IMPACT OF PSYCHOLOGICAL DISTRESS ON THE MONTREAL COGNITIVE ASSESSMENT (MOCA) AMONG GERIATRIC OUTPATIENTS

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Abstract

Geriatric patients often present with multiple and occasionally complex diseases compared to younger patients. This poses a problem to clinicians and other health care providers who must disentangle the comorbidities in order to interpret screening results accurately, diagnose disease type correctly and select treatment plan accordingly. In particular, performance on brief cognitive screening tests, such as the Montreal Cognitive Assessment (MoCA), may be influenced by the presence of clinically significant levels of depressive and anxiety symptoms. Hence, this cross-sectional study aims to assess whether presence of clinically significant levels of depressive or anxiety symptoms impact probability of success on specific MoCA questions among geriatric outpatients. Participants were recruited from two geriatric outpatient clinics in Montreal and enrolled participants were administered cognitive, depression and anxiety screening tests. Comparison of MoCA performance between low versus high levels of depression or anxiety symptoms was analyzed within a Rasch model framework via Differential Item Functioning (DIF) analysis. The results reveal that the probability of correctly answering a specific MoCA item is not influenced by the presence of clinically significant depressive or anxiety symptoms for all items on the MoCA. The present study's finding is clinically and practically applicable because it can be generalized to similar geriatric outpatient clinic settings, however further research is needed to investigate whether these findings are comparable among patients with formal psychiatric diagnoses. In conclusion, the MoCA can be used to screen for cognitive impairment amongst the general population of geriatric outpatients, regardless of recent depression and anxiety status.

Abrégé

Les patients gériatriques présentent souvent des maladies multiples et parfois complexes en comparaison à des patients plus jeunes. Ceci pose un problème aux cliniciens et autres fournisseurs en soins de santé qui doivent démêler les comorbidités afin d'interpréter les résultats de dépistage avec précision, diagnostiquer le type de maladie correctement et choisir le plan de traitement en conséquence. En particulier, la performance à un bref test de dépistage cognitif tel le Montréal Cognitive Assessment (MoCA) peut être influencé par la présence de niveaux cliniquement significatifs de symptômes d'anxiété ou de dépression. Ainsi, cette étude transversale tente de déterminer si la présence de niveaux cliniquement significatifs de symptômes d'anxiété ou de dépression ont un impact sur la probabilité de bonne réponse à des questions spécifique du MoCA chez les patients gériatriques en consultation externe. Des participants furent recrutés de deux cliniques gériatriques de consultation externe à Montréal et des tests de dépistage cognitif, de dépression et d'anxiété furent administrés aux participants sélectionnés. La comparaison entre la performance au MoCA à des niveaux bas et des niveaux élevés de symptômes d'anxiété ou de dépression fut analysée dans un cadre du modèle Rasch par une analyse de « Differential Item Functioning ». Les résultats révèlent que la probabilité de répondre correctement à des items spécifiques du MoCA n'est pas influencée par la présence de symptômes d'anxiété ou de dépression cliniquement significatifs pour tous les items du MoCA. La découverte réalisée dans cette étude est cliniquement et pratiquement applicable car elle peut être généralisée à des situations similaires de cliniques gériatriques de consultation externe. Toutefois, plus de recherche est nécessaire pour investiguer si ces découvertes sont comparables chez les patients avec des diagnostiques psychiatriques formels. En conclusion, le MoCA peut

être utilisé pour dépister la détérioration cognitive chez la population général de patients gériatrique en consultations externe, peu importe leur état récent de dépression ou d‘anxiété.

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Preface

Organization of Thesis

Chapter 1 introduces the clinical relevance of the proposed research question within the context of the aging population. Chapter 2 provides background information in cognitive impairment, depression and anxiety specifically in a geriatric setting, as well as the relationship between depression and anxiety on cognitive performance. A brief comparison between the traditional measurement model versus the Rasch measurement model is explained in Chapter 3. Chapter 4 states the objective and rationale for the thesis, which leads to the manuscript in Chapter 5 prepared for submission. Chapter 6 entails a brief comparison between the prospective data presented in the manuscript and historical data collected previously. Conclusions and additional topics for discussion are addressed in Chapter 7. Supplementary information is included in the Appendices.

Contribution of Authors

Mei Huang (MH) developed the research question with the suggestions and recommendations from her thesis supervisor, Lisa Koski (LK), and her advisory committee members, Catherine Brodeur (CB) and Susan Bartlett (SB). MH wrote and prepared the ethics protocol for submission to the McGill University Health Centre (MUHC) Research Ethics Board with the suggestions and recommendations from LK and Elena Lebedeva (EL). MH coordinated participant recruitment and conducted data collection at the geriatric outpatient clinics for the prospective study, as well as training volunteers for participant recruitment. EL also conducted a portion of data collection and trained volunteers for participant recruitment. MH extracted relevant information from patient charts and entered most of the data for the prospective study. MH coordinated and conducted data quality assurance (rescoring tests based on guidelines) with

the help of a volunteer. The historical data was extracted from the database where previous lab members, including MH, contributed to data entry. MH analyzed both the historical and prospective data with help interpreting the data from EL and LK. MH prepared and wrote the manuscript with suggestions and recommendations from lab members and co-authors (EL, CB, SB and LK).

Chapter 1 – Introduction

1.1 Statement of Problem

Brief screening for cognitive impairment is now common practice in many outpatient geriatric clinics. However, these brief screening measures are not comprehensive and only provide one numerical total score based on passed or failed items. How should a low score be interpreted? Many factors can contribute to a low score, such as physiological abnormalities in the brain, depression, anxiety, acute or chronic pain to name a few. A real issue is to ensure that there is adequate identification of the primary contributor(s) to poor performance on a screening test to ensure appropriate treatment. Depression and anxiety can contribute to poor performance in many areas, including cognitive testing (Beaudreau & O'Hara, 2008; Crocco, Castro, & Loewenstein, 2010). In fact, geriatricians are often faced with this issue of identifying the extent to which depressive symptoms contribute to impaired cognition when a patient presents both depressive symptoms and cognitive symptoms (D. Steffens, 2008). It would be highly undesirable to diagnose a depressed or anxious person with dementia when their cognitive impairment may be reversible with treatment for depression or anxiety. Similarly, depressive symptoms may accompany the early stages of a dementing disorder, but should not prevent the identification and accurate diagnosis of cognitive dysfunction (Vertesi et al., 2001). People in early stages of dementia tend to make characteristic patterns of errors on screening tests (Vertesi et al., 2001). However, it is unclear whether the cognitive impairments seen in persons with early dementia mimic those seen in persons with high levels of symptoms depressive and/or anxiety? If there are differences, these might be detectable in the pattern of item failures on cognitive screening tests.

1.2 Health Problems in Aging Population

It is well known in literature that the aging population (≥ 65 years) is steadily increasing worldwide with a projected estimate of 1.5 billion in 2050 compared to 524 million in 2010 (NIH, 2011). In particular, Canada's older adult population is estimated to constitute 20% of the population by the year 2026 (CIHR, 2010) and by 2051, one in four Canadians will be over the age of 65 (ESDC, 2011). This is a significant increase in the aging population considering that presently about one in seven Canadians are 65 years old and higher (ESDC, 2011). This trend can be explained by an increase in life expectancy, the baby boomer phenomena in Canada and a general decline in number of children born per woman.

Since the older adult population is increasing in Canada, correspondingly there is a rising concern regarding health problems that are commonly associated with old age (CIHI, 2011). Unlike younger patients who seek medical care generally for a single health problem, geriatric patients often present with multiple health problems (i.e. comorbidities). This poses an additional challenge to the health care team who needs to disentangle the impact of comorbidities in order to diagnose appropriately and select treatment plan accordingly (Nobili, Garattini, & Mannucci, 2011). Extensive research has focused on the concern for comorbidities across many diseases common to older adults such as cardiovascular diseases (CIHI report, 2011), diabetes (Fillenbaum, Pieper, Cohen, Cornoni-Huntley, & Guralnik, 2000), cancer (Yates, 2001), late-life depression (Yohannes & Baldwin, 2008) and dementia (Poblador-Plou et al., 2014) to name a few. More specifically, the prevalence of comorbidity between depression and cognitive impairment ranges between 25% to 50% (D. C. Steffens & Potter, 2008), hence there is a need to distinguish between dementia and mood or anxiety disorders via practical guidelines (Downing, Caprio, & Lyness, 2013; Seignourel, Kunik, Snow, Wilson, & Stanley, 2008). The types of

cognitive impairment, depression and anxiety among geriatric population will be outlined in the following chapter.

Chapter 2 – Cognitive Impairment, Depression and Anxiety

2.1 Identifying Cognitive Impairment in Geriatric Population

Cognitive impairment in the geriatric population is characterized into diagnostic categories that differ by severity and type. For severity, this ranges from mild cognitive impairment (MCI) to dementia of different subtypes. Recently, the Diagnostic Statistical Manual 5 (DSM-V) has included a *neurocognitive disorder* section that is comprised of *mild* and *major* neurocognitive disorders (Sachs-Ericsson & Blazer, 2015).

Namely, a mild neurocognitive disorder (mNCD), or MCI, is characterized by a decline in cognitive ability beyond that seen in normal aging and may or may not lead to dementia (Sachs-Ericsson & Blazer, 2015). The prevalence of MCI in older adults range between 10% to 20% and the risk of MCI is higher among men than women (Langa & Levine, 2014). If a patient presents with cognitive symptoms, a thorough evaluation of potential factors that may affect cognition is examined (e.g. blood, neurological and psychiatric tests) (Langa & Levine, 2014) along with cognitive screening tests. There are several cognitive screening tests that are commonly used to screen for cognitive impairment such as the Mini-Mental State Examination (MMSE), Mini-Cog, 7-Minute Screen to name a few (Lin, O'Connor, Rossom, Perdue, & Eckstrom, 2013). However, only a select few are specifically suitable for detecting mild cognitive impairment, including the Addenbrooke's Cognitive Examination Revised (ACE-R), DEMTect, Memory Alteration Test (M@T) and the MoCA (Lonie, Tierney, & Ebmeier, 2009).

