APPLICATION OF ACTIGRAPHY TO THE MEASUREMENT OF NEUROPSYCHIATRIC SYMPTOMS OF AGITATION IN DEMENTIA

by

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Abstract

This thesis evaluates the application of actigraphy to the measurement of neuropsychiatric symptoms (NPS) of agitation in older adults with dementia. There are increasing numbers of older adults with dementia and management of NPS is an important aspect of providing care for this population. This thesis examined the correlation between actigraphic measures and questionnaire-based measures of NPS, including the Cohen-Mansfield Agitation Inventory (CMAI) and other measures of NPS. The actigraphic characteristics of individuals with high and low levels of agitation were described along with an assessment of the feasibility of actigraphy for measuring NPS of agitation. A total of 15 individuals with dementia residing in geriatric psychiatry inpatient units in hospital and in long-term care (LTC) facilities were included in the study. Participants wore an actigraph device on their non-dominant wrist for seven consecutive days. Informant-rated NPS measures were completed through interviews with nursing staff familiar with participants. Participants were dichotomized into groups according to agitation status as measured by a cutoff score of ≥50 on the CMAI indicating high agitation. The mean actigraph wear time for the total sample was 6.2 days (SD=1.5). Significant positive correlations were found between overall motor activity as measured by actigraphy mean motor activity (MMA) counts and the CMAI total scores for 24-hour (r=0.70, P=0.004), daytime (r=0.75, P=0.001), and evening (r=0.72, P=0.003) time periods, while nighttime MMA counts were not correlated with CMAI scores (r=-0.03, P=0.917). Significant positive correlations were found between MMA counts and CMAI verbal and non-aggressive physical agitation subscores. Additionally, patients with high CMAI scores had higher levels of 24-hour activity (mean MMA = 169.6, SD=89.4) than patients with low CMAI scores (mean MMA=78.6, SD=35.4, P=0.016). In conclusion, actigraphy appears to be a feasible method of measuring some NPS. Actigraphic measures are strongly correlated with questionnaire-based measures of agitation and higher levels of agitation are associated with higher daytime and evening motor activity as measured by actigraphy. Individuals with high levels of agitation can be distinguished from individuals with low agitation using
actigraphy. However additional studies are required to further understand the application of actigraphy to the measurement of these important symptoms.
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List of Abbreviations

AD  Alzheimer’s disease
ADL  activities of daily living
CGI-S  Clinical Global Impression-Severity Scale
Charlson  Charlson Comorbidity Index
CMAI  Cohen-Mansfield Agitation Inventory
CPM  counts per minute
CSDD  Cornell Scale for Depression in Dementia
DLB  dementia with Lewy bodies
dMMA  daytime mean motor activity
eMMA  evening mean motor activity
FTD  frontotemporal dementia
GDS  Global Deterioration Scale
ICC  intra-class correlation
Katz ADL  Katz Index of Independence in Activities of Daily Living
LTC  long-term care
MMA  mean motor activity
MMSE  Mini-Mental State Examination
nMMA  nighttime mean motor activity
NPI  Neuropsychiatric Inventory
NPS  Neuropsychiatric symptoms
PRN  pro re nata (as needed)
ROC  receiver operating characteristic
VAD  vascular dementia
VM  vector magnitude
Chapter 1

Introduction

1.1 Statement of the research problem, rationale, and objectives

Alzheimer’s disease (AD) and related forms of dementia are becoming increasingly prevalent with the aging demographics of most developed countries.\textsuperscript{1} According to a study commissioned by the Alzheimer Society of Canada, there are currently over 500,000 older adults living with dementia in Canada, and this number is projected to increase to 2.8% (1,125,200) of the Canadian population by the year 2031.\textsuperscript{1}

Characterized by impairment in a range of cognitive and non-cognitive domains, AD and related forms of dementia interfere with an individual’s ability to perform everyday activities.\textsuperscript{2-4} The hallmark cognitive changes of dementia associated with impairments in memory, attention, judgment, reasoning, language, and communication are often accompanied by a range of non-cognitive changes, commonly referred to as neuropsychiatric symptoms (NPS). These behavioural and psychological changes have been recognized as integral features of dementia,\textsuperscript{5} and encompass a variety of symptoms such as agitation, aggression, psychosis, sleep disturbances, depression, and apathy.\textsuperscript{6} Neuropsychiatric symptoms of dementia, also known as behavioural and psychological symptoms of dementia, represent a major challenge as approximately 80% of individuals with dementia develop significant NPS at some point in their illness.\textsuperscript{7,8} These symptoms are important because they are associated with a variety of adverse outcomes and can have significant effects on cognition and behavior for individuals and caregivers.

The accurate identification and monitoring of NPS have important implications on the treatment and management of these behaviours.\textsuperscript{9} Currently, the most commonly
employed methods for measuring changes in NPS rely on caregiver or nursing staff reported questionnaires of the frequency that NPS were observed over a specified time period in the past. As such, these types of measures are subjective, which can contribute to limited reliability and validity of questionnaire-based measures when compared to other methods for measuring NPS. Although there has been considerable research on NPS in older adults with dementia, one of the main difficulties in assessing these symptoms is the limited availability of objective quantitative measures for NPS.\(^\text{10}\)

One method that has received recent attention is the potential application of actigraphy for the measurement of NPS. The use of actigraphy, or electronic activity monitoring, may allow behaviour to be quantified and measured in a more objective, accurate, and reliable manner when compared to the current questionnaire based methods for measuring NPS.\(^\text{11,12}\)

There has been an extensive amount of research on the use of actigraphy to measure sleep disturbances in individuals with dementia.\(^\text{9,11,13-30}\) However, to date there have been few studies evaluating the application of actigraphy to the measurement of NPS other than sleep changes. Some NPS, such as agitation, may be particularly amenable to measurement with actigraphy, as agitation has been defined as inappropriate motor or vocal activity that is not an obvious expression of need or confusion, as judged by an outside observer.\(^\text{31}\) Understanding whether actigraphy may provide a more objective measurement of agitation and other NPS in dementia may help improve the measurement and management of these challenging symptoms.

\textit{1.1.1 Thesis overview}
The goal of this research project was to evaluate the application of actigraphy to the measurement of agitation in older adults with dementia. This thesis examines the actigraphic characteristics of individuals residing in long-term care (LTC) and geriatric psychiatry inpatient units in hospital, and evaluates the association between measures obtained through actigraphy and questionnaire-based measures of NPS.

1.1.2 Objectives and Hypotheses

1.1.2.1 Objectives

The objectives of this research project are to:

1) Determine key facilitators and barriers to the use of actigraphy for measuring NPS of agitation;
2) Evaluate whether specific patterns of motor activity recorded by actigraphy are correlated with agitation in older adults with dementia; and,
3) Describe the actigraphic characteristics of individuals with low and high levels of agitation in dementia.

1.1.2.1 Hypotheses

It is hypothesized that:

1) Actigraphy will be a feasible method for measuring NPS of agitation;
2) Higher levels of agitation will be correlated with higher daytime motor activity as measured by actigraphy; and
3) Individuals with high agitation in dementia will have distinct actigraphic profiles compared to individuals with low agitation.

1.2 Definition of dementia and subtypes of dementia

1.2.1 Definition of dementia
Dementia is a term that describes a group of neurological conditions that occur as a result of brain disease or injury that have distinct clinical features affecting the brain both directly and selectively, rather than affecting multiple organs systems. According to the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition), in order to be diagnosed with dementia, an individual’s deficits must represent a decline from a previously higher level of functioning; result in functional impairment in the performance of daily activities; and not be accounted for by any other neurological disease. Many forms of dementia are chronic and progressive in nature with a gradual onset and continuing cognitive decline that results in disturbances in multiple cortical functions. There are several sources of diagnostic criteria for dementia including: the Diagnostic and Statistical Manual of Mental Disorders; the International Classification of Diseases 10th Revision; and the National Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association. The major symptoms of dementia identified using these diagnostic criteria include: memory deficits; impairments in executive functioning (such as difficulties with judgment, problem solving, planning, learning, and reasoning); and difficulties with speech, language, orientation, and comprehension. In addition, the hallmark cognitive changes associated with dementia are often accompanied by changes in behavior known as NPS (see Section 1.3 of this thesis for a more detailed description of NPS).

1.2.2 Subtypes of dementia

Alzheimer’s disease is the most common form of dementia accounting for approximately 50% to 60% of all dementia cases. Alzheimer’s disease is characterized by a gradual and late onset that occurs after the age of 65, commonly around 70 to 80
years of age, and slowly progresses with a 5 to 15 year course. Characterized by early problems with short-term memory and a lack of insight into deficits, cognitive symptoms of AD also include: impairments in attention, judgment, reasoning, language, and communication. In addition to cognitive changes, AD is also accompanied by a range of NPS. Progression into AD may also occur in individuals who have a history of mild cognitive impairment, which can be considered a prodromal phase of AD. Additionally, AD dementia can be further categorized as early onset (before age 65) or late onset (after age 65) with the earlier onset form tending to be characterized by a relatively rapid rate of disease progression and deterioration in cognition.

The second most common form of dementia is vascular dementia (VAD), which occurs in approximately 10% to 20% of individuals with dementia. This type of dementia can occur suddenly after a single large stroke or a succession of strokes; or more gradually after multiple small strokes resulting in a patchy distribution of cognitive deficits. The onset of VAD typically occurs around 60 to 70 years of age and progression is often sudden or step-wise, meaning that the individual may experience periods of deterioration after a cerebrovascular event followed by periods of plateau, followed by further deterioration if another cerebrovascular event occurs. Vascular dementia can also occur in conjunction with AD, which may be referred to as a mixed dementia.

Dementia with Lewy bodies (DLB) is another form of dementia that is seen in approximately 5% to 15% of dementia cases. This disease is characterized by cognitive problems as well as spontaneous Parkinsonism such as tremor, rigidity, akinesia, and postural instability; visual hallucinations; and fluctuations in attention and
Onset of DLB occurs at approximately 70 to 80 years of age, and often has a more rapid progression than AD.\textsuperscript{39} Supportive clinical features of DLB include repeated falls, rapid eye movement sleep disturbance, depression, delusions, and fluctuations in level of consciousness.\textsuperscript{39}

Another form of dementia is frontotemporal dementia (FTD), which has been shown to occur in approximately 5\% to 10\% of all dementia cases.\textsuperscript{35} There are variants of FTD with regard to affected brain regions; however, FTDs involve initial degeneration in the frontal and temporal lobes of the brain.\textsuperscript{4,40} Onset of FTD typically occurs around 50 to 60 years of age or younger with a rapid progression over a few years.\textsuperscript{4,40} Symptoms of FTD include disinhibition, loss of insight, eating disturbances, and impaired language and social skills.\textsuperscript{4,40}

In addition to those mentioned above, dementia can be caused as a result of other disease processes, such as dementia caused by Parkinson’s disease and Huntington disease, among others.\textsuperscript{32}

Although each dementia subtype results from different underlying pathologies, they all occur as a result of major neurological disease resulting in extensive cell death and brain atrophy.\textsuperscript{41} Depending on the area affected and the order in which brain regions are affected, dementia subtypes are associated with different cognitive and NPS profiles.\textsuperscript{41,42}

1.2.3 Prevalence of dementia in different care settings

The prevalence of dementia has been shown to vary in different care settings. For example, the prevalence of dementia in community samples has been shown to be between 5\% and 42\%.\textsuperscript{35,43} In addition, a recent review on the epidemiology of mental
health disorders in LTC\textsuperscript{8} found a reported prevalence of dementia between 50\% and 70\%.\textsuperscript{8,44-49} Prevalence rates of dementia in geriatric psychiatry inpatient units have been shown to be between 4\% and 27\%.\textsuperscript{50-53} Increased prevalence in more specialized care settings, such as LTC, may occur as a result of the severity of cognitive decline, concurrent physical decline, and the difficulty in caring for individuals with NPS of dementia.\textsuperscript{54}

1.3 Overview of neuropsychiatric symptoms

In addition to cognitive changes, dementias are often accompanied by a range of non-cognitive symptoms referred to as NPS. Neuropsychiatric symptoms of dementia have been defined as “signs and symptoms of disturbed perception, thought content, mood, or behaviour that frequently occur in patients with dementia.”\textsuperscript{55} Neuropsychiatric symptoms are common among individuals with dementia. In a population-based sample of community residents in Cache County, Utah, Lyketsos and colleagues\textsuperscript{56} found that the prevalence of these symptoms was three to four times higher among individuals with dementia when compared to age matched controls. Overall approximately 80\% of individuals with dementia display NPS at some point in their illness.\textsuperscript{7,8} Neuropsychiatric symptoms of dementia encompass a variety of non-cognitive changes in mood or behaviour, including: agitation, delusions, hallucinations, sleep and nighttime disturbances, depression, apathy, elation, anxiety, irritability, appetite and eating changes, and disinhibition. These symptoms are described in detail in the following sections of the thesis.

1.3.1 Agitation
Agitation has been operationally defined as inappropriate vocal, verbal, or motor activity that is not an obvious expression of need or confusion, as judged by an outside observer.\textsuperscript{31} Using the Cohen-Mansfield Agitation Inventory (CMAI), which measures several different symptoms of agitation, three clusters of agitation symptoms have been identified: verbal agitation (e.g., yelling, repetitive vocalizations); non-aggressive physical agitation (e.g., pacing, general restlessness); and aggressive physical agitation (e.g., hitting, kicking).\textsuperscript{57} Symptoms of agitation can manifest as socially inappropriate behaviours in a variety of ways, including: behaviours that are typically appropriate, but performed at an inappropriate frequency (e.g. constant questioning); behaviours that are inappropriate according to social standards in different situations (e.g. disrobing in the hallway of a LTC facility); or as abusive or aggressive behaviour towards the individual themselves or others.\textsuperscript{58}

Another measure of NPS, the Neuropsychiatric Inventory (NPI),\textsuperscript{59} describes symptoms of agitation as behaviors such as refusing to co-operate or accepting help from others; becoming upset with caregivers; or resisting care activities (e.g., bathing, changing clothes). Agitated individuals may also curse or shout angrily; kick furniture or throw things; attempt to hit or hurt others; or become stubborn and hard to handle. Additional symptoms of agitation that are often of concern are symptoms such as making physical or verbal sexual advances; inappropriate dress or disrobing; intentional falling; hiding or hoarding items; performing repetitious mannerisms; repetitive screaming, crying, questioning, or complaining; or constant unwarranted requests for attention or help.\textsuperscript{57}
In many studies, agitation has been classified as one of the most frequent NPS in dementia. Lyketsos and colleagues found that over 40% of individuals were reported to have symptoms of agitation from the onset of the disease. Alternatively, Zuidema and colleagues found that 85% of individuals displayed at least one agitation symptom as measured by the CMAI and that 31% of individuals met the criteria for significant agitation based on the NPI. In a longitudinal study, Aalten and colleagues found that approximately 45% of individuals displayed agitation or aggression symptoms over the two year measurement period. In a review of studies examining NPS of dementia, Zuidema and colleagues found that the prevalence of agitation and aggression ranged from 48% to 82%; with aggressive physical agitation ranging from 11% to 44%; and verbal agitation from 10% to 39%.

For many of the reasons discussed above, agitation is a concerning and challenging NPS that requires appropriate identification and monitoring in order to facilitate treatment and have the best chance of alleviating patient suffering and reducing adverse consequences.

1.3.2 Psychosis

Psychotic symptoms, such as delusion and hallucinations have been shown to occur throughout the course of dementia. When experiencing delusions, individuals have fixed-false beliefs that the observer knows are not true but that persist despite the presence of strong contradictory evidence. For example, individuals may have false beliefs that people in their lives are imposters or that they are planning to hurt them. The prevalence of delusions experienced by individuals with dementia has been shown to range from 15% to more than 80%.
In addition to having false beliefs, individuals with dementia can experience hallucinations in which the individual experiences sensory perceptions that are not actually present. Hallucinations can occur in any sensory modality, including visual, auditory, olfactory, gustatory, and tactile experiences. Common examples of hallucinations include hearing voices, and seeing or talking to people who are not there. Hallucinations have been shown to occur in 8% to 47% of individuals with dementia. Both delusions and hallucinations have been shown to occur throughout the course of dementia with higher prevalence at severe stages of cognitive decline.

1.3.3 Sleep and nighttime behavior disorders

Individuals with dementia often have difficulty sleeping. This can encompass difficulty falling or staying asleep; excessive napping during the day; multiple awakenings where they are wandering, pacing, or awakening others at night; awakening too early in the morning; or a reversal in sleep patterns where they are up in the night and asleep in the day. Sleep disturbances have been shown to occur in approximately 12% to 55% of individuals with dementia, and be most frequent at moderate stages of dementia progression.

1.3.4 Depression

The clinical picture of depression in dementia can be seen as having clinically significant depressed mood; decreased pleasure in response to usual activities; social withdrawal; fatigue; feelings of worthlessness, hopelessness, or excessive inappropriate guilt; and recurrent thoughts of suicide, ideation, plan or attempt. Depression has been shown to occur in approximately half of individuals diagnosed with dementia, with the highest prevalence at very mild to mild stages of the disease. In a study
examining sex differences in the prevalence of NPS of dementia, it has been shown that depressive symptoms are more prevalent in women than men.  

1.3.5 Apathy

Although there is substantial overlap with depressive symptoms, apathy represents a distinct group of symptoms characterized by a restricted expression of affect; feelings of indifference; and poor or no motivation, interest, or effort in engaging in goal-directed behaviour for most or all of the time.  

Symptoms of apathy have been shown to be of the most prevalent NPS experienced by individuals with dementia, and have been shown to have prevalence rates ranging from 34% to 79% of individuals from the onset of dementia.  

1.3.6 Other neuropsychiatric symptoms

Alternative NPS include persistent and abnormal feelings of elation or euphoria; anxiety; irritability; appetite and eating changes; and disinhibition. Symptoms of elation have been shown to occur in 3% to 8% of individuals with dementia from the onset of cognitive symptoms, and are characterized by an individual seeming too cheerful or happy for no apparent reason, or finding humour where others do not. Studies suggest that approximately 25% to 69% of individuals experience symptoms of anxiety such as being very nervous, worried, or frightened for no apparent reason.  

