RELATIONSHIP BETWEEN NEUROPSYCHIATRIC SYMPTOMS AND COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

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ABSTRACT

RELATIONSHIP BETWEEN NEUROPSYCHIATRIC SYMPTOMS AND COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

Introduction: Patients with Parkinson's Disease (PD) experience not only motor but also non-motor symptoms (NMSs). Neuropsychiatric symptoms (NPS) and cognitive impairment which are part of the NMSs, are prevalent among PD patients. Although NPS are more prevalent in those with PD dementia, the association is unclear. At present, there is no data describing the associations between NPS and cognitive impairment in Malaysia.

Objective: The main objective of this study is to investigate the association between NPS and cognitive impairment in PD patients. We also explored the neuropsychiatric profile in our sample population.

Method: This is an observational, hospital-based, cross-sectional study on 94 patients with PD. Patient Demographic Questionnaire was used to record socio-demographic and clinical data. NPS were assessed using the Neuropsychiatric Inventory (NPI) and the cognitive impairment with Neuropsychiatry Cognitive Assessment Tool (NUCOG). The Hoehn and Yahr scale were used to assess the stage of Parkinson disease (Stages 1 to 5) particularly in the motor function. The Mann Whitney test was performed to investigate the association between socio-demographic/clinical factors and NPS to cognitive impairment. The Chi-Square test was performed to analyze if any one NPS significantly changes a subject's odds of having advanced cognitive deficits. Linear regression was

performed to compare the relative importance of the selected significant NPS with NUCOG scores with corrections for the bias from socio-demographic and clinical factors.

Results: The mean age was 64.89 years old (SD= 9.34). Most subjects received up to secondary education (56.4%) and 23.4 % received tertiary education. The mean duration of PD was 9.70 years (SD: 5.89). 12.7 % had advance staged PD. Subjects with advanced PD ($p<0.01$), requiring assistance in their functioning ($p<0.001$) and on Benzodiazepines ($p<0.01$) had significantly higher NPI scores. PD subjects fared worse in all cognitive domains of NUCOG with the mean score of 73.7% (SD: 19.34). The only significant factor found to be significantly associated with NUCOG score was education level ($p<0.01$). Subjects with tertiary education scored significantly higher in all cognitive domains except for executive function. Subjects with advanced PD ($p<0.001$), who required any form of assistance ($p<0.001$) and who were on anti-dementia ($p<0.05$) scored significantly lower in the total NUCOG and all domain scores. Subjects with delusion ($p<0.01$), hallucinations ($p<0.05$), agitation/ aggression ($p<0.05$), irritability ($p<0.05$) and sleep disturbances ($p<0.05$) showed overall cognitive impairment. Hallucinations ($p<0.05$), delusions ($p<0.05$) and irritability ($p<0.05$) are particularly associated with NUCOG score <80. However, after correcting for education, hallucination was the only symptom that achieved a significant negative correlation with NUCOG scores ($p<0.05$).

Conclusion: Subjects performed poorly in all 5 cognitive domains of NUCOG: language, memory, executive function, visuo-constructional and attention. This study shows an association between hallucination and cognitive impairment.

ABSTRAK

HUBUNGAN ANTARA SYMPTOM NEUROPSKIATRIK DAN KEMEROSOTAN KOGNITIF PENYAKIT PARKINSON

Pengenalan: Pesakit yang mengalami Penyakit Parkinson bukan sahaja mengalami gejala motor tetapi juga gejala-gejala bukan motor, 'non-motor symptoms' (NMSs). Simptom neuropsikiatrik, 'neuropsychiatric symptoms' (NPS) dan kemerosotan kognitif adalah sebahagian daripada gejala-gejala bukan motor yang amat lazim di kalangan pesakit Penyakit Parkinson. Walaupun NPS adalah lebih lazim di kalangan pesakit Parkinson yang mengalami dementia, 'Parkinson's Disease Dementia' (PDD), hubungan ini adalah kurang jelas. Sehingga kini, tiada maklumat mengenai perhubungan antara NPS dan kemerosotan kognitif di Malaysia.

Objektif: Objektif utama kajian ini adalah untuk menyiasat perhubungan antara NPS dan kemerosotan kognitif di kalangan pesakit Parkinson. Kami juga menyiasat profil neuropsikiatrik di kalangan populasi kajian.

Kaedah: Kajian ini dijalankan dengan kaedah pemerhatian, keratan rentas dan bertapak di hospital, pada 94 orang pesakit Parkinson. Soal selidik demografik pesakit digunakan untuk merekod maklumat social-demografik dan klinikal. Penilaian NPS adalah melalui 'Neuropsychiatric Inventory' (NPI) sementara kemerosotan kognitif adalah melalui 'Neuropsychiatry Cognitive Assessment Tool' (NUCOG). Skala 'Hoehn and Yahr' digunakan untuk menilai tahap Penyakit Parkinson (Tahap 1-5) terutamanya dari segi motor. Ujian 'Mann Whitney' dijalankan untuk menyiasat hubungan antara factor-faktor social-demografik/klinikal dan NPS kepada kemerosotan kognitif. Ujian 'Chi-Square' dijalankan untuk menganalisa sekiranya salah satu NPS menukarkan kebarangkalian seseorang subjek secara ketara ('significant') untuk mendapat kemerosotan kognitif.

Linear regresi dijalankan untuk membandingkan kepentingan relatif NPS dengan markah NUCOG dengan pembetulan untuk 'bias' daripada factor-faktor sosial-demografik dan klinikal.

Keputusan: Umur 'mean' adalah 64.89 tahun (SD= 9.34). Kebanyakan subjek menerima pengajian sehingga tahap menengah (56.4%) dan 23.4 % menerima sehingga tahap university/kolej. 'Mean' tempoh mengalami penyakit Parkinson adalah 9.70 tahun (SD: 5.89). 12.7 % mengalami tahap Parkinson yang paling ketara. Pesakit yang mengalami tahap Parkinson yang paling ketara ($p<0.01$), memerlukan pertolongan untuk berfungsi ($p<0.001$) dan yang mengambil Benzodiazepine ($p<0.01$) mempunyai markah NPS yang tinggi. Semua pesakit menonjolkan prestasi yang rendah dalam semua domain NUCOG dan 'Mean' markah adalah 73.7% (SD: 19.34). Faktor ketara yang didapati berhubung dengan markah NUCOG adalah tahap pengajian sahaja ($p<0.01$). Subjek yang menerima sehingga tahap university/kolej mempunyai markah lebih tinggi dalam semua domain kognitif kecuali fungsi eksekutif. Subjek yang bertahap Parkinson yang paling ketara ($p<0.001$), memerlukan pertolongan untuk berfungsi ($p<0.001$) dan yang mengambil ubat anti-demensia ($p<0.05$) mendapat markah NUCOG dan domain NUCOG lebih rendah. Subjek yang mengalami delusi ($p<0.01$), halusinasi ($p<0.05$), 'agitation'/ 'aggression' ($p<0.05$), 'irritability' ($p<0.05$) dan masalah tidur ($p<0.05$) menunjukkan kemerosotan kognitif. Halusinasi ($p<0.05$), delusi ($p<0.05$) dan 'irritability'($p<0.05$) mempunyai kait dengan markah NUCOG rendah (<80). Akan tetapi, selepas pembetulan untuk tahap pengajian, hanya halusinasi yang mencapai korelasi negatif dengan markah NUCOG ($p<0.05$).

Rumusan : Semua subjek mencapai prestasi yang rendah dalam semua 5 domain kognitif NUCOG: Bahasa, ingatan, eksekutif, visiokonstruksi dan tumpuan. Terdapat perhubungan antara halusinasi dan kemerosotan kognitif.

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LIST OF ABBREVIATIONS

ACE-R	Addenbrooke's Cognitive Examination-Revised
AD	Alzheimer's disease
aMCI	amnestic MCI
B*	Beta * coefficient
BDNF	Brain-derived neurotrophic factor
BDZ	Benzodiazepine
CI	Confidence Interval
DDA	Direct Dopamine Agonists
DRS	Dementia Rating Scale
DRT	Dopamine replacement therapy
EDS	Excessive daytime sleepiness
GAD	Generalized anxiety disorder
GEPAD	German Study on the Epidemiology of Parkinson's disease with Dementia
HKL	Hospital Kuala Lumpur
LB	Lewy body
MAO-B	Monoamine Oxidase-B
MCI	Mild cognitive impairment
MDS	Movement Disorder Society
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
N	Number
NMSs	Non-motor symptoms
NPI	Neuropsychiatric Inventory
NPS	Neuropsychiatric Symptoms
NUCOG	Neuropsychiatry Cognitive Assessment Tool
OSA	Obstructive Sleep Apnoea
PD	Parkinson's Disease
PDD	Parkinson's Disease Dementia
PD-NC	Parkinson's Disease without cognitive impairment
PD-ND	Non-demented Parkinson's disease
RBD	REM-sleep behavioral disturbance
REM	Rapid eye movement
RLS	Restless legs syndrome
SD	Standard Deviation
SE	Standard Error
SPSS	Statistical Package for Social Sciences
STN	Subthalamic nucleus
UMMC	University Malaya Medical Centre
UK	United Kingdom

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CHAPTER 1: INTRODUCTION

Parkinson's Disease (PD) is known as a chronic, progressive and debilitating neurodegenerative disorder. PD was named after an English doctor, James Parkinson in the 19th century who described features of PD in 6 of his patients (Parkinson, 2002). Currently, PD is known to be the second commonest neurodegenerative disorder following Alzheimer's disease (Dorsey et al., 2007). PD has been considered to be a multi-factorial disease following theories on etiology and pathogenesis of the disorder (Gandhi et al., 2005a). Interactions between genetic and environmental factors have been cited to be responsible for the cellular changes which lead to progressive neuronal degeneration. Although there had been well-described clinical and pathological phenotype, the molecular mechanisms leading to neurodegeneration remain elusive. There is abundance of evidence on the pathogenesis of PD. Evidence suggests a major causative role for mitochondrial dysfunction, oxidative mechanisms and failure of the protein degradation machinery at the cellular level in the PD pathogenesis (Gandhi et al., 2005b).

At least 11 forms of genetic parkinsonism had been discovered so far which share clinical features and possibly pathogenetic mechanisms with the more common sporadic form of the disease (Bonifati, 2005). Examples of these are mutations in alpha-synuclein, parkin, UCHL1, DJ1, PINK1 and LRRK2 with a Mendelian pattern of inheritance (Schapira, 2006). There is some indirect evidence from various epidemiological studies stating that age, sex, dietary habits, infections, environmental toxins and trauma may be contributing factors for PD (Logroscino, 2005). Toxins have been shown to cause nigrostriatal cell death by several mechanisms i.e interfering with mitochondrial function, inducing oxidative stress and modifying protease malfunction (Schapira, 2006).

The two important neuropathologic findings in Parkinson disease are the loss of pigmented dopaminergic neurones in the pars compacta of the substantia nigra as well as the presence of α-synuclein-containing Lewy bodies and Lewy neurite in the surviving neurones. The resulting dopamine deficiency leads to denervation of the nigrostriatal tract. The significant reduction of dopamine at the striatal level in turn affects the neurotransmission process for the basal ganglia circuit. As a consequence of this denervation process, there will be an imbalance in the striato-pallidal and pallido-thalamic output pathways. When these pathways are affected, major motor deficits will occur (Albin et al., 1989).

PD is thus characterized by the hallmark clinical motor symptoms; resting tremor, rigidity, bradykinesia and postural instabilities (Gelb et al., 1999). Motor features of PD start insidiously over weeks or months, with tremor being the most frequent initial symptom (Hughes et al., 1992). Postural disturbances, falls, freezing of gait, speech and swallowing difficulties are the other motor signs observed in later stages of PD (World Health Organization, 2006). As the disease progresses without treatment, PD causes significant motor deterioration resulting in loss of independence and ambulation as well as difficulties in carrying out activities of daily living (Ahlskog et al., 2001). Assistance would be crucially needed for these patients in most activities such as feeding, self-hygiene, dressing, turning in bed, rising from the sitting position and walking (Bloem et al., 2004; Chaudhuri et al., 2005). Patients who experience gait disturbances and postural instability may have frequent falls, with increased risk of fractures. Dysarthria and hypophonia which can occur leads to communication difficulties, while deglutition disorders increase the risk of aspiration pneumonia (Bloem et al., 2004; Chaudhuri et al., 2005). Parkinson's disease runs a chronic slowly progressive course, being extremely variable in patients.

The rate of mortality in PD is increased compared with a control population. A recent study showed that the standardized mortality ratio for the PD group was 1.52 compared with the controls (Herlofson et al., 2004). Contributing factors to this increased mortality include complications related to motor disability (immobility, prostration, deglutition disorders) and autonomic dysfunction resulting in falls, fractures, pneumonia, urinary tract infections, etc. (Alves et al., 2005). The course of PD is said to be prolonged with the increase in life expectancy. Long-term motor complications, owing to disease itself and treatment-related, as well as non-motor symptoms are seen more often and account for significant morbidity (Schrag et al., 2006).

In addition, some PD patients may even experience motor response complications (due to long-term dopaminergic medication) which complicate their disease (Ahlskog et al., 2001). These include motor fluctuations and dyskinesia. The "wearing-off" condition (or "OFF-medication state), which is the commonest type of motor fluctuation will improve if the patient takes a dose of PD medication leading to the "ON"-medication state. Dyskinesias are involuntary choreiform movements typically occur when patients are "ON" ("peak-dose" dyskinesia). Approximately 50% of patients experience this after five years being on L-Dopa. Less often, dyskinesia can also occur before the full effect of the medication dose and during "wearing-off" phase ("biphasic" dyskinesia) (Shen-Yang et al., 2012). Non-motor fluctuations are psychiatric and cognitive symptoms which can occur or worsen during "OFF" periods. Examples of these symptoms are; anxiety, fatigue, dysphoria, slowness of thinking, confusion, poor concentration, word finding problems and impaired memory (Witjas et al., 2002). All these features including axial motor symptoms (resistant to levodopa) could predominate in advanced PD (Kulisevsky et al., 2013).

Although PD is widely known as a movement disorder, PD also gives rise to non-motor symptoms (NMSs) which are rather prevalent and diverse. NMSs which include neuropsychiatric, autonomic and sensory disorders have important clinical consequences for both the patient and caregiver and can even dominate the clinical picture of an advanced illness. The under-recognition of NMSs by clinicians often results in the condition being untreated leading to increased disability, poor quality of life and shortened life expectancy (Chaudhuri et al., 2011).

Neuropsychiatric symptoms (NPS) which form a major part of the NMSs complicate PD (Chaudhuri et al., 2011). NPS are important in terms of prognosis, nursing home placement and mortality (Williams-Gray et al., 2006).This study will focus on exploring the NPS aspect in a study population comprising of 94 Parkinson's Disease patients. The symptoms studied include; depression, anxiety/aggression, apathy/indifference, hallucinations, delusions, irritability, cognitive impairment, elation/euphoria, sleep disturbances and appetite changes. These symptoms were assessed using the Neuropsychiatric Inventory (NPI) and the Neuropsychiatry Cognitive Assessment Tool (NUCOG) which are validated and reliable tools (Cummings et al., 1994; Walterfang et al., 2006). The NUCOG which is a comprehensive 21-item cognitive screening tool assesses on five cognitive domains often affected in PD; Attention, Visuo-constructional, Memory, Executive and Language function (Walterfang et al., 2006). On the other hand, the Neuropsychiatric Inventory (NPI) assesses the frequency and severity of 10 behavioural disturbances and two neuro-vegetative symptoms as mentioned above. Besides that, socio-demographic and clinical factors which may be associated with these 2 aspects will be explored.

Cognitive impairment which comprises a range of spectrum from mild cognitive impairment to dementia is of the particular focus of this study. Most PD patients will subsequently develop dementia and indeed these NPS are found to be common in those with Parkinson's Disease Dementia (PDD) (Aarsland et al., 1999b; Emre, 2003). It has been found that advanced motor stage of PD correlates with higher frequency and severity of NPS (Javeed et al., 2014). Therefore in this study, we used Hoehn and Yahr scale to assess the stage of Parkinson disease (Stages 1 to 5) particularly in the motor function (Hoehn et al., 1967).

Although the Braak hypothesis explained on the pathophysiology of the NMS complex, much of it remains unclear as some of the NMS did not coincide with the proposed stages (Chaudhuri et al., 2006). PD is more than a nigrostriatal dopamine deficiency disease involving multiple central and peripheral systems as non-dopaminergic and NMSs are sometimes present prior to PD diagnosis and potentially manifest with disease progression (Chaudhuri et al., 2006; Hely et al., 2008). Studies on the associations between neuropsychiatric symptoms and cognitive impairment are limited. To our knowledge, there is no data describing the above relationship in Malaysia. Therefore, this cross-sectional study was done to address this issue. The importance of understanding this relationship could provide insight into the phenotype of PD and thus provide a better understanding of its pathophysiology. Subsequently, this knowledge can be translated into a more personalized and holistic approach to the effective management of the many challenging non-motor symptoms of PD.

CHAPTER 2: LITERATURE REVIEW

The prevalence of Parkinson's Disease (PD) in developed countries is about 0·3% of the total population and around 1% in people over 60 years of age. In populous nations, the number of individuals with PD over age 50 was between 4.1 and 4.6 million in 2005 and is forecasted to double to between 8.7 and 9.3 million by 2030 (Dorsey et al., 2007). It was also reported that incidence rates of PD are 8–18 per 100 000 person-years. It has been found that a significantly higher incidence rate of PD was found among men. The relative risk was 1.5 times greater in men than women (Wooten, 2004). Approximately 15% of people with PD have a first-degree relative who has the disease (Samii et al., 2004). At least 5% of individuals are known to have forms PD that occur due to mutation of one of several specific genes (Lesage et al., 2009; Taylor et al., 1999). The disease is rare before the age of 50 years and the prevalence increases with age, up to 4% in the much older groups. In fact, a sharp increase in incidence is demonstrated after the age of 60. These statistics established PD as an age-related disease (Lau et al., 2006).

2.1 Non-motor Symptoms (NMSs)

The presentation of PD can be divided into motor and non-motor symptoms (NMSs). There is a wide spectrum of NMSs which can accompany PD. These symptoms include neuropsychiatric symptoms, fatigue, autonomic dysfunctions, sensory symptoms, gastrointestinal symptoms, sexual dysfunction and others. NMSs in PD are complex, diverse and disabling. These NMSs are challenging not only for the patient but the caregivers as well, especially in the advanced stages of the disease. The difficulties in NMSs results in limitations of effective treatment of the motor signs and thus increased

disability in PD patients. Also, the global burden of NMSs seems to have a greater impact on patient's quality of life as compared to their motor symptoms (Chaudhuri et al., 2011).

Manifestations of NMSs can be related to various factors such as effects of dopaminergic treatment i.e. dopamine dysregulation syndrome, drug-induced hallucinations or psychosis, postural hypotension and non-motor fluctuations (Chaudhuri et al., 2011). NMSs frequently correlate with advancing disease and disease severity (Martinez-Martin et al., 2007). However, there has been some evidence that certain NMSs, like rapid eye movement (REM) behavior disorder (RBD) and olfactory deficit, constipation and depression can precede the onset of motor symptoms by a few years (Chaudhuri et al., 2006). In the more advanced disease, NMSs are known to be major determinants of loss of independence, caregiver strain, and nursing home placement (Aarsland et al., 2000). In the pathogenesis of NMSs of PD, non-dopaminergic neurotransmitters such as acetylcholine, norepinephrine, and serotonin have frequently been implicated. This further provides the rationale for several pharmacological interventions for cognition and mood symptoms (Hely et al., 2008).

A recent prevalence study by Khedr et al. on NMSs of PD showed that mood/cognition was the most commonly affected domain (prevalence rate=87.5%), followed by sleep disturbance/fatigue second (78.6%). Apart from that, all other NMSs scored highly: gastrointestinal and urinary (76.8% for both), sexual dysfunction (73%), cardiovascular (70.5%) with a significantly higher percentage of predominantly akinetic/rigid patients. However, perceptual problems/hallucinations (9.9%) were infrequent (Khedr et al., 2013b).

2.2 Neuropsychiatric Symptoms (NPS)

Neuropsychiatric symptoms (NPS) have been established as one of the important parts of the constellation of NMSs in PD. The NPS in PD includes; depression, anxiety, apathy, hallucinations, delusions, cognitive impairment (dementia, mild cognitive impairment), dopamine dysregulation syndrome (could be levodopa related), impulse control disorders (related to dopaminergic drugs), panic attacks etc. (Chaudhuri et al., 2011). This group of symptoms has a significant impact not only on the quality of life of PD patients but also caregiver burden and distress as well as increase risk of nursing home placement. The health care system is also significantly affected (Aarsland et al., 2009b).

The commonest NPS in PD includes depression, anxiety, apathy and psychosis (Aarsland et al., 2009b). NPS are found to be more common in those with those having dementia i.e. Parkinson's Disease Dementia (PDD) (Emre, 2003). It has also been established that the more advanced the motor stage of PD is, the more frequent and severe the NPS may be (Javeed et al., 2014). For example, depression was found to be more frequent in patients with higher disability and psychosis with longer duration of disease and older age (Rai et al., 2015). NPS are often found to be under-treated. There are many reasons for the under-recognition and under-treated NPS which are; patient-related factors (e.g., lack of understanding of mental health problems), access-to-care issues, and lack of interest and knowledge among clinicians (Dobkin et al., 2013; Weintraub, 2013).

Knowledge on causal factor for NPS is limited. However, phenotypic variation suggests that a variety of factors contribute to NPS in PD. Specific factors such as involvement of specific brain regions and dopamine replacement therapy (DRT), genetic factors, psychological and social reactions appear to have a part in the development of NPS in PD (Leentjens et al., 2013; MacCarthy et al., 1989). In the elderly and those who

suffer from other brain diseases, symptoms like depression and anxiety are common. In PD and related disorders, there are some symptoms like visual hallucinations, misidentification syndrome, REM-sleep behavioral disturbance (RBD), and impulse control disorders which are more characteristic of the disease. Thus, the neuropsychiatric profile of PD differs from that of patients with Alzheimer's disease (AD) and even other diseases of the basal ganglia (Aarsland et al., 2001a, 2001b).

2.2.1 Depression

Depression is manifested by sadness, feeling of guilt, lack of self-esteem and remorse. Depression is very common among PD patients, with a prevalence of approximately 35% (Chaudhuri et al., 2011). Depression can occur before or at the time of the diagnosis of PD. In addition, prior history of depression has been shown to be a predictor for or a pre-motor clinical manifestation of PD (Ishihara et al., 2006). It is thought that dysfunction of dopaminergic, serotoninergic and noradrenergic pathways in the limbic system can be affected in these group of patients (Remy et al., 2005). The frequency of depression was observed to be higher in the more advanced PD and patients with cognitive impairment. Using the NPI, rates of depression were 70% in amnestic MCI (mild cognitive impairment), 60% in non-amnestic MCI, and 55% in normal cognition (Monastero et al., 2013). In another study using the Montgomery and Åsberg depression rating scale, the frequency of depression was found to increase with disease stage, and was higher in PDD (44%) than non-demented patients (PD-ND) (18%). Similar findings were found in a recent meta-analysis which has a moderately large effect size (0.52) (Tremblay et al., 2013). There were two studies which showed that higher severity of depression or a diagnosis of major depression predicted more progressive long-term cognitive decline (Mayeux et al., 1990; Starkstein et al., 1992a).

However, whether depression is a risk factor for PDD is still debatable. Several studies did not find an association between depression and rate of cognitive decline (Aarsland et al., 2004) or incident dementia (Hobson et al., 2004a; Hughes et al., 2000b). The Norwegian Park West study reported that depression score at baseline did not predict conversion to dementia (Pedersen et al., 2013). The mechanism for this association is unknown, but the vulnerability of hippocampal neurones to the increased stress-response associated with depression may be implicated. In addition to these, depression, apathy, and dementia often can overlap. Those with cognitive impairment and apathy can also have less awareness and this can influence the capacity to express depressive symptoms (Aarsland et al., 2014).