More specifically, the cognitive components captured by the MoCA are visuospatial/executive, naming, attention, language, abstraction, short-term memory and orientation (Nasreddine et al., 2005). It can be administered in five to ten minutes and a total score below 26 is indicative of MCI with a sensitivity of 90% and a specificity of 87% at correctly identifying those without cognitive impairment (Nasreddine et al., 2005).

Major neurocognitive disorders spans the different subtypes of dementia. The most common subtypes are Alzheimer's Disease (AD) accounting for 60% to 80% of dementia cases and Vascular Dementia (VaD) accounting for another 10% of dementia cases (alz.org, 2015). The DSM-V criteria for dementia diagnosis are as follows, significant cognitive decline impacting one or more cognitive domains; impairment interfering with daily independent activities; and the exclusion of delirium or other possible mental disorders (Hugo & Ganguli, 2014). The prevalence of dementia varies by countries and in high-income countries, the prevalence ranges from 5% to 10% among older adults (Hugo & Ganguli, 2014).

2.2 Identifying Depression and Anxiety in Geriatric Population

Depressive and anxiety symptoms among older adults can be difficult to detect due to the presence of comorbidities, such as loss of physical function, cognitive function and other diseases. Nonetheless late-life depression (LLD) can be diagnosed based on the spectrum of depressive severity ranging from no symptoms to sub-threshold depression to major depressive disorder (MDD) (Evans & Mottram, 2000). Commonly consulted diagnostic criteria to be used in the elderly population include the DSM-IV or the International Classification of Diseases (ICD-10) (Anderson, Slade, Andrews, & Sachdev, 2009; Birrer & Vemuri, 2004; Evans & Mottram, 2000). Not surprisingly, older adults display different sets of symptoms compared to younger adults. For example, older adults express greater concern on somatic problems and

greater feelings of hopelessness, worthlessness and guilt compared to young adults (Ismail, Fischer, & McCall, 2013).

Several screening measures for clinically significant levels of depressive symptoms were developed to tailor to geriatric patients such as the Cornell Scale for Depression in Dementia (CSDD) and the Geriatric Depression Scale (GDS) (Vieira, Brown, & Raue, 2014). The original GDS is comprised of 30 brief items that assess severity of depressive symptoms based on self-reports on a dichotomous scale (i.e. yes or no) (J. A. Yesavage et al., 1982). A condensed 15-item version (GDS-15) was later developed and is able to detect presence of clinically significant depressive status (total score greater than 5) with a sensitivity of 80% and a specificity of 75% (Almeida & Almeida, 1999; Wancata, Alexandrowicz, Marquart, Weiss, & Friedrich, 2006).

Anxiety disorders often accompany depressive disorders and increase disease burden, decrease function and complicate treatment (Pachana & Byrne, 2012). The DSM-IV outlines the criteria for Generalised Anxiety Disorder (GAD) (Flint, 2005) and although this also applies to older adults, the presentation of symptoms differ between young and old adults (Kastenschmidt & Kennedy, 2011). Older adults worry more about their health (e.g. fear of falling, sleeplessness etc…) and are more irritable, restless and have a heightened startle response compared to younger adults (Kastenschmidt & Kennedy, 2011).

Commonly used anxiety screening measures with evidence of validity and anxiety in the general population may not be suitable for a geriatric population (Kogan, Edelstein, & McKee, 2000; Therrien & Hunsley, 2012). For example, the Beck Anxiety Inventory (Beck, Epstein, Brown, & Steer, 1988) includes somatic questions which may increase false positives in this population since older adults generally have at least one or more physical health problems. An

alternative, the Geriatric Anxiety Inventory (GAI), was developed to address this issue by tailoring the questions to an older population via a greater focus on mental symptoms and simple wording of the questions (Pachana et al., 2007). This dichotomous (yes/no) 20-item questionnaire captures different domains of anxiety such as fearfulness, worry, anxious thoughts, and somatic symptoms of anxiety.

2.3 Geriatric Depression and Cognition

Statistics show that up to 30% of older adults have depressive symptoms and similarly 36% of older adults show signs of cognitive impairment (D. C. Steffens & Potter, 2008). Depressive symptoms and cognitive impairment entail lower health-related quality of life, functional decline, increased mortality and higher rates of health care utilization (Huang, Wang, Li, Xie, & Liu, 2011). Not surprisingly, many large-scale observational studies have also reported a high co-occurrence of depressive symptoms and cognitive impairment in older persons (Huang et al., 2011). However, controversy exists regarding the extent to which there are reciprocal relationships between depressive symptoms and cognitive functioning (Gale, Allerhand, & Deary, 2012; Huang et al., 2011; Poon, 1992).

A plethora of studies provide evidence on each side of the argument (Gale et al., 2012; Huang et al., 2011). Studies have shown that depressed individuals tend to perform worse on tasks assessing processing speed, attention, response inhibition, performance monitoring, memory and executive function (D. C. Steffens & Potter, 2008). In particular, slowed processing speed in older patients diagnosed with late-life depression (LLD) may be the underlying contributor to suboptimal performance in other cognitive domains (Butters et al., 2004). Moreover, there may be sex differences as well. Ng et al.'s group found relationships between cognitive impairment and depressive symptoms in older men but not in older women (Ng, Niti,

Zaw, & Kua, 2009). Conversely, in the English Longitudinal Study of Aging (ELSA), Gale et al.'s group reported no bidirectional association between depressive symptoms and cognitive ability among 8611 older adults (Gale et al., 2012). Another longitudinal study of three years with 1600 older adults showed that depressive symptoms were not associated with an increased risk of cognitive decline (Dufouil, Fuhrer, Dartigues, & Alperovitch, 1996). Many factors contribute to this controversy including differing sample demographics, varying cognitive measures, and not factoring in confounding variables such as dementia and education (Poon, 1992). A more practical and applied approach could be to investigate what can be done to improve the accuracy of screening interventions for depression and cognitive disorders.

2.4 Geriatric Anxiety and Cognition

The global prevalence of geriatric anxiety disorders ranges from 1.2 – 15% (Bryant, Jackson, & Ames, 2008). More specifically, a Canadian cross-sectional study showed that the overall prevalence of anxiety disorders in this population is around 3.5%, and up to 5% in institutions (Bland, Newman, & Orn, 1988; Scott, Mackenzie, Chipperfield, & Sareen, 2010). The literature is unclear as to whether anxiety symptoms influence cognitive performance among older persons (Beaudreau & O'Hara, 2009; Bunce, Batterham, Mackinnon, & Christensen, 2012; Hynninen, Breitve, Rongve, Aarsland, & Nordhus, 2012; Yochim, Mueller, & Segal, 2013). An observational study found that anxiety symptoms were not significantly correlated with performance on cognitive tests in a sample of geriatric and old age psychiatric patients (Hynninen et al., 2012). Conversely, a recent study shows that higher anxiety symptoms were associated with lower verbal fluency scores in older adults aged 70 years and over (Bunce et al., 2012). Furthermore, abilities in cognitive domains such as attention, verbal memory, visuospatial

function and abstraction were poorer in community-dwelling older adults with significant anxiety symptoms (Beaudreau & O'Hara, 2009; Yochim et al., 2013).

2.5 Depressive and Anxiety Symptoms Impact Cognitive Assessments

Many factors can contribute to a low score, some of which include deterioration of the brain (e.g. dementia), mood (e.g. depression, anxiety), pain, sleep and other health conditions. For example, severity of depressive symptoms, as assessed by the Hamilton Depression Rating Scale, were correlated with lower MMSE scores, delayed recall and poor executive performance in older men diagnosed with late-onset depression (Tam & Lam, 2012). As well, older women with more depressive symptoms show evidence of increased cognitive decline (Yaffe et al., 1999), more MMSE errors and poorer executive function over time (Zeki Al Hazzouri et al., 2013). Geriatric anxiety symptoms are significantly correlated with poorer verbal memory, executive function and ability to draw similarities between objects/concepts (e.g. train – bicycle) in a sample of community dwelling older adults (Yochim et al., 2013). Older adults with normal cognitive ability but presenting with high levels of anxiety symptoms performed worse on processing speed and attention tasks (Beaudreau & O'Hara, 2009). Taken together, these results suggest that depressive and anxiety symptoms often impact cognition, and vice versa in older adults; however, they do not provide guidance as to how to apply this knowledge in the context of everyday clinical experience. Hence, there is a need to develop guidelines that clinicians can use to better identify and assess concurrent mood symptoms. More in-depth analysis is needed to determine how items assessing cognitive status are impacted by depressive and anxiety symptoms. In order to capture valid and reliable cognitive status, a brief introduction to traditional and modern measurement models will be explained in the next chapter.

Chapter 3 – Rasch Analysis

3.1 Traditional Measurement Model

Performance based tests and questionnaires aim to quantify latent constructs (e.g. cognitive ability). However, is it justified to conclude that the total score obtained from these tests truly reflect one's cognitive ability? This notion can be better explained by comparing the traditional measurement model with a relatively novel measurement model called the Rasch model. The traditional measurement model (Figure 3.1, yellow box) assumes that each item on the test is weighted equally compared to another item on the test. Upon closer inspection, one may realize that some items indeed capture different "amounts" of the construct compared to other items (Figure 3.1, green box). For example, in a cognitive ability test this would mean that there are difficult items that capture a greater amount of cognitive ability. Similarly, in a depression screening test there is a gradient of items that capture severe levels of depressive symptoms to items that capture milder levels of depressive symptoms.