Previous research has shown that approximately 34% to 50% of individuals with dementia exhibit irritability symptoms including having sudden flashes of anger, trouble coping with delays, or rapid changes in mood. In addition to irritability, appetite and eating changes have been shown to be associated with dementia, including changes in appetite (increase or decrease); weight (gain or loss); eating habits; food preferences; or eating
rituals such as eating exactly the same types of foods or eating food in the same order.\textsuperscript{59} Appetite and eating changes associated with dementia have been shown to occur in approximately 24\% to 43\% of individuals.\textsuperscript{7,60,62} Disinhibition has been shown to occur in approximately 20\% of individuals with dementia from the onset of cognitive symptoms\textsuperscript{7,60,62} and includes a loss of control of impulses and acting without considering the appropriateness for the situation, the consequences, or feelings of others.\textsuperscript{59}

1.3.7 Clusters of neuropsychiatric symptoms

Neuropsychiatric symptoms of dementia encompass a variety of symptoms which can be classified into symptom clusters that commonly occur together.\textsuperscript{74} As described earlier, agitation symptoms as measured by the CMAI can be classified into three clusters that occur frequently together, including: verbal agitation (e.g., yelling, repetitive vocalizations), non-aggressive physical agitation (e.g., pacing, general restlessness), and aggressive physical agitation (e.g., hitting, kicking). A recent factor analysis of one of the most commonly utilized rating scales that measures a broad range of NPS, the NPI, found that global NPS fall into three clusters, representing psychotic, mood/apathy, and hyperactivity symptoms.\textsuperscript{74} The first factor denoted a psychotic cluster encompassing symptoms of delusions, hallucinations, and anxiety. The mood/apathy dimension had high loadings on depression, apathy, nighttime behavior disturbances, and appetite and eating abnormalities. The hyperactivity factor had high loadings on euphoria, irritability, aberrant motor behavior, disinhibition, and agitation.

1.3.8 Prevalence and correlates of neuropsychiatric symptoms

Although prevalence rates have been shown to vary depending on the study sample chosen, diagnostic criteria used, whether co-existing disorders are excluded, and
other factors, NPS of dementia have been shown to be highly prevalent among individuals with dementia. For example, two large cross-sectional population-based studies examining the prevalence of NPS in LTC and community samples of individuals with all-cause dementia, found that over 80% of participants classified as having dementia displayed at least one NPS over the course of the disease.\(^7,60\) Longitudinal studies investigating the course of NPS in patients with dementia have found even greater prevalence rates. For example, in a longitudinal study by Aalten and colleagues\(^62\) it was found that 95% of their sample of all-cause dementia patients living in the community developed at least one NPS over two years of follow-up. Additionally, a study by Chen and colleagues\(^64\) found that 98% of individuals in their sample of elderly community residents with AD displayed NPS at some point in the disease.

In addition to being highly prevalent, research has shown that individual NPS can be more prevalent at different stages of the progression of dementia,\(^62\) where some symptoms occur during specific stages of the disease, some are more intermittently present and others occur throughout the disease.\(^62,64\) The severity of NPS does not necessarily increase with disease progression.\(^62,64,75\) For example, symptoms of anxiety and depression have been shown to occur more commonly in the early stages of the disease.\(^64\) In contrast, agitation/aggression,\(^64,72,76\) paranoid/ delusional ideation,\(^64,72\) and sensory hallucinations,\(^23,64,72\) have been shown to be most prevalent in the severe stages of dementia. In an examination of stage specific prevalence of NPS, Chen and colleagues\(^64\) found that agitation was noted in about 64% of subjects at all stages of the disease. It has been found that agitation and aggression tended to increase with dementia severity,\(^64,72,76\) peaking at the severe stages of progression into the illness with 75% of
individuals displaying agitation symptoms.\textsuperscript{64} One study has found that the presentation of symptoms of agitation/aggression tend to differ between men and women. In this study it was found that men exhibit more aggressive behavior with increased violence and threats of violence, where women tend to display more verbal agitation, such as seeking help, or complaining.\textsuperscript{69} This finding has also been supported by research by Majic and colleagues\textsuperscript{77} that found that there is a significant increased risk of verbal agitation in women.

Previous research suggests that NPS can be persistent over time. For example, results from a study by Aalten and colleagues\textsuperscript{62} indicate that NPS are highly persistent, where patients who had any symptom on one occasion were highly likely to have the same symptom again over the course of the disease. Results from sample of 191 community-dwelling individuals with dementia indicate that symptoms of apathy are highly persistent and occur through advanced stages of the disease, whereas symptoms of depression are less persistent with disease progression.\textsuperscript{62} Hyperactivity symptoms were also relatively persistent in this sample, where aberrant motor behaviours, such as pacing and wandering, increased with disease progression.\textsuperscript{62} However, psychosis was the least persistent NPS in this sample.\textsuperscript{62} Furthermore, research examining NPS in 931 individuals with dementia residing in LTC has indicated that agitation, irritability, disinhibition, and apathy were the most persistent symptoms.\textsuperscript{72}

The presence and severity of NPS has been shown not only to vary by severity of cognitive decline but also among dementia types. Studies examining the neuropsychiatric profiles in dementia have shown unique neuropsychiatric profiles by dementia types. In a study by Johnson and colleagues\textsuperscript{41} examining the NPS profiles of 2,963 individuals with
mild to moderate AD, VAD, DLB, Parkinson’s disease dementia and two mixed AD/VAD and AD/DLB variants, it was found that participants with VAD consistently reported with highest prevalence of mood, psychosis, and frontal symptoms. In contrast, individuals with AD were reported to have moderate severity of mood, psychotic, and frontal symptoms; and individuals with Parkinson’s disease dementia scored the lowest for severity across these symptom domains. Individuals with DLB were shown to experience more frequent visual hallucinations. Previous research has also shown that individuals with cortical VAD have a greater prevalence of agitation and sleep disturbances, as well as greater overall NPS scores in all NPI domains, compared to those with AD.

Additionally, NPS have been shown to correlate with a variety of medical conditions. Previous research has found that individuals with a history of head injury, alcohol abuse, and stroke may increase the likelihood of individuals with dementia to experience specific NPS. For example, it has been shown that in individuals with AD, a history of head injury is associated with significant increases in NPS scores, especially inappropriate elation, compared to those without a history of head injury. Alcohol abuse has been shown to be associated with a significantly increased risk of elation and disinhibition scores in individuals with AD and VAD. Additionally, it has been found that a history of stroke increases the risk of agitation in individuals with AD, but not among individuals who are diagnosed with VAD or a VAD/AD variant.

1.3.9 Impact of neuropsychiatric symptoms in dementia

In addition to being quite common in individuals with dementia, NPS are important because they are associated with a variety of adverse outcomes. The
identification of individuals with NPS in dementia is important because individuals who experience these symptoms show significantly greater psychological, neurological, and functional impairments than their non-symptomatic counterparts.\textsuperscript{79}

For individuals with dementia, NPS add an additional burden to the compromised functioning and ultimately severely debilitating deterioration associated with dementia progression.\textsuperscript{80} Neuropsychiatric symptoms are the leading cause of admission to LTC;\textsuperscript{81-83} are associated with increased cost of care;\textsuperscript{84} and greater impairment in activities of daily living (ADL).\textsuperscript{85} Neuropsychiatric symptoms are also associated with a more rapid decline in cognition and function;\textsuperscript{83,86,87} an increased risk of mortality;\textsuperscript{83} and a decreased quality of life for both patients\textsuperscript{88} and caregivers.\textsuperscript{88,89} Symptoms of agitation are also associated with increased risk of adverse events. For example, depression scores have been shown to increase in residents who have worse agitation, and improve in residents whose agitation improved.\textsuperscript{90} In a recent study by Volicer and colleagues\textsuperscript{90} depression scores of participants were significantly higher in residents with agitation at every period of the study. Physically aggressive and verbally agitated behaviour were shown to be associated with depressive symptoms beyond the effects of dementia severity.\textsuperscript{77} Additionally psychosis scores have been shown to increase in individuals with agitation.\textsuperscript{90} Furthermore, in a cross-sectional study by Majic and colleagues,\textsuperscript{77} it was found that increased stages of dementia severity was associated with increased risk of verbally agitated behaviour, non-aggressive physical behaviour, physically aggressive behaviour, and depression.

Dementia not only has a significant impact on individuals who live with the disease, but also on their families and caregivers. When caring for individuals with
dementia, the presence of NPS results in an increased requirement for direct care when compared to dementia patients without NPS, adding to the physical and emotional strain on caregivers. Furthermore, the presence of NPS has been shown to be associated with increased caregiver stress and burnout. Of all NPS, the three symptoms most associated with caregiver burden have been shown to be agitation, apathy, and aberrant motor behaviour. As a result of the serious adverse consequences associated with NPS, management of NPS is an important component of providing care for individuals with dementia, formal and informal caregivers.

1.4 Measurement of neuropsychiatric symptoms

In order to assess and treat NPS it is important to have standardized tools that evaluate the frequency and severity of NPS. There are numerous challenges associated with the measurement of NPS in dementia. Impaired language and executive functioning may contribute to an individual’s limited capacity to convey their subjective experiences of NPS. Therefore, measurement of NPS in dementia often relies on identification and assessment of NPS by an informant who is familiar with the individual.

1.4.1 Measurement of neuropsychiatric symptoms by direct observation

Direct observation and recording of NPS could be considered the “reference standard” for evaluation of these symptoms. The Agitated Behaviour Mapping Instrument is one example of an observational assessment tool and is used to rate agitation as well as the social and environmental conditions in LTC facilities. This measure requires informants to observe an individual’s behaviour over a 3-minute observation period during each hour for 24-hours and count the number of times a list of 14 behaviours occur. Observers are required to simultaneously record information such as
potential triggers of the behaviour; the sound, light, and activity levels in the environment; and how many other people are in the room. Due to the complexity of this observational measure, extensive training is required for proper use.\textsuperscript{95} In a study by the scale creators, average inter-rater reliabilities for items on this instrument were shown to be 0.93.\textsuperscript{94} Agitated behaviours of a sample of 175 individuals with dementia residing in LTC have been examined using the Agitated Behaviour Mapping Instrument and the CMAI. Results from this study showed significant positive correlations between items describing verbal agitation ($r$=0.17 to 0.44), non-aggressive physical agitation ($r$= 0.32 to 0.56), and aggressive physical agitation ($r$=0.41) between the two measures, demonstrating convergent validity between direct observation and informant-rated measures of agitation.\textsuperscript{32}

1.4.2 Caregiver or healthcare provider questionnaires

Direct observation of behaviors is time consuming, very costly, and requires time sampling that limits the period covered by assessment,\textsuperscript{96} and therefore direct observation is not feasible in most routine dementia care settings. As a result, most of the commonly employed measures of NPS are based on caregiver or nursing staff reported questionnaires of the frequency that NPS were observed over a certain time period in the past, typically within the past two to six weeks.

There are many informant-rated questionnaires that have been developed to assess NPS. Measures have been developed and validated for use in specific dementia populations,\textsuperscript{59,97-103} elderly,\textsuperscript{57,104,105} or the general population;\textsuperscript{106-109} and designed to measure particular NPS or a variety of NPS. For a review of the characteristics of
common NPS rating scales, including the informants used, the rating method, the number of items, and the behaviours assessed, see Table 1.1.

1.4.2.1 Measures of agitation

Measurement scales have been developed to assess specific NPS, such as agitation. The CMAI is one of the most commonly utilized measures of agitation in older adults. Originally developed to assess the frequency of agitated behaviours in elderly persons, the CMAI has frequently been utilized to measure agitated behaviours in individuals with dementia. Rated by an informant familiar with the individual, the CMAI is a 29-item rating of the frequency of agitation symptoms over the preceding 2 weeks on a 7-point Likert scale between 1 (Never) and 7 (Several times an hour). Possible scores can range from 29 to 203, with higher scores representing a higher frequency of agitated behaviours. The CMAI has shown high levels of internal consistency with Cronbach’s α values of 0.86, 0.91 and 0.87 for the day, evening, and night shift raters, respectively. Interrater reliability, as measured by an intra-class correlation (ICC), for the total score, verbal agitation, non-aggressive physical agitation, and aggressive physical agitation subscores was 0.41, 0.61, 0.26, 0.66, respectively. In addition, previous research has indicated that inter-rater reliabilities range from 0.10 to 0.72 and test-retest reliability for CMAI items was shown to be as low as 0.32 and as high as 1.00. Test-retest reliabilities for CMAI total, verbal agitation, non-aggressive physical agitation, and aggressive physical agitation subscores have been shown to be 0.89, 0.86, 0.83, and 0.82, respectively. Furthermore, correlations between the direct observations and ratings obtained from the CMAI in the same individual during the same time period have been shown to be only moderately correlated (r = 0.20 to 0.38) indicating the questionnaire
ratings may have limited criterion validity when compared to direct observations of behavior. Additional details about the CMAI are presented in Section 2.3.3.1 in this thesis.

In addition to the CMAI, the Pittsburgh Agitation Scale was developed and validated for the measurement of agitation symptoms in dementia populations. Inter-rater reliability, as measured by an ICC of Pittsburgh Agitation Scale total scores in acute geriatric psychiatry inpatient units (n=4) and nursing homes (n=2) were good with ICC=0.82 and 0.93, for measures in hospital and LTC, respectively. As a measure of validity, the authors of the scale compared Pittsburgh Agitation Scale scores from when interventions of as needed (PRN) medications or restraints occurred to when these interventions did not occur. Results from this study support content validity of this measure, as mean Pittsburgh Agitation Scale scores were 2.2 ± 2.5 (range: 0 to 12) when no intervention was needed, and significantly higher at 8.9 ± 4.9 (range: 4 to 14) when interventions were needed. Additionally, ICC values for the individual items measuring motor agitation, aggressiveness, aberrant vocalizations, and resisting care activities were moderate to high, with ICC values of 0.54, 0.63, 0.64, and 0.88, respectively.

1.4.2.2 Measures of depression

In addition to measures that are used to assess NPS of agitation, scales have been developed to measures symptoms of depression. The Cornell Scale for Depression in Dementia (CSDD) was specifically developed to assess the signs and symptoms of major depression in individuals with dementia. In a study by the measure developers, it was determined that the scale has good inter-rater reliability with total CSDD score weighted kappa value of 0.67 and supported by individual item correlations
Internal consistency has been shown to be low to high, with mean ICC=0.24 among items on the CSDD, and α=0.84. Furthermore, a Kruskal-Wallis analysis of variance demonstrated that the CSDD was able to distinguish subjects with depressive symptoms of various intensity in both hospitalized and LTC residents. Cornell Scale for Depression in Dementia scores have also been shown to correlate moderately with scores on several other depression scales, including the Hamilton Depression Rating Scale (r=0.60) and the Geriatric Depression Scale (r=0.36) in 76 individuals with AD. Additional details about the CSDD are presented in Section 2.3.3 in this thesis.

The Geriatric Depression Scale was developed for use in non-demented elderly individuals and has been used to measure depression symptoms in mild to moderately cognitively impaired older adults. A recent factor analysis of the Geriatric Depression Scale has indicated that items associated with apathy, rather than dysphoric symptoms of depression, accounted for 42% of the total variance in a sample of 569 individuals with a diagnosis of probable AD. Analysis of item frequencies showed that cognitive impairment (e.g., memory problems, difficulties with concentration) and apathy were among the most frequently endorsed items on the Geriatric Depression Scale in this sample, indicating possible problems with the scale’s discriminant validity. Other scales that have been developed for the measurement of depression in populations of individuals with primary affective disorder without dementia have also been validated in populations with dementia. These scales have included the Hamilton Rating Scale for Depression and the Montgomery-Asberg Depression Rating Scale. 1.4.2.3 Measures of apathy
In addition to scales used to identify and measure symptoms of agitation\textsuperscript{56,101} and depression\textsuperscript{103,104,107,108} in dementia, scales have been used to measure symptoms of apathy.\textsuperscript{105,109} The Apathy Evaluation Scale\textsuperscript{105} was developed for use in individuals with brain related pathology. In a study by the scale creators,\textsuperscript{105} 123 individuals with probable AD, major depression, healthy elderly, and individuals with stroke were examined with the three versions (patient, clinician, and informant) of the Apathy Evaluation Scale. Internal consistency reliability, as measured by Cronbach’s $\alpha$ coefficient, was shown to be satisfactory for each version of the Apathy Evaluation Scale, ranging from 0.86 to 0.94. The ICC for two clinician raters was found to be 0.94 and mean total $k=0.58$ for the Apathy Evaluation Scale clinician version.\textsuperscript{105} Inter-rater reliability for the clinician version was 0.94, with test-retest reliability of 0.88 and internal consistency of 0.90.\textsuperscript{105}

The Apathy Inventory\textsuperscript{109} was developed to determine the presence of apathy in individuals with brain disorders using information reported from patients and caregivers. In a study by the scale developers\textsuperscript{109} concurrent validity was shown by comparing the Apathy Inventory to the apathy subscore of the NPI. In a sample of AD patients, using the caregiver reported version of the Apathy Inventory, it was found that the two items measuring lack of initiative and lack of interest were significantly correlated with the NPI-Apathy subscore with $r=0.22$ to 0.66. Internal consistency, as measured using Cronbach’s $\alpha$ coefficient, was rated at 0.84 for the overall score on the caregiver version. Furthermore, inter-rater agreement ($k=0.99$) and rest-retest reliabilities for individual items ($k=0.97$ to 0.99) and global score ($k=0.96$) were shown to be high.

