequency in patients with psychotic disorders including patients with psychotic depression (Keshavan et al, 2003). Sensory integration signs have also been shown to decrease in seriousness in the presence of a stable total NSS scores, during the clinical course of first episode schizophrenia (Bachman et al, 2005., Prikryl et al, 2012). It was therefore not unexpected in this study that the eye movement factor, which basically tests for sensory integration functions, did not show significant stability across the one year course of schizophrenia.

It has been argued that if indeed NSS are an ideal biological marker for schizophrenia, then the total NES score as well as the sub-scale scores should reflect a similar pattern of stability across the course of schizophrenia (Bachman et al, 2005., Smith et al, 1999). While this argument may have some validity, it may not be sustainable in practice. It is more likely that a group of 26 hand-picked neurological examination items would represent different aspects of a heterogenous disorder like schizophrenia. In this case, some items may have potentials as trait markers while others may have potentials for defining the different clinical aspects of the disease. Indeed, different items may contribute to the total NES score at different stages of the disease. It may also be more clinically meaningful to have a small group of signs testing for specific aspects of the disease, rather than a long battery of test for one aspect of a multi-dimensional disease. It is for this reason that factor analysis of the NES or indeed other measures of NSS became an important statistical tool for a parsimonious reduction of the signs. Nevertheless, there are studies in the literature that have found both the NES total score and some sub-scale scoreS to be stable across the course of the disease (e.g Emsley et al, 2005), while some others have found only the total NES score showing temporal stability (e.g Bachman et al, 2005., Prikryl et al, 2012).

When the functional categories of NSS were considered, this study found that the sequencing of complex motor act signs was stable across the one year course of schizophrenia. This was true when the measurements were taken at baseline, month 6 and month12. A similar study that tested the temporal stability of the functional categories of

the signs across a 14 month course of the disease also found a relative stability of the motor sequencing sign in schizophrenia (Bachman et al, 2005). However, in that study, the NES total score showed a stronger level of stability across the same time frame, compelling the authors to conclude that the NES total score may be a better trait marker, but admitted that it is quite ambiguous (Bachman et al, 2005., Smith et al, 1999). A study of the one year stability of the signs in a South-African sample also found that although the most stable factor was the factor for attention, the motor sequencing factor was also stable when measured at baseline, month 6 and month 12 (Emsley et al, 2005). However, when measurement of the signs at month 3 were entered into the analysis, the authors found that there was a significant reduction of the mean scores for motor sequencing that coincided with symptom reduction. However, the finding of a reduction at 3 months may be related to the initial effect of antipsychotics in reducing the acute symptoms of the disease, including NSS resulting from them. There is evidence from the literature on neuroleptic naive schizophrenia patients suggesting that the state defining characteristics of the active disease process may predominate during the early course of the disease as symptoms fluctuate, whereas, the trait-like characteristics that are representative of the baseline vulnerability to the disease may become more prominent after the resolution of the acute symptoms (Whitty et al, 2009., Bachman et al, 2005., Browne et al, 2000). Thus, in the background of evidence that NSS at onset of schizophrenia is associated with more severe psychopathology including positive and inattention symptoms (Mittal et al, 2007., Whitty et al, 2009), the initial response to the introduction of antipsychotics by the florid acute phase symptoms including inattention also results in an initial reduction in the NSS which are secondary to these symptoms. On

the other hand, the NSS which are intrinsic to the disease remain persistent or become more obvious after the removal of the acute phase symptoms. A corollary to this fact is the finding of increasing severity of NSS in some studies of chronically ill patients (Smith et al, 1999., Chen et al, 2000). This feature of NSS is a reflection of a genetically determined neuro-developmental origin, or an evidence for a pre-morbid acquired permanent deficit. In fact, sequencing of complex motor acts signs were recently confirmed as evidence of the latter, in so far as they were correlated with an excess of obstetric complications and pre-morbid deterioration in psycho-social functioning (Peralta et al, 2011). Indeed the study of the temporal stability of NSS in the South-African sample concluded that attentional and motor sequencing signs are replicable across studies of NSS using the methods of exploratory factor analysis (Emsley et al, 2005). Also, the description of the meaning of NSS by Heinrich and Buchanan (Heinrich and Buchanan, 1989) suggests that such motor sequencing signs better differentiate patients with schizophrenia from those of other psychosis, while Krebs and colleagues concluded that integrative motor functions differentiated patients with schizophrenia from those with mood disorders (Krebs et al, 2000). Many of the items in the sequencing of complex motor act category were also found to show significant heritability in the confirmatory factor analysis by Sanders and colleagues (Sanders et al, 2006).

The other two functional categories (motor co-ordination and sensory integration) showed significant changes across the one year course of schizophrenia, with trends towards a reduction of the signs as patients improved on treatment. The study by

Bachman and colleagues among chronically hospitalised patients also showed that sensory integration signs are not stable through the course of schizophrenia, varying as the symptom profile changed (Bachman et al 2005). In the same study, motor co-ordination signs showed only a moderate level of stability.

In all, the results of this investigation strongly support the first hypothesis: proposing that there will be no significant difference in the scores of NSS dimensions in patients with schizophrenia after three repeated measurements over a 12 month period. This is true to the extent that the neurological abnormalities that have been described as intrinsic to schizophrenia (and as such have a trait defining characteristics) remained stable after three measurements at different times in the one year course of the disease. The fact that the total NES score did not exhibit stability across this time frame may be linked to the heterogeneous nature of the 26 items contributing to this score. Different items are likely to contribute to the total score at different stages of the disease.

6.6. NEUROLOGICAL SOFT SIGNS AND THE CLINICAL CHARACTERISTICS OF SCHIZOPHRENIA

An important finding in this study is the significant correlation between baseline neurological soft signs (NSS) and certain symptom dimensions of schizophrenia when the five factor model of the Positive and Negative Syndrome Scale (PANSS) was adopted. This correlation was present when the total Neurological Evaluation Scale

(NES) score at baseline as well as the functional categories proposed by Buchanan and Heinrichs, (Buchanan and Heinrichs, 1989) were considered. It was also present when using the empirically derived factors of this study. Specifically, apart from the motor sequencing 'functional' category which correlated significantly with the depression/anxiety factor of the PANSS, the other 'functional' categories, the NES total score, as well as the empirically derived factors correlated significantly with the negative as well as the cognitive/disorganised factors of the PANSS. Factors 1 and 2 of the NES from this study, as well as the total NES score correlated significantly with the excitement factor of the PANSS. However, this correlation was only observed with the motor co-ordination sub-set when the 'functional' categories were considered. In line with this finding, the baseline NES total and subscale scores (functional or empirical) correlated with more severe psychopathology. The importance of the association between NSS, or abnormalities in specific neurological domains, and some symptom dimensions of schizophrenia is in the ability of such association to explain which neurological dysfunction is an intrinsic characteristic of the illness. Association of certain NSS with psychopathology may help to explain aspects of the underlying neurobiology of the disorder. However, some authors have suggested that NSS could be secondary to some psychiatric symptoms, such as impaired attention (Lawrie et al, 2001., Browne et al, 2000).

The finding of a relationship between NSS and a more severe schizophrenia psychopathological process, including the presence of negative symptoms, as well as cognitive/disorganization symptoms may suggest a state-like quality of some NSS

categories. A high total NSS score as well as a preponderance of sensory integration and motor coordination signs appear to be specifically suggestive of a more severe form of the disease and as such have implications for prognosis. Therefore, these signs appear to have the potentials of a state marker of severe psychopathology, and possibly poor prognosis (Chen et al, 2005., Prikryl et al, 2006., 2007., Kong et al, 2012). A similar argument has been presented previously by Mechri et al (Mechri et al, 2009) when the authors suggested that the association between some NSS categories and cognitive dysfunction, deficit or disorganized syndromes of schizophrenia may be related to a more chronic course of the disease. Also other studies of the relationship between NSS and outcome of schizophrenia has reported important associations with poor response to acute treatments (Prikryl et al,2006., 2007), higher number of relapses (Chen et al, 2005), and other characteristics of unfavourable course of the disease (Kong et al, 2012). In line with the finding of a correlation between NSS and a more severe schizophrenia psychopathology, we report that sensory integration abnormalities (functional category) correlates significantly and inversely with the age at onset of schizophrenia. Many cases of deficit and disorganised schizophrenia are also known to be associated with a younger age at onset of schizophrenia. Studies in the literature reporting similar inverse correlation between NSS and age at onset concludes that early onset schizophrenia is clearly associated with neuro-developmental abnormalities including NSS (Nicholson et al, 2000., Biswas et al, 2007). However, the failure of this study to find a relationship between DUP and NSS was perhaps unexpected given the relationship found with negative and cognitive PANSS factors.

Several studies in the literature have reported associations between NSS and negative (Schroder et al, 1992., Malla et al, 1997., Arango et al, 2000., Dazzan and Murray, 2002., Scheffer et al, 2004., Bombin et al, 2005., Ruiz-Veguilla et al, 2008., Chan et al, 2010a and b., Prikryl et al, 2012., Smit et al, 2012), cognitive (Chan et al 2009) or disorganization (Arango et al, 2000., Mechri et al, 2009) psychopathology of schizophrenia as reported in this study. The study by Malla et al, (Malla et al, 1997) relied on Liddle's three dimensions of schizophrenia. The authors found a modest relationship between a factor derived extrapyramidal domain of neurological signs (i.e, Rhomberg test, adventitious flow, and tremor) and psychomotor poverty dimensions (similar to the negative dimensions of the PANSS) in males. Whereas this same symptom dimension was associated with neurological factors reflecting attention and initiative (which was rhythm tapping in that study) in their female subjects (Malla et al, 1997). While the study by Arango and colleagues (Arango et al, 2000) found a significant relationship between the disorganization domain of schizophrenia and global neurological abnormalities. The same study reported that deficit syndrome was significantly related only to sensory integration abnormalities, while hallucination and delusions were not related to any neurological abnormalities (Arango et al, 2000). Also Browne et al. (Browne et al, 2000) described an association between NSS and total symptom severity and positive symptoms in the Irish first episode psychosis study. However, Bombin et al. (Bombin et al, 2005) suggested that negative symptoms and, less often disorganization symptoms, could be correlated to NSS, especially signs of frontal functions (motor) and those of parietal functions (sensory integration), whereas positive symptoms consistently appear unrelated

to NSS. Furthermore, Scheffer et al, (Scheffer et al, 2004) suggested that higher NSS scores correlated with persistence of negative symptoms after commencement of antipsychotic treatment. Whereas Das et al, (Das et al, 2004) argued that the relationship between a higher NSS score and negative symptoms occurred after antipsychotic medications were switch from first generation to second generation in patients with schizophrenia.

There are also some important studies in the literature finding no correlation between the symptoms dimension of schizophrenia and the baseline neurological abnormalities. For instance, Shibre et al. (Shibre et al, 2002) reporting from a study in an Ethiopian cohort did not find a relationship between NSS and negative or disorganisation symptoms. Also, Whitty et al, (Whitty et al, 2006) suggests that NSS are not specific to any of the diagnoses that share the presence of psychotic symptoms. As in many cases of such conflicting reports, methodological differences in the studies account for a majority of the variation in findings. An important methodological similarity between this study and those reporting a significant relationship is the use of out-patient hospital subjects. The report by Shibre and his colleagues (Shibre et al, 2002) is based on a rural community sample.

Consistent with the finding of relative stability of the motor sequencing sign across three measurements in the one year course of schizophrenia in this study, is the absence of a significant correlation between baseline scores for this sign and the psychopathology dimensions as measured on the Positive and Negative Syndrome scale (PANSS). It would

therefore appear that signs suggesting abnormal sequencing of complex motor acts do not to have state defining qualities for identifying certain types of schizophrenia psychopathology. By extension, their prognostic value may be somewhat doubtful. However, the characteristics of the motor sequencing NSS in this study further strengthens the already robust evidence for a trait-like characteristic of this group of signs in schizophrenia (Heinrich and Buchana, 1988., Krebs et al, 2000., Keshavan et al, 2003., Bachman et al, 2005., Sanders et al, 2006., Mayoral et al, 2012., Theleritis et al, 2012). As such, they may have endophenotype potentials. The finding that a relationship exists between baseline abnormal sequencing of complex motor acts and the depression/ anxiety factor of the PANSS may be due to the need for adequate motivation and attention in the performance of complex movement that requires repetition according to a particular pattern. The depressed schizophrenia patient may not have the required motivation or sustained attention to perform such complex movements. Indeed, Lawrie et al, (Lawrie et al, 2001) and Browne et al, (Brown et al, 2000) had proposed that some soft signs are secondary to certain aspects of the psychopathology of schizophrenia rather than being intrinsic to the disease. In this case, depression may impair the ability to perform complex sequential movements. In line with this argument is the fact that baseline NSS did not correlate significantly with the development of depression over time. It would appear that depression developing during the treatment of schizophrenia is of a different origin and process compared to neurological soft signs. Whereas depression in the course of schizophrenia may be secondary to certain psychopathological processes (such as delusions and hallucinations), treatment, or the elevated responsibility of acquiring insight, NSS on the other hand may be intrinsic to the disease.

There was a significant inverse correlation between baseline NSS and treatment emergent extra-pyramidal symptoms at 6 months and at 12 months. This is in contrast to some reports suggesting that baseline NSS predicted the presence of treatment emergent extrapyramidal symptoms , especially tardive dyskinesia (Emsley et al, 2005., Yacizi et al, 2002). In this study, in order to remove the important confounding effect of covert non-adherence, a relatively low mean dose (10 milligrams fortnightly) of depot antipsychotic (flupenthixol) was used in the treatment of patients. As such, the mean total Extra-pyramidal Symptoms Rating Scale (ESRS) score for the entire sample was generally low (0.26 ± 0.07). A closer look at the data also suggests that although there were no significant differences between the mean total ESRS scores of those who were followed up (0.31±0.75) and those who dropped out of the study (0.11±0.32), p=0.255, those who dropped out had significantly more tardive dyskinesia symptoms (0.37±1.21), p=0.022. Therefore, the attritions (22.6%) may have had the effect of diluting the overall mean ESRS at month 12, especially with respect to tardive dyskinesia which is the extra-pyramidal symptom most associated with NSS. Nevertheless, the very high rates of NSS (96.4%) at first presentation in this study, and in other first episode, antipsychotic naive schizophrenia samples around the world (Browne et al, 2000., Scheffer et al, 2004) would suggest that NSS may not be related to anti-psychotic effect. Moreover, the vast majority of studies comparing medicated and un-medicated patients, or patients with and without extra-pyramidal symptoms report no association between neurological abnormalities and antipsychotic medication or extra-pyramidal symptoms (Sheffer et al, 2004., Browne et al, 2000., Arango et al, 2000).

This study also reports a correlation between the excitement/hostility dimension of the PANSS and baseline NSS. The correlation existed for factors 1 and 2 derived from the NES as well as the motor co-ordination 'functional' category and total NES score. The excitement/ hostility factor of the PANSS is comprised of mania-like symptoms in schizophrenia, such as uncooperativeness, poor impulse control, excitement and hostility. The literature on the relationship of NSS and psychopathology dimension of schizophrenia appears to be silent on the associations with this dimension. This may be because the earlier studies of this relationship have been based on the conventional three factors of the PANSS (Kay et al, 1987), which do not include a separate factor for excitement/hostility. The five factor solution now has widespread acceptability in more recent outcome studies of schizophrenia (Monteiro et al, 2008., Llorca et al, 2011) after the establishment of its psychometric properties in clinical practice (Serreti and Olgiatti, 2004., Van de Gaag et al, 2006). Nevertheless, recent brain activation studies that have used the five factor model of the PANSS suggest that in patients with schizophrenia, the excitement score of this model positively correlates with activation in the right pre-frontal cortex and other fronto-polar regions (Nishimura et al, 2011). This finding is in congruence with studies reporting a relationship between the prefrontal activities during response inhibition and impulsivity, violent behaviour and co-morbid anti-social personality disorder in schizophrenia (Horn et al, 2003., Asahi et al, 2004., Joyal et al, 2007., Naudts and Hodgins, 2006). The pre-frontal cortex plays an important role in the control of sensory conflict, and both functional and structural abnormalities in the pre-frontal cortex have been consistently associated with both total NSS and motor co-

ordination or integration signs (Mohr et al, 1996., Dazzan et al, 2004., Rao et al, 2008., Dazzan and Piccioni, 2009). Therefore, the association between NSS and the excitement/hostility dimension of schizophrenia which was found in this study, indirectly confirm the evidence from studies reporting an association the fronto-polar region, which also sub-serves integrative functions, and the excitement factor of the PANSS. The direct association would require further verification in future studies.