2.2.2 Anxiety

Next to depression, anxiety symptoms are also common in PD and could predate the motor symptoms (Shiba et al., 2000; Weisskopf et al., 2003). The prevalence ranges around 25–40% (Park et al., 2009). Anxiety can be characterized as panic attacks, phobias or generalized anxiety disorder (GAD). In one large cohort, 34% were diagnosed to have an anxiety disorder, and GAD was the commonest, followed by panic attacks and phobias (Leentjens et al., 2011). However, in a large German study, anxiety was found to be less prevalent in PDD unlike other NPS (Riedel et al., 2010).

Anxiety can be due to certain neurobiological and neuropeptide dysfunction associated with PD (Richard et al., 1996) and, as it is frequently associated with depression, the same pathophysiology has been implicated. Clinically, anxiety symptoms are commonly seen during the "off" period due to the deficiency in dopamine (Goetz, 2010). These can improve with better dopaminergic agents and lessen ‘off’ time. Having said that, the majority of cases anxiety symptoms seem to occur without any temporal

relationship with specific motor states (Leentjens et al., 2012). Some forms of anxiety, such as the fear of dying or going insane, that are independent of dopaminergic state and that do not respond to an improvement of the dopaminergic therapy; these may be more likely to be a reaction to the diagnosis and progressive PD symptomatology (Park et al., 2009). In some cases, anxiety and mania have been reported as side effects of dopamine agonist treatment and high-dose levodopa treatment (Singh et al., 2005).

2.2.3 Psychosis

PD patients can experience rather disabling psychotic symptoms (hallucinations and delusions) which are known to be predictors of nursing home placement and mortality (Aarsland et al., 2000). The exact point prevalence is not clear, but in the long term, psychosis can affect up to 60% of PD patients (Fénelon et al., 2000; Mosimann et al., 2006). The most typical presentation is complex visual hallucinations, (e.g animals and people). Other perceptual disturbances which can occur includes; illusions, sensations of movement in the periphery and sensations of presence (extra-campine hallucination). Perceptual disturbances and visual hallucinations are most of the time benign (Fenelon et al., 2011). Hallucinations in other sensory modalities (auditory, tactile, and olfactory) can occur but are not as common (Fénelon et al., 2010b). Visual hallucinations occur in 7–25% of PD patients, but increase to 41%–87% in PDD patients (Fénelon et al., 2010a).

Delusions can be present when insight is compromised, which is associated with the degree of cognitive impairment. Paranoid delusions appear to be the recurring theme, but others like delusional misidentification can also occur in a minority of PDD patients (Pagonabarraga et al., 2008b). Delusions alone without hallucinations have a prevalence of 4%–5%, less common than hallucinations (Forsaa et al., 2010). As visual hallucinations often occur due to side effects of medication, neuronal degeneration of the

pedunculopontine nucleus, locus ceruleus and dopaminergic raphe nuclei which are implicated can be causative (Diederich et al., 2005). One of the hypothesis of the development of psychosis begins with drug-induced sleep disruption, which results in vivid dreams, hallucinations and delirium (Moskovitz et al., 1978). Lewy body pathology has been associated with hallucinations. This involves accumulation of Lewy Body in the amygdala, parahippocampus and inferior temporal cortices. The denervation of mesolimbic and mesocortical dopaminergic receptors leading to dopaminergic medication hypersensitivity ("kindling phenomenon") is also implicated in the process leading to psychosis. Genetic risk factors and a polymorphism in the cholecystokinin gene could also be involved (Goldman et al., 2004).

Psychosis can affect PD patients at any stage even at the early stage (Morgante et al., 2012). However, although it usually occurs in the later course of the disease (Forsaa et al., 2010). Risk factorsfor visual hallucinations are;severity and disease duration,ocular disorders, older age of PD onset and REM-sleep behavior disorder (Aarsland et al., 2014). The presence of visual hallucinations in PD may be a warning sign of developing dementia, or in the presence of preexisting dementia lead to more rapid decline (Aarsland D. et al., 2003; Emre et al., 2007). Also, cognitive decline in PD may be an important risk factor for visual hallucinations (Morgante et al., 2012) and it is observed that even non-demented PD hallucinators tend to have more executive dysfunction, poorer sustained attention, and worse visuoperceptual function compared with non-hallucinators (Hepp et al., 2013).

2.2.4 Apathy

Apathy is defined as a decrease in goal-directed behavior, verbalization, and mood. The prevalence is 30% to 40% in PD patients (Sockeel et al., 2006; Starkstein et al.,

1992b). Apathy is common among neurodegenerative diseases (Starkstein et al., 2009) and it is a specific symptom of PD independent of depression, somnolence, and fatigue. However, it may or may not occur with depression and seems to coexist with anxiety (Chaudhuri et al., 2011). A study demonstrated that PD patients have a higher prevalence of apathy than in patients with osteoarthritis, which indicates a neurodegenerative contribution (Alves et al., 2004). Functional imaging studies have proposed that in PD patients, reward processing in the brain is decreased (Chaudhuri et al., 2005). In some cases of apathy, a dopaminergic deficit is implicated. However in some cases, it can be unresponsive to dopaminergic therapy which indicates a probable involvement of other neurotransmitters than the dopaminergic pathways (Chaudhuri et al., 2011). Noradrenergic dysfunction along with inactivation of the frontal cortex and basal ganglia are also implicated. Lately, research has found an association between apathy and decreased cingulate, inferior frontal and orbitofrontal gyrus volumes (Aarsland et al., 2014).

In terms of cognitive impairment, PD can occur independently, but the overlap is also frequent (Starkstein et al., 1992b). In PDD patients, the prevalence is up to 50% (Aarsland et al., 2007). In a study which compared PD patients with a control group, apathy was more common in the PD group, was associated with cognitive impairment but not depression or anxiety (Pluck et al., 2002). Another study showed similar findings (Dujardin et al., 2007) and its prevalence was greater in PDD than those without dementia. All PD patients also showed a reduction in initiating actions compared with controls and PDD showed a greater impairment in this regard. In terms of cognitive domains, apathy is associated with executive deficits, memory impairment and bradyphrenia (Pluck et al., 2002; Starkstein et al., 1992b).

2.2.5 Sleep Disturbances

Sleep disturbances in PD consist of excessive daytime sleepiness (EDS) and nocturnal sleep disturbances (insomnia, sleep fragmentation, restless legs syndrome (RLS), periodic limb movements of sleep, circadian dysrhythmia, Obstructive Sleep Apnoea (OSA), sleep disordered breathing, and REM sleep behavior disorder (RBD)). Both are very common in PD, with a prevalence of up to 80% and 90% of patients respectively (Stacy, 2002). RBD is common as well with a prevalence range of 46%–58% (Vendette et al., 2007), and can predate the onset of PD by up to few decades (Claassen et al., 2010). It has been found that the incidence of EDS increases with disease duration. EDS can be detrimental with interference with activities of daily living, particularly driving (Frucht et al., 1999). There is emerging evidence on an association between the severity of cognitive impairment and EDS in PD (Goldman et al., 2013).

Although the etiology is not well understood, neuropathological changes to sleep-wake centres in the brainstem and hypothalamus (hypocretin-secreting neurons) have been implicated (Videnovic et al., 2013). The atrophy of cortical grey matter and nucleus basalis of Meynert appear more often in PD patients with EDS, even without cognitive impairment and hallucinations (Kato et al., 2012). Damage to the brainstem, in particular to the descending reticular formation and reduced striatal dopaminergic activity has been implicated in RBD (Aarsland et al., 2014). The occurrences of sleep disturbances are reported to be no difference in PD patients with and without MCI (Monastero et al., 2013). Evidence on whether there is an association between nocturnal sleep disturbances and severity of cognitive impairment or with certain cognitive domains is lacking (Goldman et al., 2013). However, it was found that in PD patients with RBD, rates of MCI are about six to seven times higher than those without RBD (Gagnon et al., 2009). It is a precursor for earlier onset of dementia compared with PD patients without RBD (Vendette et al.,

2007). Patterns of cognitive deficits similar to PDD are observed impaired attention, visuo-constructional and visuo-perceptual abilities, but with relatively preserved memory and naming (Vendette et al., 2007).

2.2.6 Cognitive Impairment

Cognitive impairment is increasingly recognized as a significant NMSs of PD as it is particularly prevalent and could occur even in the early stages of the disease. A wide spectrum of cognitive impairment is seen in PD patients, ranging from mild to a more severe degree called mild cognitive impairment (PD-MCI) and Parkinson's Disease Dementia (PDD) respectively (Caviness et al., 2007). According to the guideline by Movement Disorder Society (MDS), PD-MCI is described as the cognitive decline that does not interfere with functional independence (Erro et al., 2012; Litvan et al., 2012). Conversely, for PDD patients, MDS defined it as deficits in at least two of the four cognitive domains (attention, memory, executive and visuo-spatial functions) which have to be sufficiently severe to impede normal functioning (Emre, 2003; Pagonabarraga et al., 2008a). Within PD-MCI, significant heterogeneity exists in terms of the number and types of cognitive domain impairments. Although impairments affect a range of cognitive domains, single domain impairment (in attention, visuo-spatial and executing tasks) is more common than multiple domains. Also, non-amnestic is shown to be more common than amnestic (Carpi et al., 2013; Goldman et al., 2011).

Studies have suggested that PD-MCI may be the earliest stage of cognitive decline and a risk factor for developing dementia in PD (Janvin et al., 2006). However, not all MCIs progress to dementia (Muslimovic et al., 2005). A study by Weintraub showed that cognitive impairment has also been found in around 10% of early, untreated PD patients

(Weintraub et al., 2015). Litvan et al. (2012) concluded that MCI is common in non-demented PD (PD-ND) patients, with a mean of 26.7% (range, 18.9–38.2%). William-Gray et al. found an even higher prevalence of PD-MCI is 57% of the early PD patients (Williams-Gray et al., 2007). This condition is found to increase with advancing age, disease duration and severity, male gender and lower levels of education (Williams-Gray et al., 2007).

Initial reports of cognitive impairment in PD were focused on frontal-type dysfunction, related to disconnection of the fronto-striatal circuits, present especially in newly diagnosed and drug naïve PD patients (Alexander et al., 1986; Lees et al., 1983; Owen et al., 1992). Specifically, parts of the basal ganglia and frontal cortex are found to be under-activated. This results in deterioration in the frontal executive function involving manipulation of information within the working memory (Lewis et al., 2003; Marklund et al., 2008).

These impairments in PDD are summarized as "subcortical dementia" syndrome with greater impairment in non-amnestic cognitive domains (e.g., executive function, attention, and visuo-spatial function) and less impairment in declarative memory, language and praxis. However, the cognitive features of PDD may be heterogeneous whereby some patients may exhibit more "cortical" profiles with impaired memory and language (Emre, 2003; Pagonabarraga et al., 2008a). The clinical presentation of aphasia, apraxia and agnosia seem to resemble patients in temporal lobe damage and cortical dementia (Williams-Gray et al., 2007).

2.2.7 Parkinson's Disease Dementia (PDD)

PDD has been accounted for at least 3% to 4% of dementia in the general population. The point prevalence is around 30–40% (Aarsland et al., 2005; Chaudhuri et

al., 2011). There is a five times higher risk of developing dementia in patients with Parkinson's Disease compared to healthy controls (Emre, 2003; Hobson et al., 2004b). According to longitudinal cohort studies, approximately 50-60% of those with PD develop dementia after ten years. Subsequently after 20 years, this figure increases to over 80 % (Cosgrove et al., 2015; Hely et al., 2008; Karrasch et al., 2015). Some of the associated factors in PDD are; older age at the disease onset, male gender, severe motor symptoms, akinetic-rigid motor phenotype, longer PD duration, psychosis, depression, and genetic factors such as APOE4 and MAPT alleles (Hughes et al., 2000a; Setó-Salvia et al., 2011; Williams-Gray et al., 2009).

2.2.8 Neuropathology and Neurochemical basis of PDD

The exact neurobiological and pathophysiology leading to the development of PDD is unknown. However, many studies emphasize on Lewy body (LB) deposition in the limbic and cortical areas and Alzheimer's-type (AD) pathology (Caballol et al., 2007). In addition to Lewy-body-type pathology, cholinergic dysfunction in the limbic system and neocortex is known to be the major pathological correlate of cognitive impairment in PD (Hall et al., 2014). Cholinergic cell loss in the nucleus of basalis Meynert is prominent. Perry et. al reported diminished activity of choline acetyltransferase (ChAT) in the frontal and temporal cortex in patients with PDD (Perry et al., 1983). Cholinergic dysfunction therefore forms the basis of cholinergic treatment for dementia in PD (Chaudhuri et al., 2006). Other monoamine transmitters like noradrenergic pathways dysfunction due to lesions in locus coeruleus and loss of serotonergic neurons have also been implicated in the cognitive deterioration in PD (Bosboom et al., 2004).

Several pathological studies have linked PDD to Alzheimer-type pathology (Caballol et al., 2007). A study by Apaydin found that besides diffuse or transitional LB

disease was the major pathological substrate, some AD-type pathology (senile plaques and neurofibrillary tangles) also correlated with neocortical LB (Apaydin et al., 2002). Jellinger (2002) also confirmed neurofibrillary tangles to correlate with PDD (Jellinger et al., 2002). De Vos reported that PDD patients have the higher degree of cortical AD-type pathology compared to patients without dementia (De Vos et al., 1995). These studies concluded that α-synuclein and AD-type pathology often found to occur. However, despite the common occurence, AD-type pathology is less predictive of PDD (Emre, 2003). Besides these, the contribution vascular pathology, as well as a possible genetic association with the APOE genotype has also been implicated. Volumetric Magnetic Resonance Imaging (MRI) studies detected that hippocampal volume is diminished in PDD, likening to that of Alzheimer's disease (Chaudhuri et al., 2006).

2.3 The association between mental illness and PD

It has been established that psychiatric disorders occur at higher rates in PD patients compared to the general population (Jacob et al., 2010). One study showed a 2.38 increased risk of developing PD in those having a psychiatric disorder (Lin et al., 2014). Both depression and anxiety disorders have shown to precede PD development and therefore could be risk factors for PD. Both of these disorders may also be associated with a more rapid deterioration in cognitive and motor functions (Uekermann et al., 2003). Depression appears to be the most frequent premorbid psychiatric illness (Jacob et al., 2010). Schizophrenia on the other hand, exhibited the highest risk of a subsequent PD diagnosis in the study by Lin and colleagues. As for Bipolar Disorder, there is still no conclusive evidence on whether there is significant increase risk of subsequent PD (Lin et al., 2014).

Underlying neurologic changes attributed to premorbid psychiatric disorders may increase the vulnerability of the brain to PD. PD and psychiatric disorders are both caused by an overall depletion of neurotransmitters (Ishihara et al., 2006a). Animal studies suggested that affective disorders are linked to disturbances in the metabolism of dopamine and other brain molecules. Lower serotonin levels found in PD led to the postulation of the serotonergic hypothesis for depression in PD. Also, both PD and depression are associated with reduced activity or lesions in the orbital frontal cortex and basal ganglia (Mayeux et al., 1988). However, it is noted that the frequency of PD and major depressive disorder is low (Tandberg et al., 1996). In the pathogenesis of Schizophrenia and PD, neurotransmitter dopamine and dopaminergic neurons have been implicated (Birtwistle et al., 1998). Negative symptoms of Schizophrenia are frequently reported in both patients with Schizophrenia and PD (Winograd-Gurvich et al., 2006).

In addition, psychiatric symptoms prior to PD may be caused by other factors contributing to PD. There are some postulations that behavioral and personality patterns may occur years before the onset of motor symptoms. These patterns include emotional and attitudinal inflexibility, lack of affect, introspective and over-controlling personality, anxious personality and vulnerabilities to depressive illnesses (Bower et al., 2010; Todes et al., 1985). Other factors may be psychosocial impact and reactive response to the early symptoms of PD (such as motor fatigue). Thus owing to the possible involvement of psychiatric disorders in PD, the etiology of PD is therefore multi-factorial (Ishihara et al., 2006b).

2.4 Neuropsychiatric Symptoms (NPS) and Cognitive impairment

Studies examining the associations between NPS and cognitive impairment are limited and inconclusive (Javeed et al., 2014). The reasons for the inconclusiveness were due to various methodological reasons including scales being used and difference in the characteristics of the sample population. For example, a study from the UK on PD-MCI patients showed a weak correlation between cognition and behavioural changes. This study used Addenbrooke's Cognitive Examination-Revised (ACE-R) and the carer-completed Cambridge Behavioral Inventory-Revised (McColgan et al., 2012). Another Mexico-based study which used the Neuropsychiatric Inventory Questionnaire (NPI) to assess NPS found no relation between disease duration, severity, cognitive impairment and NPS. The dissociation is probably due to a relative lack of advanced cases in their population (Ringman et al., 2002).

Some studies have shown that NPS even appears regardless of the stage of cognitive impairment. Leroi examined a total of 127 PD patients; subjects without cognitive impairment (PD-NC; n=54), PD-MCI (n=48), and PDD (n=25) using the NPI. Over 79% of PD patients regardless of cognitive stage, reported at least one NPS. There seems to be no significant difference in the frequency or severity of NPS between PD-NC and PD-MCI, apart from the domain of apathy. The proportion in each group who had significant NPI (scores of ≥4) was: PD-NC, 64.8%; PD-MCI, 62%; PDD 76%. Apathy was noted in almost 50% of those with PD-MCI and PDD, and thus it was an important NPS differentiating PD-MCI from PD-NC. The intensity in the PD-MCI group for apathy was 3.79 (SD 4.91) which was almost three times more than the PD-NC group. An association between early cognitive impairment and NPS, particularly mood symptoms was also observed in de novo PD (Poletti et al., 2012). NPS have also been

found to be increasingly common in those with mild cognitive impairment (MCI) compared with cognitively normal PD patients, particularly for those with amnestic MCI (aMCI) (Monastero et al., 2013).

A study by Kulisevsky et. al in PD patients without dementia (PD-ND) showed that 87% of them reported at least one neuropsychiatric symptom. The most common reported symptoms were depression (70%), anxiety (69%), apathy (48%), and irritability (47%). In terms of depression, 50% of the patients had HADS-depression scores ranging from possible (8–10; 22%) to probable (>or=11; 28%) depression. Executive impairment and excessive daytime somnolence (EDS) were found in 41% and 26% of subjects respectively. These considered variables were significantly more common with longer duration and more severe disease. Of all the psychiatric symptoms, only depression appeared to be influenced by the type of medication as it was found to be less prevalent among patients treated with Dopamine Agonists. This study also identified 5 Neuropsychiatric Inventory (NPI) clusters among patients scoring >or=1 on the NPI (87.3%): patients having predominantly apathy (12.7%), psychosis (3%), depression (13%), anxiety (15.6%), and "low-total NPI" (43.2%). Kulisevsky et al concluded that neuropsychiatric symptoms are common in PD-ND patients and thus suggests that they are an integral part of PD from the beginning of the disease and appears more related to disease progression than to the type of anti-parkinson medication (Kulisevsky et al., 2008).

Another study by Aarsland on early untreated PD using the NPI found that >50% of PD patients had positive scores in at least one domain compared to a 22% of non-PD controls ($p<0.001$). Of these, nearly 35% of subjects had two or more NPI items present. The most common NPS were depression (37%) and apathy (27%) followed by sleep disturbance (18%) and anxiety (17%). In the PD group also, 27% of them had clinically

significant symptoms as compared to only 3% in the control group ($p<0.001$). It was noted that those with significant clinical NPS had more severe parkinsonism than those without. Aarsland then concluded that although the majority of early untreated PD do not have clinical significant NPS, these symptoms are more prevalent in PD patients than in people without PD. Factors likely to contribute to the higher frequencies are related to both psychological stress and brain changes (Aarsland et al., 2009a).

In contrary, studies have demonstrated an association between NPS and more severe cognitive decline. The profile, frequency and severity of NPS have been shown to be associated with PDD. A study on 139 patients in Norway found that psychiatric symptoms assessed by NPI were significantly correlated with cognitive impairment assessed by the Mini-Mental State Examination (MMSE) (Aarsland et al., 1999b). PDD had more frequent and severe neuropsychiatric morbidity on the NPI compared with PD-ND and questionable dementia patients. This study found significant relations between dementia and delusions ($p<0.001$), hallucinations ($p<0.001$), apathy ($p<0.05$), and aberrant motor behaviour ($p<0.001$). There also reported correlations between total NPI, hallucination, delusion, and agitation scores with MMSE, most DRS (Dementia Rating Scale) subscales, and memory tests. In addition, a significant correlation was found between apathy and executive functioning as measured by the number of errors on the Stroop test (Aarsland et al., 1999b).

A large German Study on the Epidemiology of Parkinson's Disease with Dementia (GEPAD study) with 1449 PD outpatients showed that 70% had at least one NPS (including dementia as an NPS). The study also demonstrated that there is increased frequency of psychotic symptoms in PDD compared to PD without dementia. However, there were no differences in anxiety symptoms, depression and insomnia (Riedel et al., 2010). Aarsland et al. (2007) found that 89% of 537 PDD patients presented at least one

symptom on the NPI, 77% had two or more symptoms and 64% had at least one symptom with a score >4 (Aarsland et al., 2007). Notably, the most common symptoms were depression (58%), apathy (54%), anxiety (49%) and hallucinations (44%). Those with more severe dementia and advanced PD had more NPS. There were 5 NPI clusters identified: one group with few and mild symptoms (52%); a mood cluster (11%, high scores on depression, anxiety and apathy); apathy (24%; high apathy and low scores on other items); agitation (5%, high score on agitation and high total NPI score); and a psychosis cluster (8%; high scores on delusions and hallucinations). The following 2 clusters: psychosis and agitation had the lowest Mini-Mental State Examination (MMSE) score and the highest Unified Parkinson's Disease Rating Scale (higher motor symptom severity) and caregiver distress scores (Aarsland et al., 2007).

Symptoms like hallucinations and comorbid symptoms were found to be characteristic for PDD. However, sleep or mood symptoms were exclusively more common in PD without dementia (Bronnick et al., 2005). Lee Wei-Ju et al. demonstrated an association between hallucination and cognitive impairment in PDD patients (Lee et al., 2012). Leroi also found that psychosis (including hallucinations and delusions) seem to increase linearly with cognitive impairment: 12.9% in PD-NC; 16.7% in PD-MCI; 48% in the PDD group. Risk for psychosis in PD involves cholinergic deficits and presence of Lewy bodies in the temporal lobe (Aarsland et al., 2009b). Thus, identifying NPS in PD-MCI has implications for ascertaining conversion to dementia in PD (Leroi et al., 2012). There are several postulations for the co-occurrence of dementia and NPS. Factors found to be related to PDD and can potentially contribute to NPS are; Dementia-associated neocortical pathologies (e.g., tau, amyloid and synuclein inclusions) and neurotransmitter changes (cholinergic and monoaminergic changes in addition to dopaminergic deficits). Besides that, cognitive decline could lead to anxiety and depression.

2.5 Pathophysiology of Non-motor symptoms (NMSs) and the Braak Hypothesis

Studies have been done to demonstrate the role of non-dopaminergic dysfunction in PD in the complexity of the development of NMSs. From a neuropathological perspective, there are involvements of multiple neuronal systems in PD owing to changes developing in a few susceptible types of nerve cells. Neuropathological diagnosis of α-synuclein-immunopositive Lewy neurites and Lewy bodies are essential. As mentioned earlier on, the pathological process in PD begins by the degeneration of dopaminergic neurones in the substantia nigra (Chaudhuri et al., 2006). Braak and colleagues challenged this theory with their introduction of the six-stage pathological process of PD. This theory greatly contributed to the awareness of the association between symptoms and the neuro-pathological lesions affecting the nervous system. This pathological process involves the intracerebral formation of Lewy bodies and Lewy neuritis which begins at specific induction sites and advances in a topographically predictable sequence.