1.4.2.4 Global measures of neuropsychiatric symptoms
In addition to measures used to assess NPS of agitation,\textsuperscript{57,102} depression,\textsuperscript{103,104,107,108} and apathy,\textsuperscript{105,109} such as those discussed above, scales have been developed to assess global NPS symptomology. The 12-item NPI\textsuperscript{59} is one of the most commonly utilized global measures of NPS. The NPI has shown high levels of internal consistency with Cronbach’s $\alpha$ values ranging from 0.76\textsuperscript{117} to 0.88.\textsuperscript{59} A majority (78\%) of scale items showed no correlation to each other\textsuperscript{59} indicating that NPI subscale items are assessing different behaviours and also indicating that item scores may be more relevant than NPI total score. However, other psychometric properties of this measure highlight some limitations of questionnaire-based measures.\textsuperscript{110,111} Inter-rater reliabilities have been shown to range from 0.12 to 0.70.\textsuperscript{111} In a study by Cummings and colleagues\textsuperscript{118} test-retest reliability of two interviews three weeks apart was shown to range from 0.79 to 0.86 for overall symptom frequency and severity, respectively. However, lower correlation coefficients were found for specific items, such as the severity of agitation ($r=0.51$) and irritability ($r=0.53$), as well as the frequency of anxiety and irritability symptoms ($r=0.51$ for both items).\textsuperscript{118} Test-retest reliability was shown to range from 0.23 to 0.80 in some samples.\textsuperscript{111} Additional details about the NPI are presented in Section 2.3.3.2 in this thesis.

Additional global measures of NPS have been developed to evaluate the severity of NPS in individuals with AD following pharmacological interventions\textsuperscript{97} and as baseline measures.\textsuperscript{98,99} These measures include the Alzheimer’s Disease Assessment Scale-Non-Cognitive Subscale;\textsuperscript{97} the Behaviour Pathology in Alzheimer’s Disease\textsuperscript{98} scale; and the Consortium to Establish a Registry for Alzheimer’s Disease-Behaviour Rating Scale for Dementia.\textsuperscript{99} There are some limitations associated with these measures. For example,
previous research has indicated that the Alzheimer’s Disease Assessment Scale-Non Cognitive subscale has a lack of discriminant validity due to having significant
correlations with a measure assessing the severity of cognitive symptoms associated with
dementia, the Alzheimer’s Disease Assessment Scale-Cognitive subscale ($r=0.67$).\textsuperscript{119} Previous research utilizing the Behaviour Pathology in Alzheimer’s Disease scale has
found that kappa coefficients on rater agreement of the presence or absence of symptoms,
ranged from as low as 0.43 to as high as 1.0.\textsuperscript{120} The Consortium to Establish a Registry
for Alzheimer’s Disease-Behaviour Rating Scale for Dementia assumes that patients are
able to verbalize NPS\textsuperscript{121} and as such is only suitable for assessing NPS in individuals
with mild to moderate AD.

Other global NPS measures have been developed for the use in other populations
and utilized in the measurement of NPS in individuals with dementia. For example, the
Neurobehavioural Rating Scale;\textsuperscript{101} was initially developed to assess the cognitive,
personality, and behavioural disturbances resulting from traumatic closed head injury.
Another example is the Brief Psychiatric Rating Scale\textsuperscript{106} that was developed and
validated in the general population to assess the presence of psychotic and non-psychotic
symptoms in individuals with major psychiatric illnesses such as schizophrenia and has
been used without modification in individuals with dementia. Some limitations of these
measures have been found in studies examining their use. For example, the reliability of
Neurobehavioural Rating Scale factor scores has been shown to vary substantially
between raters, ranging from 0.50 on measures of verbal disturbances to 0.91 on
measures of behavioural retardation.\textsuperscript{122} Previous research utilizing the Brief Psychiatric
Rating Scale has indicated limited construct validity as a measure of NPS, as the scale
measures a variety of cognitive and non-cognitive symptoms. In previous studies, inter-rater reliability has ranged from low to high depending on the symptom measured with kappa values ranging from 0.13 to 1.00.
| Measure       | Source (First Author, Year) | Informant                         | Rating Method                 | No. Of Items | Agi | Sle | Dep | Psy | Apa | Irr | Ela | Dis | App | Anx | Mot |
|--------------|----------------------------|-----------------------------------|-------------------------------|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| **Agitation**|                            |                                   |                               |              |     |     |     |     |     |     |     |     |     |     |     |     |
| Elderly      |                            |                                   |                               |              |     |     |     |     |     |     |     |     |     |     |     |     |
| CMAI         | Cohen-Mansfield, 1989      | Caregiver/nursing staff           | Self-administered             | 29           | ●   |     |     |     |     |     |     |     |     |     |     |     |
| Dementia     |                            |                                   |                               |              |     |     |     |     |     |     |     |     |     |     |     |     |
| ABMI         | Cohen-Mansfield, 1989      | Direct obs Clinician              | Clinician                     |              |     |     |     |     |     |     |     |     |     |     |     |     |
| PAS          | Rosen, 1994                | Caregiver/nursing staff           | Self-administered             | 4            | ●   |     |     |     |     |     |     |     |     |     |     |     |
| **Depression**|                           |                                   |                               |              |     |     |     |     |     |     |     |     |     |     |     |     |
| Dementia     |                            |                                   |                               |              |     |     |     |     |     |     |     |     |     |     |     |     |
| CSDD         | Alexopoulos, 1988          | Caregiver/nursing staff           | Clinician/trained technician interview | 19           |     |     |     |     |     |     |     |     |     |     |     |     |
| Elderly      |                            |                                   |                               |              |     |     |     |     |     |     |     |     |     |     |     |     |
| Geriatric Depression |                    |                                   |                               |              |     |     |     |     |     |     |     |     |     |     |     |     |
| Scale        | Yeseavage, 1983            | Patient                           | Self administered/technician interview | 15-30        |     |     |     |     |     |     |     |     |     |     |     |     |
| Apathy       |                            |                                   |                               |              |     |     |     |     |     |     |     |     |     |     |     |     |
| Elderly      |                            |                                   |                               |              |     |     |     |     |     |     |     |     |     |     |     |     |
| AES          | Marin, 1991                | Patient/caregiver/nursing staff   | Patient/caregiver/clinician self-administered | 18           |     |     |     |     |     |     |     |     |     |     |     |     |
| Measure | Source (First Author, Year) | Informant | Rating Method | No. Of Items | Agi | Sle | Dep | Psy | Apa | Irr | Ela | Dis | App | Anx | Mot |
|---------|-----------------------------|-----------|---------------|--------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| All     |                             |           |               |              |     |     |     |     |     |     |     |     |     |     |     |     |
| AI      | Robert, 2002                | Patient/caregiver/nursing staff | Patient/caregiver/clinician interview | 3   |     |     |     |     |     |     |     |     |     |     |     |     |
| Global NPS |                             |           |               |              |     |     |     |     |     |     |     |     |     |     |     |     |
| Dementia |                             |           |               |              |     |     |     |     |     |     |     |     |     |     |     |     |
| ADAS-NonCog | Rosen, 1984               | Patient/caregiver | Technician interview | 10  | ●   | ●   | ●   |     |     |     |     |     |     |     |     |     |
| BEHAVE-AD | Reisberg, 1987           | Caregiver | Clinician interview | 25  | ●   | ●   | ●   |     |     |     |     |     |     |     |     |     |
| CERAD-BRSD | Tariot, 1995              | Caregiver | Interview trained technician | 17-46 | ●   | ●   | ●   | ●   | ●   |     |     |     |     |     |     |     |
| NRS     | Levin, 1987                | Patient/Caregiver/nursing staff | Structured interview/technician | 28  | ●   | ●   | ●   | ●   |     |     |     |     |     |     |     |     |
| NPI     | Cummings, 1994            | Patient/Caregiver/nursing staff | Structured interview/technician | 12  | ●   | ●   | ●   | ●   | ●   | ●   | ●   | ●   |     |     |     |     |
| All     |                             | Patient/caregiver/nursing staff | Clinician unstructured interview/Direct obs | 16-24 | ●   | ●   | ●   | ●   | ●   | ●   | ●   | ●   | ●   | ●   | ●   | ●   |

*Note.* CMAI=Cohen-Mansfield Agitation Inventory; ABMI=Agitated Behaviour Mapping Instrument; PAS=Pittsburgh Agitation Scale; CSDD=Cornell Scale for Depression in Dementia; AES=Apathy Evaluation Scale; AI=Apathy Inventory; ADAS-NonCog=Alzheimer’s Disease
Assessment Scale-Non Cognitive Subscale; BEHAVE-AD= Behaviour Pathology in Alzheimer’s Disease; CERAD-BRSD= Consortium to Establish a Registry for Alzheimer’s Disease-Behaviour Rating Scale for Dementia; NRS= Neurobehavioural Rating Scale; NPI= Neuropsychiatric Inventory; BPRS= Brief Psychiatric Rating Scale; No.= Number; Agi= Agitation; Sle= Sleep disturbances; Dep= Depression; Psy= Psychosis; Apa= Apathy; Irr= Irritability; Ela= Elation; Dis= Disinhibition; App= Appetite changes; Anx= Anxiety; Mot= Motor activity; Direct obs= Direct observation.
1.4.2.5 Challenges with measurement of neuropsychiatric symptoms of dementia

Although there are numerous NPS specific scales, as well as measures designed to rate global NPS symptomology, there are significant limitations associated with current standard measures of NPS and a need for more objective and reliable measurement methods that can be employed in routine care settings. Commonly utilized scales to measure NPS, like the CMAI and NPI, depend on observers which may provide information of varying quality\textsuperscript{124} for a variety of reasons which are discussed below.

Previous research has indicated that the accuracy and reliability of these measures rely on a variety of factors.\textsuperscript{15,125} For example, in a LTC or hospital inpatient setting, reports rely on how frequently the same staff are available to observe an individual patient; how often they interact with the individual; the duration of time they have to observe the individual; how well they know the individual’s normal behaviour to detect change in symptoms; and the informant’s memory of a particular individual’s NPS over the past few weeks. Research examining sleep disturbances among nursing home patients found that nursing staff reports of patient sleep was limited by decreased nursing staff at night, and staff lack of attention to individuals who are not requesting attention.\textsuperscript{15} As a result, it is suggested that individuals who experience NPS, yet do not cause excessive workload for caregivers or staff may not be recognized or reported accurately.\textsuperscript{9,15} In support of this point, Most and colleagues\textsuperscript{9} found that the predictive value of caregiver reports were extremely limited, as caregivers did not reliably report the participant’s actual sleep by frequently underreporting symptoms.

In addition, research by Hoekert and colleagues\textsuperscript{11} found that caregivers overestimated the actual sleep time of individuals with dementia, whereas individuals
appear to have disturbed sleep through objective measures of motor activity using actigraphy. It was suggested that caregivers may underreport symptoms and disturbances if the caregiver’s sleep itself goes undisturbed.\textsuperscript{9} Furthermore, it has been suggested that professional caregivers may underreport symptom frequency and severity in an attempt to demonstrate their competence in caring for the patient.\textsuperscript{126} Possible underreporting of symptoms can result in symptoms remaining undetected and untreated, further contributing to increases in challenging behaviours and the adverse consequences associated with NPS.

Another limitation associated with utilizing caregiver or nursing staff reported questionnaires are that the scoring of these measures only account for behaviour the informant can see.\textsuperscript{9,10} In many circumstances, for example, in the measurement of sleep disturbances in individuals with dementia, it is not reasonable to expect caregivers to be aware of behaviors that occur throughout the night.\textsuperscript{25} Previous research has also found that caregivers are highly stressed and as a result compliance with completing observational measures can be poor.\textsuperscript{26} In addition, in a study examining the effect of melatonin on sleep, Serfaty and colleagues\textsuperscript{25} indicate that after participants refused to comply with the study protocol, sleep diary sheets were rarely filled out by their caregiver. It has also been suggested that some difficulties in measuring NPS may arise as family caregivers may exaggerate symptoms due to the stress they cause.\textsuperscript{126}

Additional problems with measurement of NPS in individuals with dementia may be encountered during longer periods of study where a change in observer for some participants may change the quality of data collected.\textsuperscript{124} Therefore, there are significant limitations associated with current standard measures of NPS utilizing subjective
caregiver or nursing staff reports and a need for more objective and reliable measurement methods that can be employed in routine care settings.

1.4.3 Use of actigraphy to measure neuropsychiatric symptoms of dementia

The use of actigraphy, or electronic activity monitoring, may provide a more accurate and reliable measurement of NPS when compared to the current methods for measuring these symptoms.\textsuperscript{11,12} Important potential advantages of actigraphy are that it is a non-invasive, continuous method that can be used for monitoring motor activity for extended periods of time without requiring an observer. Furthermore, previous research has shown that individuals with dementia show differences in movement patterns compared to controls that can be detected using actigraphy.\textsuperscript{21,127}

Previous research utilizing actigraphy to examine the movement patterns of individuals with dementia has shown a broad range of activity disturbances in dementia patients.\textsuperscript{11,12,17,128-130} Actigraphy has been used most extensively in the measurement of motor activity related to circadian rhythm variations and sleep patterns.\textsuperscript{9,11,20,24,128,131,132} However, it has also been used in the quantification and description of symptoms of apathy,\textsuperscript{10,127,133-135} and agitated behaviour.\textsuperscript{124,125,131}

1.4.3.1 Assessment of agitation in dementia

There have been few studies evaluating the application of actigraphy to the measurement of behavioural symptoms other than sleep disturbances and apathy in dementia. Some NPS, such as agitation, may be particularly amenable to measurement with actigraphy, as many of the symptoms of agitation are motor activities, such as wandering, or pacing.
In the study of agitation in dementia, actigraphy has been used to measure the effects of treatments such as melatonin,\textsuperscript{125} bright light treatment,\textsuperscript{23,136} acetylcholinesterase inhibitors,\textsuperscript{137} antipsychotics,\textsuperscript{24} and the cannabinoid dronabinol.\textsuperscript{125,138} These studies have shown convergent validity between subjective measures and actigraphy measures, with clinical observations supported by actigraphy measures.\textsuperscript{24,125,136,138} Furthermore, in a study by Mahlberg and Walther\textsuperscript{125} examining the effect of melatonin, dronabinol, or placebo on nighttime and 24-hour activity, both actigraphy and the NPI were able to distinguish between treatment and placebo groups, and actigraphic measures changed over time with treatment.

In addition to using actigraphy to corroborate questionnaire-based NPS measures, other studies have examined the relationship between actigraphic measurements and measures of agitation.\textsuperscript{124,131} Nagels and colleagues\textsuperscript{124} examined the correlation between actigraphy and the CMAI. In this study, participants were dichotomized into groups based on agitation, with those with a score over 50 on the CMAI representing those high in agitation and those with a score below 50 representing those that are low in agitation. Results from this study indicate that patients with high CMAI scores had higher levels of activity during the day compared with those patients with low CMAI scores.\textsuperscript{124} Additionally, correlations between actigraphic data and CMAI scores were moderate but highly significant. For example, correlations examining CMAI total scores and actigraphic variables ranged from $r=0.29$ to $0.35$. Furthermore, when examining the clusters of agitation symptoms examined in the CMAI, aggressive physical agitation and verbally agitated behaviour did not correlate significantly with actigraphic parameters.
However, the CMAI cluster of physically non-aggressive behaviour showed moderate correlations ranging from $r=0.32$ to 0.35.

An additional study examined the use of actigraphy in the quantitative evaluation of NPS severity and changes in physical activity over a 24-week follow-up period in 51 individuals with VAD. In this study, low correlation coefficients were found between changes in NPI total score and changes in diurnal, evening, and nighttime activity ($r=0.39, 0.47, \text{and} 0.32; P=0.820, 0.809, \text{and} 0.670, \text{respectively}$). Furthermore, results of this study demonstrate a strong correlation between change in Agitation and Irritability subscores on the NPI and change in diurnal activity (6am to 6pm) as measured by actigraphy ($r=0.67, P=0.043$).

1.4.3.2 Assessment of sleep disturbances in dementia

In study samples involving individuals with dementia, actigraphy has been more extensively used in the measurement of sleep and circadian rhythm disturbances. A majority of these studies have used actigraphy as an objective measurement of changes in sleep patterns in intervention studies. Many of these studies have examined the role of melatonin, bright light treatment, acetylcholinesterase inhibitors, antipsychotics, the effect of withdrawal of antipsychotic medications, or other treatments on reducing sleep disturbances in individuals with dementia.

In a majority of these studies actigraphy data has been supported by the clinical ratings of nursing staff, showing comparable direction of change in symptoms, indicating convergent validity. In a study by Ruths and colleagues exploring the effect of withdrawal of anti-psychotic medication on sleep in individuals with dementia, subjective behavioural measures using the NPI were found to be significantly associated
with mean daytime, nighttime, and 24-hour activity recorded by actigraphy, with strong correlations ($r=0.60$ to 0.64). Conversely, a study by Serfaty and colleagues\textsuperscript{25} found no correlation between reports from diary sheets completed by caregivers and objective sleep information from actigraphs. Other studies have used actigraphy to measure the prevalence and characteristics of sleep disturbances in individuals with dementia;\textsuperscript{15,21,28} how these sleep disturbances may change as a results of disease progression;\textsuperscript{18,30} and predictors of circadian rhythm maintenance.\textsuperscript{29} Research by Paavilainen and colleagues\textsuperscript{21} examined how sleep-wake and circadian rhythm pattern activities differ between those with or without dementia and found that the activity patterns of those with dementia were distinct from those without dementia, where those with dementia showed lower daytime and higher nighttime activity compared with those without dementia.

Research examining characteristics of sleep in dementia patients using actigraphy have found that some sleep parameters correlate well between actigraphy and subjective questionnaire-based measures. For example, Fetveit and Bjorvatn\textsuperscript{15} found that nursing staff observations of sleep onset latency and early morning awakenings were consistent with actigraphic measurements. However, nocturnal awakening registered by nursing staff showed poor correlation with high values of actigraphically measured awakenings after sleep onset. Possible explanations offered for this variation suggest that differences in reports were due to the reduced number of nursing staff during the night compared to daytime shifts or staff’s lack of attention to patients who woke and did not require staff attention during the night shifts by remaining quiet yet awake in bed.

1.4.3.3 Assessment of apathy in dementia
Apathy is another NPS that has been examined using actigraphy in dementia patients. These studies have focused on understanding the relationship between apathy and locomotor activity and sleep-wake patterns. In a study by David and colleagues, examining the relationship between apathy and locomotor activity in individuals with mild AD, it was found that individuals exhibiting symptoms of apathy had decreased motor activity over a 75 minute assessment period when compared to both those without apathy and healthy controls.