This study could not replicate the findings of Peralta et al, (Peralta et al, 2011) that certain neurological abnormalities were associated with poorer pre-morbid functioning. This association was also not found in earlier studies such as those of Gupta et al, (Gupta et al, 1995) and Buchanan et al, (Buchanan et al, 1990). In the study by Peralta and colleagues, an argument was presented for the relevance of sequencing of complex motor acts NSS as a marker of poor pre-morbid functioning because of its association with obstetric complications among a cohort of 177 medication naive first episode schizophrenia patients. The possibility exists that this relationship was not confirmed because this study did not directly measure the association between obstetric complications and NSS. Nevertheless, this study confirmed, to a large extent, our second hypothesis which proposed that a preponderance of NSS at baseline will be associated with negative and disorganization psychopathology, as well as earlier age at onset of schizophrenia.

6.7. NEUROLOGICAL SOFT SIGNS AND THE OUTCOME OF SCHIZOPHRENIA.

A striking and consistent finding in this study is the pattern of the sequencing of the complex motor acts 'functional' category signs across the one year course of schizophrenia. This category of signs did not only remain stable after measurements across time intervals from baseline through month 6 and month 12, it had no significant relationships with the psychopathology dimensions at presentation. The baseline scores for the sequencing of complex motor acts was also not related to the outcome of schizophrenia as measured by the percentage changes in the PANSS scores, as well as the social and occupational functioning and the quality of life at one year. As earlier highlighted, abnormalities of these signs reflect difficulties with organization and planning (Piccioni and Dazzan, 2009). This is a recognized frontal lobe executive function (Bersani et al, 2005., Rao et al, 2008). Abnormalities of sequencing of complex motor acts have been shown, and reported to be specific to schizophrenia (Heinrichs and Buchanan, 1988., Krebs et al, 2000., Keshavan et al, 2003., Emsley et al, 2005., Bombin et al, 2005., Delevoye-Turell et al, 2003., Sullivan et al, 2001). They have also been demonstrated to be more prevalent in high risk individuals (Theleritis et al, 2012), and siblings of patients (Prasad et al, 2009., Neelam et al, 2012) compared with normal controls. Furthermore, many individual items in the category have been shown to exhibit significant heritability (Sanders et al, 2006). Similar to previous studies, this category of signs did not load as a separate factor in the exploratory factor analysis of this study. They have also repeatedly loaded together combination with other individual signs, in

previous factor analyses of the signs in schizophrenia (Malla et al, 1997., Sanders et al, 2000., Keshavan et al, 2003., Emsley et al, 2005). And as previously highlighted, the motor sequencing NSS has been shown to be stable across the course of schizophrenia in first episode medication-naive cases (Emsley et al, 2005., Mayoral et al, 2012), and in chronic patients with the disorder (Bachman et al, 2005). In sum, this feature of the motor sequencing signs strengthens the idea that motor abnormalities, especially those involving the performance of complex motor acts may constitute a reliable vulnerability marker for schizophrenia. This assertion has previously been made by Bombin et al, (Bombin et al, 2006) and Gourion et al (Gourion et al, 2003), and reported by Mechri et al, (Mechri et al, 2009). The profile of the motor sequencing sign as a vulnerability marker was recently confirmed by Peralta and colleagues (Peralta et al, 2011). In that study, signs of sequencing of complex motor acts were associated with obstetric complications as well as deterioration in pre-morbid functioning among a cohort of 177 medication-naive first episode schizophrenia patients. For this reason, the authors argued that the sign is more of an environmental marker for schizophrenia, rather than a genetic marker for the disease (Peralta et al, 2011).

The baseline scores of the other functional categories (i.e, motor co-ordination and sensory integration), as well as those of the derived NES factors of this study were found to correlate with the percentage changes in negative and cognitive/disorganization symptoms of the PANSS. This finding is a corollary of the evidence demonstrated in this study, and elsewhere that a preponderance of NSS is associated with negative and

cognitive/disorganization dimensions of the PANSS (Schroder et al, 1992., Malla et al, 1997., Arango et al, 2000., Dazzan and Murray, 2002., Scheffer et al, 2004., Bombin et al, 2005., Ruiz-Veguilla et al, 2008., Chan et al, 2010a and b., Prikryl et al, 2012., Chan et al 2009., Mechri et al, 2009).

A clearer reflection of the relationship between NSS and outcome is the finding that a higher cumulative number of NSS at baseline is associated with a poorer level of functioning, not only at 6 months, but also at 12 months in some cases. This association was present for the derived NES factors and the functional categories. However, the most interesting finding in the relationship between NSS and outcome is that a preponderance of motor co-ordination signs at baseline correlates with a poor quality of life rating at month 12. This is especially so for the ratings on the psychological domains of quality of life. This finding was consistent for both the derived motor co-ordination/graphaesthesia factor and the motor co-ordination functional category of Buchanan and Heinrichs, (Buchanan and Heinrichs, 1989). It also confirmed the third hypothesis of this study that a preponderance of NSS at baseline will be associated with a poorer outcome of schizophrenia at one year.

This study reports a relationship between NSS and functioning independent of psychopathological limitations. In relying on the Social and Occupational Functioning Scale (SOFAS), functioning was rated independent of illness related confounders. The literature on the use of the SOFAS in investigating the relationship between NSS and functional outcome appears to be very sparse. A previous assessment of the relationship

between NSS and functioning has relied on the Global Assessment of Functioning (GAF) (Mechri et al, 2009), a measure of functioning that is heavily influenced by psychopathology. The authors found a relationship between NSS total score and GAF score while using a comparative case control design. Earlier attempts at establishing a relationship between NSS and functioning in the later stages of the course of the disease reported absence of a relationship (Sanders et al, 1994., Dazzan and Murray, 2002). However, the consensus in the literature is that baseline NSS is associated with a poorer current social functioning (Whitty et al, 2009.,Bombin et al, 2005., Galderisi et al, 1999).

To the best of the knowledge of this investigator, this is the first description of the relationship between NSS and quality of life. Most of the previous investigations of NSS and outcome of schizophrenia have relied on symptom reduction (Emsley et al, 2005., Das et al, 2004), relapse rates (Emsley et al, 2005), length of hospital stay (Gureje, 1987), or global functioning using the GAF (Mechri et al, 2008) in describing and inferring the relationship between NSS and the outcome of schizophrenia.

CHAPTER SEVEN

LIMITATIONS

7.1. SELECTION BIAS

In this study, the recruitment of patients was based on contact with psychiatric services, either as in- or out-patients. Every patient presenting to the psychiatric units in the study location within a particular time frame was asked to take part in the study. Given the observation suggesting that many patients with psychosis in the community have not sought formal biomedical care, it is likely that the sample studied may have been self-selected on the basis of access to the facilities and by illness severity. A large scale community study would eliminate a possible referral bias. Also, this study did not include a control group. The presence of several types of controls such as unaffected relatives, or normal comparison group would have allowed blinding of the unvestigators and clarified the differential prevalence of NSS along this spectrum of exposure levels.

7.2. SAMPLE SIZE

This study is further limited by a relatively small sample size especially at follow-up. Similar to most longitudinal studies of patients with psychosis, there was a problem with attrition. Although 84 subjects were recruited into study at inception, only 65 subjects completed one year assessment. Nevertheless, the follow-up rate of 77.45 still provided sufficient power (90%) to detect differences in the variables explored.

7.3. MEASUREMENT BIAS

The investigator was not blind to the clinical state of the subjects. This may have introduced an observer bias in the measurement of Neurological Soft Signs (NSS). Similarly, some of the improvements observed may have been due to learning effects on some of the signs.

7.4. STATISTICAL ANALYSIS

Corrections for multiple testing were not carried as part of the statistical analysis, because of the exploratory nature of this study. Such corrections would have clearly delineated the key points of change in the total or sub-scale scores of NSS in the one year course of schizophrenia.The investigator have relied on exploratory factor analysis in describing the structure of NSS in this population in line with previous studies of NSS in the

literature. Only one previous confirmatory factor analysis had been done on the NES previously (Sanders et al, 2006), and the finding was not less difficult to interprete compared to those using exploratory methods.

CHAPTER EIGHT

CONCLUSIONS

The presence of a high prevalence of Neurological Soft Signs (NSS) at first presentation with schizophrenia or schizophreniform disorder in this study, as well as in some other similar studies in the literature, even before exposure to antipsychotics, would suggest that NSS are intrinsic to the process of schizophrenia. They therefore have potential as biological markers for the disease. They appear more common when compared to some of the more frequently suggested phenotypes of the schizophrenia syndrome.

Some of the NSS categories exhibit significant temporal stability across the short to medium term course of the disease. The categories of sequencing of complex motor acts as well as the signs of cognitive processing of perceptual stimuli remained persistently abnormal across the one year course of the disease. The sequencing of complex motor act signs were especially resistant to the influence of the clinical profile of the disease throughout the duration of the study. The evidence from this finding and others in the literature lends credence to the conceptualization of NSS as a trait marker for schizophrenia. It is however doubtful if all available heterogenous items in a neurological examination scale have this trait defining characteristic. The sequencing of complex motor act signs, as well as signs representing cognitive processing of perceptual stimuli appear to be markers of the vulnerability to

schizophrenia. Future studies should help clarify if these abnormalities are genetically determined or they are acquired permanent pre-morbid defects.

Other NSS categories as well as the NES total scores are markers of a more severe negative and disorganization psychopathology. A preponderance of NSS may also be related to higher degree of hostility in patients with schizophrenia. Positive symptoms were not significantly associated with NSS at presentation. This finding may suggest that some NSS or the ability to perform some of the test may be secondary to the influence of the psychopathology dimensions. It may also suggest that these NSS are markers of a poorer prognosis in terms of residual symptoms and possibly the potentials for relapse. Such patients may therefore require longer term treatment even in the first episode.

The NSS that were related to certain psychopathology dimensions before treatment with antipsychotics also decreased in frequency and severity as the relevant psychopathology decreased in severity in response to treatment. This finding is in support of the previous suggestion that some NSS categories may be secondary to certain psychopathology dimensions.

A higher cumulative number of NSS at baseline is associated with a poorer level of functioning at 6 months, and also at 12 months in some cases. Although the assessment of functioning in this study was independent of psychopathology, this finding is in support of the argument that the relationship between a cumulative

amount of NSS and a more severe schizophrenia psychopathology may also be a marker for poor prognosis, including functional outcome in this case.

Also in line with the previous finding on outcome, a preponderance of motor co-ordination abnormalities is associated with a poorer quality of life at one year. This is especially related to outcome in terms of psychological health. This finding may be related to a possible presence of residual symptoms at one year in patients with predominant motor co-ordination abnormalities at baseline. This may suggest a need for longer term monitoring and treatment for patients with such signs at presentation**.**

8.1. RECOMMENDATIONS

Attempts at replicating the theoretical categories of signs compiled by Buchanan and Heinrichs from the Neurological Evaluation Scale (NES) using statistical derivations have often failed. It has also been difficult to replicate any of the previous factor analyses in the many attempts around the world. This probably reflects the heterogeneity in symptom expression of the illness. The nearest approximation to replicating a previous factor analysis has been achieved by studies that relied on similar items or number of items. Many of these approximations have also been achieved while relying on the same subject sample.

The functional categories of Buchanan and Heinrichs appear more meaningful compared to any factor derived category. As such, it is the recommendation of this investigator that in the mean time, the functional categories be relied upon in the many attempts at unravelling the true meaning of NSS in schizophrenia until a standard and replicable sub-categories of NSS is found.

The total NES score which is a combination of the scores for 26 items may be too heterogenous to tell any specific story about the process of schizophrenia. It is also too long and time consuming to be meaningful for the clinician. It is the recommendation of this investigator that a shorter version of the NES be designed from the original 13 items that made up the three main functional categories of Buchanan and Heinrichs. This version of the NES should be standardized for use in research and in clinical settings, using first episode antipsychotic naive samples.

There is presently no agreement on what constitutes an abnormality in most of the scales for assessing NSS around the world. As such researchers have used several thresholds in defining abnormalities. It is the recommendation of this investigator that a standardized shorter version of the NES should also include an agreed cut-off for abnormalities. This cut-off point should be the point with the best validity for identifying the vulnerability to schizophrenia or a poorer prognosis in patients. This may help the clinician with identification and early initiation of effective therapies in patients or high risk persons.

Ongoing advances in imaging techniques may help to further clarify the underlying neural substrates of NSS in general. In this way, such studies should also provide important information on the pathogenetic processes that underlie schizophrenia and other neurodevelopmental disorders such as Attention Deficit and Hyperactivity Disorders, Autistic spectrum disorders, and Obscessive Compulsive Disorders.

Future studies should also help to clarify the point of influence of the vulnerability marking NSS along the pathway to the overt disease. This may lead to novel interventions in schizophrenia.

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ADDENDA

ADDENDUM A

Consent Form (English)

IRB Research approval number:
This approval will elapse on: dd/mm/yy

Title of the research: A study of the profile and determinants of outcome in recent onsetschizophrenia.

Name and affiliations of researchers
This study is being conducted by Professor Oye Gureje of the Department of Psychiatry, University of Ibadan. Nigeria.

Who are the sponsors of research?
The purpose of this research is to study patients with a first episode of schizophrenia and related psychotic disorder and follow the, up over some years. Schizophrenia and its related disorders are chronic and sometimes disabling disorders. We are conducting the study to learn more about the illness, particularly ways of improving the outcome. In order to do so, we plan to study 80 people with the illness, treat them all with the same medication and follow them up for one or two years. Medication is often used treat people with psychiatric conditions, and for your illness it is absolutely necessary.

What happens during the research?
You will be interviewed and physically examined during some of your visits during the research. We may need to take a blood sample as part of a general investigation of your health. These procedure are not dangerous but can cause some local pain. Your blood will not be used for any other purpose aside from what has been stated. You will also be placed on free drug treatment after recruitment into the study. The compound that will be used to treat you is called Fluanxol depot. Although oral medication (tablets) is available, there are several benefits to using this long acting injection. First it ensures that the medication is being taken correctly since people often find it difficult to remember to take tablets everyday, or sometimes, when they become ill they don't believe that they need any medication. At each visit you will be asked several questions related to your illness by the doctor and nurse. As some of the visits your blood pressure, pulse and weight will be taken.

Expected duration of research and of participants' involvement:
In total, the study will last 5b years, but we expect you to be involved in this research for 2 years. You should not spend more than 1hour at each clinic visit.

What do I benefit by participating in the research?
The possible benefits of participating are that you will receive expert care and you will be assisting us to learn more about your illness so that we can provide improved care to you and others in future. You will also be receiving free medication and detailed assessment of your health at more frequent intervals than is usual.

Confidentiality
All information collected in this study will be kept strictly confidential. No stored information can be linked to you in anyway and your name or nay identifier will not be used in nay publication or reports from this study.

Am I free to opt out of the study any time?
You are free to choose whether or not you want to take part in this study. If you do not, it will not affect the way you are looked after. You can also choose to withdraw from the research at anytime. Please note that some of the information that has been obtained about you before you choose to withdraw may have been modified or used in reports and publications. These cannot be removed anymore. However the researchers promise to make good faith effort to comply with your wishes as much as is practicable.

What if suffer any injury or unwanted effect because I participated in the study?
If you suffer any injury as a result of your participation in this research, you will be treated at the University College Hospital Ibadan and the research will bear the cost of this treatment.

If you wish to participate in this study, you are requested to kindly go home with this form, discuss the study and your participation in the study with your relatives before signing the form.

Statement of person obtaining informed consent:
I have fully explained this research to ----------and have given sufficient information, including risks and benefits, to make an informed decision.

DATE:---------- SIGNATURE:---------- Thumb print----------

NAME:----------

Statement of person giving consent:
I have read the description of the research or have had it translated into language understand.
I have also talked it over with the doctor to my satisfaction. I understand that my participation is voluntary. I know enough about the purpose, methods, risks and benefits of the research study to judge that I want to take part in it. I understand that I may freely stop being part of this study at any time. I have received a copy of this consent form additional information sheet to keep for myself.

DATE:----------SIGNATURE:----------

NAME:----------

NAME OF RELATIVE and RELATIONSHIP (if applicable)----------

SIGNATURE OR RELATIVE (if applicable)----------

WITNESS' SIGNATURE (if applicable):----------

WITNESS' NAME (if applicable):----------

Detailed contact information including contact address, telephone, fax, e-mail and any other contact information of researcher, institutional HREC and head of institution:
This research has been approved by the Health Research Ethics committee of the University of Ibadan and the chairman of this committee can be contacted at the Biode building, Room T10, IMRAT, College of Medicine, University of Ibadan. The e-mail address is uiuchr@yahoo.com. In addition if you have any question about your participation in this research, you can conct the principal investigator, Professor Gureje at his office at the psychiatry department, College building, third floor University College Hospital, Ibadan. The phone number and e-mail address are +234-8033464284, e-mail ogureje@comui.edu.ng.