The targeted specific induction sites are namely degeneration of the olfactory bulb, anterior olfactory nucleus, dorsal motor nucleus of the glossopharyngeal and vagal nerves. At stage 2, the pathological process progresses to the lower brain stem. The pathological processes in these preclinical areas are implicated in NMSs such as olfactory dysfunction, sleep homeostasis and other autonomic disturbances. The lower brain stem involves several brain-stem nuclei which are centers for mediating these NMSs. The pathological process in the brain stem follows an ascending course with little inter-individual variation. On the other hand, the disease process in the anterior olfactory nucleus makes fewer incursions into related areas than that developing in the brain stem (Braak et al., 2003, 2004).

The Braak theory, therefore, has popularized the concept of a 'bottom-up' pathogenesis of PD. Therefore concurrent with this theory, several NMSs of PD, such as hyposmia, RBD, constipation and depression, are now recognized as possible pre-motor features of PD. Subsequently, as the neurodegenerative process affects the substantia nigra and other deep nuclei of midbrain and forebrain in Stages 3 and 4, the typical motor triad of tremor, rigidity and bradykinesia ensues. At this stage, PD crosses from a premotor to a motor disorder and thus is clinically diagnosed. Following that, Stages 5 and 6 involves the presence of Lewy Bodies in limbic structures and mature neocortex. Cortical involvement begins with the anteromedial temporal mesocortex and then the neocortex succumbs, commencing with a high order sensory association and prefrontal areas. After that, the first order sensory association/premotor areas and primary sensory/motor fields follow suit. NPS like depression, cognitive decline and visual hallucinations would emerge at this point (Braak et al., 2003, 2004; Chaudhuri et al., 2006).

However, there are many controversies surrounding this theory as it is based on Lewy-Body distribution instead of neuronal degeneration. For instance, the clinical presentation of parkinsonism with cognitive difficulties like hallucinations and dementia as observed in Lewy Body Dementia are unexplainable using this theory (Chaudhuri et al., 2006). Also, it has been found that NPS and cognitive impairment may occur before the development of motor symptoms of PD (Weintraub et al., 2015). Therefore the neuropathological progression did not reflect the phenotype of PD seen in clinical practice.

Significant correlations were demonstrated between the severity of bradykinesia and impaired visual-spatial reasoning and psychomotor speed. The severity of tremor was also associated with better performance on a spatial orientation memory test (Mortimer et al., 1982). In another study on early PD, dissociation of cognition and motor control

was demonstrated, which suggests that cognitive impairment is largely independent of fronto-striatal dopamine deficiency underlying motor disability (Cooper et al., 1991). PD-MCI was shown to precede the loss of motor function in a novel rodent model of PD (Li et al. 2013). Slowing of thought which was often reported in PD also did not appear to accompany bradykinesia and thus may not be related to dopaminergic dysfunction (Rafal et al. 1984). 34% of early-stage PD patients exhibit cognitive impairment, which is associated to disease severity, bradykinesia, rigidity, axial symptoms and more symmetric distribution of motor symptoms (Pfeiffer et al., 2014).

Higher prevalence of NPS preceding the onset of PD also hypothesized the possibility of dissociation between NPS of PD and motor presentation. In a registry study, 9.2% of PD patients had depression preceding the onset of PD (Leentjens et al. 2003). If depression in PD is due to the underlying neuroanatomical degeneration, rather than simply a reaction to the psychosocial stress and disability, this may indicate there could be a separate neuro-mechanism for depression and motor symptom in PD (McDonald et al. 2003). Therefore, it is obvious the evolution of clinical presentation of PD does not follow the linear progression as suggested in Braak's staging. Some studies based on axonal tracing on monkey model suggests that the basal ganglia is organised into sensorimotor, associative, and limbic regions (Parent et al., 1995). There are some PD patients who undergo deep brain surgery with the aim of improving motor disability through the stimulation of subthalamic nucleus (STN). However, this procedure has been reported to modify cognitive, emotional, and motivational functions. There is anatomical evidence that suggest that STN may integrate the cognitive, emotional, motivational and motor symptoms in PD. The STN is topographically organized by inputs from the sensorimotor, associative, and limbic regions of the basal ganglia. Furthermore, the pallido-subthalamic projection is associated with most of the non-motor functions of the

basal ganglia (Karachi et al., 2005).Of late, the insula, which was primarily thought to be just a limbic cortical structure, has also been implicated in NMSs of PD. The insula is found to be affected in PD by alpha-synuclein deposition, disruptions of neurotransmitter functions, alterations in connectivity as well as metabolic and structural changes. This structure is recently being recognized to be involved in integrating somatosensory, autonomic and cognitive-affective information to guide behaviour. Despite limited studies being done on the role of the insula in PD, there is emerging evidence from neuroimaging studies linking the insula to cognitive decline, behavioural and somatosensory disturbances (Christopher et al., 2014).

CHAPTER 3: RATIONALE AND OBJECTIVES

3.1 Rationale of the study

The importance of understanding the relationship between neuropsychiatric symptoms and cognitive impairment are not only provide understanding of the phenotype of PD and thus provide better understanding of its pathophysiology and neurobiological changes; it is also important in terms of a personalised approach to PD management

3.2 Primary Objective

To investigate the association between the neuropsychiatric symptoms and the cognitive impairment in Parkinson's Disease patients.

3.3 Secondary Objective

To explore the neuropsychiatric profile in Parkinson's Disease patients.

3.4 Research Hypothesis

The research hypothesis is that there is a relationship between the neuropsychiatric symptoms of Parkinson's disease and cognitive impairment.

3.5 Null Hypothesis

There is no association between neuropsychiatric symptoms and cognitive impairment.

CHAPTER 4 : METHODOLOGY

4.1 Study setting

This multi-centre study was conducted at the Neurology Clinic of University Malaya Medical Centre (UMMC), Neurology (Parkinson's) Clinic in Hospital Kuala Lumpur (HKL) and the Neuropsychiatric Clinic in the Psychiatric Clinic of HKL. Both UMMC and HKL are national tertiary medical referral centers situated in Kuala Lumpur, the capital of Malaysia.

UMMC was set up as a teaching hospital for the designated medical faculty of the university and it falls under the jurisdiction of Ministry of Higher Education. The centre has a bedded hospital which serves the population from Klang Valley to Petaling Jaya. In 2010, 988,132 patients were treated at the hospital, 55,826 were inpatients and the rest were out-patients HKL is located in the heart of Kuala Lumpur. It is also the largest hospital under the Ministry of Heath of Malaysia and one of the biggest in Asia. It is a government referral hospital with 82 wards, 2143 beds and 565,386 number of out-patient attendees at Specialist Clinics as of the year 2015 (*HKL Health Facts 2015*, 2015).

The Neurology (Parkinson's) Clinic of HKL has allocated clinics days for managing Parkinson's disease patient which is held every Wednesdays (afternoon session) with approximate attendees of ten patients. The Neuropsychiatry Clinic in the Psychiatric Clinic at HKL is held every Monday, Tuesday and Thursday mornings providing services to approximately 10 patients each clinic session. Total of patients with Parkinson's Disease varies from 2-5 patients per week. Neurology Clinic in UMMC is conducted every Tuesdays (morning until afternoon) and Fridays (afternoon only) whereby the

Parkinson 's disease patients would be seen with other patients with neurological disorders.

4.2 Study design

We conducted a hospital-based, multicentre, observational, cross-sectional study.

4.3 Study period

The study period was from February 2015 until January 2017. Data collection was done from January 2016 until October 2016. The data analysis and write-up were carried out from June 2016 till December 2016.

4.4 Study population

The study populations were patients with Parkinson's Disease who attended the Neurology Clinic in UMMC, Neurology (Parkinson's) Clinic in HKL and Neuropsychiatric Clinic in the Psychiatric Clinic of HKL. These centers were the most strategic locations to obtain subjects for this study. (Because the prevalence of NPS in normative PD population in Malaysia is unknown and the study seeks to determine relationship of NPS to cognitive impairment in PD patients, we intentionally select neuropsychiatric clinic to increase the likelihood of PD patients with NPS. The NPS prevalence reported is not meant to reflect the nationwide true prevalence as this was not the main goal of the study. Rather the goal is to examine with sufficient statistical power, the relationship between NPS and cognitive impairment in PD patients).

4.5 Sampling Method

The subjects were recruited by convenience sampling from the list of Parkinson's patients scheduled for the day. The subjects were approached and recruited into the study based on inclusion and exclusion criteria.

The diagnosis of PD was made by the neurologist of the respective centers. The PD diagnosis was based on the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria of PD (Hughes et al., 1992). The diagnostic criteria include: bradykinesia and at least one of the following: muscular rigidity, 4-6 Hz rest tremor and postural instability. The patients' socio-demographic variables as well as clinical data will be collected. Only patients who were present with their caregivers and either of them who could provide consent were selected for the study. A caregiver is defined as a person who spends at least four hours per day at least 4 days a week with the patient and is knowledgeable about the patient's day and night time behaviours (Cummings et al., 1994).

4.6 Inclusion criteria

1. Subjects diagnosed with Parkinson's disease by a neurologist according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria.
2. Patients/ carers who agreed to participate in this study.
3. Patients accompanied by carers.
4. Patients with adequate conversant and literacy skills in Malay or English language

4.7 Exclusion criteria

1. Patients with a diagnosis of Parkinson's Plus Syndrome.
2. Patients with a diagnosis of Secondary Parkinsonism.
3. Patients with neurodegenerative disorder other than PD.
4. Patients with co-morbid substance and alcohol use disorder.
5. Patients who were not able to cooperate with the assessment (eg.: "off-fluctuation" phase, severely psychotic, agitated or aggressive).
6. Poor conversational & literacy skills in Malay/ English
7. Patients who declined to participate in the study.

4.8 Study Variables

1. The socio-demographic data obtained include: the subject's age, gender, ethnicity, marital status, employment status. The clinical data obtained were: duration of illness (PD) since diagnosis, functional dependence, medical illnesses (vascular risk factors), past psychiatric history, history of head injury and other neurological disorders, family history of Parkinson's disease, alcohol and substance history as well as the patient's medication. The data was obtained from the subjects or through the patient's record or case notes. Duration of illness (PD), other medical illnesses (vascular risk factors) and medications were obtained from the patient's case notes.

2. The English or Malay NUCOG, NPI and the Hoehn and Yahr Scale were assessed by the researcher.

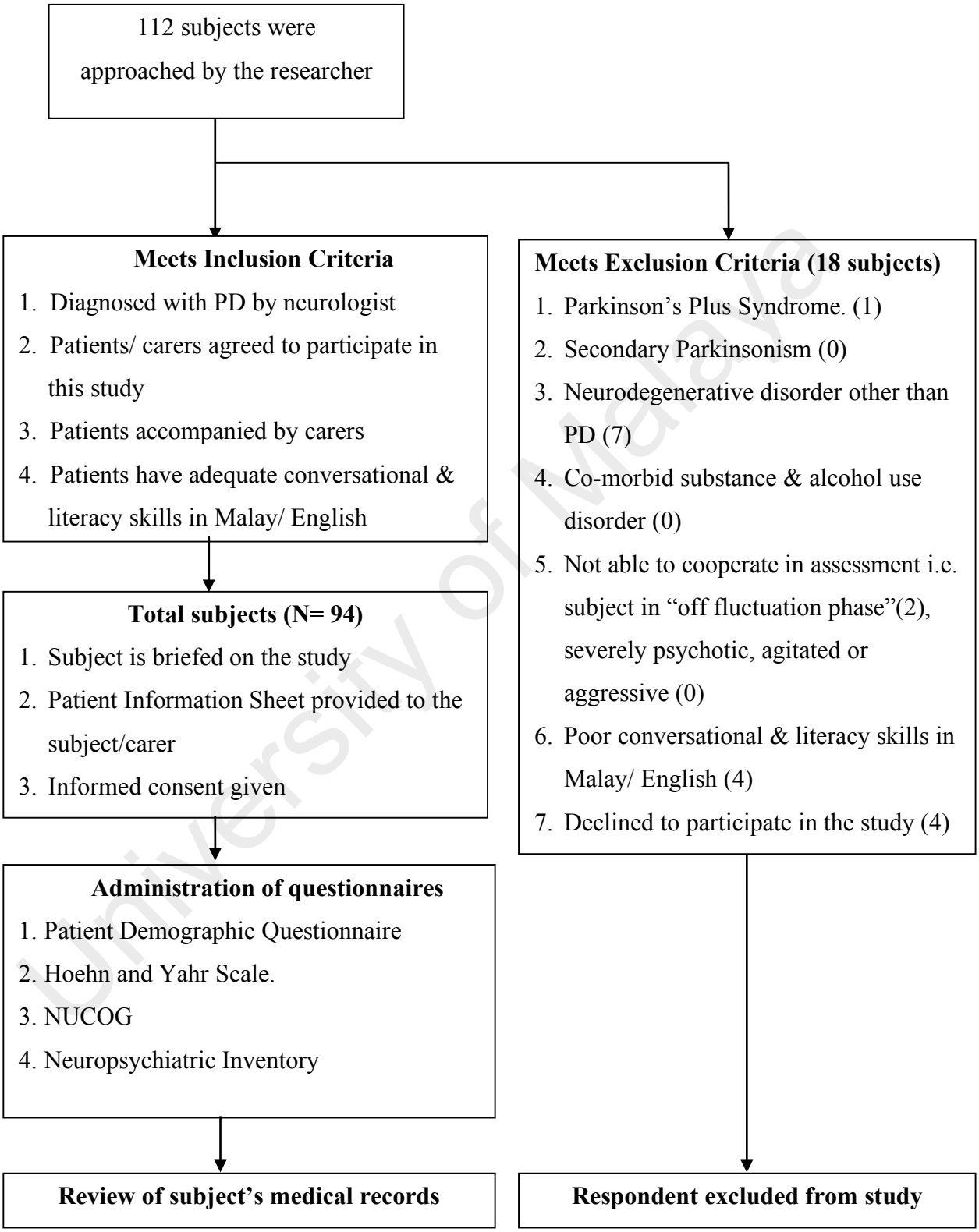
4.9 Data collection

A single researcher performed the data collection. Subjects were sampled from a pool of Parkinson's patients from 3 clinics namely the Parkinson's Disease Clinic of HKL, the Neuropsychiatry Clinic of HKL and the Neurology Clinic of UMMC. For each clinic day, 3-4 subjects were selected by randomly sampling their number in the patient register using computer-generated random numbers. Subjects and their caregivers were approached and briefed about the nature and aim of the study. They were given the Patients Information Sheet. Participation was on a voluntary basis. Written consent from the subjects was taken prior to participation in the study. Both subjects and carers were taken into a private interview room which is quiet and conducive to ensure privacy and confidentiality of the subjects. Four sets of questionnaire forms were administered to all study subjects;

1. Patient Demographic Questionnaire
2. Hoehn and Yahr Scale
3. NUCOG
4. Neuropsychiatric Inventory

The total duration of assessment and interview session for each subject was approximately 45 minutes to 1 hour. During the administration of the questionnaires, the researchers remained in neutrality so as not to lead or mislead the subjects and the carers. The data collection was completed by procuring the remaining clinical variables from the patient's case notes or records.

Figure 4.1 Flow Chart showing the Inclusion and Exclusion Process of Study Respondents



Total of 112 subjects were approached to participate in this study. Two subjects were excluded due to having "off-fluctuation phase" during the time of the interview. Seven subjects were excluded due to prior or co-morbid cerebrovascular disease and there was one subject was excluded due to a possible diagnosis of Parkinson Plus Syndrome. Four subjects declined to participate in the study and thus were not included in the study. Another four subjects who did not have adequate literacy skills in the Malay or English language. There was none who were severely psychotic, agitated and aggressive. After accounting for inclusion and exclusion criteria, a total of 94 subjects qualified for this study.

4.10 Sample Size Estimation

In this study, we wish to assess if subjects who have NPS will have poorer cognitive performance, measured through the NUCOG scale, compared to subjects who have no NPS. Since we do not know if NUCOG scores are normally distributed, we will perform the Mann-Whitney U test to assess if the distributions of NUCOG scores significantly differ between the cohorts with and without NPS. The power of this statistical test to distinguish differences between the two cohorts is limited by the sample size and the effect size. The effect size is the minimum difference between the mean NUCOG scores of both cohorts that is worthy of attention. In this study, we consider only large effect size as this is likely to result in significant decline in quality of life and functional ability and thus meriting clinical, interventional and rehabilitative attention. Thus, we choose effect size, δ=0.8 times the standard deviation of the mean, as recommended by Cohen [*]. We also wish to consider only those neuropsychiatric symptoms that have common prevalence in PD patients.

Literature reports the prevalence of common NPS to be between 10% – 30%. Symptoms with lower prevalence impose more stringent sample size conditions so we consider a 10% prevalence to estimate sample size. To choose the best sample size, we perform a simulation using G*Power software to identify the tradeoff between sample size versus statistical power. From the graph in Figure MM, a 2/3rd chance of correctly rejecting the null hypothesis is satisfactory, and this suggests an achievable sample size of 90 subjects is needed.

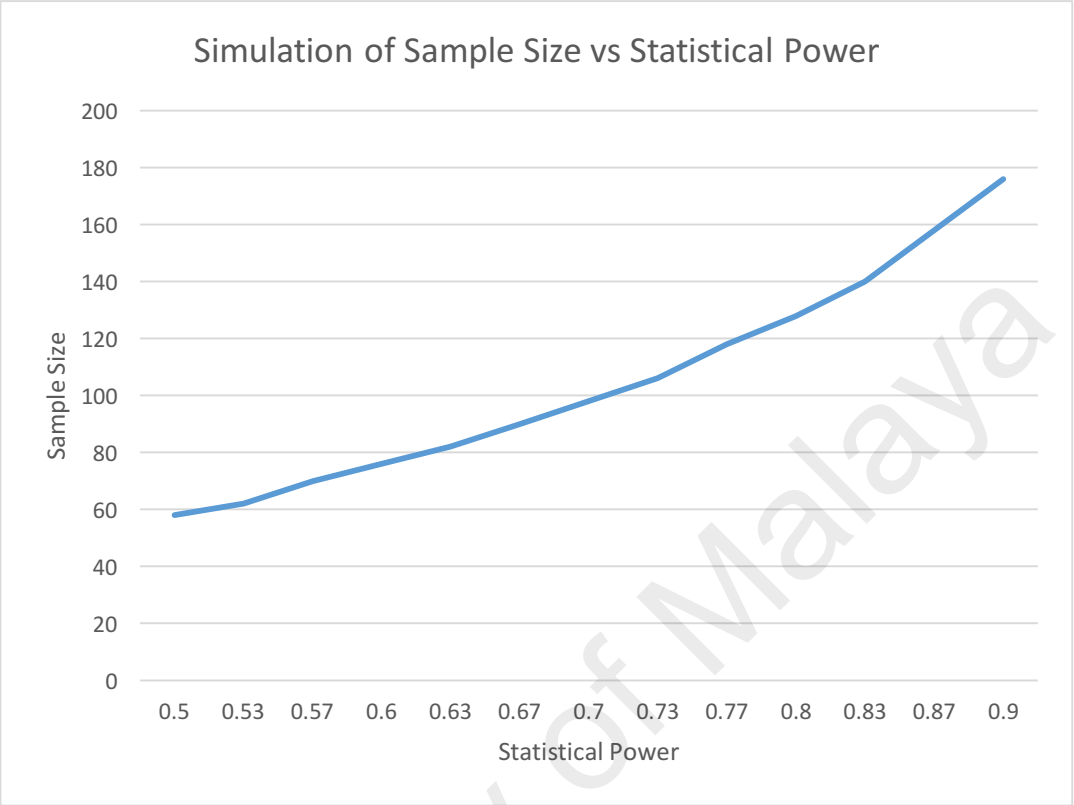


Figure 4.2 Simulation of sample size versus statistical power using G*Power software at effect size 0.8 S.D., type 1 error probability 0.05 and prevalence of 10%

4.11 Study instruments

4.11.1 Patient Demographic Questionnaire

This questionnaire was developed by the researcher to procure information of relevant data on the socio-demographic and clinical data of all the study subjects.

Socio-demographic and personal characteristics:

1. Gender

2. Age

3. Ethnicity

4. Marital status

5. Current employment status

6. Education level

Clinical data

1. Duration of illness (Parkinson's Disease) since diagnosis

2. Functional dependence

4. Medical illnesses (vascular risk factors)

5. History of head injury and other neurological disorders,

6. Family history of Parkinson's Disease

7. Past psychiatric history

8. Substance and alcohol history

9. Medications

4.11.2 Hoehn and Yahr Scale

The Hoehn and Yahr scale is a clinical rating scale which is widely used in Parkinson's Disease patients (Goetz et al., 2004). The scale is used to describe the symptom progression of PD, particularly in the motor function. The scale was originally described in 1967 and includes stages 1 through 5 (Hoehn et al., 1967). It provides an overall estimate of clinical function in PD, combining functional deficits (disability) and objective signs (impairment). The scale has since been modified as "the modified HY scale" that includes 0.5 increments i.e. addition of stages 1.5 and 2.5. The modification on the HY scale is to account for the intermediate course of Parkinson disease. However, even though this scale has been used widely, no clinometric data are available on this

adaptation (Goetz et al., 2004). In this study, the original Hoehn and Yahr scale was applied. The scale is principled on the concept that the severity of overall parkinsonian impairment relates to bilateral motor involvement and compromised balance or gait. Thus the progression of motor impairment is charted as below (Goetz et al., 2004) (Hoehn et al., 1967):

Stage 0	No signs of disease
Stage 1	Symptoms are very mild; unilateral involvement only
Stage 2	Bilateral involvement without impairment of balance
Stage 3	Mild to moderate bilateral disease; some postural instability; physically independent
Stage 4	Severe disability; still able to walk or stand unassisted
Stage 5	Wheelchair bound or bedridden unless aided

Although many studies have used the HY scale as the gold standard to assess validity of other scales, the validity of the HY scale was never formally studied (Goetz et al., 2004). Studies show moderate to significant inter-rater reliability (non-weighted and weighted Kappa scores ranging between 0.44 and 0.71) but no studies are available on the intra-rater reliability. Likewise, no validity and reliability studies of the HY scale have been done in the Malaysian context.

4.11.3 Independent variable

Neuropsychiatry Inventory (NPI) (Cummings, 1997; Cummings et al., 1994)

The Neuropsychiatric Inventory (NPI) is an instrument used to assess 10 behavioural disturbances occurring in dementia patients; delusions, hallucinations, dysphoria/depression, anxiety, agitation/aggression, elation/euphoria, disinhibition, irritability/lability, apathy/indifference and aberrant motor activity. Two neuro-vegetative areas are also included in the NPI: Sleep and Night-time Behavior Disorders, Appetite and Eating Disorders. Both frequency and severity of each behavior are recorded using this tool. It is a valid tool with high inter-rater and test-retest reliability. The NPI can obtain information on the presence of psychopathology in patients with brain disorders. The NPI was developed for application to patients with Alzheimer's disease and other dementias, but it may be useful in the assessment of behavioral changes in other conditions. NPI has been widely used in clinical research in Parkinson's disease (Guo et al., 2015; Oh et al., 2015; Pérez-Pérez et al., 2015).

The administration of NPI is based on responses from an informed caregiver, preferably one living with the patient. The informant or caregiver would be asked in the presence or absence of each NPS with an initial screening question followed by a series of yes or no questions. Each NPS which were present was scored by assigning a "1" and a "0" for its absence. The symptoms were then rated on level of severity; 1 = mild, 2 =moderate, 3 = severe(range: 0–4). The total intensity score for each symptom domain is the product of the frequency score multiplied by the severity score (range: 0–12 for each NPS). The highest possible score (frequency X severity) of any domain is 12. Finally, the NPI total score is obtained by adding all the intensity total scoresof the 12 domains (range: 0–144). A measure of the level of caregiver distress is also given in the NPI, but is not

included in the NPI total score. NPI is available without charge for all non-commercial research and clinical purposes(Connor et al., 2008; Cummings et al., 1994).