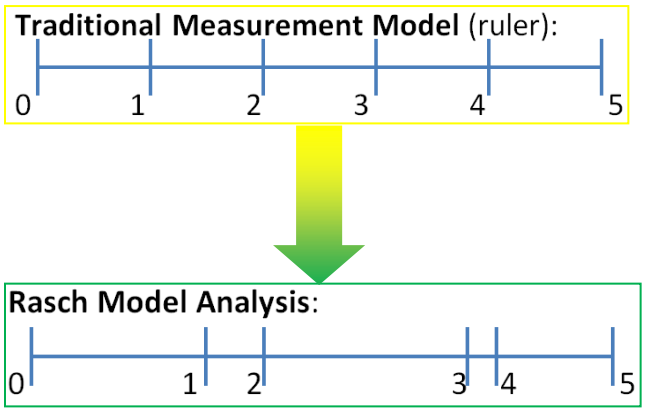

Figure 3.1 – Schematic for comparison between traditional measurement model and Rasch model

3.2 Rasch Measurement Model

Rasch analysis is a statistical approach based on item-response theory (IRT) and it is used to rigorously evaluate the extent to which a set of test questions measures a unidimensional construct. More specifically, it evaluates the goodness of fit of a data set to a unidimensional Rasch model, in which the probability of responding correctly to any question on the test can be fully determined by a person's ability and the difficulty of that question (Tennant & Conaghan, 2007). For example, Rasch analysis of the MoCA has yielded good unidimensional fit and thus the total score is a valid measure of the construct, cognitive ability (Koski, Xie, & Finch, 2009). The Rasch model aims to convert ordinal data onto an interval scale. More specifically, the Rasch model ranks the items from easiest/mild items to most difficult/severe items based on all the responses on a test within a data set. An item is labeled easy/mild to difficult/severe depending on the frequency of a specific response for each item. For example, if many persons pass item A on a cognitive ability test, item A is easy. Correspondingly, if very few persons (or no persons) pass item Z on a cognitive ability test, then item Z is most difficult. This applies to depression screening tests where mild items are items endorsed by many persons (i.e. even those with low levels of depressive symptoms) and severe items are items endorsed by fewer persons (i.e. only persons with high levels of depressive symptoms). Once the items are ranked on a scale from easy/mild items to difficult/severe items, then each person can be "mapped" onto this scale based on their set of responses for a given test. For example, if person A only passes easy cognitive items and fails more difficult cognitive items, then person A has low cognitive ability. Correspondingly, if person Z passes all the easy items and also passes a few difficult items, then person Z has high cognitive ability. On this scale, the items that are directly adjacent to persons have a 50% probability of pass/endorsement (applies only to dichotomous response items). If the

data set does not fit the Rasch model, several modifications can be explored as outlined in appendix A.2.

Rasch analytic tools include methods for determining whether responses to a given question are associated with characteristics of an individual *apart from their overall ability level*, a phenomenon known as differential item functioning (DIF). DIF occurs when participants with similar ability perform differently on a specific item because they are from different groups (e.g. low, medium, high depressive/anxiety symptoms). DIF is analyzed by a two-way analysis of variance (ANOVA) where each person is first categorized by the severity of depressive/anxiety symptoms, then divided by overall ability level (e.g. low, medium or high cognitive ability). ANOVAs are used to test for effects of these factors on the probability of passing each item on the MoCA. Uniform DIF is present when there is a main effect of a group characteristic on the probability of passing an item. Non-uniform DIF is present when a group characteristic only influences the probability at specific levels of cognitive ability. Thus, we will conduct analyses of DIF within a Rasch measurement model to assess the extent to which high levels of depressive symptoms and high levels of anxiety symptoms affect MoCA performance.

Chapter 4 – Rationale and Objective

4.1 Objective

The aim of this study is to estimate the extent to which clinically significant levels of self-reported depression, and clinically significant levels of self-reported anxiety, contribute to performance on specific MoCA items used to assess cognitive impairment in geriatric outpatients.

Geriatric patients endorsing clinically significant depressive symptoms were predicted to perform poorly on items assessing processing speed, executive function, attention and memory compared to those with low depressive symptoms (Crocco et al., 2010; D. C. Steffens & Potter, 2008). These domains are represented by drawing digits on the clock, tapping A's and 7s subtract (processing speed & attention); trail, copy cube and clock (executive function); and recall words and orientation (memory). Geriatric patients endorsing clinically significant anxiety symptoms were predicted to perform poorly on tests of attention, verbal memory, visuospatial function and abstraction compared to those with low anxiety symptoms (Beaudreau & O'Hara, 2009; Yochim et al., 2013). These domains are represented by digits, tapping A's and 7s subtract (attention); recall words and repeat sentence (verbal memory); trail, copy cube and clock (visuospatial function); and similarities between words (abstraction).

4.2 Rationale

Results of this study may have immediate applicability to clinical settings because these brief cognitive screening tools are widely used by geriatricians and geriatric nurses. They are low-cost and time efficient, yet results may be confounded by the presence of high levels of depressive and/or anxiety symptoms. Thus, improving interpretation of low test scores can

potentially aid clinicians in the differential diagnosis between dementing disorders and mood disorders in individuals with low cognitive scores. More specifically, by identifying questions on the MoCA that are answered differently among older adults with varying degrees of depressive or anxiety symptoms, this could lead to improved sensitivity for detecting mood disorders. It is current practice for clinicians to omit administering depression or anxiety screening tests at their discretion if patients do not look visibly depressed or anxious. However, identifying patterns of responses to different items related to depressive or anxiety symptoms, could prompt clinicians to more carefully evaluate where there is evidence of clinically relevant mental health issues and appropriately treat the patient to improve their quality of life.

Chapter 5 – Manuscript

Manuscript prepared for submission to the journal entitled Journal of American Geriatrics Society

TITLE: The Impact of Depressive and Anxiety Symptoms on the Montreal Cognitive Assessment (MoCA) among Geriatric Outpatients

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5.1 Preamble

The manuscript presents data collected in a prospective study. Since the manuscript only allows three graphics (figures, tables, graphs), additional relevant graphics such as the participant recruitment flow diagram, frequency distributions of test scores and correlation graphs are embedded in this chapter. Additionally, historical data (MoCA and GDS only) collected from retrospective medical chart reviews (n=155, 2005 to 2014) will be presented in the next chapter and comparisons will be drawn between the prospective data and historical data.

5.2 Abstract

Objectives: To assess the extent to which self-reported symptoms of depression and anxiety influences scores on the Montreal Cognitive Assessment (MoCA) in ambulatory geriatric patients.

Design: Cross-sectional study (August 2014 - March 2015).

Setting: Geriatric outpatient clinics in large urban hospitals.

Participants: 146 older adults (>60 years, Mean=82.0 years, SD=6.3) fluent in English or French, without significant hearing impairments or acute medical illness.

Measurements: The MoCA, the Geriatric Depression Scale (GDS-15) and the Geriatric Anxiety Inventory (GAI) were used to assess cognitive function, depressive symptoms and anxiety symptoms, respectively. Differential item functioning (DIF) was assessed using Rasch analysis.

Results: Although, the GDS-15 and GAI were moderately correlated (rho=0.50, p<0.001), no systematic relationship was found between between MOCA scores and GDS-15 or GAI (rho=0.047, p=0.577 and rho=0.050, p=0.552, respectively). There was no evidence of DIF on individual MoCA items between persons with low versus high scores on the GDS-15 and GAI.

Conclusions: Our results contribute initial evidence supporting the validity of MOCA scores, even in the presence of clinically significant levels of depression and anxiety.

KEYWORDS: Cognition, depression, anxiety, geriatrics, MoCA

5.3 Introduction

Diagnosing cognitive disorders in geriatric patients is often complicated by the presence of other complex and multiple health problems (Poblador-Plou et al., 2014). More specifically, the prevalence of comorbidity between depressive disorders and cognitive impairment ranges between 25% to 50% (D. C. Steffens & Potter, 2008). This poses an additional challenge to the health care team who must disentangle the impact of depressive and anxiety symptoms, in order to interpret screening results correctly, diagnose cognitive disorders appropriately and select treatment plan accordingly (Downing et al., 2013; Nobili et al., 2011; Seignourel et al., 2008). Hence, there is a need to distinguish between cognitive disease and depressive or anxiety symptoms at the level of cognitive screening tests.

Brief cognitive screening tools are commonly used to detect clinically significant cognitive impairment in geriatric settings (Ismail, Rajji, & Shulman, 2010; Lonie et al., 2009). Previous studies have found an association between depressive and anxiety symptoms and cognitive test scores on the MoCA (Del Brutto et al., 2015; Dierckx, Engelborghs, De Deyn, Van der Mussele, & Ponjaert-Kristoffersen, 2014). This is problematic because it would be inappropriate to diagnose a neurocognitive disorder in individuals with significant levels of depressive or anxiety symptoms when their cognitive impairment may be reversible with appropriate treatment for depression or anxiety. Thus, it is necessary to ensure that brief cognitive screening tests are not biased by the presence of high levels of depressive and/or anxiety symptoms.

The Rasch measurement framework can be used to more rigorously assess the validity of psychological test scores and identify potential limitations of a test at an individual item level (Koski et al., 2009; Tennant & Conaghan, 2007). For example, differential item functioning

(DIF) analysis can be used to assess whether response to individual test questions differ by patient characteristics. More specifically, when the probability of success or failure on specific items is influenced by another factor (e.g., sex, test language), test validity is weakened in the sub-population with this particular characteristic. When DIF is identified, alternate scoring methods or different cut-off values can be be applied to subgroups to increase the accuracy of the assessments. Diversely, when there is no evidence of significant DIF, then the test can be used in the target audience with no additional revisions. In relevance to this context, the cognitive screening test could be used to screen for cognitive impairment amongst the general population of geriatric outpatients, regardless of current mood status. Moreover, this may be especially important when older adults are being evaluated for changes in cognitive function where the implications of testing could trigger distress in some patients. Thus, the goal of this study was to assess the extent to which symptoms of depression and anxiety influence scores obtained on the Montreal Cognitive Assessment (MoCA) in older patients seen in ambulatory care settings. We hypothesized that older adults with clinically significant symptoms of depression will perform poorer on visuospatial/executive, abstraction, short-term memory and orientation (time and place) MoCA items and no difference in MoCA performance due to symptoms of anxiety.

5.4 Methods

Study Population and Design

A prospective cross-sectional study was conducted between August 2014 to March 2015 among individuals referred for cognitive evaluations at the geriatric outpatient clinics, McGill University Health Centre (MUHC), Montreal, Canada. All clinic patients were screened for eligibility; individuals who were not fluent in English or French, had significant hearing impairments that could not be, at least, partially corrected, had significant acute medical or psychiatric illness (e.g. psychotic symptoms) or were deemed inappropriate by health care staff (e.g. due to severe dementia) were excluded. Eligible patients were approached on the same day of their appointment to complete all study tests. After providing written informed consent, participants completed the MoCA before their appointment and screening tests for depression and anxiety before, during or after their appointment. Study procedures were approved by the MUHC Research Ethics Board (14-101-PSY).