A cross-sectional study examining Apathy Evaluation Scale ratings and actigraphic measures of daytime activity over 5 consecutive days in a sample of 32 individuals with dementia and 21 individuals with mild cognitive impairment residing in nursing homes found similar results to those of David and colleagues. Results from this study indicate that apathy was associated with decreased daytime activity independent of diagnosis, although the effect was greater in the dementia with apathy group than the mild cognitive impairment with apathy group.

In a subsequent study by David and colleagues, individuals with AD were dichotomized into groups based on their apathy subscores on the NPI, where individuals with scores greater than four indicate those with significant signs of apathy, and those with scores lower than four indicate the absence of apathy symptoms. The motor activity of participants was measured for seven 24-hour periods, and apathy symptoms were measured using the NPI and the Apathy Inventory. The results of this study indicate that those with apathy have significantly lower daytime motor activity than those without apathy. Additionally, daytime mean motor activity (MMA) as measured by actigraphy
was significantly correlated with the apathy item on the NPI, whereas nighttime MMA did not differ between the groups.

In addition, research examining the relationships between daytime activity and apathy in a sample of individuals with FTD residing in the community\textsuperscript{135} found similar results to samples examining participants with AD\textsuperscript{127,133} and all-cause dementia.\textsuperscript{134} Research by Merrilees and colleagues found that there were strong positive correlations between apathy and lower levels of activity, increased bouts of immobility, and longer immobility bout duration in a sample of individuals with FTD ($n=13$) over 2 weeks of actigraphic measurement.\textsuperscript{135}

One study, examining the relationship between apathy and sleep-wake patterns has found that AD patients with symptoms of apathy have less consolidated nocturnal sleep than those without apathy.\textsuperscript{10} Interestingly, in this study there were no differences in scores on the sleep disturbances subscale of the NPI between participants with and without apathy, whereas there were actigraphic differences in sleep parameters. Researchers explain these results as being due to a lack of sensitivity of the NPI sleep domain as the scoring of these measures relies on accounts from informants for behaviour that they can directly observe.

1.4.3.4 Potential advantages of actigraphy in the measurement of neuropsychiatric symptoms

To date, actigraphy has been used to examine some common NPS in individuals with dementia. Research examining agitation, sleep disturbances, and apathy in individuals with dementia has indicated that actigraphy may be a useful, simple, and objective measurement of NPS. Some researchers have suggested that it may be the one
most reliable method of evaluating NPS currently available. It has also been suggested that as a result of the positive correlations between actigraphy and staff observations, that actigraphy can replace systematic behavioural observation by specialized nursing staff.

Previous research examining treatment interventions for agitation and disordered sleep patterns in elderly individuals with and without dementia have shown that actigraphy provides a responsive outcome measure that is sensitive to change in symptoms. Research examining treatment effects on symptoms of sleep and agitation show that data from actigraphy are supported by clinical ratings of symptoms, showing comparable direction of change in symptoms, and indicating that actigraphy has convergent validity with subjective measures of these symptoms.

Furthermore, research examining the relationship between actigraphy and standard NPS rating-scales has indicated that actigraphy has moderate to strong correlations between subjective measures of sleep, apathy, and agitation. However, some research has found no correlations or a trend to significant correlations between actigraphy and subjective measures of NPS.

Additionally, previous research has found that actigraphy is a measurement tool that can be used to discriminate between those that are high or low in symptoms of apathy and agitation as measured by standard informant questionnaire-based measures of NPS, between those that are demented or non-demented, and between treatment and placebo groups receiving treatment for symptoms of agitation.

To date there have been many studies examining the application of actigraphy in the measurement of sleep in dementia, but relatively few studies on the application of
actigraphy to the measurement of other NPS, such as agitation.\textsuperscript{124,131} Although the relationship between actigraphic measurements and validated assessment scales of agitation have been examined in a few studies,\textsuperscript{124,125,131} the distinct actigraphic characteristics of individuals with agitation have not been described. Furthermore, research has yet to examine the relationships between specific types of agitation and actigraphic movement, as well as how movement patterns of individuals with high levels of agitation may differ during daytime, evening, and nighttime time periods from those with low agitation symptoms.

Agitation is an important NPS to understand as it can contribute to depression,\textsuperscript{77,90} cognitive impairment,\textsuperscript{77} and caregiver burden.\textsuperscript{92} Therefore, recognizing agitation problems at an early stage of the disease progression is a first prerequisite of intervention and monitoring of progress. As a result of some of the limitations identified with relying on caregiver or nursing staff reports of symptoms, it is important to objectively assess and measure change in NPS in order to not only identify NPS but subsequently ensure that behavioural and psychological problems do not go untreated and receive necessary care. In this thesis, the application of actigraphy as an objective measure of NPS of agitation in older adults with dementia is examined.
Chapter 2

Methods

2.1 Study sites

All individuals who met the eligibility criteria outlined below who reside in long-term care (LTC) or geriatric psychiatry inpatient units in the Kingston and surrounding area were eligible for inclusion in the study.

Participants were recruited from Hastings Manor LTC facility in Belleville, Ontario, Canada and the geriatric psychiatry inpatient unit at Providence Care, Mental Health Services in Kingston, Ontario, Canada. These sites were selected as they are two sites under the clinical practice of geriatric psychiatrist Dr. Seitz. Hastings Manor is a 253 bed facility with secure Alzheimer’s disease (AD) units designated to address the special needs of individuals with dementia. The Providence Care Mental Health Services geriatric psychiatry inpatient unit is a 28 bed secure unit that provides care for seniors with dementia complicated by significant neuropsychiatric symptoms (NPS).

2.2 Participant recruitment and eligibility

Participants were recruited and data was collected from September 2013 to January 2014. If unable to provide consent, participant substitute decision makers were contacted in person or via telephone; provided with a letter of information or a verbal description of the study purpose, methods, risks, and impact; and after being informed about the study, were asked if they would like to provide consent for the participant to be included in the study.

All individuals with a diagnosis of AD or related forms of dementia were potentially eligible to participate in the study. Diagnosis of dementia was established by physician as recorded in the participant’s medical chart, as well as by clinical examination by a physician (Dr.
Seitz) to confirm diagnosis using the Diagnostic and Statistical Manual of Mental Disorders (Fifth Version) criteria for major neurocognitive disorders and complete cognitive testing. Inclusion criteria were individuals who were ambulatory and able to mobilize independently; who were able to wear an actigraph; and who had no changes in psychotropic medications in the two weeks preceding enrolment in the study. No restrictions were placed on the gender of participants selected to participate in the study. Individuals were excluded from the study if they were experiencing uncontrolled pain; were currently receiving palliative care or had a life expectancy of less than six months; were awaiting transfer to another LTC facility or hospital; or had severe cerebrovascular disease, a diagnosis of Parkinson’s disease or related movement disorders as they present potential confounders to the analysis of movement patterns. The presence of exclusionary diagnoses was established by a physician as recorded in the participant’s medical chart.

2.2.1 Ethics

Participants were assessed to determine if they were capable of providing informed consent for the study. For individuals who were not able to provide consent for themselves, consent was obtained from their substitute decision makers (Appendix A). Authorization of the Queen’s University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board and institutional approval from the participating LTC and hospital sites were granted for this study (Appendix B).

2.3 Measures

2.3.1 Participant demographic characteristics and baseline information

Demographic information collected from review of participant medical charts at the study sites included: age, gender, place of residence, and duration of time in hospital or LTC. The
duration of time in hospital or LTC was determined through intake date and reported in months. Information related to participant characteristics collected from review of participant medical charts included: participant height (centimeters), body weight (kilograms), dementia diagnosis, duration of dementia diagnosis, presence of chronic medical conditions, regularly scheduled and as needed (PRN) medications, and impairment in activities of daily living (ADL). Height and body weight were determined through review of medical chart as measured on intake into the facility and monthly measurements, respectively. Dementia diagnosis was classified as either AD, vascular dementia (VAD), dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), or other types of dementia. The duration of dementia diagnosis was determined through a review of patient medical history as recorded in their medical chart and reported in months.

Participant medical comorbidity was determined using the Charlson Comorbidity Index (Charlson) using information obtained from the participant’s medical chart. This index assesses participant disease comorbidity and associated comorbidity-adjusted life expectancy. The Charlson assesses the presence of 16 diseases with participant age factored into the score, resulting in possible scores ranging from 0 to 37, where higher scores indicate a higher disease comorbidity and poorer life expectancy. Medical comorbidity scores were calculated by summing the relevant items on the Charlson for all participants.

Regularly scheduled and PRN medications were recorded from participant’s medical charts and classified as antipsychotics, antidepressants, benzodiazepines, cholinesterase inhibitors, cognitive enhancers, sedatives, N-methyl-D-aspartate receptor antagonists, or other.

The degree of impairment in ADL was assessed using the Katz Index of Independence in Activities of Daily Living (Katz ADL). The Katz ADL scale was completed by a nursing staff
informant who was familiar with the participant. The index rates the ability of the participant in independently performing six activities, including bathing, dressing, toileting, transferring, continence, and feeding. Items are scored from 0 (*Dependence*) to 1 (*Independence*), for each of the items. Item totals are summed to provide a total score, where a score of six indicates full function, four indicates moderate impairment, and two or less indicates severe functional impairment in independently performing ADL. Prior to analyzing the data, Katz ADL scores were calculated for all participants by summing all items on the index.

### 2.3.2 Measures of cognitive impairment

The Mini-Mental State Examination\textsuperscript{143} (MMSE), and the Global Deterioration Scale (GDS)\textsuperscript{144} were used to measure the severity of cognitive impairment. Mini-Mental State Examinations were completed through an interview with the participant by a trained interviewer (A.L.K). The GDS was completed by clinician interview (Dr. Seitz) with participants.

#### 2.3.2.1 Mini-Mental State Examination

The MMSE is a 30-item measure completed by a trained interviewer with the individual to measure the severity of cognitive impairment where decreasing scores indicate more severe cognitive impairment.\textsuperscript{143} The scale consists of two sections: the first examining participants verbal responses to items that address the individual’s orientation to time, place, memory recall, and attention; and the second examining the individual’s ability to perform verbal and written commands and assessing calculation, language, and motor skills. The scores for each item, rated from 0 (*Incorrect response*) and 1 (*Correct response*), are summed to provide a total score with a maximum score of 30. One suggestion of MMSE classification of cognitive impairment indicates stages where a score of 30 represents no cognitive impairment; a score between 26 to 29 represents questionable cognitive impairment; a score of 21 to 25 represents mild cognitive
impairment; a score between 11 to 20 for moderate cognitive impairment; and a score of 0 to 10 for severe dementia.\textsuperscript{145}

The MMSE has been shown to be a valid and reliable instrument that has been used extensively in research and clinical assessments. In a study by the original authors,\textsuperscript{143} the MMSE was shown to identify individuals with cognitive impairment from cognitively normal individuals, record changes in cognition over time, as well as demonstrate concurrent validity with other measures of cognition. However, other studies have found that the MMSE was less sensitive in identifying individuals with mild cognitive impairment compared to those with more severe cognitive impairment and controls.\textsuperscript{146,147} In addition, 24-hour and 28-day test-retest, and inter-rater reliabilities have been shown to be high, with correlations of $r=0.89$, $r=0.98$ and $r=0.827$, ($P<0.001$) respectively.\textsuperscript{143} Furthermore, one-week test-retest reliabilities have been shown to be significantly high, ranging from 0.90 to 0.97 ($P<0.001$) with acceptable internal consistency (above $\alpha=0.80$).\textsuperscript{148}

The MMSE was used in this thesis to describe the global cognitive impairment of all individuals in the sample. Prior to analyzing the data, MMSE scores were calculated by summing participant scores on all items on the MMSE.

2.3.2.2 Global Deterioration Scale

The GDS rates the stage of cognitive decline from 1 (\textit{No cognitive impairment}) to 7 (\textit{Very severe cognitive decline}),\textsuperscript{144} with higher scores indicating more severe cognitive decline. The GDS assesses an individual’s functional and cognitive abilities, by taking into account an individual’s difficulty performing complex tasks such as handling finances; memory recall; language skills; orientation to date, day of the week, season and place; ability to independently perform ADL; as well as presence of NPS. In a retrospective analysis of the relationship between
GDS score and independent psychometric assessments of patients with very mild to moderately severe cognitive decline, GDS scores were shown to correlate significantly with 38 psychometric measures, including measures of reaction time, delayed recall, verbal learning, orientation, attention, and memory. Additionally, GDS scores have been shown to correlate significantly with anatomic brain changes associated with dementia utilizing positron emission tomography and computerized tomographic scans.

The GDS was used in this thesis as a measure of the progression of dementia. All participants were scored by clinician interview to fall into one of the following seven dementia stages: subjectively and objectively normal; very mild cognitive impairment; mild cognitive impairment; early dementia; moderate dementia; moderately severe dementia; or severe dementia.

2.3.3 Measures of neuropsychiatric symptoms

Standard NPS rating scales were completed through interviews with nursing staff familiar with the participants and experienced in observing NPS. Agitation was measured using the Cohen-Mansfield Agitation Inventory (CMAI) as our primary outcome measure. The Neuropsychiatric Inventory (NPI), the Cornell Scale for Depression in Dementia (CSDD), and the Clinical Global Impression-Severity (CGI-S) scales were used to measure the severity of comorbid NPS and depression. A single rater (A.L.K) performed the interviews and ratings of the interview-based NPS measures for each participant in the study after training from an experienced interviewer, Dr. Seitz. The CGI-S was completed as a global clinical measure of the severity of psychiatric behaviours and completed by clinician interview (Dr. Seitz) with participants.

2.3.3.1 Cohen-Mansfield Agitation Inventory
The CMAI\textsuperscript{57} was used as our primary outcome measure to measure the frequency of agitated behaviours present in participants. The CMAI is a 29-item rating of the frequency of agitation symptoms over the preceding two weeks rated on a seven-point Likert scale between 1(\textit{Never}) and 7 (\textit{Several times an hour}). Possible scores can range from 29 to 203, with higher scores representing a higher frequency of agitated behaviours. The CMAI groups agitated behaviors into three clusters: verbal agitation, non-aggressive physical agitation, and aggressive physical agitation. Items assessing verbal agitation include behaviours such as repetitive questioning, unwarranted requests for help, screaming or cursing. Non-aggressive physical agitation items include behaviours such as pacing, wandering, and general restlessness. Aggressive physical agitation items include behaviours such as hitting, kicking, pushing, biting, and scratching. Although the CMAI does not contain items rating the severity of behaviour, scale developers\textsuperscript{58} have suggested that the nature of most behaviour items reflect the severity of the behaviours, for example screaming is by nature more severe than repetitive sentences or questions. Please see \textbf{Section 1.4.2.1} in this thesis for a description of the psychometric properties of the CMAI scale.

Prior to examining or analyzing the data, the CMAI total score and subscale scores were calculated for each individual in the sample. Agitation subscores were computed by summing the appropriate items in the CMAI corresponding to verbal agitation (CMAI items 22 to 29), non-aggressive physical agitation (CMAI items 12 to 21), and aggressive physical agitation (CMAI items 1 to 11), respectively. In order to determine the actigraphic characteristics of individuals with agitation in dementia, participants were classified based on agitation status. After removing any outliers from the sample (see \textbf{Section 3.1.1} of this thesis for a more detailed description of outliers), participants were dichotomized into groups based on the severity of agitation using a
cutoff score found in previous research. To group those that were high and those that were low in agitation a cutoff score of greater or equal to 50 on the CMAI was used to indicate high levels of agitation. Using this cutoff score, six out of 15 participants were classified as having high levels of agitation.

2.3.3.2 Neuropsychiatric Inventory

The NPI is a 12-item rating scale which is based on a structured interview conducted by a trained interviewer with an informant who is familiar with the patient. This instrument assesses the frequency, severity, and caregiver distress associated with 12 NPS, including: delusions, agitation/aggression, anxiety, hallucinations, depression/dysphoria, irritability, aberrant motor behaviour, elation/euphoria, apathy/indifference, appetite/eating behaviours, and nighttime behaviours. Of these NPS, the NPI assesses four agitation items, including agitation, disinhibition, irritability, and aberrant motor behaviour. The NPI is administered by first asking screening questions that provide an overview of each behaviour item. If the initial screening question indicates the presence of behaviour problems for the item in question an additional seven or eight subquestions are asked to the informant to ascertain the frequency and severity of the behaviour of interest. A four-point frequency rating (1=Occasionally to 4=Very frequently) is multiplied by a three-point severity rating (1=Mild to 3=Severe) to produce a subscale score for each behaviour, and the summation of all subscale scores produces a total NPI score. The overall NPI score can range from 0 to 120, with higher scores indicating more frequent and severe behaviour problems. Please see Section 1.4.2.4 in this thesis for a description of the psychometric properties of the NPI scale.

Prior to examining or analyzing the data, total NPI scores were computed for all participants. All NPI subscale scores were then computed by averaging the relevant items for all
individuals for the delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behavior, sleep and nighttime behavior disorders, and appetite and eating changes subsections.

2.3.3.3 Cornell Scale for Depression in Dementia

The CSDD is a 19-item depression screening tool that rates the severity of depression symptoms over the previous week between 0 (Absent) to 2 (Severe) with a score of a representing that the informant was unable to evaluate the symptom in question. The summation of all items produces a CSDD total score. Possible scores on the CSDD can range from 0 to 38, with higher scores indicating more severe depression symptoms. The CSDD is completed through a structured interview with an informant who is in frequent contact with the patient. The CSDD includes items that measure mood related signs of depression (e.g., sadness); behavioural disturbances (e.g., slowing in movements or speech); physical signs (e.g., loss of appetite or weight); cyclic functions (e.g., difficulty falling asleep or multiple awakenings during sleep); and ideational disturbances (e.g., suicidal ideation, feelings of self-deprecation, or pessimism). A score of below six is associated with an absence of significant depressive symptoms; a score of greater than 10 indicates probable major depression; and a score of greater than 18 represents that the individual is experiencing significant symptoms of depression. Please see Section 1.4.2.2 in this thesis for a description of the psychometric properties of the CSDD scale. Prior to examining or analyzing the data in this thesis, CSDD total scores were calculated by summing all items on the CSDD for all participants.