In the original report, the NPI scale demonstrated good content validity, concurrent validity, inter-rater reliability (93.6% to 100% for different behaviors) and 3 week test-retest reliability (correlation = 0.79 for frequency and 0.86 for severity ratings) (Cummings, 1997).

In Malaysia, the Malay Translated Version of NPI (MvNPI) is a valid and reliable tool for assessing Behavioural and Psychological Symptoms of Dementia (BPSD) among Malay speaking populations of Malaysia (Rosdinom et al., 2014). Content validity indicated mild and inverse relationship between MMSE scores and severity, and distress score (-0.281 and -0.268, respectively, with $p<0.001$). Discriminant validity calculated using Mann-Whitney U test was found to be significant ($p<0.001$) in differentiating severity of cognitive impairment. The individual items and total scale score of MvNPI had high internal consistency, with Corrected Item-Total Correlation ranging from satisfactory to good (0.41 to 0.77). The Cronbach's alpha for all the NPI domains showed high internal consistency (0.83), and subtotal for severity and distress scores were perfect (0.998 to 1.00). There was no significant difference between test-retest mean scores ($p>0.05$) and their correlations were perfect (0.996 to 1.00).

4.11.4 Dependent variable

Neuropsychiatry Cognitive Assessment Tool (NUCOG) (Walterfang et al., 2006)

The NUCOG is a 21-item cognitive screening tool which combines a broad range of the main cognitive domains. The fivecognitive domains or subscales are; Attention, Visuo-constructional, Memory, Executive and Language function. The NUCOG can be

administered in approximately 20 minutes or less by trained clinicians. However, administration of the NUCOG may take longer time for example in elderly individuals who have dementia. The total score of NUCOG for a subject is 100, and for each of the five cognitive domains, the total score is 20.

In the original report, the NUCOG tool is a valid and reliable cognitive tool that is also sensitive and specific for the detection of dementia. Patients who score less than 80/100 is highly predictive of having a dementing illness, although not all scores of less than 80/100 are indicative of dementia (sensitivity of 0.84 and specificity 0.86). The NUCOG can differentiate dementia and psychiatric subgroups. Therefore, NUCOG provides a comprehensive, multidimensional profile of an individual's cognitive status. It is also well-tolerated, reliable and highly useful clinical tool (Walterfang et al., 2006). Permission from the authors was required to use the NUCOG tool and was obtained from the authors Mark Walterfang and Dennis Velakoulis.

In Malaysia, the Malay NuCOG tool is a valid and reliable cognitive instrument that is sensitive and specific for the detection of dementia (Thong et al., 2016). It demonstrated good internal consistency and reliability (Cronbach's alpha = 0.895). The Malay NuCOG also has 100% sensitivity and 87.5% specificity at the cutoff score of 78.50/100. Permission to use the Malay NUCOG was also obtained from the authors Ng Chong Guan and Chee Kok Yoon.

4.12 Statistical Analysis

The Statistical Package for Social Sciences (SPSS), version 22 was used for data analysis in this study. The significance level was set at $p<0.05$. The prevalence of NPS, Hoehn Yahr stage and sociodemographic characteristics were analyzed using descriptive

statistics. Univariate analysis was conducted on the NPI and NUCOG scores against socio-demographic and clinical factors. The study cohort was separated into two groups according to each socio-demographic and clinical factor. Since we did not assume that scores were normally distributed, the Mann-Whitney test was performed to assess for any significant difference in scores between the 2 groups. The same test was used to assess significant differences in NUCOG scores between subjects with or without any NPS and subsequently, for each NPS separately. The Chi-Square test was performed to analyze if any NPS score significantly changes the subject's odds of scoring less than 80, which is the NUCOG threshold indicative of dementia. Linear regression was done to compare the relative importance of the selected significant NPS with NUCOG scores before and after correction of any bias from the socio-demographic and clinical factors.

4.13 Ethical consideration

This study was approved by the University Malaya Ethics Committee (MECID.NO: 20158-1531). Approval from the Malaysia Research Ethic Committee, Ministry of Health, Malaysia was obtained (Reference Number: NMRR-15-1050-25616). The written informed consent was obtained from all the patients or caregivers. Confidentiality was also ensured by utilizing a coding system to identify subjects. Subjects were not given access to the data of the study but they had the right to know about their respective results. The results of the study published will have no reference to any specific individual.

CHAPTER 5: RESULTS

5.1 Socio-demographic Data

A total of 94 subjects who fulfilled the inclusion criteria were recruited for this study. Most of the subjects recruited were from the Parkinson's Disease Clinic in HKL (n=58, 61.7%), followed by the Neuropsychiatric Clinic in HKL (n=24 subjects, 25.5%) and the rest were from the UMMC Neurology Clinic (n=12, 12.8%). Data from these 94 subjects were analyzed.

The mean age was 64.89 years old (SD= 9.34). The majority of the subjects were of the male gender (68.1%) and the remaining 31.9% were female. The subjects grouped by ethnicity had the following distribution; Malay at 38.3%, Chinese at 37.2%, Indians at 23.4% and 1.1% from other ethnicities. The majority of the subjects were married (80.9%), 10.6% were widowed, 5.3 % were divorced and 3.2 % were single. Most subjects were retired individuals (92.6%). Most subjects received up to secondary education, between 6 to 11 years (56.4%), 23.4 % received tertiary education and the rest received a primary education (20.2%). Table 5.1 summarizes the socio-demographic factors of the study subjects.

Table 5.1: Socio-demographic factors of the study subjects

Sociodemographic factors		**N (%)**	**Mean (SD)**
Age	Total of subjects	94	64.89 (9.34)
	<50 years old	2 (2.2%)	41.5 (9.19)
	≥50 years old	92 (97.8%)	65.40 (8.71)
Gender	Male	64 (68.1%)	
	Female	30 (31.9%)	
Ethnicity	Malay	36 (38.3%)	
	Chinese	35 (37.2%)	
	Indian	22 (23.4%)	
	Others	1 (1.1%)	
Marital Status	Single	3 (3.2%)	
	Married	76 (80.9%)	
	Widow/widower	10 (10.6%)	
	Divorced	5 (5.3%)	
Occupation	Retired	87 (92.6%)	
	Part-time	5 (5.3%)	
	Home-maker	1 (1.1%)	
	Full-time	1 (1.1%)	
Education level	< 6 years	19 (20.2%)	
	6 to 11 years	53 (56.4%)	
	> 11 years	22 (23.4%)	

5.2 Clinical characteristics

Table 5.2 describes the clinical characteristics of the study subjects. The mean duration of illness (Parkinson's disease) since diagnosis was 9.70 years (SD: 5.89). Regarding functional dependence, 31.9% of them were fully independent, and the rest required various forms of assistance ranging from some activities to 24-hour care. A slight majority of subjects, 51.1 % have either Diabetes Mellitus Type 2, Hypertension, Dyslipidaemia, Ischemic Heart Disease or combinations of these. However, a minority of the subjects (16%) have a family history of Parkinson's disease. There were no subjects who had any past psychiatric history. Prior to PD diagnosis, only two subjects complained of depressive symptoms and one subject complained of anxiety symptoms but all 3 subjects were not clinically diagnosed to have a psychiatric disorder.

All of the subjects (n=94, 100%) were on 1 or more type of anti-parkinson medication (s). 95.7% were prescribed Levodopa or Levodopa-based medications, 54.3% were treated with Direct Dopamine agonist (non –ergot), 27.7 % Anticholinergics, 22.3% with MAO-B Inhibitor (Selegiline) and 20.2 %, Amantadine. 64.9% of subjects were receiving psychiatric medications: anti-dementia 30.9%, Benzodiazepines 42.6%, Antipsychotics 20.2 %, Antidepressant 11.7% and mood stabilizer 1.1 %.

The Hoehn and Yahr score reflects the severity of motor impairment, and this is used in the staging of the PD. The mean Hoehn and Yahr was 2.5 (SD: 0.94). 87.3% had mild to moderate PD (Stage 1: 14.9 %; Stage 2:33 %; Stage 3: 39.4%), and 12.7 % had advanced staged PD (Stage 4: 10.6%; Stage 5: 2.1%).

Table 5.2: Clinical characteristics of the study subjects

Clinical Variables		N(%)	Mean (SD)
Duration of Illness	<5years	20 (21.3%)	9.70 (5.89)
	5-10 years	39 (41.5%)	
	11-15 years	19 (20.2%)	
	16-20 years	12 (12.7%)	
	>20 years	4 (4.3%)	
Functional Dependence	Independent	30 (31.9%)	
	Required assistance with some activities	49 (52.1%)	
	Required assistance with most activities	10 (10.6%)	
	Requires 24 hour care	5 (5.3%)	
Medical illness	Yes	48 (51.1%)	
	No	46 (48.9%)	
Family history of PD	Yes	15 (16%)	
	No	79 (84%)	
Anti-PD Medications	Levodopa	90 (95.7%)	
	1 type	65 (69.1%)	
	2 types	20 (21.3%)	
	3 types	5 (5.3%)	
	Anti-parkinsonian agents		
	1 type	26 (27.7%)	
	2 types	23 (24.5%)	
	3 types	24 (25.5%)	
	4 types	15 (16.0%)	
	5 types	3 (3.2%)	
	6 types	3 (3.2%)	

Table 5.2, continued

Clinical Variables		N(%)	Mean (SD)
Anti-PD Medications	Direct Dopamine Agonists (DDA)	51 (54.3%)	
	MAO-B Inhibitor	21 (22.3%)	
	Anticholinergic	26 (27.7%)	
	Amantadine	19 (20.2%)	
	Deep Brain Stimulation	2 (2.1%)	
Psychiatric medications	Any	61 (64.9%)	
	Antipsychotic	19 (20.2%)	
	Benzodiazepines	40 (42.6%)	
	Antidepressant	11 (11.7%)	
	Antidementia	29 (30.9%)	
	Mood stabilizer	1 (1.1%)	
Past psychiatric history	No	94 (100%)	
Hoehn and Yahr	Stage 1	14 (14.9%)	2.5 (0.94)
	Stage 2	31 (33.0%)	
	Stage 3	37 (39.4%)	
	Stage 4	10 (10.6%)	
	Stage 5	2 (2.1%)	

5.3 Total Mean and Domain Scores of Neuropsychiatric Inventory (NPI)

Table 5.3 displays the total mean scores for the NPI and the individual NPI domain score for all subjects. The mean NPI score was 6.44 (SD=7.95). Among the highest

domain scores which indicate greater frequency and severity of symptoms were measured for the domains of sleep disturbances, depression/dysphoria, hallucination and apathy.

Table 5.3: Total Mean and Domains Score of NPI

Psychometric Scale	Mean (SD)	Median	Range	
			Lowest	Highest
Total Mean NPI Score	6.44 (7.95)	4.0	0	39
Delusion	0.21 (0.96)	0.0	0.0	8.0
Hallucination	0.73 (1.49)	0.0	0.0	6.0
Agitation and aggression	0.49 (1.09)	0.0	0.0	6.0
Depression/ dysphoria	1.22 (2.06)	0.0	0.0	12.0
Anxiety	0.62 (1.44)	0.0	0.0	8.0
Euphoria	0.01 (0.10)	0.0	0.0	1.0
Apathy	0.69 (1.87)	0.0	0.0	12.0
Disinhibition	0.03 (0.18)	0.0	0.0	1.0
Irritability and lability	0.41 (1.06)	0.0	0.0	6.0
Aberrant motor behavior	0.13 (0.68)	0.0	0.0	6.0
Sleep disturbances	1.54 (2.43)	0.0	0.0	12.0
Appetite change	0.34 (1.01)	0.0	0.0	6.0

5.4 Prevalence of Neuropsychiatric Symptoms (NPS)

Table 5.4 shows the Prevalence of Neuropsychiatric Symptoms in PD patients using the using the Neuropsychiatric Inventory (NPI) and its relation to the PD stage (based on Hoehn and Yahr). Our findings show that 81.9% (N=77) of our subjects report 1 or more NPS on the NPI. There were 17 (18.1%) subjects who reported not having any NPS. The most prevalent NPS reported were; depression (45.7%), sleep and night-time behavior disorder (44.7%) followed by hallucination (27.7%) and anxiety (27.7%). The lowest common symptoms were disinhibition (3.2%) and elation/euphoria (1.1%). Table 5.4.a shows the mean total NPI score and the prevalence if only clinically significant NPI symptoms are considered, that is if individual domain scores are equal or greater than 4.0. The prevalence of at least one clinically significant NPI is 40.4% in the study cohort.

5.4.1 Intensity of Neuropsychiatric symptoms in relation to Stages of Parkinson's Disease

Table 5.4.1 shows the intensity (frequency x severity) NPS scores in relation to Stages of PD (based on Hoehn and Yahr Score). Table 5.4.1 shows that the NPI scores (intensity) for advanced PD was significantly greater than the mild to moderate PD cohort. Advanced PD patients suffered from a greater number, frequency and severity of NPS. Although the cumulative burden of NPS is significantly worse in advanced PD, only hallucination and sleep disturbances scores were significantly higher in advanced PD patients compared to patients with mild to moderate PD. Elation/euphoria could not be analyzed because there was only 1 sample.

Table 5.4: Prevalence of NPS in mild/ moderate and advanced Parkinson's Disease

Neuropsychiatric symptoms		Total Prevalence N(%)	Mild & moderate PD (Stage 1 – 3)	Advanced PD (Stage 4-5)
			Prevalence N	Prevalence N
Total NPI	Yes	77(81.9)	66	11
	No	17(18.1)	16	1
Delusion	Yes	9 (9.6)	7	2
	No	85(90.4)	75	10
Hallucination	Yes	26(27.7)	20	6
	No	68(72.3)	62	6
Agitation / Aggression	Yes	22(23.4)	17	5
	No	72(76.6)	65	7
Depression / Dysphoria	Yes	43(45.7)	38	5
	No	51(54.3)	44	7
Anxiety	Yes	26(27.7)	21	5
	No	68(72.3)	61	7
Elation / Euphoria	Yes	1(1.1)	0	1
	No	93(98.9)	82	11
Apathy / Indifference	Yes	20(21.3)	16	4
	No	74(78.7)	66	8
Disinhibition	Yes	3(3.2)	2	1
	No	91(96.8)	80	11
Irritability	Yes	17(18.1)	15	2
	No	77(81.9)	67	10
Aberrant Motor Behavior	Yes	6(6.4)	5	1
	No	88(93.6)	77	11
Sleep and NBS	Yes	42(44.7)	33	9
	No	52(55.3)	49	3
Appetite / Eating	Yes	16(17.0)	13	3
	No	78(83.0)	69	9

Table 5.4a: Prevalence of NPS by clinically significant severity thresholds (NPI domain score ≥ 4.0 only)

Neuropsychiatric symptoms		Total Prevalence N(%)	Mean NPI Score
Total NPI	Yes	38 (40.4)	6.3
	No	56 (59.6)	1.0
Delusion	Yes	2 (2.1)	6.0
	No	92 (97.9)	0.1
Hallucination	Yes	9 (9.6)	4.7
	No	85 (90.4)	0.3
Agitation / Aggression	Yes	4 (4.3)	4.5
	No	90 (95.7)	0.3
Depression / Dysphoria	Yes	16 (17.0)	5.1
	No	78 (83.0)	0.4
Anxiety	Yes	7 (7.4)	5.1
	No	87 (92.6)	0.3
Elation / Euphoria	Yes	0 (0)	0.0
	No	94 (100.0)	0.0
Apathy / Indifference	Yes	7 (7.4)	6.6
	No	87 (92.6)	0.2
Disinhibition	Yes	0 (0.0)	0.0
	No	94(100.0)	0.0
Irritability	Yes	4 (4.3)	4.5
	No	90 (95.7)	0.2
Aberrant Motor Behavior	Yes	1 (1.1)	6.0
	No	93 (98.9)	0.1
Sleep and NBS	Yes	22 (23.4)	5.4
	No	72 (76.6)	0.4
Appetite / Eating	Yes	2 (2.1)	6.0
	No	92 (97.8)	0.2

Table 5.4.1: Intensity of Neuropsychiatric Symptoms in relation to mild/moderate and advanced Parkinson's Disease

	Mild & moderate PD (Hoehn Yahr Stage 1–3)		**Advanced PD (Hoehn Yahr Stage 4 – 5)**		
Neuropsychiatric symptoms	**Mean**	**SD**	**Mean**	**SD**	**p-value**
Total NPI	5.66	7.48	11.75	0.24	0.006*
Delusion	0.18	0.93	0.42	1.16	0.357
Hallucination	0.61	1.40	1.58	1.83	0.038*
Agitation / Aggression	0.39	0.89	1.17	1.95	0.090
Depression / Dysphoria	1.24	2.13	1.08	1.56	0.926
Anxiety	0.49	1.28	1.50	2.11	0.097
Elation / Euphoria	-	-	0.08	0.29	-
Apathy / Indifference	0.51	1.37	1.92	3.73	0.199
Disinhibition	0.02	0.16	0.08	0.29	0.281
Irritability	0.43	1.10	0.33	0.78	0.906
Aberrant Motor Behavior	0.13	0.72	0.08	0.29	0.789
Sleep	1.30	2.31	3.17	2.72	0.007*
Appetite / Eating	0.34	1.06	0.33	0.65	0.478

5.5. Association between Socio-demographic and Clinical Factors with Neuropsychiatric Symptoms

Table 5.5a shows the univariate analysis of NPI scores demonstrating the association between socio-demographic factors and neuropsychiatric symptoms (NPS) whereas Table 5.5b shows the univariate analysis of NPI scores demonstrating the association between clinical factors and neuropsychiatric symptoms.

Assessing by socio-demographic factors, females have anxiety scores significantly compared to males (Mean 1.4 vs. 0.3). There was no association between depression with any of the socio-demographic factors. Malays scored significantly lower in anxiety compared to the non-Malays (Mean: 0.1 vs. 0.9). Higher irritability scores were seen in those educated 11 years and below (Primary and Secondary Education) as compared to those who received a tertiary education (Mean: 0.5 vs. 0.0). However, the reverse is seen in aberrant motor behavior whereby those with tertiary education had higher scores than those who had Primary or Secondary education (Mean: 0.5 vs. 0.0).

Referring to Table 5.5b, subjects in the following categories had significantly greater NPI scores: advanced PD, subjects requiring assistance in their functioning and subjects on Benzodiazepines.

Subjects who required any assistance for their functioning scored significantly higher in; delusions, hallucinations, irritability, agitation, sleep disturbances and appetite. Subjects with advanced PD scored significantly higher in hallucinations, elation/euphoria and sleep disturbances. Subjects with longer duration of PD illness (≥ 11 years) scored significantly higher in disinhibition and aberrant motor behavior. Those who had a medical illness and no family history of PD had higher scores in irritability significantly.

Of specific note, depression scores were not significantly associated with any clinical factors, especially: duration of illness, functional dependence and stage of PD.

Subjects on Benzodiazepines were noted to have significantly higher scores in depression, aberrant motor behavior and sleep disturbances. Subjects with antipsychotics and anti-dementia medications had significantly higher hallucination scores. Also, subjects with antipsychotics had significantly higher agitation scores. On the other hand, subjects on anti-dementia had lower depression scores.

Table 5.5a Univariate analysis of NPI scores demonstrating the association between socio-demographic factors and neuropsychiatric symptoms

Total NPI

Socio-demographic factors		**Mean**	**SD**	**p value**
Gender	Male	5.4	7.0	0.112
	Female	8.6	9.5	
Ethnicity	Malay	7.0	8.3	0.693
	Others	6.1	7.8	
Marital Status	Married	6.4	8.0	0.178
	Others	8.7	4.7	
Education	>11 years	4.0	4.1	0.207
	≤ 11years	7.2	8.7	

Table 5.5a, continued

Delusions

Socio-demographic factors		Mean	SD	p value
Gender	Male	0.1	0.3	0.336
	Female	0.5	1.6	
Ethnicity	Malay	0.1	0.3	0.698
	Others	0.3	1.2	
Marital Status	Married	0.2	1.0	0.792
	Others	0.0	0.0	
Education	>11 years	0.0	0.0	0.083
	≤ 11years	0.3	1.1	

Hallucination

Socio-demographic factors		Mean	SD	p value
Gender	Male	0.6	1.3	0.318
	Female	1.0	1.8	
Ethnicity	Malay	0.8	1.6	0.763
	Others	0.7	1.4	
Marital Status	Married	0.7	1.4	0.224
	Others	2.3	3.2	
Education	>11 years	0.4	1.3	0.106
	≤ 11years	0.8	1.5	

Table 5.5a, continued

Agitation

Socio-demographic factors		Mean	SD	p value
Gender	Male	0.5	1.1	0.453
	Female	0.5	1.2	
Ethnicity	Malay	0.5	1.2	0.916
	Others	0.5	1.0	
Marital Status	Married	0.5	1.1	0.497
	Others	0.0	0.0	
Education	>11 years	0.2	0.6	0.083
	≤ 11years	0.6	1.2	

Depression

Socio-demographic factors		Mean	SD	p value
Gender	Male	1.2	2.2	0.293
	Female	1.4	1.8	
Ethnicity	Malay	1.6	2.6	0.222
	Others	1.0	1.6	
Marital Status	Married	1.2	2.1	0.096
	Others	2.3	1.5	
Education	>11 years	0.7	1.2	0.255
	≤ 11years	1.4	2.2	

Table 5.5a, continued

Anxiety

Socio-demographic factors		Mean	SD	p value
Gender	Male	0.3	0.7	0.002*
	Female	1.4	2.2	
Ethnicity	Malay	0.1	0.3	0.003*
	Others	0.9	1.7	
Marital Status	Married	0.6	1.5	0.952
	Others	0.3	0.6	
Education	>11 years	0.3	0.9	0.232
	≤ 11years	0.7	1.6	

Elation

Socio-demographic factors		Mean	SD	p value
Gender	Male	1.0	0.0	0.144
	Female	0.0	0.2	
Ethnicity	Malay	0.0	0.0	0.431
	Others	0.0	0.0	
Marital Status	Married	0.0	0.1	0.984
	Others	0.0	0.0	
Education	>11 years	0.0	0.0	0.580
	≤ 11years	0.0	0.1	

Table 5.5a, continued

Apathy

Socio-demographic factors		Mean	SD	p value
Gender	Male	0.7	2.0	0.186
	Female	0.8	1.6	
Ethnicity	Malay	0.7	1.7	0.636
	Others	0.7	2.0	
Marital Status	Married	0.7	1.9	0.178
	Others	1.3	1.2	
Education	>11 years	0.5	1.3	0.631
	≤ 11years	0.8	2.0	

Disinhibition

Socio-demographic factors		Mean	SD	p value
Gender	Male	0.0	0.1	0.192
	Female	0.1	0.3	
Ethnicity	Malay	0.1	0.2	0.307
	Others	0.0	0.1	
Marital Status	Married	0.0	0.2	0.936
	Others	0.0	0.0	
Education	>11 years	0.1	0.3	0.074
	≤ 11years	0.0	0.1	

Table 5.5a, continued

Irritability

Socio-demographic factors		Mean	SD	p value
Gender	Male	0.4	1.0	0.781
	Female	0.4	1.2	
Ethnicity	Malay	0.5	1.2	0.785
	Others	0.4	1.0	
Marital Status	Married	0.4	1.1	0.610
	Others	0.0	0.0	
Education	>11 years	0.0	0.0	0.013*
	≤ 11years	0.5	1.2	

Aberrant Motor Behavior

Socio-demographic factors		Mean	SD	p value
Gender	Male	0.1	0.3	0.916
	Female	0.2	1.1	
Ethnicity	Malay	0.3	1.1	0.132
	Others	0.0	0.2	
Marital Status	Married	0.1	0.7	0.855
	Others	0.0	0.0	
Education	>11 years	0.5	1.3	0.009*
	≤ 11years	0.0	0.2	

Table 5.5a, continued

Sleep

Socio-demographic factors		Mean	SD	p value
Gender	Male	1.5	2.5	0.266
	Female	1.7	2.4	
Ethnicity	Malay	2.0	2.9	0.273
	Others	1.3	2.0	
Marital Status	Married	1.5	2.4	0.484
	Others	2.3	2.1	
Education	>11 years	1.0	1.7	0.510
	≤ 11years	1.7	2.6	