Measures

Cognitive Ability

The MoCA is a brief (30 item) screening tool used to screen for the presence of cognitive impairment (Dong et al., 2012; Smith, Gildeh, & Holmes, 2007). It has items that cover different cognitive aspects including visuospatial/executive, naming, short-term memory (delayed recall), attention, language, abstraction and orientation (time and place) (Nasreddine et al., 2005). Scores range from 0 to 30; a score of ≤25 is indicative of mild cognitive impairment (MCI) with a sensitivity of 90% and a specificity of 87% (Nasreddine et al., 2005), although some argue this

cut-off may need to be adapted to local populations (Gil, Ruiz de Sanchez, Gil, Romero, & Pretelt Burgos, 2015; Kaya et al., 2014; Waldron-Perrine & Axelrod, 2012).

Depressive and Anxiety Symptoms

Severity of depressive symptoms over the previous week was assessed with the Geriatric Depression Scale Short Form (GDS-15) (Jerome A. Yesavage & Sheikh, 1986). Scores ≥6 out of 15 are indicative of clinically significant levels of depressive symptoms with a sensitivity of 80% and a specificity of 75% (Almeida & Almeida, 1999; Wancata et al., 2006). Severity of anxiety over the previous week was assessed with the 20-item Geriatric Anxiety Inventory (GAI) (Pachana et al., 2007). Scores ≥9 out of 20 are indicative of clinically significant levels of anxiety with a sensitivity of 73% and a specificity of 80% (Byrne et al., 2010; Pachana et al., 2007; Ribeiro, Paul, Simoes, & Firmino, 2011). Both the GDS and the GAI are available in English and French scales and were developed and validated in geriatric populations (Almeida & Almeida, 1999; Byrne et al., 2010; Wancata et al., 2006). They contain simple and easy to understand questions with dichotomized scoring and minimal bias due to somatic symptoms (Pachana et al., 2007; Jerome A. Yesavage & Sheikh, 1986).

Statistical Analyses

Descriptive statistics were calculated for all variables. MoCA data were normally distributed ($p=0.125$, Shapiro-Wilk test), whereas the GDS and GAI data were not normally distributed ($p<0.001$, Shapiro-Wilk test) as presented in figure 5.5.2. Hence, correlations between total MoCA, total GDS and total GAI were examined using Spearman's rho. DIF analysis was used to compare individual item responses between people with low versus high GDS and GAI scores with group classification based on the clinical cut points. More specifically,

effects of depressive and anxiety symptoms on the probability of passing each item on the MoCA were evaluated separately using two-way analysis of variance (ANOVA) with alpha set at p=0.05 and using Bonferroni correction for multiple comparisons.

A sample size of 100 is required for Rasch analysis to ensure that difficulty levels of the items are estimated within 0.5 logits of their real values with 95% confidence (Chen et al., 2014; Guilleux, Blanchin, Hardouin, & Véronique, 2014; Linacre, 1994). Original response options for Subtract 7s (i.e. 0, 1, 2 or 3) were modified to 0 (0 correct subtractions), 1 (1, 2 or 3 correct subtractions) and 2 (4 or 5 correct subtractions) to improve psychometric properties of this item (Koski et al., 2009). Total MoCA scores were not available for four participants due to missing scores for visual items (Trails, Cube Drawing, Clock Drawing and Naming Animals) from three participants with visual impairment and one participant for refusal to complete items Clock Drawing and Subtract 7s, as detailed in table A.1 (Appendices section). All available data on other items were used in the DIF analyses. In the GDS and GAI data, one item from each data set was missing due to preference not to answer. The total GAI and GDS scores were accordingly prorated. Statistical analyses were performed using SPSS version 19 and DIF was performed using RUMM2030 (RUMM Laboratory, PTY Ltd, 2010)

5.5 Results

As presented in figure 5.5.1, of 670 patients attending appointments during the data collection period, 257 (38%) individuals were invited to participate. The remaining 413 patients were not approached due to unavailable study personnel to recruit participants (200), patients who were not fluent in English or French (156), patients who had no time or were requested not to be approached by medical staff (54), patients who could not understand study procedures (2), and significant hearing impairment (1). Of the 257 invited to participate, 25 declined and 6 encountered problems during testing (e.g. patient cried during testing, caregiver influenced patient's response). Of the 226 patients tested, 80 (35%) patients were not administered the MoCA due to significant cognitive impairment. Only patients with complete MoCA data (n=146) are included in the analysis.

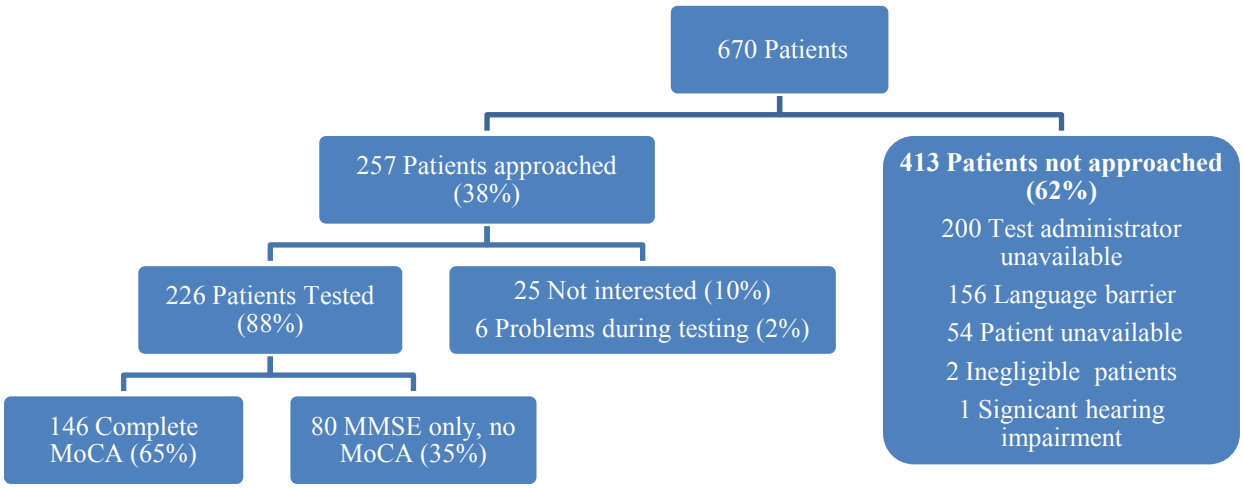

Figure 5.5.1 – Participant recruitment flow diagram

Table 5.5.1 presents sample demographics and clinical characteristics for the whole sample, and by GDS and GAI status. Cognitive diagnoses were extracted from medical charts based on physicians' formal or follow-up written letters. There were equal proportions of males

and females, half of the sample (51%) received post-secondary education and most participants (75%) elected to complete the tests in English. The mean (SD) MoCA score was 20.2 (4.6) and most participants (86%) performed lower than the clinical cut-off for MCI. The median scores for GDS and GAI were 3 and 2, respectively. Clinically significant depressive and anxiety symptoms were present in only 21% and 14% of the participants, respectively. Severity of anxiety symptoms and severity of depressive symptoms were moderately correlated (rho=0.501, $p<0.001$). However, no systematic relationship was evident between cognitive ability and severity of depressive or anxiety symptoms (rho=0.047, p=0.577 and rho=0.050, p=0.552, respectively), as shown in figure 5.5.3.

Table 5.5.1 – Sociodemographic and clinical characteristics of older patients referred for evaluation of cognitive function by clinically significant depressive and anxiety symptoms status (n=146)

			GDS-15		GAI	
		All	Low (≤5) N=115	High (≥6) N =31	Low (≤8) N=125	High (≥9) N=21
Sex	Female	78 (53%)	61 (53%)	17 (55%)	64 (51%)	14 (67%)
Age (y.o.)	Mean ±(SD)	82.0 (6.3)	81.7 (6.6)	83.2 (5.2)	82.0 (6.4)	82.6 (5.9)
	Min – Max	62 – 97	62.3-96.9	69.5-91.2	62.3-96.9	69.5-91.5
Education (years)	Elementary (0-8)	17 (12%)	12 (10%)	5 (16%)	12 (10%)	5 (24%)
	High school (9-12)	50 (34%)	34 (30%)	16 (52%)	39 (31%)	11 (52%)
	College (>13)	74 (51%)	66 (57%)	8 (26%)	70 (56%)	4 (19%)
	Missing	5 (3%)	3 (3%)	2 (6%)	4 (3%)	1 (5%)
Test Language	English	109 (75%)	88 (77%)	21 (68%)	97 (78%)	12 (57%)
Cognitive Ability (total MoCA score)	Normal (≥26)	16 (11%)	14 (12%)	2 (6.5%)	16 (13%)	0
	MCI Cut-off (≤25)	126 (86%)	99 (86%)	27 (87%)	107 (86%)	19 (90%)
	Mean (SD)	20.2 (4.6)	20.1 (4.6)	20.3 (4.6)	20.3 (4.7)	19.3 (3.9)
	Median (IQR†)	20 (17-24)	20 (17-24)	22 (17-24)	20 (17-24)	20 (17-22)
	Missing*	4 (3%)	2 (2%)	2 (6.5%)	2 (1%)	2 (10%)
Depressive symptoms (GDS score)	Normal (≤5)	115 (79%)				
	Clinical Cut-off (≥6)	31 (21%)				
	Median (IQR)	3 (1-5)				
Anxiety symptoms (GAI score)	Normal (≤8)	125 (86%)				
	Clinical Cut-off (≥9)	21 (14%)				
	Median (IQR)	2 (0-6)				
Cognitive Diagnosis	Normal	14 (10%)	9 (8%)	5 (16%)	12(10%)	2 (10%)
	MCI	39 (27%)	32 (28%)	7 (23%)	34 (27%)	5 (24%)
	Dementia	56 (38%)	47 (41%)	9 (29%)	49 (39%)	7 (33%)
	No Cognitive Diagnosis	35 (24%)	25 (22 %)	10(32%)	28 (22%)	7 (33%)
	Missing	2 (1%)	2 (1%)	0	2 (2%)	0

*missing too many visual items to prorate (3) and did not want to do clock drawing & Sub7s (1)

†IQR (Interquartile range)