2.3.3.4 Clinical Global Impression-Severity

The CGI-S is a seven-item global rating of severity of psychiatric symptoms from 1 (Normal, not ill at all) to 7 (Among the most extremely ill patients) considering the rating
clinicians total clinical experience with the population of interest. Higher scores on this measure indicate greater cognitive decline. The CGI-S scale has been shown to correlate well with a variety of scales, including the Hamilton Rating Scale for Depression and the Brief Psychiatric Rating Scale among others, across a variety of psychiatric conditions.\textsuperscript{152-155} 

The CGI-S was used as a global clinical measure of the severity of psychiatric behaviors in this thesis. All participants were scored by clinician interview and severity of behaviors were classified as normal; borderline mentally ill; mildly ill; moderately ill; markedly ill; severely ill; or among the most extremely ill patients.

2.3.4 Actigraph equipment

Participant activity variables were collected using wireless wGT3x+ activity monitors from ActiGraph, LLC (Pensacola, Florida).\textsuperscript{156} Actigraphy allows for continuous, objective, and unobtrusive data collection through the use of a piezoelectric accelerometer. The wGT3x+ activity monitors consist of a tri-axis accelerometer which converts acceleration of the vertical (Axis 1), horizontal (Axis 2), and diagonal (Axis 3) body positions into an electrical signal. When attached to the participant, the sensor continuously records any movement it undergoes. The data can then be downloaded and analysed to examine movement patterns.

Activity monitors are housed in a hard plastic case that is 4.6cm x 3.3cm x 1.5cm in size, weighing 19 grams. The wGT3x+ monitors can store up to 512 MB of data for 40 days at 30Hz, with a battery life lasting up to 30 days when fully charged. Actigraph monitors are also water resistant for up to one meter for 30 minutes.

Actigraph monitors were set to collect at a sample rate of 30 Hertz starting a minimum of five minutes after the device was attached to the participant’s wrist. Data from the wGT3x+ monitor was downloaded in raw binary format with file extension, exported to ActiLife 6.8.1
data analysis software (ActiGraph, LLC, Pensacola, Florida), and analyzed in 10 second epochs.

**Figure 2.1** shows an example of actigraphy data collected from one participant with low agitation for seven 24-hour measurement periods.
Figure 2.1 Example of actigraphy data for seven 24-hour measurement periods of one participant in the low agitation group. The vertical lines indicate activity counts for the corresponding time period (located along x-axis). The height of the vertical lines indicate activity intensity (light, moderate, vigorous, or very vigorous). Red, orange, and blue lines represent Axis 1 (vertical), Axis 2 (horizontal), and Axis 3 (diagonal) activity counts, respectively.
2.3.5 Actigraphic measures

After completing questionnaire measures with nursing staff, wGT3x+ actigraph monitors (Actigraph, LLC, Pensacola, Florida)\(^{156}\) were attached to the participant’s non-dominant wrist using a wrist band. The non-dominant wrist was chosen as the actigraph wear site in order to limit interference with daily activities (e.g., eating), as well as to be more consistent with previous research.\(^9^{12},^{14},^{20},^{22},^{24},^{27-30},^{124,125,127,131,133,137,138}\) Participants were asked to wear the wrist actigraph continuously over seven consecutive 24-hour periods within one week. The participant and nursing staff were instructed that the actigraph monitor could be left on throughout the measurement period and participants could go about their normal day, including bath time and other care activities. Participants and nursing staff were informed that the actigraph monitors could be removed at any time if participants wished to no longer participate or if participants were observed to be attempting to remove the actigraphs.

In order to examine whether actigraphy is a feasible method for measuring agitation in older adults with dementia, actigraph wear time (days) for the entire measurement period was also examined. In order to examine the actigraphic characteristics of individuals with agitation in dementia, actigraphic parameters were calculated for actigraph axes one, two, and three. In addition, the sum of the activity counts on all three axes, referred to as vector magnitude (VM) was calculated. Vector magnitude activity counts were used to calculate mean motor activity (MMA) counts, as our primary actigraphic outcome measure. Actigraph parameters collected included the 24-hour MMA which is the mean of all activity count epochs throughout each 24-hour period. Mean motor activity was then examined in three separate time periods during the day: daytime MMA (dMMA), the mean of all activity count epochs between the hours of 6am and 2pm; evening MMA (eMMA), the mean of all activity count epochs between the hours of
2pm and 10 pm; and nighttime MMA (nMMA), the mean activity count epochs between the hours of 10pm and 6am.

Actigraphic parameters were calculated to examine 24-hour, daytime, evening, and nighttime activity intensity per day, normalized to participant wear time. Activity intensity variables were classified into time (minutes) in light activity (activity intensity ranging from 0 to 2690 counts per minute; CPM); moderate activity (activity intensity ranging from 2691 to 6166 CPM); vigorous activity (activity intensity ranging from 6167 to 9642 CPM); and very vigorous activity (activity intensity with 9643+ CPM). Actigraphic variables were calculated to examine sedentary bouts defined as periods with activity counts ranging from 0 to 99 CPM for a minimum of 10 minutes. Sedentary variables calculated include the total number of sedentary bouts (mean number of sedentary bouts per day, normalized to participant wear time); the average length of sedentary bouts (mean duration of sedentary bouts per day, normalized to participant wear time); and the total time in sedentary bouts (total sedentary time detected per day, normalized to participant wear time). After downloading actigraph data, the data was wear time validated to filter out intervals of time within the data set that were recorded when the device was not being worn and/or was removed during the measurement period using the ActiLife 6.8.1 data analysis software (Actigraph, LLC, Pensacola, Florida). The Wear Time Validation tool in ActiLife identifies invalid data using a definition of a non-wear period as 60 minutes of consecutive zeros with a two minute spike tolerance and allows users to manually identify wear and non-wear periods that can be included or excluded from analysis if wear/non-wear periods are known. Wear time was determined using nursing records and reports of times in which the actigraph monitor was removed from the participant. Data from non-wear times were excluded from analysis.
After wear time validation, the Data Scoring tool of ActiLife 6.8.1 data analysis software was used to generate actigraph variables listed above. Data cutpoints to determine activity intensity levels were defined using validated cutpoints for adults using industry standard algorithms with the ActiLife analysis software. Using these algorithms activity is classified into intensity groups based on falling into a range of CPM to identify light, moderate, vigorous, and very vigorous activity, as previously described. Additionally, activity data was broken down into three time periods to examine daytime (6am to 2pm), evening (2pm to 10pm), and nighttime (10pm to 6am) activity patterns.

After computing and examining all relevant variables for normality assumptions, outliers, actigraphy wear time, as well as dichotomizing the participants based on agitation levels, a series of statistical analyses, discussed below, were performed in order to explore the present research hypotheses discussed in Section 1.1.2.2 in this thesis.

2.4 Data analysis

2.4.1 Preliminary analyses

After computing all relevant NPS and cognitive impairment variables, all questionnaire and actigraphy variables in the present data set were examined for missing data, univariate outliers, and normality by assessing the standardized scores, histograms, and scatterplots. Examination of the standardization scores and histogram plots indicated that one participant’s actigraphy scores fell above the acceptable range of three standard deviations above or below the mean for all time points examined in the study, and as a result their data was excluded from the present sample.

2.4.1.1 Demographic, cognitive, and neuropsychiatric symptom characteristics
Demographic characteristics of participants were summarized using mean ± standard deviations for continuous variables, and the number of participants and percentages for categorical variables for the total sample and for the low and high agitation subgroups. Mean ± standard deviation of the measures of cognitive impairment and NPS measures were calculated for the total sample and for the two subgroups. After verifying the normality of distribution, group comparisons between participants rated high and low in agitation were made to determine if there were differences between the demographic characteristics, cognitive impairment, or NPS presentation of participants the low and high agitation subgroups using a $t$-test for continuous variables or a $X^2$ test for categorical variables. An intra-class correlation (ICC) was used to examine the consistency with which participants were classified as high-agitation or low-agitation across the different days of actigraphic measurement.

2.4.2 Main analyses

2.4.2.1 Feasibility of actigraphy as a measure of agitation

In order to examine the hypothesis that actigraphy would be a feasible method for measuring NPS of agitation a variety of analyses were performed. The number of participants who completed the full seven days of actigraphic recording was recorded. For participants with less than seven days of actigraphic recording, the duration of time the actigraph was worn was calculated. Descriptive statistics were used to summarize nursing staff reports of actigraph removal. The mean actigraph wear time between high and low agitation groups was examined using independent samples $t$-tests to examine whether individuals high in agitation differ from participants with low agitation in the tolerability of wearing the actigraph device for a period of seven days, where lower scores indicate less tolerability.

2.4.2.2 Correlations between actigraphy and neuropsychiatric symptom measures
In order to examine the hypothesis that higher levels of agitation would be correlated with higher daytime motor activity as measured by actigraphy, Pearson’s r correlation coefficients were used to examine the relationship between CMAI (total score and verbal agitation, non-aggressive physical agitation, and aggressive physical agitation subscores) and actigraph VM-derived MMA counts for daytime, evening, and nighttime time periods. Additionally the relationships between NPI, NPI agitation related items (i.e., Agitation + Disinhibition + Aberrant Motor Behaviour + Irritability subscores), and CSDD total scores and VM-derived MMA counts were examined using Pearson’s r correlation coefficients.

2.4.2.3 Actigraphic profiles of participants in low and high agitation subgroups

Study participants were dichotomized into low or high agitation subgroups based on CMAI total scores ≥ 50 representing high agitation and CMAI total scores <50 representing low agitation. Baseline characteristics of individuals in subgroups were examined using a t-test for continuous variables or Χ² test for categorical variables.

In order to evaluate the hypothesis that individuals with agitation in dementia would have distinct actigraphic profiles, analyses were undertaken to evaluate the differences in the VM-derived MMA counts between participants rated high and participants rated low in agitation in the daytime, evening, and nighttime time periods, as well as for the total 24-hour measurement periods using independent samples t-tests. The relationships between 24-hour, daytime, evening, and nighttime activity intensity between participants high and low in agitation were examined using independent samples t-tests for time in light, moderate, vigorous, and very vigorous activity. The relationships between the total number of sedentary bouts; total time in sedentary bouts; and average length of sedentary bouts between participants rated high and participants rated low in agitation were examined using independent samples t-tests. Moving averages of
participant actigraph data in the low and high agitation subgroups were also calculated and summarized to provide a description of how activity quantity and intensity corresponded and changed throughout the 24-hour day.

2.4.2.3.1 Accuracy of actigraphy to diagnose low or high levels of agitation

In addition, a receiver operating characteristic (ROC) analysis was performed to determine the accuracy of using actigraphy to discriminate between individuals with low and high agitation by determining how much 24-hour activity delineates high agitation from low agitation. To determine the optimal VM-derived MMA cutpoint to diagnose agitation, the sensitivity, specificity, Type I, and Type II error rates corresponding to a variety of 24-hour MMA cutoff scores (ranging from 20 to 270) were calculated using the CMAI total score ≥50 as an identifier of true agitation status. The number of participants above a certain MMA cutoff and also classified as agitated using the CMAI cutoff score was identified as a true positive (sensitivity) classification. The number of participants below the MMA cutoff who were not agitated as classified by the CMAI total score ≥50 were considered true negatives (specificity). The number of participants above the MMA cutoff when they were not considered agitated using the CMAI cutoff were considered false positives (Type I error). The number of participants below the MMA cutoff when they were classified as agitated using the CMAI cutoff score were considered to be a false negative (Type II error). True positive rates (sensitivity) were plotted against false positive rates (1-specificity) for all possible MMA thresholds. A balanced approach for sensitivity and specificity was used to identify an optimal cutoff of mean 24-hour MMA activity counts to correctly classify individuals with low or high levels of agitation.

Microsoft Office Excel 2007 (Microsoft Corporation, Redmond, Washington) and SAS version 9.3 (SAS Institute Inc., Cary, North Carolina) were used to compute summary statistics,
$t$-tests, and $X^2$. The intra-class coefficient was calculated using SAS version 9.3 (Cary, N.C., U.S.A.).
Chapter 3

Results

3.1 Demographic, cognitive, and neuropsychiatric symptom characteristics of the total sample

3.1.1 Participant recruitment

Substitute decision makers for 19 individuals were approached to obtain proxy consent for participant inclusion in the study and all provided their consent. After examining participant medical charts, two individuals were excluded from the study for not meeting inclusion criteria and as a result no data was collected from them. Our study sample included 17 individuals with a diagnosis of Alzheimer’s disease (AD) or a related form of dementia who met inclusion criteria. Using the modified z-score calculation, the actigraphic data from one participant was found to exceed 3.5 for all time points examined in this study, and as a result the data from this participant was excluded from the analysis. In addition, actigraphy data for one participant in the low agitation group was lost after the participant removed the monitor and the device was unable to be retrieved. As a result, the data included were from the remaining 15 participants for whom complete and accurate data were available.

3.1.2 Participant demographic and baseline characteristics of the total sample

Demographic and baseline characteristics of participant of the total sample are presented in Table 3.1. The mean age of participants in the total sample was 74 years (SD=9) and 46% were 75 years of age or older. A majority of the sample (73%) was male and 80% were residents in the geriatric psychiatry inpatient unit at the Providence Care, Mental Health Services hospital site. The duration of time in long-term care (LTC) or hospital ranged from one month to 30 years.
and five months, with a median duration of 18 months and a mean duration of 42 months 
($SD=90$) for the total sample.

In an examination of the dementia characteristics of participants it was found that of the 
dementia diagnoses of participants, AD was the most common, occurring in one-third ($n=5$) of 
the study sample. However, 47% ($n=7$) of the participant dementia diagnoses were classified as 
other types of dementia, including mixed dementia, Korsakoff’s syndrome, and unspecified 
dementia. The mean duration of dementia diagnosis was 52 months ($SD=45$; with 5 unknown).

Mean medical comorbidity scores, as measured by the Charlson Comorbidity Index 
(Charlson), ranged from 3 to 8, with a mean score for the total sample of 5.5 ($SD=1.5$) indicating 
that participants had relatively few of the co-occuring disorders identified on the Charlson.

In a review of the regularly scheduled and as needed (PRN) medications prescribed to the 
total sample it was found that a majority of the sample (93%) received either regularly scheduled 
or PRN psychotropic medication, including antipsychotics, antidepressants, benzodiazepines, or 
sedatives. Antipsychotic medications were the most prevalent medication prescribed to 
participants in both regularly scheduled (73%) and PRN (53%) medications.

Participant scores for the degree of impairment in activities of daily living (ADL), as 
measured by the Katz Index of Independence in Activities of Daily Living (Katz ADL), ranged 
from 1 ($Low$) to 6 ($High$), with a mean score of 2.5 ($SD= 1.7$), indicating that participants in this 
study had a wide range of independence in ADL ranging from being very dependent on others 
for assistance to being independent in performing ADL with moderate dependence on others 
overall.

3.1.3 Participant cognitive impairment of the total sample
Cognitive impairment scores on the Mini-Mental State Examination (MMSE) and the Global Deterioration Scale (GDS) for the total sample are presented in Table 3.1. Participant MMSE scores ranged from 0 to 21 with a mean score of 10.2 \((SD=9.4)\) for the total sample, representing a severe level of cognitive impairment for a majority of the sample. Mean GDS scores of participants ranged from 5 \((Moderately severe cognitive decline)\) to 6 \((Severe cognitive decline)\) with a mean score of 5.7 \((SD=0.5)\) for the total sample, indicating that all participants in the study were either moderately severe or severely cognitively impaired.

3.1.4 Neuropsychiatric symptoms of the total sample

Table 3.1 displays the neuropsychiatric symptom (NPS) scores on the Cohen-Mansfield Agitation Inventory (CMAI), the Neuropsychiatric Inventory (NPI), the Cornell Scale for Depression in Dementia (CSDD), and the Clinical Global Impression-Severity Scale (CGI-S) of participants of the total sample. Participant CMAI total scores ranged from 29 to 80 out of a possible range of 29 to 203, with a mean score of 47.1 \((SD=13.9)\) for the total sample, indicating that agitation symptoms occur at a moderate frequency in this sample overall. The mean CMAI subscores for verbal agitation, non-aggressive physical agitation, and aggressive physical agitation for the total sample were 6.1 \((SD=2.0)\), 10.8 \((SD=5.9)\), and 12.9 \((SD=4.4)\), respectively. These results indicate that in the total sample symptoms of aggressive physical agitation seem to be the most prevalent of the three agitation subtypes, followed by symptoms of non-aggressive physical agitation. Verbal agitation items were the least endorsed symptoms in this sample.

Participant NPI total scores ranged from 3 to 34 out of a possible 120, with a mean score of 15.8 \((SD=9.3)\) for the total sample, indicating that overall the sample had relatively few or infrequent NPS other than agitation.
Depressive symptom scores, as measured by the CSDD, ranged from 0 to 8 with a mean CSDD score of 3.7 ($SD=2.6$) for the total sample, indicating that there was an absence of significant depressive symptoms in the total sample overall and no participants met the criteria for probable major depression by having a score of 10 or more on the CSDD.