Appetite

Socio-demographic factors		Mean	SD	p value
Gender	Male	0.2	0.5	0.527
	Female	0.6	1.6	
Ethnicity	Malay	0.4	1.2	0.708
	Others	0.3	0.9	
Marital Status	Married	0.4	1.0	0.624
	Others	0.0	0.0	
Education	>11 years	0.3	1.3	0.096
	≤ 11years	0.4	0.9	

Table 5.5b Association between clinical factors and NPI scores

Total NPI

Clinical factors		Mean	SD	p value
Duration of illness	<11years	6.3	8.5	0.173
	≥11years	6.7	7.0	
Medical illness	Yes	6.2	7.8	0.991
	No	6.7	8.2	
Family history of PD	Yes	6.7	5.9	0.493
	No	6.4	8.3	
Hoehn & Yahr	Mild	5.7	7.5	0.006*
	Advanced	11.8	9.4	
Functional Dependence	Independent	1.8	1.9	0.000*
	Assisted	8.6	8.8	
Psychiatric Medications	Antipsychotics	8.5	8.9	0.065
	None	5.9	7.7	
	Benzodiazepines	8.3	7.8	0.001*
	None	5.1	7.9	
	Antidepressants	9.9	14.4	0.920
	None	6.0	6.7	
	Antidementia	6.6	8.1	0.847
	None	6.4	7.9	

Table 5.5b, continued

Delusions

Clinical factors		Mean	SD	p value
Duration of illness	<11years	0.3	1.1	0.342
	≥11years	0.1	0.7	
Medical illness	Yes	0.2	0.7	0.101
	No	0.2	1.2	
Family history of PD	Yes	0.1	0.5	0.708
	No	0.2	1.0	
Hoehn & Yahr	Mild	0.2	0.9	0.357
	Advanced	0.4	1.2	
Functional Dependence	Independent	0.0	0.0	0.032*
	Assisted	0.3	1.2	
Psychiatric Medications	Antipsychotics	0.6	1.9	0.052
	None	0.1	0.5	
	Benzodiazepines	0.3	1.3	0.569
	None	0.2	0.6	
	Antidepressants	0.0	0.0	0.254
	None	0.2	1.0	
	Antidementia	0.4	1.5	0.330
	None	0.1	0.5	

Table 5.5b, continued

Hallucination

Clinical factors		Mean	SD	p value
Duration of illness	<11years	0.7	1.5	0.345
	≥11years	0.8	1.5	
Medical illness	Yes	0.8	1.7	0.969
	No	0.7	1.3	
Family history of PD	Yes	1.1	2.2	0.890
	No	0.7	1.3	
Hoehn & Yahr	Mild	0.6	1.4	0.038*
	Advanced	1.6	1.8	
Functional Dependence	Independent	0.1	0.5	0.002*
	Assisted	1.0	1.7	
Psychiatric Medications	Antipsychotics	1.9	2.2	0.000*
	None	0.4	1.1	
	Benzodiazepines	0.9	1.6	0.308
	None	0.6	1.4	
	Antidepressants	0.5	1.8	0.207
	None	0.8	1.5	
	Antidementia	1.2	1.8	0.042*
	None	0.5	1.3	

Table 5.5b, continued

Agitation/ Aggression

Clinical factors		Mean	SD	p value
Duration of illness	<11years	0.4	0.8	0.340
	≥11years	0.7	1.5	
Medical illness	Yes	0.6	1.3	0.596
	No	0.4	0.8	
Family history of PD	Yes	0.4	0.7	0.845
	No	0.5	1.2	
Hoehn & Yahr	Mild	0.4	0.9	0.090
	Advanced	1.2	1.9	
Functional Dependence	Independent	0.1	0.4	0.008*
	Assisted	0.7	1.3	
Psychiatric Medications	Antipsychotics	0.7	0.9	0.012*
	None	0.4	1.1	
	Benzodiazepines	0.6	1.0	0.143
	None	0.4	1.2	
	Antidepressants	0.9	1.3	0.072
	None	0.4	1.1	
	Antidementia	0.5	0.9	0.307
	None	0.5	1.2	

Table 5.5b, continued

Depression

Clinical factors		Mean	SD	p value
Duration of illness	<11years	1.2	2.2	0.582
	≥11years	1.2	1.9	
Medical illness	Yes	1.1	1.7	0.848
	No	1.3	2.4	
Family history of PD	Yes	0.7	1.4	0.261
	No	1.3	2.2	
Hoehn & Yahr	Mild	1.2	2.1	0.926
	Advanced	1.1	1.6	
Functional Dependence	Independent	0.8	1.4	0.066
	Assisted	1.4	2.3	
Psychiatric Medications	Antipsychotics	1.0	1.8	0.466
	None	1.3	2.1	
	Benzodiazepines	1.8	2.6	0.011*
	None	0.8	1.4	
	Antidepressants	3.2	4.1	0.066
	None	1.0	1.5	
	Antidementia	0.6	1.4	0.020*
	None	1.5	2.3	

Table 5.5b, continued

Anxiety

Clinical factors		Mean	SD	p value
Duration of illness	<11years	0.8	1.7	0.336
	≥11years	0.3	0.8	
Medical illness	Yes	0.8	1.7	0.397
	No	0.5	1.1	
Family history of PD	Yes	0.2	0.6	0.182
	No	0.7	1.5	
Hoehn & Yahr	Mild	0.5	1.3	0.097
	Advanced	1.5	2.1	
Functional Dependence	Independent	0.2	0.4	0.154
	Assisted	0.8	1.7	
Psychiatric Medications	Antipsychotics	1.1	2.2	0.491
	None	0.5	1.2	
	Benzodiazepines	0.9	1.6	0.056
	None	0.4	1.3	
	Antidepressants	1.1	2.3	0.206
	None	0.6	1.3	
	Antidementia	0.7	1.9	0.450
	None	0.6	1.2	

Table 5.5b, continued

Elation/ Euphoria

Clinical factors		Mean	SD	p value
Duration of illness	<11years	0.0	0.0	0.194
	≥11years	0.0	0.2	
Medical illness	Yes	0.0	0.1	0.328
	No	0.0	0.0	
Family history of PD	Yes	0.0	0.0	0.663
	No	0.0	0.1	
Hoehn & Yahr	Mild	0.0	0.0	0.009*
	Advanced	0.1	0.3	
Functional Dependence	Independent	0.0	0.0	0.494
	Assisted	0.0	0.1	
Psychiatric Medications	Antipsychotics	0.0	0.0	0.615
	None	0.0	0.1	
	Benzodiazepines	0.0	0.0	0.389
	None	0.0	0.1	
	Antidepressants	0.0	0.0	0.716
	None	0.0	0.1	
	Antidementia	0.0	0.0	0.504
	None	0.0	0.1	

Table 5.5b, continued

Apathy

Clinical factors		Mean	SD	p value
Duration of illness	<11years	0.9	2.3	0.152
	≥11years	0.3	0.8	
Medical illness	Yes	0.5	1.4	0.119
	No	0.9	2.3	
Family history of PD	Yes	1.3	3.4	0.919
	No	0.6	1.4	
Hoehn & Yahr	Mild	0.5	1.4	0.199
	Advanced	2.0	3.7	
Functional Dependence	Independent	0.1	0.4	0.051
	Assisted	1.0	2.2	
Psychiatric Medications	Antipsychotics	0.5	1.1	0.948
	None	0.7	2.0	
	Benzodiazepines	0.7	1.7	0.881
	None	0.7	2.0	
	Antidepressants	0.7	1.8	0.876
	None	0.7	1.9	
	Antidementia	0.7	2.3	0.740
	None	0.7	1.7	

Table 5.5b, continued

Disinhibition

Clinical factors		Mean	SD	p value
Duration of illness	<11years	0.0	0.0	0.023*
	≥11years	0.1	0.3	
Medical illness	Yes	0.0	0.1	0.535
	No	0.0	0.2	
Family history of PD	Yes	0.1	0.3	0.406
	No	0.0	0.2	
Hoehn & Yahr	Mild	0.0	0.2	0.281
	Advanced	0.1	0.3	
Functional Dependence	Independent	0.0	0.0	0.231
	Assisted	0.0	0.2	
Psychiatric Medications	Antipsychotics	0.0	0.0	0.378
	None	0.0	0.2	
	Benzodiazepines	0.1	0.2	0.393
	None	0.0	0.1	
	Antidepressants	0.0	0.0	0.524
	None	0.0	0.2	
	Antidementia	0.0	0.0	0.242
	None	0.0	0.2	

Table 5.5b, continued

Irritability

Clinical factors		Mean	SD	p value
Duration of illness	<11years	0.4	1.1	0.424
	≥11years	0.4	0.9	
Medical illness	Yes	0.6	1.2	0.032*
	No	0.3	0.9	
Family history of PD	Yes	0.0	0.0	0.050*
	No	0.5	1.1	
Hoehn & Yahr	Mild	0.4	1.1	0.906
	Advanced	0.3	0.8	
Functional Dependence	Independent	0.0	0.0	0.002*
	Assisted	0.6	1.2	
Psychiatric Medications	Antipsychotics	0.5	1.5	0.872
	None	0.4	0.9	
	Benzodiazepines	0.3	0.8	0.210
	None	0.5	1.2	
	Antidepressants	0.9	2.1	0.799
	None	0.3	0.8	
	Antidementia	0.5	1.4	0.976
	None	0.4	0.9	

Table 5.5b, continued

Aberrant Motor Behavior

Clinical factors		Mean	SD	p value
Duration of illness	<11years	0.0	0.1	0.016*
	≥11years	0.3	1.1	
Medical illness	Yes	0.1	0.2	0.915
	No	0.2	0.9	
Family history of PD	Yes	0.4	1.5	0.913
	No	0.1	0.3	
Hoehn & Yahr	Mild	0.1	0.7	0.789
	Advanced	0.1	0.3	
Functional Dependence	Independent	0.0	0.0	0.085
	Assisted	0.2	0.8	
Psychiatric Medications	Antipsychotics	0.1	0.2	0.807
	None	0.1	0.7	
	Benzodiazepines	0.3	1.0	0.036*
	None	0.0	0.1	
	Antidepressants	0.0	0.0	0.360
	None	0.1	0.7	
	Antidementia	0.1	0.3	0.923
	None	0.2	0.8	

Table 5.5b, continued

Sleep

Clinical factors		Mean	SD	p value
Duration of illness	<11years	1.3	2.4	0.070
	≥11years	1.9	2.4	
Medical illness	Yes	1.3	2.0	0.588
	No	1.8	2.8	
Family history of PD	Yes	1.9	2.4	0.625
	No	1.5	2.5	
Hoehn & Yahr	Mild	1.3	2.3	0.007*
	Advanced	3.2	2.7	
Functional Dependence	Independent	0.4	0.9	0.007*
	Assisted	2.1	2.7	
Psychiatric Medications	Antipsychotics	1.7	2.4	0.663
	None	1.5	2.5	
	Benzodiazepines	2.3	2.8	0.002*
	None	1.0	2.0	
	Antidepressants	1.7	3.6	0.887
	None	1.5	2.3	
	Antidementia	1.4	2.1	0.975
	None	1.6	2.6	

Table 5.5b, continued

Appetite

Clinical factors		Mean	SD	p value
Duration of illness	<11years	0.3	0.9	0.261
	≥11years	0.5	1.2	
Medical illness	Yes	0.3	0.9	0.826
	No	0.4	1.1	
Family history of PD	Yes	0.5	1.6	0.801
	No	0.3	0.9	
Hoehn & Yahr	Mild	0.3	1.1	0.478
	Advanced	0.3	0.7	
Functional Dependence	Independent	0.0	0.2	0.015*
	Assisted	0.5	1.2	
Psychiatric Medications	Antipsychotics	0.4	1.4	0.433
	None	0.3	0.9	
	Benzodiazepines	0.4	1.1	0.700
	None	0.3	1.0	
	Antidepressants	0.8	1.8	0.285
	None	0.3	0.8	
	Antidementia	0.4	1.2	0.666
	None	0.3	0.9	

5.6 Total Mean and Domains Score NUCOG

Table 5.6 depicts statistics of the total NUCOG scores and the individual domain scores. Our subjects had a mean NUCOG score of 73.7% (SD: 19.34). The highest NUCOG score was 98% and the lowest score was 8%. Figure 5.1 is a plot which compares the NUCOG domain scores of our study cohort against mean, two and three standard deviation scores among healthy control (Walterfang et al., 2006). Our study cohort performed significantly worse in all domains compared with the healthy population. Language and memory were the lowest domain which was more than three SDs below, followed by executive function and visuo-constructional (both below two SDs) and then attention (below 1 SD). As a point of comparison, dementia patients will score less than two standard deviations below the mean in 4 out of 5 domains.

Table 5.6 Total Mean and Domains Score NUCOG

Psychometric Scale	Mean (SD)	Median	Range	
			Lowest	Highest
Total Score	73.74 (19.34)	80	8	98
Attention	14.77 (4.39)	16.0	1.0	20.0
Visuo-constructional	16.54 (3.37)	17.5	5.0	20.0
Memory	12.84 (4.78)	13.0	0.0	20.0
Executive function	13.13 (5.06)	14.25	0.0	20.0
Language	16.46 (4.08)	18.0	0.0	20.0

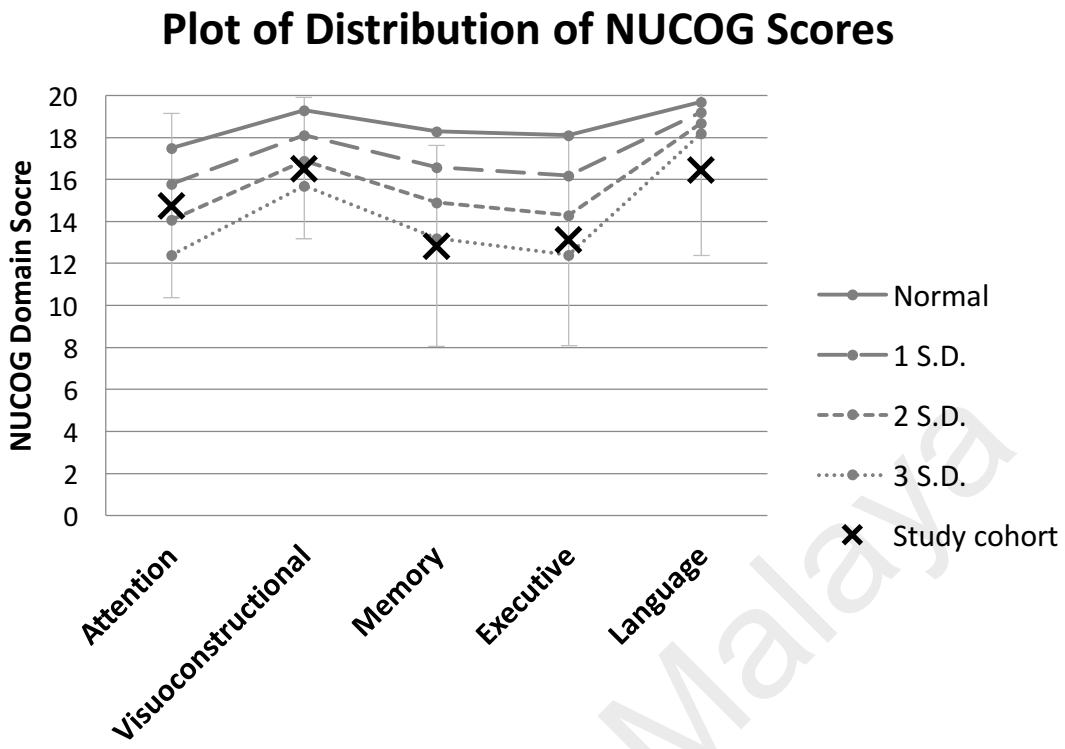


Figure 5.1 Plot of Distribution of NUCOG domain scores

(healthy controls vs. study cohort)

5.7 Univariate analysis of socio-demographic factors for NUCOG score

Table 5.7 summarizes the univariate analysis of NUCOG scores. The Mann-Whitney test was used to assess the association between socio-demographic factors and cognitive performances. For each test the study cohort was sub-divided into 2 groups according to a socio-demographic factor.

The analysis showed that education level was the only factor found to be significantly associated with NUCOG score. Subjects with tertiary education (more than 11 years) scored significantly higher in all cognitive domains except for executive function. The mean total score for tertiary educated subjects was 83.82% (SD: 11.9)

Table 5.7 Univariate analysis of social demographic factors for NUCOG score

Socio-demographic Variables		Total NUCOG		Attention		Visuo-constr'l	
		Mean(SD)	p value	Mean(SD)	p value	Mean(SD)	p value
Gender	Male	74.4 (20.2)	0.293	14.9 (4.6)	0.411	16.7 (3.5)	0.108
	Female	72.4 (17.6)		14.5 (4.0)		16.2 (3.1)	
Ethnicity	Malay	77.4 (16.0)	0.242	14.6 (4.1)	0.695	16.8 (2.8)	0.981
	Others	71.5 (21.0)		14.9 (4.6)		16.4 (3.7)	
Marital Status	Married	73.2 (19.4)	0.067	14.6 (4.4)	0.02*	16.5 (3.4)	0.538
	Others	90.2 (8.9)		19.0 (1.7)		17.7 (2.3)	
Education	>11 years	83.8 (11.9)	0.002*	16.5 (3.5)	0.006*	18.3 (2.0)	0.000*
	≤ 11 years	70.7 (20.1)		14.2 (4.5)		16.0 (3.5)	

Socio-demographic Variables		Memory		Executive		Language	
		Mean (SD)	p value	Mean (SD)	p value	Mean (SD)	p value
Gender	Male	13.1 (4.8)	0.369	13.1 (5.3)	0.779	16.5 (4.1)	0.403
	Female	12.3 (4.7)		13.1 (4.6)		16.3 (4.1)	
Ethnicity	Malay	13.8 (4.5)	0.091	14.3 (4.5)	0.122	17.9 (2.1)	0.008*
	Others	12.2 (4.9)		12.4 (5.3)		15.6 (4.7)	
Marital Status	Married	12.7 (4.8)	0.075	13.0 (5.1)	0.145	16.4 (4.1)	0.200
	Others	17.3 (3.1)		17.2 (2.5)		19.0 (0.0)	
Education	>11 years	15.6 (3.4)	0.001*	14.8 (4.3)	0.103	18.6 (1.5)	0.001*
	≤ 11 years	12.0 (4.8)		12.6 (5.2)		15.8 (4.4)	

*p<0.05,**p<0.01

whereas subjects with fewer years of education (11 years and below) had a mean score of70.7% (SD: 20.1). Malays significantly scored higher in the language domain (17.89 vs. non-Malays: 15.58). The subjects who were single had significantly higher scores in attention (19.00 vs. not-single: 14.63).

5.8 Univariate analysis of clinical factors for NUCOG score

Table 5.8 summarizes the univariate analysis of NUCOG scores to demonstrate the association between clinical factors and cognitive performance. Subjects were also divided into two groups by each clinical factors, and the Mann-Whitney test was used to assess significant differences in NUCOG scores.

The subjects who had mild PD (Hoehn and Yahr's Stage 1 and 2) scored significantly higher on total NUCOG scores (p=0.000) and in all domain scores. Conversely, subjects with advanced PD (Hoehn and Yahr's Stage 4 and 5) scored significantly lower in the NUCOG total and in all domain scores.

Functionally independent subjects also had significantly higher mean total NUCOG scores (p=0.000) and NUCOG domain scores compared with subjects who required any form of assistance (some, moderate assistance or 24-hour care).

Subjects with medical illness (vascular risk factors), scored significantly lower in the NUCOG visuo-constructional domain (p=0.021). However, it is of special note that duration of illness does not affect cognitive scores significantly in all domains of the NUCOG.

Subjects on anti-dementia medications had significantly lower (p= 0.017) mean total NUCOG scores, memory (p=0.002) and executive functions (p=0.010) compared to subjects who were not prescribed this medication. Similarly, subjects on antipsychotics

also had significantly lower performance in memory domain (p=0.021). On the other hand, subjects who were prescribed antidepressants have significantly higher visuo-constructional function (p=0.034, 18.09 vs 16.34)

Table 5.8 Univariate analysis of clinical factors for NUCOG score

Clinical Factors		Total NUCOG		Attention		Visuo-constructional	
		Mean (SD)	p value	Mean (SD)	p value	Mean (SD)	p value
Duration of illness	<11years	74.2 (19.2)	0.870	14.8 (4.4)	0.746	16.5 (3.4)	0.946
	≥11years	73.0 (19.9)		14.7 (4.5)		16.6 (3.4)	
Medical illness	Yes	70.3 (20.9)	0.072	14.1 (4.7)	0.208	15.9 (3.7)	0.029*
	No	77.4 (17.0)		15.4 (4.0)		17.2 (3.0)	
Family history of PD	Yes	72.6 (28.2)	0.427	14.4 (5.8)	0.577	16.2 (4.7)	0.696
	No	73.9 (17.4)		14.8 (4.1)		16.6 (3.1)	
Hoehn & Yahr	Mild	77.3 (15.8)	0.000*	15.5 (3.6)	0.002*	17.1 (2.7)	0.000*
	Adv	49.2 (23.9)		10.1 (6.3)		12.5 (4.7)	
Functional Dependence	Indep	82.7 (14.1)	0.000*	16.1 (3.8)	0.013*	18.4 (1.8)	0.000*
	Assisted	69.5 (20.1)		14.1 (4.5)		15.7 (3.6)	
Psychiatric Medications	Antipsy	66.2 (24.9)	0.125	14.1 (5.7)	0.683	15.4 (4.5)	0.289
	None	75.6 (17.4)		14.9 (4.0)		16.8 (3.0)	
	BDZ	71.9 (17.6)	0.069	14.6 (4.3)	0.522	16.2 (3.4)	0.147
	None	75.1 (20.6)		14.9 (4.5)		16.8 (3.4)	
	Antidep	81.1 (11.3)	0.239	16.1 (2.7)	0.473	18.1 (1.8)	0.034*
	None	72.8 (20.0)		14.6 (4.5)		16.3 (3.5)	
	Antidem	66.3 (22.4)	0.017*	14.0 (5.2)	0.355	15.6 (3.9)	0.062
	None	77.1 (17.0)		15.1 (4.0)		17.0 (3.0)	

*p<0.05,**p<0.01
Adv = Advanced, Indep = Independent, Antipsy = Antipsychotics, BDZ=Benzodiazepene, Antidep = Antidepressant, Antidem = Antidementia

Table 5.8, continued

Clinical Factors		Memory		Executive		Language	
		Mean (SD)	p value	Mean(SD)	p value	Mean (SD)	p value
Duration of illness	<11years	13.0 (4.7)	0.781	13.2 (5.1)	0.894	16.7 (4.1)	0.303
	≥11years	12.6 (5.0)		13.1 (5.0)		16.1 (4.1)	
Medical illness	Yes	12.0 (5.2)	0.167	12.3 (5.1)	0.067	15.9 (4.5)	0.106
	No	13.7 (4.1)		14.0 (4.9)		17.1 (3.5)	
Family history of PD	Yes	13.1 (6.1)	0.495	12.9 (7.1)	0.634	16.0 (6.3)	0.432
	No	12.8 (4.5)		13.2 (4.6)		16.5 (3.6)	
Hoehn & Yahr	Mild	13.5(4.4)	0.001*	14.2(4.4)	0.000*	17.1(3.3)	0.001*
	Adv	8.2(4.9)		6.1(3.6)		12.3(6.4)	
Functional Dependence	Indep	14.6(3.5)	0.016*	15.9(3.9)	0.00*	17.8(3.1)	0.001*
	Assisted	12.0(5.1)		11.9(5.1)		15.8(4.4)	
Psychiatric Medications	Antipsy	10.6(5.1)	0.021*	11.3(6.0)	0.147	14.7(5.7)	0.123
	None	13.4(4.6)		13.6(4.7)		16.9(3.5)	
	BDZ	12.3 (4.5)	0.185	12.4 (4.5)	0.102	16.4 (3.7)	0.251
	None	13.3 (5.0)		13.6(5.4)		16.5 (4.4)	
	Antidep	13.9 (3.5)	0.633	15.4 (3.3)	0.143	17.6 (2.9)	0.177
	None	12.7 (4.9)		12.8 (5.2)		16.3 (4.2)	
	Antidem	10.5 (5.0)	0.002*	11.1 (5.3)	0.010*	15.2 (5.2)	0.0903
	None	13.9 (4.3)		14.1 (4.7)		17.0 (3.4)	

*p<0.05,**p<0.01
Adv = Advanced, Indep = Independent, Antipsy = Antipsychotics, BDZ=Benzodiazepene, Antidep = Antidepressant, Antidem = Antidementia

5.9 Association of Neuropsychiatric symptoms with NUCOG scores

Table 5.9 shows the association between the presence of NPS with NUCOG scores. Here again, subjects were divided into two groups according to presence or absence of each NPS. The Mann-Whitney test was applied to assess if NUCOG scores were significantly different when NPS was present.