Consent Form (Yoruba)

IWE ATEWOBO PE MO GBA (TI MOLEBI)
IRB Research approval number:
This approval will elapse on: dd/mm/yy

Title of research: A STUDY OF THE PROFILE AND DETERMINANTS OF OUTCOME IN RECENT ONSET SCHIZOPPHRENIA

ORUKO ATI AWON TO GBE ETO IWADI YII KALE:
A gbe eto iwadi yi kale inpase Ojogbon Oye Gureje ti eka awon to n toju alarun opolo ni ile iwosan Oritamefa, Ibadan.

AWON WO LO SE AGBATERU RE?
Awon to se agbeteru eto iwadi ni awon to fowosowopo ki ile adulawo le dara si (New Partnership for Africa's Development NEPAD)

KI NI IDI GAN TI A FI GBE ETO IWADI YII KALE?
A gbe iwadi yi kale lori awon alaisan to ni apeere arun opolo fun igbe akoko ati awon miran to far ape. Asi maa toju won fun odun die. Aun se eto iwadi yi lati mo inpa aisan yii, paapaa julo awon ona ti a le gba lati je ki ara eni naa da ti ko ni fe si wahala Kankan mo. Lati le se yi, a fen i imo ijinle lori awon ogorin eniyan ti won ni iru ailera yi, a o fun won ni ogun kan naa, a o si ma wo fun bi odun kan si meji. A ma n saba lo ogun lati fi toju awon alarun opolo, fun ailera ti molebi yin ni yii, lilo oogun se Pataki.

KI NI YO SELE NIGBA TI A BA N SE ETO IWADI YII?
A o gba oro lenu molebi yin, a o si ye ara re won nigba ti o ba n wa fun ayewo lee kookan. Ni ekookan yii, a le gba eje die ni ara re fun awon iwadi Kankan nipa ilera re. Eje gbigba yi ko le wu sugbon o le dun yin die. A o ni lo eje re fun nkankan yato si iwadi ti a fe se yi, e ma jaya. A o fun n ni ogun ofe leyin ti a ba gba a wole sinu eto iwadi yi. A ti se eto abere sile fun won ti an pen i Fluanxol depot. Ogun oniworo naa wa pelu, anfani pupo lo wa nipa lilo abere yi ti yo sise fun igba pipe:
Ekini, o je ki aridaju wa wipe a n lo ogun yi bo se ye ka lo, nitoripe awon eniyan wa o n fe logun ni ojoojumo paapaa nigba ti won ban i ailera kan. Bi o ba se n wa a o ma beere awon ibeere to jo mo ailera yi lati enu dokita ati noosi lo wo re. ni ekookan bi o bat i n wa a o si ma ye ifunpa re wo, ati bi o se gbe iwon si.

IWONGBA TI ETO IWADI YI MA WA ATI IGBA TI A MA NILO YIN SI?
Ni apapo, a o se eto iwadi yi fun odun marun sugbon a fe ki o darapo mow a ninu iwadi yi fun odun meji. A o si ripe ko loju wakati kan lo ti o bat i wa.

KINI AWON ANFANI TI A MA RI GBA NINU BI BAYIN SEPO NINU ETO IWADI YI?

Anfani ti o romo kikopa yi ni pe, molebi yin o gba itoju ti o peye, yio sit un ma ran wa lowo lati ni imo si nipa ailera yi, eyi yio si jeki awa naa le ma pese ojulowo itoju fun yin ati awon miran ni ojo iwaju. Oogun ofe ari ekunrere itoju bi ailera re se ri ni e o ma gba

ASIRI

Gbogbo oro tie yin tabi molebii yin ba so fun wa nipa molebii yin yoo je nkan asiri. A ko ni lo oruko, bee sin i oro akole Kankan ti aba ko lori eto iwadi yi.

NJE MO LE FI ETO YII SILE PE MI KO SE MO NIGBA KANKAN

Molebi yin ni anfani lati ko pa tabi lati ma ko pa. Ti o ba se ipinu lati ma ko pa,
Ko ni di bi a se n se itoju re lowo leyin naa. O ni anfani lati so wipe nko se mo nigbakugba.
A fe ki e mop e, awon idahun ti e ba ti fun wa, a ti le lowon lati koi we ko to dipe e pinu lat ma kopa, mo, akosile wa ko le kuro mo. Bakana oluwadi ti yo ma ko pa ninu itoju yin yio ma sa ipa won lati faramo ipinu yin ati lati fowosowopo pelu yin.

KI LO MA SELE TI MO BA FARAPA TABI TI OHUN BURUKU KAN BA SELE NITORIPE MO KO PA NINU IWADI YIN?

Ti molebi yin ba farapa nipa iwadi yi, yio o gba itoju lati ile iwosan Oritamefa, Ibadan ati wipe awon eleeto iwadi yin i yio ma san owo itoju yin.

STATEMENT OF PERSON OBTAINING CONSENT:

MO TI SALAYE ETO IWADI YI NI KIKUN FUN----------

ATI WI PE MO TI SO NI KIKUN NIPA ANFANI ATI EWU TO RO MO LATI LE SE IPINU.

DEETI---------- IBOWOLUWE---------- ITEKA----------

ORUKO----------

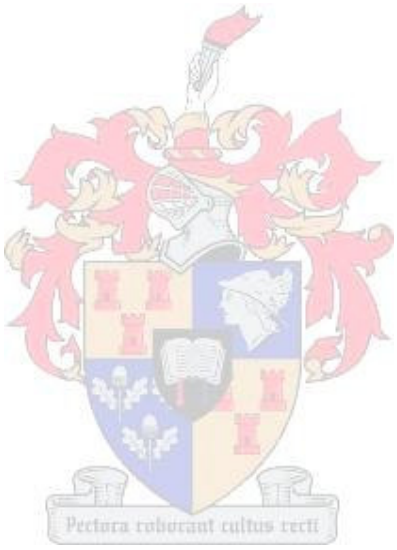
STATEMENT OF PERSON GIVING CONSENT.

MO TI KA GBOGBO NKAN TI A SO NIPA ETO IWADI, WON SI TI KO NI EDE TI MO MOO KA, TO SI TI YE MI.

MO SITI MO NI KIKUN LATI ODO DOKITA TO SI YE MI. MO WIPE KIKOPA MI JE KO PO DANDAN. MO MO DARADARA NIPA NKAN TI WON FE SE. ONA TI WON FE GBE GBA, EWU ATI ANFANI ETO IWADI YI, LA TI SE IPINU NI KOKO PE MO FE DARAPO MO. O SI TI YE MI WIPE MO LE PINU LATI MA KO PA NIGBAKUGBA. MO TI GBA IKAN NINU ILEWO TI MO FI DARAPO YI ATI ELEYI TI MO LE MU LO SILE.

DEETI---------- IBOWOLUWE----------

ORUKO----------



INSTITUTE FOR ADVANCED MEDICAL RESEARCH AND TRAINING (IAMRAT)
COLLEGE OF MEDICINE, UNIVERSITY OF IBADAN. IBADAN, NIGERIA.
Director: **Prof. A. Ogunniyi,** B.Sc(Hons), MBChB, FMCP, FWACP, FRCP (Edin), FRCP (Lond)
Tel: **08023038583, 08038094173**
E-mail: **aogunniyi@comui.edu.ng**

UI/UCH EC Registration Number: **NHREC/05/01/2008a**

Notice of Renewal of Approval

Re: ***A Study of the Profile and Determinants of Outcome in Recent Onset Schizophrenia***

UI/UCH Ethics Committee Assigned Number: UI/EC/08/0077

Name of Principal Investigator: **Prof. O. Gureje**

Address of Principal Investigator: Department of Psychiatry,
College of Medicine,
University of Ibadan, Ibadan

Date of receipt of valid application: 26/01/2012

Status: **4th Year Approval**

This is to inform you that we have received and reviewed your 3rd year report on the above named research. The report indicates the number of patients recruited since the commencement of the study. It does not show any adverse events due to the study.

The Committee notes the contents of the report and hereby gives retrospective approval to your request for the renewal of approval for one year of study only.

This renewed approval dates from 26/01/2012 to 25/01/2013. Note that no participant accrued or activity related to this research may be conducted outside of these dates. All informed consent forms used in this study must carry the UI/UCH Ethics Committee assigned number and duration of UI/UCH EC approval of the study. It is expected that you submit your annual report as well as an annual request for the project renewal to the UI/UCH EC early in order to obtain renewal of your approval to avoid disruption of your research.

The National Code for Health Research Ethics requires you to comply with all institutional guidelines, rules and regulations and with the tenets of the Code including ensuring that all adverse events are reported promptly to the UI/UCH EC. No changes are permitted in the research without prior approval by the UI/UCH EC except in circumstances outlined in the Code. The UI/UC EC reserves the right to conduct compliance visit to your research site without previous notification.

Prof. A. Ogunniyi
Director, IAMRAT
Chairman, UI/UCH Ethics Committee
E-mail:uiuchirc@yahoo.com

ADDENDUM C

SCID-I/P VERSION 2.0 (for DSM IV)

OVERVIEW

Ma beere lowo yin nipa idamu tabi wahala te e le tini ri, ma de ma ko si le bi mo se n biyin ni
ibere ka to beere
DEMOGRAPHIC DATA –
SEXOKUNRIN
(male)
OBIRIN (female)
DOB (Igbawo ni a biyin) - ------ --------- ------ AGE----------
OSU OJO ODUN
MARITAL STATUS
Se ni iyawo(if male)
tabi oko(If female)?
To ba je rara se ti loko tabi iyawo ri?
(1) Married (wa nipo lokolaya)
(2) Widowed (Ti di opo)
(3) Divorced (ko oko tabi aya sile)
(4) Separated (Ti ya pa)
(5) Never married (Ko loko laya)
Any children? (what are their ages?) Se e ti bi omo (omo dun melo ni won) ----------
If yes: How many? To ba je beeni,melo ni won?---------
Where do you live? Ibo ni won gbe----------
Who do you live with? Tani iwo ‘n ba gbe? ----------
Education and Work History
How far did you get in school? Iwe meelo le e ka?
(1) Primary 6 certificate or did not graduate
(2)Graduated from secondary school
(3)Did not graduate from secondary school
(4)NCE, Grade2, Hsc/A-levels
(5) Graduated from university
(6)Did not graduate from university
(7)Professional/masters
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If failed to complete a programme in which they were enrolled: Why didn’t you finish?
Ki lo de te e fi pari----------
What kind of work do you do? (do you work outside your home?)
Ise wo len se----------
ONSET OF PRESENT IILNESS/EXACERBATION
When did this beging
Ni gba wo lo beere?----------

(Igbawo le ripe nkan kan sele)----------
When were you last feeling o.k?
Igba wo le rip e ara ya gbeyin?
NEW SYMPTOM OR RECURRENCE

Is there something new or a return of something you have had before? (What made you come for
help now?)
Se nkan to sese sele ni tabi aisan to pada si yin lara-(Ki lo gbe yin wa si ile iwosan)----------
---

ENVIRONMENTAL CONTEXT AND POSSIBLE PRECIPITANTS OF PRESENT ILLNESS OR EXACERBATION (USE CODE AXIS 10)
What was going on in your life when thid began?
Ki lo n sele laye yin nigba ti nkan yii sele----------

Did anything happen or changed just before anything started?
Se iyato kan wa ki iyato yii to sele tabi leyin to sele----------
---
COURSE OF PRESENT ILLNESS OR EXACERBATION
Nigba to beere ki lo tun sele ----------
(se awon nkankan n damu yin lokan?)

Igba ti isele yii sele,igba wo le ripe o buru jayi----------

IF MORE THAN A YEAR AGO: To ba je bii odun kan seyin ,igba wo le leri pe o buru jayi?
Se e n sise nisi yii? ----------
♉TO BA JE BEENI: Lati igba wo leti n sise nibe? ----------
TO BA JE OSU MAFA SI SIYIN:ki lo de tefi kuro nise ten se tele?----------
---
Se e ti ma n se ise yen tele? ----------
♉To ba je rara:ki lo de tofi jebe?----------
Iru ise wo le ti se ri? ----------
179
Bawo le se n toju ara yin nisi yii? ----------
TI E BA MO:Nje igba kankan wa ti e ko le sise tabi losi ile iwe?----------
---
To ba je beeni:Nigbawo ni?Ki lo de to fi sele bee?----------

OVERVIEW OF PRESENT ILLNESS
Ti e ko ba mo: CURRENT TREATMENT STATUS
(PAST MONTH)
Se e ti gba itoju kankan lawon osu to ti koja? 1. Current in patient (including residential treatment)
2.Current outpatient
3. Other (e.g. 12 step program)
4. No current treatment
IF CURRENTLY IN TREATMENT: Date admitted on that kind of treatment
Or outpatient fascility for present illness:

Number of weeks since admission to fascility
1. <1week
2.1-4weeks
3. >4weeks
When did you come to the (hospital, clinic) ----------
CHIEF COMPLAINT AND
DESCRIPTION OF PRESENTING PROBLEM
Ki lo je ki e wa ni asiko yii?atipe kini isoro ten la koja te fi wa----------
---

If does not give details of presenting problem: E so fun mi ni kikun atipe ki ni itumo re----
---

TREATMENT HISTORY
I gbawo le ri enikankan nipa ero okan yin tabi arun opolo?(Ki lo wa fun)----------
---

Awon ogun wo ni won ko fun yin atipe itoju wo le gba?----------
---

Nje e ti gba ogun ri fun ogun oloro kankan tabi oti mimu?----------
---

THE LIFE CHART ON PAGE V1 OF OVERVIEW MAY BE USED TO DOCUMENT
A
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COMLICATED HISTORY OF PSYCOPATHOLOGY AND TREATMENT
Nje e ti fi igbakan je ailasan ni ile iwosan awon to ni arun opolo? Bi emelo ni won ti da
yin duro nibe(do not include transfers) 0
1
To ba je beeni,ki lo wa fun? 2
E meelo ni? 3
4
5(or more)
IF GIVES AN INADEQUATE ANSWERS, CHALLENGE GENTLY:
e.g Ti ko ba si nkan mi nibe,awon eniyan okan saa dede lo si ile iwosan awon to ni arun
opolo
boya nitoripe o re won tabi fun eru tabi aya jija----------

Se ti wa si ile iwosan ri fun aisan ara miran----------

To baje beeni?fun ki ni?----------

OTHER CURRENT PROBLEMS
Nje e ni ailera kankan losu to ko ja? ----------

♉Bawo le se le sowipe e sen farada nkan ti awon ba se fun si? ----------
---

Ba wo le se le sowipe ara yin daa si tabi se e ti ni arun kankan ri ti o gba itoju?(use this information on code axis 111----------
---

Se e ma mu ogun to yato si eleyi te ti so fun mi tele bii ogun a teje se? ----------
---

To baje beeni : meelo le ma n mu atipe e meelo ni lojumo?----------
Se won ti so fun yin wipe ke d a kan duro ke si ma lokan ri? ----------
---

Bawo lese mu oti si seyin? ----------

Se e ti ma n mu ogun oloro kankan ri bii igbo,kokaini ati awon ogun oloro miiran----------
---

CURRENT SOCIAL FUNCTIONING
Ba wo le sen lo asiko yin si?----------

Ta le ma n ba lo asiko yin?----------
Most likely current diagnoses: ----------

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Diagnoses that need to be ruled out: ----------

AGE (OR DATE) Description (symptoms,triggering events) Treatment
---------- ---------- ----------
---------- ---------- ----------
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RETURN TO OVERVIEW PAGE 1V, OTHER CURRENT
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SCID (DSM-IV)VERSION 2.0(FEB 1996 FINAL)Screening Questions screening –page1

SCID SCREENIG MODULE (OPTIONAL)
Ni bayi mo fe beere awon ibeere kan
Nipato nipa isoro ti e le ti niri .a o ma
yan nana re to baya.

RESPONSED TO POSITIVE RESPONSES WITH: We'll talk more about that later.

1. Nje e ti mu oti ri nigbakan nigbesi aye yin Circle"NO"on E 1
Circle"yes"on E 1
bii burukutu, emu ,gulder ni idiwon tumbila mewa
ati paraga,ogogoro ni idiwon tumbila meta nijoko ekan

2. Nje e ti mu oogun oloro kankan ri? Circle"NO"on E 10
Circle"yes "on E 10
(Bii igbo,kokain ati bebe lo)

3. Nje oogun kan ti dokita ko tabi ti e ra ni chemist Circle"NO"on E 10
Circle"yes "on E 10
Ti di baraku fun yin ti e lo ju iye to ye ki e lo lo

4. Nje e ti ni idojuko eru tabi ijaya ojiji ti o mu ki Circle"NO"on F.1
Circle"yes F. 1
awon apere kankan ma fi ara han lara yin

5. Nje o ti sele ri wipe eru ati jade ninu ile Circle"NO"on F 7
Circle"yes "F.7
Ma n nba yin,wiwa ni arin ero,diduro
lori ila tabi ririn irin ajo ninu oko
tabi reluwe?