Participant CGI-S scale scores ranged from 3 (Mildly ill) to 5 (Markedly ill) with a mean score of 3.9 ($SD=1.0$) for the total sample, indicating that on average participants in the sample demonstrated moderately severe psychiatric behaviours compared to others in this population.
Table 3.1 Demographic, cognitive, and neuropsychiatric symptom characteristics of the total sample and of the low and high agitation subgroups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total sample (n=15)</th>
<th>Low agitation (n=9; CMAI&lt;50)</th>
<th>High agitation (n=6; CMAI ≥50)</th>
<th>Test statistic #</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, Mean (SD)</td>
<td>74 (9)</td>
<td>77 (7)</td>
<td>71 (11)</td>
<td>1.19</td>
<td>0.254</td>
</tr>
<tr>
<td>Male gender, N (%)</td>
<td>11 (73)</td>
<td>8 (89)</td>
<td>3 (50)</td>
<td>2.78</td>
<td>0.095</td>
</tr>
<tr>
<td>Residing in hospital, N (%)</td>
<td>12 (80)</td>
<td>8 (89)</td>
<td>4 (67)</td>
<td>1.11</td>
<td>0.292</td>
</tr>
<tr>
<td>Duration of time in LTC or hospital, months (SD)</td>
<td>42 (90)</td>
<td>18 (13)</td>
<td>77 (141)</td>
<td>-1.27</td>
<td>0.227</td>
</tr>
<tr>
<td><strong>Dementia characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia diagnoses, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>5 (33)</td>
<td>2 (22)</td>
<td>3 (50)</td>
<td>4.16</td>
<td>0.041*</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>2 (13)</td>
<td>2 (22)</td>
<td>0 (0)</td>
<td>3.67</td>
<td>0.056</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>1 (7)</td>
<td>1 (11)</td>
<td>0 (0)</td>
<td>1.83</td>
<td>0.176</td>
</tr>
<tr>
<td>Other types of dementia</td>
<td>7 (47)</td>
<td>4 (44)</td>
<td>3 (50)</td>
<td>3.55</td>
<td>0.059</td>
</tr>
<tr>
<td>Duration of dementia diagnosis (months), Mean (SD)</td>
<td>52 (44)†</td>
<td>51 (52)</td>
<td>52 (18)</td>
<td>-0.02</td>
<td>0.986</td>
</tr>
<tr>
<td><strong>Medical comorbidity</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson Score, Mean (SD)</td>
<td>5.5 (1.5)</td>
<td>5.9 (1.2)</td>
<td>4.8 (1.8)</td>
<td>1.37</td>
<td>0.193</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regularly scheduled medications, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>11 (73)</td>
<td>7 (78)</td>
<td>4 (67)</td>
<td>5.73</td>
<td>0.017*</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>8 (53)</td>
<td>5 (56)</td>
<td>3 (50)</td>
<td>4.09</td>
<td>0.043*</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>3 (20)</td>
<td>2 (22)</td>
<td>1 (17)</td>
<td>1.66</td>
<td>0.197</td>
</tr>
<tr>
<td>Sedatives</td>
<td>3 (20)</td>
<td>1 (11)</td>
<td>2 (33)</td>
<td>3.08</td>
<td>0.079</td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>1 (17)</td>
<td>2.25</td>
<td>0.134</td>
</tr>
<tr>
<td>As needed (PRN) medications, N (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>8 (53)</td>
<td>4 (44)</td>
<td>4 (67)</td>
<td>4.51</td>
<td>0.034*</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>7 (47)</td>
<td>5 (56)</td>
<td>2 (33)</td>
<td>4.41</td>
<td>0.035*</td>
</tr>
<tr>
<td>Variable</td>
<td>Total sample (n=15)</td>
<td>Low agitation (n=9; CMAI&lt;50)</td>
<td>High agitation (n=6; CMAI ≥50)</td>
<td>Test statistic #</td>
<td>P-value</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------</td>
<td>------------------------------</td>
<td>-------------------------------</td>
<td>------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Sedatives</td>
<td>2 (13)</td>
<td>1 (11)</td>
<td>1 (17)</td>
<td>1.13</td>
<td>0.289</td>
</tr>
<tr>
<td>Independence in activities of daily living</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Katz ADL, Mean (SD)</td>
<td>2.5 (1.7)</td>
<td>2.8 (1.9)</td>
<td>2.2 (1.5)</td>
<td>0.66</td>
<td>0.522</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE Scores</td>
<td>10.4 (7.8)</td>
<td>14.7 (6.3)</td>
<td>4.0 (4.9)</td>
<td>2.85</td>
<td>0.022*</td>
</tr>
<tr>
<td>GDS Score</td>
<td>5.7 (0.5)</td>
<td>5.7 (0.5)</td>
<td>5.7 (0.5)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Neuropsychiatric symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohen-Mansfield Agitation Inventory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMAI Total Score</td>
<td>47.1 (13.9)</td>
<td>37.9 (6.1)</td>
<td>60.8 (10.0)</td>
<td>-5.57</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>CMAI Verbal Agitation Subscore</td>
<td>13.3 (5.3)</td>
<td>10.9 (3.6)</td>
<td>17.0 (5.6)</td>
<td>-2.59</td>
<td>0.022*</td>
</tr>
<tr>
<td>CMAI Non-Aggressive Physical Agitation Subscore</td>
<td>17.8 (6.0)</td>
<td>14.0 (4.2)</td>
<td>23.5 (2.4)</td>
<td>-4.96</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>CMAI Aggressive Physical Agitation Subscore</td>
<td>15.9 (7.5)</td>
<td>13.0 (1.9)</td>
<td>20.3 (10.7)</td>
<td>-2.05</td>
<td>0.062</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI Total Score</td>
<td>15.8 (9.3)</td>
<td>11.6 (6.3)</td>
<td>22.2 (9.9)</td>
<td>-2.56</td>
<td>0.024*</td>
</tr>
<tr>
<td>NPI Agitation Subscore</td>
<td>3.1 (2.9)</td>
<td>1.4 (1.2)</td>
<td>5.7 (2.9)</td>
<td>-3.86</td>
<td>0.001***</td>
</tr>
<tr>
<td>Cornell Scale for Depression in Dementia</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSDD Score</td>
<td>3.7 (2.6)</td>
<td>2.8 (2.5)</td>
<td>5.0 (2.4)</td>
<td>-1.71</td>
<td>0.112</td>
</tr>
<tr>
<td>Clinical Global Impression-Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI-S Score</td>
<td>3.9 (1.0)</td>
<td>3.3 (0.7)</td>
<td>4.8 (0.4)</td>
<td>-4.67</td>
<td>&lt;0.001***</td>
</tr>
</tbody>
</table>

Note. *≤0.05; **≤0.01; ***≤0.001. #=Comparisons made between low and high agitation subgroups using χ² tests for categorical variables with one degree of freedom and t-tests for continuous variable testing. For all neuropsychiatric symptom scales, higher scores are indicative of higher levels of neuropsychiatric symptoms. † n=5 unknown; Charlson= Charlson Comorbidity Index; Katz ADL=Katz Index of Independence in Activities of Daily Living; MMSE=Mini Mental State Examination; GDS= Global Deterioration Scale; CMAI=Cohen-Mansfield Agitation Inventory.
Inventory; NPI=Neuropsychiatric Inventory; CSDD=Cornell Scale for Depression in Dementia; CGI-S=Clinical Global Impressions-Severity; SD=Standard deviation; N= Number; n=sample size. See Section 2.3 in this thesis for a description of the measures included in this table.
3.2 Actigraphic characteristics of the total sample

In an examination of activity quantity, it was found that for the 24-hour period, the mean motor activity (MMA) counts were 115.0 (SD=75.5) for the total sample. An intra-class correlation (ICC) examining the consistency with which participants were classified as high agitation or low agitation across the different 24-hour days of actigraphic measurement was shown to have a value of 0.64, indicating moderate levels of agreement of agitation classification across measurement days.

The quantity of MMA was found to vary across the 24-hour day. For the total sample, the daytime time period was associated with the second highest level of MMA throughout the 24-hour day (M=149.8, SD=104.1), and the evening period was associated with the highest levels of MMA (M=156.1, SD=101.3). As expected, the nighttime time period had the lowest amount of recorded MMA (M=32.9, SD=38.6). Additional actigraphic variables for participants of the total sample are presented in Table 3.2.
### Table 3.2 Actigraphy measurements of participants of the total sample and of the low and high agitation subgroups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total sample (n=15)</th>
<th>Low agitation (n=9; CMAI&lt;50)</th>
<th>High agitation (n=6; CMAI ≥50)</th>
<th>t-test #</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean motor activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour</td>
<td>115.0 (75.5)</td>
<td>78.6 (35.4)</td>
<td>169.6 (89.4)</td>
<td>-2.78</td>
<td>0.016*</td>
</tr>
<tr>
<td>dMMA</td>
<td>149.8 (104.1)</td>
<td>96.8 (73.5)</td>
<td>229.3 (133.2)</td>
<td>3.04</td>
<td>0.009**</td>
</tr>
<tr>
<td>eMMA</td>
<td>156.1 (101.3)</td>
<td>108.7 (74.0)</td>
<td>227.1 (156.1)</td>
<td>2.66</td>
<td>0.019*</td>
</tr>
<tr>
<td>nMMA</td>
<td>32.9 (38.6)</td>
<td>30.9 (33.1)</td>
<td>35.8 (56.4)</td>
<td>0.23</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Activity intensity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-hour activity levels (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in light activity</td>
<td>1330.9 (92.3)</td>
<td>1375.0 (40.7)</td>
<td>1264.8 (111.6)</td>
<td>2.75</td>
<td>0.017*</td>
</tr>
<tr>
<td>Time in moderate activity</td>
<td>109.1 (92.3)</td>
<td>65.0 (40.7)</td>
<td>175.3 (111.6)</td>
<td>-2.75</td>
<td>0.017*</td>
</tr>
<tr>
<td>Daytime activity levels (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in light activity</td>
<td>429.3 (50.6)</td>
<td>456.5 (21.5)</td>
<td>388.6 (55.8)</td>
<td>3.35</td>
<td>0.005**</td>
</tr>
<tr>
<td>Time in moderate activity</td>
<td>47.4 (43.3)</td>
<td>26.4 (19.6)</td>
<td>78.8 (51.6)</td>
<td>-2.80</td>
<td>0.015*</td>
</tr>
<tr>
<td>Evening activity levels (min)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in light activity</td>
<td>429.9 (47.0)</td>
<td>450.3 (17.8)</td>
<td>399.3 (61.6)</td>
<td>2.38</td>
<td>0.033*</td>
</tr>
<tr>
<td>Time in moderate activity</td>
<td>51.49 (44.4)</td>
<td>30.5 (18.1)</td>
<td>82.9 (54.9)</td>
<td>-2.7</td>
<td>0.018*</td>
</tr>
<tr>
<td>Nighttime activity levels (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in light activity</td>
<td>471.7 (22.8)</td>
<td>468.2 (17.2)</td>
<td>476.9 (30.6)</td>
<td>-0.71</td>
<td>0.489</td>
</tr>
<tr>
<td>Time in moderate activity</td>
<td>10.2 (15.2)</td>
<td>8.1 (7.7)</td>
<td>13.5 (23.0)</td>
<td>-0.67</td>
<td>0.514</td>
</tr>
<tr>
<td><strong>Sedentary analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of sedentary bouts</td>
<td>21.2 (6.8)</td>
<td>23.6 (5.4)</td>
<td>17.7 (7.8)</td>
<td>1.74</td>
<td>0.105</td>
</tr>
<tr>
<td>Total time in sedentary bouts (min)</td>
<td>644.8 (169.9)</td>
<td>659.2 (173.2)</td>
<td>623.3 (178.6)</td>
<td>0.39</td>
<td>0.704</td>
</tr>
<tr>
<td>Average length of sedentary bouts (min)</td>
<td>5.5 (2.7)</td>
<td>4.4 (1.2)</td>
<td>7.2 (2.6)</td>
<td>-2.85</td>
<td>0.014*</td>
</tr>
<tr>
<td><strong>Actigraph wear time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actigraph wear time (days)</td>
<td>6.2 (1.5)</td>
<td>6.6 (1.2)</td>
<td>5.7 (1.7)</td>
<td>1.19</td>
<td>0.255</td>
</tr>
</tbody>
</table>
Note. *≤0.05; **≤0.01. #= Comparisons made between low and high agitation subgroups using t-tests for continuous variable testing. Vector magnitude= Sum of activity counts of each actigraph axis; dMMA= Daytime mean motor activity (6am - 2pm); eMMA= Evening mean motor activity (2pm - 10pm); nMMA= Nighttime mean motor activity (10pm - 6am); min= minutes; SD= Standard deviation; n= sample size.
3.3 Feasibility of actigraphy as a measure of agitation

In order to examine the hypothesis that actigraphy will be a useful and feasible method for measuring NPS of agitation, participant adherence to actigraphy and duration of actigraphic measurement between agitation subgroups were examined. Tolerability and adherence to actigraphs were examined using descriptive statistics of nursing staff reports of actigraph removal and confirmed with review of actigraph non-wear period data. Complete seven 24-hour periods of actigraph data were available for nine of 17 participants (53%). However, less than seven 24-hour periods of actigraphic recording were completed for the remaining eight participants. The removal of actigraph devices occurred for eight participants due to a variety of reasons, including: one participant leaving the care facility due to a scheduled hospital visit; one actigraph was accidentally removed by staff; and six actigraphs were removed by participants.

Of the six actigraphs removed by participants, three were restarted and were able to collect a full seven consecutive 24-hour period of measurement; two were removed multiple times; and one was removed by participant part way through the seven day measurement period and partial data was only available for this individual. Of the actigraphs removed by participants and reapplied to collect a full measure, two participants had low agitation; one participant had high agitation; and data from one of the participants with low agitation was not used for data analysis due to being an outlier as described previously. Of the two actigraphs removed by participants multiple times throughout the measurement period, we were able to retrieve data from the actigraph of one participant with high agitation, and were unable to retrieve actigraph data from one participant with low agitation as the actigraph monitor was lost. In addition, the actigraph monitor removed by the participant part way through the seven day measurement
period and applied to another individual by nursing staff was from a participant in the high agitation group.

Of the eight actigraph monitors that had been removed, actigraph data for six participants was able to be utilized for analysis after meeting a requirement of a minimum of one 24-hour measurement period. In summary, actigraph removal occurred equally in the two agitation subgroups, where three participants in the low agitation subgroup and three participants in the high agitation subgroup removed the actigraph devices before the completion of seven 24-hour measurement periods.

The mean actigraph wear time for the total sample was close to the aim of seven 24-hour measurements ($M=6.2$ days, $SD=1.5$). Actigraph wear time did not differ between participants with low ($M=6.6$ days, $SD=1.2$) and high agitation ($M=5.7$ days, $SD=1.7$, $P>0.05$) (See Table 3.2).

3.4 Correlations between actigraphy and neuropsychiatric symptom measures

In order to examine the hypothesis that higher levels of agitation will be correlated with higher daytime motor activity as measured by actigraphy, the relationships between NPS measures and mean actigraph vector magnitude (VM)-derived (the sum of activity counts on the three actigraph axes) MMA counts for daytime, evening, and nighttime time periods were examined. Correlations between the CMAI, NPI, and CSDD NPS measure scores and MMA counts for daytime, evening, and nighttime time periods are presented in Table 3.3.

Strong statistically significant correlations were found between CMAI total scores for 24-hour ($r=0.70$, $P=0.004$), daytime ($r=0.75$, $P=0.001$, See Figure 3.1A), and evening MMA counts ($r=0.72$, $P=0.003$, See Figure 3.1B), indicating that higher levels of agitation are associated with higher levels of 24-hour, daytime, and evening activity as measured by
actigraphy. The percentage of shared variance ($r^2$) between CMAI total scores and 24-hour, daytime, and evening MMA (eMMA) counts is 49%, 57%, and 51%, respectively, demonstrating that approximately half of the variability in 24-hour MMA, daytime MMA (dMMA), and eMMA can be explained by agitation symptoms. No correlations were found between CMAI total scores and nighttime MMA (nMMA; $r=-0.03$, $P=0.917$, See Figure 3.1C), indicating no statistically significant relationships between agitation symptoms and nMMA. In support of the strong significant correlations found between agitation as measured by the CMAI and 24-hour, daytime, and evening motor activity; there were strong correlations found between agitation as measured by the NPI (Agitation + Disinhibition + Aberrant Motor Behaviour + Irritability Subscores) and 24-hour ($r=0.63$, $P=0.012$), dMMA ($r=0.67$, $P=0.006$), and eMMA ($r=0.62$, $P=0.014$).

In an examination of the subtypes of agitation that may be correlated with MMA, it was found that CMAI non-aggressive physical agitation subscores were significantly correlated to 24-hour ($r=0.60$, $P=0.018$), dMMA ($r=0.63$, $P=0.012$), and eMMA ($r=0.58$, $P=0.022$) counts. These strong correlations demonstrate that higher levels of non-aggressive physical agitation are associated with higher 24-hour, dMMA, and eMMA. Results show that approximately 35% of variance in 24-hour, dMMA, and eMMA can be explained by non-aggressive physical agitation symptoms ($r^2= 36\%, 40\%, \text{and} 34\%$, respectively).

Results also indicate that CMAI verbal agitation subscores had strong positive correlations with 24-hour ($r=0.69$, $P=0.005$), dMMA ($r=0.69$, $P=0.005$), and eMMA counts ($r=0.58$, $P=0.024$). These results illustrate that higher levels of verbal agitation are associated with higher 24-hour, dMMA, and eMMA. Results indicate that CMAI aggressive physical agitation subscores had a trend to significance with eMMA ($r=0.45$, $P=0.094$). However, no significant correlations were found between CMAI aggressive physical agitation subscores for
the 24-hour, dMMA, and nMMA periods. Furthermore, no statistically significant correlations were found between agitation subtypes as measured by the CMAI subscores (verbal agitation, non-aggressive physical agitation, and aggressive physical agitation) and nMMA (See Table 3.3), indicating that activity in the nighttime was not associated with agitation symptoms in this sample.

No significant correlations were found between NPI total scores, CSDD total scores and MMA counts at any of the time periods examined (See Table 3.3), indicating that there is no linear relationship between alternative NPS, or depression and nighttime activity, as measured by actigraphy. However, in support of the significant correlations found between CMAI total scores and actigraphy MMA for 24-hour activity and during the daytime and evening, there were significant correlations found between the agitation items on the NPI (i.e., NPI Agitation + Disinhibition + Aberrant Motor Behaviour + Irritability subscores) and 24-hour ($r=0.63$, $P=0.012$), daytime ($r=0.67$, $P=0.006$), and evening ($r=0.62$, $P=0.014$) MMA counts.
Table 3.3 Correlations between neuropsychiatric symptom measures and 24-hour, daytime, evening, and nighttime mean motor activity counts.