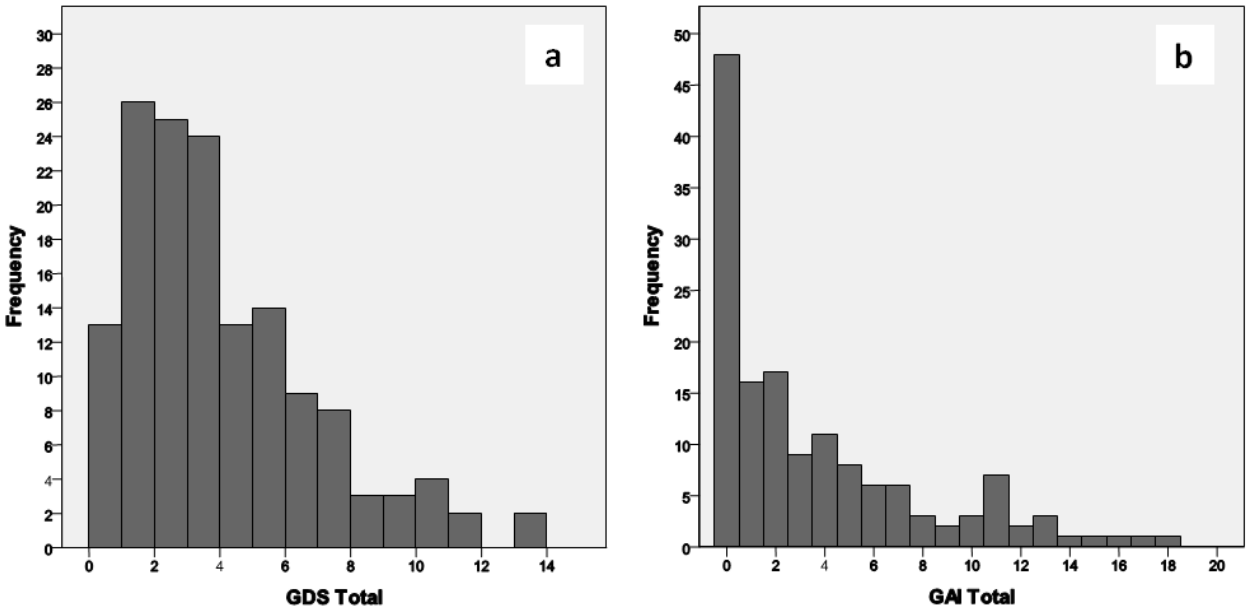

Figure 5.5.2 – Frequency distribution of (a) total GDS scores and (b) total GAI scores

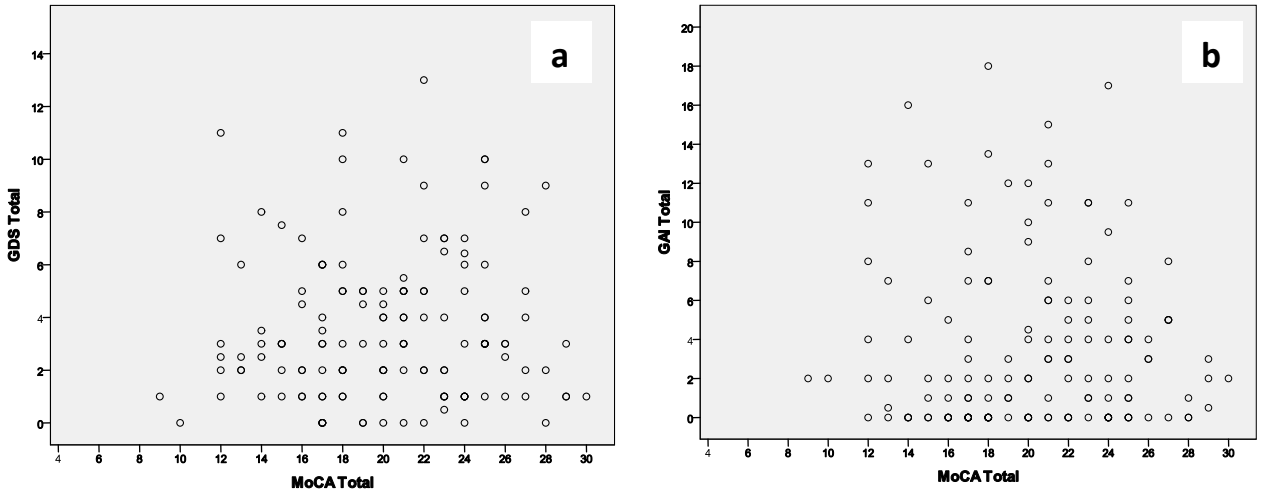

Figure 5.5.3 – Correlation between (a) cognitive ability (MoCA total scores) and severity of depressive symptoms (GDS total scores) and (b) cognitive ability (MoCA total scores) and severity of anxiety symptoms (GAI total scores)

Figure 5.5.4 presents the distribution of persons (top bars) and items (bottom bars) on the same cognitive ability scale in logit values. The persons are ordered ranging from low cognitive ability towards the negative end of the axis (left), to high cognitive ability towards the positive

end of the axis (right). Similarly, the items are ordered from easiest at the negative end, to most difficult at the positive end. The MoCA items are relatively evenly distributed between -3 to +3 logits and mostly align with the persons distribution, demonstrating that it can assess a reasonable spectrum of cognitive ability level for this sample. The relative distribution of persons along this hierarchy of ability is slightly shifted towards the positive axis indicating that the participants in this study are performing better than the average difficulty of the test questions (average is location 0). In particular, there are some high performing individuals (> +3 logits) whose cognitive ability cannot be accurately assessed due to missing items of greater difficulty (> +3 logits). Individuals are divided into two groups based on severity of depressive (Figure 5.5.4a) or severity of anxiety (Figure 5.5.4b), respectively. Diagonal lined bars represent persons reporting low levels of depressive (GDS ≤5) symptoms or anxiety (GAI ≤8) symptoms, while horizontal lined bars represent persons reporting clinically significant levels of depressive (GDS ≥6) or anxiety (GAI ≥9) symptoms. As shown, participants were relatively evenly interspersed along the continuum, indicating that group performance on the MoCA was comparable.

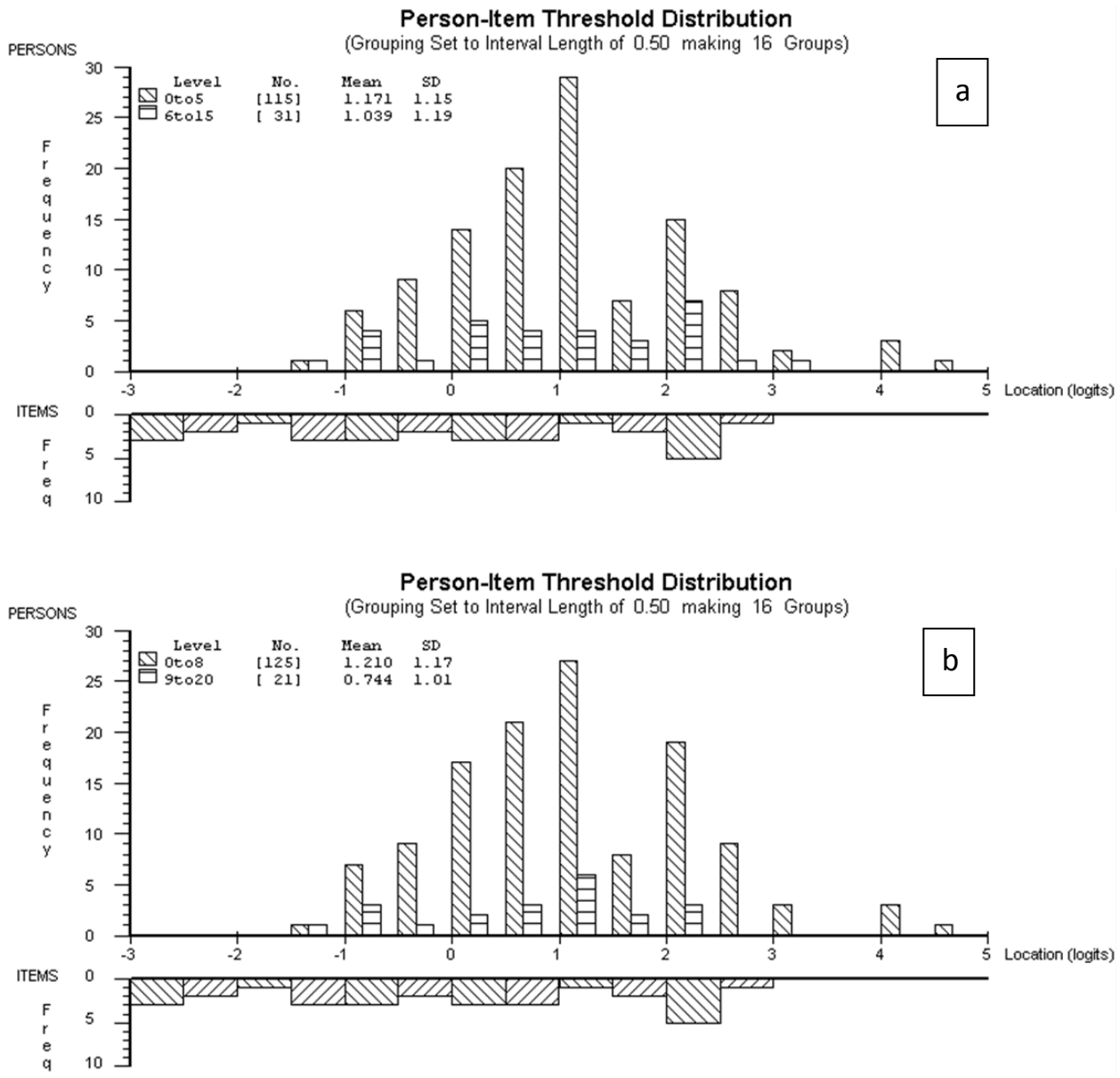

Figure 5.5.4 – Person-Item distribution graph categorized between (a) persons reporting low levels of depressive symptoms (GDS ≤5) in diagonal lines and persons reporting clinically significant levels of depressive symptoms (GDS ≥6) in horizontal lines and (b) persons reporting low levels of anxiety symptoms (GAI ≤8) in diagonal lines and persons reporting clinically significant levels of anxiety symptoms (GAI ≥9) in horizontal lines. Top bars represent persons and bottom bars represent items. Persons are ordered from low cognitive ability (towards negative logits) to high cognitive ability (towards positive logits) and items are likewise ordered from easiest items (negative logits) to most difficult items (positive logits).