6. Nje ohun kankan wa ti eru e ma n bayin Circle"NO"on F. 11
Circle"yes"on F . 11
ati se,tabi ti ara yin ki bale ati se laarin
awon elomiran bi sisoro, jijeun,
tabi ki a ma kowe?

7. Nje awon nkankan wa ti e n beru ni pato Circle"NO"on F16
Circle"yes"on F16
bi fifo ninu balu,riri eje,iro ibon,ibi giga,
alafo ti o di pa tabi awon eranko kan tabi kokoro

8. Nje o ti sele ri wipe ki ero ti ko mogbon dani Circle"NO"on F20
Circle"yes"on F20
ma damu okan yin kosi tun ma wa leralera ti
e ba ti e gbiyanju ati ma ro?

9. Nje awon ohun kan wa ti e ko le ma se,ti e si ma Circle"NO"on F 2 1
Circle"yes"on F 2 1
nse leralera bi ka fo owo nigbogbo igba,tabi ki a ye
nkan wo ni igba pupo lati le mo boya a ti se daradara?

10. Ni osu mefa sehin see se alaifara bale tabi gbon riri? Circle"NO"on F. 3 1
Circle"yes"on F. 3 1

11. Nje igba kankan wa ti o je wipe iwon yin diku si Circle"NO"on H. 1
Circle"yes "on H. 1
ohun ti awon eniyan ro wipe iwon yin je?

12. Nje e ma nsaba ni awon igba ti o je wipe e ma Circle"NO"on H. 4
Circle"yes "on H. 4
n jeun lai bikita?

SCID-I/P VERSION 2.0 (for DSM IV)

PSYCHOTIC AND ASSOCIATED SYMPTOMS

Ipale yii wa fun awon to ni arun opolo ati awon to fara pee to ti leni ri

♉If already has acknowledged psychotic symptoms:
Eti so fun mi nipa arun opolo te ni, mo wa fe bere lowo yin nipa nkan to ti le se yin ri.
Nje igbakan ti wa to dabi pe awon kan soro nipa yin ninu okan yin ti won si n ba yin soro lona oto

DELUSION
♉ False belief based on incorrect inference about external reality and firmly sustained in spite
of what almost everyone else believes in spite of what constitutes incontrovertible and obvious

proof or evidence to the contrary. The belief is not one ordinarily accepted by other members of
person's culture or subculture. Code overvalued ideas(unreasonable and sustained beliefs that are
maintained with less than delusional intensity)as "2"

Delusion of reference i.e. events, objects, or ? Other people in the individuals immediate Environment has a particular or unusual significance.

To ba je beeni, se erope won soro Nipa yin tabi erongba okan re ni Eso ni kikun: Nje awon yii ma n fun yin ni imoran lati ori television tabi redio tabi ninu iwe iroyin tabi bii ati se to nkan Se e le so wipe awon to n ba yin soro yin tabi mu inira bayin tabi se yin ni ijanba ?

Persecutory delusion i.e. the individual
(or his or her group)is being attacked,harassed,cheated,persecuted,or conspired against you
Eso ni kikun Nje e ti ro ri wipe e je eniyan

Grandiose delusion i.e content involves ?
Pataki ni ilu wa yii tabi eni agbara exaggerated power, knowledge,or importance
lati se nkan ti ara yoku ole se or a special relationship to a deity or famous person
Describe:
N je e ti sa ki a si wipe e

Somatic Delusion i.e content involves? change or disturbance in body appearance or functioning
ni ailara kan ni ara yin botile sepe dokita yin ni ko si nkankan mu yin bii arun jejere tabi awon arun miiran Nje e ti mo ni pato wipe eya Eso ni kikun Ara kan ko se daradada tabi bi o se ri? N je e ti sa kiyesi wipe nkan ti o ye Kan se le bi nkan ajeji n se le si Eya ara yin kankan? N je e ti gba esin sodi ri?
Other Delusion ?

Check if:
-Religious delusions
-Delusion of Guilt
-Jealous Delusions
-Eromatic Delusions

N je e ti se nkan ti o da fun yan ri tabi ese kan
to le je ki e jebi idajo
I f never had a delusion and there is no suspicion
Of any psychotic features
Descibe(eso ni kikun):

Check here and Go to

Delusion of being controlled i.e feelings impulses, thoughts, or actions are experienced as being Under control of same external force

N je e ti ro wipe eniyan kankan Tabi nkankan nita ara yin soro Sinu okan yin tabi pe ke e se

Nkan ti e Fe se.

Check if:

-thought insertion
-thought withdrawal

Nje o ti seleri wipe awon ero Kan ti ko se tiyin ti man wa si okan yin
Se awon ero yii ma n jade Kuro lokan yin

Describe: (Eso ni kikun)

Thought Broadcasting i.e the delusion that one's thought are audible to others
ma so sita ki awon ara yoku

N je e ti ro wipe awon ero yii legbo nkan ti e n ro lokan
Se e ti ro wipe awon Kan le mo nkan Ti e n ro lokan tabi ti e fe so

Describe (E so ni kikun)

How do you explain content Of delusion?

Bizarre Delusion i.e. involving a individual's Subculture would regard as totally Implausible e.g. the person's brain has been removed and replaced with someone else's brain
Describe;

Auditory Hallucination

Hallucinations (psychotic)
A Sensory perception that has the compelling sense of reality of a true perception but occurs without external stimulation of relevant sensory organ. Code 2 for hallucination that is as transparent as to be without Diagnostic significance.

Auditory Hallucinations when ?fully awake, heard either inside or outside your head

A voice keeping up a running connection on the individual's behaviour or thoughts as they occur

Tabi oro awon kan ti a so kelekele N je e ti ma n gbo nkan ti A won kan ole gbo tabi ariwo Si yin leti (nje e ko sun ni gba yen)

To ba je beeni: ki le n gbo? E so ni kikun B awo le se ma n saba gbo ohun Yii?

To ba je ohun (voices): se won fesi si nkan ti e n se tabi ro lokan

Go to visual hallucination below

Visual Hallucinations

Visual Hallucination ?
N je e ma ri iran tabi Ri nkan ti awon yoku o ri Describe (se e e ko sun nigba yen)

NOTE: Distinguish from an Illusion i.e a misperception of A real external stimulus.
Nj e e ma n ri ki nkankan Ma run lara yin?

Describe:
Nj e e ma n gborun ti awon Miiran ko gbo
Other Hallucination e.g gustatory, olfactory
Check if:
-gustatory
-olfactory
Describe:

Other Symptoms

I f No suggestion that there have ever been psychotic symptoms,Check Here --- and skip to
module D
(Let me stop for a minute and make some full notes…….)

The following items are rated Catatonic behaviour based on observation And history consults Old charts, other observers E.g. family members, Therapeutic staff)

-tabi ko kotikun si nkan ?
-lilera laisepe won so fun yin ?
-tabi ko ma sare malo bii ko ma se giragira laisepe e so fun te ba ni ko ma se bii ko gbese kuro legbe ina ,ko si ma dahun
-bii ko ma rin ni ona to je pe ohun nikan lo ye bii gbowo lejika fun igba pipe ? 1 2 3
-so oro tele yin tabi se ohun te ba n se ?

Describe:

Grossly Disorganised Behaviour
E yi tile beere lati igba to wa ni Kekere ti o ma n se ipanle si ailenisuru Ti o ma ri bi eni ti won toju tabi mura ni,ma woso ti o bar a mu bii wo aso meeji meta po tabi wo aso erun nigba ojo,ati bi ko ma yo oko sita ladubgbo, tabi si dile,ati ki o ma pa ariwo laito tabi sepe

Describe:

Grossly Inapproprite Affect:
Nje igba kan leti wa ti oro re ko Ba tara ye yoku mu,bii ko ma Dun nu ju,tabi sokun laito , Idunnu yii le wa fun igba pipe Tabi ki e ma ba soro ko ma tara ye mu

Describe:

Disorganized Speech:

Eyi ma n sele nigba mi bii ko o Ma a soro ti oni jora won tabi Fo lati ori oro kan si oro mii ti a Ko bii tabi ti o jo mo oro to n so, Tabi ko kan farape die.Awon Oro mi ko ni mu ero gidi lowo Tobege wipe awon oro yen o ni Itumo.

DESCRIBE:

N egative Symptoms

F or any Negative Symptoms Coded 3 ,Determine whether the symptoms is definitely Primary or whether it is possible or definitely Secondary i.e related to another mental disorder e.g(depression),a substance or a general medical condition (e.g medication induced Akinesia) or to a psychotic symptoms(e.g) command hallucinations not to move

IF UNKNOWN;
Bawo lese ma n lo asiko yin?

AVOLITION:
Nje gbogbo nkan ti e ba gbero Pe e fe se le ma n lese?Se e ti ro wipe e fe paro ise kan si kan Tabi e n le lati se nkan,tabi e fe Se itoju ara yin,se e ma n le se?

ALOGIA:
nje o ma n Ro ero miiran ti a ko ni ri itumo Kankan mu jade tabi ni iwuwa,
Idahun re nigbami le kere si oroTe bi,oro re nigbami le ma to iye ti afe so tabi ko je pe awon oro to
Ni itumo re le ma po,tabi ko maMu ogbon wa,tabi ko ma so tele yin Tabi ko ma ni patterni kan

Affective Flattening:
Eyi ma n sele nigbati ko fe e Si tabi ko sin kan to feran tabi Ko ma fi apeere han ti nkan ayo Tabi nkan buruku ba sele

C. Differential Diagnosis of Psychotic Disorders

Note: Both primary psychotic system and psychotic systems that are substance induced or due to a general medical condition may be present in the same individual at the time. this may
require multiple ‘passes’ through the algorithms in this module.
If: All psychotic symptoms in module B are due to a substance or A general medical Condition, Go to Gmd substance C16.
If: there are no items coded 3 in B psychotic and associated symptoms
Check Here_____ and skip to next module

SCHIZOPHRENIA CRITERIA
CHECK FOR PRESENCE OF ACTIVE PHASE SYMPTOMS
REFER TO ITEMS CODED “3” IN THE PSYCHOTIC AND ASSOCIATED

(NOTE: CRITERIA ARE IN DIFFERENT ORDER THAN IN DSM-IV)
A. Two (or more) of the following, each present for
a significant portion of time during a one month
period (or less id successfully treated):

SYMPTOMS MODULE (MODULE B)

1) Delusions
2) Hallucinations
3) Disorganized speech (e.g., frequent derailment or incoherence)
4) Grossly disorganized or cataonic behavior
5) Negative symptoms, i.e., affective flattening, alogia, or avolitio.

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

D. Schizoaffective Disorder and mood Disorder with Psychotic Features have been ruled out because either:

IF UNCLEAR: Has there ever been a time when you had (SXS FROM ACTIVE PHASE) concurrently with at the same time that you were (down/high/ irritable / OWN EQUIVALENT)?

1) No major Depressive, Manic or Mixed episodes have occurred

the active phase symptoms (i.e., the "A" Symptoms listed above)

NOTE: CODE "3" IF NEVER ANY MAJOR DEPRESSIVE OR MANIC EPISODES OR IF ALL MAJOR DEPRESSIVE AND MANIC EPISODES OCCURRED DURING THE PRODROMAL OR RESIDUAL PHASE.
CODE "1" IF ANY MOOD EPISODES OVERLAP WITH PSYCHOTIC SYMPTOMS.

NOTE: BECAUSE OF THE DIFFICULTY IN DISTINGUISHING THE PRODROMAL AND

RESIDUAL SYMPTOMS OF SCHIZOPHRENIA FROM A MAJOR DEPRESSIVE SYNDROME, THE RATER SHOULD RECONSIDER ANY PREVIOUSLY CODED MAJOR DEPRESSIVE EPISODE TO BE SURE IT IS UNEQUIVOCAL.

IF UNCLEAR: How much of the time episodes
that you have had (SXS FROM ACTIVE disturbance) has been
AND RESIDUAL PHASES) would you say brief relative to the total duration of the
you have also been (depressed / high/irritable/ active and residual phases.
OWN EQUIVALENT)?

2) the total duration of mood (occurring during the

NOTE: CODE “1” IF SYMPTOMS MEETING CRITERIA FOR A MAJOR DEPRESSIVE, MANIC, OR MIXED EPISODE HAVE BEEN PRESENT FOR A SUBSTANTIAL PORTION OF THE TOTAL DURATION OF THE ACTIVE AND RESIDUAL PHASES

NOWMAKE A DIFFERENTIAL
DIAGNOSIS BETWEENSCHIZOPHRENIA
AND SCHIZOPHRENI FORM DISORDER

C. Continuous signs of the disturbance
persist for at least six months.
This six -
month period must include at least one

Month of symptoms that meet

criterion A

(i.e., active phase symptoms), and may include periods of prodromal or residual symptoms. During these residual periods, the signs of the disturbance may be manifested by only negative sxs (i.e., affective flattening, alogia, avolition) or two or more symptoms listed in

IF UNCLEAR: Between (MULTIPLE EPISODES), were you back to your prodromal or normal self? How long did each episode last?

criterion A
present in an attenuated form
(e.g., odd
beliefs, unusual perceptual
experiences).

IF NOT ALREADY KNOWN: When you
time since
(HAD "A" CRITERION SXS), were
or more
You (working, having a social life, taking
as work,
care of yourself)?
care is

achieved prior to

childhood

expected

or

B. For a significant portion of the

the onset of the disturbance, one

major areas of functioning such

Interpersonal relations or self-

markedly below the level

the onset (or when the onset is in

or adolescence, failure to achieve

level of interpersonal academic,

occupational achievement).

IF NOT KNOWN: Were you taking any
the direct
drugs of medicines during this time?
substance (e.g., a

a general
IF NOT KNOWN: Were you physically ill
at this time?

E. The disturbance is not due to

Physiological effects of a

drug of abuse, a medication) or to

medical condition.

IF THERE IS ANY INDICATION THAT THE PSYCHOTIC SXS MAY BE SECONDARY (I.E., A DIECT PHYSIOLOGICAL CONSEQUENCE OF A GMC OR SUBSTANCE, GO TO *GMC/SUBST* C. 16, AND RETURN HERE TO MAKE A RATING OF "1" OR "3".

conditions

Etiological general medical

include: neurological conditions

(e.g., neoplasms, cerebrovascular disease, Huntington's disease epilepsy, auditory nerve injury, deafness, migraine, central nervous system infections); endocrine conditions (e.g., hyper – and hypothyroidism, hyper – and hypoparathyroidism, hypocortisolism); metabolic conditions (e.g., hypoxia, hyper carbia, hypoglycemia); fluid or electrolyte imbalances; hepatic or renal diseases; and autoimmue disorders with central nervous system involvement (e.g., systemic lupus erythematosis).

Etiological substances include:

alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids (meperidine), phencyclidine sedatives, hypnotics, and anxiolytics, and other or known substances.

SCHIZOPHRENIA TYPES
NOW DETERMINE THE CURRENT PHENOMENOLOGIC TYPE:

Paranoid Type: currently:

A. Preoccupation with one or more delusions or frequent auditory hallucinations.

B. None of the following is prominent: disorganized speech, disorganized behavior, flat of inappropriate affect or catatonic

PARANOID TYPE

behavior.

Catatonic Type: currently the clinical picture is dominated by at least two of the following:

1) Motoric immobility as evidenced by catalepsy (including waxy flexibility) or stupor.
2) Excessive motor activity (that is apparently purposeless and not influenced by external stimuli)
3) Extreme negativism (an apparently motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism.
4) Peculiarities of voluntary movement as evidenced by posturing (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, prominent mannerisms, or prominent grimacing.
5) Echolalia or echopraxia.

CATATONIC TYPE

DISORGANIZED TYPE

IF UNKNOWN, DETERMINE WETHER FLAT OR IN APPROPRIATE AFFECT HAS BEEN PRESENT.

Disorganized Type: currently the following criteria are met:

A. All of the following are prominent:

   1) Disorganized speech
   2) Disorganized behavior
   3) Flat or inappropriate affect

B. Does not meet criteria for Catatonic type.

UNDIFFERENTIATED TYPE

Undifferentiated Type: currently symptoms meeting criterion A for Schizophrenia are present, but the Criteria are not met for the Paranoid, Catatonic, or Disorganized Types.

RESIDUAL TYPE

Residual Type: currently, the following criteria are met:

A. Absence of prominent delusions, hallucinations, disorganized speech, and grossly disorganized or catatonic behavior.
B. There is continuing evidence of the disturbance, as indicated by the presence of negative symptoms or two or more symptoms listed in criterion A for Schizophrenia, Present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

***SCHIZOPHRENIFORM DISORDER* SCHIZOPHRENIFORM DISORDER CRITERIA**

SCHIZOPHRENIA HAS BEEN RULED OUT BECAUSE THE DURATION IS LESS THAN SIX MONTHS

IF NOT KNOWN:How long did (PSYCHOTIC SXS) LAST?

IF NOT KNOWN:
NJE EN LOGUN KANKAN NIGBA NAA

IF NOT KNOWN:
Nje aisan Kankan ti a le toju ri nseYin Ni gba naa?

B.An episode of the disorder (including prodromal, active and residual phases) lasts at least one month but less than six months
(se o sele fun osu kan Sugbon ko to mefa)

GO TO*BRIEF PSYCHOTIC DISORDER C.14

C. The disturbance is not due to direct physiological effects of substance (eg a drug Of abuse,medication)or to a General medical condition

GO TO *PSYCHOTIC DISORDER NOS C.20

SCHIZOPHRENIFORM DISORDER

IF THERE IS ANY INDICATION THAT THE PSYCOTIC SXS MAY BE SECONDARY(I.E A DIRECTION PHYSIOLOGICAL CONSEQUENCE OF A GMC OR SUBSTANCE,GO TO GMC*/SUBST*C.16 AND RETURN HERE TO MAKE A RATING OF “1”OR “3”

IF OTHER PERIODS OF PSYCHOTIC SXS NOT DUE TO A SUBSTANCE OR GMC RETURN TO C.1 OTHERWISE GO TO NEXT MODULE

REFER TO LIST OF GENERAL MEDICAL CONDITIONS AND SUBSTANCES C.5

When diagnoses is made without waiting For recovery, it should be qualified as“Provisional”

N OTE: CODE”2” IF THE EXPECTEDRECOVERY HAS NOT YET OCCURRED CODE”3”IF THERE HAS BEEN A FULL RECOVERY

PROVISIONAL DX

DEFINITE DX

CONTINUE ON NEXT PAGE

NOW DETERMINE IF GOOD PROGNOSTIC FEATURES ARE PRESENT

At least two of the following features that is generally associated with good prognosis

(1) Onset of prominent psychotic symptoms Within 4 weeks of first noticeable chang In usual behaviour or functioning

(2) Confusion or perplexity at the height Of the psychotic episode

(3) Good premorbid social and occupational functioning

(4) Absence of blunted or flat affect

AT LEAST TWO GOOD PROGNOSTICS FEATURES CODED “3”

SCHIZOAFFECTIVE DISORDER

SCHIZOPHRENIA AND SCHIZOPHRENIFORM A DISORDER HAVE BEEN RULED OUT BECAUSE OF PROMINENT MOOD SYMPTOMS. CONSIDER. A DIAGNOSIS OF SCHIZOAFFECTIVE DISORDER

SCHIZOAFFECTIVE DISORDER CRITERIA

A. An uninterrupted period of illness during which, at some time, there is either a Major Depressive Episode (which must include (1) depressed mood), a Manic or a Mixed episode concurrent with symptoms that Meet Criterion A for Schizophrenia

Note: The Major Depressive Episode must Include criterion A1: depressed mood

B. Nigba ti ara yin ko ya yi, se o ti sele ri wipe e ma n gbo ohun ajeji tabi ri iranti awon eniyan miran fun bi ose meji lai si awon aperemiran.

GO TO CHRONOLOGICAL *C.21
GO TO PSYCOTIC DISORDER NOS*C2

C. Awon apere to le so fun wa wipe gan n waye Ni gbogbo igba ti ailera yi fi wa.

IF NOT KNOWN: Nje e n lo oogun kankan nigba na

IF NOT KNOWN: Nje e se aisan kankan ti a le foru ri

D. The disturbance is not due to the direct Physiological effects of a substance (e.g. a Drug of abuse, medication) or to a general

GO TOPSYCOTIC DISORDER NOS*C.20

SCHIZOAFFECTIVE DISORDER.SELECT SUBTYPE

DUE TO SUBSTANCE OR GMC;IF OTHER PERIODS OF PSYCHOTIC SXS NOT DUE TO A SUBSTANCE OR GMC

REFER TO LIST OF GENERAL MEDICAL CONDITIONS AND SUBSTANCES ON PAGE C5

SCHIZOAFFECTIVE DISORDER SUBTYPES

Manic Episode or Mixed Episode (or a Manic Or Mixed Episode and Major Depressive Episodes) during the course of the disturbance

DEPRESSIVE TYPE. BIPOLAR TYPE

GO TO CHRONOLOGICAL *C.21

ADDENDUM D

Neurological Evaluation Scale

(Buchanan, Heinrichs – 1989)

1. Tandem Walk

Instructions: Subject to walk, in a straight line, 12 feet, heel to toe.
Assessment: 0 = no missteps after subject has completed first full step; 1 = one or two missteps after completion of first full step; 2 = 3 or more missteps, grabbing or falling.

2. Romberg Test

Instructions: Subject to stand with his/her feet together, eyes closed, his/her arms held parallel to the floor, and fingers spread apart. The subject is to maintain this position for 1 min.
Assessment: 0 = relatively stable, minimal swaying;
1 = marked swaying; 2 = subject steps to maintain balance or falls.

3. Adventitious Overflow

Instructions: Same as Romberg Test.
Assessment: 0 = absence of movement of fingers, hands, or arms; 1 = irregular fluttering movement of fingers only;
2 = irregular fluttering movement extended to hands and/or arms.

4. Tremor

Instructions: Same as Romberg Test.
Assessment: 0 = no tremor; 1 = mild, find tremor;
2 = marked, find or coarse tremor.

5. Cerebral Dominance

a. Handedness

Instructions: Ask subject to demonstrate how he/she would write, throw a ball, use a tennis racket, strike a match, use scissors, thread a needle, use a broom, use a shovel, deal cards, use a hammer, brush teeth, and unscrew the lid of a jar.
Assessment: R – Subject write with right hand and performs at least seven other activities with right hand; M – Subject write with right hand but performs less than seven other activities with right/left hand; L – Subject writes with left hand and performs at least seven other activities with left hand.

b. Footedness

Instructions: Ask subject to demonstrate how he/she would kick a ball.
Assessment: R – Subject kicks ball with right foot;
L – Subject kicks ball with left foot.

c. Eyedness

Instructions: Ask subject, with both eye open, to look at a distant object through a hole in the center of a 3-inch x 5-inch index card that is held with both hands 18 inches in front of the subject. The subject is to close one eye at a time and tell the examiner with which eye closed did he/she lose sight of the object.

Assessment: R – Subject loses sight of object with right eye closed; L – Subject loses sight of object with left eye closed.

6. Audio-Visual Integration

Instructions: The subject is asked to match a set of tapping sounds with one of three sets of dots presented on a 5-inch x 7-inch index card. The subject is instructed to close his/her eyes during the tapping. Three practice trials are performed first to ensure that the subject understands the directions.

Assessment: 0 = no error; 1 = one error; 2 = two or more errors.

7. *Stereognosis

Instructions: Subject, with eyes closed, is asked to identify an object placed in his/her hand. Subject is instructed to feel the object with one hand and to take as much time as needed. If subject cannot name the object, he/she is asked to describe for what purpose the object is used. The subject starts with the dominant hand, based on the prior evaluation of handedness, or the hand with which he/she writes, if there is mixed hand dominance. The instructions are repeated at the beginning of the second trial.

Assessment: 0 = no errors; 1 = one error; 2 = more than one error.

8. *Graphesthesia

Instructions: Subject with eyes closed, is asked to identify the number written on the tip of his/her forefinger. The order of hands is determined as with stereogenosis.

Assessment: 0 = no errors; 1 = one error; 2 = more than one error.

9. *Fist-Ring Test

Instructions: The subject is asked to alternate placing his/her hand on the table, in the position of a first, with the thumb placed either over the knuckles or over the middle phalanges and placing his/her hand, on the table, in the position of a ring, with the tips of the thumb and forefinger touching and the remaining three fingers extended. The subject is to bring his/her arm into the upright position between each change in hand position. If the subject does not perform the movement accurately or in a manner that can be appropriately assessed, he/she is to be stopped to be reinstructed, and to start the test again. The subject is to repeat each set of hand position changes 15 times.

Assessment: 0 – *no major disruption of motion after first repetition;* errors limited to incomplete extension of fingers in ring position and no more than two hesitancies in the transition from fist to ring or vice versa and no more than one fist/ring confusion; 1 = *no major disruption of motion after first repetition or complete breakdown of motion;* more than two hesitancies in the transition from fist to ring, difficulty in developing and maintaining a smooth, steady flow of movement, three to four fist/ring confusions, or any total of three but not more than four errors; 2 = *major disruption of movement or complete breakdown of motion, or more than four fist/ring hesitations or confusions.*

10. *Fist-Edge-Palm Test

Instructions: Ask the subject, using a smooth and steady rhythmic pattern, to touch the table with the side of his/her fist, the edge of his/her hand, and the palm of his/her hand. The subject is to break contact with the surface of the table between each change in hand position, but not to bring the arm back in full flexion. The subject is to repeat this sequence of position changes 15 times.

Assessment: 0 = *no major disruption of motion after first repetition;* errors limited to no more than two hesitancies in the transition from one position to the next and no more than one mistake in hand position; 1 = *no major disruption of motion after first repetition of complete breakdown of motion;* more than two hesitancies in the transition from one position to another, difficulty in developing and maintaining a smooth, steady flow of movement, three to four position confusions, or any total of three or four errors; 2 = *major disruption of movement or complete breakdown of motion or more than four hesitations or position confusions.*

11. Ozeretski Test

Instructions: The subject is to place both hands on the table, one hand palm down and the other hand in the shape of a fist. The subject is then asked simultaneously to alternate the position of his/her hand sin a smooth and steady motion. The subject is asked to repeat this motion 15 times.

Assessment: 0 = *no major disruption of motion after first repetition;* errors limited to no more than two hesitancies in the transition from one position to the next and no more than one mistake in hand position; 1 = *no major disruption of motion after first repetition or complete breakdown of motion;* more than two hesitancies in the transition from one position to another, difficulty in developing and maintaining a smooth, steady flow of movement, three to four position confusions, or any total of three, but no more than four errors; 2 = *major disruption of movement or complete breakdown of motion; more than four hesitations or position confusions.*

12. Memory

Instructions: Subject is told four words and is asked to repeat them immediately after they are all presented. If the subject is unable to repeat the four words correctly, they are represented. If the subject still cannot repeat the four words after a total of three presentations of the words, the test is terminated and the subject is given a score of 2 for both parts of the item. If the subject is able to repeat the four words after the initial or two subsequent presentations, he/she is then asked to remember the words as well as possible and told that he/she will be asked to repeat the words twice later on during the interview. The subject is then asked to recall the four words at 5 and 10 min.

Assessment: 0 = Subject remembers all words;
1 = Subject remembers three words; 2 = Subject remembers fewer than three words.

13. Rhythm Tapping Test

Part A

Instructions: Ask the subject to reproduce exactly the series of taps heard while the subject has eyes closed. The subject may have eyes open while reproducing series of taps.

Assessment: 0 = no errors; 1 = one error of either nondiscrimination between soft and hard sounds, rhythm, or error in number of taps; 2 = more than one error.

Part B

Instructions: Ask the subject to produce a series of taps as instructed.

Assessment: 0 = no errors; 1 = one error; 2 = more than one error.

14. *Rapid Alternating Movements

Instructions: Ask the subject to place his/her hand palms down on legs. The subject is to start with his/her dominant hand and is to slap his/her leg distinctly with the palm and the back of his/her hand in an alternating motion. The determination of dominance is as described above (see item 8). The subject is to perform the task 20 times, with both hands, one hand at a time.

Assessment: 1 – no major disruption of motion, hesitation, or mistake in hand placement; 1 = no major disruption of motion or one to two hesitations or mistakes in hand placement;
2 = major disruption of motion or three or more hesitations or mistakes in hand placement.

15. *Finger-Thumb Opposition

Instructions: Ask the subject to place both hand palms up with fingers fully extended on his/her legs. The subject is to start with his/her dominant hand and is to touch the tip of his/her fingers with the tip of his/her thumb, from forefinger to pinky, returning to forefinger, for a total of 10 repetitions.

Assessment: 0 = no major disruption of motion and no more than one mistake; 1 = no major disruption of motion or two to three mistakes; 2 = major disruption of motion or four or more mistakes.

16. *Mirror Movements

Instructions: The subject's hand, which is not performing the Finger-Thumb Opposition Test, is observed for parallel movements of the fingers and thumb.

Assessment: 0 = no observable movements of the fingers;
1 = minor, inconsistent, or repetitive movements of the fingers; 2 = consistent, distinctive movements of the fingers.

17. Extinction (Face-Hand Test)

Instructions: The subject is seated, with hands resting palm down, on his/her knees and with eyes closed. The subject is told that he/she will be touched on either the cheek, hand, or both, and is to say where he/she is asked – the first time this occurs only – if he/she felt a touch anywhere else. The simultaneous touching is done in the following order: right

cheek-left hand, left cheek-right hand, right cheek-right hand, left cheek-left hand, both hands, and both cheeks.
Assessment: 0 = no errors; 1 = one error; 2 = more than one error.

18. Right/Left Confusion
Instructions: Subject is asked to point to his/her right foot, left hand; place his/her right hand to left shoulder, left hand to right ear; point to examiner's left knee, right elbow; with examiner's arms crossed, point to examiner's left hand with his/her right hand, and with examiner re-crossing arms, point to examiner's right hand with his/her left hand.
Assessment: 0 = no errors; 1 = one error; 2 = two or more errors.

19. Synkinesis
Instructions: Subject is instructed to follow the cap of a pen with his/her eyes only as it is moved between extremes of horizontal gaze. If the subject moves his/her head, the subject is asked to keep his/her head still and follow the cape of a pen with the eyes only.
Assessment: 0 = no movement of the head;
1 = movement of the head on first trial but not when specifically told to keep head still; 2 = movement of the head even when told to keep head still.

20. Convergence
Instructions: Subject is instructed to follow the cap of a pen with his/her eyes as it is moved toward the subject's nose.
Assessment: 0 = both eyes converge on object; 1 = one or both eyes are unable to converge completely, but can converge more than halfway; 2 = one or both eyes fail to converge more than halfway.

21. Gaze Impersistence
Instructions: Subject is instructed to fix his/her gaze on the cape of a pen at a 45^{o} angle in the horizontal place of the right and left visual fields for 30 sec.
Assessment: 0 = no deviation from fixation; 1 = deviation from fixation after 20 sec; 2 = deviation from fixation before 20 sec.

22. Finger to Nose Test
Instructions: The subject is instructed to close eyes and touch the tip of his/her nose with the tip of his/her index finger.
Assessment: 0 = no intention tremor or pass- pointing;
1 = mild intention tremor or pass-pointing; 2 = marked intention tremor or pass-pointing.

23. Glabellar Reflex
Instructions: Subject is instructed to fix his/her gaze on a point across the room. The subject is approached from above the forehead outside of the visual field, and the examiner taps the glabellar region 10 times with the index finger.
Assessment: 0 = three or fewer blinks; 1 = four or five full blinks, or more than six partial or full blinks; 2 – six or more full blinks.

24. Snout Reflex
Instructions: Subject is instructed to relax, and the examiner presses his

finger against the subject's philtrum.
Assessment: 0 = no contraction of the orbicularis orris (or puckering of the lips); 2 = any contraction of the orbicularis orris (or puckering of the lips).

25. Grasp Reflex
Instructions: The subject is instructed not to grab, and the examiner strokes the inside of the subject's palm between the index finger and thumb. This procedure is repeated a second time with the subject being asked to spell the word "help" backwards.
Assessment: 0 = no flexion of the subject's fingers; 1 = mild flexion of the subject's fingers on first trial or flexion of any kind on second trial; 2 = marked flexion of the subject's fingers on first trial.

26. Suck Reflex
Instructions: The examiner places the knuckle of a flexed index finger or tongue depressor between the subject's lips.
Assessment: 0 = no movement; 2 = any pursing or sucking motion by the subject's lips.