<table>
<thead>
<tr>
<th>Variable</th>
<th>24-hour MMA (r-value, P-value)</th>
<th>Daytime MMA (r-value, P-value)</th>
<th>Evening MMA (r-value, P-value)</th>
<th>Nighttime MMA (r-value, P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMAI Total Score</td>
<td>0.70 (0.004)**</td>
<td>0.75 (0.001)*****</td>
<td>0.72 (0.003)****</td>
<td>-0.03 (0.917)</td>
</tr>
<tr>
<td>CMAI Verbal Agitation Subscore</td>
<td>0.69 (0.005)****</td>
<td>0.67 (0.005)****</td>
<td>0.58 (0.024)***</td>
<td>0.21 (0.454)</td>
</tr>
<tr>
<td>CMAI Non-Aggressive Physical Agitation Subscore</td>
<td>0.60 (0.018)*</td>
<td>0.63 (0.012)*</td>
<td>0.58 (0.022)***</td>
<td>0.07 (0.806)</td>
</tr>
<tr>
<td>CMAI Aggressive Physical Agitation Subscore</td>
<td>0.33 (0.227)</td>
<td>0.40 (0.138)</td>
<td>0.45 (0.094)</td>
<td>-0.26 (0.356)</td>
</tr>
<tr>
<td>NPI Total Score</td>
<td>0.47 (0.081)</td>
<td>0.44 (0.098)</td>
<td>0.41 (0.127)</td>
<td>0.26 (0.355)</td>
</tr>
<tr>
<td>NPI Agitation Related Items Subscore*</td>
<td>0.63 (0.012)*</td>
<td>0.67 (0.006)****</td>
<td>0.62 (0.014)***</td>
<td>0.04 (0.897)</td>
</tr>
<tr>
<td>CSDD Total Score</td>
<td>0.19 (0.502)</td>
<td>0.19 (0.507)</td>
<td>0.15 (0.594)</td>
<td>0.08 (0.769)</td>
</tr>
</tbody>
</table>

Note. *≤0.05; **≤0.01; ***≤0.001. CMAI=Cohen-Mansfield Agitation Inventory; NPI= Neuropsychiatric Inventory; CSDD= Cornell Scale for Depression in Dementia; MMA=Mean motor activity. *NPI Agitation related items subscore includes the sum of NPI subscores for Agitation, Disinhibition, Aberrant Motor Behaviour, and Irritability.
**Figure 3.1** Correlation between Cohen-Mansfield Agitation Inventory total scores and mean motor activity counts for daytime (A), evening (B), and nighttime (C).
3.5 Comparison of demographic, cognitive, and neuropsychiatric symptom characteristics of participants in low and high agitation subgroups

3.5.1 Participant demographic and baseline characteristics in low and high agitation subgroups

The study sample was dichotomized into low and high agitation subgroups based on the CMAI total score as previously described. The demographic and baseline characteristics of individuals in the two agitation subgroups were then examined to identify potential confounders. A comparison of demographic and baseline characteristics of participants in the low and high agitation subgroups is presented in Table 3.1.

There were no significant differences found between agitation subgroups for the demographic variables of mean age, gender, place of residence, and duration of time in LTC or hospital.

When examining dementia characteristics of participants in the low and high agitation subgroups it was found that there was no significant difference between groups for the duration of dementia diagnosis. However, there were significant differences between low \((n=2, \%e=22)\) and high \((n=3, \%e=50, P=0.041)\) agitation subgroups in dementia diagnosis, where there were a greater percentage of participants with AD in the high agitation subgroup compared to the low agitation subgroup and no differences between subgroups for participants diagnosed with other types of dementia (See Table 3.1).

There were no significant differences found between low \((M=5.9, SD=1.2)\) and high \((M=4.8, SD=1.8, P=0.193)\) agitation subgroups for medical comorbidity, as measured by the Charlson.
Results indicate significant differences between low and high agitation groups for regularly scheduled and PRN medications, where participants with low agitation were prescribed more regularly scheduled antipsychotic and antidepressant medications, as well as more antipsychotic and benzodiazepine PRN medications (See Table 3.1). There were no differences in regularly scheduled benzodiazepines, sedatives, and cholinesterase inhibitors medication, nor PRN sedatives between participants in the high and low agitation subgroups. Additionally, of the participants with prescribed PRN medication two participants (one in the low agitation subgroup and one in the high agitation subgroup) received one dose of PRN antipsychotics and one participant in the low agitation subgroup received one dose of PRN sedatives throughout the measurement period. There were no differences in PRN use between agitation subgroups throughout the measurement period.

There were also no significant differences found between low ($M=2.8, SD=1.9$) and high ($M=2.2, SD=1.5, P=0.522$) agitation subgroups in independence in ADL, as measured by the Katz ADL.

3.5.2 Participant cognitive impairment in low and high agitation subgroups

Comparisons of cognitive impairment scores of participants in the low and high agitation subgroups are presented in Table 3.1. Results showed that there was a significant difference between MMSE scores of participants with low agitation ($M=16.6, SD=7.6$) and high agitation ($M=2.8, SD=4.2, P=0.002$), where participants in the high agitation subgroup had lower scores indicating more severe cognitive impairment. There were no significant differences in GDS scores found between participants in the low ($M=5.7, SD=0.5$) and high ($M=5.7, SD=0.5, P=1.000$) agitation subgroup, demonstrating
that both groups were characterized as being between moderately severe and severe cognitive decline, and as described in the GDS, they may require assistance in performing ADL and maintaining hygiene.\textsuperscript{144}

3.5.3 Neuropsychiatric symptoms in low and high agitation subgroups

In support of the classification of participants as low or high in agitation in this study, there were significant differences between CMAI total scores of participants with low agitation ($M=37.9$, $SD=6.1$) and high agitation ($M=60.8$, $SD=10.0$, $P<0.001$) as anticipated. Further support of the agitation classification used in this thesis was provided by the significant differences found between the NPI Agitation subscores of participants with low agitation ($M=1.4$, $SD=1.2$) and high agitation ($M=5.7$, $SD=2.9$, $P=0.001$), indicating that participants in the high agitation subgroup have significantly greater levels of agitation symptoms as measured by the NPI. Examination of CMAI agitation subscores that may have differed between subgroups, demonstrated that participants in the two subgroups had significantly different levels of verbal agitation and non-aggressive physical agitation, and trend to significance in aggressive physical agitation CMAI subscores (See Table 3.1), where individuals in the high agitation group experienced significantly more levels of all three agitation types.

In an examination of potential differences in alternative NPS that could act to confound results, there was a significant difference between total NPI scores of participants with low agitation ($M=11.6$, $SD=6.3$) and high agitation ($M=22.2$, $SD=9.9$, $P=0.024$). However, when the agitation subscore items were removed, there were no significant differences found between the NPI score of participants with low agitation ($M=10.1$, $SD=6.2$) and high agitation ($M=16.5$, $SD=8.6$); $t(13)=-1.68$, $P=0.116$. 

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Furthermore, there were no significant differences found in depression found between low ($M=2.8$, $SD=2.5$) and high ($M=5.0$, $SD=2.4$, $P=0.112$) agitation subgroups, as measured by the CSDD.

Low ($M=3.3$, $SD=0.7$) and high ($M=4.8$, $SD=0.4$, $P<0.001$) agitation subgroups were found to differ significantly on CGI-S scores, where participants with high agitation had higher scores indicative of increased global severity of psychiatric symptoms. Individuals with low agitation were shown to fall between the mildly and moderately ill category, whereas individuals high in agitation were shown to have more advanced severity and fall within the moderately to markedly ill category.

### 3.6 Actigraphic profiles in low and high agitation subgroups

In order to evaluate the hypothesis that individuals with agitation in dementia will have distinct actigraphic profiles, subgroup analyses were undertaken to evaluate the differences in actigraphic variables in the two agitation subgroups. Actigraphic variables including MMA quantity and activity intensity were examined for across the 24-hour measurement period and then broken down to examine dMMA, eMMA, and nMMA, controlling for participant actigraph wear time. Sedentary analysis was performed to examine potential differences in the total number, average length, and total time in sedentary bouts per day, controlling for participant actigraph wear time. Examination of actigraphic movement activity between participants in the low and high agitation subgroups included a description of movement throughout the day using moving averages of VM-derived MMA counts. Additionally, a receiver operating characteristic (ROC) analysis was performed to determine the diagnostic accuracy of various cut-points of MMA in correctly classifying participants within the low or high agitation subgroups.
Actigraphy measurements of participants in the total sample and the low and high agitation subgroups are presented in Table 3.2.

A significant difference was found between the mean 24-hour MMA counts of participants with low agitation ($M=78.6$, $SD=35.4$) and high agitation ($M=169.6$, $SD=89.4$, $P=0.016$), where individuals with high agitation had significantly more 24-hour movement activity than individuals with low agitation. In an examination of the time periods in which activity quantity may have differed between subgroups, a significant difference in dMMA was found between participants with low agitation ($M=96.8$, $SD=73.6$) and high agitation ($M=229.3$, $SD=133.2$, $P=0.009$). Differences between eMMA of participants with low ($M=108.7$, $SD=74.0$) and high ($M=227.1$, $SD=156.1$, $P=0.019$) agitation were also statistically significant. However, there were no significant differences between agitation subgroups for nMMA (See Table 3.2). These results indicate that individuals with high agitation can be differentiated from individuals with low agitation in dementia by having significantly greater levels of 24-hour activity, as well as greater activity in the daytime and evening compared to individuals with low agitation symptoms in dementia.

The time participants spent in light and moderate activity throughout the 24-hour, daytime, evening, and nighttime time periods are presented in Table 3.2 for the low and high subgroups. Due to no participants registering any activity in the vigorous or very vigorous activity levels, this information was not summarized. Participants in the low agitation subgroup ($M=1375.0$, $SD=40.7$) spent significantly more time in 24-hour light activity per day compared to the high agitation subgroup ($M=1264.8$, $SD=111.6$; $P=0.017$). These results indicate that individuals with low agitation spend more time in
light levels of activity than individuals with high agitation. Significant differences were also found between participants low in agitation ($M=65.0$, $SD=40.7$) and high in agitation ($M=175.3$, $SD=111.6$, $P=0.017$) for 24-hour measures of time in moderate activity. These results indicate that high levels of agitation are associated with greater amounts of more intensive activity.

When examining whether the time period in which activity intensity may have differed between agitation subgroups, it was found that participants low in agitation and participants high in agitation differed significantly in time spent in both light and moderate activity in the daytime and evening. These results indicate that participants in the low agitation groups had greater amounts of light activity, where individuals with high agitation had greater amounts of more intense activity during the daytime and evening. However, there were no significant differences found between agitation subgroups for nighttime activity intensity (See Table 3.2).

Sedentary analysis of participants in low and high agitation subgroups are presented in Table 3.2 (see Section 2.3.5 in this thesis for the definition of sedentary bouts). Results of the sedentary analysis indicate that there was a significant difference between the average length of sedentary bouts for participants low in agitation ($M=4.4$, $SD=1.2$) and high in agitation ($M=7.2$, $SD=2.6$, $P=0.014$), where individuals in the high agitation subgroup had longer sedentary bouts on average than individuals with low agitation. However, there were no differences between participant subgroups for total number of sedentary bouts and total time in sedentary bouts when controlling for participant actigraph wear time (See Table 3.2).
The moving averages of participant actigraph data in the low and high agitation subgroups were calculated and summarized to provide a graphic representation of how activity quantity and intensity corresponds to time of day. Examination of actigraphic movement patterns indicate that activity in individuals with low agitation tends to rise and then plateau between the hours of 1pm and 9pm, whereas the activity of individuals with high agitation tends to rise steadily until peak around 7pm and 8pm where it begins to decline. The highest point or peak of activity in each 24-hour period was at approximately 9pm for both low and high agitation groups; however activity in the low agitation group did not reach the amplitude of the activity in the high agitation group. Additionally, low levels of activity in the low agitation group occurred for approximately 8 to 11 hours between the hours of 1am and 12pm, where the lowest activity for the high agitation group occurred for approximately 7 to 10 hours between 12am and 11am.

3.5.1 Accuracy of actigraphy to diagnose low or high levels of agitation

Furthermore, a ROC analysis was performed to examine the use of actigraphy to discriminate between individuals with low and high levels of agitation by determining how much 24-hour activity delineates high agitation from low agitation. Using a balanced approach for sensitivity (83%) and specificity (56%), an optimum measure was obtained using a cutoff of 24-hour MMA over seven 24-hour periods equal to 80 (Arbitrary actigraph units). Using these cutoffs, the area under the curve was 0.82 for the actigraph correctly classifying individuals with low or high levels of agitation (See Figure 3.2).
Figure 3.2 Receiver operating characteristic (ROC) analysis with varying threshold of 24-hour vector magnitude-derived mean motor activity in diagnosing low or high agitation as defined by Cohen-Mansfield Agitation Inventory total scores. True positive rates (sensitivity) were plotted against false positive rates (1-specificity) for all possible mean motor activity thresholds, indicated under the points on the ROC curve.
Chapter 4

Discussion

4.1 Thesis summary

This thesis is one of the first studies to compare the actigraphic movement patterns of individuals with low and high levels of agitation in dementia for several days of measurement. This thesis examined the actigraphic profiles of 15 individuals with dementia and compared questionnaire–based measures of neuropsychiatric symptoms (NPS) with actigraphic measures of motor activity. Results from this thesis indicate that despite some challenges in collecting actigraphic measures in individuals with dementia, actigraphy appears to be a feasible method of measuring NPS of agitation in this population. Higher levels of actigraphic movement activity were shown to have significantly strong positive correlations between agitation with Cohen-Mansfield Agitation Inventory (CMAI) total scores, as well as CMAI verbal agitation and non-aggressive physical agitation subscores for both the daytime and evening time periods. Furthermore, individuals with high agitation were shown to have distinct actigraphic profiles characterized by significantly more activity with higher intensity throughout the measurement period than individuals with low agitation. Results from this thesis indicate that individuals with high agitation in dementia can be differentiated from individuals with low levels of agitation by their movement patterns.

4.2 Main findings

4.2.1 Feasibility of actigraphy as a measure of agitation

The first objective of this thesis was to determine key facilitators and barriers to the use of actigraphy for measuring NPS of agitation; of which we hypothesized that
**Actigraphy will be a feasible method for measuring NPS of agitation.** In partial support of the first hypothesis, results of the duration of actigraphic measurement indicate that actigraphy appears to be a feasible method for measuring NPS of agitation. However, the results of the adherence to actigraphy point to some potential challenges to utilizing actigraphy in dementia populations.

Examination of the adherence to wearing the actigraph device indicates that there were some difficulties in collecting actigraphic measures on individuals with dementia residing in long-term care (LTC) or geriatric psychiatry units in hospital. For the total sample, the full seven 24-hour actigraphic measurements were available for 53% of the sample. However, in eight out of 17 (47%) individuals in our sample of individuals with dementia, less than seven full 24-hour actigraphy measurements were available.

Collection of less than seven 24-hour actigraph measurements was associated with participants removing the devices before the full seven 24-hour measurements were completed (35% of total sample), a scheduled hospital visit (n=1), and accidental removal and disposal by staff (n=1). In two instances less than a full seven 24-hour measurement were completed due to miscommunications with nursing staff. However, of the six actigraph monitors removed by participants in this study there were no differences in agitation status of the participants who removed them, indicating that high agitation status did not appear to be a factor in the adherence to wearing actigraph monitors. This result was further supported by the fact that there were no differences in actigraph wear time between participants high and low in agitation.

4.2.2 *Correlations between actigraphy and neuropsychiatric symptom measures*
The second objective of this thesis was to evaluate whether specific patterns of motor activity recorded by actigraphy are correlated with agitation in older adults with dementia; of which we hypothesized that higher levels of agitation will be correlated with higher daytime motor activity as measured by actigraphy. In support of the second hypothesis, strong positive correlations were found between 24-hour, daytime, and evening mean motor activity (MMA) counts for and CMAI total scores, indicating that higher levels of agitation are associated with higher levels of activity throughout the daytime and evening.

Upon examination of the correlations between agitation subtypes and MMA counts, it was found that there were strong positive correlations between CMAI verbal and non-aggressive physical agitation subscores and 24-hour, daytime, and evening MMA. These results indicate that motor activity is particularly related to the non-aggressive physical and verbal agitation CMAI dimensions within the high agitation group. There were no significant correlations between aggressive physical agitation and 24-hour, daytime, evening, or nighttime MMA. However, there could be a possible association between CMAI aggressive physical agitation subscores and MMA counts in the evening as evidenced by the trend to significance.

In the present study, no significant correlations were found between depression as measured by the Cornell Scale for Depression in Dementia (CSDD) or alternative NPS as measured by the Neuropsychiatric Inventory (NPI) and actigraphy at any period throughout the 24-hour measurement periods. However, upon examination of the correlation between actigraphy variables and agitation related items on the NPI (i.e., the Agitation + Disinhibition + Aberrant Motor Behaviour + Irritability subscores), it was
found that there were significant correlations between 24-hour, daytime, and evening MMA. These results provide further support to the relationships found between agitation and actigraphy. One potential reason for not finding significant correlations between activity throughout the day and the NPI total score is that the NPI is a global NPS measure that assesses a group of 12 distinct NPS. Whereas significant correlations were found between the CMAI and some of it’s subscores because the CMAI measures NPS of agitation specifically.

4.2.3 Actigraphic movement characteristics of individuals with low or high levels of agitation

The third objective of this thesis was to describe the actigraphic characteristics of individuals with agitation in dementia; of which we hypothesized that individuals with agitation in dementia will have distinct actigraphic profiles.

In support of the third hypothesis in this thesis, individuals with high agitation in dementia were shown to have distinct actigraphic profiles compared to individuals with low agitation.

In an examination of quantity of MMA, results indicated that individuals with high levels of agitation have significantly higher 24-hour, daytime, and evening mean motor activity levels than individuals with low agitation. There were no differences between agitation groups for actigraphically measured nighttime mean motor activity, indicating that activity of participants at night does not appear to be influenced by agitation status. These results imply that the 24-hour MMA counts are principally driven by agitation in the daytime and evening.
In addition to individuals with high agitation having significantly more 24-hour, daytime, and evening activity, low and high agitation groups were differentiated by differences in activity intensity. Results from our study indicate that individuals with high agitation spent significantly more time in moderate activity compared to individuals with low agitation over the 24-hour period. Examination of the mean time spent in light activity for the 24-hour period between agitation subgroups indicate that individuals with low agitation spent significantly more time in light activity.