As shown in Table 5.5.2, the DIF analysis revealed that the between-group differences in performance on MoCA items were not statistically significant between persons with low versus high depressive symptoms. Similarly, differences in performance on individual MoCA items also were not statistically significant between persons with low versus high anxiety. Notably, since Bonferroni correction is relatively conservative, performance on item Cube may be biased by high depressive symptoms ($p=0.003$) and high anxiety symptoms ($p=0.001$) if a more liberal correction criterion was applied. These results suggest that the probability of correctly answering a specific MoCA item is not statistically biased by the presence of clinically significant depressive and anxiety symptoms for any single MoCA item, except for probable item Cube.

Table 5.5.2 – DIF statistics (ANOVA) for each MoCA item by depressive symptoms and anxiety symptoms (Bonferroni corrected, p <0.0006)

		Depressive Symptoms (GDS)		Anxiety Symptoms (GAI)	
Cognitive Subdomain	**MoCA item**	F	p	F	p
Visuospatial/Executive	**Trail**	1.91	0.169	0.171	0.680
	Cube	9.33	0.003	11.239	0.001
	Contour (Clock)	1.11	0.293	0.791	0.375
	Numbers (Clock)	0.02	0.885	0.150	0.699
	Hands (Clock)	0.10	0.749	0.236	0.628
Naming	**Lion**	0.44	0.506	1.431	0.234
	Rhino	6.61	0.011	0.302	0.584
	Camel	0.37	0.541	0.093	0.761
Attention	**Digits Forward**	0.09	0.760	0.147	0.702
	Digits Backward	3.99	0.048	0.599	0.440
	Tapping A's	1.42	0.236	0.285	0.594
	Subtract 7's	0.01	0.921	0.489	0.485
Language	**Sentence 1 Repeat**	0.01	0.925	0.988	0.322
	Sentence 2 Repeat	1.50	0.223	0.012	0.913
	Verbal Fluency F's	6.16	0.014	4.686	0.032
Abstraction	**Train-Bicycle**	4.10	0.045	0.229	0.633
	Watch-Ruler	0.23	0.634	0.106	0.746
Short-term Memory (Delayed Recall)	**Face**	1.84	0.177	0.002	0.966
	Velvet	5.27	0.023	0.799	0.373
	Church	6.25	0.014	2.506	0.116
	Daisy	0.66	0.417	0.299	0.586
	Red	0.73	0.393	1.128	0.290
Orientation (Time and Place)	**Date**	0.52	0.472	0.826	0.365
	Month	0.50	0.480	4.913	0.028
	Year	0.28	0.597	1.105	0.295
	Day of Week	1.37	0.245	1.876	0.173
	Place	0.02	0.883	0.292	0.590
	City	1.11	0.294	0.014	0.907

5.6 Discussion

The prevalence in this sample of individuals with significant depressive symptoms (21%) and significant anxiety symptoms (14%) based on clinical cut-offs is relatively low, while the majority (86%) of participants reached clinical cut-off for MCI. The results of this study show that in this outpatient sample, clinically significant levels of depressive and anxiety symptoms did not influence the probability of passing individual items on the MoCA, nor does it impact the total scale on the MoCA among geriatric outpatients.

The impact of the severity of depressive and anxiety symptoms on cognitive performance is widely studied in the literature, however findings are inconsistent and results vary depending on which measures were used (e.g. screening tests, full neuropsychological assessments) (Beaudreau & O'Hara, 2008; McDermott & Ebmeier, 2009). In particular, relatively little is known about how depressive and anxiety symptoms impact the MoCA. Surprisingly, even among the few studies assessing the influence of depressive and anxiety symptoms on MoCA performance, results differ as to which specific cognitive domains might be impacted. A cross-sectional study conducted in a remote village in rural Ecuador of 280 community dwelling older adults found that depressed individuals (n=33, 12%), as assessed by the Depression Anxiety Stress Scale (DASS-21), performed significantly poorly on total MoCA compared to non-depressed individuals (Del Brutto et al., 2015). Moreover, depressive symptoms were associated with lower scores in short-term memory (delayed recall), orientation (time and place) and abstraction, after adjustment for age, sex and education (Del Brutto et al., 2015). In contrast, a Belgian study of 41 older adults with depressive symptoms (GDS-30 > 10) reported significantly lower scores in only the visuospatial/executive cognitive domains compared to age and gender matched controls (Dierckx et al., 2014). Interestingly, the present study also found a marginal effect for item Cube, a visuospatial/executive item, suggesting that the performance of this item

may be biased by high levels of depressive symptoms. In the present study, clinically significant anxiety symptoms were not associated with a lower MoCA score or poorer performance on individual MoCA items, except for probable item Cube. Similarly, the Ecuador study found that MoCA total and subdomain scores were not significantly different between anxious and non-anxious individuals, after adjusting for age, sex and education (Del Brutto et al., 2015).

Explanations for the discordant findings between our sample and previous studies may be due to differences in sampling technique, sample demographics (e.g. geographic location, education) and measures used to classify individual with significant depressive symptoms. The Ecuador study was conducted via door-to-door surveys in order to recruit all older individuals (≥60) in the remote rural village of Atahualpa, whereas our sample is based on older adults referred for likely cognitive impairment in a large urban hospital. The difference in participant composition is also apparent in the level of education attainment, where 19% of the participants received either partial high school or higher education in the Ecuador study versus 85% in our sample. Similarly, the total mean MoCA score was slightly lower for the Ecuador study (18.5±4.6) compared to our sample (20.2±4.6). The majority of rural Ecuadorian older adults never visited large urban centres and migration is minimal (Del Brutto et al., 2015), hence some MoCA items may be less familiar and accessible (e.g. abstraction: train vs. bicycle) due to different cultural lifestyles. The present study had a higher prevalence of individuals with clinically significant levels of depressive symptoms (21%) compared to the Ecuador study (12%) and since different depression screening measures were used (GDS-15 versus DASS-21, respectively), test criteria for categorization as depressed vs. non-depressed may also vary. Moreover, differences in overall findings and/or categorization of clinically significant

depression status may also be attributed to the Spanish translation and cultural adaption of the DASS-21 to the target population.

Cognitive screening tests provide only a crude estimate of cognitive ability; they do not accurately predict performance in specific cognitive domains as measured from a full neuropsychological battery (Moafmashhadi & Koski, 2013). Consequently, results demonstrated in studies administering extensive neuropsychological tests may not be reflected in brief cognitive screening tests since they are unable to capture specific cognitive domains comprehensively. Cognitive components that are more sensitive to the influence of depressive and anxiety symptoms, such as found in neuropsychological batteries, may not be apparent or replicable in the MoCA. For example, slowed processing speed could contribute to the cognitive impairments seen in depressed older adults (Nebes et al., 2000; Sheline et al., 2006), however this effect would not be apparent in the current study because processing speed is not formally assessed by the MoCA (Moafmashhadi & Koski, 2013)

Strengths of this study can be emphasized by the clinical relevance of the present study's findings. The study design was a prospective study targeting a geriatric outpatient clinic, all variables were obtained on the same day and exclusion criteria were minimal for better generalizability. A thorough detailed analysis at the individual item level was conducted on a widely and commonly used cognitive screening tool. Limitations of this study include binary categorization of individuals with depressive and anxiety symptoms that may contribute to misclassification of individuals near the clinical cut-off values; no documentation of duration of significant levels of depressive or anxiety symptoms (i.e. only recently within past week); and a large portion of participants (65%) diagnosed with significant cognitive impairment (i.e. MCI or dementia) that may impinge on their ability to report accurately on the mood scales.

Nevertheless, a previous study found that cognitive status, from clinical consensus diagnoses, did not significantly bias item response on the GDS (Fieo et al., 2014). Future research should consider investigating whether the influence of depressive and anxiety symptoms vary between different cognitive screening tests, due to different item composition, and whether the findings in this study based on the MoCA is comparable among patients with formal psychiatric diagnoses.

In summary, the goal of this study was to contribute evidence towards interpreting the MoCA as a cognitive screening tool in the presence of significant levels of depressive and anxiety symptoms. The findings suggest that MoCA scores are not biased by elevated depressive and anxiety symptoms amongst the general population of geriatric outpatients, however further research is needed to compare these findings with other cognitive screening tests and among patients with formal psychiatric diagnoses.

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Conflict of Interest: None.

Author Contributions: Study concept and design: MH, LMK, SJB, CB. Data acquisition: MH, EL. Data analysis and interpretation: MH, EL, LMK. Drafting of manuscript: MH. Critical revision of manuscript for important intellectual content: EL, LMK, SJB, CB. All authors approved the final version of the manuscript to be published and agree to be accountable for all aspects of the work.

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Chapter 6 – Comparison between Historical and Prospective Data

6.1 Sample Composition

Only selected patients were administered the GDS at the discretion of the geriatrician in the historical data, hence the prospective study was conducted to address potential selection bias. The selection bias would evolve from patients who were not chosen to receive a GDS and consequently these patients would be omitted from the analysis. The historical sample demographics are presented in table 6.1 in comparison with the prospective sample. The mean age (M=79.1, SD=6.9) for the historical group is significantly younger compared to the prospective group ($t(299)=3.8$, $p<0.001$). The explanation for this difference is that the GDS is typically administered on the very first appointment at the clinic as part of the initial intake procedures. If depressive symptoms are low, the GDS may not be administered in subsequent visits. Another notable difference is that there are more patients (49%) in the historical sample self-reporting clinically significant depressive status (total GDS ≥ 6) compared to the prospective sample (21%). This provides evidence that the historical group is comprised of patients that were particularly selected by the health care staff to receive GDS screening. Possible reasons may be that the patient appeared visibly depressed or other evidence of depression (e.g. caregiver, relative, family physician reporting). There is no statistical difference in mean total MoCA score between the historical and prospective sample ($t(299)=1.2$, $p=0.233$). The GAI was not previously administered in the clinic.