27. Palmomental Reflex

Neurological Evaluation Scale (NES)

Name: _____ **Date:** _____

Visit Nr: _____

		Absent	Present	Marked
1	Tandem Walk	0	1	2
2	Romberg Test	0	1	2
3	Adventitious Flow	0	1	2
4	Tremor	0	1	2
5	Cerebral Dominance			
	(a) Handedness	L	M	R
	(b) Footedness	L		R
	(c) Eyedness	L		R
6	Audio-visual Integration	0	1	2
7	Stereognosis	0	1	2
8	Graphesthesia	0	1	2
9	Fist-Ring Test	0	1	2
10	Fist-Edge-Palm Test	0	1	2
11	Ozeretski Test	0	1	2
12	Memory	0	1	2
13	Rhyth Tapping Test			
	Part A	0	1	2
	Part B	0	1	2
14	Rapid Alternating Movements	0	1	2
15	Finger Thumb Opposition	0	1	2
16	Mirror Movements	0	1	2
17	Extinction (Face-Hand Test)	0	1	2
18	Right/Left Confusion	0	1	2
19	Synkinesis	0	1	2
20	Convergence	0	1	2
21	Gaze Impersistence	0	1	2
22	Finger to Nose Test	0	1	2
23	Glabellar Reflex	0	1	2
24	Snout Reflex	0		2
25	Grasp Reflex	0	1	2
26	Suck Reflex	0		2
27	Palmomental Reflex	0		2
TOTAL SCORE				

ADDENDUM E

CLINICAL AND OUTCOME ASSESSMENT INSTRUMENTS

Premorbid Adjustment Scale

CRF No:..... Date:.....

	Score
Childhood: up through age 11	
1. Sociability and withdrawal	
2. Peer relationships	
3. Scholastic performance	
4. Adaptation to school	
Early Adolescence: Ages 12-15	
1. Sociability and withdrawal	
2. Peer relationships	
3. Scholastic performance	
4. Adaptation to school	
5. Social-sexual aspects of life during early adolescence	
Late Adolescence: Ages 16-18	
1. Sociability and withdrawal	
2. Peer relationships	
3. Scholastic performance	
4. Adaptation to school	
5. Social-sexual aspects of life during adolescence and immediately beyond.	
Adulthood: Age 19 and above.	
1. Sociability and withdrawal	
2. Peer relationships	
3a Aspects of social-sexual life. *Married presently or formerly.*	
3b Aspects of social-sexual life. *Never married, over 30.*	
3c Aspects of social-sexual life. *Never married, age 20-29.*	
General:	
1. Education	
2. During a period of 3 years up to 6 months before first hospitalisation or onset of first episode, subject was employed for pay or functioning in school.	
3. Within a period of a year up to 6 months before first hospitalisation or first episode change in work or school performance occurred.	
4. During period of 3 years up to 6 months before first hospitalisation of first episode, frequency of job change if working, or interruption of school attendance was	
5. Establishment of independence	
6. Global assessment of highest level of functioning achieved in subject's life.	
7. Social-personal adjustment	
8. Degree of interest in life	
9. Energy level	

P3. Hallucinatory behaviour. Verbal report or behaviour indicating perceptions which are not generated by external stimuli. These may occur in the auditory, visual, olfactory, or somatic realms. **Basis for rating:** verbal report and physical manifestations during the course of interview as well as reports of behaviour by primary care workers or family.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - One or two clearly formed but infrequent hallucinations, or else a number of vague abnormal perceptions which do not result in distortions of thinking or behaviour.

4 **Moderate** - Hallucinations occur frequently but not continuously, and the patient's thinking and behaviour are affected only to a minor extent.

5 **Moderate severe** - Hallucinations are frequent, may involve more than one sensory modality, and tend to distort thinking and/or disrupt behaviour. Patient may have delusional interpretation of these experiences and respond to them emotionally and, on occasion, verbally as well.

6 **Severe** - Hallucinations are present almost continuously, causing major disruption of thinking and behaviour. Patient treats these as real perceptions, and functioning is impeded by frequent emotional and verbal responses to them.

7 **Extreme** - Patient is almost totally preoccupied with hallucinations, which virtually dominate thinking and behaviour. Hallucinations are provided a rigid delusional interpretation and provoke verbal and behavioural responses, including obedience to command hallucinations.

P4. Excitement. Hyperactivity as reflected in accelerated motor behaviour, heightened responsivity to stimuli, hypervigilance, or excessive mood lability. **Basis for rating:** behavioural manifestations during the course of interview as well as reports of behaviour by primary care workers or family.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Tends to be slightly agitated, hypervigilant, or mildly overaroused throughout the interview, but without distinct episodes of excitement or marked mood lability. Speech may be slightly pressured.

4 **Moderate** - Agitation or overarousal is clearly evident throughout the interview, affecting speech and general mobility, or episodic outbursts occur sporadically.

5 **Moderate severe** - Significant hyperactivity or frequent outbursts of motor activity are observed, making it difficult for the patient to sit still for longer than several minutes at any given time.

6 **Severe** - Marked excitement dominates the interview, delimits attention, and to some extent affects personal functions such as eating and sleeping.

7 **Extreme** - Marked excitement seriously interferes in eating and sleeping and makes interpersonal interactions virtually impossible. Acceleration of speech and motor activity may result in incoherence and exhaustion.

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P5. Grandiosity. Exaggerated self-opinion and unrealistic convictions of superiority, including delusions of extraordinary abilities, wealth, knowledge, fame, power, and moral righteousness. **Basis for rating:** thought content expressed in the interview and its influence on behaviour.

1 **Absent** - Definition does not apply

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Some expansiveness or boastfulness is evident, but without clear-cut grandiose delusions.

4 **Moderate** - Feels distinctly and unrealistically superior to others. Some poorly formed delusions about special status or abilities may be present but are not acted upon.

5 **Moderate severe** - Clear-cut delusions concerning remarkable abilities, status, or power are expressed and influence attitude but not behaviour.

6 **Severe** - Clear-cut delusions of remarkable superiority involving more than one parameter (wealth, knowledge, fame, etc.) are expressed, notably influence interactions, and may be acted upon.

7 **Extreme** - Thinking, interactions, and behaviour are dominated by multiple delusions of amazing ability, wealth, knowledge, fame, power, and/or moral stature, which may take on a bizarre quality.

P6. Suspiciousness/persecution. Unrealistic or exaggerated ideas of persecution, as reflected in guardedness, a distrustful attitude, suspicious hypervigilance, or frank delusions that others mean one harm. **Basis for rating:** thought content expressed in the interview and its influence on behaviour.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Presents a guarded or even openly distrustful attitude, but thoughts, interactions, and behaviour are minimally affected.

4 **Moderate** - Distrustfulness is clearly evident and intrudes on the interview and/or behaviour, but there is no evidence of persecutory delusions. Alternatively, there may be indication of loosely formed persecutory delusions, but these do not seem to affect the patient's attitude or interpersonal relations.

5 **Moderate severe** - Patient shows marked distrustfulness, leading to major disruption of interpersonal relations, or else there are clear-cut persecutory delusions that have limited impact on interpersonal relations and behaviour.

6 **Severe** - Clear-cut pervasive delusions of persecution which may be systematised and significantly interfere in interpersonal relations.

7 **Extreme** - A network of systematised persecutory delusions dominates the patient's thinking, social relations, and behaviour.

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P7. Hostility. Verbal and nonverbal expressions of anger and resentment, including sarcasm, passive-aggressive behaviour, verbal abuse, and assaultiveness. **Basis for rating:** interpersonal behaviour observed during the interview and reports by primary care workers or family.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Indirect or restrained communication of anger, such as sarcasm, disrespect, hostile expressions, and occasional irritability.

4 **Moderate** - Presents an overtly hostile attitude, showing frequent irritability and direct expression of anger or resentment.

5 **Moderate severe** - Patient is highly irritable and occasionally verbally abusive or threatening.

6 **Severe** - Uncooperativeness and verbal abuse or threats notably influence the interview and seriously impact upon social relations. Patient may be violent and destructive but is not physically assaultive toward others.

7 **Extreme** - Marked anger results in extreme uncooperativeness, precluding other interactions, or in episode(s) of physical assault toward others.

NEGATIVE SCALE (N)

N1. Blunted affect. Diminished emotional responsiveness as characterised by a reduction in facial expression, modulation of feelings, and communicative gestures. **Basis for rating:** observation of physical manifestations of affective tone and emotional responsiveness during the course of the interview.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Changes in facial expression and communicative gestures seem to be stilted, forced, artificial, or lacking in modulation.

4 **Moderate** - Reduced range of facial expression and few expressive gestures result in a dull appearance.

5 **Moderate severe** - Affect is generally "flat", with only occasional changes in facial expression and a paucity of communicative gestures.

6 **Severe** - Marked flatness and deficiency of emotions exhibited most of the time. There may be unmodulated extreme affective discharges, such as excitement, rage, or inappropriate uncontrolled laughter.

7 **Extreme** - Changes in facial expression and evidence of communicative gestures are virtually absent. Patient seems constantly to show a barren or "wooden" expression.

009

N2. Emotional withdrawal. Lack of interest in, involvement with, and affective commitment to life's events. **Basis for rating:** reports of functioning from primary care workers or family and observation of interpersonal behaviour during the course of the interview.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Usually lacks initiative and occasionally may show deficient interest in surrounding events.

4 **Moderate** - Patient is generally distanced emotionally from the milieu and its challenges but, with encouragement, can be engaged.

5 **Moderate severe** - Patient is clearly detached emotionally from persons and events in the milieu, resisting all efforts at engagement. Patient appears distant, docile, and purposeless but can be involved in communication at least briefly and tends to personal needs, sometimes with assistance.

6 **Severe** - Marked deficiency of interest and emotional commitment results in limited conversation with others and frequent neglect of personal functions, for which the patient requires supervision.

7 **Extreme** - Patient is almost totally withdrawn, uncommunicative, and neglectful of personal needs as a result of profound lack of interest and emotional commitment.

N3. Poor rapport. Lack of interpersonal empathy, openness in conversation, and sense of closeness, interest, or involvement with the interviewer. This is evidenced by interpersonal distancing and reduced verbal and nonverbal communication. **Basis for rating:** interpersonal behaviour during the course of the interview.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Conversation is characterised by a stilted, strained, or artificial tone. It may lack emotional depth or tend to remain on an impersonal, intellectual plane.

4 **Moderate** - Patient typically is aloof, with interpersonal distance quite evident. Patient may answer questions mechanically, act bored, or express disinterest.

5 **Moderate severe** - Disinvolvement is obvious and clearly impedes the productivity of the interview. Patient may tend to avoid eye or face contact.

6 **Severe** - Patient is highly indifferent, with marked interpersonal distance. Answers are perfunctory, and there is little nonverbal evidence of involvement. Eye and face contact are frequently avoided.

7 **Extreme** - Patient is totally uninvolved with the interviewer. Patient appears to be completely indifferent and consistently avoids verbal and nonverbal interactions during the interview.

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N4. Passive/apathetic social withdrawal. Diminished interest and initiative in social interactions due to passivity, apathy, anergy, or avolition. This leads to reduced interpersonal involvements and neglect of activities of daily living. **Basis for rating:** reports on social behaviour from primary care workers or family.

1 **Absent** - Definition does not apply

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Shows occasional interest in social activities but poor initiative. Usually engages with others only when approached first by them.

4 **Moderate** - Passively goes along with most social activities but in a disinterested or mechanical way. Tends to recede into the background.

5 **Moderate severe** - Passively paticipates in only a minority of activities and shows virtually no interest or initiative. Generally spends little time with others.

6 **Severe** - Tends to be apathetic and isolated, participating very rarely in social activities and occasionally neglecting personal needs. Has very few spontaneous social contacts.

7 **Extreme** - Profoundly apathetic, socially isolated, and personally neglectful.

N5. Difficulty in abstract thinking. Impairment in the use of the abstract-symbolic mode of thinking, as evidenced by difficulty in classification, forming generalisations, and proceeding beyond concrete or egocentric thinking in problem-solving tasks. **Basis for rating:** responses to questions on similarities and proverb interpretation, and use of concrete vs. abstract mode during the course of the interview.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Tends to give literal or personalised interpretations to the more difficult proverbs and may have some problems with concepts that are fairly abstract or remotely related.

4 **Moderate** - Often utilises a concrete mode. Has difficulty with most proverbs and some categories. Tends to be distracted by functional aspects and salient features.

5 **Moderate severe** - Deals primarily in a concrete mode, exhibiting difficulty with most proverbs and many categories.

6 **Severe** - Unable to grasp the abstract meaning of any proverbs or figurative expressions and can formulate classifications for only the most simple of similarities. Thinking is either vacuous or locked into functional aspects, salient features, and idiosyncratic interpretations.

7 **Extreme** - Can use only concrete modes of thinking. Shows no comprehension of proverbs, common metaphors or similes, and simple categories. Even salient and functional attributes do not serve as a basis for classification. This rating may apply to those who cannot interact even minimally with the examiner due to marked cognitive impairment.

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N6. Lack of spontaneity and flow of conversation. Reduction in the normal flow of communication associated with apathy, avolition, defensiveness, or cognitive deficit. This is manifested by diminished fluidity and productivity of the verbal-interactional process. **Basis for rating:** cognitive-verbal processes observed during the course of interview.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Conversation shows little initiative. Patient's answers tend to be brief and unembellished, requiring direct and leading questions by the interviewer.

4 **Moderate** - Conversation lacks free flow and appears uneven or halting. Leading questions are frequently needed to elicit adequate responses and proceed with conversation.

5 **Moderate severe** - Patient shows a marked lack of spontaneity and openness, replying to the interviewer's questions with only one or two brief sentences.

6 **Severe** - Patient's responses are limited mainly to a few words or short phrases intended to avoid or curtail communication. (E.g., "I don't know," "I'm not at liberty to say.") Conversation is seriously impaired as a result, and the interview is highly unproductive.

7 **Extreme** - Verbal output is restricted to, at most, an occasional utterance, making conversation not possible.

N7. Stereotyped thinking. Decreased fluidity, spontaneity, and flexibility of thinking, as evidenced in rigid, repetitious, or barren thought content. **Basis for rating:** cognitive-verbal processes observed during the interview.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Some rigidity shown in attitudes or beliefs. Patient may refuse to consider alternative positions or have difficulty in shifting from one idea to another.

4 **Moderate** - Conversation revolves around a recurrent theme, resulting in difficulty in shifting to a new topic.

5 **Moderate severe** - Thinking is rigid and repetitious to the point that, despite the interviewer's efforts, conversation is limited to only two or three dominating topics.

6 **Severe** - Uncontrolled repetition of demands, statements, ideas, or questions which severely impairs conversation.

7 **Extreme** - Thinking, behaviour, and conversation are dominated by constant repetition of fixed ideas or limited phrases, leading to gross rigidity, inappropriateness, and restrictiveness of patient's communication.

009

GENERAL PSYCHOPATHOLOGY SCALE (G)

G1. Somatic concern. Physical complaints or beliefs about bodily illness or malfunctions. This may range from a vague sense of ill-being to clear-cut delusions of catastrophic physical disease. **Basis for rating:** thought content expressed in the interview.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Distinctly concerned about health or somatic issues, as evidenced by occasional questions and desire for reassurance.

4 **Moderate** - Complains abour poor health or bodily malfunction, but there is no delusional conviction, and overconcern can be allayed by reassurance.

5 **Moderate severe** - Patient expresses numerous or frequent complaints about physical illness or bodily malfunction, or else patient reveals one or two clear-cut delusions involving these themes but is not preoccupied by them.

6 **Severe** - Patient is preoccupied by one or a few clear-cut delusions about physical disease or organic malfunction, but affect is not fully immersed in these themes, and thoughts can be diverted by the interviewer with some effort.

7 **Extreme** - Numerous and frequently reported somatic delusions, or only a few somatic delusions of a catastrophic nature, which totally dominate the patient's affect and thinking.

G2. Anxiety. Subjective experience of nervousness, worry, apprehension, or restlessness, ranging from excessive concern about the present or future to feelings of panic. **Basis for rating:** verbal report during the course of interview and corresponding physical manifestations.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Expresses some worry, overconcern, or subjective restlessness, but no somatic and behavioural consequences are reported or evidence.

4 **Moderate** - Patient reports distinct symptoms of nervousness, which are reflected in mild physical manifestations such as fine hand tremor and excessive perspiration.

5 **Moderate severe** - Patient reports serious problems of anxiety which have significant physical and behavioural consequences, such as marked tension, poor concentration, palpitations, or impaired sleep.

6 **Severe** - Subjective state of almost constant fear associated with phobias, marked restlessness, or numerous somatic manifestations.

7 **Extreme** - Patient's life is seriously disrupted by anxiety, which is present almost constantly and, at times, reaches panic proportion or is manifested in actual panic attacks.

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G3. Guilt feelings. Sense of remorse or self-blame for real or imagined misdeeds in the past. **Basis for rating:** verbal report of guilt feelings during the course of interview and the influence on attitudes and thoughts.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Questioning elicits a vague sense of guilt or self-blame for a minor incident, but the patient clearly is not overly concerned.

4 **Moderate** - Patient expresses distinct concern over his responsiblity for a real incident in his life but is not preoccupied with it, and attitude and behaviour are essentially unaffected.

5 **Moderate severe** - Patient expresses a strong sense of guilt associated with self-deprecation or the belief that he deserves punishment. The guilt feelings may have a delusional basis, may be volunteered spontaneously, may be a source of preoccupation and/or depressed mood, and cannot be allayed readily by the interviewer.

6 **Severe** - Strong ideas of guilt take on a delusional quality and lead to an attitude of hopelessness or worthlessness. The patient believes he should receive harsh sanctions for the misdeeds and may even regard his current life situation as such punishment.

7 **Extreme** - Patient's life is dominated by unshakable delusions of guilt, for which he feels deserving of drastic punishment, such as life imprisonment, torture, or death. There may be associated suicidal thoughts or attribution of other's problems to one's own past misdeeds.

G4. Tension. Overt physical manifestations of fear, anxiety, and agitation, such as stiffness, tremor, profuse sweating, and restlessness. **Basis for rating:** verbal report attesting to anxiety and, thereupon, the severity of physical manifestations observed during the interview.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Posture and movements indicate slight apprehensiveness, such as minor rigidity, occasional restlessness, shifting of position, or fine rapid hand tremor.

4 **Moderate** - A clearly nervous appearance emerges from various manifestations, such as fidgety behaviour, obvious hand tremor, excessive perspiration, or nervous mannerisms.

5 **Moderate severe** - Pronounced tension is evidenced by numerous manifestations, such as nervous shaking, profuse sweating, and restlessness, but conduct in the interview is not significantly affected.

6 **Severe** - Pronounced tension to the point that interpersonal interactions are disrupted. The patient, for example, may be constantly fidgeting, unable to sit still for long, or show hyperventilation.

7 **Extreme** - Marked tension is manifested by signs of panic or gross motor acceleration, such as rapid restless pacing and inability to remain seated for longer than a minute, which makes sustained conversation not possible.

009

G5. Mannerisms and posturing. Unnatural movements or posture as characterised by an awkward, stilted, disorganised, or bizarre appearance. **Basis for rating**: observation of physical manifestations during the course of interview as well as reports from primary care workers or family.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Slight awkwardness in movements or minor rigidity of posture.

4 **Moderate** - Movements are notably awkward or disjointed, or an unnatural posture is maintained for brief periods.

5 **Moderate severe** - Occasional bizarre rituals, or contorted posture are observed, or an abnormal position is sustained for extended periods.

6 **Severe** - Frequent repetition of bizarre rituals, mannerisms, or stereotyped movements, or a contorted posture is sustained for extended periods.

7 **Extreme** - Functioning is seriously impaired by virtually constant involvement in ritualistic, manneristic, or stereotyped movements or by an unnatural fixed posture which is sustained for most of the time.

G6. Depression. Feelings of sadness, discouragement, helplessness, and pessimism. **Basis for rating:** verbal report of depressed mood during the course of interview and its observed influence on attitude and behaviour.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Expresses some sadness or discouragement only on questioning, but there is no evidence of depression in general attitude or demeanour.

4 **Moderate** - Distinct feelings of sadness or hopelessness, which may be spontaneously divulged, but depressed mood has no major impact on behaviour or social functioning, and the patient usually can be cheered up.

5 **Moderate severe** - Distinctly depressed mood is associated with obvious sadness, pessimism, loss of social interest, psychomotor retardation, and some interference in appetite and sleep. The patient cannot be easily cheered up.

6 **Severe** - Markedly depressed mood is associated with sustained feelings of misery, occasional crying, hopelessness, and worthlessness. In addition, there is major interference in appetite and/or sleep as well as in normal motor and social functions, with possible signs of self-neglect.

7 **Extreme** - Depressive feelings seriously interfere in most major functions. The manifestations include frequent crying, pronounced somatic symptoms, impaired concentration, psychomotor retardation, social disinterest, self-neglect, possible depressive or nihilistic delusions, and/or possible suicidal thoughts or action.

009

G7. Motor retardation. Reduction in motor activity as reflected in slowing or lessening of movements and speech, diminished responsiveness to stimuli, and reduced body tone. **Basis for rating:** manifestations during the course of interview as well as reports by primary care workers or family.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Slight but noticeable diminution in rate of movements and speech. Patient may be somewhat underproductive in conversation and gestures.

4 **Moderate** - Patient is clearly slow in movements, and speech may be characterised by poor productivity, including long response latency, extended pauses, or slow pace.

5 **Moderate severe** - A marked reduction in motor activity renders communication highly unproductive or delimits functioning in social and occupational situations. Patient can usually be found sitting or lying down.

6 **Severe** - Movements are extremely slow, resulting in a minimum of activity and speech. Essentially the day is spent sitting idly or lying down.

7 **Extreme** - Patient is almost completely immobile and virtually unresponsive to external stimuli.

G8. Uncooperativeness. Active refusal to comply with the will of significant others, including the interviewer, hospital staff, or family, which may be associated with distrust, defensiveness, stubbornness, negativism, rejection of authority, hostility, or belligerence. **Basis for rating:** interpersonal behaviour observed during the course of interview as well as reports by primary care workers or family.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; maybe at the upper extreme of normal limits.

3 **Mild** - Complies with an attitude of resentment, impatience, or sarcasm. May inoffensively object to sensitive probing during the interview.

4 **Moderate** - Occasional outright refusal to comply with normal social demands, such as making own bed, attending scheduled programs, etc. The patient may project a hostile, defensive, or negative attitude but usually can be worked with.

5 **Moderate severe** - Patient frequently is incompliant with the demands of his milieu and may be characterised by others as an "outcast" or having "a serious attitude problem." Uncooperativeness is reflected in obvious defensiveness or irritability with the interviewer and possible unwillingness to address many questions.

6 **Severe** - Patient is highly uncooperative, negativistic, and possibly also belligerent. Refuses to comply with most social demands and may be unwilling to initiate or conclude the full interview.

7 **Extreme** - Active resistance seriously impacts on virtually all major areas of functioning. Patient may refuse to join in any social activities, tend to personal hygiene, converse with family or staff, and participate even briefly in an interview.

009

G9. Unusual thought content. Thinking characterised by strange, fantastic, or bizarre ideas, ranging from those which are remote or atypical to those which are distorted, illogical, and patently absurd. **Basis for rating:** thought content expressed during the course of the interview.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Thought content is somewhat peculiar or idiosyncratic, or familiar ideas are framed in an odd context.

4 **Moderate** - Ideas are frequently distorted and occasionally seem quite bizarre.

5 **Moderate severe** - Patient expresses many strange and fantastic thoughts (e.g., being the adopted son of a king, being an escapee from death row) or some which are patently absurd (e.g., having hundreds of children, receiving messages from outer space through a tooth filling).

6 **Severe** - Patient expresses many illogical or absurd ideas or some which have a distinctly bizarre quality (e.g.,having three heads, being a visitor from another planet)

7 **Extreme** - Thinking is replete with absurd, bizarre, and grotesque ideas.

G10. Disorientation. Lack of awareness of one's relationship to the milieu, including persons, place, and time, which may be due to confusion or withdrawal. **Basis for rating:** responses to interview questions on orientation.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - General orientation is adequate but there is some difficulty with specifics. For example, patient knows his location but not the street address; knows hospital staff names but not their functions; knows the month but confuses the day of week with an adjacent day; or errs in the date by more than two days. There may be narrowing of interest evidenced by familiarity with the immediate but not extended milieu, such as ability to identify staff but not the Mayor, Governor, or President.

4 **Moderate** - Only partial success in recognising persons, places, and time. For example, patient knows he is in a hospital but not its name; knows the name of his city but not the borough or district; knows the name of his primary therapist but not many other direct care workers; knows the year and season but is not sure of the month.

5 **Moderate severe** - Considerable failure in recognising persons, place, and time. Patient has only a vague notion of where he is and seems unfamiliar with most people in his milieu. He may identify the year correctly or nearly so but not know the current month, day of week, or even the season.

6 **Severe** - Marked failure in recognising persons, place, and time. For example, patient has no knowledge of his whereabouts; confuses the date by more than one year; can name only one or two individuals in his current life.

7 **Extreme** - Patient appears completely disoriented with regard to persons, place, and time. There is gross confusion or total ignorance about one's location, the current year, and even the most familiar people, such as parents, spouse, friends, and primary therapist.

G11. Poor attention. Failure in focused alertness manifested by poor concentration, distractibility from internal and external stimuli, and difficulty in harnessing, sustaining, or shifting focus to new stimuli. **Basis for rating:** manifestations during the course of the interview.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Limited concentration evidenced by occasional vulnerability to distraction or faltering attention toward the end of the interview.

4 **Moderate** - Conversation is affected by the tendency to be easily distracted, difficulty in long sustaining concentration on a given topic, or problems in shifting attention to new topics.

5 **Moderate severe** - Conversation is seriously hampered by poor concentration, distractibility, and difficulty in shifting focus appropriately.

6 **Severe** - Patient's attention can be harnessed for only brief moments or with great effort, due to marked distraction by internal or external stimuli.

7 **Extreme** - Attention is so disrupted that even brief conversation is not possible.

G12. Lack of judgment and insight. Impaired awareness or understanding of one's own psychiatric condition and life situation. This is evidenced by failure to recognise past or present psychiatric illness or symptoms, denial of need for psychiatric hospitalisation or treatment, decisions characterised by poor anticipation of consequences, and unrealistic short-term and long-range planning. **Basis for rating:** thought content expressed during the interview.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Recognises having a psychiatric disorder but clearly underestimates its seriousness, the implications for treatment, or the importance of taking measures to avoid relapse. Future planning may be poorly conceived.

4 **Moderate** - Patient shows only a vague or shallow recognition of illness. There may be fluctuations in acknowledgement of being ill or little awareness of major symptoms which are present, such as delusions, disorganised thinking, suspiciousness, and social withdrawal. The patient may rationalise the need for treatment in terms of its relieving lesser symptoms, such as anxiety, tension, and sleep difficulty.

5 **Moderate severe** - Acknowledges past but not present psychiatric disorder. If challenged, the patient may concede the presence of some unrelated or insignificant symptoms, which tend to be explained away by gross misinterpretation or delusional thinking. The need for psychiatric treatment similarly goes unrecognised.

6 **Severe** - Patient denies ever having had a psychiatric disorder. He disavows the presence of any psychiatric symptoms in the past or present and, though compliant, denies the need for treatment and hospitalisation.

7 **Extreme** - Emphatic denial of past and present psychiatric illness. Current hospitalisation and treatment are given a delusional interpretation (e.g., as punishment for misdeeds, as persecution by tormentors, etc.), and the patient may thus refuse to cooperate with therapists, medication, or other aspects of treatment.

009

G13. Disturbance of volition. Disturbance in the wilful initiation, sustenance, and control of one's thoughts, behaviour, movements, and speech. **Basis for rating:** thought content and behaviour manifested in the course of the interview.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - There is evidence of some indecisiveness in conversation and thinking, which may impede verbal and cognitive processes to a minor extent.

4 **Moderate** - Patient is often ambivalent and shows clear difficulty in reaching decisions. Conversation may be marred by alternation in thinking, and in consequence verbal and cognitive functioning are clearly impaired.

5 **Moderate severe** - Disturbance of volition interferes in thinking as well as behaviour. Patient shows pronounced indecision that impedes the initiation and continuation of social and motor activities, and which also may be evidenced in halting speech.

6 **Severe** - Disturbance of volition interferes in the execution of simple, automatic motor functions, such as dressing and grooming, and markedly affects speech.

7 **Extreme** - Almost complete failure of volition is manifested by gross inhibition of movement and speech, resulting in immobility and/or mutism.

G14. Poor impulse control. Disordered regulation and control of action on inner urges, resulting in sudden, unmodulated, arbitrary, or misdirected discharge of tension and emotions without concern about consequences. **Basis for rating:** behaviour during the course of interview and reported by primary care workers or family.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Patient tends to be easily angered and frustrated when facing stress or denied gratification but rarely acts on impulse.

4 **Moderate** - Patient gets angered and verbally abusive with minimal provocation. May be occasionally threatening, destructive, or have one or two episodes involving physical confrontation or a minor brawl.

5 **Moderate severe** - Patient exhibits repeated impulsive episodes involving verbal abuse, destruction of property, or physical threats. There may be one or two episodes involving serious assault, for which the patient requires isolation, physical restraint, or p.r.n. sedation.

6 **Severe** - Patient frequently is impulsively aggressive, threatening, demanding, and destructive, without any apparent consideration of consequences. Shows assaultive behaviour and may also be sexually offensive and possibly respond behaviourally to hallucinatory commands.

7 **Extreme** - Patient exhibits homicidal attacks, sexual assaults, repeated brutality, or self-destructive behaviour. Requires constant direct supervision or external constraints because of inability to control dangerous impulses.

G15. Preoccupation. Absorption with internally generated thoughts and feelings and with autistic experiences to the detriment of reality orientation and adaptive behaviour. **Basis for rating:** interpersonal behaviour observed during the course of the interview.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Excessive involvement with personal needs or problems, such that conversation veers back to egocentric themes and there is diminished concern exhibited toward others.

4 **Moderate** - Patient occasionally appears self-absorbed, as if daydreaming or involved with internal experiences, which interferes with communication to a minor extent.

5 **Moderate severe** - Patient often appears to be engaged in autistic experiences, as evidenced by behaviours that significantly intrude on social and communicational functions, such as the presence of a vacant stare, muttering or talking to oneself, or involvement with stereotyped motor patterns.

6 **Severe** - Marked preoccupation with autistic experiences, which seriously delimits concentration, ability to converse, and orientation to the milieu. The patient frequently may be observed smiling, laughing, muttering, talking, or shouting to himself.

7 **Extreme** - Gross absorption with autistic experiences, which profoundly affects all major realms of behaviour. The patient constantly may be responding verbally and behaviourally to hallucinations and show little awareness of other people or the external milieu.

G16. Active social avoidance. Diminished social involvement associated with unwarranted fear, hostility, or distrust. **Basis for rating:** reports of social functioning by primary care workers or family.

1 **Absent** - Definition does not apply.

2 **Minimal** - Questionable pathology; may be at the upper extreme of normal limits.

3 **Mild** - Patient seems ill at ease in the presence of others and prefers to spend time alone, although he participates in social functions when required.

4 **Moderate** - Patient begrudgingly attends all or most social activities but may need to be persuaded or may terminate prematurely on account of anxiety, suspiciousness, or hostility.

5 **Moderate severe** - Patient fearfully or angrily keeps away from many social interactions despite other's efforts to engage him. Tends to spend unstructured time alone.

6 **Severe** - Patient participates in very few social activities because of fear, hostility, or distrust. When approached, the patient shows a strong tendency to break off interactions, and generally he appears to isolate himself from others.

7 **Extreme** - Patient cannot be engaged in social activities because of pronounced fears, hostility, or persecutory delusions. To the extent possible, he avoids all interactions and remains isolated from others.

1230009

Pt Initials:…… Visit:…… CRF No:……
Date:…….

CLINICAL GLOBAL IMPRESSION OF ILLNESS (CGI)

	D – 7	D – 6	D – 5	D – 4	D – 3	D – 2	D – 1	D – 0
Date								
Rating								

CLINICAL GLOBAL IMPRESSION OF IMPROVEMENT OF ILLNESS (CGI-I)
NB: Compare to visit D – 7

	D – 7	D – 6	D – 5	D – 4	D – 3	D – 2	D – 1	D – 0
Date								
Rating								

CLINICAL GLOBAL IMPRESSION OF ILLNESS (CGI-I)

	W2	W4	W6	M3	M6	M9	M12	M15
Date								
Rating								

CLINICAL GLOBAL IMPRESSION OF IMPROVEMENT OF ILLNESS (CGI-1)
NB: Compare to visit D-7

	W2	W4	W6	M3	M6	M9	M12	M15
Date								
Rating								

CLINICAL GLOBAL IMPRESSION OF ILLNESS (CGI)

	M18	M21	M24					
Date								
Rating								

CLINICAL GLOBAL IMPRESSION OF IMPROVEMENT OF ILLNESS (CGI-I)

	M18	M21	M24					
Date								
Rating								

CALGARY DEPRESSION SCALE FOR SCHIZOPHRENIA

Interviewer: Ask the first question as written. Use follow up probes or qualifiers at your discretion. Time framerefers to last two weeks unless stipulated. **N.B.** The last item, #9, is based on observations of the entire interview.

1. DEPRESSION: How would you describe your mood over the last two weeks? Do you keep reasonably cheerful or have you been very depressed or low spirited recently? In the last two weeks how often have you (own words) every day? All day?
0. Absent
1. Mild Expresses some sadness or discouragement on questioning.
2. Moderate Distinct depressed mood persisting up to half the time over last 2 weeks: present daily.
3. Severe Markedly depressed mood persisting daily over half the time interfering with normal motor and social functioning.

2. HOPELESSNESS: How do you see the future for yourself? Can you see any future? - or has life seemed quite hopeless? Have you given up or does there still seem some reason for trying?
0. Absent
1. Mild Has at times felt hopeless over the last two weeks but still has some degree of hope for the future.
2. Moderate Persistent, moderate sense of hopelessness over last week. Can be persuaded to acknowledge possibility of things being better.
3. Severe Persisting and distressing sense of hopelessness.

3. SELF DEPRECIATION: What is your opinion of your self compared to other people? Do you feel better, not as good, or about the same as others? Do you feel inferior or even worthless?
0. Absent
1. Mild Some inferiority; not amounting to feeling of worthlessness.
2. Moderate Subject feels worthless, but less than 50% of the time.
3. Severe Subject feels worthless more than 50% of the time. May be challenged to acknowledge otherwise.

4. GUILTY IDEAS OF REFERENCE: Do you have the feeling that you are being blamed for something or even wrongly accused? What about? (Do not include justifiable blame or accusation. Exclude delusions of guilt.)
0. Absent
1. Mild Subject feels blamed but not accused less than 50% of the time.
2. Moderate Persisting sense of being blamed, and/or occasional sense of being accused.
3. Severe Persistent sense of being accused. When challenged, acknowledges that it is not so.

5. PATHOLOGICAL GUILT: Do you tend to blame yourself for little things you may have done in the past? Do you think that you deserve to be so concerned about this?
0. Absent

1. Mild Subject sometimes feels over guilty about some minor peccadillo, but less than 50% of time.
2. Moderate Subject usually (over 50% of time) feels guilty about past actions the significance of which he exaggerates.
3. Severe Subject usually feels s/he is to blame for everything that has gone wrong, even when not his/her fault.

6. MORNING DEPRESSION: When you have felt depressed over the last 2 weeks have you noticed the depression being worse at any particular time of day?
0. Absent No depression.
1. Mild Depression present but no diurnal variation.
2. Moderate Depression spontaneously mentioned to be worse in a.m.
3. Severe Depression markedly worse in a.m., with impaired functioning which improves in p.m.

7. EARLY WAKENING: Do you wake earlier in the morning than is normal for you? How many times a week does this happen?
0. Absent No early wakening.
1. Mild Occasionally wakes (up to twice weekly) 1 hour or more before normal time to wake or alarm time.
2. Moderate Often wakes early (up to 5 times weekly) 1 hour or more before normal time to wake or alarm.
3. Severe Daily wakes 1 hour or more before normal time.

8. SUICIDE: Have you felt that life wasn't worth living? Did you ever feel like ending it all? What did you think you might do? Did you actually try?
0. Absent
1. Mild Frequent thoughts of being better off dead, or occasional thoughts of suicide.
2. Moderate Deliberately considered suicide with a plan, but made no attempt.
3. Severe Suicidal attempt apparently designed to end in death (i.e.: accidental discovery or inefficient means).

9. OBSERVED DEPRESSION: Based on interviewer's observations during the entire interview. The question "Do you feel like crying?" used at appropriate points in the interview, may elicit information useful to this observation.
0. Absent
1. Mild Subject appears sad and mournful even during parts of the interview, involving affectively neutral discussion.
2. Moderate Subject appears sad and mournful throughout the interview, with gloomy monotonous voice and is tearful or close to tears at times.
3. Severe Subject chokes on distressing topics, frequently sighs deeply and cries openly, or is persistently in a state of frozen misery if examiner is sure that this is present.

Birchwood Insight Scale

Each item is scored:

0 – no insight (yes to 2, 3, 6, and 8; no to the others)

1 – unsure (all items)

2 – insight (no to 2, 3, 6 and 8; yes to the others)

1. Some of my symptoms are made by my mind.
2. I am mentally well.
3. I do not need medication.
4. My stay in hospital is necessary.
5. The doctor is right in prescribing medication for me.
6. I do not need to be seen by a doctor or psychiatrist.
7. If someone said I have a nervous or a mental illness then they would be right.
8. None of the usual things I experience are due to an illness.

Social and Occupational Functioning Assessment Scale (SOFAS)	
Consider social and occupational functioning on a continuum from excellent functioning to grossly impaired functioning. Include impairment due to physical limitations, as well as those due to mental impairments. To be counted, impairment must be a direct consequence of mental and physical health problems; the effects of lack of opportunity and other environmental limitations are not to be considered.	
Code (Note: Use intermediate codes when appropriate, e.g., 45, 68, 72) Score:	
100 I 91	Superior functioning in a wide range of activities
90 I 81	Good functioning in all areas, occupationally and socially effective.
80 I 71	No more than a slight impairment in social, occupational, or school functioning (e.g., infrequent interpersonal conflict, temporary failing behind in schoolwork).
70 I 61	Some difficulty in social, occupational, or school functioning, but generally functioning well, has some meaningful interpersonal relationships.
60 I 51	Moderate difficulty in social, Occupational, or school functioning (e.g., few friends, conflicts with peers or co-workers).
50 I 41	Serious impairment in social, occupational, or school functioning (e.g, no friends, unable to keep a job).
40 I 31	Major impairment in several areas, such as work or school, family relations (e.g depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).
30 I 21	Inability to function in almost all areas (e.g., stays in bed all day; no job, home, or friends).
20 I 11	Occasionally fails to maintain personal hygiene; unable to function independently.
10 I 1	Persistent inability to maintain minimal personal hygiene. Unable to function without harming self or others or without considerable external support (e.g nursing care and supervision).
0	Inadequate information.

WHOQOL-BREF

The following questions ask how you feel about your quality of life, health, or other areas of your life. I will read out each question to you, along with the response options. Please choose the answer that appears most appropriate. If you are unsure about which response to give to a question, the first response you think of is often the best one.

Please keep in mind you standards, hopes, pleasures and concerns. We ask that you think about your life in the last four weeks.

		Very poor	Poor	Neither poor nor good	Good	Very good
1.	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied not dissatisfied	Satisfied	Very satisfied
2.	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last four weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3.	To what extent do you feel that physical pain prevents you from doing what you need to do?	5	4	3	2	1
4.	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1
5.	How much do you enjoy life?	1	2	3	4	5
6.	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7	How well are you able to concentrate?	1	2	3	4	5
8.	How safe do you feel in your daily life?	1	2	3	4	5
9.	How healthy is your physical environment?`	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

		Not at all	A little	Moderately	Mostly	Completely
10	Do you have enough energy for everyday life?	1	2	3	4	5
11	Are you able to accept your bodily appearance?	1	2	3	4	5
12	I have you enough money to meet your needs?	1	2	3	4	5
13	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor nor good	Good	Very good
15	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16.	How satisfied are you with your sleep?	1	2	3	4	5
17.	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18.	How satisfied are you with your capacity for work?	1	2	3	4	5
19.	How satisfied are you with yourself?	1	2	3	4	5
20.	How satisfied are you with your personal relationships?	1	2	3	4	5
21	How satisfied are you with your sex life?	1	2	3	4	5
22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23	How satisfied are you with the conditions of your living place?	1	2	3	4	5

24.	How satisfied are you with your access to health services?	1	2	3	4	5
25	How satisfied are you with your transport?					

The following question refers to how often you have felt or experienced certain things in the last four weeks.

		Never	Seldom	Quite often	Very often	Always
26	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1

Do you have any comments about the assessment?

_____

_____

[the following table should be completed after the interview is finished]

		Equations for computing domain scores	Raw score	Transformed scores*	
				4-20	0-100
27	Domain 1	(6-Q3) + (6-Q4) + Q10+Q15 + Q16+Q17+Q18 + + + + + +	a.=	b:	c:
28	Domain 2	Q5 + Q6 + Q7 + Q11 + Q19 + (16 – Q26) + + + + +	a.=	b:	c:
29	Domain 3	Q20 + Q21 + Q22 + +	a.=	b:	c:
30	Domain 4	Q8 + Q9+Q12+Q13 + Q14 + Q23+Q24 + Q25 + + + + + + +	a.=	b:	c:

EXTRAPYRAMIDAL SYMPTOM RATING SCALE

I. PARKINSONISM, DYSTONIA AND DYSKINESIA

QUESTIONNAIRE AND BEHAVIORAL SCALE (Physician or Nurse).

Enquire into the status of each symptom and rate accordingly.
For nurses, rate also the behavior observed

Status:
0 = Absent
1 = Mild
2 = Moderate
3 = Severe

1. Impression of slowness or weakness, difficulty in carrying out routine tasks	☐
2. Difficulty walking or with balance	☐
3. Difficulty swallowing or talking	☐
4. Stiffness, stiff posture	☐
5. Cramps or pains in limbs, back or neck	☐
6. Restless, nervous, unable to keep still	☐
7. Tremors, shaking	☐
8. Oculogyric crisis, abnormal sustained posture	☐
9. Increased salivation	☐
10. Abnormal involuntary movements (dyskinesia) of extremities or trunk	☐
11. Abnormal involuntary movements (dyskinesia) of tongue, jaw, lips or face	☐
12. Dizziness when standing up (especially in the morning)	☐

ESRS-1

EXTRAPYRAMIDAL SYMPTOM RATING SCALE

II. PARKINSONISM : PHYSICIAN'S EXAMINATION

1. Expressive automatic movements (facial mask/speech) ☐

0 = normal
1 = very mild decrease in facial expressiveness
2 = mild decrease in facial expressiveness
3 = rare spontaneous smile, decreased blinking, voice slightly monotonous
4 = no spontaneous smile, staring gaze, low monotonous speech, mumbling
5 = marked facial mask unable to frown, slurred speech
6 = extremely severe facial mask with unintelligible speech

2. Bradykinesia ☐

0 = normal
1 = global impression of slowness in movements
2 = definite slowness in movements
3 = very mild difficulty in initiating movements
4 = mild to moderate difficulty in initiating movements
5 = difficulty in starting or stopping any movement or freezing on initiating voluntary act
6 = rare voluntary movement, almost completely immobile

3. Rigidity Total ☐

right arm _____
left arm _____
right leg _____
left leg _____

0 = normal muscle tone
1 = very mild, barely perceptible
2 = mild (some resistance to passive movements)
3 = moderate (definite resistance to passive movements)
4 = moderately severe (moderate resistance but still easy to move the limb)
5 = severe (marked resistance with definite difficulty to move the limb)
6 = extremely severe (nearly frozen)

4. Gait & posture ☐

0 = normal
1 = mild decrease of pendular arm movement
2 = moderate decrease of pendular arm movement, normal steps
3 = no pendular arm movement, head flexed, steps more or less normal
4 = stiff posture (neck, back), small step (shuffling gait)
5 = more marked, festination or freezing on turning
6 = triple flexion, barely able to walk

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EXTRAPYRAMIDAL SYMPTOM RATING SCALE

II. PARKINSONISM : PHYSICIAN'S EXAMINATION (cont'd...)

5. Tremor Total [ ]

					Occasional	Frequent	Constant or almost so
right upper limb _____	head _____	none	=	0			
left upper limb _____	jaw/chin _____	borderline	=	1			
right lower limb _____	tongue _____	small amplitude	=		2	3	4
left lower limb _____	lips _____	moderate amplitude	=		3	4	5
		large amplitude	=		4	5	6

6. Akathisia [ ]

0 = none
1 = looks restless, nervous, impatient, uncomfortable
2 = needs to move at least one extremity
3 = often needs to move one extremity or to change position
4 = moves one extremity almost constantly if sitting, or stamps feet while standing
5 = unable to sit down for more than a short period of time
6 = moves or walks constantly

7. Sialorrhea [ ]

0 = absent
1 = very mild
2 = mild
3 = moderate; impairs speech
4 = moderately severe
5 = severe
6 = extremely severe; drooling

8. Postural stability [ ]

0 = normal
1 = hesitation when pushed but no retropulsion
2 = retropulsion but recovers unaided
3 = exaggerated retropulsion without falling
4 = absence of postural response, would fall if not caught by examiner
5 = unstable while standing, even without pushing
6 = unable to stand without assistance

ESRS-3

EXTRAPYRAMIDAL SYMPTOM RATING SCALE

III. DYSTONIA: PHYSICIAN'S EXAMINATION

1. Acute torsion dystonia — Total [ ]

right upper limb	_____	head	_____
left upper limb	_____	jaw	_____
right lower limb	_____	tongue	_____
left lower limb	_____	lips	_____
		trunk	_____

0 = absent
1 = very mild
2 = mild
3 = moderate
4 = moderately severe
5 = severe
6 = extremely severe

2. Non acute or chronic or tardive dystonia — Total [ ]

right upper limb	_____	head	_____
left upper limb	_____	jaw	_____
right lower limb	_____	tongue	_____
left lower limb	_____	lips	_____
		trunk	_____

0 = absent
1 = very mild
2 = mild
3 = moderate
4 = moderately severe
5 = severe
6 = extremely severe

EXTRAPYRAMIDAL SYMPTOM RATING SCALE

IV. DYSKINETIC MOVEMENTS : PHYSICIAN'S EXAMINATION

		Occasional*	Frequent**	Constant or almost so
1. Lingual movements (slow lateral or torsion movement of tongue)				
	none = 0			
	borderline = 1			
☐	clearly present, within oral cavity =	2	3	4
	with occasional partial protrusion ... =	3	4	5
	with complete protrusion =	4	5	6
2. Jaw movements (lateral movement, chewing, biting, clenching)				
	none = 0			
	borderline = 1			
☐	clearly present, small amplitude =	2	3	4
	moderate amplitude, but without mouth opening =	3	4	5
	large amplitude, with mouth opening =	4	5	6
3. Bucco-labial movements (puckering, pouting, smacking, etc.)				
	none = 0			
	borderline = 1			
☐	clearly present, small amplitude =	2	3	4
	moderate amplitude, forward movement of lips =	3	4	5
	large amplitude; marked, noisy smacking of lips =	4	5	6
4. Truncal movements (rocking, twisting pelvic gyrations)				
	none = 0			
	borderline = 1			
☐	clearly present, small amplitude =	2	3	4
	moderate amplitude =	3	4	5
	greater amplitude =	4	5	6
5. Upper extremities (choreoathetoid movements only: arms, wrists, hands, fingers)				
	none = 0			
	borderline = 1			
	clearly present, small amplitude, movements of one limb =	2	3	4
☐	moderate amplitude, movement of one limb or movement of small amplitude involving two limbs =	3	4	5
	greater amplitude, movement involving two limbs =	4	5	6

* when activated or rarely spontaneous;
** frequently spontaneous and present when activated

ESRS-4

EXTRAPYRAMIDAL SYMPTOM RATING SCALE

IV. DYSKINETIC MOVEMENTS : PHYSICIAN'S EXAMINATION (cont'd...)

	Occasional*	Frequent**	Constant or almost so
6. Lower extremities (choreoathetoid movements only: legs, knees, ankles, toes)			
none = 0			
borderline = 1			
clearly present, small amplitude, movement of one limb =	2	3	4
moderate amplitude, movement of one limb or movement of small amplitude involving two limbs =	3	4	5
greater amplitude, movement involving two limbs =	4	5	6
7. Other involuntary movements (swallowing, irregular respiration, frowning, blinking, grimacing, sighing, etc.)			
none = 0			
borderline = 1			
clearly present, small amplitude =	2	3	4
moderate amplitude =	3	4	5
greater amplitude =	4	5	6

* when activated or rarely spontaneous;
** frequently spontaneous and present when activated

SANDOZ
CLINICAL RESEARCH

EXTRAPYRAMIDAL SYMPTOM RATING SCALE

V. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF DYSKINESIA

Considering your clinical experience, how severe is the dyskinesia at this time? ☐

0 = absent	3 = mild	6 = marked
1 = borderline	4 = moderate	7 = severe
2 = very mild	5 = moderately severe	8 = extremely severe

VI. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF PARKINSONISM

Considering your clinical experience, how severe is the parkinsonism at this time? ☐

0 = absent	3 = mild	6 = marked
1 = borderline	4 = moderate	7 = severe
2 = very mild	5 = moderately severe	8 = extremely severe

VII. CLINICAL GLOBAL IMPRESSION OF SEVERITY OF DYSTONIA

Considering your clinical experience, how severe is the dystonia at this time? ☐

0 = absent	3 = mild	6 = marked
1 = borderline	4 = moderate	7 = severe
2 = very mild	5 = moderately severe	8 = extremely severe

VIII. STAGE OF PARKINSONISM (Hoehn & Yahr)

☐

0 = normal
1 = unilateral involvement only, minimal or no functional impairment (stage I)
2 = bilateral or midline involvement, without impairment of balance (stage II)
3 = mildly to moderately disabling: first signs of impaired righting or postural reflex (unsteadiness as the patient turns or when he is pushed from standing equilibrium with the feet together and eyes closed), patient is physically capable of leading independent life (stage III)
4 = severely disabling: patient is still able to walk and stand unassisted but is markedly incapacitated (stage IV)
5 = confinement to bed or wheelchair (stage V)

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