The following NPI domains had significantly lower mean total NUCOG scores: delusions, hallucinations, agitation/aggression, irritability and sleep disturbances. Subjects with depression/dysphoria, anxiety, elation/euphoria, disinhibition, aberrant motor behavior, appetite/ eating changes did not have significant difference in NUCOG scores compared to subjects without these NPI.

In our study, subjects with delusion or hallucination scored significantly lower in all NUCOG domains (memory, visuo-constructional, executive function and language) except attention. All the subjects with delusions also experience hallucinations except for one. Subjects experiencing agitation/aggression and sleep disturbances scored significantly lower in attention, visuo-constructional and memory domains. Subjects who experienced apathy had lower visuo-constructional scores whereas subjects with irritability scored lower in the memory domain.

Table 5.9 Association of Neuropsychiatric symptoms with NUCOG scores

Neuropsychiatric symptoms		Total NUCOG		Attention		Visuo-constructional	
		Mean (SD)	p value	Mean (SD)	p value	Mean (SD)	p value
Delusion	Yes	56.4 (22.0)	0.005*	11.7 (5.1)	0.062	13.6 (4.6)	0.008*
	No	75.6 (18.2)		15.1 (4.2)		16.9 (3.1)	
Hallucination	Yes	64.8 (23.8)	0.014*	13.4 (5.6)	0.215	14.8 (4.3)	0.005*
	No	77.2 (16.3)		15.3 (3.7)		17.2 (2.7)	
Agitation / Aggression	Yes	65.7 (21.0)	0.013*	12.9 (4.7)	0.007*	15.2 (4.1)	0.031*
	No	76.2 (18.3)		15.3 (4.1)		17.0 (3.0)	
Depression / Dysphoria	Yes	75.5 (16.2)	0.685	15.4 (3.6)	0.393	16.5 (3.0)	0.356
	No	72.3 (21.7)		14.2 (4.9)		16.6 (3.7)	
Anxiety	Yes	73.8 (16.7)	0.803	15.5 (3.7)	0.514	16.4 (3.2)	0.762
	No	73.7 (20.4)		14.5 (4.6)		16.6 (3.4)	
Elation / Euphoria	Yes	38.0 (-)	0.128	8.0 (-)	0.191	10.0 (-)	0.149
	No	74.1 (19.1)		14.8 (4.4)		16.6 (3.3)	
Apathy / Indifference	Yes	67.1 (25.4)	0.219	13.8 (5.4)	0.428	14.9 (4.5)	0.046*
	No	75.5 (17.1)		15.0 (4.1)		17.0 (2.9)	
Disinhibition	Yes	61.2 (25.6)	0.538	13.0 (5.0)	0.497	15.3 (4.7)	0.684
	No	74.0 (19.3)		14.8 (4.4)		16.6 (3.3)	
Irritability	Yes	66.5 (18.7)	0.048*	13.6 (4.1)	0.085	15.3 (3.8)	0.069
	No	75.3 (19.2)		15.0 (4.4)		16.8 (3.2)	
Aberrant Motor Behavior	Yes	65.6 (18.9)	0.178	12.7 (5.6)	0.333	14.8 (4.5)	0.223
	No	74.3 (19.4)		14.9 (4.3)		16.7 (3.3)	
Sleep	Yes	70.2 (18.1)	0.013*	13.9 (4.3)	0.014*	16.0 (3.3)	0.026*
	No	76.6 (20.0)		15.5 (4.4)		17.0 (3.4)	
Appetite / Eating	Yes	68.7 (22.3)	0.355	14.6 (4.3)	0.405	15.7 (4.1)	0.382
	No	74.8 (18.7)		14.8 (4.4)		16.7 (3.2)	

*p<0.05,**p<0.01

Table 5.9, continued

Neuropsychiatric symptoms		Memory		Executive		Language	
		Mean (SD)	p value	Mean (SD)	p value	Mean (SD)	p value
Delusion	Yes	8.9 (4.0)	0.008*	9.1 (5.2)	0.018*	13.1 (5.5)	0.010*
	No	13.2 (4.7)		13.6 (4.9)		16.8 (3.8)	
Hallucination	Yes	10.8 (5.0)	0.011*	11.2 (5.5)	0.031*	14.7 (5.1)	0.007*
	No	13.6 (4.5)		13.9 (4.7)		17.2 (3.4)	
Agitation / Aggression	Yes	10.9 (4.7)	0.023*	11.2 (5.4)	0.051	15.5 (4.6)	0.186
	No	13.4 (4.7)		13.7 (4.8)		16.8 (3.9)	
Depression / Dysphoria	Yes	13.0 (4.6)	0.781	13.5 (4.9)	0.523	17.0 (2.8)	0.789
	No	12.7 (5.0)		12.8 (5.2)		16.0 (4.9)	
Anxiety	Yes	12.7 (4.8)	0.691	13.1 (4.2)	0.669	16.2 (3.4)	0.356
	No	12.9 (4.8)		13.2 (5.4)		16.6 (4.3)	
Elation / Euphoria	Yes	5.0 (-)	0.170	7.0 (-)	0.340	8.0 (-)	0.106
	No	12.9 (4.7)		13.2 (5.0)		16.6 (4.0)	
Apathy / Indifference	Yes	11.5 (5.4)	0.227	12.0 (5.8)	0.345	15.0 (5.9)	0.338
	No	13.2 (4.6)		13.4 (4.8)		16.9 (3.4)	
Disinhibition	Yes	11.0 (5.3)	0.567	12.8 (5.5)	0.887	15.0 (6.1)	0.639
	No	12.9 (4.8)		13.1 (5.1)		16.5 (4.0)	
Irritability	Yes	10.4 (4.9)	0.026*	11.7 (5.1)	0.154	15.5 (3.4)	0.079
	No	13.4 (4.6)		13.5 (5.0)		16.7 (4.2)	
Aberrant Motor Behavior	Yes	10.3 (5.8)	0.261	11.6 (4.8)	0.314	16.2 (2.3)	0.283
	No	13.0 (4.7)		13.2 (5.1)		16.5 (4.2)	
Sleep	Yes	11.8 (4.7)	0.026*	12.3 (4.8)	0.062	16.3 (3.7)	0.194
	No	13.7 (4.7)		13.8 (5.2)		16.6 (4.4)	
Appetite / Eating	Yes	11.3 (4.9)	0.160	12.1 (5.4)	0.373	15.0 (5.0)	0.158
	No	13.1 (4.7)		13.3 (5.0)		16.8 (3.8)	

*p<0.05,**p<0.01

5.10 Neuropsychiatric symptoms (NPS) in NUCOG category

Table 5.10 summarizes our statistical assessment of the co-occurrence of NPS with NUCOG scores <80.

NUCOG score of <80 is an important threshold because the NUCOG study reported that subjects with dementia consistently scored <80 with a sensitivity of 0.84 and specificity of 0.86 (Walterfang et al., 2006). We applied the Chi-Square test to analyze if any NPS significantly changes the subject's odds of scoring less than 80. We find that the presence of at least 1 NPS increases the likelihood for a subject to score below 80 on the NUCOG. The odds are 3.9 times greater compared to subject without any NPS.

The NPS of hallucinations, delusions and irritability are particularly associated with lower NUCOG score (<80). Delusional subjects have almost 10-fold odds while hallucination or irritability increases the odds by three-fold.

Table 5.10 Neuropsychiatric symptoms in NUCOG category

Presence of NPS		Prevalence		Chi^2	Odds Ratio	95% CI		p value
		NUCOG ≥80	NUCOG <80			Lower	Upper	
Any NPS	Yes	35	42	5.361	3.900	1.17	13.04	0.021*
	No	13	4					
Delusions	Yes	1	8	6.358	9.895	1.19	82.63	0.012*
	No	47	38					
Hallucination	Yes	8	18	5.924	3.214	1.227	8.418	0.015*
	No	40	28					
Agitation	Yes	8	14	2.484	2.188	0.817	5.859	0.115
	No	40	32					
Depression	Yes	23	20	0.186	0.836	0.371	1.885	0.666
	No	25	26					
Anxiety	Yes	12	14	0.347	1.313	0.530	3.248	0.556
	No	36	32					
Elation	Yes	0	1	1.055	-	-	-	0.304
	No	48	45					
Apathy	Yes	10	10	0.012	1.056	0.393	2.835	0.915
	No	38	36					
Disinhibition	Yes	1	2	0.390	2.136	0.187	24.398	0.532
	No	47	44					
Irritability	Yes	5	12	3.894	3.035	0.975	9.454	0.048*
	No	43	34					
Aberrant Motor	Yes	1	5	3.035	5.732	0.643	51.086	0.082
Behavior	No	47	41					
Sleep	Yes	17	25	3.406	2.171	0.948	4.971	0.065
	No	31	21					
Appetite	Yes	7	9	0.413	1.425	0.482	4.208	0.521
	No	41	37					

*p<0.05,**p<0.01 , CI=Confidence Interval

5.11 Significant factors with total NUCOG scores

We performed a linear regression to compare the relative importance of the selected significant NPS with NUCOG scores. Linear regression was chosen as the multivariate analysis tool because NUCOG scores are assumed to be normally distributed. Table 5.11a summarizes the regression results, and only hallucination achieved a significant negative correlation with NUCOG scores. This means that the presence of hallucination will significantly reduce total NUCOG scores.

A second multivariate analysis was also performed to correct for the bias from the socio-demographic and clinical factors. Although NUCOG scores were found to be significantly biased by stage of PD (Hoehn and Yahr), functional dependence and anti-dementia medications (Table 5.5a and 5.5b), we only performed a linear regression to correct for education, summarized in Table 5.11b.

Linear regression requires that the independent variables namely the NPS, clinical and socio-demographic factors must be truly independent of each other. However, this is not the case in our study. As shown in Table 5.5a and 5.5b, the occurrence of several NPS is biased by clinical factors. The stage of PD, functional dependence and use of benzodiazepines are significantly related to the occurrence of hallucination, agitation, irritability and sleep disturbances in the study cohort, and therefore their bias cannot be corrected through regression. Similarly, we cannot include delusion as a neuropsychiatric variable in the regression also. The cohort with delusion is not independent of the cohort with hallucination; in fact, they are the same persons, except for one subject.

After correction for education, hallucination was still found to be the only significant neuropsychiatric factor affecting NUCOG scores. However, the causality

between NUCOG scores to education and occurrence of hallucination cannot be established by this test.

5.12 Sub-analysis on sub-cohort excluding subjects from Neuropsychiatric Clinic

PD patients recruited from the Neuropsychiatric Clinic could represent a unique cohort with a different etiology for cognitive impairment as compared to PD subjects recruited from the Neurology Clinic or Parkinson's Clinic. It is unclear if including patients from the Neuropsychiatric Clinic would bias the study findings. Therefore, additional analysis was performed on a subset of PD subjects recruited from only the Neurology and Parkinson's Clinics to investigate if the results are significantly changed.

Sub-analysis excluding patients from Neuropsychiatric Clinic showed no significant difference in the main finding, hallucination is significantly associated with cognitive impairment in PD patients.

5.12.1 Univariate analysis of clinical factors for NUCOG score

Table 5.12a and 5.12b shows the association of socio-demographic and clinical factors to NUCOG scores in this sub-cohort of PD subjects from the Neurology and PD clinics. (Tables 5.7 and 5.8 can be referred for the equivalent analysis on the whole study population). Similar to the whole study population, the subjects in this sub-cohort with advanced PD and functional dependence scored significantly lower in the total NUCOG score and in all individual NUCOG domains. Likewise, subjects in the sub-cohort with more than 11 years of education also showed a significantly higher total NUCOG score.

Table 5.11a Multivariate analysis of significant factors with total NUCOG scores using linear regression

Variables	B* (SE)	p-value	95%CI	
			Lower	Upper
Hallucinations	-10.15 (4.41)	0.024*	-18.90	-1.4
Agitation	-6.37 (4.85)	0.192	-16.00	3.26
Irritability	-4.47 (3.92)	0.257	-12.26	3.32
Sleep	-3.08 (5.34)	0.566	-13.69	7.53

B*= Beta coefficient, SE= Standard error, CI=Confidence Interval

Table 5.11b Multivariate analysis of significant factors with total NUCOG scores using linear regression (education corrected)

Variables	B* (SE)	p-value	95%CI	
			Lower	Upper
Hallucinations	-9.10 (4.34)	0.039*	-17.72	-0.47
Agitation	-5.39 (4.77)	0.261	-14.87	4.09
Irritability	-0.76 (5.34)	0.887	-11.37	9.85
Sleep	-4.65 (3.84)	0.230	-12.28	2.99
Education	10.08 (4.62)	0.032*	0.91	19.25

B*= Beta coefficient, SE= Standard error , CI=Confidence Interval

There were a few differences between this sub-cohort and the whole study population. Subjects in the sub-cohort on Benzodiazepines showed significantly poorer total NUCOG scores and were also differentiated by marital status. In contrast, if neuropsychiatric subjects were included in the analysis, anti-dementia medication appeared to be a significant discriminant but not Benzodiazepines nor marital status.

5.12.2 Association of Neuropsychiatric symptoms with NUCOG scores

Table 5.12c and 5.12d show results of the univariate and multivariate analysis to extract the association between NPS to NUCOG scores in this sub-cohort of PD subjects. (Tables 5.9 and 5.11 can be referred for the equivalent analysis on the whole study population). Univariate analysis of the sub-cohort revealed that delusions, hallucinations, agitation/aggression, irritability, and sleep disturbances significantly had lower total NUCOG scores. Appetite changes is the only significant NPS to be added, the other NPS are like those found in the whole study cohort as described in section 5.9.

Multivariate analysis with corrections for social demographic factors show that the sub-cohort without neuropsychiatric subjects still show only a significant association with the presence of hallucination.

5.12.3 Association of Severity of Neuropsychiatric symptoms with NUCOG scores

In the previous sections, the multivariate analysis demonstrated the relationship between total NUCOG score with the presence of NPS. In this section, we investigate this association in more depth by attempting to relate the severity of NPS to NUCOG score. Table 5.12f shows the multivariate association between NPS severity and total NUCOG scores in the whole study cohort. Table 5.12g shows a similar multivariate association but on the sub-cohort without neuropsychiatric subjects.

Table 5.12a Univariate analysis of social demographic factors for NUCOG score

Socio-demographic Variables		Total NUCOG		Attention		Visuo-constr'l	
		Mean(SD)	p value	Mean(SD)	p value	Mean(SD)	p value
Gender	Male	76.5 (20.0)	0.182	15.4 (4.2)	0.284	16.8 (3.6)	0.069
	Female	70.7 (21.2)		14.5 (4.3)		15.9 (3.5)	
Ethnicity	Malay	79.1 (16.1)	0.204	15.2 (3.9)	0.924	16.8 (2.9)	0.737
	Others	72.1 (22.6)		15.1 (4.5)		16.5 (4.0)	
Marital Status	Married	74.5 (20.3)	0.021*	15.1 (4.2)	0.005*	16.6 (3.6)	0.174
	Others	95.0 (4.2)		20.0 (0.0)		19.0 (0.0)	
Education	>11 years	85.8 (10.4)	0.002*	17.1 (2.9)	0.005*	18.5 (2.0)	0.000*
	≤ 11 years	70.8 (21.7)		14.5 (4.5)		15.9 (3.8)	

Socio-demographic Variables		Memory		Executive		Language	
		Mean (SD)	p value	Mean (SD)	p value	Mean (SD)	p value
Gender	Male	13.6 (4.9)	0.159	13.7 (5.3)	0.354	16.9 (4.0)	0.387
	Female	11.7 (5.3)		12.7 (4.9)		15.9 (5.0)	
Ethnicity	Malay	14.4 (4.4)	0.080	14.7 (4.5)	0.110	18.0 (2.2)	0.043*
	Others	12.2 (5.4)		12.5 (5.5)		15.7 (5.1)	
Marital Status	Married	13.0 (5.0)	0.035*	13.3 (5.2)	0.174	16.6 (4.3)	0.438
	Others	19.0 (1.4)		18.0 (2.8)		19.0 (0.0)	
Education	>11 years	16.1 (3.2)	0.002*	15.2 (3.9)	0.087	19.0 (0.9)	0.001*
	≤ 11 years	12.0 (5.2)		12.7 (5.5)		15.8 (4.7)	

*p<0.05,**p<0.01

Table 5.12b Univariate analysis of clinical factors for NUCOG score

Clinical Factors		Total NUCOG		Attention		Visuo-constructional	
		Mean (SD)	p value	Mean (SD)	p value	Mean (SD)	p value
Duration of illness	<11years	76.0 (19.5)	0.750	15.3 (4.0)	0.980	16.7 (3.5)	0.660
	≥11years	73.3 (22.0)		15.0 (4.7)		16.4 (3.8)	
Medical illness	Yes	71.0 (22.0)	0.070	14.4 (4.6)	0.062	15.9 (4.0)	0.031*
	No	79.6 (17.5)		16.2 (3.6)		17.5 (2.9)	
Family history of PD	Yes	73.7 (32.9)	0.173	14.6 (6.3)	0.525	16.1 (5.4)	0.419
	No	75.3 (17.4)		15.3 (3.8)		16.7 (3.2)	
Hoehn &Yahr	Mild	79.4 (15.4)	0.000*	16.0 (3.2)	0.000*	17.4 (2.7)	0.000*
	Adv	45.8 (25.8)		9.4 (6.1)		11.7 (4.8)	
Functional Dependence	Indep	86.1 (8.6)	0.001*	17.0 (2.6)	0.005*	18.8 (1.0)	0.000*
	Assisted	70.0 (22.1)		14.4 (4.6)		15.6 (3.9)	
Psychiatric Medications	Antipsy	62.4 (29.8)	0.081	13.6 (6.2)	0.345	14.3 (5.4)	0.069
	None	77.4 (17.3)		15.5 (3.8)		17.1(3.0)	
	BDZ	72.4 (19.3)	0.048*	14.8 (4.4)	0.345	16.1 (3.6)	0.050*
	None	76.9 (21.0)		15.5 (4.1)		17.0 (3.5)	
	Antidep	89.5 (9.2)	0.268	18.0 (1.4)	0.239	19.0 (0.0)	0.174
	None	74.6 (20.4)		15.1 (4.3)		16.6 (3.6)	
	Antidem	67.4 (25.3)	0.127	14.8 (5.1)	0.724	15.9 (4.7)	0.332
	None	77.3 (18.2)		15.3 (4.0)		16.9 (3.1)	

*p<0.05,**p<0.01
Adv = Advanced, Indep = Independent, Antipsy = Antipsychotics, BDZ=Benzodiazepene, Antidep = Antidepressant, Antidem = Antidementia

Table 5.12b, continued

Clinical Factors		Memory		Executive		Language	
		Mean (SD)	p value	Mean(SD)	p value	Mean (SD)	p value
Duration of illness	<11years	13.6 (4.8)	0.424	13.6 (5.2)	0.632	16.8 (4.2)	0.854
	≥11years	12.4 (5.6)		13.1 (5.2)		16.4 (4.6)	
Medical illness	Yes	12.3 (5.6)	0.222	12.5 (5.3)	0.091	16.0 (4.6)	0.068
	No	14.1 (4.3)		14.4 (4.9)		17.4 (3.8)	
Family history of PD	Yes	13.4 (7.1)	0.369	13.8 (7.9)	0.213	15.8 (7.3)	0.422
	No	13.1 (4.7)		13.3 (4.6)		16.8 (3.5)	
Hoehn &Yahr	Mild	14.0 (4.5)	0.001*	14.6 (4.3)	0.000*	17.4 (3.1)	0.003*
	Adv	7.3 (5.4)		5.8 (4.0)		11.6 (7.1)	
Functional Dependence	Indep	15.2 (3.0)	0.044*	16.5 (3.3)	0.000*	18.7 (1.6)	0.001*
	Assisted	12.2 (5.5)		12.0 (5.3)		15.7 (4.8)	
Psychiatric Medications	Antipsy	9.9 (6.3)	0.044*	10.7 (6.9)	0.155	13.9 (7.1)	0.189
	None	13.7 (4.6)		13.9 (4.7)		17.2 (3.4)	
	BDZ	12.4 (5.0)	0.264	12.6 (4.8)	0.128	16.5 (3.9)	0.184
	None	13.6 (5.1)		14.0 (5.4)		16.8 (4.6)	
	Antidep	17.0 (2.8)	0.299	15.5 (4.9)	0.581	20.0 (0.0)	0.17
	None	13.0 (5.1)		13.4 (5.2)		16.6 (4.3)	
	Antidem	10.3 (5.5)	0.012*	11.1 (5.7)	0.049*	15.5 (6.1)	0.627
	None	14.0 (4.7)		14.1 (4.8)		17.0 (3.6)	

*p<0.05,**p<0.01
Adv = Advanced, Indep = Independent, Antipsy = Antipsychotics, BDZ=Benzodiazepene, Antidep = Antidepressant, Antidem = Antidementia

Table 5.12c Association of Neuropsychiatric symptoms with NUCOG scores (subcohort)

Neuropsychiatric symptoms		Total NUCOG		Attention		Visuo-constructional	
		Mean (SD)	p value	Mean (SD)	p value	Mean (SD)	p value
Delusion	Yes	55.9 (23.4)	0.005*	11.9 (5.4)	0.064	13.3 (4.8)	0.008*
	No	77.5 (18.7)		15.6 (3.9)		17.1 (3.2)	
Hallucination	Yes	62.6 (25.8)	0.009*	13.1 (5.8)	0.060	14.4 (4.7)	0.003*
	No	79.7 (15.7)		16.0 (3.2)		17.5 (2.6)	
Agitation / Aggression	Yes	61.0 (22.1)	0.001*	12.8 (4.8)	0.006*	14.1 (4.4)	0.001*
	No	78.6 (18.4)		15.8 (3.9)		17.3 (3.1)	
Depression / Dysphoria	Yes	73.8 (17.4)	0.257	15.2 (3.9)	0.644	16.3 (3.0)	0.028*
	No	76.2 (22.8)		15.2 (4.6)		16.9 (4.0)	
Anxiety	Yes	75.6 (17.8)	0.956	16.1 (3.1)	0.511	16.7 (3.2)	0.912
	No	74.9 (21.2)		14.9 (4.5)		16.6 (3.7)	
Elation / Euphoria	Yes	38.0 (-)	-	8.0 (-)	-	10.0 (-)	-
	No	75.6 (19.9)		15.3 (4.2)		16.7 (3.5)	
Apathy / Indifference	Yes	64.5 (28.8)	0.134	13.6 (5.9)	0.335	14.6 (4.9)	0.060
	No	77.7 (16.9)		15.6 (3.7)		17.1 (3.0)	
Disinhibition	Yes	67.2 (25.6)	0.386	13.0 (5.0)	0.386	15.3 (4.7)	0.660
	No	75.4 (20.2)		15.3 (4.2)		16.7 (3.5)	
Irritability	Yes	63.3 (19.1)	0.010*	13.2 (4.2)	0.021*	15.0 (3.9)	0.018*
	No	77.7 (19.7)		15.6 (4.1)		17.0 (3.4)	
Aberrant Motor Behavior	Yes	64.3 (20.8)	0.118	12.0 (6.0)	0.217	14.3 (4.8)	0.162
	No	75.9 (20.2)		15.4 (4.0)		16.8 (3.4)	
Sleep	Yes	69.9 (20.5)	0.017*	14.2 (4.3)	0.027*	15.8 (3.6)	0.011*
	No	78.5 (19.6)		15.9 (4.1)		17.2 (3.5)	
Appetite / Eating	Yes	63.5 (23.1)	0.028*	13.7 (4.4)	0.028*	14.8 (4.2)	0.029*
	No	77.4 (19.0)		15.5 (4.2)		17.0 (3.3)	

*p<0.05,**p<0.01

Table 5.12c, continued

Neuropsychiatric symptoms		Memory		Executive		Language	
		Mean (SD)	p value	Mean (SD)	p value	Mean (SD)	p value
Delusion	Yes	8.5 (4.0)	0.004*	9.5 (5.5)	0.026*	12.8 (5.7)	0.005*
	No	13.7 (4.9)		13.9 (4.9)		17.2 (3.8)	
Hallucination	Yes	10.4 (5.4)	0.006*	10.7 (6.0)	0.017*	14.0 (5.6)	0.001*
	No	14.2 (4.6)		14.4 (4.5)		17.6 (3.2)	
Agitation / Aggression	Yes	9.4 (4.8)	0.003*	10.2 (5.3)	0.007*	14.6 (5.2)	0.023*
	No	14.1 (4.7)		14.2 (4.8)		17.2 (3.9)	
Depression / Dysphoria	Yes	12.7 (5.0)	0.437	12.9 (5.1)	0.380	16.7 (2.9)	0.081
	No	13.5 (5.2)		13.9 (5.2)		16.7 (5.3)	
Anxiety	Yes	13.1 (5.6)	0.907	13.3 (4.5)	0.646	16.5 (3.4)	0.383
	No	13.2 (4.9)		13.5 (5.4)		16.7 (4.5)	
Elation / Euphoria	Yes	5.0 (-)	-	7.0 (-)	-	8.0 (-)	-
	No	13.3 (5.0)		13.5 (5.1)		16.8 (4.2)	
Apathy / Indifference	Yes	11.3 (6.0)	0.190	11.3 (6.2)	0.135	13.7 (6.6)	0.021*
	No	13.6 (4.7)		14.0 (4.8)		17.4 (3.2)	
Disinhibition	Yes	11.0 (5.3)	0.453	12.8 (5.5)	0.806	15.0 (6.1)	0.488
	No	13.2 (5.1)		13.5 (5.2)		16.7 (4.2)	
Irritability	Yes	9.6 (5.1)	0.009*	10.9 (4.8)	0.028*	14.5 (3.2)	0.002*
	No	13.9 (4.7)		14.0 (5.1)		17.1 (4.4)	
Aberrant Motor Behavior	Yes	10.4 (6.5)	0.304	11.0 (5.1)	0.217	16.6 (2.3)	0.326
	No	13.3 (4.9)		13.6 (5.2)		16.7 (4.4)	
Sleep	Yes	11.7 (5.4)	0.045*	12.2 (5.0)	0.055	16.1 (4.3)	0.102
	No	14.1 (4.7)		14.2 (5.2)		17.1 (4.3)	
Appetite / Eating	Yes	10.3 (5.1)	0.024*	11.0 (5.4)	0.061	13.8 (5.1)	0.002*
	No	13.7 (4.9)		13.9 (5.0)		17.3 (3.9)	

*p<0.05,**p<0.01

Table 5.12d Multivariate analysis of significant factors (Prevalence of NPS) with total NUCOG scores using linear regression with correction for education and marital status (on sub-cohort)

Variables	B* (SE)	p-value	95%CI	
			Lower	Upper
Hallucinations	-12.348 (5.20)	0.021*	-22.749	-1.948
Agitation	-10.808 (5.72)	0.063	-22.238	0.622
Irritability	-0.097 (6.33)	0.988	-12.745	12.551
Sleep	-4.090 (4.62)	0.380	-13.329	5.149
Appetite	-8.758 (6.00)	0.150	-20.757	3.240
Education	7.217 (5.24)	0.174	-3.268	17.702
Marital Status	-14.76 (13.45)	0.277	-41.646	12.126

B*= Beta coefficient, SE= Standard error , CI=Confidence Interval

Although presence of hallucination is associated with lower total NUCOG scores in the whole-study cohort, the severity of hallucination is not significantly associated with total NUCOG score in the whole study cohort. In contrast, severity of hallucination becomes significantly associated with total NUCOG scores when the neuropsychiatric subjects are removed from consideration.

Table 5.12e Multivariate analysis of Severity of NPS with total NUCOG scores on whole study cohort

Variables	B* (SE)	p-value	95%CI	
			Lower	Upper
Hallucinations	-2.605 (1.36)	0.058	-5.297	0.087
Agitation	-2.985 (1.97)	0.134	-6.902	0.932
Irritability	2.232 (2.07)	0.284	-1.879	6.343
Sleep	-0.969 (0.85)	0.259	-2.664	0.727
Education	11.435 (4.50)	0.013*	2.491	20.379

B*= Beta coefficient, SE= Standard error , CI=Confidence Interval

Table 5.12f Multivariate analysis of Severity of NPS with total NUCOG scores on sub-cohort without neuropsychiatric subjects

Variables	B* (SE)	p-value	95%CI	
			Lower	Upper
Hallucinations	-4.572 (1.72)	0.010*	-8.000	-1.144
Agitation	-3.258 (2.33)	0.166	-7.909	1.393
Irritability	-2.026 (3.11)	0.517	-8.233	4.181
Sleep	0.159 (1.28)	0.901	-2.405	2.724
Appetite	-2.778 (2.51)	0.272	-7.791	2.235
Education	8.379 (5.09)	0.105	-1.801	18.560
Marital Status	-21.88 (14.01)	0.125	-50.01	6.255

B*= Beta coefficient, SE= Standard error , CI=Confidence Interval

CHAPTER 6: DISCUSSION

In this study, we aimed to investigate the relationship between neuropsychiatric symptoms and cognitive impairment in a cohort of Parkinson's Disease patients. To the best of our knowledge, this is the first study addressing this question and reporting the prevalence of neuropsychiatric symptoms among PD patients in the Malaysian community.

6.1 Socio-demographic background and clinical characteristics of the study sample

A total number of 94 subjects were included in this study with the completion of all the cognitive, motor and neuropsychiatric scales and the socio-demographic questionnaire. The mean age of the study population was around 65 years old, and this is consistent with the fact that incidence of PD commonly emerges after the age of 60. The majority of the subjects were male gender and ethnically Malay. The higher prevalence of men in this study coincides with previous findings that men are found to be at greater risk of PD than women (Wooten, 2004). The ethnic distribution reflects the population of Malaysia with Malays being the majority. Employment status was not evaluated in this study as there was difficulty categorizing and defining employment: for instance, would a home maker be considered jobless or would an elderly subject who switched to a simpler job be considered as having full or part-time employment? Most received between 6-11 years of education corresponding to some secondary education. It is important to record each subject's level of education as education is significantly associated with cognitive scales like NUCOG (Walterfang et al., 2006).

The mean duration of PD illness was almost ten years. In PD, it is important to know this duration because a longer duration of illness is found to be a significant risk factor for several NPS and cognitive impairment (Aarsland et al., 2014). The majority of the subjects in this study required some form of assistance in basic activities of daily living whether it be for some or most activities, or full 24-hour care. Poorer cognitive outcome predicts greater functional dependency (Macleod et al., 2016). Another community-based study found that PD patients showed a high rate of dependency (Macleod et al., 2016) which reflects the morbidity of the disease progression which leads to loss of dependence, disability and poorer quality of life.

Half of the study population has vascular risk factors which is consistent with some studies which demonstrated some association between vascular risk factors and cognitive impairment (Marttila et al., 1976; Pilotto et al., 2016). The genetic factor may be an important component in the aetiology of PD among our subjects. The earliest PD studies of prevalence reported that family history was present in 15% of the study sample (Gowers, 1902). Mjones (1949) found a higher prevalence of positive family histories, up to 41% (Henry Mjones, 1949). More recently, Elbaz et al. (1999) reported that positive family history was present in 10.3% of his patients as compared to 3.5% of controls (odds ratio = 3.2; 95% confidence interval = 1.6 to 6.6) (Elbaz et al., 1999). In our study, we observed a 16% prevalence of family history of Parkinson's disease. Although vastly different prevalence rates are reported, these various epidemiological studies concur that family history of PD is an important factor and it is widely accepted clinically that genetic risk factors increase the risk to develop PD (Taylor et al., 1999). The wide variation in prevalence could be due to differences in study parameters such as methodology, unstandardized populations and definitions of family history.

All our study subjects were prescribed anti-parkinsonian medication(s). Some anti-parkinsonian medications are known to cause neuropsychiatric symptoms. For example, dopamine agonists, anti-cholinergic agents and amantadine are known to cause psychosis in PD patients. Also, hallucinations or illusions are observed in up to 40% of PD patients treated with dopaminergic drugs (Fénelon et al., 2000, 2010a) whereas conflicting evidence exists for anxiety caused by dopamine agonists (Aarsland et al., 2014). Other types of medications may also influence the symptomatic outcomes of the study subjects. More than half of the subjects in this study were already on psychiatric medications and long-term use of benzodiazepines can worsen cognitive impairment (Yarnall et al., 2013).

This study population comprised subjects at all stages of the Hoehn and Yahr rating scale but the majority (87.3%) had mild to moderate PD (HY-stage 1-3). It is important to assess the staging of PD in the study as it has been shown that advanced PD stage is correlated with increased NPS frequency and severity (Kulisevsky et al., 2008; Litvan et al., 2012; Riedel et al., 2010).

6.2 Neuropsychiatric Symptoms (NPS)

There is a recent focus on NPS in the context of PD owing to the increasing impact upon the quality of life of patients as well as caregivers. There was a high prevalence of 81.9% at least one NPS in this study population. This is a high prevalence number, and although it is consistent with other reports, for instance: 96.4% in Egypt (Khedr et al., 2013a) and 79% in UK (Leroi et al., 2012), interpretation of the results must be done with care.

The prevalence of NPS in this study does not reflect the true prevalence of NPS in the PD patient population in Malaysia. Several of the study subjects were recruited from a neuropsychiatry clinic, and this may introduce a sampling bias because these subjects had a much higher likelihood of suffering from NPS. The bias is justifiable because the main objective of this study is to investigate the relationship between NPS and cognitive impairment in PD. Recruitment from the neuropsychiatry clinic improved the likelihood of capturing PD subjects with NPS. As a result, our study had sufficient number of subjects reporting NPS which then permitted statistically significant conclusions to be made on its association to cognitive impairment, which will be discussed later in this chapter.

The most prevalent neuropsychiatric symptoms reported were; depression (45.7%), sleep and night-time behavior disorder (44.7%), hallucination (27.7%) and anxiety (27.7%). In another study, Aarsland showed similar results whereby prevalence of depression was 38%, hallucinations: 27% and anxiety : 20% (Aarsland et al., 1999b). Riedel et al. (2010) also found similar prevalence of anxiety and sleep disturbances of 20% and 49% respectively. However, the reported prevalence of psychosis, 12.7% (Riedel et al., 2010) was lower compared to our study. The prevalence of delusions in this study was lower than hallucinations which corroborates another similar study (Forsaa et al., 2010).

In contrast, Khedr et al. (2013) found a much higher prevalence of sleep disturbance (78.6%), mood (87.5%) and much lower prevalence of hallucinations (9.9%), which could be due to differences in medication use. In their study, fewer patients (30 of the 112 patients) received regular anti-parkinsonian drugs (dopaminergic and anticholinergic drugs) and the results are aligned with the fact that dopaminergic agents are known to cause psychosis (Khedr et al., 2013b). A cross-sectional study based in Malaysia concluded that the prevalence of sleep disorders (quantified by

Polysomnography) in PD patients were high at 81.8% (Norlinah et al., 2009). In this study, sleep disturbances affected almost half of the study population which follows this trend. Differences in methodology could account for the variation in prevalence as questionnaires rather than polysomnography was used in this study to detect sleep disorders. Furthermore, 42.6% of our study subjects were taking benzodiazepines and thus received treatment for their sleep disturbances.

Female subjects scored significantly higher in anxiety which is consistent with the greater prevalence of anxiety disorders among women and the contributing factors include differences in hormonal balance, coping styles and response to stress between genders (Guo et al., 2015). On the other hand, Malays had lower anxiety as compared to non-Malay subjects. This result concurs with a previous study of Malaysian cancer patients which found that depression and anxiety were less prevalent among Malays. A possible explanatory factor could be that Malay subjects tend toward greater prominence of faith and religiosity in coping with their illness and this strong spirituality enhances their ability to counter psychological distress (Ng et al., 2016).

Subjects who scored significantly higher in irritability were more likely to have less than 11 years of education, a higher prevalence of other medical illness and a lower prevalence of PD history in their family. Literature investigating the relationship between irritability, medical illness and family history of PD is non-existent. From this data set, it is not possible to distinguish if this is due to neurological or causal relationship to PD or just a reflection of disparity in coping mechanisms. One simple explanation could be that this group of patients find it more challenging to manage the burden of PD over and above the other chronic diseases or have a poorer understanding and preparedness against the difficulties imposed by PD. It is also not obvious why subjects with tertiary education

were more prone to aberrant motor behavior as this observation is not easily explained by neurological nor psychiatric causes.

In the introductory paper on the NPI, Cummings (1997) studied the NPI profiles in 40 non-demented subjects with MMSE scores above 25 points. It was reported that mean scores in all NPI symptoms were 0 except in depression/dysphoria, disinhibition, and irritability. The mean scores in the latter symptoms were 0.25, 0.13 and 0.05 respectively in this control population. In our study, all NPI scores were elevated compared to Cumming's control groups and this indicates the presence of psychopathology which may be caused by PD (Cummings, 1997). However, the average severity of NPS reported by our subjects is broadly lower than the clinically significant threshold of 4.0 (Aarsland 2005, Leroi 2012).

If only clinically significant reports of NPS are considered (NPI domain score ≥ 4.0), the prevalence of NPS in our study cohort is 40.4% (see table 5.4a) and this prevalence somewhat lower than the 64.8% prevalence reported by Leroi (2012) in his group of normal PD controls. It implies that the NPS observed in the study cohort are serious, despite the low mean NPI scores. The mean NPI scores in this study is 6.44 which is lower compared to the mean score of 11.6 reported in the study by Leroi (2012). Leroi's study subjects were taken from a randomized clinical trial of Memantine from a community-based PD clinic.

Leroi did not report if this study cohort was on other anti-dementia or psychiatric medications whereas, in the present study, almost 65% of the subjects were already on these medications. Our study subjects were sampled from a tertiary level care hospital; hence any NMS or NPS would have been recognized and clinically managed. Thus, it is possible that our subjects experience milder symptoms because the NPS were being treated through medication to some extent. Anti-dementia and psychiatric medications

may effectively lower the intensity of NPS in PD patients and may also have contributed to an overall decrease in the magnitude of NPI score.

With regards to the stage of disease (PD) and neuropsychiatric symptoms (NPS), advance Parkinson's disease was found to correlate with higher intensity (frequency and severity) of NPS on the NPI. Several studies have shown that advanced stages of PD correlate with higher intensity of NPS (Aarsland et al., 2007, 2009a; Kulisevsky et al., 2008). Riedel (2010) also concluded that in PD outpatients, prevalence and intensity of all NPS (on the NPI) increase with increasing PD severity (Riedel et al., 2010). Our study found significantly higher intensity scores on NPI for hallucination and sleep disturbances, indicating a greater frequency and severity of these symptoms among advanced PD patients. Aarsland reported that patients with advanced Parkinson's disease had higher scores on delusions ($p<0.001$), hallucinations ($p<0.001$), apathy ($p=0.001$) and aberrant motor behaviour ($p=0.008$). Unexpectedly, the depression and delusion did not differ significantly between the advanced and mild-moderate PD group whereas Riedel (2010) showed an increased likelihood of depression and psychosis occurring (between 2 and 10 times higher respectively) in subjects at HY stages 4 and 5 as compared to subjects at Stages 1 and 2 (Riedel et al., 2010).

This study did not show any relationship between NPI depression scores with all the socio-demographic factors and is contrary to Riedel (2010) which demonstrated that depression was significantly associated with the female gender (OR = 1.99; 95% CI: 1.42–2.79) (Riedel et al., 2010). Also, our findings that depression was not significantly related to the severity of PD stage and functional dependency contradicted the study by Goyal (2015) which reported higher motor disability in depressed PD patients (Rai et al., 2015).

Collectively, these disparities in our findings with previous reports may be due to limitations in statistical power and sample size in our study. Riedel and Aarsland had investigated on 1449, and 537 subjects respectively and thus achieved greater statistical power (Aarsland et al., 2007; Riedel et al., 2010).

Similar to subjects with advanced PD, subjects requiring assistance in their functioning and subjects on Benzodiazepines also have significantly higher total intensity NPI scores. These patient cohorts experienced both higher frequency of NPS and the greater severity of the symptoms. Subjects who were dependent on others for functioning in daily activities had higher intensity scores for delusions, hallucinations, irritability, agitation, sleep disturbances and appetite. Results from Forsaa (2010) on the association between decreased activities in daily function with psychosis partially support our findings (Forsaa et al., 2010).

Our findings show that intake of medications had a significant relationship with intensity scores of several NPS. Instead of interpreting the medication as causing the NPS, a more likely explanation is that the medications were prescribed to alleviate the greater intensity of NPS. Our subjects on Benzodiazepines reported higher intensity of NPS especially in depression, aberrant motor behavior and sleep disturbances. Benzodiazepines are often clinically used to treat patients with insomnia (Kupfer et al., 1997). A community-based study reported higher usage of sedatives including benzodiazepines in PD patients compared to healthy controls (Tandberg et al., 1998). Furthermore, as depression often coexists with sleep disorders, this further increases the need for benzodiazepine prescriptions to PD patients affected by these select NPS.

Our study also showed that subjects taking antipsychotics had a significantly higher hallucination and agitation scores while subjects were taking anti-dementia medications also had higher hallucination scores but lower depression scores. Again,

these medications are often used clinically in treating NPS albeit the paucity of data on some of the medications (Shen-Yang et al., 2012). Many RCTs have shown effectiveness on cholinesterase-inhibitors to manage NPS (Aarsland et al., 2002; Emre et al., 2004) and psychosis (Emre et al., 2010).

Our study subjects with longer duration of PD illness (≥ 11 years) experienced greater frequency and severity only disinhibition and aberrant motor behavior. These findings are not coherent with Kulisevsky's report that the prevalence of depression, anxiety, apathy, irritability and sleep disturbances were associated with longer duration of disease (Kulisevsky et al., 2008). Aarsland's study was also not in line with our study by showing that hallucinations, depression and sleep disturbances were associated with greater disease duration (Aarsland et al., 2014). Forsaa (2010) also reported a higher frequency of psychosis amongst patients with a longer duration of illness (Forsaa et al., 2010). The possible reason we did not find any association between illness duration with the rest of the NPS could be due to limited sample size and the study being a cross-sectional study, not a prospective, longitudinal study like Forsaa's.

There is possibility that other stronger and more overriding factors / influences in cognitive impairment rather than duration of illness itself i.e. age, education, medications which may mask out the weaker association due to the illness. A study by Riggeal et. al concluded that cognitive decline within their PD cohort correlated with motor impairment but not disease duration. Cognitive impairment may start early in the disease process but may be very mild and often undetected. Therefore a PD patient with "mild disease" may have had PD for several years with minimal motor and, therefore, cognitive impairment; while a patient with an aggressive disease course may be significantly impaired (physically and cognitively) sooner (Riggeal et al., 2007). Longitudinal studies are needed to confirm this observation.

In our investigation, we did not study impulse control disorders and dopamine dysregulation syndrome. Although these NPS are of relevant interest as suggested by some literature (Chaudhuri et al., 2011), these NPS are not part of the NPI scale and therefore were ignored.

6.3 Cognitive impairment and cognitive domains (subscales) with the NUCOG

In the validation study of the NUCOG scale, it was reported that the mean total NUCOG score among healthy controls across all ages was 93.1% (SD 4.5). Across 60-70- year-olds, the mean total score was 91.9%. With a cut-off score of 80/100, the sensitivity of the NUCOG for detecting dementia was 0.84, and the specificity was 0.86 (Walterfang et al., 2006). This result shows that a score below 80 is highly predictive of a dementing illness, but not all scores below 80 are indicative of dementia. Cognitive impairment is determined by a NUCOG score between 2 or 3 standard deviations (82.5 and 78.8) below the age-adjusted mean in a healthy population. Therefore, in this study, our study subjects scored a 73.7% mean score which exceeds 3 SDs below the mean of healthy controls, thus indicating that this study population is affected by some form of cognitive impairment. The cognitive impairment seen here is more than expected for normal ageing and indicative of dementia in PD.

The PD patients in this study performed poorly in all cognitive domains with the greatest decline in language and memory (both below 3 SDs), followed by executive function and visuo-constructional (both below 2 SDs) and finally, attention (below 1 SD). This finding coincides with Walterfang's study where it was observed that patients with any form of dementia scored not exceeding two standard deviations below the mean of healthy controls in at least 4 out of 5 domains (Walterfang et al., 2006). Our finding is

also contrary to the traditional view that dementia in PD reflects a "subcortical dementia" with predominance in executive function, attention, and visuo-spatial function impairment, but less in declarative memory, language and praxis. The patients in this study population exhibit more "cortical" profiles with impaired memory and language. This is fitting with studies suggesting other contributions to the dementia process in PD patients beyond the typical Lewy-type pathology such as AD-type and vascular pathology (Apaydin et al., 2002; Caballol et al., 2007; Chaudhuri et al., 2006; De Vos et al., 1995; Jellinger et al., 2002). The neuroanatomical implications of a more cortical dementia would further suggest more temporal-limbic deficits in addition to the fronto-striatal deficits of PDD.

Education was the only socio-demographic factor found to be significantly associated with NUCOG scores. Subjects with tertiary level education had a significantly higher mean NUCOG score as compared to subjects with education upto the secondary level or less. This result matches the findings in the validation study of NUCOG which showed education to be significantly associated with NUCOG scores (Walterfang et al., 2006). There were also several subsequent studies demonstrating the association between educational attainment with overall improvements in cognitive performance and reduced risk of cognitive impairment and dementia in later life (Brayne et al., 1990; Farmer et al., 1995).

Evidence linking education to Parkinson's disease is scarce. There were conflicting findings between 2 studies where one supported this notion (Kierzynka et al., 2011) while another study was in disagreement (Pai et al., 2001). Nevertheless, researchers in this field still promote adjustments for education and age when designing appropriate cut-offs in studies screening for cognitive impairment in PD patients (Cullen et al., 2005; Karrasch et al., 2015).

In our study, Malay subjects had significantly higher scores in the language domain. This confirms results of a previous study on the psychometric properties of the Malay NUCOG whereby Malay subjects with Alzheimer's disease performed significantly better in the language area compared to counterparts from other ethnicities (Thong et al., 2016). Since the Malay subjects were assessed using a Malay language version of the NUCOG, they have a possible advantage as the assessment interview was conducted in their primary language, as compared to subjects of other ethnicities who were assessed with either the English or Malay version of NUCOG, both of which are likely to be a second language.

Another significant association was that subjects who were single scored higher in the NUCOG attention domain. However, this may not imply that being unmarried leads to better NUCOG scores and better cognitive function. Only 3 subjects were single and the 2 elder subjects received a tertiary education, (NUCOG scores are significantly higher for the cohort with tertiary education) and one received secondary education. Therefore, the limited sample size and the presence of other factors that could co-influence make it insufficient to evaluate the association in this study.

Contrary to previously reported studies, we did not find that duration of illness was a significant factor in the decline of cognitive function (Hely et al., 2008; Litvan et al., 2011). These other studies reported that prevalence of cognitive impairment in Parkinson's disease increases with age, disease duration, and disease severity (Litvan et al., 2011) and approximately 50-60% of those with PD develop dementia after ten years. According to the Sydney Multicentre Study by Hely and colleagues, dementia is present in 83% of 20-year survivors of Parkinson's Disease (Cosgrove et al., 2015; Hely et al., 2008). Here again, the difference in our findings could be due to limitations of sample

size. Approximately 63% of our study population had a duration of illness ≤ 10 years. We may be under-sampling the patient population with longer disease duration.

Studies have also shown an association between vascular illness and decline in specific cognitive domains. Pilotto et. al (2016) demonstrated that in patients with hypertension, heart disease, and diabetes, their performance in executive and attention were significantly worse ($p < 0.05$).(Pilotto et al., 2016). Martilla and Rinne (1976) conducted a study in Finland showing that PD patients with arteriosclerosis were more likely to be demented than those without (Marttila et al., 1976). For our subjects with medical illness, we only found significant impairments in the visuo-constructional domain as compared to subjects without vascular illness.

We observed that advanced stage PD (Stage 4 and 5) correlates with overall cognitive dysfunction and decline across all cognitive domains which is in agreement with the study by Litvan (Litvan et al., 2011). Similarly, another study by Riedel (2010) on 1449 PD patients showed that the dementia was more likely to occur at advanced stages than at early stages of PD (HY; OR = 1.72, 95% CI: 1.10–2.70) (Riedel et al., 2010).

The NUCOG scores for the subjects who required assistance (some/moderate assistance and 24-hour care) for their functioning were significantly lower than those who did not require any assistance. This can be readily explained as follows: Due to motor disabilities, subjects with an advanced stage of PD are very likely to depend on others for the daily activities of living. As discussed in the previous paragraph, this same group of advanced PD patients is also more likely to suffer from cognitive decline. Therefore there is a link between subjects requiring assistance and cognitive decline because these subjects are likely to have advanced stage PD. Macleod et al. (2016) identified poorer

cognition as an independent predictor for dependency in addition to older age, smoking and higher axial impairment (Macleod et al., 2016).

Our analysis revealed significant associations between several types of medications and cognitive domains in the NUCOG. Some of these findings also seem counter-intuitive. Thus, no studies relating cognitive domains to use of medication were found. Therefore, care must be taken not to attribute direct causality naively.

Subjects on anti-dementia medications scored lower on NUCOG scores in the domains of memory and executive function. However, anti-dementia medications are known to improve dementia in PD hence the expectation for this cohort to also have better cognitive performance. There is evidence supporting the use of cholinesterase inhibitors like rivastigmine and donepezil for Parkinson's Disease Dementia. Rivastigmine is proven to improve executive functions especially in attentional tasks. Also, rivastigmine can improve psychotic symptoms, agitation, anxiety and even apathy (Oh et al., 2015). Instead, it is likely that the cohort on anti-dementia medications may already be biased towards subjects who already have a serious cognitive impairment or PDD, and are receiving anti-dementia medications to manage their symptoms. Therefore, it is understandable why subjects on anti-dementia medications have lower scores in memory and executive function.

Our study also found that subjects on antipsychotics had lower performance in memory. Antipsychotics are used clinically for psychosis in PD and only Clozapine has evidence on a positive outcome for psychosis in PD patients with possible dementia. Although Quetiapine is also being used widely for PD psychosis, there is no evidence for its efficacy (Shotbolt et al., 2010). Data on the association with these antipsychotics with cognition is rather limited. However, there is evidence that quetiapine has been found to affect cognition in Alzheimer's Disease patients (Ballard et al., 2005). Some of the

reasons postulated were suppression of brain-derived neurotrophic factor (BDNF) and its anti-muscarinic properties (Ballard et al., 2005). Besides this, our study found that subjects on antidepressants had significantly higher visuo-constructional performance. A study by Butters (2000) found that elderly depressed patients with baseline cognitive impairment may experience improvement in domains of memory and executive function following antidepressant therapy. However, they may not necessarily achieve normal levels of performance (Butters et al., 2000).

6.4 Association of Neuropsychiatric Symptoms and Cognitive Impairment

The association between NPS and cognitive impairment in PD patients has been investigated by numerous groups in the past 15 years. However the findings have been contradictory and a recent review summarized that the association is still inconclusive (Javeed et al., 2014). There were studies which showed weak correlations (McColgan et al., 2012) or no correlations between NPS and cognitive impairment in PD patients (Guo et al., 2015; Ringman et al., 2002). Several other studies (Aarsland et al., 1999b, 2007, 2009a; Leroi et al., 2012; Riedel et al., 2010). Aarsland (1999) of Norway concluded that NPS were significantly correlated with cognitive impairment assessed by the MMSE and Dementia Rating Scale (DRS) (Aarsland et al., 1999b). NPS were seen more prevalently in patients with PDD compared to those without cognitive impairment (Aarsland et al., 1999b, 2007; Leroi et al., 2012).

We noted that the studies with no or weak associations included subjects with relatively mild cognitive and motor symptoms. McColgan's study excluded dementia patients and only included PD-MCI in their sample (McColgan et al., 2012). The study by Ringman based in Mexico had the limitation of relative lack of advanced PD patients

in their study. This is a selection bias, and their results are therefore not reflective of the general population of PD patients (Ringman et al., 2002). The study by Guo in Taiwan found a significant association between almost all cognitive domains of the ACE-R test. However, they argue for a weak association due to the small magnitude of the correlations. It is unclear if this is a justifiable conclusion from their data. A small reduction in ACE-R scores (18% from the maximum score) is indicative of dementia and the difference in the quality of life between a subject with dementia and normal cognition is not small (Guo et al., 2015; Ringman et al., 2002).

In our study, NPS and cognitive impairment are found to be significantly associated. PD patients with the following NPS; delusion, hallucinations, agitation/ aggression, irritability and sleep disturbances showed greater overall cognitive impairment (evidenced by the lower mean total NUCOG scores) than those who do not have these NPS. Of particular note, PD patients with NPS have significantly lower NUCOG score (<80) signifying the presence of dementia.

Our analysis shows that a PD patient with NPS has almost four times greater chance of having dementia (and therefore PDD) than a patient without NPS. Among all the NPS assessed by the NPI scale, hallucinations, delusions and irritability are significantly associated with dementia (lower NUCOG score <80). A PD patient with delusions has almost ten times greater chance of having dementia than a patient without delusions. A PD patient with hallucination or irritability has a three times greater chance of having PDD than a patient without hallucination or irritability.

Further analysis on individual NPS reveal significant associations between psychosis (both hallucinations and delusions) and dementia in our study. These results are compatible with findings from several studies (Aarsland et al., 1999b, 2007; Leroi et al., 2012; Riedel et al., 2010). We only studied hallucinations as we did not have sufficient

statistical power to further assess the effect of delusions against other significant NPS, due to low prevalence (only nine subjects). Hallucination appeared to be of significance to cognitive impairment after adjusting for differences in education, which is a confounding variable for cognitive impairment. This is consistent with the study by Lee Wei-Ju et al. (2012) who demonstrated an association between hallucination and cognitive impairment in PD patients after adjusting for education as well (Lee et al., 2012). The possible mechanisms underlying both hallucination and cognitive impairment will be discussed in depth in the next section (6.5).

In addition to psychosis, we also found a significant association between cognitive impairment, agitation and irritability. Neuropathological studies have linked Alzheimer neuropathology (high neurofibrillary burden in orbitofrontal cortex) with agitation (Caballol et al., 2007). Similarly in PDD patients with agitation, Alzheimer's disease-like changes may be more marked (Aarsland et al., 2007). The study by Monastero demonstrated an association between irritability and cognitively impaired PD patients (Monastero et al., 2013). Related studies have found significance in other NPS to cognitive impairment, but not found in our study. Aarsland found significant relations between dementia and apathy, aberrant motor behavior (Aarsland et al., 1999b) and agitation (Aarsland et al., 2007). Leroi also found a higher rate of aberrant motor behavior in PDD patients besides psychosis (Leroi et al., 2012).

Upon further investigation with multivariable analysis, our findings suggest that hallucination is the only significant NPS, which implies that the other NPS are only significant through their relationship with hallucination. Results from the sub-analysis enforce the conclusion that the presence and the severity of hallucination alone is significantly associated with lower total NUCOG scores. This further suggests that a detailed investigation into the co-occurrence between NPS is necessary to completely

answer the link between NPS and cognitive impairment in PD. Aarsland conducted a factor analysis and found that several NPS tend to co-occur (Aarsland et al., 1999b). This is preliminary evidence supporting the existence of inter-relationship between NPS. It is possible that the significance of several NPS to cognitive deficits found by these groups could be dependent only on interaction with very few NPS. Thus, it will be important to identify what these core NPS are, if any and any common neurological cause which links them.

Despite a high prevalence of depression and anxiety in the study subjects, there was no statistically significant relationship between these NPS with the total and individual domain scores of the NUCOG. This finding is in line with the GEPAD (German Study on Epidemiology of Parkinson's Disease with Dementia) study which also did not find any cognitive changes in PDD patients with depression and anxiety. Several other studies also found no association between depression and cognitive function (Aarsland et al., 2004; Hobson et al., 2004a; Pedersen et al., 2013). However, depression was found to correlate with worse cognitive function in PD patients with non-severe cognitive decline. Monastero studied only PD-MCI patients, and Tremblay excluded PDD patients (Monastero et al., 2013; Tremblay et al., 2013). In all these studies, the effect of the medication is not well controlled for thus making it difficult to arrive at a consistent conclusion. Antidepressant medication, in particular, can lead to improvement of depression-associated cognitive impairment (Aarsland et al., 2014).

There is a lack of data on the associations between NPS and specific cognitive domains. We performed this analysis in our study and now compare our results with published studies where available. The presence of delusion and hallucination correlates with significantly lower performance in the all cognitive domains except attention. This is like the study by Hepp et al. which reported that PD patients with hallucinations have

poorer executive and visuo-perceptual function compared with those who did not hallucinate. However, Hepp also observed poorer sustained attention in PD patients with hallucinations (Hepp et al., 2013). We did not did not detect an association between attention and hallucination in our study.

On the association of sleep disturbances with impaired cognitive function, this study found significance in the domains of attention, visuo-constructional and memory functions. Vendette (2007) found similar associations except that there was no impact on memory (Vendette et al., 2007). Contradictory results were observed in the GEPAD study which did not show any differences in cognitive performance between PDD patients with insomnia with patients without (Riedel et al., 2010). This apparent contradiction may be resolved by the detailed findings of Goldman (2013). In her study, she found that daytime sleepiness was significantly associated with PDD and deficits in all cognitive domains whereas no evidence of cognitive deficits could be linked to night time sleep disturbance, which is also a symptom that affects all PD patients across the cognitive spectrum (Goldman et al., 2013).

Our study also discovered a significant association between irritability with lower memory scores and agitation/aggression with poorer attention, visuo-constructional and memory performance. This agrees with Aarsland's study (1999) which also concluded that in the cluster of PD patients with psychosis, agitation and irritability, memory scores were lower. Aarsland added that these 3 NPS are grouped into 1 cluster based on cognitive and motor measures. This is preliminary evidence that hallucinations, delusions, agitation and irritability can be closely linked or co-occur and therefore suggests that this cluster of NPS result in impairment in similar cognitive domains (Aarsland et al., 1999b). Further investigation is needed to confirm and explain the pathophysiological basis of this association if any.

Despite the high prevalence of subjects with apathy, this study did not find a significant association between apathy and deficits in overall cognitive function. Only poorer visuo-construction performance was observed. This is contrary to several studies which found a higher prevalence of apathy in cognitively impaired and demented PD patients (Dujardin et al., 2007; Pluck et al., 2002). Pluck reported that patients with apathy suffered from a poorer executive function, memory and slowness of thought (via time-dependent tasks) (Pluck et al., 2002; Starkstein et al., 1992b) whereas Aarsland (1999) found poorer executive function. These differences with our study could be due to the different rating scales used i.e. Stroop test (Aarsland et al., 1999b), Lille Apathy Rating Scale (Dujardin et al., 2007), modified Wisconsin card sort test (WCST) and a test for verbal fluency (the controlled word association test, "COWAT") (Pluck et al., 2002; Starkstein et al., 1992b) as compared to the NPI in our study.

6.5 Neuropathological, neurochemical and genetic mechanisms underlying hallucination and cognitive impairment

Our findings reveal an association between hallucination and cognitive impairment. Therefore, any shared neurochemical and neuropathological mechanisms between hallucination and cognitive impairment are of special interest to explain the etiology of these symptoms in PD. Previous studies show evidence of common pathological mechanisms due to cholinergic deficits (Burn et al., 2006). PDD patients developed more pronounced cholinergic deficits and atrophy of the nucleus basalis compared to PD patients without dementia (Whitehouse et al., 1983). Cholinergic deficits have also been associated with psychosis in delirium, Alzheimer's Disease and Lewy Body dementia. Taken together, the evidence suggests that cholinergic deficits in PDD

contributes to the emergence of psychosis (Aarsland et al., 1999a). Burn et. al (2006) found that PDD patients with visual hallucinations experienced greater improvements in cognition and NPS in response to cholinesterase inhibitors than those without the hallucinations. The observed benefits are consistent with the hypothesis that patients with hallucinations have greater cholinergic deficits (Burn et al., 2006).

Lewy Body pathology (Williams-Gray et al., 2006) is another neuropathology common in subjects with both hallucination and impaired cognition. In PDD patients, cortical Lewy Bodies are more prevalent and a preferential paralimbic distribution is linked to psychosis and dementia (Perry et al., 1996). In autopsy examinations, PDD patients were often found with the pathology of Alzheimer's Disease. AD patients are known to have a high prevalence of psychosis (Mega et al., 1996) which suggests that Lewy Body pathology increases the susceptibility to psychosis.

Genetic factors underpinning possible links between hallucination and cognitive impairment are not well understood. A small case-control study reported a positive association between the MAPT H1/H1 genotype and hallucinations in PD, thus implicating MAPT as a common genetic risk factor for both dementia and hallucinations in PD (Papapetropoulos et al., 2007). Contrasting evidence from a large cross-sectional study (500 patients) however showed no association between MAPT H1/H1, SNCA-REP1 (alpha-synuclein promoter polymorphism) or APOE with psychosis. It is possible that the presence of psychosis was underestimated in the larger study because psychosis was determined solely from subject responses to one item on the UPDRS scale on a single occasion (Factor et al., 2011).

Understanding the common pathophysiology underlying NPS and cognitive impairment in PD is crucial to the development of targeted therapeutic strategies (Aarsland et al., 2013). Studies have established a link between psychosis and dementia

through cholinergic deficits, cortical Lewy Bodies and Alzheimer's-type cortical pathologic changes (Aarsland et al., 1999a). Genetic factors are poorly understood and there is a lack of studies on candidate genes which may jointly influence protein aggregation, cholinergic transmission and the development of psychosis in PD.

6.6 Summary of Findings

In this section, the main findings of this study are summarized for easy reference. First, significant relationships between the NPI domains and socio-demographic and clinical factors are highlighted. Next, the important associations between NUCOG scores with socio-demographic and clinical factors are briefly summarized. Finally, the association between NUCOG scores and NPI scores, which is the primary result of this study, are succinctly described.

NPI scores were significantly higher for subjects with advanced PD, subjects which are functionally dependent and subjects on Benzodiazepines. In advanced PD patients, only hallucination and sleep disturbances scores were significantly higher compared to patients with mild to moderate PD. Subjects who were functionally dependent scored significantly higher in; delusions, hallucinations, irritability, agitation, sleep disturbances and appetite. Subjects with longer duration of PD illness ($\geqslant$ 11 years) had significantly higher scores in disinhibition and aberrant motor behavior. Females have significantly higher anxiety scores compared to males. Malays scored significantly lower in anxiety compared to the non-Malays.

This study found that PD patients fared worse in all cognitive domains of the NUCOG (with a mean score of 73.7%) compared to the healthy population. Language and memory were the lowest domain (more than three SDs below), followed by executive

function and visuoconstructional (both below two SDs) and then attention (below 1 SD). Education level was the only factor found to be significantly associated with NUCOG score. Subjects with tertiary education scored significantly higher in all cognitive domains except for executive function. Malays scored significantly higher in the language domain. Subjects with advanced PD and who were functionally dependent scored significantly lower both in the total NUCOG score and in all domain scores.

Total NUCOG scores were significantly lower in PD subjects who suffered from the following NPS: delusions, hallucinations, agitation/aggression, irritability and sleep disturbances. Subjects with delusion or hallucination scored significantly lower in all NUCOG domains except attention. Subjects experiencing agitation/aggression and sleep disturbances scored significantly lower in attention, visuo-constructional and memory domains. Subjects who experienced apathy had lower visuo-constructional scores whereas subjects with irritability scored lower in the memory domain.

The presence of at least 1 NPS increases the likelihood for a subject to score below 80 on the NUCOG. The odds are 3.9 times greater compared to the subject without any NPS. Subjects with hallucinations, delusions or irritability are associated with lower NUCOG score (<80). Delusional subjects have almost 10-fold increase in odds of scoring below 80 on the total NUCOG scale while having hallucination or irritability increases the odds by three-fold. Hallucination was found to have a significant negative correlation with NUCOG scores. After correction for education, hallucination was still found to be the only significant neuropsychiatric factor affecting NUCOG scores. If subjects from the neuropsychiatric clinic are excluded, the association between total NUCOG scores with hallucination is strengthened. Both presence and severity of hallucination are significantly associated with lower total NUCOG scores.

6.7 Limitations

There were several limitations of this study:

1. Convenience sampling method

This method can lead to selection bias as the eligible subject of a population will not have an equal chance of being selected in a sample (Skowronek et al., 2009). In this study, only patients who attend the neurology or neuropsychiatric clinic on a specific day were included into the sample. A random sampling method is the preferred method to reduce the bias.

2. Cross-sectional study

With cross-sectional study design, we could only find an association between hallucination and cognitive impairment. We could not provide evidence that due to hallucination, the person develops cognitive impairment. Further, given that the estimates here are cross-sectional and considered only over the previous month, they are probably underestimates of the cumulative prevalence of NPS over the course of PD. Moreover, behavioral disturbances often fluctuate and may not be present at the time of examination. A longitudinal study could be more accurate in reflecting the frequency of NPS and cognitive impairment.

3. Lack of representation

This study is a hospital-based study which is based in urban areas of Malaysia; thus, our results should not be regarded as representative of all PD patients in the general population. The prevalence may not be reflective of Malaysian PD population because

sampling from neuropsychiatric clinic automatically biases patients to have neuropsychiatric symptoms.

4. Recall bias

The NPI is prone to recall bias as caregivers would give their account of observed behaviour (Javeed et al., 2014). Moreover, some of the NPS with more subjective quality may have been missed.

5. Time-consuming

This study used two psychometric scales and one scale which required the researcher to perform a neurological examination on the subjects. This posed much effort from the subjects as they were Parkinson's patients. Some were also exhibited emotional distress and expressed their discouragement when they were slow or incapable of performing the tests. All these may lead to inconsistent responses as they feel pressured to rush through the questions and tasks.

6. Language

Some subjects used Mandarin or Tamil as their primary language. As both scales used were administered only in 2 languages, English and Malay Language.

6.8 Recommendations to improve the methods for future replication of the study

1. Prospective study

A longitudinal, prospective study may more accurately study the development of NPS in a cohort of Parkinson's disease patients and the effects of medications can be controlled for. This can also determine the frequency of NPS and study the associations concern in the study with more exact results.

2. Random sampling method

Random sampling method can represent the target population and further reduces sampling biasness.

3. Generalizability

The sampling should be more generalized (eg. include subjects from general outpatient clinics and wards) as our study population was from specialty clinics. Rates and patterns of NPS and cognitive impairment in inpatient and outpatient settings might be considerably different.

4. Assessment tools

Movement Disorder Society (MDS)-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al., 2008). The MDS-UPDRS can be used instead as it is a more comprehensive instrument offering a more detailed description of motor impairment (eg. tremor severity, laterality). Besides being one of the most widely used scales for measuring motor symptoms in PD patients it is the evaluated, valid, and reliable scale available. It is also efficient and flexible enough to monitor the disabilities

and impairment in PD. Besides it also includes the Hoern and Yahr scale which makes the assessment of motor symptoms more complete (Ramaker et al., 2002).

5. Impulse Control Disorders (ICDs)

Impulse control disorders are also part of NPS. As the prevalence of ICDs is around 6% among treated PD patients (Chaudhuri et al., 2011) it is worthwhile to include this NPS in future studies. Also, PD patients with ICDs have been shown to have impairment in a range of cognitive domains including executive abilities and spatial planning (Aarsland et al., 2014). Questionnaire for Impulsive Compulsive Disorders in Parkinson's Disease (QUIP), a screening instrument with high discriminant validity for Impulse Control Disorders in PD can be used. The QUIP covers a wide range of symptoms occurring at any time since PD onset and lasting for one month (Weintraub et al., 2009)

6. Control group

A control group (healthy population) can be included to estimate the exact prevalence of psychiatric symptoms specific to Parkinson's disease with certainty. However, there is evidence that the frequency and severity of NPI items is low in healthy elderly people and in those without dementia (Cummings, 1997).

6.9 Strengths

Despite the limitations mentioned above, there were also strengths in this study:

1. This is the first study to be carried out in Malaysia.

2. This study has a representative sample with sufficient duration of illness to enable neuropsychiatric symptoms to develop.

3. Psycho-metrics used in this study were validated and reliable diagnostic instrument covering a wide range of neuropsychiatric symptoms commonly occurring in patients with neurological disorders used. Also, the NUCOG Malay version was recently validated (Thong et al., 2016), making it easier for the subjects in this study to be assessed especially those who are more proficient in the Malay Language.

CHAPTER 7 : CONCLUSION

7.1 Conclusion

This study found that neuropsychiatric symptoms become increasingly prevalent as cognitive deficits progress in severity in PD, especially since dementia emerges. PD patients with delusion, hallucinations, agitation/ aggression, irritability and sleep disturbances showed greater cognitive deficits than those who do not have these NPS. After correcting for education in multivariate analysis, hallucination is the only significant variable associated with cognitive impairment. When Neuropsychiatric Clinic subjects were excluded the association is even stronger. Not only the presence but the severity of hallucination is found to be associated with cognitive impairment. We conclude from our study that that there is an association between NPS (specifically hallucination) and cognitive impairment in PD patients. Therefore, if a PD patient develops hallucinations, it is important for clinicians to look into dementia. The association between hallucination and cognitive impairment likely reflects the shared neurobiological basis between hallucination and cognitive impairment which are cholinergic deficits and Lewy Body pathology. Thus, this study not only aids our understanding of the pathogenesis of the neurobiological features of PD but also proposes new links to possible psychiatric manifestations of this pathology.

The findings in our study suggest a possibility to identify conversion from normal baseline cognition to dementia in PD patients through the emergence of NPS, particularly hallucination. The present results have identified a link between hallucination and decline in cognitive function, which is believed to be a non-dopaminergic mediated function. This

finding supports the hypothesis that multiple neurotransmitter systems, other than dopamine, are involved in the pathophysiology of psychosis in PD.

Our findings are a contribution to the advancement of knowledge on the diverse presentation of NPS in PD. This body of knowledge must continue to grow to improve clinical understanding and precision in diagnosing subtypes of PD. In time to come, we hope this knowledge will become a foundation to design more effective management of PD and in the use of neuro-protective therapies.

7.2 Recommendations

More studies and research should be done on this topic in future. There are few recommendations for further research on this study:

1. Investigate the co-occurrence of clusters of NPS to identify pathogenesis and the common pathophysiology.
2. Investigate the common pathophysiology between hallucination, motor symptoms of PD and cognitive decline
3. Use a larger sample size to obtain greater statistical power or detect subtle effects and use random sampling in future studies.

CHAPTER 8: REFERENCES

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