Table 6.1 – Sample demographics for prospective sample and historical sample

		Prospective sample [n=146]	Historical sample [n=155]
Sex	Male	68 (47%)	69 (45%)
	Female	78 (53%)	86 (55%)
Age (years)†	Mean ±(SD)	82.0 (6.3)	79.1 (6.9)
	Min – Max	62 – 97	62 – 91
Education (years)	Low (0-8 years)	17 (12%)	31 (20%)
	Med (9-12 years)	50 (34%)	48 (31%)
	High (>13 years)	74 (51%)	57 (37%)
	Missing	5 (3%)	19 (12%)
Test Language	English	109 (75%)	103 (66%)
	French	37 (25%)	52 (34%)
Cognitive Ability (MoCA score)	Normal (≥26)	16 (11%)	16 (10%)
	Clinical Cut-off for MCI (≤25)	126 (86%)	138 (89%)
	Mean (SD)	20.2 (4.6)	20.8 (4.1)
	Median (IQR)	20 (17-24)	21 (18-24)
	Missing*	4 (3%)	1 (1%)
Depressive symptoms (GDS score)	Normal (≤5)	115 (79%)	79 (51%)
	Clinical Cut-off (6-15)	31 (21%)	76 (49%)
	Median (IQR)	3 (1-5)	5 (3-8)

*Prospective Data: missing too many visual items to prorate (3 cases) and refused clock drawing & Sub7s items (1 case). Historical Data: missing too many visual items to prorate (1 case)

†statistical difference ($t(299)=3.8$, $p<0.001$)

6.2 DIF Analyses

The historical data fit the Rasch model after a minor modification to the scoring structure for item Subtract 7s, as described in the manuscript. Similarly, there was no statistically significant difference between individual MoCA item performance between individuals with low and high levels of depressive symptoms in the historical group. This can also be seen in the person-item distribution graph (Figure 6.2) where the individuals with low depressive symptoms (blue) are interspersed between the individuals with high depressive symptoms (red), suggesting that overall MoCA performance does not differ by level of depressive symptoms. When comparing the probability of passing specific MoCA items strictly between the historical sample

and the prospective sample, DIF occurs for item Clock Hands. This could be explained by the standardized rescoring of MoCA procedure applied exclusively to the prospective data only. All prospective completed MoCA tests were rescored based on the MoCA scoring guidelines provided by their official website (MoCAtest.org, 2010). This was done to reduce inconsistencies in subjective scoring between different test administrators (e.g. doctors, nurses, medical students, research personnel etc…), in particular for the visuospatial/executive items and to correct errors in understanding how to correctly score Subtract 7s. The historical MoCA tests were not rescored because they were not readily available. In addition, physical paper forms are inaccessible due to the recent transition of an online documentation system at the MUHC. Since participants in the historical group had a higher probably of passing item Clock Hands compared to the participants in the prospective group, this could be attributed to a more lenient and liberal scoring method among clinical staff (historical data) compared to the rescoring guidelines which were more structured and conservative (prospective data).

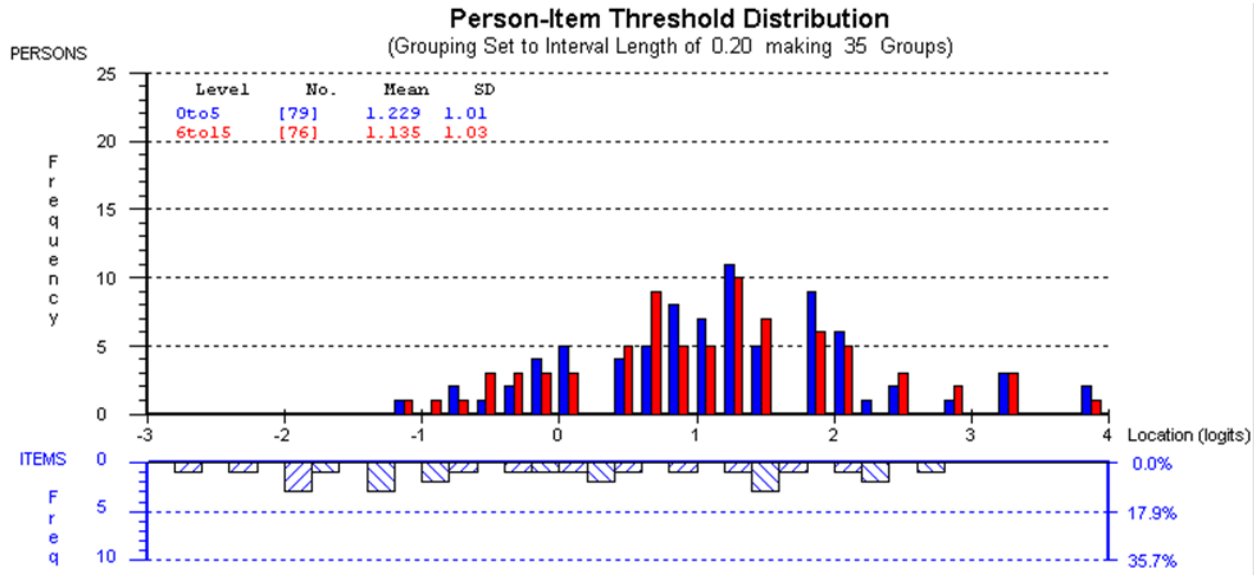

Figure 6.2 – Person-Item distribution graph categorized between persons reporting low levels of depressive symptoms (GDS ≤5) in blue and persons reporting clinically significant levels of depressive symptoms (GDS ≥6) in red, for historical data only.

When comparing the prospective sample and the historical sample, a minor detail to note is that some participants have completed the MoCA and GDS at multiple time points (Table 6.2). For example, a patient who completed the MoCA and GDS test form in a previous clinic appointment (historical data) was then approached again for the prospective study. There are also four participants who have complete test forms at different time points within the historical data. The total number of completed MoCA and GDS is 301 (from historical and prospective), hence 11% of the total data is comprised of a set of multiple test forms from the same individuals. These multiple test forms are neither a strength nor a flaw to the analysis because Rasch analysis evaluates each item independently of the test responder.

Table 6.2 - Multiple complete test forms from same participant between historical and prospective sample

Number of consecutive appointment visits	Participant cases	Multiple test forms from same participant
2	24	24
3	2	4
4	2	6
	Total	34/301 (11.3%)

Chapter 7 – Conclusions

7.1 Discussion

Performance on individual MoCA items was not statistically different between individuals with low levels of depressive symptoms and individuals with clinically significant levels of depressive symptoms, as mentioned in the manuscript. The same finding also applies when comparing MoCA performance between individuals with low levels of anxiety symptoms versus individuals with clinically significant levels of anxiety symptoms. These results do not support the prediction that specific cognitive domains (i.e. depressive symptoms: processing speed, executive function, attention and memory; anxiety symptoms: attention, verbal memory, visuospatial function and abstraction), would be impaired among patients with clinically significant levels of depressive/anxiety symptoms. Moreover, the mean MoCA score were comparable between the group with low depressive symptoms (M=20.1, SD=4.6) and the group with clinically significant depressive symptoms (M=20.3, SD=4.6). Similarly, the group with low anxiety symptoms (M=20.3, SD=4.7) and the group with clinically significant anxiety symptoms (M=19.3, SD=3.9) did not statistically differ in mean MoCA score ($t(144)=0.92$, $p=0.36$). Severity of depressive symptoms or severity anxiety symptoms were not correlated with total MoCA score, however severity of depressive and anxiety symptoms correlated significantly.

As discussed in the manuscript, several possible reasons were outlined to explain the differences between the present study results and previous relevant studies that also administered MoCA as the outcome measure. On a broader comparison among studies that use neuropsychological batteries, inconsistent findings are presented. Previous studies in older persons have listed several cognitive domains shown to be associated with depressive symptoms,

namely memory (Hamilton et al., 2014; Johnson et al., 2013; O'Shea et al., 2015; Reppermund et al., 2011), executive function (Hamilton et al., 2014; O'Shea et al., 2015) and processing speed (Hamilton et al., 2014). Similar cognitive domains are also affected in older adults diagnosed with major depressive disorder (MDD), including memory (Dumas & Newhouse, 2015; Mantella et al., 2007; Nebes et al., 2000), processing speed (Nebes et al., 2000; Sheline et al., 2006) and executive function (Lockwood, Alexopoulos, & van Gorp, 2002). In contrast, there are also disagreements in the literature where some studies found a null effect of depressive symptoms on cognitive function (Bunce et al., 2012; Gale et al., 2012). Altogether, these incongruous results demonstrate that an important emphasis needs to be placed on the type of measures and tests used to capture cognitive function which could ultimately entail differing findings.

Similar patterns are seen in previous studies in older persons assessing the influence of anxiety symptoms or formal types of anxiety disorders on cognitive function. There are studies that report a negative impact of anxiety symptoms on cognitive function, positive effects depending on severity of anxiety symptoms, and possibly a curvilinear relationship between anxiety symptoms and cognitive performance. Cognitive components that are negatively impacted among older adults with significant anxiety symptoms include attention (Beaudreau & O'Hara, 2009), verbal fluency (Bunce et al., 2012), visuospatial ability (Stillman, Rowe, Arndt, & Moser, 2012), memory (Stillman et al., 2012; Yochim et al., 2013) and executive functioning (Yochim et al., 2013). Conversely, a recent study from a sample of 955 community dwelling older adults demonstrated that performance in verbal fluency and overall cognitive function is higher among individuals self-reporting mild to moderate levels of state anxiety (Potvin et al., 2013). Alternatively, anxiety symptoms may have a curvilinear relationship with cognitive ability such that mild anxiety symptoms improve, whereas severe anxiety symptoms worsen,

scores on the MMSE (Bierman, Comijs, Jonker, & Beekman, 2005). Individuals (n=19) with a formal diagnosis, based on DSM-IV criteria, for Generalized Anxiety Disorder (GAD), had significantly lower scores in short-term and delayed memory compared to age and education matched controls (Mantella et al., 2007).

Surprisingly, even in studies specifically administering the MoCA, a consensus cannot be reached about which cognitive domains are influenced by depressive symptoms, as outlined in the manuscript. Of note, Del Brutto et al.'s study sample consisted of rural community dwelling older adults who were, on average ten years younger (i.e. Mean age 70 +/- 8 years versus Mean age 82.0 +/- 6.3 years, respectively) and statistically different from the present study's sample ($t(424)=15.7$, $p<0.001$). Moreover, in their sample only 81% completed primary school or less, whereas only 12% of the individuals in the present study had eight years of school or less. Both this study and Del Brutto et al.'s study found no difference in MoCA scores globally and at the domain specific level between older adults with high versus low levels of anxiety symptoms. Speculatively, this could be partially explained by the positive/curvilinear relationships of anxiety symptoms on cognitive performance mentioned previously (Bierman et al., 2005; Potvin et al., 2013), suggesting that anxiety symptoms could help or hinder depending on the severity, individual and context.

Finally, there is a subtle yet important distinction to be emphasized between statistical significance versus clinical significance (Houle & Stump, 2008). Findings can be statistically significant in a controlled laboratory setting, yet not meaningful or even apparent when applied in a clinic setting. On a global scale, many other well established factors, such as age and education, are known to affect cognition. In particular, a study investigating the degree to which individual demographic factors (i.e. age, education, level of depressive symptoms etc) explain

scores on specific cognitive domains demonstrated that depressive symptoms predict less than 2% for each cognitive domain (Ganguli, Snitz, Vander Bilt, & Chang, 2009). Specifically, depressive symptoms, as assessed by the modified Center for Epidemiological Studies - Depression scale (mCES-D), explained executive function at 1.22%, visuospatial ability at 0.95%, language at 0.79%, memory at 0.64% and attention at 0.28% (Ganguli et al., 2009). This effect is minimal when compared with other factors such as age and education that range from 6.68% to 14.5% and 2.69% to 4.68% (except attention), respectively (Ganguli et al., 2009). Moreover, the effect of depressive symptoms on cognitive performance may be negligible when interpreting cognitive screening scores for clinical purposes, particularly since depressive symptoms did not significantly explain total MoCA score variance in comparison to other significant factors such as age and education (49%) (Freitas, Simoes, Alves, & Santana, 2012). Since the effect of depressive symptoms is minimal, this may partially explain the varying results in the literature and further support the possibility that different findings can arise due to different sample demographics and various types of measures used.

Despite previous studies reporting significant findings between measures of cognitive function, and measures of depression and anxiety, it is important to emphasize that the difference in the actual cognitive measures used (e.g. neuropsychological tests vs. brief screening tests) may contribute to differences in findings as discussed in the manuscript. Some of these previous studies administer more extensive neuropsychological batteries that assess specific cognitive domains in more depth (Beaudreau & O'Hara, 2009; Yochim et al., 2013), whereas other studies administer different cognitive screening tests, such as the MMSE (Tam & Lam, 2012; Yaffe et al., 1999; Zeki Al Hazzouri et al., 2013). In this current study, there was no statistically significant difference in total MMSE score between individuals ($M = 25.5$, $SD = 2.6$) with high

depressive symptoms and individuals (M = 25.6, SD = 3.1) with low depressive symptoms ($t(144) = 0.1$, $p = 0.9$) . Similarly, total MMSE score did not statistically differ between individuals (M = 25.6, SD = 2.6) with high anxiety symptoms and individuals (M = 25.6, SD = 3.1) with low anxiety symptoms ($t(144) = 0.06$, $p = 0.9$). A previous study reported sex differences in cognitive ability (based on MMSE) such that depressive symptoms are associated with cognitive impairment in older males (Ng et al., 2009). In this sample, the difference in total MMSE score between older males (M = 24.7, SD = 2.2) and females (M = 26.2, SD = 2.8) with high depressive symptoms did not reach statistical significance ($t(29) = 1.6$, $p = 0.13$), however this trend may be more apparent with greater individuals with high depressive symptoms.

7.2 Limitations

Several points should be considered when interpreting the results and these include the present study's sample size, patient characteristics, precision of depression and anxiety tests, and potential impact of medication. To examine sample size as a potential contributor to the null effects in this study, a power analysis was done based on the estimated effect size (Cohen's d = 0.60) from a similar study that reported significant effects of depression status on total MoCA score (Del Brutto et al., 2015). Power in the current study with a sample size of 146 was estimated at 84%, which is acceptable although it does not rule out the possibility that significant effects might be seen with a larger sample size. Since the study sample is derived from a general geriatric outpatient clinic, very few participants self-reported severe levels of depressive or anxiety symptoms. Hence, the study's findings may not generalize to patients with higher levels of depression or anxiety (i.e. from a psychiatric setting). Instead, these conclusions are applicable to situations when geriatric patients are presenting with minimal to mild depressive or anxiety symptoms.

The precision of the tests used to assess depressive and anxiety symptoms should be considered because comparison was based on binarizing participants into low versus high depressive or anxiety symptoms. For example, item "problems with memory" on the GDS has been shown to not fit within the Rasch model (Chachamovich, Fleck, & Power, 2010; Chiang, Green, & Cox, 2009; Tang, Wong, Chiu, Lum, & Ungvari, 2005), indicating that it may not be a meaningful contributor in assessing depression status. This is particularly relevant for individuals who score near the clinical cut-off for significant levels of depressive and anxiety symptoms, since the increment from five to six on the GDS is essentially the deciding factor for group categorization. Alternatively, it would be interesting to compare between individuals with low versus severe depressive or anxiety symptoms in order to address this minor issue. However, due to the composition of the study sample, there is insufficient numbers of individuals with severe levels of depressive or anxiety symptoms to examine the proposed comparison.

The effect of medications, such as antidepressants or anxiolytics, was not incorporated in the analyses and could contribute to cognitive performance. For example, if a patient diagnosed with a depressive disorder reported low levels of depressive symptoms due to treatment for depressive disorder, does cognitive function remain the same as pre-treatment or change post-treatment? Depending on the presence and directionality, or absence, of change in cognitive function post-treatment, this may affect the results. More specifically, if there is cognitive improvement following treatment for depressive disorder, then this effect would support the prediction that individuals with low levels of depressive symptoms perform cognitively better than individuals with high levels of depressive symptoms. A recent review article, for all adult age groups, suggested that certain types of antidepressants may have beneficial effects in cognitive components, namely learning, memory and executive function (Baune & Renger,

2014). Nevertheless, the current sample is based from general geriatric outpatient clinics and only a small portion, 9 participants (6%) and 4 participants (3%) , have documented clinician notes via medical chart reviews of clinically significant depressive or anxiety status, respectively.

7.3 Future Directions

As mentioned in the manuscript, it would be relevant to demonstrate whether the findings from this study are comparable among patients with a formal diagnosis in the various types of depressive or anxiety disorders (e.g. geriatric psychiatric clinics). Presumably, these patients would have higher levels of depressive and anxiety symptoms that may result in cognitive domain specific deficits statistically significant enough to be detected in the MoCA. Moreover, it would also be possible to examine the relationship between antidepressants or anxiolytics and MoCA performance within this context.

The MoCA is a widely used common cognitive screening tool, however it is not the only one designed to detect early stages of significant cognitive impairment. There exist others (Lonie et al., 2009) and since each screening test is unique in assessing cognition in terms of the specific items included, the findings in this study focused on the MoCA may not be replicable in other screening tests. For example, the effects of depression may be more apparent in a cognitive screening test that implements higher difficulty and more elaborate memory, processing speed or executive function items. Hence, future studies can shed light on whether the present study's findings on the MoCA are comparable to other brief cognitive screening tests.

In conclusion, the purpose of this thesis was to contribute evidence as to whether the presence of clinically significant levels of depressive and anxiety symptoms impact performance on specific items of the MoCA among general geriatric outpatients. This research question is practically and clinically relevant because geriatric patients often present with various health

problems and the MoCA is commonly used in geriatric settings. The results of this thesis suggest that clinically significant levels of depressive or anxiety symptoms do not influence the probability of successfully passing individual MoCA questions and this finding can be generalized to general geriatric outpatient settings.

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Appendices

A.1 Missing MoCA, GDS and GAI Data

In the MoCA data, there are four test forms that have missing data, as outlined in table A.1. This is due to three participants who have visual impairments and hence could not complete visual items (trails, cube drawing, clock drawing and naming animals) and one participant who refused to complete clock drawing and Subtract 7s. In both the GDS data and GAI data, only one item from one participant was missing due to preference not to answer.

Table A.1 – Frequency and reasons for missing MoCA, GDS and GAI data

Test	**Items**	**Missing cases**	**Reasons why (number of cases)**
MoCA	Trails	3	-visual impairment (3)
	Cube	3	-visual impairment (3)
	Clock Drawing all components (Contour, Numbers and Hands)	4	-refuse to do item (1) -visual impairment (3)
	Animal Naming all components (Lion, Rhino and Camel)	3	-visual impairment (3)
	Subtract 7s	1	-refuse to do item (1)
GDS	1 item missing (Q11)	1	-prefer not to answer (1)
GAI	1 item missing (Q13)	1	-prefer not to answer (1)

A.2 Procedures for establishing data fit to the Rasch Model

The units in Rasch are called logits (natural logarithm linear units). Items are standardized to a normal distribution with a mean of 0 and a standard deviation of 1. In order to capture the full range of the construct, the items should span a range of +/- 4 standard deviations. The data set fits the Rasch model when (1) there is a global non-significant x^2 (chi-squared) AND (2) items and persons have standardized fit residuals between +/- 2.5. If the data set does not fit the Rasch model several modifications can be explored:

- Check if the variance is significantly explained by a secondary factor other than the main factor (principal components). Several items may cluster together to form this secondary factor, hence items can be rescored appropriately.
- Check for disordered thresholds among polytomous items. Disordered thresholds arise when the probability of successfully passing an item is higher for a difficult item than an easy item. Items with disordered threshold can be rescored appropriately.
- Check for unstable items (items with DIF) and stratify based on group characteristic.
- Check for residual correlations between items. If two items are highly correlated, delete one of the two items to reduce redundant test items.
- Check for misfit items with fit residuals greater than +/- 2.5. If this item remains a misfit item after undergoing above modifications then delete misfit item.

This list is not exhaustive nor is there a specific order in implementing these modifications, several combinations and iterative processes may be required in order to balance reliability and validity of a test.