Furthermore, in an examination of the time periods in which activity intensity differed between agitation groups, results indicate that individuals with low agitation spent significantly more time in light activity in the daytime and evening compared to individuals with high agitation. In contrast, individuals with high agitation spent significantly more time in moderate activity in the daytime and evening compared to individuals with low agitation. Again, there were no significant differences found between agitation groups for any level of nighttime activity intensity.

Results from sedentary analyses support the activity intensity results, and indicate that high agitation is associated with significantly greater average length of sedentary bout. However, individuals with low and high agitation did not differ in the total number of sedentary bouts or total time spent in sedentary activity.

Examination of the patterns of actigraphic movement for participants indicated that activity in individuals with low agitation tends to rise in the morning and then plateau during the evening and decline thereafter. In comparison, activity of individuals with high agitation tends to increase steadily throughout the daytime and evening and then peak around 9pm before declining. Although the activity in both low and high
agitation groups, in this study, tended to peak around the same time, the quantity and intensity of activity was significantly different between the groups, indicating that individuals with high agitation in dementia have significantly more activity in quantity and intensity compared to individuals with low agitation.

4.2.3.1 Accuracy of actigraphy to diagnose low or high levels of agitation

Results from a receiver operating characteristic (ROC) analysis indicate that by using a mean 24-hour MMA of 80 over seven 24-hour periods, actigraphy can be used to correctly identify individuals with agitation with 83% sensitivity, and correctly identify people without agitation with 56% specificity. Furthermore, results indicate that 82% of variance in agitation classification can be explained by utilizing MMA actigraphy counts.

4.3 Synthesis of findings with previous research

4.3.1 Demographic, cognitive, and neuropsychiatric symptom correlates of agitation

The association between increased agitation and more severe levels of cognitive impairment as measured by the Mini-Mental State Examination (MMSE) is consistent with previous research.\textsuperscript{56,64,72,77,158-161} Previous studies have found dementia severity to be associated with increased risk of agitation in LTC,\textsuperscript{77,160,72,161} hospital,\textsuperscript{158} and community\textsuperscript{56,64} samples of individuals with dementia. Furthermore, increasing stages of dementia and cognitive impairment have been shown to be associated with a higher risk of all agitation subtypes, including verbal agitation, non-aggressive physical agitation, and aggressive physical agitation.\textsuperscript{77,159} The higher levels of verbal and non-aggressive physical agitation in our sample of individuals in the high agitation group who also have a mean MMSE score of 2.8, are in agreement with previous research that has indicated
that the frequency of agitated behaviours increase with dementia severity, particularly for individuals with MMSE scores within the 0 to 4 range.\(^{159}\)

Results from this thesis indicate that agitation subgroups differed on MMSE scores while having no significant differences in Global Deterioration (GDS) scores. The dissimilarity in these cognitive impairment measures could be due to differences in items included in the measures. The MMSE measures items related to cognitive impairment, including orientation to time and place, memory recall, attention language ability, calculation, and motor skills.\(^{143}\) Whereas the GDS assesses items related to both cognitive and functional abilities by taking into account an individual’s difficulty in performing complex tasks such as handling finances, the ability to perform activities of daily living (ADL), toileting, eating, dressing.\(^{144}\) Similarities in functional abilities between the groups may account for the lack of significant differences found in GDS scores.

4.3.2 Feasibility of actigraphy as a measure of agitation

Difficulties associated with collecting actigraph measures on individuals with dementia have been reported in previous research.\(^{14,19,22,25,26,128,162-164}\) Previous research has reported difficulties collecting complete actigraphic measures of participants with dementia due to technical difficulties,\(^{14,22,159,164}\) monitors lost or misplaced by participant or caregiver;\(^{72,164}\) refusal to wear actigraph monitor;\(^{14,22,56,131,160,164}\) repeated removal of the monitor;\(^{124,158}\) and participant illness.\(^64\) Comparable adherence rates have been found in previous studies that have reported having insufficient actigraph data from 43\% of participants, with 20\% repeatedly removing actigraphs, 16\% refusing the wear actigraphs; and 2\% due to acute participant illness.\(^25\)

4.3.3 Correlations between actigraphy and neuropsychiatric symptom measures
The results that CMAI total score correlations are significantly correlated with daytime and evening activity, as measured by actigraphy, are similar to results previously observed in a samples of individuals diagnosed with dementia. The significant correlations, found in this study, between CMAI total scores and daytime and evening activity, as measured by actigraphy, are similar to the results of a study by Nagels and colleagues that found moderate but highly significant correlations between CMAI total scores and daytime actigraphy counts, with daytime classified as any activity between 9am and 9pm. These results are also supported by research by Pan and colleagues evaluating the severity of NPS in individuals with vascular dementia (VAD) that found moderate significant correlations between changes in NPI agitation plus irritability subscores and changes in diurnal activity.

In support of the significant correlation between non-aggressive physical agitation and MMA counts in the daytime and evening, previous research validating actigraphy as an assessment tool for symptoms of agitation and aggression has found similar results. In a sample of 110 individuals with dementia there was a moderate significant correlation between CMAI non-aggressive physical agitation subscores and daytime activity counts. Similar to the results presented in this thesis, there was no significant correlation was found between CMAI aggressive physical agitation subscores and measures of actigraphic activity during the day. However, in contrast to the significant correlation between verbal agitation and MMA counts in the daytime evening, previous research has found no significant correlation between verbally agitated behavior and actigraphic parameters. Possible reasons for the differences concerning specific
correlations of agitation subtypes may be due to differences in study samples and the frequency of agitated behaviours observed in participants.

4.3.4 Actigraphic movement profiles of individuals with low and high levels of agitation

The results that individuals in the current study with high agitation have significantly more daytime and evening MMA are similar to results previously observed in individuals with dementia and classified by agitation status. These results are comparable to previous research that has shown that participants with agitation have significantly more actigraphic activity through the hours between 9am and 9pm than participants without agitation.

The results that the activity in individuals high in agitation have a gradual increase in activity with a peak of activity followed by a gradual decrease are supported by results from previous research indicating that there is a temporal pattern of NPS of agitation where the agitation symptoms of individuals with high levels of agitation and aggression follow an inverted U-shaped curve with a peak just before sunset.

4.4 Project impact and clinical relevance

4.4.1 Impact on measurement of neuropsychiatric symptoms

Actigraphy is an objective and non-invasive method of examining symptoms of agitation in individuals with dementia, who may be difficult to examine by other means. Actigraphy is a method capable of providing comprehensive, detailed, and objective measurements for extended periods of time that are representative of daily variations and uninfluenced by caregiver stress, expectations, recall bias, or other limitations of subjective measurements. The use of actigraphy provides an opportunity for improved data collection as it provides a wireless alternative to collect data in real-time that is non-
invasive to the participant, allows for continuous monitoring, permits analysis of day-to-day fluctuations in activity, and uses a widely available device. Results from this thesis provide strong preliminary evidence for the use of actigraphy in the measurement of NPS of agitation in individuals with dementia.

4.5 Limitations and Strengths of dissertation

As with any research study, there are limitations and strengths of this thesis study, which are discussed in the following section.

4.5.1 Limitations

One limitation of this thesis relates to the informants that were used to obtain questionnaire-based measures. Although the informants were full-time nurses who were familiar with the participants, they were typically only present for one of the three time periods, the daytime, which may have impacted the accuracy and reliability of rating of NPS at the time periods when they were not present. Furthermore, the ratings of participants who exhibit frequent symptoms that may not impact the burden on nursing staff might have been rated as less severe, impacting the accuracy of subjective questionnaire-based measures. For these reasons, the methods of assessing NPS of agitation using informant-rated questionnaire-based measures and actigraphy may be best used to complement each other as actigraphy does not give details of the specific agitation symptoms experienced by an individual.

Additionally, a small number of participants were evaluated. A priori sample size calculations indicated that a total sample size of 30 participants was required to detect a correlation of 0.40 or higher with a power of 0.80 and an α of 0.05. However, results of this study indicate that our conservative sample size calculation was larger than needed
and the associations between actigraphy and NPS measures were much stronger than anticipated.

Another limitation of this study is that the study sample was a more advanced dementia sample and as a result, the findings of this study may not be generalizable to groups of individuals with less severe cognitive impairment. However, the strong associations found in this thesis support the use of actigraphy in the measurement of agitation in individuals with severely cognitively impaired individuals with dementia.

One limitation of this study was the difficulty in collecting seven full 24-hour periods of actigraphic measurement on all the participants with dementia. Previous research has indicated that the tolerance of wearing actigraphic devices can be difficult in this population. However, despite these difficulties, actigraphy data was only unusable for two participants and these data were lost due to miscommunications with nursing staff. These results indicate that one method of facilitating improved actigraphic measurement of individuals with dementia could be by improving the communication between all members of the care team.

Although there are some barriers associated with utilizing actigraphy to assess symptoms of agitation in dementia, actions can be taken to improve the facilitation of using this method as an objective measurement of NPS of agitation in individuals with dementia.

4.5.2 Strengths

The study design represents the strength of this study. The collection of seven 24-hour periods of actigraphy data is one of the strengths of this study. Previous research has indicated that three days of accelerometer data are needed to accurately predict physical
activity levels in older adults and when examining specific intensities. In addition, gathering seven days of actigraphy data at the participant’s residence may reflect a more naturalistic spectrum of activity rather than actigraphic data gathered in other settings such as in memory clinics or laboratories. Moreover, home-based assessments may improve the feasibility of collecting actigraphy data for individuals who may not tolerate unfamiliar environments. The results of this study indicating that there are stronger correlations for daytime activity between symptoms of agitation and actigraphy, indicate that the division of the 24-hour measurement period into daytime, evening, and nighttime time periods, may be beneficial for a more detailed classification of the relationship between actigraphy and agitation in dementia. Furthermore, the use of actigraphy to measure NPS of agitation provides the capability of objective measurements that are representative of daily variations and tend not to be influenced by informant stress, expectations, or other bias. The use of actigraphy may improve the measurement of NPS of agitation by providing an objective and easy to use method of examining symptoms of agitation in individuals with dementia, who may be difficult to examine by other means.

4.6 Future research directions

This thesis examined the actigraphic characteristics of individuals with advanced dementia in institutionalized settings. One possibility for future research therefore could be to extend the study scale and scope to examine the use of actigraphy in individuals with agitation and dementia in other settings, including community samples, and/or explore the relationship between actigraphic movement patterns of individuals with agitation throughout the progression of dementia severity. Due to the small sample size and cross-sectional design of this study, future research could examine the application of
actigraphy to the measurement of symptoms of agitation in a larger sample size or in a longitudinal design.

In addition, the use of actigraphy may be used to facilitate early identification and diagnosis of these behaviours, which would result in earlier access to support, information, and available treatment options that benefit not only the individual with dementia, but also their caregivers. Results from our study indicate that there is potential for actigraphy to be used both as a diagnostic tool for identifying symptoms of agitation in individuals with dementia, as well as a measurement of change in these symptoms as a result of pharmacological or non-pharmacological interventions. Given the relatively strong correlations noted in day-to-day actigraphic measures in this thesis, actigraphy may be able to classify individuals as having agitation earlier than a more prolonged period of observation, as well as examine fluctuations of agitation symptoms corresponding to different activities throughout the day (e.g., during care times).

Future research could examine differences in study design and the effect that may have on actigraphic outcomes. For example, future research could compare the actigraphic data collected from participant’s dominant versus non-dominant wrist to examine whether there are differences in actigraphic activity recorded from these sites. Additionally, research can be completed to examine whether there are changes in MMA after the initial application of the device and whether an acclimatization period to the device’s presence would have an effect on MMA (e.g., the Hawthorne effect).

In addition, future research could examine the potential application of actigraphy to the clinical care of other populations with mental illnesses or neurological conditions who experience symptoms of agitation.
4.7 Conclusion

This thesis is one of the first studies to evaluate the application of actigraphy to the measurement of NPS among older adults with dementia. The results of our study indicate that actigraphic measures of motor behaviors are correlated with some symptoms of agitation supporting the potential future use of actigraphy as a method for measuring agitation. Furthermore, although there are some challenges associated with utilizing actigraphy to assess symptoms of agitation in dementia, these challenges appear to be possible to overcome and are outweighed by the possible benefits of utilizing actigraphy as an objective measure of agitation in individuals with dementia, who may be difficult to examine by other means.
References


18. Fetveit A, Bjorvatn B. Sleep duration during the 24-hour day is associated with the severity of dementia in nursing home patients. *International Journal of Geriatric Psychiatry*. 2006;21(10):945-950.


Appendix A

Dr. Dallas Seitz
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LETTER OF INFORMATION / CONSENT FORM
FOR CLIENTS

The Application of Actigraphy to the Measurement of Neuropsychiatric Symptoms of Dementia

Principal Investigator: Dr. Dallas Seitz
Co-Investigator: Ms. Amber Knuff

Purpose of the Study
You are invited to take part in this study to understand whether an actigraph or portable electronic sensor can be used to measure behavioural and psychological symptoms and whether you find it to be acceptable. If found to be effective, we plan to expand the program to other long-term care facilities or hospital inpatient settings, with the intent of facilitating better clinical outcomes by detecting behavioural and psychological symptoms earlier and assessing treatment response. This study will be carried out by Dr. Dallas Seitz and Ms. Amber Knuff.

What will happen during the study?
Your involvement in this study will consist of wearing the electronic sensor for 1 to 7 sessions spread over a few days, with each session lasting 24-hours.

The electronic sensor housed in a plastic case that is approximately 4.6cm x 3.3cm x 1.5cm in size. The sensor can be simply attached to a belt. Prior to wearing the sensor, we will collect some information about you from your patient chart and nursing staff such as your age, body weight, height, the severity of your cognitive impairment, degree of impairment in activities of daily living, and measures pertaining to your behaviour.

While wearing the sensor, simply go about your normal day. The sensor will record your movement activity. While you are wearing the electronic sensor, a member of the research team may be present at your long term care home. The research team member may monitor and record your behaviour for brief periods of 3 minutes. We will compare the information from the team member’s recordings to the recordings on the electronic sensor to determine whether it is working well or not.

Are there any risks to doing this study?
There are no anticipated risks associated with your participation in this study. Every effort will be made to make wearing the sensor comfortable and unobtrusive, however it is possible that you may find it uncomfortable. Should you wish, you can withdraw (stop taking part) at any time.
Are there any benefits to doing this study?
By participating in this study, you are helping us to learn more about how motor behaviours can be identified earlier in persons with dementia in long term care, which can in turn lead to quicker treatment.

Confidentiality
We will undertake a number of steps to safeguard the confidentiality of your provided information. When conducting analyses, we will not use your name or any information that would allow you to be identified. The information you provide will be kept in a locked cabinet only accessible by members of the research team. Information kept on a computer will be protected by a password. Once the study has been completed, the data will be destroyed after a period of five years.

What if I change my mind about being in the study?
It is your choice to be part of this study or not. If you decide to be part of the study, you can decide to stop (withdraw), at any time, even after signing the consent form or part-way through the study. If you decide to withdraw, there will be no consequences to you or the usual care you receive. If you withdraw part-way through the study, you will no longer wear the sensor and no new data will be collected from that point forward.

How do I find out what was learned in this study?
We expect to have this study completed by approximately August 2014. If you would like a brief summary of the results, please let us know how you would like it sent to you.

Questions about the Study
Any questions about study participation may be directed to Amber Knuff (graduate student) at 613-548-5567 ext. 5821/ 72ak1@queensu.ca or Dr. Dallas Seitz (principal investigator) at 613-548-5567 ext. 5942/ seitzd@providencecare.ca. You may also contact Dr. Roumen Milev at 613-548-5567 ext. 5823/ milevr@providencecare.ca, Head of the Department of Psychiatry at Queen’s University. If you have any questions regarding your rights as a research participant, you may contact Dr. Albert Clark, Chair of the Queen’s Health Sciences & Affiliated Teaching Hospitals Research Ethics Board at clarkaf@queensu.ca or 613-533-6081.
CLIENT CONSENT

I have read the information presented in the information letter about a study being
carried out by Dr. Dallas Seitz, of Queen’s University. I have had the opportunity to ask
questions about my involvement in this study and to receive additional details I
requested. I understand that if I agree to participate in this study, I may withdraw from
the study at any time. I have been informed that I will be given a copy of this form for my
own files. I, ______________________________, agree to participate in the study.

1. □ Yes, I would like to receive a summary of the study’s results. Please send them
to this email address ___________________________ or to this mailing address
___________________________________________________________.
□ No, I do not want to receive a summary of the study’s results.

Participant Signature: __________________________ Date: ____________________
Name of Participant (Printed) _____________________________________________
Signature of Project Investigator: _____________________ Date: ________________
Signature of Person explaining consent process: ______________________________
Appendix A

June 12, 2012

Dr. Dallas Seitz
Department of Psychiatry
Providence Care, Mental Health Services

Dear Dr. Seitz

Title: PSIY-363-12 Use of Portable Electronic Sensors to Measure Motor and Vocal Behaviors in Long-Term Care Residents with Dementia: A Feasibility Study

File # 6007054

Co-Investigators: Mr. A. Fage

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol, Mini Mental Status, Cohen-Mansfield Agitation Inventory, Neuropsychiatric Inventory, Connell Scale for Depression, Data Extraction Form, ABMI – Agitation Behavior Mapping Instrument, revised information/consent form for clients, revised information/consent form for substitute decision makers and letter of information/assent form for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following listing of ethics requirements you must fulfill over the course of your study:

Reporting of Amendments: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. Please use event form: HSREB Multi-Use Amendment/Full Board Renewal Form associated with your post review file # 6007054 in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Serious Adverse Events: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information. Serious Adverse Event forms are located with your post-review file 6007054 in your Researcher Portal (https://eservices.queensu.ca/romeo_researcher/)

Reporting of Complaints: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

Annual Renewal: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

Chair, Research Ethics Board

June 12, 2012

Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete