Apathy: Why Care? The Relationship between Apathy and Cognition in Young Adults and Individuals with Cerebrovascular Disease

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Abstract

Apathy is characterized by diminished goal-directed behaviour (e.g., lack of effort, initiative, and/or productivity), decreased goal-directed cognition (e.g., lack of interest in learning/pursuing new experiences), and blunted emotion (e.g., unchanging affect; Marin, 1991). Greater apathy is correlated with poorer social, physical, and functional outcomes (Kaufer et al., 1998; Starkstein, Federoff, Price, Leiguarda, & Robinson, 1993). Apathy may be present in both clinical and non-clinical populations, including individuals with stroke, dementia, depression, and healthy adults. Apathy is related to depression and is a common characteristic of dysexecutive syndromes. It may occur in conjunction with a variety of other clinical difficulties and comorbidities, complicating assessment and treatment (Marin, 1990).

The purpose of the current dissertation was to advance our understanding of apathy, its relationship to depression, and its influence on cognition, in individuals with cerebrovascular disease and in young adults. This dissertation had three primary goals, which were addressed in five chapters. First, it explored how symptoms of apathy (i.e., decreases in goal-oriented behaviour, goal-oriented cognition, and/or emotional blunting) were related to cognition (i.e., memory and executive functioning) beyond the influence of depressive symptoms in individuals with cerebrovascular disease (Articles 1 and 2). Second, it examined the relative contribution of apathy and depression on cognition (particularly neutral and emotional memory) in young educated adults (N = 96), positing that apathy may impair *overall* cognitive performance to a greater degree than depression, but that depression may impact the *type* of emotional content that is remembered (Article 3). Last, it extended upon findings from Articles 1 and 2 by designing and implementing a randomized controlled trial (N = 72 stroke patients) to evaluate whether goal-setting could improve cognitive performance in the chronic phase after stroke (Article 4).

These studies demonstrate the importance of a) screening for apathy (even in the absence of depressive symptoms), b) differentiating between apathy and depression, c) appreciating the relationship between apathy and cognition (e.g., executive function and memory) in young educated adults and in individuals with cerebrovascular disease, and d) demonstrating the utility of intervention tools (e.g., goal-setting) to enhance cognitive performance.

CHAPTER 1: Conceptual and Theoretical Background

General Introduction

Over the past few decades, apathy, defined as a lack of motivation, has been increasingly recognized as a distinct psychiatric syndrome. Apathy is characterized by diminished goal-directed behaviour (e.g., lack of effort, initiative, and/or productivity), decreased goal-directed cognition (e.g., lack of interest in learning/pursuing new experiences), and blunted emotion (e.g., unchanging affect; Marin, 1991). As a syndrome, apathy cannot be attributable to emotional distress or a diminished level of consciousness (e.g., drowsiness and/or diminished attentional capacity; Marin, 1991).

Greater apathy has been correlated with poorer social, physical, and functional ability (Kaufer et al., 1998; Starkstein, Federoff, Price, Leiguarda, & Robinson, 1993). Apathy is related to decreases in rehabilitation service participation (Medley & Powell, 2010; Skidmore et al., 2010), poorer coping skills (Finset & Andersson, 2000), increases in length of hospital stay (Galynker et al., 1997), and greater caregiver burden (George, 2013; Leroi et al., 2012). Apathy is also an independent risk factor for other diseases, including vascular diseases and dementia (Eurelings et al., 2014; Robert et al., 2006).

Apathy is present in both clinical and non-clinical populations, including individuals with stroke, Parkinson's disease, dementia, depression, as well as healthy adults (Adams, 2001; Lyketsos et al., 2002; Okada et al., 1997; Starkstein et al., 1993). Meta-analyses posit that apathy occurs nearly as frequently as depression in neurological disorders; however, apathy has only gained research interest over the past few decades as an important neuropsychiatric construct (Caeiro, Ferro, & Costa, 2013; Marin, 1990; Van Dalen, Moll van Charante, Nederkoorn, van Gool, & Richard, 2013). Apathy may occur in conjunction with a variety of other clinical difficulties and comorbidities, and may complicate assessment and treatment (Marin, 1990).

Broadly, the purpose of the current dissertation was to advance our understanding of apathy, its association to depression, and its relationship with cognition, in individuals with cerebrovascular disease and in young educated adults. This dissertation contains five chapters that reflected three primary goals. First, it intended to explore how symptoms of apathy (i.e., decreases in goal-oriented behaviour, goal-oriented cognitions, and/or emotional blunting) correlate with cognitive functioning (i.e., memory and executive functioning) beyond the influence of depressive symptoms in individuals with cerebrovascular disease. Given that apathy is both related to depression and is a common characteristic of dysexecutive syndromes, I explored whether apathy may be a better predictor of cognition than depressive symptoms. Chapter 2 (Articles 1 and 2) differentiated the relationships between apathy and depressive symptoms with verbal learning and memory in stroke patients, and examined apathy as a predictor of executive function in patients with cerebrovascular disease.

Second, researchers have yet to examine how apathy relates to cognition in young, educated adults without neurological or cerebrovascular diseases. Research suggests that apathy is present in healthy older adults (Adams, 2001; Ishizaki & Mimura, 2011; Onyike et al., 2007). In some instances, symptoms of apathy have been more commonly reported than symptoms of depression (Adams, 2001). My second goal (Chapter 3) was to differentiate the role of apathy and depressive symptoms on various tests of memory (e.g., neutral episodic memory, emotional episodic memory, autobiographical memory) executive function (e.g., verbal fluency), and working memory (e.g., digit span) in young educated adults. I proposed that greater apathy symptoms may be related to poorer cognitive performance to a greater degree than depressive symptoms, but that depressive symptoms may be related to the type of emotional content that is remembered.

Last, studies that elucidate the role of apathy on cognitive, emotional, and physical function across neurological and psychiatric populations have highlighted the importance of goal-setting. Given that apathy is defined as a lack of goal-oriented behaviour, cognition, and emotion, goal-setting techniques offer a way to increase goal-oriented cognition and behaviour in individuals (Locke & Latham, 1990, 2002). In Chapter 4 (Article 4), I explored the effectiveness of a short-term goal-setting intervention in improving cognitive performance in stroke patients. If goal-setting instructions were found to enhance cognitive performance, it would indicate that treatments targeting apathy (as opposed to sad mood in depression) may serve as a novel approach to improving cognitive outcomes and enhancing patient quality of life in the chronic phase after stroke.

Overview of the General Introduction

This introduction will define apathy, distinguish this syndrome from depressive symptoms, and discuss apathy within the context of dysexecutive syndromes. Specific relationships between cognition (i.e., memory, executive functions, attention, and speed of processing) and apathy will be reviewed, as well as the relationship between depression and cognition. Apathy, depression, and cognitive function will then be explored together, using research supporting that apathy may have a stronger relationship with cognition than sad mood. The introduction will conclude with a discussion of the gaps in the literature and the specific aims of each study in the dissertation.

What is Apathy?

Apathy has been described as a "simultaneous decrease in the behavioral, cognitive and emotional concomitants of goal-directed behavior" (Figure 1.1; Marin, 1991). Goal-directed behaviours include accomplishing tasks, putting effort into activities, carrying out activities

independently, spending time doing tasks that are of interest to the individual, and having friends (Marin, 1991). Goal-directed cognitions encompass the thoughts required to elaborate on action plans. Goal-directed cognitions include being interested in having new experiences, learning new skills, completing tasks, and setting goals for the future. Lastly, emotional-affective deficits comprise of flat affect and lack of reactivity to various situations.

A. Lack of motivation relative to the patient's previous level of functioning or the standards of his or her age and culture as indicated either by subjective account or observation by others.

B. Presence, while with lack of motivation, of at least 1 symptom belonging to each of the following three domains:

Diminished goal-directed behavior.

1. Lack of effort.

2. Dependency on others to structure activity.

Diminished goal-directed cognition

3. Lack of interest in learning new things, or in new experiences.

4. Lack of concern about one's personal problems.

Diminished concomitants of goal-directed behavior.

5. Unchanging affect.

6. Lack of emotional responsivity to positive or negative events.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to diminished level of consciousness or the direct physiological effects of a substance (e.g., a drug of abuse, a medication).

Figure 1.1 Diagnostic criteria for apathy (copied directly from Marin, 1991)

These criteria were revised by Robert and colleagues in 2009, and again by Robert and colleagues in 2018 (see Figure 1.2). This revision emphasized using the terminology "goal-directed behaviour/activity," which the researchers posit is easier to observe and objectively quantify than the term "motivation." Robert et al. (2018) used symptom clusters to reflect three categories, including behaviour/cognition (reflecting high correlations between behaviour and cognitive symptoms [e.g., Mulin et al., 2011]), emotion, and social interaction.

Criterion A: A quantitative reduction of goal-directed activity either in behavioral, cognitive, emotional or social dimensions in comparison to the patient's previous level of functioning in these areas. These changes may be reported by the patient himself/herself or by observation of others.
Criterion B: The presence of at least 2 of the 3 following dimensions for a period of at least four weeks and present most of the time:
B1. BEHAVIOUR & COGNITION: Loss of, or diminished, goal-directed behaviour or cognitive activity as evidenced by at least one of: **General level of activity:** the patient has a reduced level of activity either at home or work, makes less effort to initiate or accomplish tasks spontaneously, or needs to be prompted to perform them.
Persistence of activity: He/she is less persistent in maintaining an activity or conversation, finding solutions to problems or thinking of alternative ways to accomplish them if they become difficult.
Making choices: He/she has less interest or takes longer to make choices when different alternatives exist (e.g., selecting TV programs, preparing meals, choosing from a menu, etc.).
Interest in external issue: He/she has less interest in or reacts less to news, either good or bad, or has less interest in doing new things.
Personal wellbeing: He/she is less interested in his/her own health and wellbeing or personal image (general appearance, grooming, clothes).
B2. EMOTION: Loss of, or diminished, emotion as evidenced by at least one of the following:
Spontaneous emotions: the patient shows less spontaneous (self-generated) emotions regarding their own affairs, or appears less interested in events that should matter to him/her or to people that he/she knows well.
Emotional reactions to environment: He/she expresses less emotional reaction in response to positive or negative events in his/her environment that affect him/her or people he/she knows well (e.g., when things go well or bad, responding to jokes, or events on a TV program or a movie, or when disturbed or prompted to do thing she/she would prefer not to do).
Impact on others: He/she is less concerned about the impact of his/her actions or feelings on the people around him/her.
Empathy: He/she shows less empathy to the emotions or feelings of others (e.g., becoming happy or sad when someone is happy or sad, or being moved when others need help).
Verbal or physical expressions: He/she shows less verbal or physical reactions that reveal his/her emotional states.
B3. SOCIAL INTERACTION: Loss of, or diminished engagement in social interaction as evidenced by at least one of the following:
Spontaneous social initiative: the patient takes less initiative in spontaneously proposing social or leisure activities to family or others.
Environmentally stimulated social interaction: He/she participates less, or is less comfortable or more indifferent to social or leisure activities suggested by people around him/her.
Relationship with family members: He/she shows less interest in family members (e.g., to know what is happening to them, to meet them or make arrangements to contact them).
Verbal interaction: He/she is less likely to initiate a conversation, or he/she withdraws soon from it.
Homebound: Hes/he prefer to stays at home more frequently or longer than usual and shows less interest in getting out to meet people.
CRITERION C: These symptoms cause clinically significant impairment in personal, social, occupational, or other important areas of function.
CRITERION D: The symptoms are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), to motor disabilities, to a diminished level of consciousness, to the direct physiological effects of a substance (e.g. drug of abuse, medication), or to major changes in the patient's environment.

Figure 1.2 Diagnostic criteria for apathy in 2018 (copied directly from Robert et al., 2018)

Apathy may be considered as both a neuropsychiatric syndrome associated with specific aspects of brain damage and a psychological syndrome closely associated with depression (Marin, 1991). Depending on its etiology, apathy may be the primary clinical disturbance, a symptom of another disorder, or a coexisting disorder requiring independent diagnosis and management.

Distinguishing Apathy and Depression

Although depression and apathy are related to each other, they can occur separately from one another (Brodaty et al., 2005; Starkstein et al., 1992); individuals can experience depressive symptoms but not apathetic symptoms, and vice versa (Kirsch-Darrow, Fernandez, Marsiske, Okun, & Bowers, 2006; Starkstein et al., 1992). In contrast to apathy, depression is characterized by feelings of sadness, low mood, and helplessness (American Psychiatric Association, 2013). Accompanying symptoms of depression may include guilt, suicidal ideation, sleep irregularities, and appetite abnormalities (American Psychiatric Association, 2013). In contrast to depression, individuals with apathy experience decreases in motivation and initiation, and increases in emotional indifference. However, individuals with either apathy or depression may experience a reduction in interest, energy, or insight (Figure 1.3).

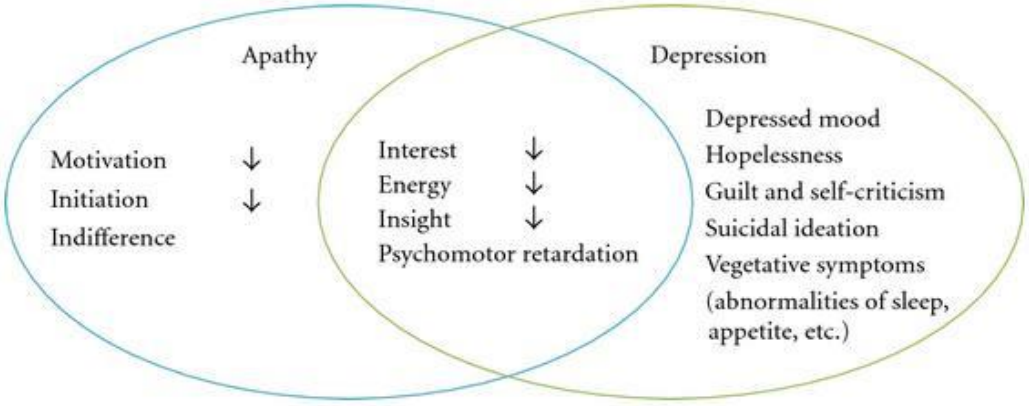

Figure 1.3 Comparing characteristics of apathy and depression (copied from Ishizaki, 2011)

Within stroke populations, apathy has also been differentiated from depression. In stroke patients, reports of crying and overt sadness correlate with greater depression severity, but not apathy (Carota et al., 2005). Additionally, Marin (1991) found that individuals with poststroke apathy do not report the same emotional experiences of loss and sadness as individuals with poststroke depression. Furthermore, patients with poststroke depression without apathy have significantly higher depression scores than individuals with poststroke apathy without depression (Yang et al., 2013).

Hama and colleagues (2007) found both apathy and depression were present in 21% of stroke patients, apathy without depression in 20%, depression without apathy in 12%, and neither apathy nor depression in 47% of patients. In a separate stroke study, Hama (2010) found both apathy and depression in 15% of stroke patients, apathy without depression in 28%, depression without apathy in 12%, and neither depression nor apathy in 45% of patients. In addition, healthy young adults who scored in the clinical range for apathy were not significantly more depressed (as assessed using the Depression, Anxiety, Stress Scale; Lovibond & Lovibond, 1995) than individuals who were not apathetic (Bonnelle, Manohar, Behrens & Husain, 2016). Together, these findings support a differentiation between these syndromes.

Additionally, factor analyses of depression scales have revealed distinct phenomenological symptom clusters, with apathy and sadness often represented by different factors. For example, a principal factor analysis of the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) in stroke survivors with depression yielded three phenomenological symptom clusters, including sadness, distress, and apathy (Kanellopoulos et al., 2020). The “sadness” factor was represented by apparent and reported sadness, pessimistic thoughts, and suicidal thoughts, the “distress” factor was represented by reduced appetite,

concentration difficulty, and inner tension, and the "apathy" factor was represented by lassitude and reduced interest. A factor analysis of the Post-Stroke Depression Rating Scale (PSDRS; Gainotte et al., 1997) revealved a three-factor solution including depressive/anxious symptoms, lack of emotional control, and reduced motivation (Quarranta, Marra, & Gainotti, 2012). The "reduced motivation" factor, consisting of items representing anhedonia and apathy, was the only factor that negatively correlated with a measure of global cognition. Additionally, in healthy community-dwelling adults who completed the Geriatric Depression Scale, dysphoric mood, withdrawal-apathy-vigor, hopelessness, worry/anxiety, and concentration were the factors revealed in a principal components analysis (Adams et al., 2004). Relatedly, small to moderate correlations observed between apathy and depressive symptoms are frequently due to a subset of items (diminished work/interest, psychomotor retardation, lack of energy, and lack of insight) commonly seen in apathetic syndromes (Ishii, Weintraub, & Mervis, 2009). When these overlapping items are excluded from analysis in individuals with normal aging, stroke, Alzheimer's disease, and major depression, correlations between apathy and depression are not significant (Ishii et al., 2009; Marin et al., 1993).

Apathy and depression have also been differentiated at the neuroanatomical and neurophysiological level. Neuroanatomical findings examining depressive and apathetic dimensions of poststroke depression (PSD) separately demonstrated that depression severity is associated with left frontal lobe (but not basal ganglia) damage, and apathy severity is related to damage to the bilateral basal ganglia (but not to the frontal lobe; Hama, 2011). Other studies have also supported relationships between poststroke depression and left anterior lesions (Brodaty et al., 2005; Hama et al., 2007), whereas poststroke apathy has been associated with right hemispheric subcortical lesions (e.g., basal ganglia, anterior cingulate cortex [Andersson,

Korgstad, & Finset, 1999; Caeiro et al., 2013; Okada et al., 1997]). These findings are consistent with previous demonstrations that depressive symptoms are associated with left frontal lobe functioning (Brodaty et al., 2005), whereas the apathetic symptoms are associated with basal ganglia functioning (Carod-Artal, Egido, Gonzalez, & De Seijas, 2000; Jorge, Starkstein, & Robinson, 2010).

Furthermore, both poststroke depression and poststroke apathy have been associated with poor functional recovery and lower quality of life (Hama et al., 2007; van Dalen et al., 2013). Recent studies have reported relationships between greater apathy severity and clinical characteristics (e.g., cognitive impairment and functional decline), without observing these relationships with greater depressive symptoms (Starkstein et al., 2005). Several studies have also shown that apathy has stronger associations with cognitive and functional impairment than depression (e.g., Butterfield, Cimino, Oelke, Hauser, & Sanchez-Ramos, 2010; Hama et al., 2007; Oguru, Tachibana, Toda, Okuda, & Oka, 2009). Similarly, Kanellopoulos et al. (2020) found that when the Montgomery-Asberg Depression Scale (MADRS) was divided into sadness, distress, and apathetic dimensions using factor analysis, only the apathy dimension was associated with greater impairment in EF, memory, and global cognition in individuals with moderate-to-severe depression. However, other studies have found that individuals with depression performed worse than nondepressed individuals on tests of processing speed, memory, learning, problem solving, and executive function (Castaneda et al., 2008; Elderkin-Thompson, Mintz, Haroon, Lavretsky, & Kumar, 2007); Notably, these studies did not account for symptoms of apathy.

Anhedonia. Anhedonia, characterized by "an inability to derive pleasure," is a symptom that is related to both depression and apathy (Husian & Rosier, 2018). Anhedonia and apathy

were correlated in healthy adults, suggesting these constructs share overlapping symptoms (Ang et al., 2018). However, apathy and anhedonia differ in that apathy involves a reduction in goal-oriented behavior and a reduction in emotion expression whereas anhedonia specifically characterizes a loss of pleasure (Calamia, 2014). Apathy and anhedonia have been differentiated from one another in individuals with Parkinson's disease (PD), whereby they were classified as separate constructs in factor analyses (Kirsch-Darrow et al, 2011; Zahodne, Marsiske, Okun, & Bowers, 2012). In both of these studies, a reduction in interest/pleasure was distinct from behavioural symptoms of apathy (e.g., reduced motivation and engagement in activities). Moreover, Batail et al. (2017) found that individuals with depression who were apathetic were able to maintain their ability to feel pleasure despite motivational deficits. In light of these findings, it is also important to highlight that anhedonia can be divided into two categories: anticipatory and consummatory (Thomsen, Whybrow, & Kringelbach, 2015). Anticipatory anhedonia, or "wanting", is related to one's willingness to work for a reward, whereas consummatory pleasure, or "liking", is related to one's in-the-moment experience of pleasure (Thomsen et al., 2015). Anticipatory pleasure is commonly associated with motivation and goal-directed behavior, whereas consummatory pleasure refers to a liking that results from fulfilling a desire (Batail et al., 2017). In summary, the discrepancy between subtypes of anhedonia and between dimensions of apathy elucidate why apathy and anhedonia are related but do not represent identical syndromes.

Prevalence of Apathy

Apathy has been found to occur across psychological, cerebrovascular, and neurodegenerative diseases. Apathy has been shown to affect individuals with stroke, Parkinson's disease, dementia, depression, as well as healthy adults. Apathy is present in 25-50%

of individuals with Alzheimer's disease (Levy et al., 1998; Starkstein et al., 1992), 20-45% of individuals with Parkinson's disease (Aarsland et al., 1999; den Brok et al., 2015), 46% of individuals with traumatic brain injury (Andersson et al., 1999), 30% of individuals with Huntington's disease (Mason & Barker, 2015), and in 20-50% of stroke patients (Brodaty et al., 2005; Starkstein et al., 1993). The prevalence of apathy is similar for left- and right-sided hemispheric stroke lesions and for ischemic and hemorrhagic stroke types (Caeiro et al., 2013).

Across numerous disorders, symptoms of apathy have been reported either to the same extent or more frequently than depressive symptoms. For example, the prevalence of apathy and depression in Alzheimer's disease was shown to be 67% and 25%, respectively (Aarsland et al., 1999). In a sample of individuals with Parkinson's disease, apathy was present in 60% of patients, and depression in 56% (Oguru et al., 2009). In patients with Huntington's disease, apathy was present in 52% of patients, whereas depression was present in 12% of patients (Naarding, Janzing, Eling, van der Werf, & Kremer, 2009). In a systematic review, Caeiro et al. (2013) posited that the rate of 'pure apathy' (without concomitant depression) is twice as frequent as the rate of 'pure' depression (without concomitant apathy) in stroke patients.

Fewer studies have examined the rates of apathy in healthy adults. In a sample of healthy older adults above 65 years old, Adams (2001) found that items representing apathy using the Geriatric Depression Scale were more frequently endorsed (75.2%) than items representing depression (37.8%) or anxiety (25.1%). Onyike et al. (2007) found that apathy was present in 1.4% of community-dwelling older adults without evidence of cognitive impairment above age 65. Lyketsos et al. (2002) and Ishizaki and Mimura (2011) found prevalence rates of 3.2% and 7.0%, respectively, in older adults. These findings illuminate that apathy is measurable and detectable in community-dwelling populations (primarily older adults) but with lower prevalence

rates than in populations with neuropsychiatric conditions.

Instruments Used to Measure Apathy

Numerous validated instruments may be used to measure apathy, including the Apathy Evaluation Scale (AES; Marin, 1991), the Neuropsychiatric Inventory (Cummings et al., 1994), Apathy Inventory (Robert et al., 2002), and Lille Apathy Rating Scale (Sockeel et al., 2006). The Apathy Inventory (Robert et al., 2002) and Lille Apathy Rating Scale (Sockeel et al., 2006) include subscales measuring specific components of apathy (i.e., different diagnostic criteria such as loss of interest and lack of initiative). A review by Clarke et al. (2011) determined that the AES is the most psychometrically robust and widely used measure to assess apathy.

The Apathy Evaluation Scale is an 18-item apathy measure (Marin, 1991). Marin and colleagues (1991) described four subscales for the AES; behavioural, cognitive, emotional, and "other". The behavioural subscale has six items (e.g., "I get things done during the day", "I spend time doing things that interest me"), the cognitive subscale has five items (e.g., "I am interested in things", "I am interested in having new experiences"), the emotional subscale has two items (e.g., "When something good happens, I get excited"), and the "other" subscale has three items (e.g., "I have initiative", "I have motivation"). AES items are reverse coded (except for items 6,10, and 11) and AES scores range from 18 to 60, with higher scores indicating greater apathy. Internal consistency for the AES ranges from .86 to .94, and test-retest reliability ranges from .76 to .94 (Marin, Biedrqcki, & Firinciogullari, 1991). The AES has been utilized across a variety of age groups (Resnick, Zimmerman, Magaziner, & Adelman, 1998; Kohn & Rosman, 1972) and across neurodegenerative (Sockeel et al., 2006; Starkstein et al., 1993) and cerebrovascular disease (Brodaty et al., 2005; Sagen et al., 2010) populations and healthy individuals (Marin, 1991; Santa et al., 2008). The AES has self-rated (AES-S), informant-rated

(AES-I), and clinician-rated (AES-C) versions.

	Clinician			Informant			Self	
	Apathy	**Depression**	**Anxiety**	**Apathy**	**Depression**	**Anxiety**	**Apathy**	**Depression**
Clinician								
Apathy								
Depression	0.39							
Anxiety	0.35[3]	0.87						
Informant								
Apathy	0.62	0.23[2]	0.15[1]					
Depression	0.56	0.53	0.41	0.65				
Anxiety	0.46	0.67	0.45	0.43	0.74			
Self								
Apathy	0.72	0.35[3]	0.37	0.43	0.46	0.42		
Depression	0.41	0.74	0.71	0.27[3]	0.53	0.56	0.42	
Anxiety	0.36	0.56	0.63	0.23[2]	0.42	0.55	0.42	0.78

Note. Intercorrelations are shown among clinician-, informant-, and self-rated measures of apathy, depression, and anxiety. Apathy scores are self, informant, and clinician (R.C.B.) scores on the Apathy Evaluation Scale. Clinician measures of depression and anxiety are from the Hamilton Rating Scales for Depression and the Hamilton Rating Scale for Anxiety, respectively. Informant- and self-rated measures for depression and anxiety are both from the Zung Rating Scale for Depression and the Zung Rating Scale for Anxiety, respectively. Underlined items are convergent validity coefficients.

Figure 1.4 Convergent and discriminant validity of the AES (copied from Marin, 1991)

Figure 1.4 shows that clinician-rated and self-rated versions of the AES can discriminate apathy from depression. It also shows that informant ratings may not be as effective in discriminating between apathy and depression. Despite informants' familiarities with subjects, they may not know more subjective information, such as subjects' moods or appraisals of their own efforts and values, which are critical for discriminating apathy and depression (Marin, 1991). In other studies, however, self-rated apathy was highly correlated with informant-rated apathy, establishing the validity of using self-rated apathy instead of, or in combination with, informant-rated assessments of apathy in future studies (Mason & Barker, 2015).

Apathy and Cognition

Researchers have explored the relationship between apathy and cognition in individuals with neurological diseases. Overall, researchers have reported correlations between apathy severity and global measures of cognition (e.g., Mini Mental Status Exam [MMSE]; Folstein, Folstein, & McHugh, 1975). Brodaty et al. (2005) found that apathetic stroke patients performed significantly worse on the MMSE than nonapathetic stroke patients. Yamagata, Yamaguchi, and

Kobayashi (2004) found that apathetic stroke patients performed significantly lower on a global cognition test (Hasegawa Dementia Rating Scale; Katoh, 1991) than nonapathetic individuals. Mayo, Fellows, Scott, Cameron, and Wood-Dauphinee (2009) and Starkstein et al. (1993) also noted correlations between apathy severity and poorer MMSE. Global brain atrophy is strongly associated with post-stroke apathy (and not post-stroke depression), and this relationship is independent of both stroke lesion and comorbid post-stroke depression (Douven et al., 2020). As a result, cumulative brain pathology may play a role in the development of post-stroke apathy by damaging microstructural networks that are involved in the regulation of mood and motivational processes (Douven et al., 2020). Research regarding the relationship between apathy and specific cognitive functions are addressed below.

Apathy and Executive Function. Executive functions (EFs) are a set of cognitive processes that are involved in controlling behaviours, including self-monitoring, planning, organization, and reasoning. As such, the term "dysexecutive syndrome" is used to describe difficulties with initiating, coordinating, and completing self-monitoring, planning, organizing, and reasoning tasks (Repovs & Baddeley, 2006). Across neurodegenerative and cerebrovascular diseases, apathy is correlated with (and is also a common characteristic of) impairments in executive functions, including difficulties with verbal fluency, task shifting, planning, inhibition, and cognitive flexibility (Liang, Liang, Ungvari, & Tang, 2016).

Damage to frontal subcortical circuits are well-known causes of dysexecutive syndromes, encompassing emotional and behavioural changes in affected individuals (Shallice & Burgess, 1991; Stuss et al., 1994). Ardila (2013) described two prefrontal circuits supporting two types of dysexecutive syndromes: metacognitive dysexecutive syndrome and emotional/motivational dysexecutive syndrome. Metacognitive executive dysfunction is mediated by the lateral

prefrontal cortex (e.g., dorsolateral prefrontal cortex [dlPFC]), and involves difficulties with task shifting and responding to new and/or complex stimuli, as well as organizing goal-directed activities (Fuster, 2002). Emotional/motivational dysexecutive syndrome involves damage to the orbitofrontal and medial frontal cortex (e.g., anterior cingulate cortex [ACC]; Sallet et al., 2011), and encompasses difficulties with value-based decision-making (Ardila, 2013). This dysexecutive syndrome is associated with difficulties with inhibitory control, personality changes, emotional lability, apathy, and lack of insight (Eslinger & Damasio, 1985).

The anterior cingulate cortex and dorsolateral prefrontal cortex are also functionally interconnected; research regarding ACC-dlPFC connectivity suggest that the ACC may modulate dlPFC activity, while the dlPFC may drive ACC activity (Sallet et al., 2011). Studies of resting state cingulate functional connectivity found a relationship between activity in certain regions of the ACC with dlPFC activity (Habas, 2010; Margulies et al., 2007). Kouneiher, Charron, and Koechlin (2009) have posited that the interaction between these regions is related to motivational control. In addition, both the anterior cingulate and dorsolateral prefrontal circuits involve projections to the striatum (followed by the globus pallidus, substantia nigra, and the thalamus; Bonelli & Cummings, 2007; Tekin & Cummings, 2002; Van Dalen et al., 2013). Damage to these prefrontal cortex-basal ganglia circuits have been associated with apathy symptoms (Kimura et al., 2003; Levy, 2012; Middleton & Strick, 2000). For example, lesions to the striatum have been associated with very severe apathetic states (Levy & Dubois, 2006).

Individuals with Parkinson's disease or Alzheimer's disease who were apathetic performed worse on a fluid reasoning task (i.e., Raven's Colored Progressive Matrices; Carlesimo, Caltagirone, & Gainotti, 1996) than individuals with Parkinson's disease or Alzheimer's disease who were not apathetic (Grossi et al., 2013). Individuals with Alzheimer's

disease who were apathetic performed worse on a test of set-shifting, cognitive flexibility, and inhibition (i.e., Stroop Colour-Word Interference Test; Barbarotto et al., 1998) than nonapathetic individuals with Alzheimer's disease. Individuals with traumatic brain injury (TBI) who were apathetic performed worse on an executive function and inductive reasoning task (Wisconsin Card Sorting Task; Heaton, 1993) when compared to individuals with TBI without apathy (Andersson & Bergedalen, 2002). In addition, stroke patients with more severe apathy performed worse on an executive function task (Executive Interview; Stokholm, Vogel, Gade, & Waldemar, 2005) than individuals with less severe apathy and individuals without apathy (Isella et al., 2002).

Apathy and Fluency. Verbal fluency is a measure of verbal ability and executive function. Verbal fluency tasks examine individuals' abilities to retrieve information according to specific criteria within a time limit (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Category (semantic) fluency is assessed by asking participants to generate words belonging to a specific category (e.g., animals or vegetables; Newcombe, 1969), and letter (phonemic) fluency is assessed by asking participants to generate words that begin with particular letters (Benton & Hamsher, 1976). Successful word retrieval requires executive control abilities including attention, inhibition, and task shifting (Fisk & Sharp, 2004; Miyake et al., 2000; Miyake & Friedman, 2012).

Apathy and verbal fluency are correlated with one another, such that individuals with apathy typically generate fewer words on letter and category fluency tasks (Isella et al., 2002; Yamagata et al., 2004). Apathy in individuals with Parkinson's disease is correlated with verbal fluency task performance, such that greater apathy is related to fewer words generated on letter and category fluency tasks (Isella et al., 2002). Apathetic individuals with TBI demonstrated

impairments in category (but not letter) fluency compared to nonapathetic individuals with TBI (Andersson & Bergedalen, 2002). Apathy was negatively correlated with verbal fluency in individuals with first-episode psychosis (Faerden et al., 2009). Additionally, stroke survivors with apathy had poorer category fluency than stroke survivors without apathy (Yamagata et al., 2004).

Apathy and Working Memory. Working memory (WM), a multi-component system that holds and manipulates information in short-term memory (Baddeley & Hitch, 1974), is also related to apathy. Baddeley's (2000) model of working memory postulates that working memory consists of the central executive, visuospatial sketchpad, phonological loop, and the episodic buffer. The central executive supervises and coordinates the other systems ("attention-controlling" system), the visuospatial sketchpad manipulates visual and spatial images, the phonological loop manipulates auditory information, and the episodic buffer integrates material from different modalities and is controlled by the central executive (Baddeley, 2000). Complex WM span tasks are more strongly correlated with higher-order cognitive tasks (i.e., EFs) than simple WM span tasks, which measure short-term storage capacity (Conway et al., 2005; Unsworth & Engle, 2006). Furthermore, similar to the proposed neurobiological underpinnings of apathy, the highly interrelated complex WM span and EF tasks both activate prefrontal-subcortical networks in the brain (Ardila, 2013; Osaka et al., 2004). Working memory performance in HIV-1 infection correlated with apathy severity, such that individuals with apathy performed worse on working memory tasks than individuals without apathy (no relationship was observed between depression scores and working memory; Castellon, Hinkin, Wood, & Yarema, 1998). In patients with first-episode psychosis, apathy severity was negatively correlated with working memory (Faerden et al., 2009).

Apathy and EF in Adults without Cerebrovascular or Neurodegenerative Diseases. More limited research has examined the relationship between apathy and executive function in neurotypical populations. Older adults with apathy had difficulties with inhibition (Esposito et al., 2010), cognitive flexibility (Onyike et al., 2007), multitasking (Esposito et al., 2010), and future planning tasks (Raffard et al., 2013), compared to nonapathetic older adults. Additionally, individuals with apathy performed worse on tasks of overall cognition, category fluency, executive functioning, constructional praxis, and processing speed, regardless of depressive symptoms (Montoya-Murillo, Ibarretxe-Bilbao, Peña1, & Ojeda, 2019; Onyike et al., 2007). In older adults with depression, apathy severity was most strongly correlated with two verbal executive measures (i.e., Stroop Colour-Word Interference Task and letter fluency) and one nonverbal executive measure (i.e., Wisconsin Card Sorting Test-Other Responses; Feil, Razani, Boone, & Lesser, 2003).

Apathy and Memory. Researchers have examined the relationship between apathy and memory in a variety of cerebrovascular and neurodegenerative conditions. Apathetic individuals with Alzheimer's disease performed worse on long-term free and cued recall than individuals with Alzheimer's disease without apathy after accounting for age, sex, education, and depression severity (Montgomery & Asberg, 1979). Apathetic individuals with mild cognitive impairment (MCI) had greater impairment in long-term free recall (but not cued recall) on an episodic memory task and a greater decline in long-term free recall performance after one year than nonapathetic individuals with MCI (Robert et al., 2006). In individuals with TBI, greater apathy was associated with poorer verbal acquisition and delayed recall (Andersson & Bergedalen, 2002). Apathetic individuals with Parkinson's disease had more deficits in verbal memory (immediate and delayed) than nonapathetic individuals with Parkinson's disease (Starkstein et

al., 1992). In stroke patients, apathetic individuals had greater impairment on verbal learning and memory tasks than nonapathetic individuals (Hama, Yamashita, Yamawaki, & Kurishu, 2011; Yamagata et al., 2004). Researchers have also reported negative correlations between apathy and long-term verbal memory in stroke patients (Calamia, 2014; Chiaravalloti & DeLuca, 2003; Hama et al., 2011; Kuzis et al., 1999).

Apathy and Memory in Adults without Cerebrovascular or Neurodegenerative Diseases. More limited research has been conducted to evaluate the relationship between apathy and cognition in adults without cerebrovascular or neurodegenerative diseases. However, the few studies suggest that apathy is correlated with cognitive and functional impairment in healthy older adults (Onyike et al., 2007). Apathy in adults without neurological/neurodegenerative diseases correlated with prospective memory, even after controlling for global cognitive functioning, working memory, processing speed, and negative mood (Esposito, Rochat, Van der Linden, & Van der Linden, 2012). Lack of initiative in healthy older adults also correlated with poorer verbal memory (Esposito et al., 2014), poorer episodic memory (Robert et al., 2006), and poorer prospective memory (Esposito et al., 2012).

Although memory consolidation is dependent on the medial temporal lobe (e.g., hippocampus, entorhinal cortex, perirhinal cortex; Achim & Lepage, 2005; Schacter & Wagner, 1999), the prefrontal cortex is also important for memory encoding and retrieval (Alvarez & Squire, 1994; Squire, Knowlton, & Musen, 1993; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Research has shown that the prefrontal cortex is activated by memory recall tasks (Badre & Wagner, 2007; Wheeler, Stuss, & Tulving, 1997). Specifically, the dorsolateral prefrontal cortex (dlPFC; Blumenfeld & Ranganath, 2006) and ventrolateral prefrontal cortex (vlPFC; Blumenfeld & Ranganath, 2006; Levy & Dubois, 2006) have been found to contribute to

memory performance. These regions are essential to frontal-subcortical circuitry. Lesions or damages to this circuit (which includes projections to the caudate nucleus) have also been found to impact motivational control (Bonelli & Cummings, 2007; Tekin & Cummings, 2002), and cause severe apathy (Kumral, Evyapan, & Balkir, 1999). Taken together, this research supports a relationship between apathy and memory at the neurophysiological level.

Apathy and Processing Speed. Processing speed (PS) may be evaluated using reaction time for motor, verbal, and/or visual tasks. In individuals with Parkinson's disease, apathy severity was negatively correlated with attention and PS after accounting for age and depression (Brodaty et al., 2005). Lohner, Brookes, Hollocks, Morris and Markus (2017) found that apathy (and not depression) was negatively correlated with PS in patients with cerebral small vessel disease. Furthermore, apathetic stroke survivors had poorer attention (Harris, Elder, Schiff, Victor, & Goldfine, 2014) and PS (Brodaty et al., 2005) than nonapathetic stroke survivors.

Apathy and PS in Adults without Cerebrovascular or Neurodegenerative Diseases. Marin (1991) found that apathy scores correlated with the amount of time that healthy individuals chose to play a game and the average response time for indicating they intended to play again, as well as the difficulty level at which participants chose to play. Other studies reported psychomotor slowness in apathetic older adults (Onyike et al., 2007). In older adults with depression, apathy severity strongly correlated with information processing speed (Feil et al., 2003).

Summary of Cognitive Findings. Together, these findings support relationships between apathy and verbal memory, executive functioning (e.g., verbal fluency), and psychomotor speed, across a variety of neurodegenerative and cerebrovascular diseases. The limited research conducted with healthy older adults supports poorer memory, verbal fluency, multitasking, and processing speed in apathetic compared to nonapathetic individuals (Montoya-

Murillo et al., 2019; Onyike et al., 2007). For individuals with depression, apathy has also been correlated with cognitive impairment (Feil et al., 2003). To the best of our knowledge, researchers have not examined the relationships between apathy, depression, and other constructs related to memory (e.g., autobiographical memory, episodic memory, and emotional memory) and executive functioning (e.g., verbal fluency, working memory) in young adults.

Summary of Neurophysiological Findings. Impairments in frontal-subcortical circuitry, which includes the anterior cingulate cortex, dorsolateral prefrontal cortex, ventral striatum, globus pallidus, substantia nigra, and thalamus, have frequently been associated with apathy (Bonelli & Cummings, 2007; Tekin & Cummings, 2002; van Dalen et al., 2013). Damage to these circuits (e.g., anterior cingulate circuit and dorsolateral prefrontal circuit), which project to the basal ganglia, are thought to underlie symptoms of apathy (Chase, 2011; Levy & Dubois, 2006). Lesions to the ACC, basal ganglia, temporal cortex, and medial thalamic regions are also associated with more severe symptoms of apathy (Apostolova et al., 2007; Lanctôt et al., 2007; Migneco et al., 2001; Okada et al., 1997).

Section Summary. These findings suggest that apathy may act as both a syndrome related to depression (and anhedonia) as well as a characteristic of dysexecutive syndromes commonly resulting after frontal brain injuries (Ardila, 2013). Importantly, the association between apathy and cognitive impairment may be bidirectional and/or result from shared frontostriatal brain damage. The reviewed studies highlight the shared etiological substrates of apathy and cognition (especially EF and WM), which complement other case reports that focus on apathy's onset after strokes to frontostriatal circuits that mediate EF (Manning & Taylor, 2020). Apathy may also be related to alterations in reward circuitry (e.g., in ventral striatum and ACC), including reward anticipation and reward sensitivity (Treadway et al., 2012), and/or a

reduced willingness to expend effort (Treadway et al., 2012). Furthermore, the relationship between apathy and cognition may be bidirectional, as individuals with poorer cognitive function may be more likely to develop apathy, and individuals with apathy may be more likely to deteriorate cognitively or be cognitively impaired (Palmer et al., 2010). For instance, post-stroke apathy has been shown to predict poorer recovery of cognitive function (Mikami et al., 2013), while greater baseline cognitive impairment, particularly in EF, is related to subsequent increases in symptoms of apathy (Douven et al., 2018).

Depression and Cognition

Researchers have also examined the relationship between depression and cognitive function. Individuals with depression have been found to perform worse on processing speed, memory, learning, problem solving, and EF tasks than nondepressed individuals (Castaneda et al., 2008; Elderkin-Thompson et al., 2007; Keilp, Gorlyn, Oquendo, Burke, & Mann, 2008; Landrø, Styles, & Sletvold, 2001). Individuals with depression have exhibited cognitive deficits on tests of episodic verbal learning (Asmundson, Stein, Larsen, & Walker, 1995; Smith, Muir, & Blackwood, 2006), working memory (Walter, Wolf, Spitzer, & Vasic, 2007), and long-term memory (Leposavic, Leposavic, & Gavrilovic, 2010), when compared to healthy individuals. Some studies have reported negative correlations between depression severity and cognitive performance (Egeland et al., 2005; Hill, Keshavan, Thase, & Sweeney, 2004).

In stroke patients, depression (as assessed using the Beck Depression Inventory; Beck, Steer, & Brown, 1996) has been associated with poorer global cognitive function (e.g., Abbreviated Mental Test [Jitapunkul, Pillay, & Ebrahim, 1991], MMSE [Folstein, Maiberger, & McHugh, 1977]) (Saxena, 2006; Starkstein, Robinson, & Price, 1988). Depression has also been correlated with impairment in WM, EF, and memory (Hommel, Carey, & Jaillard, 2015;

Kauhanen et al., 1999). However, some studies have not replicated these results, noting nonsignificant correlations between depression and cognition (Parikh, Lipsey, Robinson, & Price, 1987; Robinson & Spaletta, 2010). Some of these studies have posited that more severe depression is associated with greater cognitive impairment, and mild depression is only associated with mild or no cognitive impairment (Robinson & Spaletta, 2010). Although there is evidence to support this hypothesis (Paradiso & Robinson, 1999; Raskin, Friedman, & DiMascio, 1982; Robinson, Bolla-Wilson, Kaplan, Lipsey, & Price, 1986), given the relationship between apathy and cognition, apathy symptomatology should also be considered when examining these constructs (Benitez, Horner, & Bachman, 2011).

Apathy, Depression, and Cognition

Researchers have suggested that the relationship between depression and cognition is largely due to a deficiency in motivation (Scheurich et al., 2008). Motivation, defined as "the ability to initiate appropriate activity either spontaneously or in response to environmental cues" (Lezak, 1995), is central to apathy (Marin, 1991). As a result, researchers have suggested that apathy may predict cognitive performance over and above depression (Pluck & Brown, 2002).

Several studies have shown that when apathy is included in analyses, apathy has stronger associations with cognitive and functional impairment than depression (Brodaty et al., 2005; Butterfield, Cimino, Oelke, Hauser, & Sanchez-Ramos, 2010; Hama et al., 2007). Butterfield et al. (2010) reported that after controlling for depressive symptoms, apathy predicted impairment in short-term memory, whereas after controlling for apathy, depression did not predict memory impairment. Santangelo and colleagues (2009) and Cohen, Weingartner, Smallberg, Pickar, and Murphy (1982) found that apathy alone was sufficient in predicting cognitive dysfunction. Extending these findings, researchers found that apathy mediated the relationship between

cognitive control (but not memory) and depression in older adults with depression (Funes, Lavretsky, Ercoli, St. Cyr, & Siddarth, 2018). Furthermore, Scheurich and colleagues (2008) found that goal-setting instructions improved cognitive performance in individuals with depression when compared with standard instructions. When these goal-setting strategies were utilized, individuals with depression performed as well as non-depressed individuals on memory and EF measures (Scheurich et al., 2008). As such, apathy, which encompasses decreases in goal-directed behaviours, goal-directed cognitions, and increases in emotional indifference, may predict overall cognitive performance to a greater degree than depression (Lezak, 1995; Santangelo et al., 2009; Scheurich et al., 2008).

Although these studies suggest that apathy may be correlated with cognition to a greater degree than depression, depression may impact the type of emotional content that is remembered (Chepenik, Cornew, & Farah, 2007). Laboratory-induced sad mood and clinical depression in young adults share neurophysiological similarities with one another, including hypoactivity in the dorsolateral prefrontal cortex (Aalto et al., 2002; Murphy, Nimmo-Smith, & Lawrence, 2003), hyperactivity in the amygdala (for a review, see Drevets, 2003), and abnormal activation in the medial prefrontal cortex (Bush, Luu, & Posner, 2000; Kennedy et al., 2001). Sad mood induction has been associated with biases towards remembering negatively valenced emotional words and faces better than positively-valenced stimuli (Bouhuys, Geerts, & Mersch, 1997; Chepenik, Cornew, & Farah, 2007; Williams, Mathews, & MacLeod, 1996). Sad mood induction and clinical depression have also been associated with a relative difficulty in accessing specific autobiographical memories in response to emotion-related word cues, particularly for positive memories (Dalgleish et al., 2007; Werner-Seidler & Moulds, 2011). However, sad mood induction and mild levels of depression have not been associated with impaired performance on

tests of executive functioning, working memory, attention, or memory for neutral material (Chepenik et al., 2007; Wang, LaBar, & McCarthy, 2006). These results demonstrate that sad mood may not exert an effect on *overall* cognition (but can affect the *valence* of the emotional content that is remembered) and that factors other than sad mood (e.g., apathy) may be responsible for the cognitive changes observed in individuals with depression.

Dissertation Objectives

Broadly, the purpose of the current dissertation was to advance our understanding of apathy, its relationship to depression, and its relationship with cognition, in individuals with cerebrovascular disease and in young adults. This dissertation contains five chapters that reflected three primary goals.

Specific Aim #1: To differentiate the impact of depressive and apathy symptoms on verbal memory impairment and verbal fluency in patients with cerebrovascular disease. Given that apathy is both related to depression and is a common characteristic of dysexecutive syndromes, I explored whether apathy may be a better predictor of cognitive difficulties than depressive symptoms. This aim was addressed in Chapter 2 (Articles 1 and 2).

Hypothesis 1a-c: Apathetic (as assessed using the AES) stroke patients will have poorer memory acquisition, short-term recall, and long-term recall (on the California Verbal Learning Test [CVLT-II]) than nonapathetic stroke patients after adjusting for age, education, and depressive symptoms.

Hypothesis 1d-f: Depressed (as assessed using the Center for Epidemiologic Studies Depression Scale [CES-D]) stroke patients will have similar memory acquisition, short-term free recall, and long-term free recall (using the CVLT-II) as nondepressed stroke patients after adjusting for age, education, and apathy.

Hypothesis 1g-h: Apathy symptoms (as assessed using the AES) will predict letter fluency (on the Controlled Oral Word Association Test) and category fluency (on the Semantic Fluency Test) after adjusting for age, education, and depressive symptoms in individuals with cerebrovascular disease.

Hypothesis 1i-j: Depressive symptoms (as assessed using the CES-D) will not predict letter fluency or category fluency after adjusting for age, education, and apathy symptoms in patients with cerebrovascular disease.

Specific Aim #2: To investigate the relative contribution of apathy and depressive symptoms on memory and executive function in educated young adults. The limited research available suggests that apathy is present in healthy older adults and that symptoms of apathy may be more commonly reported than depression in this population (Adams, 2001). Given that few studies have evaluated the relationship between depression and apathy in young adults and their contribution to cognition across multiple domains, I explored whether apathy in healthy adults impaired *overall* cognitive performance to a greater degree than depression, and whether depression instead impacted the *type* of emotional content that was remembered. This aim was addressed in Chapter 3 (Article 3).

Hypothesis 2a. Apathy will be negatively associated with cognitive performance, such that individuals with higher levels of apathy will perform worse on working memory (as assessed by the Digit Span and Reading Span Test), verbal acquisition and long-term memory for neutral words (CVLT-II) and emotional images (Emotional Pictures Task [EPT]), after controlling for depressive symptoms and the number of fluent languages spoken.

Hypothesis 2b. Depressive symptoms (as assessed by the CES-D) will have a valence-related effect on memory for affective images, such that individuals with higher levels of

depressive symptoms will learn and recall a larger proportion of negatively valenced images on the EPT after controlling for apathy and the number of fluent languages spoken.

Hypothesis 2c. Depressive symptoms (as assessed by the CES-D) will have a valence-related effect on emotional memory, such that individuals with higher levels of depressive symptoms will recall a larger proportion of specific memories in response to negatively-valenced cues than positively-valenced cues on the AMT after controlling for apathy and the number of fluent languages spoken.

Specific Aim #3: To investigate the impact of goal-setting instructions in improving cognitive performance in stroke survivors relative to standard instructions. Given that apathy is defined as a lack of goal-oriented behaviour, cognition, and emotion, goal-setting techniques offer a way to increase goal-oriented cognition and behaviour in individuals (Locke & Latham, 1990, 2002). This aim was addressed in Chapter 4 (Article 4). If goal-setting instructions were found to improve cognitive performance, it would indicate that treatments targeting apathy (as opposed to sad mood in depression) may serve as a novel approach to improving cognitive outcomes and enhancing patient quality of life in the chronic phase after stroke.

Hypothesis 3a. Individuals in the goal-setting condition will perform significantly better than individuals in the standard instruction condition on tests of memory (CVLT-II), executive function (Controlled Oral Word Association Test, Semantic Fluency Test, Trail Making Test – Part B), and attention/working memory (Trail Making Test – Part A, Digit Span Test), after adjusting for age and years of education.

Hypothesis 3b. Stroke survivor motivation will significantly increase in the goal-setting condition, where there will be a significant increase in motivation from baseline to after goal-setting instructions are delivered.

CHAPTER 2: The Relationship between Apathy, Depression, and Cognition in Cerebrovascular Disease

Article 1

The role of apathy and depression on verbal learning and memory performance after stroke[1]

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Abstract

Objective: Psychiatric symptoms, including depression and apathy, may significantly impede functional and cognitive capabilities following a cerebrovascular event. This study examined the role of apathy and depression on learning and memory performance in stroke patients. *Method:* Stroke patients (n = 140 [119 ischemic, 21 hemorrhagic], mean age = 60.6 [SD = 15.1]) completed the Apathy Evaluation Scale (AES), the Center for Epidemiologic Studies Depression Scale (CES-D), and the California Verbal Learning Test - Second Edition (CVLT-II). *Results:* Using a 2 × 2 MANOVA with depression (CES-D ≥ 16) and apathy (AES ≥ 34) as the independent variables and cognitive performance (i.e., verbal acquisition, short-term free recall, and long-term free recall) as the dependent variables, we found a main effect for apathy (F[3,134] = 2.98, p = .034), such that apathetic stroke patients (n = 24) performed significantly worse on verbal acquisition (F[1,136] = 6.44; p = .012), short-term free recall (F[1,136] = 7.86; p = .006), and long-term free recall (F[1,136] = 8.37; p = .004) than nonapathetic stroke patients (n = 116). There was no main effect of depression on cognitive performance (F[1,136] = 1.72, p = .155). *Conclusions:* These results suggest that apathy, not depression, is related to verbal memory performance in stroke patients. Future research should explore whether treatment of apathy (e.g., improving motivation) could be a novel target for improving cognition after stroke. Researchers should also examine whether this model can be applied to other aspects of cognition, including executive function and other areas of memory including autobiographical and working memory.

Keywords: Learning and Memory; Apathy; Motivation; Cerebrovascular disease/accident and stroke; Cognition; Depression

The role of apathy and depression on verbal learning and memory performance after stroke

1. Introduction

Apathy, meaning "lack of passion," is characterized by diminished goal-directed behavior (e.g., lack of effort), decreased goal-directed cognition (e.g., lack of interest in learning/pursuing new experiences), and blunted emotion (e.g., unchanging affect; Marin, 1991). Apathy has been shown to be related to poorer functional status, social engagement, and physical ability (Kaufer et al., 1998; Starkstein, Federoff, Price, Leiguarda, & Robinson, 1993). Apathy has been found to occur in clinical and non-clinical populations, including stroke, Parkinson's disease, dementia, depression, and healthy adult populations (Adams, 2001; Lyketsos et al., 2002; Okada, Kobayashi, Yamagata, Takahashi, & Yamaguchi, 1997). Apathy is related to depression and is also a symptom of dysexecutive syndromes (Levy & Dubois, 2006).

In contrast to apathy, depression is characterized by feelings of sadness, low mood, and helplessness (American Psychiatric Association, 2013). Accompanying symptoms may include guilt, suicidal ideation, sleep irregularities, and appetite abnormalities (American Psychiatric Association, 2013). Individuals with either apathy or depression may also experience a reduction in interest, energy, or insight. Although depression and apathy are related to each other, they can occur separately from one another (Brodaty et al., 2005; Starkstein et al., 1992).

Psychiatric symptoms, including depression and apathy, may be related to poorer functional and cognitive capabilities following a vascular event (Hosking, Marsh, & Friedman, 2000). Apathy is present in approximately 20%–50% of individuals after experiencing a stroke (Brodaty et al., 2005; Van Reekum, Stuss, & Ostrander, 2005). Similarly, approximately 33% of stroke survivors exhibit depressive symptoms after a stroke (Hackett, Yapa, Parag, & Anderson,

2005). Furthermore, meta-analyses posit that apathy occurs nearly as frequently as depression in neurological disorders, although apathy has only gained attention over the past few decades as an important neuropsychiatric construct (Caeiro, Ferro, & Costa, 2013; Van Dalen, Moll van Charante, Nederkoorn, van Gool, & Richard, 2013).

Both apathy and depression have been related to cognitive impairment after stroke, but in different studies. Cognitive impairment is three times more frequent in stroke patients with apathy than without apathy (Hama et al., 2007; Yamagata, Yamaguchi, & Kobayashi, 2004). Deficits in attention, working memory, reasoning, and processing speed have been commonly observed in apathetic stroke survivors (Caeiro et al., 2013; Withall, Brodaty, Altendorf, & Sachdev, 2011). Stroke survivors with apathy had lower memory performance than individuals without apathy (Hama, Yamashita, Yamawaki, & Kurishu, 2011). Impairments in verbal fluency (Fishman et al., 2018; Yamagata et al., 2004) and executive dysfunction (Feil, Razani, Boone, & Lesser, 2003; Withall, Brodaty, Altendorf, & Sachdev, 2011) have also been correlated with greater apathy scores.

A similar relationship exists between post-stroke depression (PSD) and cognitive impairment (Andersen, Vestergaard, Ingemann-Nielsen, & Lauritzen, 1995; Bour et al., 2010; Donnellan et al., 2016; Kauhanen et al., 1999). Memory, attention, and psychomotor speed are the domains most commonly affected among patients with PSD (Kauhanen et al., 1999). Additionally, stroke patients with executive dysfunction are more depressed than stroke patients without executive dysfunction (Bour et al., 2010).

Apathy is also a feature of dysexecutive syndromes (Ardila, 2013). Dysexecutive syndrome encompasses difficulties with planning, organizing, problem solving, initiating, and completing tasks (Levy & Dubois, 2006). Damage to the frontal lobes and frontal subcortical

circuits commonly cause dysexecutive syndromes, which may include emotional and behavioral changes in individuals (Repovs & Baddeley, 2006). Impairments in the frontal-subcortical circuit have frequently been associated with apathy (Bonelli & Cummings, 2007; Van Dalen et al. 2013). Additionally, although memory consolidation is dependent on the medial temporal lobe (e.g., hippocampus, entorhinal cortex, perirhinal cortex; Achim & Lepage, 2005), the prefrontal cortex is believed to underlie memory encoding and retrieval (Alvarez & Squire, 1994). Research has shown that the prefrontal cortex is activated by memory recall tasks (Badre & Wagner, 2007). Specifically, the dorsolateral prefrontal cortex (dlPFC; Blumenfeld & Ranganath, 2006) and ventrolateral prefrontal cortex (vlPFC; Badre & Wagner, 2007) have been found to contribute to memory performance, and these regions are essential to frontal-subcortical circuitry. The ACC and dlPFC are also functionally interconnected (Sallet et al., 2011). Lesions or damage to ACC and/or dlPFC frontal-subcortical circuits (which involve projections to the caudate nucleus) have been found to impact motivational control (Bonelli & Cummings, 2007; Tekin & Cummings, 2002), and cause severe apathy (Kumral, Evyapan, & Balkir, 1999).

Researchers have posited that apathy may be negatively related to learning and memory, regardless of depression (Pluck & Brown, 2002). In support of this notion, Butterfield, Cimino, Oelke, Hauser, and Sanchez-Ramos (2010) reported that after controlling for depressive symptoms, apathy accounted for marginally significant impairment in short-term memory, whereas after controlling for apathy, depression did not predict memory impairment in patients with Parkinson's disease. Scheurich et al. (2008) and Benitez, Horner, and Bachman (2011) also found that individuals with depression who either used goal-setting techniques or provided adequate effort did not perform worse on neuropsychological tasks than non-depressed individuals. Additionally, Santangelo et al. (2009) and Cohen, Weingartner, Smallberg, Pickar,

and Murphy (1982) did not find any relationship between depression and performance on any neuropsychological tasks but found that apathy alone predicted cognitive dysfunction in individuals with Parkinson's disease and depression, respectively. These studies suggest a greater role of apathy than depression on memory performance, but in a different population.

Although studies have examined the relationship betwen depression and apathy with cognition in stroke patients, few studies have examined these constructs in the same study. As a result, specific mood–memory relationships remain understudied and underappreciated in vascular populations. Many studies have also used small sample sizes (Hochstenbach, Mulder, van Limbeek, Rogier, & Schoonderwaldt, 1998) or assessed learning and memory impairment in very specific types of stroke (Van der Werf et al., 2003). Additionally, the association between apathy and cognitive function may be confounded by age, education, or other medical conditions (e.g., diabetes; Clarke, Ko, Lyketsos, Rebok, & Eaton, 2010; Mayo, Fellows, Scott, Cameron, & Wood-Dauphinee, 2009).

The current study aimed to help clarify the roles of apathy and depression on verbal learning and memory performance in stroke patients by examining these constructs together, including a substantially larger sample size, by considering the age and education of participants, as well as other potential medical confounds. Given the role of apathy as a symptom of dysexecutive syndromes and a construct that may overlap with depression, apathetic stroke patients may exhibit deficits in learning and memory regardless of depression diagnosis.

We hypothesized that apathetic stroke patients (Apathy Evaluation Scale ([Marin, 1991]) ≥ 34, consistent with Andersson, Krogstad, and Finset ([1999]), and Kant, Duffy, and Pivovarnik ([1998])) would have impaired cognitive performance (measured by memory acquisition, short-term free recall, and long-term free recall on the California Verbal Learning Test-II; Delis,

Kramer, Kaplan & Ober, 2000) after scaling scores by age and years of education, regardless of depression (as measured by the Center for Epidemiologic Studies Depression Scale ([Radloff, 1977]) ≥16, consistent with Lewinsohn, Seeley, Roberts, and Allen ([1997])).

2. **Methods**

This research project was conducted as part of the "Depression, Obstructive Sleep Apnea, and Cognitive Impairment" Study, which examined the use of a brief screening tool to assess patients for common post-stroke comorbidities (Swartz et al., 2017).

All testing took place at the Secondary Stroke Prevention Clinic at Sunnybrook Health Sciences Centre in Toronto, Canada. The Institute's ethics board approved all study procedures. The research was completed in accordance with the Helsinki Declaration.

2.1 **Participants**

Participants were individuals with stroke at the Secondary Stroke Prevention Clinic in Toronto. One hundred fifty-eight non-aphasic, English speaking stroke patients without motor/visual impairments consented to complete a neuropsychological examination. Multivariate outliers (n = 2) and participants with over 80% of missing data for the tests related to this study (n = 11) were excluded from analysis. Participants who did not complete any memory testing were also excluded (n = 5). In total, 140 stroke patients participated in this study. The study took place between April 23, 2012 and April 30, 2014.

The mean age of study participants (N = 140) was 60.50 (SD = 15.3, range = 17–95) years and 44.3% (n = 63) were female. Participants reported on average 15.5 years (SD = 4.4, range = 5–30) of education. Forty-one participants were classified as "depressed," consistent with the cut-off score of greater than or equal to 16 (Lewinsohn et al., 1997) on the CES-D (Radloff, 1977). Twenty-four participants were classified as "apathetic," consistent with the cut-

off score of greater than or equal to 34 (Andersson et al. 1999; Kant et al. 1998; Sagen et al., 2010) on the AES (Marin, 1991). Seventeen individuals were both apathetic and depressed, seven individuals were only apathetic, 24 individuals were only depressed, and 92 individuals were neither apathetic nor depressed.

Of the 140 stroke patients, 119 (83.8%) had ischemic events and 23 (16.2%) had hemorrhagic events. There were no differences in age, sex, years of education, or medical diagnoses (e.g., diabetes, history of vascular disease) between individuals with ischemic versus hemorrhagic strokes, There were no differences in verbal acquisition ($F = 1.96$, $p = .16$), short-term free recall ($F = 1.10$, $p = .29$), long-term free recall ($F = .82$, $p = .37$), education ($F = 3.73$, $p = .06$), sex ($F = 1.56$, $p = .21$), or age ($F = 1.93$, $p = .167$) for individuals with ischemic versus hemorrhagic strokes. Additionally, there were no differences in verbal acquisition ($F = .02$, $p = .88$), short-term free recall ($F = .68$, $p = .41$), long-term free recall ($F = .06$, $p = .81$), education ($F = 3.73$, $p = .06$), sex ($F = 1.56$, $p = .21$), or age ($F = 1.93$, $p = .167$) for individuals with left- versus right-hemisphere strokes. There were significantly more depressed (CES-D ≥ 16) apathetic stroke patients than nonapathetic stroke patients, $\chi^2 = 23.97$, $p < .001$. Participants did not differ from excluded participants ($n = 18$) in terms of age, years of education, location of cerebrovascular event, type of stroke, smoking status, family history of cerebrovascular disease, or diabetes/autoimmune disease/obstructive sleep apnea diagnosis. There were no sex differences in apathy severity ($F = 1.51$, $p = .222$) or apathy classification (AES ≥ 34; $\chi^2 = 1.15$, $p = .367$).

Additional participant information is included in Table 2.1.

Table 2.1

Participant Characteristics

	Stroke Patients (N = 140)	Apathetic (n = 24)	Not Apathetic (n = 116)	Statistical Difference
Age	*M* = 60.6 (*SD* = 15.1), range 17-95	*M* = 61.3 (*SD* = 14.6), range 21-87	*M* = 57.3 (*SD* = 17.6), range 17-95	*t*(138) = 1.19, *p* = .238
Women:men	62:78 (44.3% female)	13:11	49:67	χ^2 = 1.14, *p* = .286
Years of education	*M* = 15.5 (*SD* = 4.4), range 5-30	*M* = 15.7 (*SD* = 5.2), range 7-30	*M* = 15.6 (*SD* = 3.7), range 5-26	*t*(138) = -.08, *p* = .936
Location of event[a]				
left hemisphere	58 (55.8%)	8 (57.1%)	50 (55.6%)	χ^2 = .01, *p* = .931
right hemisphere	39 (37.5%)	5 (35.7%)	34 (37.8%)	
bilateral	7 (6.7%)	1 (7.1%)	6 (6.7%)	
Type of Stroke				
ischemic	118 (85.0%)	19 (79.2%)	99 (86.1%)	χ^2 = .74, *p* = .391
hemorrhagic	21 (15.0%)	5 (20.8%)	16 (14.0%)	
Smoking status[b]				
current	15 (11.7%)	3 (15.0%)	12 (11.1%)	χ^2 = 7.24, *p* = .007
reformed	11 (8.6%)	6 (30.0%)	5 (4.6%)	
non-smoker	102 (79.7%)	11 (55.0%)	91 (84.3%)	
Family history of cardiovascular disease[c]	37 (26.4%)	5 (20.8%)	32 (27.6%)	χ^2 = .46, *p* = .496
Diabetes (diagnosed)[c]	25 (17.9%)	4 (16.7%)	21 (18.1%)	χ^2 = .03, *p* = .868
Autoimmune disease[c]	5 (3.6%)	2 (8.3%)	3 (2.6%)	χ^2 = 1.89, *p* = .169

Alcohol use[c]				
> 2 drinks/day	8 (6.7%)	2 (11.1%)	6 (5.9%)	
< 2 drinks/day	15 (12.5%)	0	15 (14.7%)	$\chi^2 = 1.90$, $p = .168$
rare/social	61 (50.8%)	8 (44.4%)	53 (52.0%)	
never/not currently	36 (30.0%)	8 (44.4%)	28 (27.5%)	
Obstructive sleep apnea (diagnosed)	18 (12.9%)	1 (4.2%)	17 (14.7%)	$\chi^2 = 1.94$, $p = .164$
CES-D score	*M* = 11.9 (*SD* = 10.1), range 0-49			$\chi^2 = 23.97$, $p < .001$
# depressed	41	17	24	
AES score	*M* = 28.3 (*SD* = 8.1), range 18-56			
# apathetic	24			
CVLT acquisition score scaled	*M* = -.12 (*SD* = 1.1), range -3.5-2.4			
CVLT short-term recall score scaled	*M* = -.36 (*SD* = 1.2), range -3.0-3.0			
CVLT long-term recall score scaled	*M* = -.52 (1.2), range -3.0-2.5			

Note. [a] 36 missing cases; [b] 28 missing cases; [c] 38 missing cases.

2.2 **Materials**

DOC Case Report Form (DOC-CRF). The DOC-CRF extracted information on demographic status and prior medical history, including previous cerebrovascular disease risk factors, alcohol intake, BMI, diagnosis, smoker status, as well as other diagnoses (e.g., cancer, diabetes).

Apathy Evaluation Scale (AES; Marin, 1991). Participants answered 18 questions regarding participants' interest in learning and having new experiences, taking initiative, being motivated, and putting effort into tasks. They responded to these statements using a Likert-type scale ranging from 1 (*Not at all*) to 4 (*A lot*). AES scores range from 18 to 60, with higher scores indicating greater apathy. Cronbach's alpha for the AES was .87 in this study.

Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). The CES-D is a 20-item questionnaire that measures depressive symptomatology over the past week (Radloff, 1977). Participants were asked questions about their sleep patterns, appetite, as well as feelings of fear, loneliness, and hopelessness. Participants responded to statements using a Likert-type scale ranging from 0 (*Rarely or none of the time*) to 3 (*Most or almost all of the time*). CES-D scores range from 0 to 60, with higher scores indicating greater depressive symptomatology. Cronbach's alpha for the CES-D was .90 in this study.

California Verbal Learning Test-Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000). The CVLT-II is a frequently used neuropsychological measure that assesses auditory-verbal learning, recall, and recognition of words. The word list was created from four unrelated semantic categories; furniture, modes of transportation, animals, and vegetables (Delis et al., 2000). In the current study, only verbal acquisition, short-term free recall, and long-term free recall scores were utilized for analysis.

2.3 **Procedure**

Participants at the Secondary Stroke Prevention Clinic completed a 5-min, brief screen for depression, obstructive sleep apnea, and cognitive impairment ("DOC" screen), as part of clinical standard of care. Patients were approached by research assistants, nurses, or doctors and asked to consent to participate in more detailed neuropsychological assessments at a time

suitable for the participant. Research assistants obtained informed consent from all participants. Out of the larger battery, for the purposes of this study, participants completed the CES-D, AES, and CVLT-II.

2.4 **Data Analysis**

SPSS version 21, 64-bit edition, was used for data analysis. Of the patients retained for analysis, there were 24 (.5%) missing cells from the AES, and 51 (.9%) missing cells from the CES-D. This missing data were handled using expectation maximization. The results of Little's MCAR test indicated that the data were missing completely at random, $\chi^2 = 584.89$, $df = 519$, $p = .824$.

Scores for memory acquisition, short-term free recall, and long-term free recall were scaled according to age, sex, and years of education (Delis et al., 2000).

We conducted a 2 × 2 MANOVA to examine whether apathy and depression (two independent variables) impacted (1) verbal memory acquisition (i.e., word learning), (2) short-term free recall, and (3) long-term free recall in stroke patients. Depression (CES-D ≥ 16) and apathy (AES ≥ 34) were entered into the MANOVA as independent variables, and verbal acquisition, short-term free recall, and long-term free recall were entered into the MANOVA as dependent variables. A 2 × 2 MANCOVA was also conducted to control for potential medical confounds, including past stroke, family history of cardiovascular disease, diabetes, smoking status, alcohol use, obstructive sleep apnea, past stroke, and time since stroke.

3. **Results**

A two-way MANOVA revealed a significant multivariate main effect for apathy, Wilks' $\lambda = .94$, $F(3,134) = 2.98$, $p = .034$, partial $\eta^2 = .063$. There was no significant multivariate main effect for depression ($p = .155$). The interaction between apathy and depression on cognitive

performance was also not significant (p = .622; see Table 2.2).

Table 2.2

Multivariate Analysis of Variance (MANOVA) for the Role of Apathy and Depression on Cognitive Performance

	Wilks' λ	*F*	*df*	*p*	partial η^2
Apathy	.94	2.98	3, 134	.034*	.063
Depression	.96	1.77	3, 134	.155	.038
Apathy x Depression	.99	.59	3, 134	.622	.013

*p < .05

Significant univariate main effects for apathy were found for verbal acquisition (F[1,136] = 6.44, p = .012), short-term free recall (F[1,136] = 7.86, p = .006), and long-term free recall (F[1,136] = 8.37, p = .004), such that apathetic stroke patients performed significantly worse than nonapathetic stroke patients on these tasks. These results remained significant after implementing a Bonferroni correction (0.05/3 = .016). Specifically, apathetic stroke patients (verbal acquisition: M = −.46, SD = 1.21; short-term free recall: M = −.88, SD = 1.28; long-term free recall: M = −1.02, SD = 1.30) had significantly worse learning and memory than nonapathetic stroke patients (verbal acquisition: M = −.06, SD = 1.05; short-term free recall: M = −.27, SD = 1.12; long-term free recall: M = −.43, SD = 1.09; see Fig. 2.1). The results did not change after controlling for depression (CES-D ≥ 16).

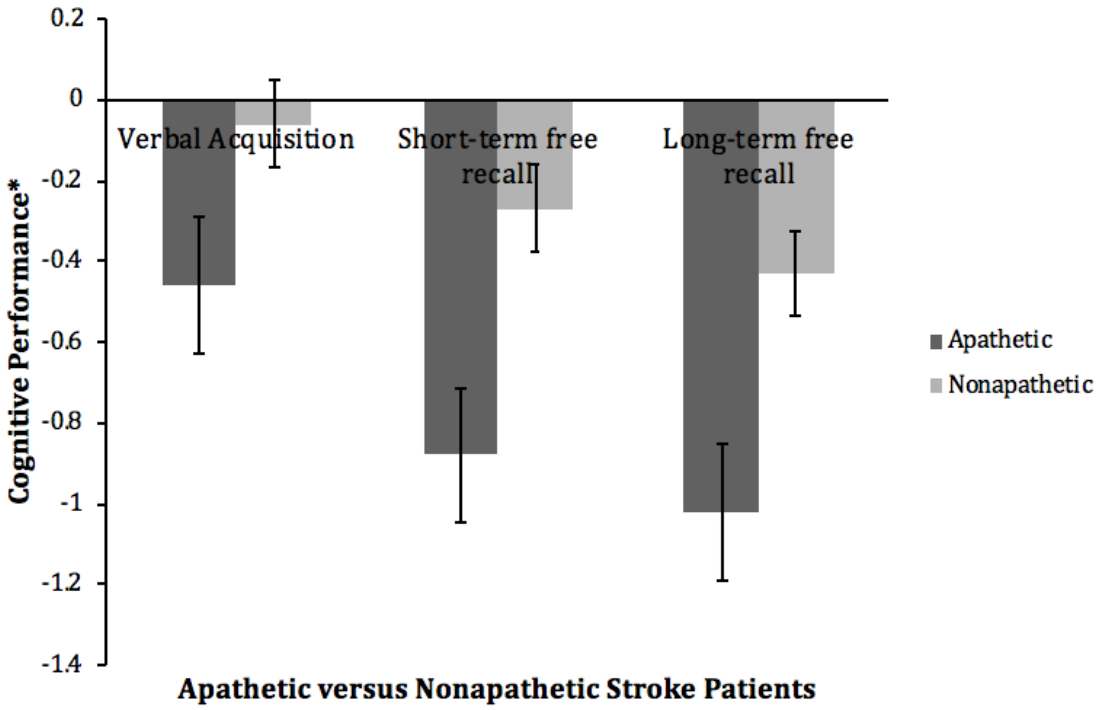

Figure 2.1. Main effect of apathy on verbal acquisition, short-term free recall, and long-term free recall in stroke patients.
*Raw scores were scaled by age and years of education (Delis et al., 2000).

The univariate post-hoc analyses for depression revealed a main effect of depression on verbal acquisition, such that depressed stroke patients (M = .04, SD = 1.01) had significant better verbal acquisition scores than non-depressed stroke patients (M = −.20, SD = 1.11), $F(1,136)$ = 5.37, p = .022 (see Fig. 2). However, this effect did not remain statistically significant when the Bonferroni correction (.05/3 = .016) was applied. No significant effects were observed for depression on short-term (p = .108) or long-term (p = .085) recall.

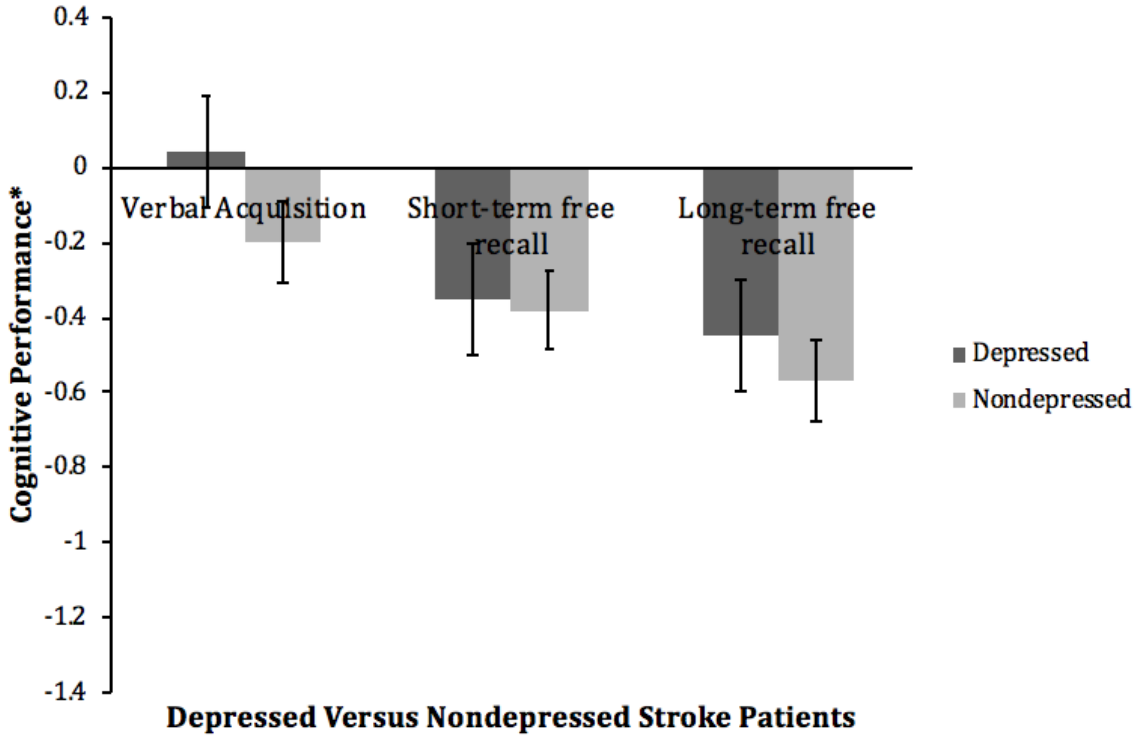

Figure 2.2. Main effect of depression on verbal acquisition, short-term free recall, and long-term free recall in stroke patients.
*Raw scores were scaled by age and years of education (Delis et al., 2000).

3.1 **Medical Confounds**

A 2 × 2 MANCOVA was also conducted to examine whether these findings could be accounted for by other medical considerations associated with cognitive functioning in stroke patients, including diabetes diagnosis, family history of cardiovascular disease, past stroke, time since most recent stroke, alcohol use, smoking status, and obstructive sleep apnea. As shown in Table 3, none of the covariates were significant in the model. In addition, the results did not change after controlling for these variables, as there was a significant main effect of apathy on cognitive performance (Wilks' $\lambda = .89$, $F(3,101) = 4.35$, $p = .006$, partial $\eta^2 = .12$).

Table 2.3

Multivariate Analysis of Covariance (MANCOVA) for the Role of Apathy and Depression on Cognitive Performance[a]

	Wilks' λ	*F*	*df*	*p*	partial η^2
Diabetes	.96	1.37	3, 101	.256	.04
Family history of cardiovascular issues	.98	.69		.558	.02
Past stroke	.96	1.25		.296	.04
Days since most recent stroke	.95	1.44		.235	.04
Smoking	.98	.78		.507	.02
Obstructive sleep apnea	.97	.95		.418	.03
Alcohol Use	.99	.45		.721	.01
Apathy	.89	4.35		.006*	.12
Depression	.95	1.92		.132	.05
Apathy x Depression	.98	.80		.493	.02

*$p \leq .05$
[a]26 cases were missing.

4. **Discussion**

In this study, 140 stroke patients from a Secondary Stroke Prevention Clinic underwent neuropsychological testing to examine the relationship between apathy and depression with verbal learning and memory performance. Memory acquisition, short-term free recall, and long-term free recall were assessed using the CVLT-II (Delis et al., 2000). Using a 2 × 2 MANOVA and a 2 × 2 MANCOVA, we found a main effect of apathy on memory performance, such that

apathetic stroke survivors performed significantly worse than nonapathetic stroke survivors on verbal acquisition, short-term free recall, and long-term free recall on the CVLT-II, regardless of depression. There was no difference in memory performance on the CVLT-II between depressed versus non-depressed individuals, apart from verbal acquisition (i.e., depressed individuals performed superior to non-depressed individuals). However, this effect was no longer significant after applying the Bonferroni correction. Therefore, this result should be interpreted with reservations. These results provide support that apathy is a separate construct from depression, and that apathy may play a more pivotal role in learning and memory performance than depression in stroke patients.

Researchers have suggested that the relationship between depression and memory performance is largely due to a deficiency in motivation. Motivation, defined as "the ability to initiate appropriate activity either spontaneously or in response to environmental cues" (Lezak, 1995), is the crucial component of apathy (Marin, 1991). As such, apathy, which encompasses decreases in goal-oriented behavior/cognition and increases in emotional indifference, may be the key link between depression and cognitive performance (Lezak, 1995; Santangelo et al., 2009; Scheurich et al., 2008). This theory complements the results of our study. Scheurich et al. (2008) found that goal-setting significantly improved verbal memory performance in patients with depression when compared with standard instructions. When these goal-setting strategies were utilized, depressed patients performed similarly on memory measures as healthy controls (Scheurich et al., 2008). Another study found that depressed individuals performed significantly worse than non-depressed individuals on immediate memory, language, delayed memory, and attention (Benitez et al. 2011). However, when individuals were excluded who did not provide adequate effort, there were no group differences in cognitive performance, regardless of

depression diagnosis (Benitez et al. 2011). These results support that cognition may be more affected by symptoms of apathy than symptoms of depression.

The results of this study exemplify a link between apathy and cognitive performance in stroke patients, but not between depression and cognitive performance. The stronger ties between apathy and memory, rather than depression and memory, have been previously reported in Parkinson's disease (Pluck & Brown, 2002; Varanese, Perfetti, Ghilardi, & Di Rocco, 2011). Santangelo et al. (2009) and Cohen and colleagues (1982) did not find any relationships between depression and neuropsychological test performance, but found that apathetic patients were more cognitively impaired than nonapathetic patients with Parkinson's disease and depression, respectively. These studies support our findings that apathy is related to poorer cognitive performance, regardless of (and after controlling for) depression (CES-D $\geq$ 16), and is consistent with our findings that apathy and cognitive performance are also linked in stroke populations. Apathy may be a better indicator of impaired learning and memory (due to low motivational resources) than depression in stroke patients.

It is also important to distinguish between depression and apathy in order to optimize treatment outcomes. Widely prescribed antidepressant medications for treatment of depressive disorders include selective serotonin reuptake inhibitors (SSRIs; e.g., citalopram, escitalopram, fluoxetine, sertraline; De Lima & Hotopf, 2003). However, SSRIs are associated with increased behavioral and affective indifference (Barnhart, Makela, & Latocha, 2004; Lee & Keltner, 2005; Wongpakaran, Van Reekum, Wongpakaran, & Clarke, 2007). Qualitative studies have reported decreases in emotional expression and reduced motivation in individuals taking SSRIs (Garland & Baerg, 2004). Wongpakaran et al. (2007) reported that individuals being treated for depression with SSRIs described more apathetic symptoms than individuals being treated with non-SSRIs,

although they experienced a decrease in depressive symptoms. Medication-induced apathetic symptoms were also found with serotonin-noradrenaline reuptake inhibitors and mood stabilizers (Price, Cole, & Goodwin, 2009). However, brain-injured individuals who were prescribed dopamine stimulants (bromocriptine and amantadine) reported decreases in apathy symptoms and improved cognitive function (Kraus & Maki, 1997; Powell, Al-Adawi, Morgan, & Greenwood, 1996). No changes in depressive or anxiety symptoms were observed using bromocriptine treatment (Powell et al., 1996). As such, improperly identifying neuropsychiatric symptoms may detrimentally affect treatment outcomes and, in turn, may further impair cognitive functioning (Powell et al., 1996; Price et al., 2009; Wongpakaran et al., 2007).

Limitations to this study include the self-report nature of assessing apathy. Given that apathetic individuals may have poor insight into their symptoms, rates of apathy may have been underestimated, as observed in Njomboro and Deb's (2012) study. In addition, individuals were classified as apathetic if their AES score was equal to or greater than 34, consistent with Andersson and colleagues (1999), Kant and colleagues (1998), and Sagen et al. (2010). Individuals were identified as depressed when their CES-D score was greater than or equal to 16, consistent with Lewinsohn and colleagues (1997). Although these cutoffs have excellent sensitivity and specificity (e.g., Beekman et al., 1997), a clinical interview, such as the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), may reduce the rate of potential false positives (American Psychiatric Association, 2013). Given the larger variability in CVLT-II acquisition, short-term recall, and long-term free recall performance (which may be expected with a range of brain damage severity), future studies should focus on replicating these findings in order to strengthen the study's conclusions and implications. Lastly, there were missing cases regarding stroke laterality and the degree of

anterior cerebrovascular damage, which may affect depression prevalence (Narushima, Kosier, & Robinson, 2003).

Despite these limitations, there are a number of strengths to the current study. To our knowledge, this is one of few studies that has examined the relationship between apathy and depression with learning and memory performance in the same study in a stroke sample. Other studies have either ignored the role of apathy (Donnellan et al., 2016) or depression (Mayo, Fellows, Scott, Cameron & Wood-Dauphinee, 2009) in neuropsychological evaluations. We also controlled for a range of potential medical confounders, including diabetes, past stroke, days since most recent stroke, family history of cardiovascular disease, obstructive sleep apnea, smoking status, and alcohol use, which did not impact the study findings.

The results of this study offer preliminary support for the role of apathy, and not depression, in verbal learning and memory in stroke patients. As both an important feature of dysexecutive syndromes (Ardila, 2013) and a construct related to depression, these results suggest that apathy may potentially better indicate difficulties with verbal learning and memory than depression. However, additional research should continue to explore the role of apathy in cognitive functioning. Future research should also examine whether this model can be applied to other populations and other aspects of learning and memory, such as autobiographical memory and working memory. Additionally, given that emotional indifference is a hallmark symptom of apathy, and apathetic individuals experience greater difficulty with emotional recognition (Hanby, 2014), it may be of interest to examine apathy's role in emotional verbal memory (e.g., Emotional Verbal Learning Test; Strauss & Allen, 2013). These studies would allow researchers to further explore the emotion–cognition interaction.

Given its prevalence across neurodegenerative diseases, acquired brain injuries,

psychiatric disorders, and healthy adults, as well as its relationship to poorer social and physical ability, functional recovery, and treatment optimization, it is surprising that apathy has not received more attention in the literature (Kaufer et al., 1998; Starkstein et al., 1993). There is a need to better understand the unique effect of apathy, to appropriately identify symptoms of apathy, and to improve neuropsychological models of its relationship with other constructs in individuals with vascular pathology. Future work may then determine whether treatments targeting apathy could serve as a novel approach to improving cognitive outcomes and to enhancing patient and caregiver quality of life after stroke.

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Article 2

Apathy, not depressive symptoms, as a predictor of semantic and phonemic fluency task performance in stroke and transient ischemic attack[2]

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Abstract

Objectives: This study examined the relationship between apathy and cognition in patients with cerebrovascular disease. Apathy may result from damage to frontal subcortical circuits causing dysexecutive syndromes, but apathy is also related to depression. We assessed the ability of apathy to predict phonemic fluency[3] and semantic fluency performance after controlling for depressive symptoms in 282 individuals with stroke and/or transient ischemic attack. *Method:* Participants (N = 282) completed the Phonemic Fluency Test, Semantic Fluency Test, Center for Epidemiologic Studies Depression Scale, and Apathy Evaluation Scale. A cross-sectional correlational design was utilized. *Results:* Using hierarchical linear regressions, apathy scores predicted semantic fluency performance (β = –.159, p = .020), but not phonemic fluency performance (β = –.112, p = .129) after scaling scores by age and years of education and controlling for depressive symptoms. Depressive symptoms entered into the first step of both hierarchical linear regressions did not predict semantic fluency (β = –.035, p = .554) or phonemic fluency (β = –.081, p = .173). Apathy and depressive symptoms were moderately correlated, $r(280) = .58$, $p < .001$. *Conclusions:* The results of this study are consistent with research supporting a differentiation between phonemic and semantic fluency tasks, whereby phonemic fluency tasks primarily involve frontal regions, and semantic fluency tasks involve recruitment of more extended networks. The results also highlight a distinction between apathy and depressive symptoms and suggest that apathy may be a more reliable predictor of cognitive deficits than measures of mood in individuals with cerebrovascular disease. Apathy may also be

[3]We recognize that phonemic fluency is more accurately referred to as “letter fluency”, and that semantic fluency is more accurately referred to as “category fluency.” We used this term in these manuscripts because they have already been published. In manuscripts that have been submitted but not yet published, we have used “letter” and “category” fluency to describe verbal fluency tasks.

more related to cognition due to overlapping motivational and cognitive frontal subcortical circuitry. Future research should explore whether treatments for apathy could be a novel target for improving cognitive outcomes after stroke.

Keywords: Cerebrovascular disorders; motivation; neuropsychology; neuropsychological tests; verbal behavior

Apathy, not depressive symptoms, as a predictor of semantic and phonemic fluency task performance in stroke and transient ischemic attack

1. Introduction

Verbal fluency tasks are frequently utilized in neuropsychological examinations to assess executive functioning and verbal ability. These tasks examine the ability to retrieve information according to specific criteria within a time limit (Lezak, Howieson, Loring, Hannay, & Fischer, 2004). Semantic fluency is assessed by asking participants to generate words belonging to a specific category (e.g., animals or vegetables; Newcombe, 1969), and phonemic fluency is assessed by asking participants to generate words that begin with particular letters (e.g., F, A, and S; Benton, 1968).

Verbal fluency tasks are widely used because they allow researchers and clinicians to efficiently and reliably test both verbal ability and executive functioning simultaneously (Ettenhofer, Hambrick, & Abeles, 2006). Executive functions are a set of cognitive processes that are involved in controlling behaviors, including self-monitoring, planning, organization, and reasoning. Successful word retrieval requires executive control abilities including attention, inhibition, and task shifting (Fisk & Sharp, 2004; Miyake & Friedman, 2012; Miyake et al., 2000). Individuals with damage to frontal brain regions and frontal subcortical circuits (e.g., anterior cingulate circuit and dorsolateral prefrontal circuit; Fuster, 2002; Sallet et al., 2011) have shown impairments on verbal fluency tasks (Baldo & Shimamura, 1998; Schwartz & Baldo, 2001), supporting verbal fluency tasks as behavioral indices of frontally mediated cognitive function. In terms of verbal ability, the validity of these tasks is supported by findings that individuals with smaller vocabularies produce fewer words than participants with larger vocabularies (Sauzeon et al., 2011).

Impairments in verbal fluency have been found for a variety of psychiatric disorders and neurodegenerative diseases, including individuals with traumatic brain injuries (Kavé, Heled, Vakil, & Agranov, 2011), Parkinson's disease (Pettit, McCarthy, Davenport, & Abrahams, 2013), depression (Okada, Okamoto, Morinobu, Yamawaki, & Yokota, 2003), and Alzheimer's disease (Drijgers, Verhey, Leentjens, Köhler, & Aalten, 2011). Patients with focal nonfrontal injuries have also been found to perform poorly on tests of verbal fluency (Loring, Meador, & Lee, 1994; Martin, Loring, Meador, & Lee, 1990). Stroke patients have also demonstrated impaired performance on tasks of verbal fluency (Hochstenbach, van Spaendonck, Cools, Horrstink, & Mulder, 1998; Rafnsson et al., 2007; Tatemichi et al., 1994). Viswanathan et al. (2015) reported that 67% of stroke patients fell below the 15th percentile for semantic fluency performance when compared with age-, education-, and gender-adjusted norms.

Apathy, defined as a lack of motivation and goal-oriented behavior, cognition, and emotion (Marin, 1991), has been shown to be negatively correlated with functional recovery, social ability, and physical ability (Kaufer et al., 1998; Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1993; Starkstein, Petracca, Chemerinski, & Kremer, 2001). Apathy is related to depression and it is also a feature of dysexecutive syndromes (Levy & Dubois, 2006). Minimal research has examined the relationship between apathy and verbal fluency in stroke patients, while controlling for depressive symptoms. Research has shown that although depression and apathy are related to each other, they can occur separately from one another (Brodaty et al., 2005; Starkstein et al., 1992). Whereas apathy encompasses decreased motivation, decreased initiation, and indifference, depression is commonly characterized by feelings of sadness, low mood, appetite disturbance, suicidal ideation, and helplessness (American Psychiatric Association, 2013). Individuals with either apathy or depression may also experience a reduction

in interest, energy, or insight. In stroke patients, reports of crying and overt sadness have been correlated with greater depression, but not greater apathy (Carota et al., 2005). Additionally, Marin (1991) stated that individuals with poststroke apathy frequently do not report the same emotional experiences of loss as individuals with poststroke depression.

Apathy may also be a feature of dysexecutive syndromes (Levy & Dubois, 2006). "Dysexecutive syndrome" is a term used to define difficulties with initiating, coordinating, and completing self-monitoring, planning, organization, and reasoning tasks (Repovs & Baddeley, 2006). Damage to the frontal lobes and frontal subcortical circuits are well-known causes of dysexecutive syndromes, encompassing emotional and behavioral changes in affected individuals (Shallice & Burgess, 1991; Stuss et al., 1994). Ardila (2013) described two prefrontal circuits supporting two types of dysexecutive syndromes: metacognitive dysexecutive syndrome and emotional/motivational dysexecutive syndrome. Metacognitive executive dysfunction is mediated by the lateral prefrontal cortex (e.g., dorsolateral prefrontal cortex, dlPFC) and involves difficulties with task shifting and responding to new and/or complex stimuli, as well as organizing goal-directed activities (Fuster, 2002). Emotional/motivational dysexecutive syndrome involves damage to the orbitofrontal and medial frontal cortex (e.g., anterior cingulate cortex, ACC; Sallet et al., 2011) and encompasses difficulties with value-based decision making (Ardila, 2013). This dysexecutive syndrome is associated with difficulties with inhibitory control, personality changes, emotional lability, apathy, and lack of insight (Eslinger & Damasio, 1985).

The ACC and DLPFC are also functionally interconnected; research regarding ACC–DLPFC connectivity suggests that the ACC may modulate dlPFC activity, while the dlPFC may drive ACC activity (Sallet et al., 2011). Studies of resting-state cingulate functional connectivity

found a relationship between activity in certain regions of the ACC with dlPFC activity (Habas, 2010; Margulies et al., 2007). Kouneiher, Charron, and Koechlin (2009) have posited that the interaction between these regions is related to motivational control. In addition, both the anterior cingulate and dorsolateral prefrontal circuits involve projections to the striatum (followed by the globus pallidus, substantia nigra, and the thalamus; Bonelli & Cummings, 2007; Tekin & Cummings, 2002; van Dalen, Moll van Charante, Nederkoorn, van Gool, & Richard, 2013). Damage to these prefrontal cortex-basal ganglia circuits have been associated with apathy symptoms (Kimura et al., 2003; Levy, 2012; Middleton & Strick, 2000). For example, lesions to the striatum have been associated with very severe apathetic states (Levy & Dubois, 2006).

Apathy is present in approximately 20–50% of individuals after experiencing a stroke (Brodaty et al., 2005; Starkstein et al., 1993; van Reekum, Stuss, & Ostrander, 2005). Apathy has been found to be negatively correlated with cognition, rehabilitation, medication adherence, and physical ability (Kaufer et al., 1998; Starkstein et al., 1993, 2001). After stroke, individuals with apathy had lower semantic fluency performance than individuals without apathy (Yamagata, Yamaguchi, & Kobayashi, 2004). Apathy has been negatively correlated with both phonemic and semantic verbal fluency performance in stroke patients (Okada, Kobayashi, Yamagata, Takahashi, & Yamaguchi, 1997). Other studies using global measures of cognition (e.g., Mini-Mental State Examination [MMSE]) have yielded non-domain-specific effects of apathy on cognition (Jarzebska, 2007; Onoda et al., 2011). However, many researchers have only examined the role of either semantic fluency (Brady, Spiro, McGlinchey-Berroth, Milberg, & Gaziano, 2001; Viswanathan et al., 2015; Yamagata et al., 2004) or phonemic fluency in their studies (Shapiro, Mahoney, Zingman, Pogge, & Verghese, 2013). This is problematic because semantic and phonemic fluency tasks have been found to involve both overlapping and distinct brain

regions. Specifically, semantic fluency tasks have been associated with greater activation in left temporal neocortex and medial temporal cortex than phonemic fluency tasks, whereas phonemic fluency tasks rely more heavily on frontal brain areas than do semantic fluency tasks (Gourovitch et al., 2000; Schmidt et al., 2017).

Clinical correlates of behavioral symptoms (e.g., apathy) after stroke include global cognitive impairment and executive dysfunction (Liang, Liang, Ungvari, & Tang, 2016). Given the importance of frontal subcortical circuits (substantia nigra, globus pallidus, thalamus, caudate nucleus) in apathy and in carrying out executive functions, it seems reasonable that apathy and tasks of verbal fluency (executive functioning tasks) would be related to one another (Houk, 2001; Litvan, 2001; Stuss, van Reekum, & Murphy, 2000). As a result, apathy and verbal fluency may be related due to overlapping brain damage, whereby damage to the same regions drives both apathy and lower fluency performance, and/or a uni/bidirectional influence between diminished motivation and fluency, whereby individuals with poorer cognitive function may be more likely to develop apathy and individuals with apathy may be more likely to deteriorate cognitively or be cognitively impaired (Palmer et al., 2010). For instance, post-stroke apathy has been shown to predict poorer recovery of cognitive function (Mikami et al., 2013), while greater baseline cognitive impairment, particularly in EF, is related to subsequent increases in symptoms of apathy (Douven et al., 2018).

In this study, we hypothesized that symptoms of apathy (as measured by the Apathy Evaluation Scale, AES; Marin, 1991) could predict semantic and phonemic fluency performance in stroke patients after controlling for depressive symptoms (as measured by the Center for Epidemiologic Studies Depression Scale, CES-D; Radloff, 1977), such that higher apathy scores could predict poorer fluency performance. These hypotheses were tested using multiple

regressions controlling for depressive symptoms, as well as subscale analyses to determine whether specific AES subscales (emotional, cognitive, or behavioral) predicted performance on these cognitive tasks.

To the best of our knowledge, no study to date has examined the relationship between apathy symptoms with both semantic and phonemic fluency test performance in patients with cerebrovascular disease after controlling for depressive symptoms. As individuals with depression have been found to be impaired on tests of verbal fluency, it is important to control for the influence of depressive symptoms (e.g., sad mood, appetite/sleep disturbance) before examining the role of apathy (for a review, see Veiel, 1997). This study was performed to extend research investigating the relationship between apathy and cognition across psychiatric and neurodegenerative diseases (Cohen, Iglesias, & Minor, 2009; Dujardin, Sockeel, Delliaux, Destée, & Defebvre, 2009; Starkstein et al., 1992).

In this study, 147 stroke and 135 transient ischemic attack (TIA) patients at a secondary stroke prevention clinic in Ontario completed tests of phonemic fluency, semantic fluency, apathy, and depression. As apathy has been shown to affect frontal cortex functionality (Benton, 1968; Milner, 1964), the purpose of the current study was to examine the role of apathy in predicting phonemic and semantic fluency in patients with stroke and TIA after scaling scores by age and years of education and controlling for depressive symptoms.

2. **Method**

This study was conducted as part of a larger study, known as the “DOC” study. The DOC study examined the reliability and validity of a brief screening tool to assess stroke patients for depression, obstructive sleep apnea, and cognitive impairment compared with a comprehensive neuropsychological battery of cognitive, psychological, and sleep tests.

All testing took place at the Secondary Stroke Prevention Clinic at Sunnybrook Health Sciences Centre in Toronto, Canada. The Institute's ethics board approved all study procedures, and the research was completed in accordance with the Helsinki Declaration.

2.1 **Participants**

Between 23 April 2012 and 30 April 2014, all referrals to a Secondary Stroke Prevention Clinic were eligible to undergo a brief cognitive screening test. The initial brief cognitive screening (DOC screen) was completed by 1503 participants. Three hundred and fifty-three patients were non-English speaking, aphasic, or possessing motor/visual impairments, or had illnesses that would interfere with neuropsychological testing, and thus were not approached for additional testing. Among patients who completed the DOC screen, 437 gave written informed consent to undergo more detailed neuropsychological assessments by research assistants. Of those 437 patients, 95 were referred to the Secondary Stroke Prevention Clinic for nonvascular-related issues (e.g., headaches, blurry vision), and 43 were referred to the clinic for other vascular issues without a TIA and/or stroke (e.g., asymptomatic carotid artery disease) and therefore were excluded from analysis. As a result, 299 individuals referred to the Secondary Stroke Prevention Clinic with stroke (n = 158) or TIA (n = 141) were eligible participants. Patients with over 80% of missing data for the tests related to this study were not included in analysis (n = 6 stroke). Participants who did not complete a fluency test were also excluded from analysis (n = 11 for phonemic fluency, n = 12 for semantic fluency). Thus, 282 participants (n = 147 stroke, n = 135 TIA) were included in phonemic fluency analyses and 281 for semantic fluency analyses. Participants who were excluded did not differ from sample participants in terms of age, years of education, diagnosis, location of cerebrovascular event, smoking status, family history of cardiovascular disease, diabetes diagnoses, autoimmune disease diagnoses, or

alcohol consumption (Table 1). A significantly higher proportion of females were in the excluded subjects group than in the participants group.

2.2 **Materials**

DOC Case Report Form (DOC-CRF). The DOC-CRF contains medical information including previous cerebrovascular history, vascular risk factors, alcohol intake, diagnosis, date of cerebrovascular event, smoker status, as well as other diagnoses (e.g., cancer, autoimmune disorders).

Phonemic fluency test (Leach, Kaplan, Rewilak, Richards, & Proulx, 2000). In this task, participants were given a letter (i.e., F) and were asked to name as many words as possible that begin with that letter for 1 min. This procedure was replicated with another two letters (i.e., A and S). Performance for phonemic fluency was computed as the number of correct items generated in response to all three letters. Items were scored as correct if they belonged to the category and were not repetitions. This test has been frequently used to evaluate phonemic fluency in clinical populations (Weinstein et al., 2014).

Semantic fluency test (Darvesh, Leach, Black, Kaplan, & Freedman, 2005). In this test, participants were asked to name as many animals as they could within a 1-min period. Performance for semantic fluency was computed as the number of correct items generated. Items were scored as correct if participants correctly generated animals, and they were not repetitions. The semantic fluency test has been used in clinical populations, including stroke patients, as well as in patients with frontal and nonfrontal lobe damage (Baldo, Schwartz, Wilkins, & Dronkers, 2006; Costafreda et al., 2006).

Apathy Evaluation Scale (AES; Marin, 1991). The Apathy Evaluation Scale is an 18-item self-report questionnaire that addresses individuals' thoughts, feelings, and activities over

the past two to three weeks. The AES has three subscales that measure overt goal-directed cognitions, goal-related behaviours, and goal-related emotions. The questions examined the extent to which patients are interested in learning and having new experiences, taking initiative, being motivated, and putting effort into tasks. Participants responded to these statements using a Likert-type scale ranging from 1 (*Not at all*) to 4 (*A lot*). AES score range from 18 to 60, with higher scores indicating greater apathy. The AES has satisfactory reliability and has previously been utilized in stroke populations (Marin, 1991; Sagen et al., 2008, 2010). Internal consistency for the AES ranges from .86 to .94, and test-retest reliability ranges from .76 to .94 (Marin, Biedrqcki, & Firinciogullari, 1991; Marin, Firinciogullari, & Biedrzycki, 1993, 1994). Cronbach's alpha for the AES in this study was .86.

Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). The CES-D is a 20-item questionnaire that measures depressive symptomatology over the past week (Radloff, 1977). Participants were asked questions about their sleep patterns, appetite, and feelings of fear, loneliness, and hopelessness. Participants responded to statements using a Likert-type scale ranging from 0 (*Rarely or none of the time*) to 3 (*Most or almost all of the time*). Total CES-D scores range from 0 to 60, with higher scores indicating greater depressive symptomatology. The CES-D has been utilized across various age groups and cultures (Lewinsohn, Seeley, Roberts, & Allen, 1997; Roth, Ackerman, Okonkwo, & Burgio, 2008). The CES-D has high reliability (Cronbach's alpha = .90) and high convergent validity with the Beck Depression Inventory–II (BDI–II; Beck, Steer, & Brown, 1996) and the Hamilton Depression Inventory (HDI; Reynolds & Kobak, 1995). Cronbach's alpha for the CES-D in this study was .91.

2.3 **Procedure**

Participants at the Secondary Stroke Prevention Clinic were approached by research assistants, nurses, or doctors and were asked to complete a 5-min, brief screen for depression, obstructive sleep apnea, and cognitive impairment as part of routine clinical care. After completing the DOC screen, participants were asked whether they were interested in completing a full neuropsychological battery at a later time suitable for the participant. If individuals expressed an interest in participating, a date was booked with the research assistant. Upon arrival, research assistants obtained informed consent from all participants. For the purposes of this study, participants completed the phonemic fluency test (Leach et al., 2000), the semantic fluency test (Darvesh et al., 2005), the AES (Marin, 1991), and the CES-D (Radloff, 1977). Relevant data were extracted from patient files to complete the case report form. Research assistants administered the phonemic and semantic fluency tasks to participants. Participants completed the CES-D and the AES as self-report measures. After study completion, individuals were thanked for their participation and were given a free parking card to cover their parking fee at the hospital.

2.4 **Data analyses**

Missing data were handled using expectation maximization. There were 24 (0.5%) missing fields from the AES, and 51 (0.9%) missing fields from the CES-D. The results of Little's Missing Completely at Random (MCAR) test indicated that the data were missing completely at random, $\chi^2(519) = 584.89$, $p = .824$. SPSS Version 21, 64-bit edition, was used for data analysis.

Scores for semantic and phonemic fluency were scaled according to age and years of education, consis- tent with Tombaugh, Kozak, and Rees (1999).

3. **Results**

3.1 **Participant characteristics**

Participant information is shown in Table 2.4. The mean age of study participants (N = 282) was 63.00 (*SD* = 15.0) years, ranging from 17 to 95 years old. One hundred forty-three participants (50.7%) were female. There were no sex differences in apathy severity ($F = 0.22$, $p = .636$).

Table 2.4

Participant Characteristics

Characteristic	Participants (*N* = 282)	Excluded subjects (*N* = 16)	Statistical test
Age (years)	*M* = 63.0 (*SD* = 15.0)	*M* = 62.8 (*SD* = 4.28)	*t* = –0.05
Range	17–95	30–85	*p* = .959
17–40	21 (7.4%)	2 (12.5%)	
41–60	96 (34.0%)	5 (31.3%)	
61–80	130 (46.1%)	6 (37.5%)	
81+	35 (12.4%)	3 (18.7%)	
Men:women	139:143 (50.7% female)	4:12 (75% female)	$\chi^2 = 4.00$
			p = .045
Years of education	*M* = 15.5 (*SD* = 3.9)	*M* = 16.9 (*SD* = 0.96),	*t* = 1.45
Range	4–30	10–24	*p* = .148
Cerebrovascular disease type	147 stroke (52.1%)	11 stroke (68.8%)	*t* = 1.37
	135 TIA (47.9%)	5 TIA (31.2%)	*p* = .187
Location of event[a]			
Left hemisphere	111 (39.3%)	5 (31.2%)	$\chi^2 = 0.11$
Right hemisphere	76 (27.0%)	4 (25.0%)	*p* = .947
Bilateral	16 (5.7%)	1 (6.3%)	
Smoking status[b]			
Current	28 (9.9%)	1 (7.1%)	$\chi^2 = 1.29$
Reformed	16 (5.7%)	N/A	*p* = .523
Nonsmokers	208 (73.8%)	13 (92.9%)	
Family history of cardiovascular disease[c]	86 (30.5%)	5 (31.2%)	$\chi^2 = 0.01$
			p = .949
Diabetes (diagnosed)[c]	46 (16.3%)	4 (25.0%)	$\chi^2 = 0.81$
			p = .366
Autoimmune disease[c]	11 (3.9%)	1 (6.2%)	$\chi^2 = 0.22$
			p = .642
Alcohol use[c]			
>2 drinks/day	18 (6.4%)	N/A	$\chi^2 = 2.86$
<2 drinks/day	44 (15.6%)	3 (18.8%)	*p* = .414
rare/social	122 (43.3%)	6 (37.5%)	
never/not currently	59 (20.9%)	6 (37.5%)	
CES-D score	*M* = 11.2 (*SD* = 10.5)		
Range	0–53		
AES score	*M* = 27.5 (*SD* = 7.6)		
Range	18–56		
Phonemic fluency	*M* = 10.0 (*SD* = 3.2)		
Range	2–18		
Semantic fluency	*M* = 17.7 (*SD* = 5.9)		
Range	1–36		

Note. TIA = transient ischemic attack; CES-D = Center for Epidemiologic Studies Depression Scale; AES = Apathy Evaluation Scale.
[a]There were 79 missing cases for the sample and 6 missing cases for the excluded subjects. [b]There were 30 missing cases for the sample and 2 missing cases for the excluded subjects. [c]There were 40 missing cases for the sample and 1 missing case for the excluded subjects.

3.2 **Apathy and Depressive Symptoms**

Scores on the AES and the CES-D were moderately correlated, $r(280) = .58$, $p < .001$.

3.3 **Semantic Fluency**

All scores were analyzed as continuous variables. We conducted a hierarchical linear regression to examine whether self-reported apathy could predict semantic fluency in stroke and TIA patients. Depressive symptoms, as assessed by the CES-D, were entered into the first step of the model, and apathy scores were entered in the second step, with scaled semantic fluency score as the dependent variable. We found that the overall final model significantly predicted semantic fluency after controlling for depressive symptoms ($R^2 = .173$), $F(2,278) = 12.95$; $p = .015$ (see Table 2.5). Depressive symptoms entered in Step 1 did not predict semantic fluency ($\beta = -.035$; $p = .554$). In Step 2 of the model, apathy was a significant predictor of semantic fluency scores, such that higher apathy scores were predictive of lower performance on the semantic fluency task ($\beta = -.210$; $p = .004$).

Table 2.5

Linear Regression of Apathy Predicting Semantic Fluency Scores after Controlling for Depressive Symptoms

Predictor	*df*	*B*	*SE*	β	*t*	*F*	*p*	R^2	95% CI
Step 1	1,280							.001	
CES-D		-.004	.01	-.04	-.59	.35	.554		[-.018, .009]
Step 2	2,280							.030	
CES-D		.01	.01	.09	1.21	4.30	.229		[-.006, .027]
AES		-.03	.01	-.21	-2.87		.004		[-.057, -.011]

Note. CES-D = Center for Epidemiologic Studies Depression Scale; AES = Apathy Evaluation Scale; CI = confidence interval.

We conducted post-hoc analyses to examine which AES subscale (i.e., cognitive, behavioural, emotional) significantly predicted semantic fluency score, after controlling for depressive symptoms. We conducted three hierarchical linear regressions. Depressive symptoms, as assessed by the CES-D, were entered into the first step of the model, and the cognitive, behavioural, or emotional AES subscale score was entered in the second step, with scaled semantic fluency score as the dependent variable. We used a Bonferroni correction (.05/3 = .016) to determine statistical significance. The cognitive subscale significantly predicted semantic fluency score (β = -.190, p = .005), even after using the Bonferroni correction. Additionally, the behaviour subscale significantly predicted semantic fluency score (β = -.157, p = .027), but it was not statistically significant after the Bonferroni correction was applied. Lastly, the emotional subscale did not predict semantic fluency score (β = -.106, p = .102).

We also conducted a post-hoc analysis to examine whether apathy symptoms significantly predicted semantic fluency after controlling for the anhedonia subscale of the CES-D, which contains some items that overlap with apathy (Radloff, 1977). After controlling for the anhedonia subscale (which did not predict semantic fluency score; β = .061, p = .385), apathy scores still significantly predicted semantic fluency score (β = -.192; p = .007).

3.4 **Phonemic Fluency**

We examined whether apathy could predict phonemic fluency in stroke and TIA patients using a hierarchical linear regression. Depressive symptoms, as assessed by the CES-D, were entered into the first step of the model, and apathy scores were entered in the second step, with scaled phonemic fluency score as the dependent variable. We found that the overall final model did not significantly predict phonemic fluency (R^2 = .015), F(2,279) = 2.09, p = .125 (see Table 2.6). Depressive symptoms entered in Step 1 did not predict phonemic fluency (β = -.081; p =

.173). Additionally, in Step 2 of the model, apathy was not a significant predictor of phonemic fluency score after controlling for depressive symptoms (β = -.112; p = .129).[1]

Table 2.6

Linear Regression of Apathy Predicting Phonemic Fluency Scores after Controlling for Depressive Symptoms

Predictor	*df*	*B*	*SE*	β	*t*	*F*	*p*	R^2	95% CI
Step 1	1,280							.007	
CES-D		-.03	.02	-.08	-1.37	1.87	.173		[-.061, .011]
Step 2	2,281							.015	
CES-D		-.01	.02	-.02	-.21	2.09	.835		[-.049, .040]
AES		-.05	.03	-.11	-1.52		.129		[-.109, .014]

Note. CES-D = Center for Epidemiologic Studies Depression Scale; AES = Apathy Evaluation Scale; CI = confidence interval.

4. **Discussion**

The purpose of this study was to examine the ability of apathy, as assessed by the AES, to predict phonemic and semantic fluency task performance in individuals with stroke and/or TIA. We found that apathy significantly predicted semantic fluency, but not phonemic fluency, after scaling the scores by age and education and controlling for depressive symptoms. Specifically, the cognitive subscale and the behavioral subscale[2] of the AES predicted semantic fluency scores, whereas the emotional subscale of the AES was unrelated to semantic fluency. In addition, apathy predicted semantic fluency scores after controlling for the anhedonia subscale on the CES-D, which shares some overlapping features with apathy. Lastly, depressive symptoms did not predict phonemic or semantic fluency scores.

Our findings extend and are consistent with research demonstrating that apathy is correlated with verbal fluency in a variety of psychiatric disorders and neurological diseases (Cohen et al., 2009; Dujardin et al., 2009; Viswanathan et al., 2015). However, the predictive ability of apathy on phonemic fluency was not supported, even though correlations between these variables have previously been found in individuals with strokes and other diseases (Okada et al., 1997; Stolar, Berenbaum, Banich, & Barch, 1994).

Both phonemic and semantic verbal fluency tasks have been used as behavioral indices of frontally mediated cognitive functioning (Schwartz & Baldo, 2001). Semantic fluency tasks have also been associated with greater activation of the left temporal neocortex and medial temporal cortex than phonemic fluency tasks (Baldo et al., 2006; Gourovitch et al., 2000). A meta-analysis by Henry and Crawford (2004) found that individuals with temporal lobe damage had larger deficits in semantic fluency than phonemic fluency, supporting the notion that semantic fluency tasks recruit more extended networks than phonemic fluency tasks. Semantic fluency tasks involve information retrieval from semantic memory (operating in the temporal lobe), which stores information for concepts, general facts, and vocabulary that are not related to specific experiences. As a result, the execution of executive processes that are recruited in semantic fluency tasks may be affected indirectly by nonfrontal impairments in long-term verbal memory or word knowledge. Furthermore, both hippocampi are proportionally activated during semantic fluency tasks, and their involvement is even greater than in phonemic fluency tasks (Glikmann-Johnston et al., 2015). Martin et al. (1990) found that patients with primarily memory-related difficulties were impaired on a semantic fluency test. Moreover, apathetic stroke patients had impaired memory performance relative to nonapathetic stroke patients (Hama, Yamashita, Yamawaki, & Kurishu, 2011). Numerous studies have also reported correlations between apathy

and long-term verbal memory (Calamia, 2014; Chiaravalloti & DeLuca, 2003; Hama et al., 2011). Those studies support a more influential role of apathy in verbal memory tasks that trigger effortful and conscious processes (free recall), which may also play a role in word finding and retrieval. It may also be that this sample had more temporal infarcts than frontal infarcts.

Given that deficits in executive processes are commonly observed in individuals who are apathetic, we had expected that apathy scores would also predict phonemic fluency. This may not have occurred due to methodological reasons, including task order and/or sample type. It may be that the inclusion of participants with lesions or damage to the right hemisphere (approximately 27% of the sample) attenuated effects of the phonemic fluency tasks, as participants have been found to be more impaired on phonemic fluency tasks with left-hemisphere damage, but equally impaired on semantic fluency tasks with right- and left-hemisphere damage (Joanette & Goulet, 1986; Robinson, Shallice, Bozzali, & Cipolotti, 2012). As the right hemisphere is also involved in accessing the semantic meaning of words, the effect of apathy on semantic fluency would not have been diminished by including these individuals in the analysis (Chiarello, 1988; Searleman, 1977). In our sample, there was no difference in semantic fluency or phonemic fluency performance in individuals with right- versus left-hemisphere damage after stroke.

Lack of motivation, the main characteristic of apathetic behavior, has also previously been correlated with semantic and not phonemic fluency (Meyer et al., 2015; Naarding et al., 2007). There may be deficits in long-term memory storage in apathetic individuals, which would also contribute to impaired semantic fluency task performance (Calamia, 2014; Chiaravalloti & DeLuca, 2003). However, given that motivation has been extensively linked to frontal processes, it was unexpected that apathy symptoms did not predict phonemic fluency performance (Meyer

et al., 2015; Naarding et al., 2007). The literature supports phonemic fluency tasks as requiring more effortful processing than semantic fluency tasks (Troyer & Moscovitch, 2006). It may be that because more effort was required for this task, it motivated participants to try harder on the activity. It is also important to consider that both phonemic and semantic fluency tasks encompass elements of clustering (involving temporal-lobe processes including verbal memory and word storage) and switching (involving frontal-lobe processes such as strategic search, which is critical for cognitive flexibility in shifting from one subcategory to another; Troyer & Moscovitch, 2006). Clustering is thought to be relatively automatic, and involves semantic categorization (Rende, Ramsberger, & Miyake, 2002). Switching, which requires cognitive flexibility in shifting from one subcategory to another, is a more effortful process (Rende et al., 2002; Troyer, Moscovitch, & Winocur, 1997). These components of fluency performance may be differentially impacted by various neurological disorders. Clustering is related to temporal lobe functioning, whereby clustering performance among patients with Alzheimer's disease is impaired (Troyer, Moscovitch, Winocaur, Leach, & Freedman, 1998). Clustering is relatively unaffected by focal frontal lesions (Troyer et al., 1998). Conversely, switching is related to frontal functioning, whereby switching performance among patients with left dorsolateral and/or superior medial frontal-lobe lesions is impaired (Troyer et al., 1998). As a result, it may be that the relationship observed between apathy symptoms and semantic fluency performance is due, in part, to a reduction in switching, as opposed to cluster size, consistent with Fossati, Guillaume, Egris, and Allilaire's (2002) study. Kavé et al. (2011) also found that impaired switching on semantic tasks was the most useful measure for demonstrating executive deficits in individuals with traumatic brain injuries. Future research may be needed to explore this possibility.

Finally, the inability of depressive symptoms to predict either phonemic or semantic fluency supports a differentiation between apathy and depressive symptoms. Although they are related constructs, apathy and depression can occur separately from one another (van Dalen et al., 2013; Wu, Liu, Chau, & Chang, 2010). Researchers have suggested that a lack of motivation, which is largely characteristic of apathy (Marin, 1991), contributes to impaired performance on cognitive tasks to a significantly greater degree than mood (i.e., depressive) symptoms (Naarding et al., 2007). Apathy is also an important feature of dysexecutive syndromes (Ardila, 2013). Damage to the frontal lobes and frontal subcortical circuits are well-known causes of dysexecutive syndromes, encompassing emotional and behavioral changes in affected individuals (Levy & Dubois, 2006). Both the anterior cingulate and dorsolateral prefrontal circuits involve projections to the striatum (Bonelli & Cummings, 2007; Tekin & Cummings, 2002; van Dalen et al., 2013). Damage to these prefrontal cortex-basal ganglia circuits have also been associated with apathy symptoms (Levy, 2012; Middleton & Strick, 2000; Kimura et al., 2003). Together, this research suggests that apathy may be a more reliable predictor of deficits in verbal fluency tasks than mood symptoms in individuals with cerebrovascular disease.

Other studies have demonstrated that motivation level is negatively correlated with performance on semantic fluency tasks (Janzing, Naarding, & Eling, 2005; Naarding et al., 2007). Janzing et al. (2005) also failed to find a correlation between depressive symptoms or mood symptoms with verbal fluency tasks. Additionally, Masai et al. (2016) found that verbal fluency negatively correlated with one's reported difficulty to initiate and perform everyday activities, and not depressed mood, in individuals with major depressive disorder. As a result, it is reasonable that the cognitive and behavioral AES subscales, encompassing items including getting things done during the day, putting effort into things, and being interested in new

experiences, predicted semantic fluency performance. The emotional subscale may not have been related to performance as it is only composed of two items, and given the neutral tone of the tasks completed, it may not have impacted cognitive performance. If the tasks examined fluency for emotional words, however, this subscale may have been important to task performance. Another important study finding is that after controlling for the anhedonia subscale on the CES-D (which overlaps with apathy), apathy still significantly predicted semantic fluency scores. The results of this study suggest that apathy may be a more reliable predictor of deficits in verbal fluency tasks than mood symptoms in individuals with cerebrovascular disease.

The distinction between apathy and depression is important, since treatments and outcomes may be different for individuals with depression and apathy (Wongpakaran, van Reekum, Wongpakaran, & Clarke, 2007). Certain pharmacological agents recommended for individuals with depression, including selective serotonin reuptake inhibitors, may exacerbate apathy symptoms (Barnhart, Makela, & Latocha, 2004; Lee & Keltner, 2005; Wongpakaran et al., 2007). Preliminary research has supported the use of cilostazol (Toyoda et al., 2011), dopamine stimulants (Kraus & Maki, 1997; Powell, Al-Adawi, Morgan, & Greenwood, 1996), and methylphenidate (Lanctôt et al., 2014; Rosenberg et al., 2013) in improving apathy symptoms and cognitive functioning. Potentially treatable sleep and circadian rhythm disorders may also be contributing (Cosin et al., 2015). Therefore, it is imperative to identify neuropsychiatric symptoms accurately, as improper identification of psychiatric issues may exacerbate maladaptive symptoms (Lee & Keltner, 2005; Wongpakaran et al., 2007).

Limitations of the current study include that only self-reported apathy scores were assessed. Since individuals with apathy may have poor insight into their symptoms ("anosognosia"), rates of apathy may have been underestimated (Njomboro & Deb, 2012).

However, self-reported apathy has significantly correlated with both clinician-rated and informant-rated apathy (Marin, 1991; Mason & Barker, 2015). Future research should examine whether informant or clinician-rated apathy significantly predicts semantic or phonemic fluency deficits. Additionally, we did not characterize our sample using a dichotomous depression diagnosis; depressive symptomatology was analyzed along a continuum of severity. Although future research could examine those with a specific diagnosis of depression, it was important for the researchers to examine the range of depressive symptoms in order to distinguish these symptoms from apathy. It should also be noted that this study did not include a healthy control group. An examination of deficits in phonemic and semantic fluency in vascular patients relative to healthy controls may assist in highlighting the clinical importance of assessing apathy in these populations. Utilizing cued recall in memory tasks may assist in differentiating whether impairments may be attributable to retrieval deficits or degradation of semantic memory stores. Given that apathetic individuals experience greater difficulty with emotional recognition (Hanby et al., 2014), it may be of interest to examine the relationship between apathy and emotional verbal fluency performance (e.g., Sass, Fetz, Oetken, Habel, & Heim, 2013) in this population. This would allow researchers to further explore the emotion–cognition interaction.

Strengths of this study include the large sample size, as many researchers have utilized fewer numbers of participants in their studies (Hochstenbach, van Spaendonck, Cools, Horstink, & Mulder, 1998; van der Werf et al., 2003). Including patients with stroke and/or transient ischemic attack affecting any brain area also allowed this study to be more inclusive and, as a result, more generalizable to individuals with cerebrovascular disease. Importantly, this study assessed both depressive symptoms and apathetic symptoms, whereas other studies have ignored

the role of either apathy (Bour et al., 2010) or depressive symptoms (Mayo et al., 2009) in neuropsychological evaluations.

The results of the current study support the notion that apathy is related to memory (i.e., temporal-related processes), that apathy is more pertinent to semantic processing than depressive symptoms in individuals with cerebrovascular disease, and that semantic and phonemic fluency have different cognitive demands. An examination of clustering and switching may assist in further understanding the role of apathy on verbal fluency task performance. A more comprehensive examination of apathy's role in verbal long-term memory, word knowledge, and verbal attention, which can subserve word fluency, is supported. Further investigations of the ways in which apathy is related to neuropsychological test performance may elucidate cognitive functions affected by apathy and provide future directions of whether treating apathy symptoms could be a novel target for improving cognitive outcomes after stroke.

5. Footnotes

[1]When these analyses were conducted excluding all missing data, the results did not change. Apathy symptoms significantly predicted semantic fluency performance after depressive symptoms were controlled (β = −.034, p = .004). Apathy symptoms did not predict phonemic fluency performance after controlling for depressive symptoms (β = -.046, p = .142).

[2]The behavioral subscale of the AES significantly predicted semantic fluency performance before the Bonferroni correction (β = -.157; p = .027). However, after the Bonferroni correction was implemented, the behavioral subscale did not significantly predict semantic fluency performance.

6. Acknowledgments

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7. Contributions

Articles 1 and 2 utilized data collected as part of a larger study, the Depression, Obstructive Sleep Apnea, and Cognitive Impairment (“DOC”) study, with Dr. Swartz as the Principal Investigator (Swartz et al., 2017). The DOC study examined the reliability and validity of a brief screening tool to assess stroke patients for depression, obstructive sleep apnea, and

cognitive impairment compared with a comprehensive neuropsychological battery of cognitive, psychological, and sleep tests.

With regards to Articles 1 and 2, Keera Fishman, the primary author, conducted a secondary data analysis based upon the DOC data. Keera Fishman led the study conceptualization, conducted data analysis, and wrote both manuscripts. She also participated in data collection for DOC in 2013.

Dr. Andrea R. Ashbaugh, research supervisor, and Dr. Richard H. Swartz, stroke neurologist at Sunnybrook Health Sciences Centre, met with Ms. Fishman frequently to discuss the research questions and data analysis. Throughout the process, Drs. Ashbaugh and Swartz provided guidance and recommendations regarding article content and edited the full manuscripts. Megan L. Cayley provided the DOC dataset. Dr. Krista Lanctôt, Dr. Brian J. Murray, Dr. Nathan Herrmann, Karen Lien, and Michelle Sicard provided feedback on manuscript drafts.

With regards to the DOC study, Dr. Richard H. Swartz was involved in conceptualization, funding acquisition, investigation, methodology, project administration, resources, and supervision. Dr. Krista L. Lanctôt was involved in conceptualization and methodology. Karen Lien, Michelle Sicard, and Megan Cayley were involved in the initial analysis, investigation, and visualization for the DOC study. Dr. Brian J. Murray was involved in conceptualization and methodology. Dr. Kevin E. Thorpe was involved in conceptualization and methodology. Dr. Demetrios J. Sahlas and Dr. Nathan Herrmann were involved in conceptualization for the DOC study.

CHAPTER 3: The Relationship Between Apathy, Depression, And Cognition in Young Adults

i. **Preamble**

In Article 1 (Chapter 2), I found that stroke patients with apathy performed worse than stroke patients without apathy on verbal word-list learning, short-term free recall, and long-term free recall, regardless of depression. In Article 2 (Chapter 2), I found that apathy predicted category fluency after controlling for depressive symptoms. As hypothesized, depressive symptoms did not predict performance on neuropsychological tests in individuals with cerebrovascular disease. Together, and complementing findings from studies in the context of neurodegenerative diseases, I suggested that apathy may better predict impairment in verbal memory and verbal fluency than depressive symptoms. I highlighted that future research should examine whether this model could be applied to other populations (e.g., individuals without cerebrovascular disease) and to extend the model to include aspects of memory and EF, such as autobiographical memory and working memory.

Consistent with this recommendation, Chapter 3 (Article 3) examined the relationship between apathy and cognitive functioning in young educated adults. Given the elevated risk for depression and other mental health disorders in young adults between the ages of 18-29 (Ceyhan, Ceyhan, & Kurtyılmaz, 2009), it may be particularly important to acquire an understanding of the rates and impact of apathy in this population. My first goal was to explore the prevalence of apathy (and depression) in young adults attending university. My second goal was to examine whether apathy and depression could be differentiated from one another in this sample. I also expanded the neuropsychological battery to include measures of autobiographical memory, working memory, and emotional memory. Inclusion of these measures allowed for a more comprehensive examination of the relationship between apathy and cognition. I hypothesized that apathy would be related to poorer overall cognitive performance to a greater degree than

depression, but that depression may impact the type of emotional content that was remembered. This study served as a novel contribution to the literature, given that the role of apathy had yet to be examined in a population of exclusively young adults, nor had its relationship to neutral and emotional memory been examined in the same study.

Article 3

Mind the age gap: A comprehensive examination of apathy, depression, and cognition in young adults[4]

Revision submitted for publication

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Abstract

Depression and apathy are associated with poorer cognition in healthy older adults. We examined the role of apathy and depression on cognition in young adults (n = 96) from a bilingual university in Ontario. Participants completed measures of apathy, depression, executive function (EF), working memory (WM), autobiographical memory, neutral memory, and memory for affective images. Apathy was present in 22% of the sample. Apathy scores were correlated with poorer category fluency (r=-.20, p=.049) and the number of specific autobiographical memories recalled (r=.21, p=.041), but these relationships were not significant after correcting for multiple comparisons. Apathy in young adults was not related to performance in EF, WM, neutral memory, or memory for affective images, after adjusting for depressive symptoms and the number of self-reported fluent languages. Depressive symptoms were also not related to neuropsychological performance. However, high levels of depressive symptoms predicted greater recall of negatively-valenced than positively-valenced images (t[64] = 2.34, p = .022) and specific autobiographical memories (t[93] = 2.47, p = .015). These findings support the notion that mild-to-moderate symptoms of depression and apathy exert a minimal to negligible impact on EF, WM, and memory in young, educated adults. As a result, neuropsychologists who assess cognition in this population are encouraged to explore reasons other than psychopathology to explain deficits, particularly when evaluating clients who report mild affective or mood symptoms. Future research in this area should incorporate more EF measures and individuals with severe apathetic symptomatology in order to refine our understanding of specific indices that may possibly be differentially impacted by apathy.

Apathy; Depression; Motivation; Neuropsychology; Cognition; Emotion; Learning and Memory

Public Significance Statement: Apathy (low motivation) has been shown to be negatively

related to cognitive and functional abilities in older adults. We found that apathy is present in educated young adults (22%), but neither apathy nor depressive symptoms were related to poorer cognition. Neuropsychologists are encouraged to explore reasons other than psychopathology to explain cognitive difficulties in individuals reporting mild to moderate affective or mood symptoms.

Mind the age gap: A comprehensive examination of apathy, depression, and cognition in young adults

1. Introduction

Apathy is defined as a lack of motivation and is characterized by diminished self-generated volitional and purposeful activity, affecting behavioural (e.g., lack of effort and engagement), cognitive (e.g., lack of interest in pursuing new experiences), and affective (e.g., blunted affect) domains (Levy & Dubois, 2006; Marin, 1991). Apathy is present across psychiatric, neurological, and neurodegenerative disease populations, including individuals with stroke, Parkinson's disease, dementia, and depression (Lanctôt et al., 2017). Across these diseases, apathy impairs daily functioning, physical ability, rehabilitation, participation in rehabilitation services, and increases caregiver burden (Lanctôt et al., 2017; Skidmore et al., 2010).

1.1 Apathy and Depression

Researchers have posited that although apathy and depression are correlated with one another because they share common symptoms of diminished interest, psychomotor slowness, and low energy, however, they can also present distinctly from one other (Kirsch-Darrow et al., 2006). In contrast to apathy, depression is characterized by feelings of sadness, low mood, and helplessness (American Psychiatric Association, 2013). Symptoms of depression may include guilt, suicidal ideation, sleep irregularities, and appetite changes (American Psychiatric Association, 2013). In contrast, apathy is primarily characterized by low initiation of behaviour and emotional indifference (Ishizaki & Mimura, 2011). Apathy and depression have been successfully differentiated in older adult populations and also across psychiatric and neurological conditions, including Parkinson's disease, schizophrenia, dementia, and stroke (Kirsch-Darrow

et al., 2006; Lanctôt et al., 2017).

1.2 **Apathy in Healthy Adults**

To date, few studies have examined the rates of apathy in adults without neurodegenerative or neurological pathology. In a sample of healthy older adults above 65 years old, Adams (2001) found that items representing apathy using the Geriatric Depression Scale were more frequently endorsed (75.2%) than items representing depression (37.8%) or anxiety (25.1%). Onyike et al. (2007) found that apathy (Neuropsychiatric Inventory [NPI]-Apathy ≥ 4) was present in 1.4% of community-dwelling older adults above age 65 without evidence of cognitive impairment. Lyketsos et al. (2002), Marin (1994), and Clarke et al. (2010) found prevalence rates of 3.2% (NPI-Apathy > 0), 7.0% (AES > 38), and 23.7% (General Health Questionnaire-Apathy ≥ 6.5) respectively, in older adults. The differences in prevalence rates may be due to different instruments and cut-offs being implemented. However, these findings illustrate that apathy is measurable and detectable in community-dwelling populations, though with lower prevalence rates than in populations with neuropsychiatric conditions that have used similar instruments and cut-offs (e.g., AES ≥ 34; Fishman et al., 2018; NPI-Apathy > 0; Rush et al., 2010).

1.3 **Apathy and Cognition**

In clinical populations, higher apathy is related to poorer treatment response, risk for progression from amnestic mild cognitive impairment to dementia, risk of vascular disease, and cognitive performance (Eurelings et al., 2014; Fishman et al., 2019; Lanctôt et al., 2017). Comparatively, fewer studies to date have examined the role of apathy on cognitive functioning in community samples. Older adults with apathy performed worse of tasks of executive function (EF), including inhibition (Esposito et al., 2010), cognitive flexibility (Onyike et al., 2007),

multitasking (Esposito et al., 2010), and future planning tasks (Raffard et al., 2013), compared to older adults without apathy. Similarly, individuals with apathy performed worse on tasks of EF, as well as global cognition, constructional praxis, and processing speed, regardless of depressive symptoms (Montoya-Murillo et al., 2019; Onyike et al., 2007). Given that the neurobiological underpinnings of apathy involve altered connectivity of fronto-striatal circuitry (e.g., anterior cingulate cortex, dorsolateral prefrontal cortex, ventral striatum, globus pallidus, substantia nigra, and thalamus), it is reasonable that EF tasks including verbal fluency and WM tasks including digit span are more strongly related to apathy symptoms than other cognitive domains, including language and visuospatial ability (Chase, 2011; Levy & Dubois, 2006; Varanese et al., 2011).

1.4 **Depression and Cognition**

Researchers have also examined the relationship between depression and cognitive functioning. A meta-analysis by Goodall et al. (2018) reported that adolescents and young adults (i.e., 12-25 years old) with major depressive disorder (MDD) performed worse on attention, processing speed, verbal/visual memory, and verbal reasoning tasks than individuals without a diagnosis of MDD, though these effects were small to moderate. However, other studies have not replicated these findings, noting an absence of discrepancies in cognitive ability (e.g., EF, verbal memory, attention, processing speed) between young adults with and without mild to moderate depression (Castaneda et al., 2008; Grant, Thase, & Sweeney, 2001; Robinson & Spaletta, 2010). Furthermore, several studies have shown that when apathy is included in analyses, apathy has stronger associations with cognitive and functional impairment than depression (Butterfield et al., 2010). Scheurich et al. (2008) found that individuals with depression performed as well as individuals without depression on memory and EF when they were provided with explicit

instructions on goals to strive to achieve during cognitive tasks (i.e., presumably diminishing symptoms associated with apathy). Participants' performance improved by increasing participant motivation and attention towards goal-relevant activities (Locke & Latham, 2002; Scheurich et al., 2008). Santangelo et al. (2009) found that only apathy (and not depression) predicted cognitive dysfunction. Rohling et al. (2002) also did not report differences in neuropsychological performance between individuals with and without depressive symptoms when participants who were not motivated were excluded. Together, these results suggest that goal-directed behaviour, which is diminished in individuals with apathy, is an underlying factor related to cognitive performance that should be differentiated from depression.

Although the reviewed studies posit that apathy may impair EF, working memory (WM), and memory to a greater degree than depression (Santangelo et al., 2009), depression may impact the type of emotional content that is remembered (Chepenik et al., 2007). Sad mood induction and state low self-reported mood have been associated with biases towards remembering a larger proportion of negatively-valenced stimuli (e.g., faces, words) than positively-valenced stimuli (Gilboa-Schechtman et al., 2002; Joormann, 2004; Ridout et al., 2003; Williams, Mathews, & MacLeod, 1996). Leppänen (2006) highlighted that these memory biases in MDD are complemented by exaggerated neural activity in the putamen, globus pallidus, and amygdala in response to sad stimuli (Anand et al., 2005), which may also disrupt cortico-limbic connections that help to regulate emotional responses. Depression is also associated with a relative difficulty in accessing specific autobiographical memories (AM) in response to emotion-related word cues, particularly for positive memories (Dalgleish et al., 2007). As such, a larger proportion of negatively-valenced specific autobiographical memories (e.g., Autobiographical Memory Test; Williams & Broadbent, 1986) have been found to be recalled in individuals with depression

(Williams & Dritschel, 1988; Williams & Scott, 1988). Conversely, sad mood induction and mild levels of depression have not been associated with impaired performance on tests of EF, working memory (WM), attention, or memory for neutral material (Chepenik et al., 2007). These results demonstrate that (a) sad mood may not exert an effect on overall cognition but may affect the valence of the emotional content that is remembered, and (b) factors other than sad mood (e.g., apathy) may be responsible for the cognitive changes observed in individuals with depression.

1.5 **Study Purpose**

There is a paucity of research examining the role of apathy and differentiating its role from depression on cognitive performance in young educated adults, despite the empirical support for both the prevalence of apathy and its impact on cognition and functional indicators among healthy older adults. Evaluating apathy rates and correlations with neuropsychological abilities, while also accounting for the role of depressive symptoms, in a younger cohort of healthy individuals, fills an important gap in the literature. There is a growing concern about the mental health of university students (Ceyhan et al., 2009), whereby rates of depression are estimated to be 31% in students, and range from 10% to 85% (Ibrahim et al., 2013). Given the elevated risk for depression and other mental health disorders in young adults between the ages of 18-29 (Ceyhan et al., 2009), this age group may also experience greater (and more debilitating) levels of apathetic symptomatology. Furthermore, although apathy and depression are related, healthy adults with apathy have been found to have lower perceived quality of life, lower engagement in work, and more difficulties carrying out activities of daily living than individuals without apathy, independent of their level of depression (Groeneweg-Koolhove et al., 2014). As a result, apathy may be related to poorer cognition, functional abilities, and quality of

life in young adults, regardless of the role of depressive symptoms.

The current study has three primary goals: 1) to evaluate the rate of apathy in young adults attending university and to determine whether apathy and depression can be differentiated from one another in a sample of educated young adults, 2) to clarify the role of apathy on EF, WM, and memory, over and above the role of depressive symptoms and number of fluent languages spoken, and 3) to evaluate whether depressive symptoms have a valence-related effect on memory after controlling for apathy.

First, we examined rates of apathy and depression in our sample. We hypothesized that symptoms of apathy and depression would correlate with one another to a small-to-moderate degree. Relatedly, we expected that depressive symptoms would correlate with state and trait depression ratings (but not motivation ratings) and that apathy scores would correlate with state and trait motivation ratings (but not depression ratings). Together, these relationships would help to determine whether apathy and depression are dissociable in young adults. Second, we hypothesized that apathy symptoms would predict poorer EF (i.e., Controlled Oral Word Association Task and Semantic Fluency Test), WM (i.e., Digit Span and Reading Span Test), neutral verbal memory (i.e., California Verbal Learning Test – II), and memory for affective images (Emotional Pictures Task [EPT]), independent of depressive symptoms and the number of fluent languages spoken. We also hypothesized that depressive symptoms would have a valence-related effect on memory, such that individuals with higher levels of depressive symptoms would recall a higher proportion of negatively-valenced images than positively-valenced images on the EPT and recall a higher proportion of specific memories in response to negatively-valenced than positively-valenced cues on the AMT.

We evaluated these hypotheses by examining both apathy and depression dimensionally

and by using reliable and valid neuropsychological tools across cognitive domains of EF, WM, and verbal/visual memory. Given that data were collected at a bilingual university, a large proportion of participants spoke multiple languages. We therefore also adjusted for the number of fluent languages spoken at a bilingual university and conducted subgroup analyses with exclusively participants who indicated English as their first language learned, as well-documented research has illustrated differences in cognitive performance for verbal tasks in native English and French speaking individuals (Sheppard et al., 2015; Taler et al., 2013). A better understanding of the relationships of apathy and depression across both neutral and emotional cognitive domains is important because diminished motivation can have a significant societal and personal cost, which can impact educational performance, occupational performance, and civic engagement (Vansteenkiste et al., 2005).

2. Method

2.1 Participants

One hundred sixteen (N = 116) English-speaking undergraduate students from the University of Ottawa participated in this study. Participants were recruited through the University's psychology participant pool on a password-protected website, the Integrated System of Participation in Research (ISPR). Participants (n = 20) who did not report their first language learned were also excluded from analysis. The final sample consisted of 96 undergraduate students. Thirty-two participants did not complete the EPT (discussed below in materials) as the task was added shortly after data collection commenced and these participants were thus not included in the analysis of that test.

The sample was 62.5% female, with a mean age of 19.8 years (SD = 2.3) and ranging from 17-29 years old. Participants were of Caucasian (35.4%), Asian (25.0%), Iranian (12.5%),

African American (7.3%), Indian (5.2%), and Hispanic (2.1%) descent. Sixty-three (65.6%) participants indicated English as the first language learned. Twenty-six (27.1%) reported fluency in one language, 57 (59.4%) reported fluency in two languages, and 13 (13.5%) reported fluency in 3 or 4 languages. The majority of participants did not use cannabis (63.5%). Nineteen (19.8%) participants reported using cannabis 1-2 times over the past year, 9 (9.4%) reported using cannabis monthly, 4 (4.2%) weekly, and 2 (2.1%) almost daily. Twenty-seven (28.1%) participants reported difficulty sleeping 0-1 nights per week, 44 (45.8%) reported difficulty sleeping 2-4 nights per week, and 25 (26.0%) reported difficulty sleeping 5-7 nights per week.

2.2 **Materials**

In addition to completing the questionnaires below, participants completed a sociodemographic questionnaire to identify information including sex, age, year of study, ethnicity, and first language learned.

2.2.1 ***Clinical Measures***

Apathy Evaluation Scale (AES; Marin, 1991). The Apathy Evaluation Scale is an 18-item apathy measure (Marin, 1991). The AES has four subscales; behavioural (e.g., “I get things done during the day”), cognitive (e.g., “When something good happens, I get excited”), emotional, and “other” (e.g., “I have initiative”). Scores range from 18 to 60, with higher scores indicating greater apathy. Internal consistency for the AES ranges from .76 to .94 (Clarke et al., 2011; Marin et al., 1991). Cronbach’s alpha for the AES in this study was .74.

Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). The CES-D is a 20-item questionnaire that measures depressive symptomatology over the past week (Radloff, 1977). Participants responded to questions examining sleep patterns, appetite, mood, and hopelessness, on a Likert-type scale ranging from 0 (*Rarely or none of the time*) to 3 (*Most*

or almost all of the time). CES-D scores range from 0 to 60, with higher scores indicating greater depressive symptomatology. Cronbach's alpha for the CES-D in this study was .90.

Emotional Verbal Learning Task (EVLT) State and Trait Measures (Strauss & Allen, 2013). Modified EVLT State and Trait Measures evaluated how sad, anxious, and motivated participants felt in the moment and in general using scales from 1 (*not at all*) to 7 (*extremely*). EVLT self-report state and trait ratings were highly correlated with state and trait ratings on the Positive and Negative Affect Schedule (Crawford & Henry, 2004).

2.2.2. ***Neuropsychological Measures***

Executive Function.

Controlled Oral Word Association Test (COWAT; Benton & Hamsher, 1976). The COWAT is a measure of letter (phonemic) fluency which assesses EF and verbal ability. Participants were asked to generate as many words as possible that begin with a given letter over one minute. This procedure was replicated with another two letters. Performance for letter fluency is the number of correct items generated in response to all three letters.

Semantic Fluency Test (SFT; Darvesh et al., 2005). Similar to letter fluency, category (semantic) fluency is a measure of EF and verbal ability. In the SFT, participants were asked to name as many animals as possible over one minute. Performance is measured by the number of correct items generated in response to the animal category.

Working Memory.

Digit Span Test (DST; Wechsler, 2008). The DST assesses WM capacity (Engel & Kane, 2004). Participants listened to a set of digits (one digit per second) and were asked to repeat the digits back to the examiner in a forward, backward, or sequential order. The number of digits participants were asked to recall increased sequentially from three to nine digits. Each digit had

two separate trials. Administration was terminated if participants incorrectly recalled the digits for both trials for a specific digit. Participant performance in each category was the maximum trials of digits correctly repeated forward, backward, or in sequence. The DST has high internal consistency (.89 to .94; Wechsler, 2008).

Reading Span Test (RST; Mueller & Piper, 2014). The RST, a computerized modified version of Daneman and Carpenter's (1980) task, assesses WM. Participants were presented with between 2-7 letters sequentially on a computer screen, followed by a sentence that they were asked to define as sensical or nonsensical. Participants were then asked to recall the letters previously presented in the correct order. The RST provides additional information regarding processing speed and incorporates a secondary processing component, which may highlight greater discrepancies in WM than the non-computerized DST.

Memory.

Autobiographical Memory Test (AMT; Williams & Broadbent, 1986). The AMT assesses AM in response to positive, negative, and neutral word cues. Participants were given 60 seconds to respond to each cue with a memory of a specific event (i.e., an event that happened at a specific place and time and lasted for a day or less). Four positive (i.e., happy, hopeful, excited, lively), four negative (i.e., sad, grief, upset, guilty), and four neutral (i.e., gigantic, fashion, onion, bathe) cues were presented in a random order. The Sony Voice ICDPX333 was used to record responses. AMT inter-rater reliability ranges from .78 to .96 (Griffith et al., 2012).

California Verbal Learning Test - Second Edition (CVLT-II; Delis et al., 2000). The CVLT-II measures verbal learning, recall, and recognition of words from four unrelated semantic categories. Participants were asked to recall words presented from a 16-item word list to measure verbal acquisition over five trials. After presentation of a second word list, participants were

asked to recall words from the first list to evaluate short-delay free and cued recall. After a 20-minute delay, participants were asked to recall words from the first word list to evaluate long-delay free and cued recall. Test-retest reliability ranges from .80 to .84 (Delis et al., 2000).

Emotional Pictures Task (EPT; Ack Baraly et al., 2019; Lang et al., 2008). To examine visual memory for affective images, we followed the protocol used by Ack Baraly et al. (2019). Participants were presented with 34 images in a row from the International Affective Pictures System (IAPS; Lang et al., 2008). Eleven images were negatively valenced, 11 were positively valenced, and 12 were neutral. The images were matched on arousal. Participants were asked to recall the images immediately after they were presented and after a 20-minute delay.

2.3 **Procedure**

Participants provided their informed consent to participate and were compensated with course credit. In block one, participants completed the CVLT-II (neutral verbal memory), AMT (autobiographical memory), RST (WM), followed by the CES-D (self-report depression scale). In block two, participants completed the EPT (visual memory for affective images), COWAT (letter fluency), SFT (category fluency), DST (WM), and AES (self-report apathy scale). Participants also completed a sociodemographic questionnaire indicating their age, sex, education, ethnicity, and language abilities. The block order was counterbalanced across participants.

2.4 **Data Analysis**

Our most complex analysis for the first component of the study was a multiple regression, so we opted to use that to calculate our power analysis. A power analysis for a multiple regression analysis (single regression coefficient) with a small to medium effect size (f^2 = .09), .05 alpha, and .80 power indicated a sample size of at least 90 participants was needed

(Faul et al., 2009). Participants were overrecruited to ensure adequate power after removing outliers and missing data.

SPSS version 21, 64-bit edition, was used for data analysis (IBM Corp, 2012). There were 5 (0.26%) missing cells from the AES, and 51 (0.62%) missing cells from the CES-D. Data were missing completely at random, $\chi^2 = 445.247$, df = 439, $p = .408$, and were imputed using expectation maximization. All participants passed the reliable digit span, an indicator of performance validity (Shroeder et al., 2012). Given the narrow age range of the sample, raw scores were used for analysis. All variables had acceptable skewness (< 2) and kurtosis (< 4; Kline, 2005). Scores were analyzed as continuous variables.

First, Spearman correlations were calculated to examine the relationship between apathy and depression to determine whether or not apathy and depression could be differentiated in our sample. Correlations between apathy (AES) and depression (CES-D) with state and trait measures of both motivation and sadness (EVLT-STM) were then conducted to examine convergent and divergent validity of the AES and CES-D.

Next, we examined whether apathy predicted neuropsychological performance in young adults. In order to reduce the number of analyses, we calculated composite scores for each cognitive domain. Similar to Christodoulou et al. (1998), raw scores were converted to standardized residual scores (*z* scores), controlling for the relationships with depressive symptoms and the number of fluent languages spoken. These standardized residuals were computed using separate linear regressions with depression scores and the total number of self-reported fluent languages as independent variables, and each raw cognitive score as the dependent variable. The *z* scores were then averaged across variables within each domain (i.e., EF, WM, verbal memory, visual memory; see Table 1) to generate a composite score. Multiple

linear regressions with apathy predicting composite neuropsychological domain performance were then performed.

To conduct a double dissociation examining the role of depressive symptoms on cognition, standardized residuals for each cognitive test were calculated controlling for apathy symptoms and the number of fluent languages spoken. These residuals were then averaged to compute a composite score for each domain. Then, multiple linear regressions with depressive symptoms predicting composite neuropsychological domain performance were performed.

Pearson correlations between apathy and depression with all cognitive measures were also reported. The Benjamini-Hochberg (1995) procedure with a false discovery rate of 5% was used to control for multiple comparisons.

To examine whether depressive symptoms moderated the relationship between valence (i.e., positive and negative) and specificity of memories (i.e., number of specific memories) recalled on the AMT, we used methods to conduct moderated regressions using repeated measures variables outlined by Montoya (2019). With a medium effect size ($f^2 = .16$), .05 alpha, and .80 power, G*Power indicated a sample size of at least 64 participants was needed (Faul et al., 2009). Proportions of specific memories for positively and negatively-valenced cues on the AMT were calculated by dividing the number of specific memories recalled by four for each valence (reflecting the total number of valence-related cues).

The MEMORE macro (Montoya, 2019; Montoya & Hayes, 2017) was also used to evaluate whether depressive symptoms moderated the relationship between valence (i.e., positive and negative) and recall of images (i.e., number recalled) on the EPT on the immediate and delayed recall trials. Proportions of images recalled that were either positively or negatively-valenced on the EPT were calculated by dividing the number of images correctly recalled by 11

(the number of valence-related images presented). Moderation models were run both with and without adjusting for apathy. To examine the double dissociation, all moderated regressions were similarly conducted with apathy symptoms.

3. **Results**

3.1 **Descriptive Characteristics**

Table 3.1 illustrates descriptive statistics for all neuropsychological and psychological variables.

Table 3.1

Descriptive Statistics for Psychological and Neuropsychological Variables

Variable	*M*	*SD*	Min	Max	α (self-report scales)
Psychological Variables					
Apathy Evaluation Scale	29.83	5.12	19	44	.74
# above clinical cut-off for apathy (%)	21 (21.9)				
Center for Epidemiologic Studies Depression Scale	16.12	9.40	.67	40	.89
# above clinical cut-off for depression (%)	29 (30.2)				
Neuropsychological Variables					
Executive Function					
Controlled Oral Word Association Test[a]	33.96	13.73	3	60	
Semantic Fluency Test	19.08	7.13	1	36	
Working Memory					
Reading Span Test[a]					
Total # correct digits recalled					
Reaction time (milliseconds)	15.30	4.79	5	24	
Sentences correctly	1682.27	570.58	847.24	4382.74	
identified as T/F (%)	95.00	4.00	80	100	
Digit Span Test					

Digits Forward	10.07	2.14	6	15
Digits Backward	8.71	2.30	4	15
Digits Sequenced	9.34	1.91	5	16
Verbal Memory				
California Verbal Learning Test – II				
Short-delay free recall	11.15	3.28	0	16
Long-delay free recall	11.56	2.60	5	16
Visual Memory				
Emotional Pictures Task[b]				
Short-delay free recall overall	12.61	3.71	6	22
Positive	4.80	1.61	1	10
Negative	5.29	1.91	2	10
Neutral	2.52	1.50	0	6
Long-delay free recall overall	14.94	4.24	7	26
Positive	5.45	1.81	2	10
Negative	6.22	1.98	2	11
Neutral	3.25	1.68	0	8
Autobiographical Memory				
Autobiographical Memory Test[c]				
Total specific	10.29	1.57	4	12
Positive	3.35	.85	0	4
Negative	3.62	.63	2	4
Neutral	3.27	.84	1	4

Note. Apathetic = number above the clinical cut-off for the AES (i.e., greater than or equal to 34; Sagen et al., 2010); Depressed = number above the clinical cut-off for the CES-D (i.e., greater than or equal to 21; Henry et al., 2018).
[a]There were 4 missing cases in the sample.
[b]There were 30 cases missing in the sample.
[c]There was 1 missing case in the sample.

3.2 **Differentiation of Apathy and Depressive Symptoms**

Scores on the AES and the CES-D shared a small correlation, $r_s(94) = .29$, $p = .005$. Using cut-offs recommended by Sagen et al. (2010) and Henry et al. (2018), 21.9% of the sample scored

above the clinical cut-off for apathy[5] (i.e., AES ≥ 34), and 30.2% of the sample scored above the clinical cut-off for depression (i.e., CES-D ≥ 21). Using these cut-offs, 7.3% (n = 7) scored above the clinical cut-offs for both apathy and depression, 14.6% (n = 14) scored above the clinical cut-off for only apathy, 23.0% (n = 22) scored above the clinical cut-off for only depression, and 55% (n = 53) of individuals did not score above any clinical cut-offs. Males reported greater apathy severity (M = 31.5, SD = 4.7) than females (M = 28.8, SD = 5.1), $F(1,94) = 6.53$, $p = .012$, but there were no differences in apathy classification ($\chi^2 = 1.2$, $p = .279$).

Spearman correlations investigating discriminant and convergent validity of the CES-D and AES were conducted. A measure of state apathy from the adapted EVLT (Strauss & Allen, 2013; "In this moment, on a scale from 1[*not at all*] to 7 [*extremely*], how motivated do you feel right now?") correlated with the AES, $r_s(93) = -.33$, $p < .001$, but not with the CES-D, $r(93) = -.12$, $p = .247$. A measure of trait apathy from the adapted EVLT ("In general, on a scale from 1[*not at all*] to 7 [*extremely*], how motivated do you feel in general?") correlated with the AES, $r_s(93) = -.51$, $p < .001$, but not with the CES-D, $r_s(93) = -.19$, $p = .069$.

A measure of state sadness from the EVLT (Strauss & Allen, 2013; "In this moment, on a scale from 1[*not at all*] to 7 [*extremely*], how sad do you feel right now?") correlated with the CES-D, $r_s(93) = .51$, $p < .001$, but not with the AES, $r_s(93) = .14$, $p = .183$. A measure of trait sadness from the EVLT ("In general, on a scale from 1[*not at all*] to 7 [*extremely*], how sad do you feel in general?") correlated with the CES-D, $r_s(93) = .52$, $p < .001$, but not with the AES, $r_s(93) = .13$, $p = .199$.

[5]Independent samples *t*-tests revealed no differences between individuals with apathy (AES ≥ 34) and without apathy (AES < 34) on difficulties sleeping ($t[93] = -1.30$, $p = .197$), presence of a physical health condition ($t[25.25] = -1.43$, $p = .164$), or frequency of cannabis use ($t[93] = .66$, $p = .511$).

3.3 **Relationships between Apathy, Depression, and Neuropsychological Performance**

Pearson correlations between apathy symptoms, depressive symptoms, number of self-reported languages spoken, and cognitive performance are reported in Table 3.2. Greater apathy was related to poorer performance on category fluency and more specific autobiographical memories recalled, but these relationships were not significant after using the Benjamini-Hochberg procedure with a 5% false discovery rate to correct for multiple comparisons. Depressive symptoms did not correlate with any cognitive measure. A higher number of spoken languages was correlated with a larger number of images recalled after a short and long delay, as well as less specific autobiographical memories, but only the relationship between greater apathy and a larger number of emotional images recalled over a long delay remained significant after the multiple comparison correction.

Table 3.2

Pearson Correlation Coefficients Between Psychological, Neuropsychological and Language Variables

	Apathy Symptoms	Depressive Symptoms	# Languages Spoken	English as First Language Learned
Apathy Symptoms (AES)	---	---	---	---
Depressive Symptoms (CES-D)	.25 (.012)	---	---	---
# Languages Spoken	-.19 (.064)	-.09 (.385)	---	---
English as First Language Learned	-.01 (.960)	-.12 (.227)	.47 (<.001)	---
Letter Fluency (COWAT)	-.14 (.193)	<.01 (.986)	-.06 (.575)	-.24 (.019)
Category Fluency (SFT)	-.20 (.049)	-.01 (.909)	.043 (.680)	-.21 (.038)
Reading Span (RST)	-.19 (.065)	-.02 (.843)	-.12 (.277)	-.26 (.013)
Digit Span Total (DST)	.08 (.438)	.11 (.269)	-.20 (.056)	-.22 (.033)
Short-Delay Recall (SD-CVLT-II)	.04 (.705)	-.01 (.951)	.030 (.770)	-.01 (.906)
Long-Delay Recall (LD-CVLT-II)	-.02 (.830)	-.06 (.589)	.002 (.984)	-.081 (.433)
Short-Delay Images (SD-EPT)[a]	-.16 (.207)	-.20 (.110)	.27 (.031)	-.17 (.182)
Long-Delay Images (LD-EPT)[a]	-.17 (.176)	-.17 (.167)	.35 (.004)	-.05 (.706)
Specific Memories (AMT)	.21 (.041)	.12 (.244)	-.24 (.017)	-.28 (.006)

Note. $n = 96$. p values are included in parentheses.
[a] $n = 66$.

Linear regressions of apathy with composite domain scores showed that apathy was not related to performance across any neuropsychological domain, including EF, working memory, verbal memory, visual memory, or autobiographical memory, both with and without using the Benjamini-Hochberg procedure with a 5% false discovery rate to correct for multiple comparisons (Table 3.2).

Additionally, we reran analyses to account for potential variables that might impact cognitive performance. First, given the impact that English as a second learned language may have on verbally-mediated cognitive performance (Mann et al., 2013), analyses were recalculated in the subgroup who reported English as their first language learned (n = 63). The subgroup analysis did not yield any different interpretations than the main analysis (all *p*s > .108). Second, poor sleep may also be negatively related to cognitive performance (Alhola & Polo-Kantola, 2007). There were, however, no differences in the relationships observed between apathy and cognition between participants who indicated difficulties sleeping 0-3 times per week with participants who indicated difficulties sleeping 4 or more times per week (all *p*s > .134).

Table 3.2

Beta Weights and Models of Linear Regressions for Apathy Predicting Cognitive Performance

Neuropsychological Domain	AES	Model
Executive function	-.17	$F(1,93) = 2.92$, $p = .090$, Adj. $R^2 = .02$
Category Fluency		
Letter Fluency		
Working memory	.13	$F(1,91) = 1.67$, $p = .200$, Adj. $R^2 = .01$
Digit Span		
Reading Span Test		
Verbal memory		
CVLT-II	-.05	$F(1,91) = 1.67$, $p = .200$, Adj. $R^2 = .01$
Short-delay free recall		
Long-delay free recall		
Visual memory	-.05	$F(1,63) = 0.17$, $p = .684$, Adj. $R^2 = -.01$
Emotional Pictures Task		
Short-delay free recall		
Long-delay free recall		
Autobiographical Memory	.13	$F(1,93) = 1.67$, $p = .199$, Adj. $R^2 = .01$
AMT		
Overgeneral memories recalled		

Note. CES-D = Center for Epidemiologic Studies Depression Scale; AES = Apathy Evaluation Scale; CVLT-II = California Verbal Learning Test – Second Edition; AMT = Autobiographical Memory Test.
*Significant using the Benjamini-Hochberg (1955) procedure with a false discovery rate of 5% to control for multiple comparisons.

Linear regressions of depressive symptoms with composite domain scores were conducted to determine a possible double dissociation between apathy and depressive symptoms on cognition. Depressive symptoms did not predict performance across any neuropsychological domain, including EF (p = .678), WM (p = .284), verbal memory (p = .730), visual memory (p = .195), or autobiographical memory (p = .096). The subgroup analysis for native English speakers did not yield any different interpretations than the main analysis and therefore are not reported.

3.4 **The Role of Depressive Symptoms on Memory Valence**

To examine whether the level of depression affected recall of negative compared to positive valenced memories, we used a moderated regression for repeated-measures design used Model 2 of the MEMORE macro developed by Montoya (2019). Again, as suggested by Montoya (2019), because we were interested specifically and had predictions about the conditional effects of depression on valenced memory, we examined conditional effects regardless of whether the initial model was significant.

Autobiographical Memory

The model of depressive symptoms predicting the difference in proportion of negatively-valenced to positively-valenced specific memories was not significant, $F(1,93) = .62$, $p = .433$. However, the model indicated an effect of valence on specificity of memory recalled at specific levels of depressive symptoms. At low levels of depressive symptoms (one SD below the mean of the sample; CES-D = 6.62), there was no conditional effect of valence on specificity of memories, $t(93) = 1.35$, $p = .180$. At a CES-D score of 16.03 (mean of the sample), there was a conditional effect of valence on the specificity of memories recalled, $t(93) = 2.70$, $p = .008$, such that 6.84% more memories were specific to negatively-valenced cue words than to positively-valenced cue words. At a CES-D score of 25.44 (one SD above the mean of the sample), there

was a conditional effect of valence on the specificity of memories recalled, $t(93) = 2.47$, $p = .015$, such that 8.84% more memories were specific to negatively-valenced cue words than to positively-valenced cue words. Put differently, high levels of depressive symptoms were associated with more overgeneral memories in association with positive compared to negative cue words.

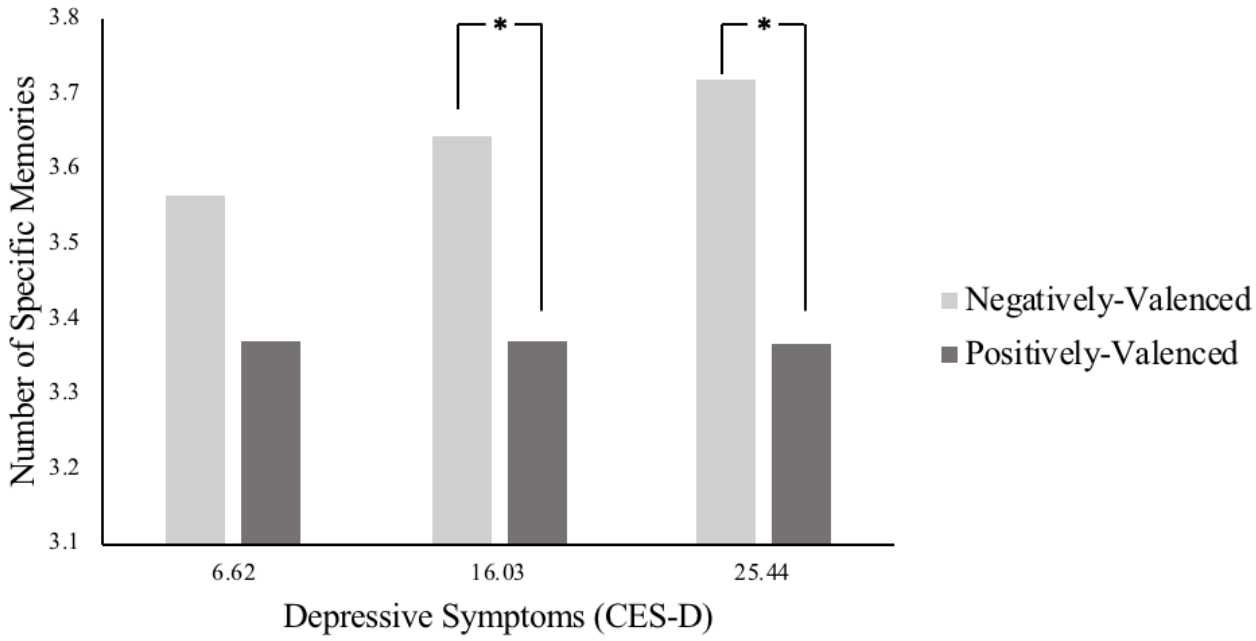

Figure 3.1. Moderation of depressive symptoms on the relationship between valence and specificity of memories recalled on the AMT ($n = 95$). 6.62 = 1 SD below the mean, 16.03 = sample mean, 25.44 = 1 SD above the mean. Error bars represent standard errors.
* indicates $p \leq .05$.

The model was also rerun controlling for apathy and the number of self-reported fluent languages. Again, higher levels of depressive symptoms (i.e., at the mean and 1 SD above the mean) had conditional effects on the relationship between valence and specificity of memory recalled (ps $\leq .008$). A double dissociation with apathy as the moderator (controlling for depressive symptoms and the number of self-reported fluent languages) revealed that apathy was not related to the difference in proportion of negatively-valenced to positively-valenced specific memories, $F(1,93) = .05$, $p = .824$.

Immediate Memory for Affective Images

In the subgroup of individuals who completed the EPT (n = 64), the model for depressive symptoms as a moderator of the relationship between valence (i.e., positive and negative) and number of images recalled on the immediate recall trial (EPT) indicated no effects, $F(1,64) = 0.19$, $p = .667$. There was no conditional effect of depressive symptoms at any level on the relationship between valence and the number of images recalled on the immediate recall trial (all ps > .065).

A double dissociation with apathy as the moderator (controlling for depressive symptoms and the number of self-reported fluent languages) similarly revealed that apathy was not related to the difference in proportion of negatively-valenced to positively-valenced images recalled on the immediate recall trial, $F(1,64) = 0.36$, $p = .551$.

Long-delay Memory for Affective Images

Using the sample of individuals who completed the EPT (n = 64), the overall linear regression model of depressive symptoms predicting the difference in proportion of negatively-valenced to positively-valenced images for delayed recall was not significant, $F(1,64) = 0.16$, $p = .686$. However, the model indicated an effect of valence on the number of images recalled on the delayed recall trial (EPT) at specific levels of depressive symptoms. At a CES-D score of 6.63 (one SD below the mean of the sub-sample), there was no conditional effect of valence on the number of images recalled on the delayed recall trial, $t(64) = 1.77$, $p = .082$. At a CES-D score of 15.30 (mean of the sub-sample), there was a conditional effect of valence on the number of images recalled on the delayed recall trial, $t(64) = 2.92$, $p = .005$, such that a higher proportion (7.02%) of negatively-valenced images were recalled than positively-valenced images after a 20-minute delay. At a CES-D score of 23.97 (one SD above the mean of the sub-sample), there was

a conditional effect of valence on the number of images recalled on the delayed recall trial, $t(64) = 2.34$, $p = .022$, such that a higher proportion (8.01%) of negatively-valenced images were recalled than positively-valenced images after 20 minutes.

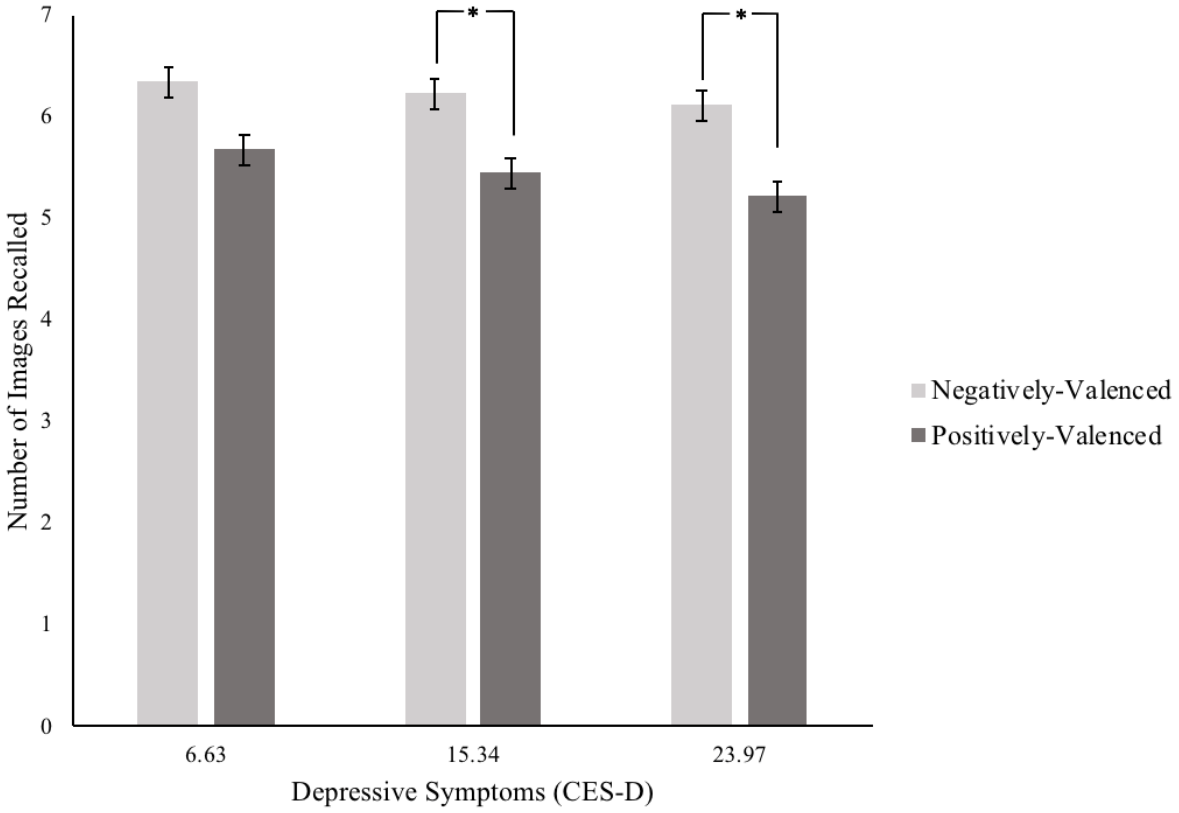

Figure 3.2. Moderation of depressive symptoms on the relationship between valence and number of images recalled on the delayed recall trial of the EPT ($n = 64$). 6.63 = 1 SD below the mean, 15.34 = sample mean, 23.97 = 1 SD above the mean. Error bars represent standard errors. * indicates $p \leq .05$.

After controlling for symptoms of apathy and number of fluent languages spoken, high levels of depressive symptoms (i.e., at the mean and 1 SD above the mean) continued to have conditional effects on the relationship between valence and images recalled (all ps $\leq .044$). A double dissociation with apathy as the moderator (controlling for depressive symptoms and the number of self-reported fluent languages) revealed that apathy was not related to the difference in proportion of negatively-valenced to positively-valenced images recalled on the EPT, $F(1,64)$

= 0.57, p = .452.

4. Discussion

To the best of our knowledge, our study is the first to examine and differentiate the role of apathy and depressive symptoms on cognition in young adults. The current study had three primary goals: (1) to examine the frequency of apathy in young adults attending university and to determine whether apathy and depression could be differentiated from one another, (2) to clarify the role of apathy on neuropsychological performance after accounting for the role of depressive symptoms and number of languages spoken, and (3) to evaluate whether depressive symptoms had a valence-related effect on memory after accounting for apathy and number of fluent languages.

We found that 22% of our sample reported clinically significant levels of apathy (AES ≥ 34; Sagen et al., 2010), which is higher than Onyike et al. (2007), Lyketsos et al. (2002), and Ishizaki and Mimura's (2011) reported apathy prevalence rates of 1.4%, 3.2%, and 7.0%, respectively, but similar to Clarke et al.'s (2010) 23.7%, in healthy older adults. Though we expected higher rates of apathy in this population given the elevated risk for mental health disorders in young adults (Ceyhan et al. 2009), the prevalence of apathy surpassed our expectations. That said, it is also important to note that the highest reported score on the Apathy Evaluation Scale was 44 out of a possible 72, indicating that mild to moderate levels of apathy, and not severe, were reported in this sample.

In the current sample, 30% of students also reported clinically elevated levels of depression. Over the past few years, the prevalence of depression in university students has increased, warranting a growing concern about the mental health of university students (Ceyhan et al., 2009). The rate reported in our study is similar to Ibrahim et al.'s (2013) weighted mean

depression prevalence of 31% of university students. Financial concerns, academic pressure, fear of academic failure, and health concerns may also contribute to elevated psychological distress (Ibrahim et al., 2013). Some research also suggests that constructs using community cut-offs may also be inflated in university students (Fernandes et al., 2018; Ibrahim et al., 2013). Furthermore, although study recruitment occurred on a steady basis throughout the academic year, self-reported mental health difficulties may have been overestimated due to seasonal fluctuations and academic pressures (Rastad, Ulfberg, & Sjödén, 2006).

Notably, apathy and depressive symptoms shared a small-to-moderate correlation in our sample of young adults. State and trait apathy correlated with AES score and not CES-D score, whereas state and trait sadness correlated with CES-D score and not AES score. These findings support the convergent and discriminant validity of the AES and CES-D, exemplifying that these constructs can be successfully differentiated from one another in young educated adults.

Contrary to our hypotheses, apathy was not related to EF, WM, verbal memory, or visual memory for affective images, in young adults. Consistent with our hypotheses, depressive symptoms were not related to any neuropsychological performance, but were related to the emotional content of what was remembered, such that individuals with higher levels of depressive symptoms recalled a greater proportion of specific negatively-valenced AMs than specific positively-valenced AMs on the AMT, and a greater proportion of negatively-valenced images than positively-valenced images after a delay on the EPT.

In older adults, apathy symptomatology has been found to correlate with EF, processing speed, constructional praxis, memory, and metacognition (Clarke et al., 2010; Montoya-Murillo et al., 2019). However, in our sample of educated young adults, apathy was only related to category fluency, and this relationship was not significant after implementing the Benjamini-

Hochberg procedure to correct for multiple comparisons. This may have occurred for a variety of reasons. First, it is possible that the mild-to-moderate severity of apathy reported in the sample was not severe enough to impact EF, WM, or memory. If a broader range of symptomatology was reported, a relationship between greater apathy and poorer cognition may have been observed. It may also be possible that the composite score calculations diluted the impact of measures that may have been more sensitive in assessing cognitive abilities. For instance, complex WM span tasks, including the RST, have shown higher correlations with higher-order cognitive tasks (i.e., EFs) than simple WM span tasks, such as the DST, which measures short-term storage capacity (Conway et al., 2005). Importantly, these findings may simply reflect that mild-to-moderate symptoms of depression and apathy exert a minimal to negligible impact on EF, WM, and memory in young, educated adults. Similar findings have been reported in outpatients with mild depressive and anxiety symptomatology (Morasco, Gfeller, & Chibnall, 2006; Tsushima et al., 2005). Studies identifying associations between psychopathology and cognitive function have also indicated that the severity of a mental health disorder, rather than the presence of symptoms alone, may account for a greater percentage of the variance in cognitive function (Burt et al., 1995; Christensen et al., 1997).

In terms of depressive symptoms, we found significant conditional effects of valence on specificity of memories recalled on the AMT, such that at higher levels of depressive symptoms, negatively-valenced cues generated a greater proportion of specific memories than positively-valenced cues. This finding is consistent with literature illustrating that individuals with depression recalled fewer specific memories (i.e., more overgeneral memories) for positive than negative cues on the AMT (Williams et al., 1996). Again, at low levels of depressive symptoms, there was no impact of valence on specificity of memories recalled. There was also a significant

conditional effect of valence on the number of affective images recalled on the delayed recall trial of the EPT, such that at higher levels of depressive symptoms, a higher proportion of negative images than positive images were recalled. Again, at low levels of depressive symptoms, there was no impact of valence on the memories recalled. It is important to note that even though these differences were consistent, the actual differences in our non-clinical sample were small (7-8%) and were accompanied by lots of variability. In addition, only a subsample of individuals completed the EPT, as the task was added after data collection commenced. Furthermore, though in the same direction, no effects on the immediate recall trial were observed. This may be because the impact of affective information tends to increase with longer retention delays (Kensinger, 2009). Overall, these patterns are consistent with the literature positing that more severe depression is associated with greater valence biases, whereas mild levels are associated with mild or no valence bias (Robinson & Spalletta, 2010).

A number of limitations are worth noting. First, our sample was comprised of young university students of predominantly White and Asian backgrounds. The present results should not be generalized to groups of individuals that differ greatly from the current population of interest, such as older adults, individuals with annual family incomes below $70,000 (less likely to attend university), or individuals with more severe psychopathology (e.g., inpatients). The combination of a smaller sample size with a restricted range of psychopathology may have reduced our power to detect more subtle differences in cognitive ability. Additionally, the internal consistency of the AES was also slightly lower (.74) than other studies (.76-.94: Clarke et al., 2011; Marin, 1991), however, reliability for the AES still fell in the acceptable range. Reliability also remained in the acceptable range after removing individuals who did not report English as their first language in the subgroup analyses. Lastly, although cognitive domains most

commonly correlated with apathy (i.e., EF, WM, memory) were assessed, measures of visuospatial ability, language, and information processing speed were not addressed in this study.

Despite these limitations, this study has a number of strengths. To the best of our knowledge, this is the first study to investigate the role of apathy on cognition in a sample of young adults; it also adjusts for the role of depressive symptoms and number of fluent languages spoken at a bilingual university. Valid and reliable measures of EF, WM, and mood were utilized (Benton & Hamsher, 1976; Darvesh et al., 2005; Marin, 1991; Mueller & Piper, 2014; Radloff, 1977; Wechsler, 2008). Furthermore, indices of neutral memory, memory for affective images, and AM were employed (Ack Baraly et al., 2019; Delis et al., 2000; Lang et al., 2008; Williams & Broadbent, 1986). No floor or ceiling effects were observed on psychological or neuropsychological measures. A number of secondary analyses were also conducted to ensure that important confounds including medical conditions, sleep quality, and cannabis use, did not impact our findings. Taken together, these provisions ensured greater comprehensiveness and methodological rigor while addressing an important gap in the psychological literature.

The results of this study suggest that apathy is prevalent, even in educated young adults, and is experienced at least to a moderate degree of severity. The high frequency estimates of approximately 1 in 5 individuals suggest that apathy is a public health problem for this age group, though it is likely underassessed (and thereby undertreated) in this population. As apathy is differentiable from depression, it may be beneficial to include apathy screening in psychological evaluations even in the absence of significant depression. Researchers may benefit from paying closer attention when studying cognitive functioning within the context of emotion-based difficulties, particularly depression, to differentiate effects based on apathy (e.g., low motivation) and depression. Future research may also determine whether distinguishing between

apathy from depression has important implications for psychological treatment.

These findings support the notion that mild-to-moderate symptoms of depression and apathy exert a minimal to negligible impact on EF, WM, and memory in young educated adults. As a result, neuropsychologists who assess cognition in this population are encouraged to explore reasons other than psychopathology to explain deficits, particularly when evaluating clients who report mild affective or mood symptoms. Still, future research should aim to explore whether more severe apathetic symptomatology is more strongly correlated with cognition than revealed in our sample of young adults.

The results also highlight that higher levels of depressive symptoms bias memory recall towards negative information. Affective verbal fluency (e.g., Emotional Verbal Fluency; Sass et al., 2013) and verbal affective memory (e.g., Cognitive-Affective Verbal Learning Test; Considine, Keatley, & Abeare, 2016) tasks may also be integrated in future research to explore whether depressive symptoms may moderate the relationship between valence and performance. Researchers may also consider incorporating indices of functional ability, self-efficacy, and wellbeing to evaluate their correlations with apathy symptoms in young adults, as performed in older adults (Tierney et al., 2018).

The growing interest in understanding the psychiatric, neurobiological, and neuropsychological mechanisms that underlie and correlate with apathy coincides with its recognition as a potential treatment target across psychiatric disorders, cerebrovascular diseases, and neurodegenerative diseases. A greater appreciation of the implications of apathy on daily living and experiences of pleasure may help to determine whether the promotion of meaningful activities and pursuit of wellbeing may be used to improve treatment for apathy in young adults.

6. Acknowledgments

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7. Contributions

The primary author, Keera N. Fishman, was involved in study conceptualization, methodology, recruitment, funding acquisition, data collection, completed data analysis, and wrote the manuscript.

Dr. Andrea R. Ashbaugh, research supervisor, met with Ms. Fishman frequently to discuss study conceptualization, research questions, methodology, data collection, data analysis, and interpretation. Throughout the process, Dr. Ashbaugh provided guidance and recommendations regarding article content and edited the full manuscript.

Titania Dixon-Luinenburg, Zoey Wilton, and Sarah Bethune provided helpful assistance with data collection, data entry, and data management.

CHAPTER 4: The Use of Goal-setting Interventions to Improve Cognitive Performance in Stroke Survivors

i. Preamble

In Chapter 2 (Articles 1 and 2), I found that apathy was negatively associated with memory and executive function in stroke patients. Despite the detrimental impact of reduced goal-directed behaviours and goal-directed cognitions on activities of daily living, rehabilitation, and cognition in stroke patients, interventions for increasing motivation to improve subsequent cognitive outcomes have been rarely examined in stroke patients. Given the empirical support for setting specific, challenging (but reasonable), and measurable goals for improving performance, goal-setting strategies may serve as a method of improving cognitive performance in stroke patients by increasing goal-directed behaviours and attention (Locke & Latham, 2002). Notably, although healthcare professionals report valuing goal-setting during stroke rehabilitation, there is a gap in implementing evidence-based goal-setting strategies into practice, in honing goal-setting strategies for use beyond physical and functional recovery, and in implementing goal-setting approaches in the chronic phase (≥ 3 months) after stroke. Thus, the final study of the current dissertation was a randomized controlled trial that explored the utility of goal-setting to enhance memory, attention/working memory, and executive function performance relative to standard instructions in patients in the chronic phase after stroke. If goal-setting instructions enhanced cognitive performance, it may indicate that treatments targeting apathy (as opposed to sad mood in depression) could serve as a novel approach to both improving cognitive outcomes and enhancing patient quality of life after stroke. With a substantially smaller word limit for this journal and consideration of the intended clinical audience, the authors opted to not include results related to apathy in the submitted publication. I have added findings from this study in relation to apathy to the “Additional Information” section following this manuscript.

Article 4

Goal-setting improves cognitive performance in a randomized trial of chronic stroke survivors[6]

Published
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ABSTRACT

Background and Purpose: Cognitive impairment after stroke, especially executive and attention dysfunction, is common, negatively affects daily functioning, and has limited treatment options. A single-blind, parallel-design, randomized controlled trial was used to examine the impact of goal setting on poststroke cognitive performance. **Methods:** Stroke survivors (*N*=72; Mean age=68.38 [*SD*=11.84], 69.4% male) in the chronic phase (≥ 3 months) after stroke from an academic stroke prevention clinic were randomly assigned to receive goal-setting instructions (*n*=36) or standard instructions (*n*=36) after completing baseline cognitive measures of executive function (primary outcome), attention/working memory, verbal learning, and verbal recall. **Results:** A one-way mixed multivariate analysis of covariance (MANCOVA) found a group by instructional manipulation interaction effect for executive function (Wilks λ=0.66; F[3,66]=11.30; $P \leq 0.001$; η^2_p=0.34), after adjusting for age and years of education. After similar adjustment, attention/working memory (Wilks λ=0.86; F[5,63]=2.10; P=0.043; η^2_p=0.16) and verbal learning (F[1,60]=5.81; P=0.019; η^2_p=0.09) also showed improvement after instruction but not verbal recall (Wilks λ=0.95; F[1,56]=2.82; P=0.099; η^2_p=0.05). There were no adverse events. **Conclusions:** Goal-setting improved executive function, attention/working memory, and learning in a heterogeneous sample in the chronic phase after stroke. This suggests that >3 months after stroke, vascular cognitive impairment is not a fixed deficit; there is a motivational contributor. Brief treatments targeting goal-oriented behaviour and motivation may serve as a novel approach or adjunct treatment to improve cognitive outcomes after stroke. Future research should investigate the use of goal-setting on functional outcomes (e.g., iADLs, vocational function) in this population, highlighting new potential avenues for treatment for vascular

cognitive impairment. **Clinical Trial Registration URL:** http://www.clinicaltrials.gov. Unique identifier: NCT03511300.

Keywords: Goal-setting, Cognition, Motivation, Executive Function; Neuropsychology, Cognitive Rehabilitation, Stroke/Cerebrovascular disorders

Non-standard Abbreviations and Acronyms

EF = Executive Function
RCT = Randomized Controlled Trial
VCI = Vascular Cognitive Impairment
COWAT = Controlled Oral Word Association Test
SFT = Semantic Fluency Test
DST = Digit Span Test
TMT = Trail Making Test
CVLT-II = California Verbal Learning Test – Second Edition
AES = Apathy Evaluation Scale
CES-D = Center for Epidemiologic Studies Depression Scale
RCI = Reliable Change Index

Goal-setting improves cognitive performance in a randomized trial of chronic stroke survivors

1. **Introduction**

Cognitive impairment after stroke is common, affecting 20-50% of stroke survivors[1,2]. Although the pattern of post-stroke cognitive deficits may encompass any domain, the most commonly affected areas include executive function (EF), processing speed, and attention[3]. Post-stroke cognitive impairment is often described as pervasive[1,4], and is associated with higher mortality[1], decreased independence in instrumental activities of daily living (iADLs)[5], and poorer quality of life[4]. Post-stroke cognitive impairment is also associated with greater apathy[6] and depression[1], contributing to poorer prognosis[1]. Notably, cognitive impairment has been found in over 50% of stroke survivors even with excellent clinical recovery[5].

Although restoration of physical function in stroke is widely researched, demonstrating significant improvements following physical rehabilitation, strategies for improving cognitive function have received substantially less attention. There are few effective options for treating post-stroke cognitive impairment[2], and few studies using randomized designs[2,7]. Cochrane reviews examining memory and EF interventions highlighted poor quality of reporting in many studies, the use of inconsistent outcome measures, and small sample sizes, concluding there was insufficient evidence to support or refute the effectiveness of cognitive rehabilitation (remediation or compensation) on function and cognition[7,8]. These reviews supported conducting high quality randomized controlled trials (RCTs) to evaluate whether cognitive rehabilitation interventions are more effective in improving cognition, quality of life, and iADLs than waitlist or sensorimotor interventions[7,8]. Some promising results have been reported for interventions which focus on meta-cognitive training to promote self-awareness of deficits and self-monitoring

of daily activities to improve EF, including enriched environments[9], strategy training[10,11], and goal management training[12]. Many of these interventions involve training over multiple sessions (e.g., 8 weeks, 1 year) and do not demonstrate objective improvements[7]. Few studies have specifically targeted motivation[10].

Locke and Latham's[13,14] goal setting theory postulates that performance will improve when specific, challenging (but attainable), and measurable goals are set, as opposed to easy, vague, or non-existent goals. They posit that goal setting impacts performance by increasing motivation and directing attention towards goal-relevant activities[14]. Unfortunately, goals for cognitive function are not always well defined or measured in stroke rehabilitation[15]. To date, only one study has examined the utility of goal-setting instructions to improve cognitive performance in individuals with any type of brain damage[16]. Using Locke and Latham's[14] goal-setting paradigm, they demonstrated that goal-setting instructions improved performance on one non-validated computerized arithmetic task relative to standard instructions in individuals with any type of brain damage in the acute phase of injury.

Cognitive impairment after stroke is often conceptualized as a fixed or static consequence of focal neuronal injury, as limited evidence of rehabilitation strategies (e.g., computer training) to improve cognition currently exist in the literature[7]. If a very brief, 20-second intervention could improve cognitive performance, this could lead to new avenues for treatment of vascular cognitive impairment (VCI).

The current study was an RCT to determine whether a simple intervention targeting goal-setting could improve cognitive performance across commonly affected domains[2,17] in the chronic phase of stroke. We expanded on Gauggel and Billino[16] by exploring a broader range of cognitive domains including EF (primary outcome), attention/working memory and verbal

memory (secondary outcomes), and incorporating validated cognitive measures in our assessment[17]. We hypothesize that goal-setting instructions would improve cognitive performance compared to standard instructions across these cognitive domains. Given that motivation and EFs (e.g., planning, initiating, problem solving) share overlapping neural circuitry involving prefrontal cortical circuits with functional connections to subcortical structures (e.g., basal ganglia, thalamus), we hypothesized that EF would be most strongly impacted by goal-setting. Moreover, as verbal EF is highly correlated with motivation measures[6] and characterizes impairment in long-term stroke survivors (with the highest rates of decline)[18], we predicted verbal EF (i.e., verbal fluency) would be particularly implicated in goal-setting.

2. **Method**

The data that support the findings of this study are available from the corresponding author upon reasonable request. Ethics approval was obtained from all participating institutions, and the research was completed in accordance with the Helsinki Declaration. All participants provided their informed consent to participate. The study is a registered clinical trial in the U.S. National Library of Medicine, NCT03511300 (https://clinicaltrials.gov/ct2/show/NCT03511300).

2.1 **Trial Design**

Single-blind, parallel design, randomized controlled trial.

2.2 **Participants**

Participants were stroke survivors recruited from the secondary Stroke Prevention Clinic at Sunnybrook Health Sciences Centre in Toronto, Canada. Inclusion criteria included English speaking, non-aphasic individuals between 35-90 years old with definite ischemic stroke diagnoses based on computed tomography and/or magnetic resonance imaging scans at least 3 months post-stroke. Participants were excluded if they had severe aphasia or dementia.

2.3 **Intervention**

The intervention occurred with the study director or research assistant over a single visit of approximately 1 hour. Participants completed baseline cognitive measures (EF, attention/working memory, verbal memory) and self-report measures (including state motivation, fatigue, and anxiety). Next, half (n=36) of the participants were randomly assigned to the goal-setting group, whereby participants were asked to set a goal to improve their performance on each task by 20%[14,19,20], with the experimenter providing a concrete number to strive to achieve (e.g., "Let's set a goal together to generate [baseline "F" x 1.2] words that start with the letter F" for the Controlled Oral Word Association Test [COWAT][21]). On the word learning task (California Verbal Learning Test-Second Edition [CVLT-II][22]), participants were asked to set a goal to recall one additional word if they correctly recalled at least 10 words, and two additional words if less than 10 words were recalled. The remainder of the participants (n=36) were assigned to the standard instruction group, whereby they received standard instructions to complete a similar set of cognitive tasks. To evaluate whether the impact of motivational instructions could transfer to different cognitive tasks, we selected two EF tasks (related to our primary outcome) including letter fluency for *P* and category fluency for supermarket. To minimize burden, we only explored transfer in the primary outcome domain (EF), not all cognitive domains. These two verbal fluency tasks were performed in both groups without a specific goal target. Finally, all participants re-rated their current motivation, fatigue, and anxiety level.

2.4 **Outcomes**

Self-report measures and neuropsychological measures were gathered during the single intervention session. A neuropsychological battery was collected to cover a range of

neuropsychological domains commonly affected after stroke, based on the National Institute of Neurological Disorders and Stroke – Canadian Stroke Network Vascular Cognitive Impairment (NINDS-CSN VCI) Harmonization Standards 30-minute battery[17], with the Digit Span Test[23] (DST) added to include an attention/working memory measure without a motor speed component.

Co-primary outcome measures

Executive Function (Verbal): (1) COWAT[21] (higher scores indicate more words generated for words beginning with three different letters) and (2) Semantic Fluency Test[24] (SFT; higher scores indicate more words generated belonging to a category).

Secondary outcome measures

Attention/Working Memory: (1) DST[23] [higher scores indicate the longest number of digits recalled in forward (0-9), backward (0-8), and in sequence (0-9), and the total number of digits recalled (0-48); Wechsler, 2008] or alternate Digit Span Test [aDST; identical to DST but each digit was replaced by another number in ordinal sequence (e.g., 0 replaced with 6, 1 with 7)], and (2) the Trail Making Test–Part A/C[25,26] [TMT-A/C; higher scores indicate slower performance connecting numbers (1-25) in ascending order (0-180 seconds).

Executive Function (Visual): (3) Trail Making Test–Part B/D[25,26] [TMT-B/D; higher scores indicate slower performance connecting numbers and letters in an alternating and ascending fashion (0-300 seconds)].

Executive Function (testing transfer of benefit from the goal-setting instructions to verbal EF tasks): (4) Letter fluency for *P*, (5) Category fluency for *supermarket.*

Verbal Memory (Learning and Recall): (6) CVLT-II[22], with verbal learning assessed over five repeated trials of a 16-item word list (0-80), short-delay free (0-16) and cued (0-16) recall after

presentation of a second interference word list, and long-delay free (0-16) and cued (0-16) recall following a 20-minute delay.

Self-report measures included: (7) Apathy Evaluation Scale[27] (AES) measuring goal-directed behaviours, goal-directed cognitions, and flat affect, with higher scores (range: 18-72) indicating greater apathy, (8) The Center for Epidemiologic Studies Depression Scale[28] (CES-D) measuring depressive symptomatology, with higher scores (range: 0-60) indicating greater depressive symptoms, (9) The Goal Commitment Questionnaire[29] assessing goal commitment in participants who were randomly assigned to the goal-setting group, with higher scores (range: 5-25) indicating greater determination to reach a goal, and (10) Single-item state indicators of current motivation, fatigue, and anxiety level separately from 1 (*not motivated/tired/anxious at all*) to 10 (*extremely motivated/tired/anxious*) measured before and after the instructional manipulation.

2.5 **Sample size**

A power analysis for a 2x2 MANCOVA with a medium effect size, .05 alpha, and .80 power indicated a sample size of 72 participants was needed[30].

2.6 **Randomization**

Participants were randomized to groups by the study director (KNF) using an online research randomizer. All protocols were prepared before recruitment began. The study director and research assistant were blinded to the randomization group before the instructional manipulation section began, and all participants were blinded to the condition. The order of the standard and alternate versions of each task (if an alternate was used) were counterbalanced across participants as to whether they were presented at baseline or during the instructional manipulation. Alternate forms were implemented for the DST and TMT in order to mitigate the

well-established practice effects of these particular tasks[31].

2.7 **Statistical methods**

Data were analyzed using SPSS Version 21, 64-bit edition[32].

Statistical analyses. Chi-square and t-tests were conducted to compare group differences on demographic and disease variables.

MANCOVAs were conducted to evaluate group differences between stroke survivors in the goal-setting and standard instruction groups across neuropsychological domains. Two separate mixed design MANCOVAs were conducted, with instruction type as the between-subjects variable, pre-post instruction manipulation as the within participants variable, and attention/working memory (Longest Digit Span Forward, Longest Digit Span Backward, Longest Digit Span Sequencing, Digit Span Total, TMT–A) or EF (COWAT, SFT, TMT–B) as the dependent variables, controlling for age and years of education. One-way repeated measures ANCOVAs were used to evaluate test-specific interaction effects within each neuropsychological domain. The Benjamini-Hochberg procedure[33] with a false discovery rate of 10% was used to correct for multiple comparisons.

A repeated measures ANCOVA was used to evaluate group differences in total learning and learning across 4 trials (Trial 2-5) on the CVLT-II, using the first trial as a baseline measure. Repeated measures ANCOVAs were also used to evaluate group differences over time for free (short- and long-delay) recall and cued (short- and long-delay) recall on the CVLT-II. An additional independent-samples one-way MANCOVA was used to evaluate group differences in verbal fluency performance for similar additional transfer tasks (i.e., words generated for the letter *P* and items found at a supermarket) after the instructional manipulation. All statistical analyses were adjusted for age and years of education because of their well-documented impact

on cognitive performance.

One-way ANOVAs were used to evaluate group differences in self-reported state motivation (secondary outcome measure), fatigue, and anxiety before and after the instructional manipulation.

Reliable change indices[34] (RCIs) were calculated for attention/working memory, EF, and verbal learning tasks. Two (goal-setting versus standard instruction group) x 3 (positive reliable change, negative reliable change, and absence of change) chi-square tests for each neuropsychological task were conducted to determine if there were group differences in the frequencies of change observed on each task.

Effect sizes were calculated using η^2_p (.01, .06, and .14 represent small, medium, and large effect sizes, respectively) and φ_c (for *df*=2; .07, .21, and .35 represent small, medium, and large effect sizes, respectively)[35].

3. **Results**

3.1 **Demographics**

The final sample consisted of seventy-two participants recruited between August 2018 to October 2019 (see Figure 4.1). Data missing at random (<5%) were imputed using SPSS's expectation maximization algorithm. Seven participants did not complete the Trail Making Test due to blindness in one eye (Goal-setting group=3; Standard instruction group=4). For cells in which the discontinue criteria for Trail Making Test A/C or B/D were met, the maximum score was used for the corresponding measure (180 seconds for TMT–A/C [n=3]; 300 seconds for TMT–B/D [n=2]).

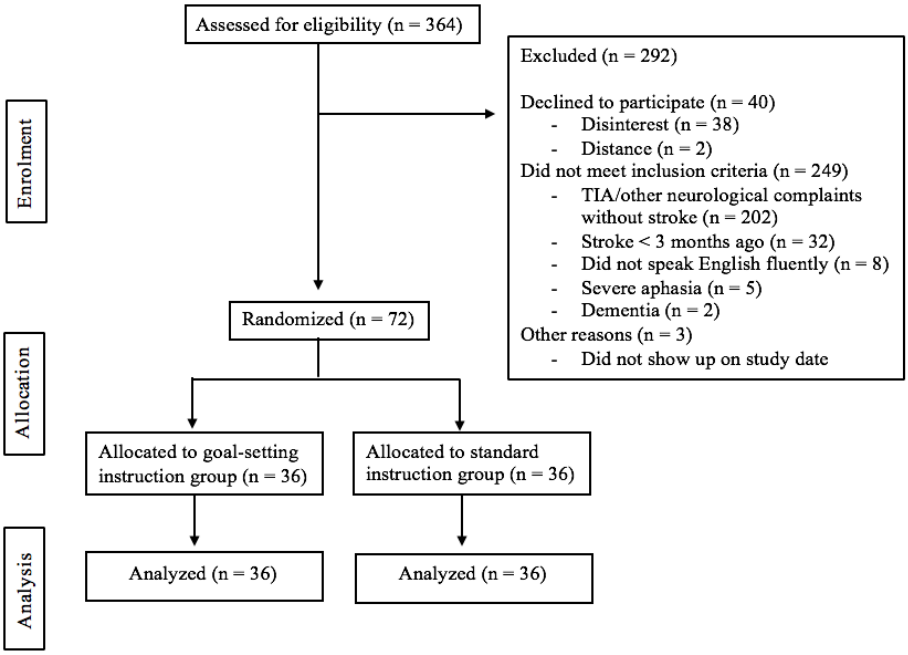


Figure 4.1. CONSORT diagram.

Participant information is presented in Table 4.1. There were no differences in the number of individuals classified as depressed or apathetic, but the goal-setting group had higher average depression scores than the standard instruction group. There were more individuals with hypertension in the standard instruction group, but this was no longer significant after using the Benjamini-Hochberg procedure[33] to account for multiple comparisons. After accounting for age, there were no differences in baseline cognitive performance between individuals with and without hypertension (*p*s .139-.497).

Table 4.1

Participant Characteristics

	Goal-setting (n = 36)	Control (n = 36)	Group comparison (goal-setting vs. standard instruction)
Age	66.4±12.3 (35-85)	70.4±11.15 (45-87)	$t(70)=1.45$, $p=.150$
Sex (% men)	23 (64%)	27 (75%)	$\chi^2=0.36$, $df=1$, $p=.548$
Years of education	15.1±2.9 (6-23)	14.1±3.91 (5-22)	$t(70)=-1.24$, $p=.221$
English first language learned	27	29	
Ethnicity			$\chi^2=6.86$, $df=6$, $p=.334$
African	1	3	
African American	2	3	
South American	1	5	
Asian	2	0	
Caucasian	14	9	
East Indian	2	0	
European	6	8	
Did not disclose	8	8	
Location: Circulation[a]			$\chi^2=1.26$, $df=2$, $p=.532$
Anterior	21	18	
Posterior	9	14	
Anterior & Posterior	4	4	

Hemisphere[a]			χ^2=1.18, *df*=2, *p*=.556
Left	18	23	
Right	14	11	
Bilateral	1	2	
Months since stroke	29±36 range 3-177	32±38 range 3-167	*t*(70)=0.45, *p*=.658
Family history of stroke[b]	20	20	*t*(57)=0.19, *p*=.853
Smoking[c]			χ^2=2.35, *df*=3, *p*=.503
Lifelong non-smoker	20	23	
Quit > 5 years ago	10	6	
Quit 1-5 yrs ago	2	3	
Current smoker	1	3	
Alcohol Use[c]			χ^2=6.30, *df*=4, *p*=.178
Never	8	13	
Not currently	5	5	
Rare/Social	10	13	
≤ 2 drinks per day	10	3	
>2 drinks per day	0	1	
Sleep difficulties over the past month (nights per week)			χ^2=0.76, *df*=4, *p*=.944
0-1	12	15	
2	4	5	
3	2	3	
4	3	2	
5-7	10	9	
General sleep difficulties over the past month			χ^2=1.72, *df*=4, *p*=.787
Not at all	10	13	

A little	5	9	
Somewhat	8	6	
Much	3	3	
Very Much	4	3	
CES-D score[d] (SD)	17.0 (9.6) range 2-40	11.9 (9.2) range 0-34	$t(70)=2.31$, $p=.024$*
# Depressed (CES-D≥16)	17	12	$\chi^2=1.43$, $df=1$, $p=.230$
AES score[d] (SD)	31.6 (8.0) range 19-53	30.6 (8.5) range 20-58	$t(69)=0.47$, $p=.641$
# Apathetic (AES≥34)	13	11	$\chi^2=0.17$, $df=1$, $p=.677$
Sleep apnea[e] (%)	10 (29%)	6 (17%)	$\chi^2=1.44$, $df=1$, $p=.230$
Hypertension[f] (%)	15 (43%)	24 (67%)	$\chi^2=4.06$, $df=1$, $p=.044$
Hypothyroidism (%)	5 (14%)	2 (6%)	$\chi^2=1.52$, $df=1$, $p=.217$
High Cholesterol[f] (%)	19 (54%)	24 (67%)	$\chi^2=1.14$, $df=1$, $p=.286$
Vision Impairment[e]	5 (19%)	5 (21%)	$\chi^2=0.20$, $df=1$, $p=.887$

Note. N = 72. Descriptive data are presented as means (and standard deviations) unless otherwise noted.
[a]2 cases missing from the goal-setting group.
[b]6 cases missing from the standard instruction group, 7 cases missing from the goal-setting group.
[c]1 case missing from the standard instruction group, 3 cases missing from the goal-setting group.
[d]Higher scores represent more severe psychopathology.
[e]12 cases missing from the standard instruction group, 10 cases missing from the goal-setting group.
[f]1 case missing from the goal-setting group.
*Significant after using the Benjamini-Hochberg procedure[33] with a false discovery rate of 10% to correct for multiple comparisons.

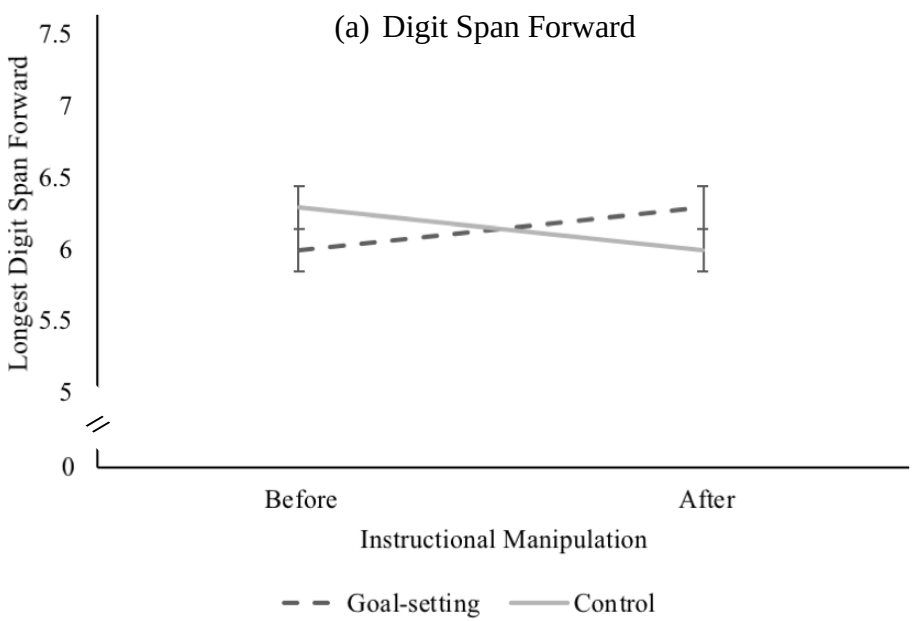
3.2 **Self-rated Motivation, Fatigue, Anxiety, and Goal Commitment**

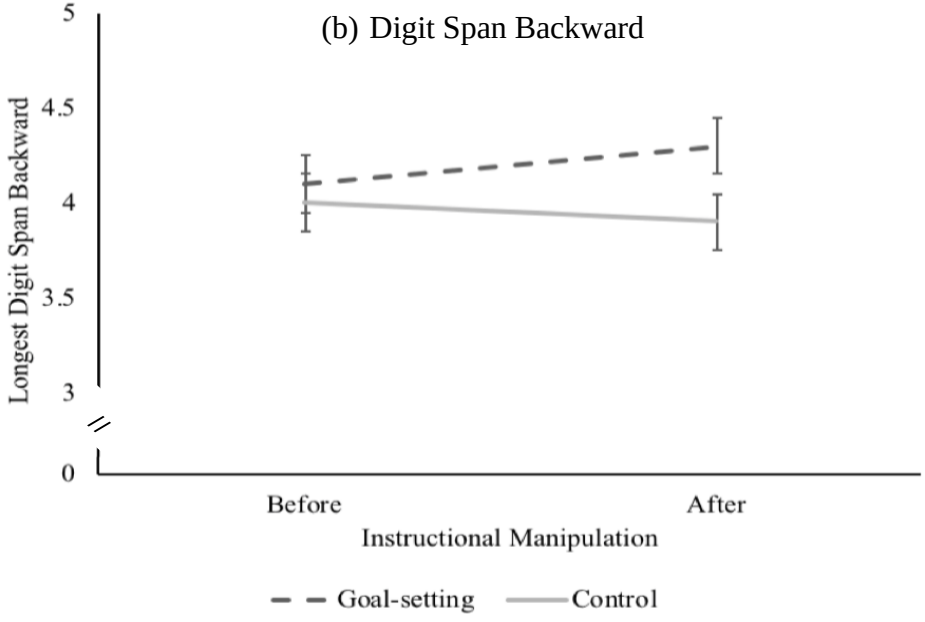
There were no group or group by time interaction effects on motivation (Wilks' λ=.99, F[1,69]=.04, p=.839, η^2_p<.01), fatigue (Wilks' λ=.97, F(1,69)=1.49, p=.227, η^2_p=.02), or anxiety (Wilks' λ=.99, F(1,28)=2.55, p=.122, η^2_p=.08). Unsurprisingly, there was a main effect of time on fatigue, such that participants reported that their fatigue level increased over time, Wilks' λ=.77, F(1,69)=20.51, p<.001, η^2_p=.23.

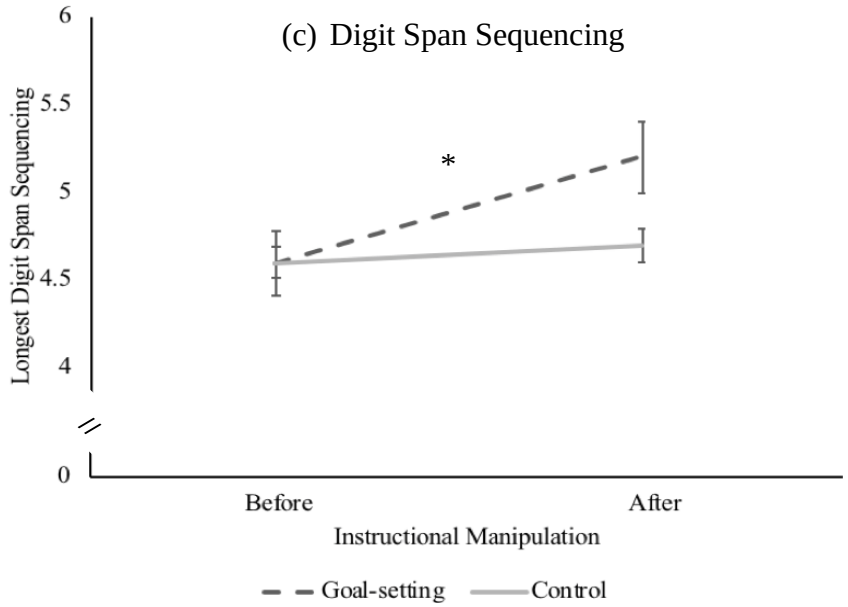
Goal Commitment. Only individuals in the goal-setting group completed the Goal Commitment Questionnaire, and the average goal commitment score was 19.55 (SD=3.54), indicating moderate to high goal commitment.

3.3 **Group Comparisons of Goal-Setting and Standard Instruction Group**

Graphical representations and a table of test-specific performance between instructional groups before and after the instructional manipulation are illustrated in Figure 4.2, Figure 4.3, and Table 4.2.


(a) Digit Span Forward
Longest Digit Span Forward
7.5
7
6.5
6
5.5
5
0
Before
After
Instructional Manipulation
Goal-setting
Control


(b) Digit Span Backward
Longest Digit Span Backward
5
4.5
4
3.5
3
0
Before
After
Instructional Manipulation
Goal-setting
Control


(c) Digit Span Sequencing
Longest Digit Span Sequencing
6
5.5
5
4.5
4
0
*
Before
After
Instructional Manipulation
Goal-setting
Control

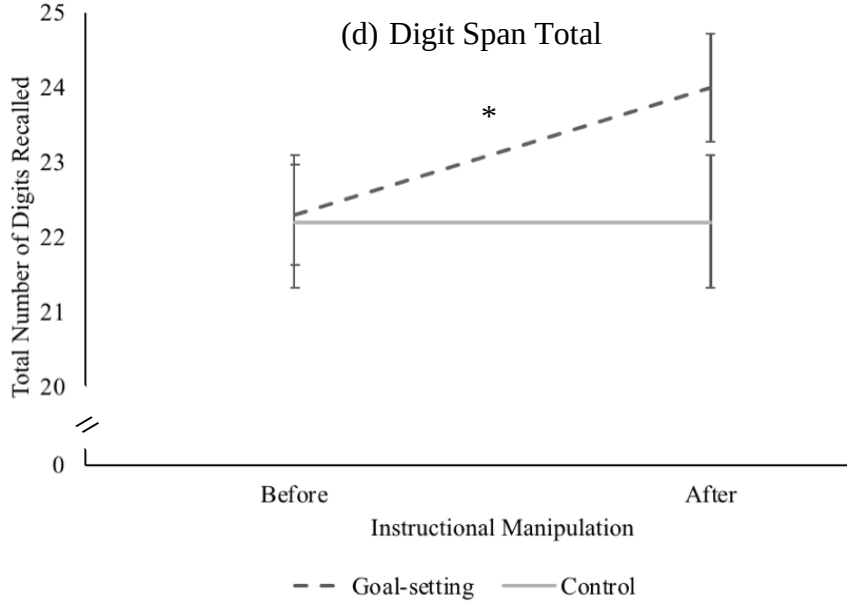
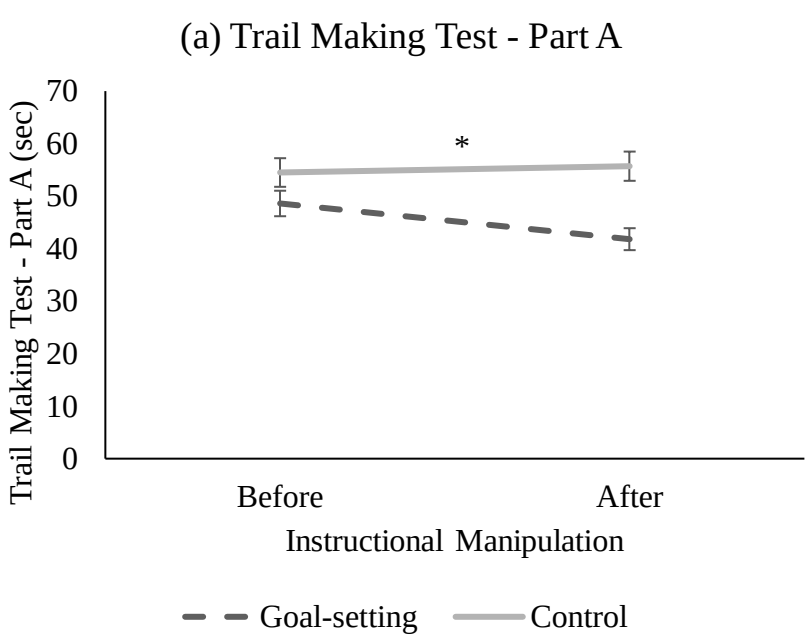

(d) Digit Span Total
Total Number of Digits Recalled
25
24
23
22
21
20
0
*
Before
After
Instructional Manipulation
Goal-setting
Control

Figure 4.2. Graphical representations of goal-setting versus standard instruction group participant performance on neuropsychological measures before and after the instructional manipulation. (a) Digit Span Forward; (b) Digit Span Backward; (c) Digit Span Sequencing; (d) Digit Span Total. Error bars indicate standard errors.
*Significant interaction after using the Benjamini-Hochberg procedure[33] with a false discovery rate of 10% to correct for multiple comparisons.


(a) Trail Making Test - Part A
Trail Making Test - Part A (sec)
70
60
50
40
30
20
10
0
*
Before
After
Instructional Manipulation
Goal-setting
Control

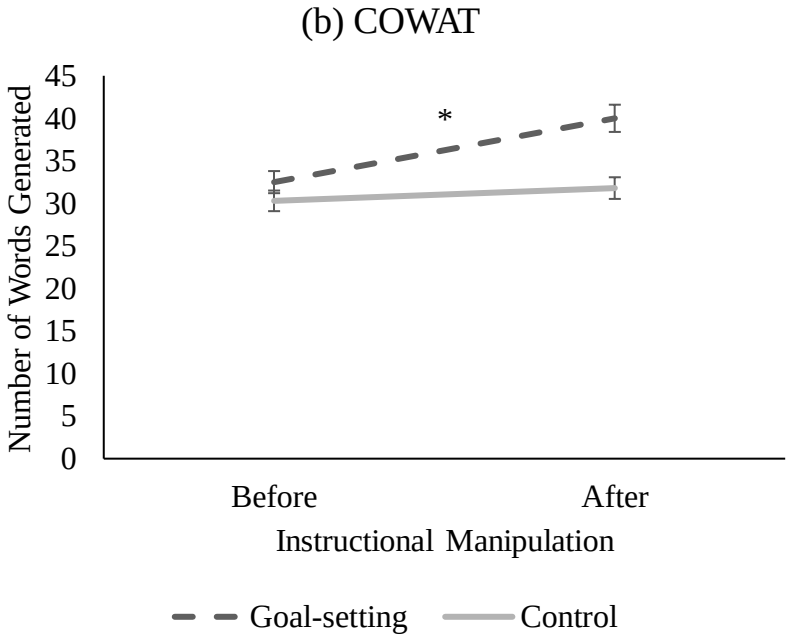

(b) COWAT
Number of Words Generated
45
40
35
30
25
20
15
10
5
0
*
Before
After
Instructional Manipulation
Goal-setting
Control

Figure 4.3 Graphical representations of goal-setting versus standard instruction group participant performance on neuropsychological measures before and after the instructional manipulation. (a) Trail Making Test – Part A; (b) Controlled Oral Word Association Test; (c) Animal Fluency; (d) Trail Making Test – Part B. Error bars indicate standard errors.
Note. COWAT = Controlled Oral Word Association Test.
*Significant interaction after using the Benjamini-Hochberg procedure[33] with a false discovery rate of 10% to correct for multiple comparisons.

Table 4.2

Comparing Test-Specific Performance Between Groups using Raw Scores

Descriptive domain & test name	Goal-setting (n=36)	Standard Instruction (n=36)	N	Group x Time Interaction[a]
Attention and working memory			72	$F(5,64)=2.45$, $p=.043$, $\eta^2_p=.16$*
Digit Span Forward			72	$F(1,68)=3.18$, $p=.079$, $\eta^2_p=.04$
Pre	6.0±1.4 (4-9)	6.3±1.3 (4-9)		
Post	6.3±1.5 (4-9)	6.0±1.7 (3-9)		
Digit Span Backward			72	$F(1,68)=1.21$, $p=.276$, $\eta^2_p=.02$
Pre	4.1±1.4 (2-7)	4.0±1.5 (0-7)		
Post	4.3±1.6 (2-8)	3.9±1.7 (0-7)		
Digit Span Sequencing			72	$F(1,68)=4.36$, $p=.040$, $\eta^2_p=.06$**
Pre	4.6±1.4 (0-6)	4.6±1.4 (1-7)		
Post	5.2±1.3 (2-8)	4.7±1.2 (2-7)		
Digit Span Total			72	$F(1,68)=4.05$, $p=.048$, $\eta^2_p=.06$**
Pre	22.3±6.8 (8-37)	22.2±6.4 (11-35)		
Post	24.0±6.1 (14-39)	22.2±7.2 (9-37)		

Trail Making Test - Part A (seconds)[b]			65	$F(1,61)=4.88$, $p=.031$, $\eta^2_p=.07$**
Pre	48.6±29.7 (18-180)	54.5±34.4 (17-180)		
Post	41.8±29.4 (14-177)	55.7±40.7 (20-180)		
Executive function			72	$F(3, 66) = 11.30$, $p<.001$, $\eta^2_p=.34$*
Letter Fluency			72	$F(1,68)=17.47$, $p< .001$, $\eta^2_p=.20$**
Pre	32.5±14.2 (4-62)	30.3±12.3 (7-66)		
Post	40.0±15.6 (14-76)	31.8±12.3 (6-62)		
Category Fluency			72	$F(1,68)=19.19$, $p<.001$, $\eta^2_p=.22$**
Pre	15.9±5.5 (4-24)	14.3±6.6 (0-29)		
Post	19.1±6.4 (3-32)	13.2±7.3 (0-24)		
Trail Making Test – Part B[b] (seconds)			65	$F(1,61)=1.27$, $p=.265$, $\eta^2_p=.02$
Pre	137.7±76.6 (40-300)	152.3±91.4 (59-300)		
Post	112.4±63.7 (39-300)	135.5±76.9 (54-300)		
Memory				

CVLT-II[c]				
Learning			64	$F(1,60)^{d}=5.81$, $p=.019$, $\eta^2_p=.09$*
Learning Trial 1	5.0±2.1 (1-11)	4.2±1.5 (2-7)		
Learning Trial 2	7.1±2.4 (4-13)	5.9±2.4 (2-11)		
Learning Trial 3	8.9±2.7 (2-15)	7.2±2.9 (3-14)		
Learning Trial 4	10.0±3.0 (3-15)	8.1±3.2 (3-14)		
Learning Trial 5	10.4±2.8 (5-15)	8.7±3.3 (2-15)		
Total Learning Trial 1-5	41.6±11.4 (18-69)	34.0±12.0 (14-56)		
Recall				
Free			62	$F(1,56)=2.82$, $p=.099$, $\eta^2_p=.05$
Short-delay Free Recall	8.2±3.3 (2-13)	6.5±3.4 (0-12)	62	
Long-delay Free Recall	8.4±3.8 (0-14)	5.9±3.8 (0-13)	62	
Cued			61	$F(1,56)=0.40$, $p=.527$, $\eta^2_p=.01$
Short-delay Cued Recall	8.8±3.5 (2-14)	7.1±3.2 (1-13)	62	
Long-delay Cued Recall	9.2±3.6 (1-15)	6.7±3.8 (0-13)	61	

Note. Test data are presented as means ± standard deviations (range) of raw test scores. CVLT-II=California Verbal Learning Test–Second Edition[25].
Digit span=longest digit span forward, longest digit span backward, longest digit span sequenced correctly.

[a]Adjusting for age and years of education.
[b]Higher scores reflect poorer performance.
[c]Thirty four participants completed this task in the goal-setting group, and 30 participants completed this task in the standard instruction group.
[d]Main effect of group on CVLT-II Trials 2-5 Total.
*$p \leq .05$
**Significant after using the Benjamini-Hochberg procedure[33] with a false discovery rate of 10% to correct for multiple comparisons.

Primary outcomes

Executive function: A one-way mixed MANCOVA revealed a significant group by time interaction effect on cognitive performance after adjusting for age and years of education (p<.001 for COWAT and SFT; see Table 2). There were no main effects of time (p=.585) or group (p=.238) on performance. Univariate tests showed that the goal-setting group improved on the COWAT and SFT relative to the standard instruction group. There were no differences in TMT – Part B performance, which was a secondary outcome measure.

Secondary outcomes

Attention and working memory: A one-way mixed MANCOVA revealed a group by time interaction effect on attention and working memory after adjusting for age and years of education (p = .043; see Table 2). There were no main effects of time (p=.052) or group (p=.943) on performance. Univariate tests showed that the goal-setting group improved on Digit Span Sequencing, Digit Span Total, and Trail Making Test – Part A relative to the standard instruction group. There were no differences in Digit Span Forward or Digit Span Backward performance.

A one-way MANCOVA showed a group difference in performance on additional verbal fluency transfer tasks after the instructional manipulation (Wilks' λ=.82, F[2,67]=7.36, p=.001, η^2_p=.18), such that participants in the goal-setting condition performed better than participants in the standard instruction condition on generating words belonging to the category *supermarket*, F(1,68)=14.92, $p\leq$.001, η^2_p=.18, but not generating words beginning with the letter *P*, F(1,68)=2.80, p=.099, η^2_p=.04.

Memory:

Learning. A repeated measures ANCOVA was used to evaluate group differences in learning across Trials 2-5 of the CVLT-II, as Trial 1 scores were accrued before the instructional

manipulation. There was no difference in Trial 1 performance on the CVLT-II between the goal-setting and standard instruction group (p=.144). There was a main effect of group (F(1,60)=5.81, p=.019, η^2_p=.09), such that the goal-setting group generated more words on the CVLT-II across Trials 2-5 than the standard instruction group. There was no main effect of time (p=.236).

Recall. Two repeated measures ANCOVAs were used to evaluate group differences for free (short-delay and long-delay) and cued (short-delay and long-delay) recall, with no group by time interaction effects.

3.4 **Group Comparisons of Goal-Setting and Standard Instruction Group with Depressive Symptoms**

Since there were group differences on the CES-D, statistical analyses were rerun controlling for CES-D scores, with similar associations observed.

3.5 **Reliable Change Indices**

Reliable change indices for attention/working memory, EF, and learning tasks are presented in Table 4.3. A larger proportion of participants in the goal-setting group showed reliable improvement in digit span total, letter fluency, category fluency, and verbal learning than participants in the standard instruction group. There were no differences in change indices for longest digit span forward, longest digit span backward, longest digit span sequencing, TMT-A/C, or TMT-B/D.

Table 4.3

Group Comparisons of Reliable Change Indices for Attention/Working Memory, Executive Function, and Memory Measures

Descriptive domain & test name	Goal-setting (n=36)		Standard Instruction (n=36)		Group x Time Interaction
	n	(%)	*n*	(%)	
Attention and working memory					
Digit Span Forward					χ^2=1.50, df=2, *p*=.472, φ_c=.14
Reliable deterioration	3	(8.3)	5	(13.9)	
No change	30	(83.3)	30	(83.3)	
Reliable improvement	3	(8.3)	1	(2.8)	
Digit Span Backward					χ^2=4.33, df=2, *p*=.115, φ_c=.25
Reliable deterioration	1	(2.8)	6	(16.7)	
No change	31	(86.1)	25	(69.4)	
Reliable improvement	4	(11.1)	5	(13.9)	
Digit Span Sequencing					χ^2=1.68, df=2, *p*=.431, φ_c=.15
Reliable deterioration	0	(0.0)	1	(2.8)	
No change	32	(88.9)	33	(91.7)	

Reliable improvement	4	(11.1)	2	(5.6)	
Digit Span Total					χ^2=7.52, df=2, *p*=.023*, φ_c=.32
Reliable deterioration	1	(2.8)	4	(11.1)	
No change	27	(75.0)	31	(86.1)	
Reliable improvement	8	(22.2)	1	(2.8)	
Trail Making Test - Part A[a]					χ^2=2.00, df=2, *p*=.368, φ_c=.17
Reliable deterioration	0	(0.0)	1	(3.1)	
No change	32	(97.0)	31	(97.0)	
Reliable improvement	1	(3.1)	0	(0.0)	
Executive function					
Letter Fluency					χ^2=5.06, df=1, *p*=.024*, φ_c=.27
Reliable deterioration	0	(0.0)	0	(0.0)	
No change	29	(80.5)	35	(97.2)	
Reliable improvement	7	(19.4)	1	(2.8)	
Category Fluency					χ^2=17.81, df=2, *p*<.001**, φ_c=.50
Reliable deterioration	2	(5.6)	6	(16.7)	

No change	18	(50.0)	29	(80.5)	
Reliable improvement	16	(44.4)	1	(2.8)	
Trail Making Test – Part B[a]					χ^2=1.42, df=2, *p*=.493, φ_c=.14
Reliable deterioration	1	(3.0)	0	(0.0)	
No change	28	(84.8)	26	(81.2)	
Reliable improvement	4	(12.1)	6	(18.8)	
Memory					
CVLT-II					
Learning Trial 1 to Trials 2-5 Total[b]					χ^2=7.57, df=1, *p*=.006**, φ_c=.28
Reliable deterioration	0	(0.0)	0	(0.0)	
No change	6	(17.6)	15	(50.0)	
Reliable improvement	28	(82.3)	15	(50.0)	

Note. N = 72 unless otherwise indicated. RCI = ([post-instructional manipulation – pre-instructional manipulation]/s_{diff}). Reliable deterioration=Reliable Change Index of less than -1.96; No change=Reliable Change Index between -1.96 to 1.96; Reliable improvement=Reliable Change Index of greater than 1.96. CVLT-II=California Verbal Learning Test–Second Edition[25].
Digit span=longest digit span forward, longest digit span backward, longest digit span sequenced correctly.
[a]Participants with visual deficits did not complete this task (n=3 in the goal-setting group, n=4 in the standard instruction group).
[b]*n*=64.
*$p \leq .05$. **$p \leq .01$.

4. **Discussion**

This randomized controlled trial examined how goal-setting influences cognitive performance across multiple neuropsychological domains in seventy-two stroke survivors in the chronic phase after stroke. We found that participants in the goal-setting instruction group improved their performance on the primary outcome of verbal EF (COWAT, SFT), as well as the secondary outcomes of attention/working memory (DST) and verbal learning (CVLT-II), but not on verbal recall (CVLT-II) or visual EF (TMT-B), after correcting for multiple comparisons. In addition, more participants in the goal-setting group showed reliable change on EF, attention/working memory, and learning measures, despite increases in fatigue over time across both groups. These effects were not attributable to differences in education, age, or depression severity, and there were no group differences in stroke location, time since stroke, substance use, sleep, or vascular risk factors after the multiple comparison correction[33]. Notably, hypertension did not have any impact on cognitive performance after correcting for age. There were also no differences between depression and cognitive performance. This study complements previous research that found goal-setting instructions improved arithmetic performance[16] and motor task performance[36] in individuals following brain injury relative to standard instructions.

4.1 **Generalizability and Interpretation**

Our findings suggest that post-stroke cognitive impairment (at least in the most common domains of EF and attention) not only results from focal neuronal injury causing fixed deficits, but also likely reflects more subtle issues, including reduced motivation. The idea that the chronic post-stroke cognitive impairment after stroke may not be permanent and can be improved to an extent by simply targeting motivation with a brief 20-second intervention, has

strong implications for daily functioning and cognition if it can be generalized beyond these specific cognitive tasks into functional cognitive goals.

With respect to treatment, some pharmacological and very limited psychological interventions for diminished motivation have been utilized in stroke populations. These approaches could be considered, like goal-setting, as attempts to increase motivation. Studies with small sample sizes and case studies have shown some impact of pharmacological treatment for diminished motivation using stimulants (e.g., methylphenidate)[37]. Even fewer studies have examined psychological interventions for motivation in stroke populations, with interventions primarily delivered acutely after stroke and with small sample sizes[10,11].

One related intervention, Goal Management Training (GMT), is based on goal-neglect theory. GMT is a standardized 20-hour metacognitive training that educates patients about their deficits and how to self-monitor their goals and has been shown to improve cognition in individuals with frontal lobe brain damage[12]. Our study nicely complements GMT - which emphasizes stopping and refocusing on goals - by highlighting the importance of engaging and educating patients to set challenging but achievable, measurable, and time-limited goals to optimize cognitive and functional performance. This poses a novel therapeutic avenue for executive/attention dysfunction, the most commonly cognitive domains affected in VCI.

Using goal-setting instructions to reliably improve EF, attention/working memory, and learning in the chronic phase of stroke highlights a potential new avenue for VCI treatment. Incorporating specific, difficult but reasonable, and measurable goals into everyday activities could improve motivation and performance on behavioural and cognitive tasks. Restructuring a patient's home/work environment to focus on identifying and setting specific goals to orient, prioritize, and organize activities (e.g., folding laundry) may be helpful to scaffold EF, improve

self-efficacy, and enhance performance[13,38]. A larger scale RCT using goal-setting in the home, and incorporating physical, functional, and cognitive measures, is needed to show persistence over time and translation to other settings. This would be a major advance for an area with few treatments and could also complement other strategies, including pharmacological treatments of apathy[37] or goal management training[12].

These findings also have important implications for neuropsychological testing. First, low scores on neuropsychological measures may not be precise reflections of stroke survivors' abilities. These participants may benefit from goal-setting instructions to an even greater degree than neurotypical individuals. Engaging more frequently in testing the limits with goals and additional time with stroke survivors may produce more accurate reflections of true capabilities. This suggestion is complemented by recent progress in considering a combined qualitative and quantitative approach to assessment of executive difficulties[39]. Testing the limits may also improve rapport and patient self-esteem[38]. Second, and more broadly, test scores may be invalid if there is diminished effort, which has been shown to partially mediate the relationship between motivation and cognitive performance on EF and attention/WM[40]. Effort testing using symptom validity measures are encouraged to be utilized during neuropsychological assessment with stroke survivors[41]. Third, it may be beneficial to design a cognitive measure with standardized goal-setting norms to quantify the extent to which a patient benefits from instructions to facilitate interpretation of neuropsychological performance.

EF, including planning, problem solving, initiating, inhibiting, and completing tasks[39] is the neuropsychological domain that is most strongly impacted by goal-setting. EFs are primarily managed by three interconnected prefrontal cortical circuits[42], with functional connections to subcortical structures including the basal ganglia and thalamus. Similar circuitry underlies

diminished motivation, or apathy[42]. Given the overlapping circuitry, it is not surprising that goal-setting had the most prominent effects on EF and attention/working memory, and not verbal recall, which has greater involvement of left medial temporal structures than EF tasks. However, collapsing short- and long-delay recall in MANCOVAs to reduce Type I error may have dampened the potential impact of goal-setting on performance by failing to appreciate unique neural circuitry involved in short- versus long-delay recall[43]. While the impact on EF may be greater if studies on goal-setting include only individuals with apathy, our study demonstrated widespread benefits of brief, clear, and simple goal-setting strategies to improve cognitive performance in stroke survivors.

4.2 **Strengths and Limitations**

There are a number of notable strengths to the current study. First, we evaluated the impact of goal-setting on cognitive performance across three neuropsychological domains in a broad sample of individuals in the chronic phase after stroke. We recruited participants with different educational histories, cognitive abilities, psychopathology, and locations of stroke in order to illuminate the generalizability of our findings. One-third of participants who disclosed their ethnic/racial background did not identify as Caucasian or European, suggesting that there was some diversity in our sample. However, further research with larger samples would be required to fully explore the impact of racial and ethnic diversity on this intervention. Additionally, we used a randomized controlled parallel group design and report our findings according to CONSORT standards. We also utilized neuropsychological tests with excellent psychometric properties, adjusted for age, years of education, and depressive symptoms in our statistical analyses, and used reliable change indices to compare changes between groups.

A number of limitations warrant mention. First, we excluded participants who were diagnosed with aphasia or dementia at the time of the study. As a result, our findings cannot be generalized to these populations. Second, self-reported motivation remained stable in both groups, regardless of instructional manipulation. Self-reported motivation was rated on a scale from 1 (*not motivated at all*) to 10 (*extremely motivated*). Although before and after instructional manipulation motivation items were correlated with self-reported AES, it may be that this single-item was not sensitive to detect subtle changes in motivation. Researchers may consider using more comprehensive measures of state motivation or using behavioural measures to quantify motivation[44]. Alternatively, autonomy support, self-agency, or attentional focus may have also contributed to improved performance as the mechanism of action for goal-setting. Lastly, although cognitive performance improved with goal-setting instructions during the intervention, it is unknown as to whether these benefits would extend to follow up measures administered after a longer duration or to more naturalistic, ecologically valid outcomes such as iADLs or home/vocational function, or neuropsychological tasks with greater verisimilitude (e.g., Test of Everyday Attention).

In summary, we found widespread benefits of a very brief and simple goal-setting intervention on cognitive performance, particularly for EF, attention/working memory, and learning. Our study supports the notion that >3 months after stroke, cognitive impairment is not a fixed deficit: there is also a motivational (or attentional) contributor to vascular cognitive impairment. Our study shows that goal-setting is a promising target for the management of VCI, given that it reliably improved EF, attention/working memory, and verbal learning in cognitive testing. If these benefits persist over time and translate to other settings, this would contribute to an area with few treatment options. It may also complement other strategies, including

pharmacological treatments of apathy, problem-solving therapy, or goal management training. Furthermore, neuropsychological testing may not precisely reflect stroke survivors' abilities, highlighting the importance of engaging in testing the limits with goals and additional time to qualitatively understand the potential influence of motivation and attention on performance in this population.

5. **Acknowledgments**

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6. **Additional Information**

All individuals accompanying stroke patients (n = 18) completed the informant-rated AES. Informant-rated AES was correlated with patients' self-rated AES, $r(16) = .54$, $p = .025$, but not with self-reported depression, CES-D, $r(16) = .22$, $p = .376$. The high correlation between self-reported apathy and informant-reported apathy on the AES supports the accuracy of self-report symptoms (Marin, 1991; Mason & Barker, 2015). Of note, informant-reported apathy scores did not correlate with self-reported depressive symptoms on the CES-D, which also supports a differentiation of symptoms of depression and apathy.

Twenty-four stroke patients (33.3% of the total number of participants) were classified as apathetic (AES ≥ 34; Sagen et al., 2010), whereby 13 individuals were apathetic in the goal-setting group and 11 individuals were apathetic in the standard instruction group. This prevalence rate is consistent with the stroke literature, which estimates that apathy affects 20-50% of stroke survivors (Van Dalen et al., 2013; Van Reekum, Stuss, & Ostrander, 2005). There were no sex differences in apathy severity, $F(1,69) = 2.66$, $p = .108$, or apathy classification, $\chi^2 = .72$, $p = .426$. Due to the small sample size, low power, and risk for type 1 and type 2 errors, we only reported the means, standard deviations, and 95% confidence intervals of neuropsychological test performance for informational purposes in Table 4.4. These descriptive statistics support the notion that the apathetic sample displayed a similar pattern of results as the entire sample. Though future research may consider only including individuals with apathy to evaluate goal-setting interventions, our study effectively demonstrated the applicability and widespread merit of using simple goal-setting strategies to improve cognitive performance in stroke patients. Future studies should collect data in larger samples of individuals with clinically significant apathy.

Table 4.4

Means, Standard Deviations, and 95% Confidence Intervals of Test-Specific Performance Comparing Apathetic Participants in the Goal-Setting and Control Group

	Apathetic participants (n = 24)	
Group	Goal-setting (n = 13)	Control (n = 11)
Descriptive domain & test name		
Attention and working memory		
Digit Span Forward		
Pre	6.38 ± 1.50 (5.48 – 7.29)	5.45 ± 1.21 (4.64 - 6.27)
Post	6.85 ± 1.57 (5.90 – 7.80)	6.38 ± 1.50 (3.60 – 5.86)
Digit Span Backward		
Pre	4.31 ± 1.32 (3.51 – 5.10)	3.09 ± 1.58 (2.03 – 4.15)
Post	4.62 ± 1.56 (3.67 – 5.56)	3.55 ± 1.75 (2.37 – 4.72)
Digit Span Sequencing		
Pre	4.40 ± 1.45 (3.67 – 5.68)	4.08 ± 1.15 (3.31 - 4.85)
Post	4.78 ± 0.73 (4.34 – 5.22)	4.14 ± 1.45 (3.17 – 5.11)
Digit Span Total		
Pre	23.32 ± 6.56 (19.36 – 27.28)	18.06 ± 5.86 (14.12 – 22.00)
Post	24.74 ± 4.84 (21.81 – 27.66)	18.19 ± 8.00 (12.81 – 23.57)
Trail Making Test – Part A (seconds)[a,b]		

Pre	46.75 ± 18.36 (35.10 – 58.41)	57.29 ± 44.47 (16.15 - 98.41)
Post	42.79 ± 20.38 (29.84 – 55.74)	63.43 ± 47.34 (19.64 – 107.21)
Executive function		
Letter Fluency		
Pre	32.23 ± 9.53 (26.47 – 38.00)	29.65 ± 16.28 (18.74 – 40.57)
Post	38.42 ± 10.38 (32.15 – 44.69)	28.15 ± 15.10 (18.01 – 38.29)
Category Fluency		
Pre	15.15 ± 5.57 (11.79 – 18.52)	12.36 ± 7.66 (7.22 – 17.51)
Post	16.98 ± 6.15 (13.26 – 20.69)	10.27 ± 7.96 (4.93 – 15.62)
Trail Making Test – Part B[a,b] (seconds)		
Pre	145.03 ± 61.50 (105.96 – 184.11)	188.14 ± 111.03 (85.45 – 290.83)
Post	123.37 ± 60.31 (85.06 – 161.69)	149.47 ± 81.27 (74.31 – 224.63)
Memory		
CVLT-II		
Learning[c]		
Learning Trial 1	4.92 ± 1.93 (3.75 – 6.09)	3.86 ± 1.57 (2.40 – 5.31)
Learning Trial 2	6.85 ± 2.38 (5.41 – 8.28)	5.29 ± 3.04 (2.47 – 8.10)
Learning Trial 3	8.08 ± 2.90 (6.32 – 9.83)	7.29 ± 3.73 (3.83 – 10.73)
Learning Trial 4	8.92 ± 2.84 (7.21 – 10.64)	6.57 ± 3.15 (3.65 – 9.49)
Learning Trial 5	9.62 ± 3.18 (7.70 – 11.53)	7.86 ± 3.44 (4.68 – 11.04)
Total Learning Trial 1-5	38.38 ± 11.21 (31.61 - 45.16)	30.86 ± 14.39 (17.55 – 44.17)

Recall[b]		
Short-delay Free Recall	7.75 ± 3.70 (5.40 – 10.10)	5.86 ± 3.29 (2.82 – 8.90)
Short-delay Cued Recall	8.75 ± 3.93 (3.52 – 9.91)	6.71 ± 3.45 (3.52 – 9.91)
Long-delay Free Recall	7.83 ± 4.41 (5.03 – 10.63)	4.86 ± 3.80 (1.34 – 8.38)
Long-delay Cued Recall[d]	9.27 ± 3.98 (6.60 – 11.94)	6.29 ± 3.82 (2.76 – 9.82)

[a] Higher scores indicate slower response speed (poorer performance).
[b] 7 apathetic participants in the control group and 12 apathetic participants in the goal-setting group.
[c] 7 apathetic participants in the control group and 13 apathetic patients in the goal-setting group.
[d] 7 apathetic participants in the control group and 11 apathetic participants in the goal-setting group.

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8. **Contributions**

The primary author, Keera Fishman, was involved in study conceptualization, methodology, patient recruitment, funding acquisition, data collection, data entry, completed data analysis, and wrote the manuscript.

Dr. Andrea Ashbaugh, research supervisor, met with Ms. Fishman frequently to discuss study conceptualization, research questions, methodology, data collection, data analysis, and interpretation. Dr. Richard Swartz, site lead and stroke neurologist at Sunnybrook Health Sciences Centre, also met with Ms. Fishman on numerous occasions to discuss study conceptualization, methodology, and study resources. Dr. Glastone, Dr. Pinto, Dr. Sundarum, and Dr. Yu also provided permission to interact with patients who satisfied the inclusion criteria for the study. Throughout the process, Dr. Ashbaugh provided guidance and recommendations regarding article content and edited the full manuscript. Dr. Richard Swartz also edited the full manuscript.

Alisia Southwell provided helpful assistance with data collection, chart reviews, and CVLT-II scoring. Elaine Xing was involved in conducting chart reviews and CVLT-II scoring. Tera Armel was involved in conducting chart reviews. Dr. Dwayne Schindler also provided valuable consultation for the statistical analyses of the manuscript.

Natalie Rashkovan, Donna Hoppenheim, Alisia Southwell, Ophelia Shen, and Rosanne Reynoso also helped with room bookings and patient coordination.

CHAPTER 5: General Discussion

General Discussion

Apathy is a syndrome characterized lack of goal-directed behaviour, cognition, and emotional indifference that negatively impacts social, physical, and functional outcomes and quality of life in both clinical and non-clinical populations (Adams, 2001; Lyketsos et al., 2002; Okada et al., 1997; Starkstein et al., 1993). The purpose of the current dissertation was to advance our understanding of apathy, its relationship to depression, and its influence on cognition in individuals with cerebrovascular disease and in young adults.

Specifically, it sought to answer the following the questions:

1) Are symptoms of apathy related to poorer memory and executive function beyond the influence of depressive symptoms in individuals with cerebrovascular disease? (Chapter 2: Articles 1 and 2)
2) What is the relative contribution of apathy and depression on cognition (including neutral and emotional memory) in young educated adults? (Chapter 3: Article 3)
    a. Is apathy related to poorer overall cognitive performance to a greater degree than depression?
    b. Are depressive symptoms related to the type of emotional content that is remembered?
3) Can goal-setting instructions, targeted to increase goal-directed behaviour and cognition, improve cognitive performance in the chronic phase after stroke? (Chapter 4: Article 4)

Chapter 1, the General Introduction, included a conceptual review of apathy, its neuroanatomical and neurophysiological underpinnings, its prevalence across clinical and non-clinical populations, its relationship to depression, and its relationship to cognition in individuals

with cerebrovascular disease and healthy adults.

Chapter 2 included two published manuscripts illustrating the relationship between apathy and cognition in cerebrovascular disease. I found that stroke patients with apathy performed worse on verbal learning, short-term free recall, and long-term free recall than stroke patients without apathy (Article 1). I also found that symptoms of apathy predicted category fluency over and above depressive symptoms in individuals with cerebrovascular disease (Article 2). The cognitive subscale in particular (e.g., interest in new experiences) predicted poorer category fluency performance in this sample. Together, and complementing findings from studies in the context of neurodegenerative diseases, I suggested that apathy may be more related to impairment in verbal memory and verbal fluency than depressive symptoms.

Chapter 3 extended this hypothesis to a sample of young, educated adults, where apathy, depression, and cognition (neutral and emotional memory) had yet to be examined together (Article 3). I learned that apathy is indeed present in young, educated adults, with 22% of the sample reporting clinically elevated levels of apathy (AES $\geq$ 34; Sagen et al., 2010). Apathy and depressive symptoms shared only a small-to-moderate correlation with one another, suggesting that these constructs could be successfully differentiated from one another in young adults. Additionally, neither apathy nor depression were related to poorer cognitive performance in EF, WM, or verbal/visual memory. These null findings were also replicated in the subsample of participants who indicated English as their first language learned. Lastly, a valence-related effect on memory was found in clinically elevated depressive symptoms. These results suggest that neuropsychologists who assess cognition in young, educated adults are encouraged to explore reasons other than psychopathology to explain deficits, particularly when evaluating clients who report mild affective or mood symptoms. These findings also offer support that depression may

impact the type of emotional content that is remembered.

Chapter 4 expanded upon Chapter 2 by implementing a short-term intervention to determine whether goal-setting could improve cognitive performance in patients in the chronic phase after stroke. This randomized controlled trial sought to highlight the importance of a) implementing evidence-based goal-setting strategies into practice, b) promoting the use of goal-setting strategies for use beyond physical and functional recovery, and c) implementing goal-setting approaches even in the chronic phase (≥ 3 months) after stroke. I found that stroke patients who received goal-setting instructions improved on neuropsychological tasks of attention/working memory, executive function, and learning, relative to stroke patients who received standard instructions. Reliable change indices for many tasks complemented these findings, whereby a larger proportion of individuals in the goal-setting group demonstrated reliable improvement during the instructional manipulation. Similar trends were observed in the descriptive statistics for the smaller subsample of apathetic stroke patients (n = 24). These findings illustrated that treatments targeting apathy may serve as a novel approach to improving cognitive outcomes after stroke.

Chapter 5 [the current chapter], the General Discussion, will address how these studies contribute to the existing literature on apathy and cognition and how they can inform psychological and pharmacological practice. In Chapters 2-4, I highlighted the direct implications of my research studies. By contrast, in the general discussion, I will extend beyond my specific research findings to the context of the broader literature regarding the assessment and treatment of apathy. Although I cannot extend the implications of my research beyond what I specifically tested, the goal of discussing these findings within a broader framework is to encourage research that can further address considerations related to neuropsychological

assessment, therapeutic efficacy of treatments for apathy, and its relation to cognition and quality of life.

Prevalence and Differentiation of Apathy

The studies in this dissertation provide support that apathy is prevalent in stroke patients and in educated young adults, and that apathy can be differentiated from depression in these populations.

Stroke Patients. Article 1 found that apathy was present in approximately 17% of stroke patients, which is slightly lower than estimated prevalence rates of 20-50% in the stroke literature (Brodaty et al., 2005; Starkstein et al., 1993). Using recommended cut-offs (Lewinsohn et al., 1997; Sagen et al., 2010), 24 participants (17%) were classified as apathetic and 41 (29%) were classified as depressed. Though 17 participants (12%) were both apathetic and depressed, 30 participants (21%) were exclusively either apathetic or depressed. In Article 2, apathy and depressive symptoms were moderately correlated with one another. Of note, there were no sex differences in apathy severity or apathy classification. These studies support the notion that apathy and depression are prevalent and that they can be differentiated from one another as categorical and continuous variables.

Young Adults. Article 3 found that apathy was present in 22% of the sample, which is higher than estimated prevalence rates of 1.4-7.0% in the healthy adult literature (Ishizaki & Mimura, 2011; Lyketsos et al., 2002; Onyike et al., 2007). Similarly, a large proportion of participants (30%) reported clinically significant levels of depression in our sample. Over the past few years, the prevalence of depression in university students has increased, warranting a growing concern about the mental health of university students (Ceyhan et al., 2009). For instance, the depression rate in university students was 24% and between 5-15% in community-

based samples (Kessler & Walters, 1998; Yeung et al., 2002). A review by Ibrahim, Kelly, Adams, & Glazebrook (2013) reported a weighted mean prevalence of depression in 30.6% of university students, with prevalence rates ranging from 10% to 84.5%. Financial concerns, academic pressure, fear of academic failure, and health concerns may also contribute to elevated psychological distress and helplessness, which may also contribute to the higher rates of apathy and depression observed in this population (Ceyhan et al., 2009; Wege, Muth, Li, & Angerer, 2016).

Males also reported greater apathy severity than females in the undergraduate sample. This pattern has similarly been found in university students attending universities in Japan (Uchida, 2010) and in the United States (Coffield, 1981). Uchida (2011) proposed that females may find greater meaning as undergraduate students because the rate of females attending university in Japan is lower than males (e.g., 36.8% versus 51.3% in 2005; Uchida, 2011). However, since the early 1990s, at least 56% of student's enrolled in Canada's public colleges and universities identified as female (Statistics Canada, 2016). Socialization differences, time of year of testing, or differences in biological pathophysiology may have contributed to these observed sex differences (Altemus, Sarvaiya, & Epperson, 2014).

Notably, however, the highest reported AES score was 44 out of a possible 72, indicating that moderate levels of apathy, and not severe levels of apathy, were reported in this sample. This may have been observed for a multitude of reasons, including that rates of severe apathy may be low in educated young adults or because individuals completing in-person university studies may be less likely to be apathetic than those completing online university studies or who do not participate in research. It would be useful to assess levels of apathy in in-person studies and online surveys to better assess whether the latter may be a possibility. It may also be helpful

to try to specifically target participants with moderate to severe apathy in future studies to address whether the relationship between apathy and cognition changes across apathy severity.

Furthermore, 7 participants were both apathetic and depressed and 36 participants were exclusively either apathetic or depressed. Apathy (Apathy Evaluation Scale [AES]) and depressive symptoms (Center for Epidemiologic Studies – Depression Scale [CES-D]) were also moderately correlated with one another. State and trait single-item measures of motivation on the Emotional Verbal Learning Test (EVLT) correlated with apathy (AES) but not depressive symptoms (CES-D), whereas EVLT state and trait single-item measures of sadness correlated with the CES-D but not the AES. These findings suggest that apathy and depression can be differentiated in educated young adults.

Lesson. Taken together, I conclude that apathy is present in young adults and in individuals with cerebrovascular disease and can be differentiated from depression in clinical and non-clinical populations. The fact that the prevalence of apathy was similar in our samples of stroke patients and young adults supports the notion that apathy is both a neuropsychiatric syndrome associated with specific aspects of brain damage and a psychological syndrome associated with depression (Marin, 1991). Thus, it is important to ask specific questions about apathy (lack of interest in pursuing new activities, lack of, low emotional responsivity) to patients at outpatient stroke clinics or those pursuing psychotherapy in order to better differentiate which syndrome is dominating the clinical picture and optimize treatment outcomes, which will be addressed further in this chapter.

Research on Apathy and Cognition: Relation to EF and Higher-Order Cognitive Tasks

The studies in this dissertation focused on cerebrovascular disease illustrated, broadly speaking, that greater apathy is associated with poorer cognition, regardless of level of depression. From

the majority of studies, I found that apathy was most strongly associated with EF and WM. These results complement other behavioural studies (Lohner et al., 2017) as well as neurophysiological studies (Le Heron, Apps, & Husain, 2018) demonstrating that apathy and EF share overlapping neural circuitry.

Stroke Patients. In Article 1, I found that stroke patients with apathy performed worse on verbal learning, immediate free-recall, and long-term free recall than stroke patients without apathy, regardless of level of depression. In Article 2, I found that apathy predicted category fluency over and above the role of depressive symptoms. Apathy, however, was not related to letter fluency. Similar to letter fluency, category fluency requires clustering (involving temporal-lobe processes including verbal memory and word storage) and switching (involving frontal-lobe processes such as strategic search, which is critical for cognitive flexibility in shifting from one subcategory to another; Troyer & Moscovitch, 2006) abilities. As a result, it may be that the relationship observed between apathy symptoms and semantic fluency performance was due, in part, to a reduction in switching, as opposed to cluster size, consistent with Fossati, Guillaume, Egris, and Allilaire's (2002) study. Kavé et al. (2011) also found that impaired switching on semantic tasks was the most useful measure for demonstrating executive deficits in individuals with TBI. Future research may be needed to explore this possibility. Moreover, depression was not related to cognitive performance in either of Articles 1 or 2. Article 4 showed that goal-setting instructions improved stroke patient performance on attention/working memory (i.e., Longest Digit Span Sequencing, Digit Span Total, and TMT-A), verbally-mediated EF (i.e., letter and category fluency), and verbal learning, but not memory. Reliable change indices indicated reliable improvement in the goal-setting group relative to the standard instruction group on digit span total, letter fluency, category fluency, and learning.

Apathy is correlated with, and is also a common characteristic of, impairment in EFs, including fluency, task shifting, planning, inhibition, and cognitive flexibility (Liang, Liang, Ungvari, & Tang, 2016). Damage to prefrontal cortex-basal ganglia circuits, encompassing the ACC and/or dlPFC, have been associated with apathy symptoms (Kimura et al., 2003; Levy, 2012; Middleton & Strick, 2000). The ACC and dlPFC are also functionally interconnected; research regarding ACC-dlPFC connectivity suggest that the ACC may modulate dlPFC activity, while the dlPFC may drive ACC activity (Sallet et al., 2011). Additionally, although memory consolidation is dependent on the medial temporal lobe (e.g., hippocampus, entorhinal cortex, perirhinal cortex; Achim & Lepage, 2005; Schacter & Wagner, 1999), the dlPFC is also involved in memory encoding and retrieval (Alvarez & Squire, 1994; Squire, Knowlton, & Musen, 1993; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). These findings support a relationship between apathy with EF and with memory.

Relationship between apathy and EF and with memory were largely observed in stroke patients in the current dissertation studies. However, in Article 4, goal-setting instructions did not improve overall free recall on the CVLT-II. Of note, only a subsample of participants (n = 60) completed the entire CVLT-II, so there may have been reduced power to detect subtle differences for this particular analysis. The post-hoc univariate ANCOVA revealed that stroke patients in the goal-setting condition performed better than stroke patients in the standard instruction condition on long-term free recall, but not on short-term free recall. Similar to findings in individuals Parkinson's disease, it may also be that long-term verbal memory is more severely impacted by apathy than short-term verbal memory (Dujardin et al., 2009; Martinez-Horta et al., 2013) or that long-term memory difficulties are a consequence of deficits in attention/working memory, which are associated with more severe apathy (Leroi et al., 2012;

Varanese et al., 2011). Continued research regarding the relationship of apathy to short- and long-delay recall should be conducted in stroke patients.

Young Adults. Article 3 elucidated that apathy symptoms were not related to EF, WM, verbal (short- and delay-recall) memory for neutral words, or visual memory (short- and delay-recall) for affective images. These null findings may have occurred for a variety of reasons. First, it is possible that the mild-to-moderate severity of apathy reported in the sample was not severe enough to impact EF, WM, or memory. If a broader range of symptomatology was reported, a relationship between greater apathy and poorer cognition may have been observed. It may also be possible that the composite score calculations diluted the impact of measures that may have been more sensitive in assessing cognitive abilities. For instance, complex WM span tasks, including the RST, have shown higher correlations with higher-order cognitive tasks (i.e., EFs) than simple WM span tasks, such as the DST, which measures short-term storage capacity (Conway et al., 2005). Notably, these findings may simply reflect that mild-to-moderate symptoms of depression and apathy exert a minimal to negligible impact on EF, WM, and memory in young, educated adults. Similar null findings have been reported in outpatients with mild depressive and anxiety symptomatology (Morasco, Gfeller, & Chibnall, 2006; Tsushima et al., 2005). Studies identifying associations between psychopathology and cognitive function have also indicated that the severity of a mental health disorder, rather than the presence of symptoms alone, may account for a greater percentage of the variance in cognitive function (Burt et al., 1995; Christensen et al., 1997).

Future research in this area may seek to recruit young adults with more apathetic psychopathology and to include indices of processing speed (e.g., Digit-Symbol Coding; Wechsler, 1997) and more indices of EF (e.g., Delis-Kaplan Executive Functioning System;

Delis, Kaplan, & Kramer, 2001), including measures of initiation (e.g., Emotional Verbal Fluency; Sass, Fetz, Oetken, Habel, & Heim, 2013), shifting, and inhibition, in order to acquire precision about certain EFs that may be impacted to a greater (or lesser) degree. For instance, EF tasks of initiation (e.g., fluency) have been shown to be impacted by apathy to a greater degree in individuals with Parkinson's disease (Meyer et al., 2015) and in individuals with psychosis (Faerden et al., 2009) than EF tasks of shifting or inhibition (Drechsler, 2007). EF tasks that incorporate reward-based decision making (e.g., Iowa Gambling Task) may also be specifically affected by apathy in young adults (Njomboro, Deb, & Humphreys, 2012). Researchers may also consider incorporating indices of functional ability, self-efficacy, and wellbeing to evaluate their correlations with apathy symptoms in young adults (Tierney et al., 2018).

Lesson. From the studies in my dissertation related to cerebrovascular disease, I found that apathy was related to EF and WM. However, important questions remain to be answered: Does severity matter? Is there a dose-response curve of apathy's impact on cognition? Does the relationship between apathy and cognition change as a function of severity of apathy symptoms? It would be interesting to consider that at mild levels of apathy, there may be a minimal impact on cognition, but at severe levels, the impact of apathy on cognition may be substantial and compromise additional cognitive domains. For instance, Funes et al. (2018) found that apathy mediated the relationship between depression and cognitive control (but not between depression and memory) in older adults with depression. Though Funes et al. (2018) sample was exclusively geriatric adults with depression, it would be interesting to see if apathy served as a moderator of cognitive performance (including EF and memory) in a sample of participants with more diverse psychopathology.

Additional considerations. The instrumentation selected to measure psychopathology in

this dissertation included the CES-D (depressive symptoms; Radloff, 1977) and the AES (apathy symptoms; Marin et al., 1991). The CES-D was incorporated in this dissertation because it is A) one of the recommended screening instruments for depression after stroke (Hachinski et al., 2006), and B) it was initially developed to screen for depression in general community samples (Radloff, 1977). However, in a review of depression scales, Fried et al. (2017) identified that the CES-D had a low symptoms overlap with other depression scales. This review, along with other research programs (Santor, Gregus, & Welch, 2006), highlighted that different instruments may capture different aspects of the heterogeneous depressive syndrome which poses a risk that the selection of a particular scale for a study may bias results. Considering these findings, it could have been useful to incorporate an additional measure of depression, such as the MADRS (Montgomery & Asberg, 1979).

Implications for Psychological Treatment of Apathy in Young Adults

In Article 3, I identified that rates of apathy were high (22%) in our young adult student sample. This rate was higher than I had expected, with possible academic/financial pressures and/or health concerns contributing to the elevated distress and helplessness observed in university students (Ceyhan et al., 2009; Wege et al., 2016). Given the prevalence and differentiation of apathy and depression in young adults, it is essential to consider how apathy may impact engagement in therapy and response to psychotherapeutic interventions. Cognitive behavioural therapy (CBT), an evidence-based, structured, and problem-focused psychotherapy, has been shown to be effective in treating a myriad of psychological disorders. When delivering CBT, it may be beneficial to implement and prioritize certain CBT strategies for individuals if apathy dominates the clinical picture in order to optimize treatment outcomes. Additionally, some interventions focused on the enhancement of motivation, such as Motivational Interviewing

(MI), may be beneficial because they provide greater attention towards assessing and reducing apathy in order to treat other mental health or substance use difficulties.

Participation. Apathy is an important determinant of client involvement in therapy, whereby more motivated clients demonstrate a greater willingness to commit to therapy and embrace conflictual themes (Maclean, Pound, Wolfe, & Rudd, 2002). Higher apathy (i.e., less motivation) is also associated with less active engagement in therapy and lower retention rates (Westra & Dozois, 2008). Some studies have also found that the presence of apathy in patients with depression is correlated with poorer treatment outcomes (Chaturvedi & Sarmukaddam, 1986; Levkovitz et al., 2011).

Cognitive Behavioural Therapy. Cognitive behavioural therapy (CBT) is an evidence-based, structured, time-limited, and goal-oriented psychological treatment that highlights the interconnectedness of thoughts, behaviours, emotions, and physical sensations. CBT protocols often encompass identifying difficulties and developing an awareness of thoughts, emotions, and beliefs about problems, engaging in activity scheduling, conducting behavioural experiments, challenging maladaptive thoughts and creating more balanced thoughts, learning relaxation strategies, and engaging in relapse prevention planning (Beck, 1993; Leahy et al., 2010). The goal of CBT is to develop a toolkit of skills and strategies to identify and challenge maladaptive thinking patterns and behaviours, in order to change how an individual feels about and reacts to a given situation (Beck, 1993). CBT has been shown to be effective in management and treatment of various psychological disorders including depression, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, social phobia, posttraumatic stress disorder, chronic pain, and somatic disorders (see Butler, Chapman, Forman, & Beck [2006] for review).

Given the differentiation between apathy and depression, it may be beneficial to

implement and prioritize certain CBT strategies in individuals if apathy dominates the clinical picture. For instance, it may be more beneficial for clinicians to focus on identifying treatment targets, setting specific, achievable short-term goals whilst providing positive feedback, adopting reward contingencies, and allotting adequate time to evaluate the benefits and drawbacks of changing (Brody, 2009; Miller, 1983; Leahy, Holland, & McGinn, 2010). Promoting autonomy by engaging individuals with apathy in decision-making, providing a rationale and psychoeducation for activities, and garnering an enhanced understanding of their perceptions (e.g., their concern about their mental health and future aspirations) may also augment positive changes (Leahy et al., 2010). Behavioural interventions may also be particularly relevant. Behavioural interventions in CBT involve behavioural monitoring and behavioural activation. Behavioural activation, which encompasses assigning and scheduling activities, can help clients to return to activities and increase goal-directed behaviours.

Conversely, if low mood rather than apathy is dominant, clinicians may place a greater emphasis on identifying and challenging automatic thoughts, maladaptive assumptions, and negative schemas, as well as developing positive self-statements (Brody, 2009). Furthermore, clinicians may focus on humanizing mistakes and replacing self-criticism with acceptance and self-reward (Leahy et al., 2010). Thus, assessing for symptoms of apathy relative to mood disturbances may have different treatment implications. Future research should continue to explore these possibilities in young adults.

Motivational Interviewing. Motivational Interviewing (MI) is a collaborative goal-directed treatment that aims to elicit behaviour change by identifying discrepancies between current behaviours and future goals, supporting self-efficacy, expressing empathy, and exploring resistance (Miller, 1983; Miller & Rollnick, 2002). Embedded in Rogers' (1959) client-centered

therapy, MI uses principles of collaboration (a supportive relationship), evocation (a client explores a given behaviour in a non-judgmental way), and autonomy (a client self-generates arguments for change) to foster increased intrinsic motivation and commitment to behaviour change. MI is typically provided over a few sessions and may be delivered as a freestanding intervention or as a prelude to other treatments (Hettema, Steele, & Miller, 2005). Meta-analyses support the efficacy of MI in treating substance use disorders, increasing physical activity, and improving medication adherence (see Burke, Arkowitz, & Menchola [2003] and Lundahl et al. [2013]). A primary goal of MI is to identify a discrepancy between a client's perception of their current progress (toward a goal) and their desired situation (the rehabilitation goal). Given that apathy is correlated with reduced treatment engagement, interventions to increase engagement may be particularly helpful in managing apathy to treat another problem.

Researchers have examined the effectiveness of combining MI and CBT in adolescents and young adults to treat mental health difficulties (Burke et al., 2003). Individuals who were provided with MI followed by CBT had greater attendance of group CBT sessions, higher treatment initiation, and higher self-rated readiness for treatment than individuals provided with a "befriending" intervention (psychoeducation about group therapy) followed by CBT (Dean, Britt, Bell, Stanley, & Collings, 2016). Additionally, Simon, Ludman, Tutty, Operskalski, and Von Korff (2004) used structured MI exercises to enhance engagement of depressed individuals in telephone CBT. These studies support a possible synergistic effect of MI with other evidence-based treatments, which may be due to reduced apathy and passivity, and a greater willingness to engage in treatment (Burke et al. 2003; Hettema et al., 2005). Thus, future research may examine whether MI may also be beneficial for reducing symptoms of apathy and improving subsequent mental health outcomes (Baker & Hambridge, 2003).

Lesson. It is important to consider and prioritize strategies to optimize treatment outcomes if apathy dominates the clinical picture. Developing a greater appreciation of how apathy and depression manifest clinically and the relevant mechanisms of change may provide fruitful avenues for improving treatment of these individuals.

Implications for Pharmacological and Non-Pharmacological Treatment of Apathy in Stroke Patients

Articles 1 and 2 of my dissertation illustrated that greater apathy is associated with poorer cognition, namely EF and memory, in stroke patients. Article 4 illustrated that goal-setting improved attention/working memory, executive function, and learning in stroke patients at least 3 months after stroke. The cognitive patterns observed for all patients were similar for the subsample of apathetic patients (n = 24) in the goal-setting and standard instruction group. Importantly, there are a few studies that have examined pharmacological treatment options for apathy, with even fewer non-pharmacological treatments for apathy investigated in the stroke literature. As Article 4 drew a link between goal-setting and reliable improvement in cognitive performance, I suggested that treatments targeting low motivation may serve as a promising target to improve cognition in the chronic phase after stroke. Before addressing non-pharmacological treatment options, I will briefly provide information on pharmacological treatments for apathy in stroke patients. Although I did not directly evaluate the effectiveness of pharmacological treatments of apathy in stroke patients in this dissertation, understanding these options and potential complicating factors, including polypharmacy and increased risks for adverse reactions to medications in geriatric populations, ultimately highlight the importance of developing non-pharmacological approaches for these individuals.

Pharmacological Treatment.

Case studies and studies with small sample sizes suggest that pharmacological treatment for apathy differs from depression. Selective serotonin reuptake inhibitors (SSRIs; escitalopram, fluoxetine, sertraline; De Lima & Hotopf, 2003), the most commonly prescribed antidepressants, have been shown to exacerbate symptoms of apathy (Barnhart, Makela, & Latocha, 2004; Levy & Dubois, 2006; Wongpakaran, Van Reekum, Wongpakaran, & Clarke, 2007). Methylphenidate, a psychostimulant which stimulates dopamine agonist and norepinephrine release, has been used to treat apathetic stroke patients (Padala, Burke, Bhatia, & Petty, 2007; Spiegel, Kim, Greene, Conner, & Zamfir, 2009). Individuals with acquired brain injuries who were prescribed dopamine stimulants (bromocriptine, amantadine) reported decreases in apathy symptoms and improved cognitive function (Barett, 1991; Catsman-Berrevoets & von Harskamp, 1988; Kraus & Maki, 1997; Powell, Al-Adawi, Morgan, & Greenwood, 1996). Moreover, single case studies have also supported the use of the dopamine agonist ropinirole (Kohno et al., 2010), zolpidem (Mathieu et al., 2011), and selegiline (Newburn & Newburn, 2005) to treat post-stroke apathy. These studies elucidate the importance of screening for apathy as improperly prescribing anti-depressant medication may exacerbate symptoms of apathy and possibly further impair cognitive functioning (Barnhart, Makela, & Latocha, 2004; Wongpakaran et al., 2007).

Furthermore, there is also a higher prescription prevalence and an increased risk for adverse reactions to medications in geriatric and stroke populations (Hanlon, Schmader, Ruby, & Weinberger, 2001; Spinewine et al., 2007). Interindividual increases in variability in health, disease, and disability across the lifespan make prescribing decisions increasingly difficult for clinicians (Gurwitz, Soumerai, & Avorn, 1990; Simonson & Feinberg, 2005). As a result, inappropriate prescribing may cause substantial morbidity and contribute clinical and economic burdens to patients and society (Spinewine et al., 2007). Given that prescription medications in

older adults has emerged into a worldwide public-health issue, it is imperative to consider other methods for treating apathy in this population (Hanlon, Schmader, Ruby, & Weinberger, 2001).

Non-pharmacological Treatment.

In Article 4, I found that goal-setting improved performance on attention/memory, EF, and learning relative to standard instructions. I also found that a larger proportion of stroke patients in the goal-setting group demonstrated more positive reliable change (using reliable change indices) across each domain than patients in the standard instruction group. This study supports the notion that >3 months after stroke, cognitive impairment is not a fixed deficit: there is a motivational contributor to cognitive impairment after stroke. Our results highlight potential new avenues for treatment or adjuncts to treatments to explore for vascular cognitive impairment, whereby there are few effective treatment options (das Nair et al., 2016; Lanctôt et al., 2019). I posit that incorporating specific, difficult (but reasonable), and measurable goals into everyday activities may lead to improved motivation and thus, facilitate improvement in performance on behavioural and cognitive tasks. Though future research may consider only including individuals with apathy to evaluate goal-setting interventions, this RCT effectively demonstrated the applicability and widespread merit of using simple goal-setting strategies to improve cognitive performance in stroke patients.

Article 4 extended upon Gauggel and Bilino (2002) and Gauggel and Fischer (2001) who found that patients with mixed acquired brain injuries who were provided with goal-setting instructions improved on a non-validated computerized arithmetic task and performance on a motor task in the acute phase of their injury, relative to patients provided with standard instructions. It also extends upon the current literature on goal-setting for functional and physical outcomes that have occurred in small sample sizes and in the acute phase after stroke. For

instance, a pilot study by Skidmore et al. (2015a) found that 15 acute stroke patients who engaged in goal-setting (e.g., strategy training using a "Goal-Plan-Do-Check" format) for 45 minutes per day for 10 days had improved functional independence (Functional Independence Measure [FIM]; Stineman et al., 1996) at 3- and 6-months when compared to a 15-patient reflective listening group. They also found that the strategy training group had greater improvement in cognitive flexibility, but not cognitive inhibition, than the reflective listening group after 6 months (Skidmore et al., 2015a). In a sample of 10 acute (i.e., <30 days) stroke patients, a strategy training group improved more than the control group (i.e., reflective questioning about rehabilitation experience) in functional independence after 6 months, despite the fact that both groups improved over time (Skidmore, Whyte, Butters, Terhorst, & Reynolds, 2015b). One study also showed that problem-solving therapy (PST) reduced apathy in stroke patients (Mikami et al., 2013). PST involves identifying specific problems, generating and evaluating possible solutions, selecting and implementing the best solution, and evaluating the selected solution (Nezu, Nezu, & Perri, 1989). Additionally, a systematic review by Hurn, Kneebone, and Cropley (2006) identified that goal attainment scaling (i.e., identifying and setting SMART goals) is effective for use in physical rehabilitation after stroke. Article 4 complements these findings from a cognitive performance perspective and as an intervention implemented in the chronic phase.

Single-case experimental designs have also investigated methods to decrease apathy in ABI. A multiple-baseline, single-case experimental design that incorporated goal-setting (through external compensation) and motivational interviewing (MI) was shown to decrease apathy in an individual with a traumatic brain injury (Lane-Brown & Tate, 2010). This intervention was successful in helping to initiate and sustain activity towards cumulative goals,

involving organizing the patient's bedroom and developing an exercise routine (Lane-Brown & Tate, 2010). Using task checklists or visual cards to facilitate cueing, establishing a sequence for vocational tasks (e.g., cleaning a bathroom), and implementing scheduled phone reminders, have also been shown to increase goal-directed behaviour in single-case experimental designs (Burke, Zencius, Wesolowski, & Doubleday, 1991; Evans, Emslie, & Wilson, 1998; Sohlberg, Sprunk, & Metzelaar, 1988). Overall, these studies demonstrate effectiveness of treatments for initiation of goal-directed behaviors via external compensation methods in single case designs.

Furthermore, Goal Management Training (GMT), based on goal-neglect theory, is a standardized 20-hour metacognitive training that aims to educate patients about their deficits and to self-monitor their goals, which has been shown to be effective in improving cognition in stroke patients (Levine et al., 2011). GMT targets sustained attention for goals by training patients to stop ongoing, unrelated behaviours and to refocus their attention on a relevant objective. Our study nicely complements GMT - which emphasizes stopping and refocusing on goals - by highlighting the importance of engaging and educating patients to set challenging but achievable, measurable, and time-limited goals in the first place, in order to optimize cognitive and functional performance. This poses a novel therapeutic avenue for executive/attention dysfunction, the most common cognitive domains affected in stroke patients (Lanctôt et al., 2019).

Paving Way for A Goal-Setting Workshop? The findings of Articles 1, 2, and 4 support the relationship between apathy and cognition and the use of goal-setting to improve cognitive performance. Thus, incorporating specific, challenging (but reasonable), and measurable goals into everyday activities may lead to improved motivation and facilitate improvement in performance on behavioural and cognitive tasks. Thus, researchers may consider delivering and

evaluating the effectiveness of a group goal-setting intervention to stroke patients and their families in the chronic phase after stroke. This 1-2 hour intervention workshop may focus on restructuring a patient's home or work environment to focus on identifying and setting specific goals whilst providing ongoing feedback (Leahy et al., 2010) and formulating goals to help identify, orient, prioritize, organize, and execute activities (e.g., folding laundry, caring for plants, cleaning) in order to scaffold executive function and improve feelings of self-efficacy and self-determination (Leahy et al., 2010). External compensation techniques, including setting phone reminders, using visual cue cards for cueing, and sequencing small goals, as performed in single-case experimental designs with ABI patients, may also be taught in the workshop (Burke et al., 1991; Lane-Brown & Tate, 2010; Evans et al., 1998; Sohlberg et al., 1988). Incorporating measures of physical, functional, and cognitive ability, as well as wellbeing, in a longitudinal design (e.g., 3 months, 6 months, 1 year) may also be helpful to evaluate the efficacy of an intervention.

Moving Forward: Addressing the Gap in Research and Clinical Practice. On a broader level, these findings also speak to the gap in knowledge translation between research and clinical practice in the rehabilitation space. Studies have illustrated that healthcare professionals value goal setting in both acute and community-based stroke rehabilitation but may not clearly define or measure outcomes of these goals in stroke rehabilitation (Scobbie, Duncan, Brady, & Wyke, 2015). Wressle, Eeg-Olofsson, Marcusson, and Henriksson (2002) found that goal-setting increased patient involvement in rehabilitation initiatives. Holliday, Antoun, and Playford (2005) reported that only 14% of rehabilitation specialists used a formalized goal-setting approach with patients for physical or functional recovery (e.g., Canadian Occupational Performance Measure [COPM; Baptiste et al., 1993], Goal Attainment Scale [GAS; Kirusek, Smith, & Cardillo, 1994],

or Contractually Organized Goal-Setting [COGS; Powell, Heslin, & Greenwood, 2002]). A review by Prescott, Fleming, and Doig (2015) highlighted that 54% of goals set during rehabilitation (functional and physical) were not realistic and that 30% of goals were not measurable. These studies exemplify that researchers value goal-setting approaches in stroke rehabilitation, but there is a gap in implementing evidence-based goal-setting strategies into practice and using goal-setting strategies outside of physical and functional recovery. With Article 4, the idea that the cognitive impairment after stroke may not be fixed (e.g., a result of disconnection/neuronal loss/capacity loss) but can be improved by simply targeting motivation, has tremendous implications for daily functioning and cognition if it can be generalized beyond these specific cognitive tasks into functional cognitive goals. Thus, we hope to elucidate the importance of using and examining the role of goal-setting for cognition and functional independence in stroke patients.

Implications for Neuropsychological Assessment in Stroke Survivors

This dissertation, namely Articles 1, 2, and 4, support the notion that there is also a motivational contributor to cognitive impairment after stroke. This has important implications for neuropsychological testing. First, low scores on neuropsychological measures may not acurrately reflect stroke patients' abilities. These patients may benefit from goal-setting instructions to an even greater degree than neurotypical individuals during neuropsychological testing. Engaging more frequently in *testing the limits* with goals and additional time with stroke patients may produce more qualitatively accurate reflections of true capabilities in which to base more helpful recommendations. This suggestion is complemented by recent progress in considering a combined qualitative and quantitative approach to assessment of executive difficulties (Hankee et al., 2013) and of individuals with epilepsy (Ogden-Epker & Munro Cullum, 2001). Testing the

limits may also positively influence rapport and help to maintain patient self-esteem (Axelrod & Schutte, 2011). Second, and more broadly, test scores may also be invalid if there is diminished effort (Meyers, Volbrecht, Axelrod, & Reinsch-Boothby, 2011; Rohling, Green, Allen, & Iverson, 2002). For instance, Rohling et al. (2002) found that there were no differences in neuropsychological performance between individuals with and without depressive symptoms when participants were excluded who did not provide sufficient effort. As such, effort testing and symptom validity measures are also encouraged to be utilized during neuropsychological assessment with stroke patients (Green & Merten, 2013; McClintock, Husain, Greer, & Cullum, 2010). Third, it may be beneficial to design a cognitive measure with standardized goal-setting norms in order to quantify the extent to which a patient benefits from instructions to facilitate interpretation of neuropsychological performance.

Limitations

Limitations to this dissertation include the self-report nature of assessing apathy, apart from Article 4. Given that apathetic individuals may have poor insight into their symptoms, rates of apathy may have been underestimated, as observed in Njomboro and Deb (2012). Although Clarke et al. (2011) concluded in a review of apathy instruments that the AES is the most psychometrically robust and widely used measure for assessing apathy, the relatively fewer items evaluating the social interaction (2 items) and emotional (2 items) dimensions (highlighted in Robert et al. [2018]) may have disproportionally weighted symptom severity towards the diminished goal-directed behaviour and cognition dimension, meaning that individuals with withdrawn social interactions and emotional indifference may not have been represented as well by the AES. However, the behaviour and cognition dimensions were arguably of the most primary interest for this dissertation. Furthermore, although self-reported apathy has significantly

correlated with both clinician-rated and informant-rated apathy (Marin, 1991; Mason & Barker, 2015), it may have been useful to implement the Robert et al. (2018) criteria to gain an even better estimate of apathy rates using consistent diagnostic criteria. Of course, this would have imposed additional time requirements for study completion that may have deterred individuals from participating. Another limitation is that Articles 1 and 2, reporting relationships between greater apathy and poorer EF (Article 1) and with poorer memory (Article 2) in stroke patients, and Article 3, reporting no relationships between apathy and cognition in educated young adults, used cross-sectional data. Some longitudinal studies have associated apathy with an accelerated decline in cognitive and functional ability (Robert et al., 2006; Starkstein et al., 2005). Future research may emphasize using a longitudinal design to evaluate how these relationships may change over time, particularly in stroke patients.

In addition, apathy was present in 22% of young educated adults, but self-reported severity fell only in the mild to moderate range with AES scores ranging between 19 – 44 out of a possible 72. Given that none of the participants reported severe apathy, it is unknown whether the effect of apathy on cognition (namely EF and complex working memory) would changes as a function of symptom severity. Thus, it would be useful to specifically target participants with moderate to severe apathy in future studies to address whether the relationship between apathy and cognition changes across apathy severity. However, it may also be possible that rates of severe apathy are low in young university-attending adults.

In stroke patients, I actively attempted to recruit across the symptomatology spectrum by approaching patients before or after their appointment with their neurologist to complete the studies. Using this approach, I was able to recruit more individuals falling in the moderate to severe range as well (Articles 1 and 2: AES between 18 - 56; Article 4: AES between 19-58).

Furthermore, I recruited stroke patients with diverse educational backgrounds (ranging from 5 to 30 years of education), medical histories, cognitive abilities, psychopathology, and locations of stroke in order to illuminate the generalizability of our findings. However, these findings cannot be generalized to patients with aphasia, with dementia, or who are not fluent in English. I also did not include a healthy control participants group (i.e., without any stroke history) in the goal-setting RCT in Article 4. Including a control group would have provided valuable information about the relative improvement in patient performance compared with the hypothesized improvement seen in control participants with goal-setting instructions. An examination of cognitive deficits in stroke patients relative to healthy controls may have also assisted in further highlighting the clinical importance of assessing apathy in this population.

Future Directions

Methodology. The current studies focused on the relationship between apathy on cognitive performance but did not assess its relationship to quality of life or activities of daily living. Future research should include additional indices of EF, including self-monitoring, organization, and flexibility (Delis et al., 2001), in order to enhance our understanding of EFs that may be affected to a greater degree than other EFs by apathy. Researchers are also encouraged to incorporate indices of functional ability and wellbeing to studies examining apathy and cognition (Tierney et al., 2018). Inclusion of these measures may allow for a more comprehensive examination of cascading impacts, via path analysis, of apathy on cognition to quality of life, particularly in stroke populations.

Complementing Funes et al. (2018), who found that apathy mediated the relationship between depression and cognitive control in older adults with depression, it may also be of interest to examine apathy as a moderator between depression and cognition (including EF and

memory), in order to understand whether these relationships may change as a function of increases in symptom severity.

As previously mentioned, this dissertation (apart from Article 4) primarily examined cross-sectional relationships between apathy, depression, executive function, and memory. Therefore, we cannot draw causal inferences regarding these associations. This means that the relationship between apathy and cognition may be a result of shared frontostriatal brain damage. The relationship between apathy and cognition may also be bidirectional, as individuals with poorer cognitive function may be more likely to develop apathy, and individuals with apathy may be more likely to deteriorate cognitively or be cognitively impaired (Palmer et al., 2010). For instance, post-stroke apathy has been shown to predict poorer recovery of cognitive function (Mikami et al., 2013), while greater baseline cognitive impairment, particularly in EF, is related to subsequent increases in symptoms of apathy (Douven et al., 2018). As a result, in order enhance our understanding of the relationship between apathy and cognition, it could be fruitful to examine if and how the associations between these constructs may evolve over time, both in stroke survivors and in healthy older adults. Alternatively, similar to the induction of sad mood, it could be interesting to induce or effect symptoms of apathy (low motivation) during the completion of cognitive and functional tasks. A randomized controlled trial that induces symptoms of apathy (as opposed to examining cross-sectionally or improving motivation) may also provide useful information regarding causality.

Assessment. As observed in Article 4, stroke patients may benefit from goal-setting instructions to an even greater degree than neurotypical individuals during neuropsychological testing. Engaging more frequently in *testing the limits* with goals and additional time with stroke patients may produce more qualitatively accurate reflections of true capabilities in which to base

more helpful recommendations. In this light, it may be useful for researchers to consider designing an EF measure with standardized goal-setting instructions to quantify the extent to which a patient may benefit from instructions to help interpret performance on neuropsychological testing.

Treatment. Given the differentiation between apathy and depression, it may be beneficial to implement and prioritize certain CBT strategies in individuals if apathy dominates the clinical picture. For instance, it may be more beneficial for clinicians to focus on identifying treatment targets, setting specific, achievable short-term goals whilst providing positive feedback, adopting reward contingencies, and allotting additional time to evaluate the benefits and drawbacks of changing (Brody, 2009; Miller, 1983; Leahy et al., 2010). Incorporating consistent diagnostic criteria in clinical practice using Robert et al. (2018) may also improve the widespread adoption of screening for apathy in neurocognitive, neurodegenerative, and psychiatric conditions. Over time, this screening approach may also help to develop clinical profiles that can be matched with specific recommendations of non-pharmacological goal-related interventions (e.g., behavioural activation, external compensation). As previously mentioned, researchers may also consider delivering and evaluating the effectiveness of a group goal-setting intervention to stroke patients and their families in the chronic phase after stroke. This 1-2 hour workshop could incorporate goal identification, organization, prioritization, and execution training strategies with external compensation techniques (e.g., phone reminders, lists, and visual cues; Lane-Brown & Tate, 2010; Leahy et al., 2010). Incorporating measures of physical, functional, and cognitive ability, as well as wellbeing, in a longitudinal design (e.g., 3 months, 6 months, 1 year) may also be helpful to evaluate the efficacy of an intervention of this nature.

Summary

The growing interest in understanding the psychiatric, neurobiological, and neuropsychological mechanisms that underlie and correlate with apathy coincides with its recognition as a potential treatment target across psychiatric disorders, cerebrovascular diseases, and neurodegenerative diseases. These studies have filled an important knowledge gap in our understanding of the relationship between apathy and cognition in young adults and in stroke patients. The current dissertation has demonstrated the importance of screening for apathy (even in the absence of depressive symptoms) and differentiating symptoms of apathy and depression. It has also highlighted the negative relationship between apathy and cognition in stroke patients, including EF and memory, and demonstrated the utility of goal-setting to enhance cognitive performance. It has also offered support that mild-to-moderate symptoms of depression and apathy exert a minimal to negligible impact on EF, WM, and memory in young, educated adults. Considering the high prevalence of apathy across different diseases and its detrimental impact on rehabilitation, quality of life, and caregiver distress, it is critical to continue investigating how to optimize non-pharmacological treatment of apathy in stroke patients and in young adults to improve mental health, cognition, and QoL of these populations.

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Appendices

Appendix A

Apathy Evaluation Scale: Self-Report

Instructions: Please think of your behaviour over last 2-3 weeks and place an X in appropriate box.

	Not at all	Slightly	Somewhat	Very Much
1. Are you interested in things?				
2. Do you get things done during the day?				
3. Is getting things started on your own important to you?				
4. Are you interested in having new experiences?				
5. Are you interested in learning new things?				
6. Do you put little effort into anything?				
7. Do you approach life with intensity?				
8. Is seeing a job through to the end important to you?				
9. Do you spend time doing things that interest you?				
10. Does someone have to tell you what to do each day?				
11. Are you less concerned about your problems than you should be?				
12. Do you have friends?				
13. Is getting together with friends important to you?				
14. When something good happens, do you get excited?				
15. Do you have an accurate understanding of your problems?				
16. Is getting things done during the day important to you?				
17. Do you have initiative?				
18. Do you have motivation?				

Appendix B

Center for Epidemiological Studies Depression Scale (CES-D)

Below is a list of some of the ways you may have felt or behaved. Please indicate how often you've felt this way during the **past week.** Respond to all items.

Place a check mark (✓) in the appropriate column. **During the past week...**	**Rarely or none of the time (less than 1 day)**	**Some or a little of the time (1-2 days)**	**Occasionally or a moderate amount of time (3-4 days)**	**All of the time (5-7 days)**
1. I was bothered by things that usually don't bother me.				
2. I did not feel like eating; my appetite was poor.				
3. I felt that I could not shake off the blues even with help from my family.				
4. I felt that I was just as good as other people.				
5. I had trouble keeping my mind on what I was doing.				
6. I felt depressed.				
7. I felt that everything I did was an effort.				
8. I felt hopeful about the future.				
9. I thought my life had been a failure.				
10. I felt fearful.				
11. My sleep was restless.				
12. I was happy.				
13. I talked less than usual.				
14. I felt lonely.				
15. People were unfriendly.				
16. I enjoyed life.				
17. I had crying spells.				
18. I felt sad.				
19. I felt that people disliked me.				
20. I could not "get going."				

Appendix C

Controlled Oral Word Association Test (COWAT)

Instructions:

"In this test, I will give you a letter of the alphabet, and I'd like you to tell me as many different words as you can think of that begin with that letter. You may say any words, but there are a couple of rules. The first rule is that you cannot give me proper names such as the names of people or places. For example, if I gave you N, you would not say Nancy, Naples or November. The second rule is that you must use different words. Do not use the same word again with a different ending. For example, if you say nap, don't say naps, napping or napped. Let's practice. If I gave you the letter P, you could say pig, put, phone, pretty and so on. Can you think of other words that fall within the rules?"

"That is fine. Now I am going to give you a letter and you are to say all of the words beginning with that letter that you can think of. Remember, no names of people of places, just ordinary words. I want you to keep on trying until the time limit is up. You will have a minute for each letter. The first letter is F. Tell me as many words as you can that begin with the letter F in 1 minute".

Secs	F	A	S
15			
30			
45			
60			

Words Recalled: ☐ ☐ ☐

Instructions Remembered? ☐

Appendix D

Category Fluency Test (Animal Naming)

Instructions: "I'm going to change things a little now. This time I'd like you to think of words that belong to a certain category. Tell me as many different kinds of animals as you can. It does not matter what letter of the alphabet the animal name begins with, as long as it's an animal! An animal is anything living that walks, crawls, swims, or flies. Tell me as many different animals as you can, go!"

Use a stopwatch or wristwatch with a second hand and note the time the individual begins to name animals as the start of the 60-second time period. It is wise to actually write down the start time (e.g. "0:23"). If the individual stops responding or becomes otherwise distracted, you should provide a prompt such as, "Keep going; remember to name as many different animals as you can". Count perseverations only if the individual does not self-correct. For example, if the individual already has said, "cat" and later on says, "Cat, dog, horse, and cow"… [pause]…"oops, I said 'cat' before, didn't I?" do not count the second cat response as a perseveration.

Secs	Animals
15	
30	
45	
60	

Number of Animals Named ☐ **Perseveration Errors** ☐

Appendix E

ISPR Recruitment for Article 3

Study name: Do you remember?

Description: There are a variety of different measures of memory that are used in populations of young adults. The purpose of the current study is to examine different types of memory and your mood. Participants will complete a series of questionnaires and memory assessments in the laboratory with a research assistant. We will be examining your working memory, short-term memory, long-term memory, and memory for past events. Assessments will involve both researcher and computer administered assessments. This study will take approximately 70 minutes to complete. This study is conducted only in English. Recruitment is on a first-come, first-served basis. This study should take about 70 minutes to complete and participants will receive 2 credits for participating.

Appendix F

Sociodemographic Questionnaire for Article 3

1. Age (in years): _____

2. The sex you were assumed at birth:

- o Male
- o Female
- o Intersex
- o Other, please specify… _____

3. The gender you identify with:

- o Man
- o Woman
- o Transman
- o Transwoman
- o Gender fluid / gender queer
- o You don't have an option that applies to me. I identify as (please specify): _____

4. Ethnic or racial background (check all that apply):

- o African
- o African American
- o Asian
- o Caucasian
- o East Indian
- o European
- o First Nations
- o Hispanic
- o Other, please specify… _____

5. University Information:

What is your university major? _____

Year of study:

- o 1st year
- o 2nd year
- o 3rd year
- o 4th year
- o More than 4th year

How many years of education have you had (starting with Grade 1)? _____

6. Relationship Status:

- o Single
- o Dating
- o Committed relationship
- o Common Law or Living together
- o Engaged
- o Married
- o Divorced
- o Widowed
- o Other, please specify... _____

7. Relationship Status:

- o Single
- o Dating
- o Committed relationship
- o Common Law or Living together
- o Engaged
- o Married
- o Divorced
- o Widowed
- o Other, please specify... _____

8. Is English your first language?

- Yes
- No

8B. Select any other languages you are fluent in:

- o French
- o Chinese
- o Japanese
- o Spanish
- o Arabic
- o German
- o Greek
- o Italian
- o Portuguese
- o Russian
- o Polish
- o Vietnamese
- o Dutch
- o Other: _____

9. Are you taking any medication(s) right now?

- Yes
- No

If yes, what kind of medication(s)? _____

If yes, for how long have you been taking these medication(s)? _____

10. Do you engage in recreational drug use? Yes No

10B. Please specify which drug(s):_____

11. In the **past year**, how often have you smoked marijuana?

Never	Once or twice	Monthly	Weekly	Daily or almost daily

12. Thinking about a typical night in the **past month**: How many nights a week do you have a problem with your sleep (e.g., trouble fall asleep, staying asleep, sleeping too much)?

0-1	2	3	4	5-7

13. Thinking about the **past month**, to what extent has poor sleep troubled you in general?

Not at all	A little	Somewhat	Much	Very Much

14. Have you been diagnosed with a physical health condition (e.g., diabetes)? _____

If yes, what kind? _____

15. Have you ever been diagnosed with any of the following mental disorders by a physician or mental health care professional? (check all that apply)

- o Neurodevelopmental disorder (e.g, intellectual disability, autism spectrum disorder, ADHD)
- o Schizophrenia spectrum or other psychotic disorder
- o Bipolar disorder
- o Depressive disorder (e.g., major depressive disorder, dysthymia)
- o Anxiety disorder (e.g., phobia, social anxiety, panic disorder)
- o Obsessive-compulsive disorder
- o Trauma- or stressor-related disorder (e.g, posttraumatic stress disorder)
- o Dissociative disorder (e.g., dissociative identity disorder, depersonalization/derealization disorder)
- o Eating or feeding disorder (e.g., bulimia, anorexia)
- o Sleep-wake disorder (e.g., insomnia disorder, narcolepsy)
- o Paraphilic disorder (e.g., pedophilic disorder, exhibitionistic disorder)
- o Sexual dysfuntion (e.g, erectile disorder)
- o Gender dysphoria (i.e., gender identity disorder)
- o Disruptive, impulse-control or conduct disorders
- o Substance-related or addictive disorders
- o Neurocogntive disorder (e.g., Alzheimer's)
- o Personality disorder (e.g., borderline personality disorder, antisocial personality disorder)
- o Other, please specify... _____
- o Not applicable. I have never been diagnosed with a mental disorder.

If you have been diagnosed with a depressive disorder…

What was your diagnosis:
_____

When did you receive this diagnosis: _____

Have you received treatment for this diagnosis?

o Yes
o No

Are you currently receiving treatment for this diagnosis?

o Yes
o No

Are you currently, or have you in the past, taken medication(s) for this diagnosis?

o Yes
o No

If yes, what medication(s): _____

If yes, when did you take this medication (Month/Year): _____

If yes, for how long have you taken this medication? _____

Appendix G

Emotional Verbal Learning Test – Adapted State and Trait Measures

Now I am going to ask you some questions about how you are feeling. At this moment, on a scale from 1 to 7, with 1 being not at all and 7 being extremely, how happy do you feel?
Using the same scale, how sad do you feel right now?
How angry?
How anxious?
How motivated?

Now I am going to ask you some questions about how you feel in general. In general, on a scale from 1 to 7, with 1 being not at all and 7 being extremely, how happy do you generally feel?
Using the same scale, how sad do you feel in general?
How angry?
How anxious?
How motivated?

Appendix H

Reading Span Test

The test begins with the following text:

"For this practice task, letters will appear on the screen one at a time. Try to remember each letter in the order they are presented. After you see 2-3 letters presented, you will see a screen with 12 possible letters. Your task is to select each letter in the order presented. Use your mouse to select the letters. When you have selected all the letters, and they are in the correct order, hit the enter button. If you make a mistake, hit the clear button to start over. If you forget one of the letters click on the blank button to mark the spot of the missing letter."

Next, participants practice the sentence reading part of the task:

"A sentence will appear on your screen that will look like this: 'I like to run in the park.' As soon as you see the sentence, you should read it and work out if it makes sense or not. An example of a sentence that does not make sense would be: 'I like to run in the sky.' On the screen after the sentence, you will see: 'This sentence makes sense, with a button marked true and a button marked false. If the sentence on the previous screen made sense, click on the true button. If the sentence did not make sense, click on the false button."

Next, participants complete both parts at the same time:

"In the next practice set, you will be given one sentence to read. Once you make your decision about the sentence, a letter will appear on the screen. Try and remember the letter. In the previous section when you only read the sentences, the computer computed your average time to read the sentences. If you take longer than your average time, the

computer will automatically move you onto the next letter part, thus skipping the true or false part and will count that problem as a sentence error. Therefore, it is important to read the sentences as quickly and as accurately as possible."

Appendix I

Autobiographical Memory Test

Instructions

"I am interested in your memory for events that have happened in your life. I am going to read to you some words. For each word I want you to think of an event that happened to you which the word reminds you of. The event could have happened recently (yesterday, last week) or a long time ago. It might be an important event, or trivial event.

Just one more thing: the memory you recall should be a specific event. So if I said the word "good" – it would not be OK to say, "I always enjoy a good party", because that does not mention a specific event. But it would be OK to say "I had a good time at Jane's party" (because that is a specific event). It is important to try retrieve a different memory or event for each cue word. Let us try some words for practice:

enjoy
friendly
bold

The participant will be cued until they get a specific memory for the practice words. After they state a specific memory, confirm that their response is the type of response that the experimenters are looking for. This will occur for at least 2 practice words."

Prompt: "Can you think of a particular time?"

Word	Specific	Extended	Categoric	Semantic associate	No response	Prompt for clarification
Happy						
Gigantic						
Sad						
Hopeful						
Fashion						
Grief						
Excited						
Onion						
Upset						
Lively						
Bathe						
Guilty						

Appendix J

Counterbalancing Conditions for Article 3

Condition 1:

1) California Verbal Learning Test-II (acquisition and short-term recall)
2) Autobiographical Memory Test
3) Reading Span Test
4) State/Trait Questions
5) CVLT-II (long-term recall)
6) Center for Epidemiological Studies Depression Scale
7) Emotional Pictures Task
8) Controlled Oral Word Association Test
9) Semantic Fluency Test
10) Digit Span Test
11) Apathy Evaluation Scale
12) Sociodemographic questionnaire
13) Emotional Pictures Recall

Condition 2:

1) Emotional Pictures Task
2) Controlled Oral Word Association Test
3) Semantic Fluency Test
4) Digit Span Test
5) Apathy Evaluation Scale
6) Sociodemographic questionnaire
7) Emotional Pictures Recall
8) Center for Epidemiological Studies Depression Scale
9) California Verbal Learning Test-II (acquisition and short-term recall)
10) Autobiographical Memory Test
11) Reading Span Test
12) State/Trait Questions
13) CVLT-II (long-term recall)

Condition 3:

1) California Verbal Learning Test-II (acquisition and short-term recall)
2) Reading Span Test
3) State/Trait Questions
4) Autobiographical Memory Test
5) CVLT-II (long-term recall)
6) Center for Epidemiological Studies Depression Scale
7) Emotional Pictures Task
8) Digit Span Test

9) Apathy Evaluation Scale
10) Controlled Oral Word Association Test
11) Semantic Fluency Test
12) Sociodemographic questionnaire
13) Emotional Pictures Task (long-term recall)

Condition 4:

1) Emotional Pictures Task
2) Digit Span Test
3) Apathy Evaluation Scale
4) Controlled Oral Word Association Test
5) Semantic Fluency Test
6) Sociodemographic questionnaire
7) Emotional Pictures Task (long-term recall)
8) Center for Epidemiological Studies Depression Scale
9) California Verbal Learning Test-II (acquisition and short-term recall)
10) Reading Span Test
11) State/Trait Questions
12) Autobiographical Memory Test
13) CVLT-II (long-term recall)

Appendix K

Consent Form for Article 3

uOttawa

CONSENT FORM FOR RESEARCH PARTICIPATION

Version: October 12, 2017

Title

Do you remember?

Researchers

Andrea R. Ashbaugh, Ph.D., C. Psych
University of Ottawa
School of Psychology

Keera Fishman, PhD Student
University of Ottawa
School of Psychology

Invitation to Participate

You are being invited to participate in this survey conducted by Andrea R. Ashbaugh, Ph.D., and Keera Fishman, Ph.D. Student, at the University of Ottawa.

Purpose of the Study

There are a variety of different measures of memory that are used in populations of young adults. The purpose of the current study is to examine different types of memory and your mood.

Participation

Your participation will consist of answering a series of questionnaires about your mood and a completing series of memory tests. We will be examining your working memory, long-term memory, and memory for past events. This study will take approximately 70 minutes to complete. Participants will also complete a demographic questionnaire, where they will identify their age, sex, gender, years of education, marital status, and any mental health diagnoses.

Benefits

There are no specific benefits to participants. This study will measure your memory and mood. The primary benefit of your participation is that you have helped with the advancement of our knowledge about mood and memory. Portions of the data gathered in this study will be used for the Ph.D dissertation of Keera Fishman.

Risks

Answering questions about your emotions and feelings when recalling memories may result in mild transient discomfort.

If these feelings persist or are too uncomfortable, below are some resources that may be helpful:

. http://www.cpa.ca/psychologyfactsheets/
. http://www.bps.org.uk/psychology-public/psychology-and-public
. Ottawa Distress Centre, 613-238-3311
. Tel-Aide Outaouais, 613-741-6433
. Centre d'Aide 24-7, 819-595-9999
. Ottawa Academy of Psychology, 613-235-2529
. University of Ottawa Student Academic Success Service, http://www.sass.uottawa.ca/about/mental-health-wellness.php

In addition, upon completion of this study, you will be provided with a list of self-help and professional resources, should you be interested in receiving more information about emotional difficulties. You may also contact Dr. Andrea Ashbaugh for other available resources.

Voluntary Participation

Your participation is voluntary. You can end your participation at any time without any negative consequence to you. You are also free to skip a question you prefer not to answer. If you refuse to participate in this study it will have no impact on your academic program.

Confidentiality and Anonymity

The information that you will share will remain strictly confidential and will be used solely for the purposes of this research. The only people who will have access to the research data are research personnel of Andrea R. Ashbaugh at the University of Ottawa. Results will be published in pooled (aggregate) format and presented at professional conferences and in academic journals. The University of Ottawa Research Ethics Board may access the study records and data to ensure the ethical conduct of this study.

Conservation of Data

All participant information and data will be stored on password-protected computers and/or password-protected external hard drives in the laboratory space of Dr. Ashbaugh (VNR 4005). In order to protect confidentiality, your information will only be identified via your ISPR identity code. Your anonymous electronic data will be stored indefinitely. The audio recording will be transferred to a password-protected computer and/or password-protected external hard drive in the laboratory space of Dr. Ashbaugh, and will be stored indefinitely. Your written test data will be stored and locked in the protected laboratory space of Dr. Ashbaugh for 7 years.

Compensation

If you signed up to participate through ISPR, you will receive 2 ISPR credits for your participation. If you choose to withdraw from the study at any time, you will still receive this compensation. If you were recruited from flyers posted around the University of Ottawa campus, you will be given a $5 gift card to a coffee shop.

Contacts

Please address your questions to Andrea R. Ashbaugh (613) 562-5800 x. 4813. If you have questions concerning your rights as a study participant, you may contact the Protocol Officer for Ethics in Research, University of Ottawa, Tabaret Hall, 550 Cumberland Street, Room 154, Ottawa, ON K1N 6N5.
Tel: (613) 562-5387
Email: ethics@uottawa.ca

Consent

Participants should retain this consent form for their records. By signing the page below, you acknowledge that you have read this document and that you consent to participate in this study:

Participant Name:	Signature:	Date:
_____	_____	_____
Experimenter Name:	Signature:	Date:
_____	_____	_____

Appendix L

Debriefing Form for Article 3

uOttawa

DEBRIEFING FORM FOR RESEARCH PARTICIPATION

Version: October 12, 2017

Thank you for participating in our research.

Title:

Do you remember?

Investigators and Institution:

The study you just participated in is being conducted by Andrea R. Ashbaugh, Ph.D., and Keera Fishman, Ph.D. student, at the University of Ottawa.

Study Purpose and Implications:

Recent studies have suggested that apathy (i.e., a lack of behavioural, cognitive, and emotional motivation) may disrupt various aspects of memory, including working memory and long-term memory, to a greater degree than depression (Lezak, 1995; Pluck & Brown, 2002; Scheurich et al., 2008). At present, limited studies have examined these psychiatric symptoms together, and their effects on emotional and neutral memory tasks in healthy young adults. This study aimed to examine the effect of apathy and depression on different measures of memory (e.g., word learning, long-term memory, working memory). We hypothesize that apathy will be related to overall memory performance, whereas depression will be related to learning and recall specifically for negatively valenced words and information. This study will allow us to further explore the differential impact of mood on neutral and emotional memories, and may provide further information regarding the potential suitability of using certain techniques (e.g., goal-setting) to improve cognitive performance.

If you would like your data to be excluded from this study now that you are aware of the goals of the study, please contact the Cognitions and Anxiety Studies Laboratory and we will ensure that your data is promptly destroyed. If you have experienced extreme distress as a result of participation in the study, you can contact the Cognitions and Anxiety Studies Laboratory. If you would like to obtain personal support or help for depression a list of potential resources in the Ottawa area is included at the bottom of this handout.

To learn more about apathy, depression, and memory performance, you can also consult the

following articles:

Adams, K. B. (2001). Depressive symptoms, depletion, or developmental change? Withdrawal, apathy, and lack of vigor in the Geriatric Depression Scale. *The Gerontologist, 41*, 768- 777.

Castaneda, A. E., Suvisaari, J., Marttunen, M., Pera, J., Saarni, S. I., Aalto-Setala, T., ... Tuulio-Henriksson, A. (2008). Cognitive functioning in a population-based sample of young adults with a history of non-psychotic unipolar depressive disorders without psychiatric comorbidity. *Journal of Affective Disorders, 110,* 36–45.

Conway, M. A., & Pleydell-Pearce, C. W. (2000). The construction of autobiographical memories in the self-memory system. *Psychological Review, 107,* 261–288.

Scheurich, A., Fellgiebel, A., Schermuly, I., Bauer, S., Wölfges, R., & Müller, M. J. (2008). Experimental evidence for a motivational origin of cognitive impairment in major depression. *Psychological Medicine, 38,* 237-246.

Wagner, A. D. (2006). Encoding and retrieval from long-term memory. In E. E. Smith & S. M. Kosslyn (Eds.), *Cognition: Mind & Brain* (pp. 192-238). Upper Saddle River, NJ: Pearson Education/Prentice Hall.

Resources for Depression:

Canadian Mental Health Association (CMHA)
Location: 1355 Bank St, Suite 301, Ottawa, Ontario
Tel: 613-737-7791
Services: Mental health information and referral service, which offers information on mental health services, referrals to needed/wanted services, needs assessments, education, advocacy, and consultation to Ottawa residents. Services in French and English.
Website: www.cmhaottawa.ca

Community Information Centre of Ottawa (CICO)
Tel: 613-241-4636 x 211 or Toll Free 1-866-540-0565
Services: Provides information about a wide range of services in the Ottawa area, including information and referral through the 241-INFO line, fax and email. Information available in French and English.
Website: www.cominfo-ottawa.org

Eastern Ottawa Resource Centre (EORC)
Location: 2339 Ogilivie Road, Main level, Ottawa, Ontario
Tel: 613-741-6025 or 613-745-4818 x6137453665 (Crisis line)
Services: Various programs and services including resource and referral, community development and mental health support. Services offered in English and French.

Website: www.eorc-gloucester.ca

Nepean, Rideau and Osgoode Community Resource Centre (NROCRC)
Location: 1642 Merivale Rd. Nepean, Ontario
Tel: 613-596-5626
Services: Non-profit organization serving Nepean, Rideau and Osgoode wards. Services include counseling, housing loss prevention and information and referrals to other services. Services in English only.
Website: www.nrocrc.org

Ottawa Academy of Psychology Referral Service
Tel: 613-235-2529
Services: Service provided by the Ottawa Academy of Psychology to help individuals find a psychologist in Ottawa (Note that not all psychologists in Ottawa are members of the Ottawa Academy of Psychology).
Website: www.ottawa-psychologists.org

Student Academic Success Service
Location: 100 Marie-Curie Private (4th Floor, MCE), Ottawa, Ontario
Tel: 613-562-5200
Fax: 613-562-5964
Email: couns@uOttawa.ca

Immediate Resources

- Ottawa Distress Centre, 613-238-3311
- Tel-Aide Outaouais, 613-741-6433
- Centre d'Aide 24-7, 819-595-9999

Self-Help Resources related to Depression

Gilbert, P. (2009). *Overcoming depression: A self-help guide using cognitive behavioural techniques.* London: Robinson.

Greenberger, D., Padesky, C. A., & Beck, A. T. (2015). *Mind over mood: Change how you feel by changing the way you think.* New York, NY: Guilford Publications.

Wright, J. H., & McCray, L. W. (2012). *Breaking free from depression: Pathways to wellness.* New York, NY: The Guilford Press.

Thank you for your participation in this study.

Appendix M

Alternate Digit Span Test (aDST)

Now I'm going to say some numbers. Listen carefully, I can only say them one time. When I am through, I want you to say them back to me in the same order. Just say what I say.

WITH GOAL-SETTING INSTRUCTIONS: Last time you completed this test, you could recall (#) numbers in a row. Now, I want you to recall (#+1) numbers for this task.

Trial		Correct?
1)	5 – 3 2 – 9	
2)	1 – 4 – 8 2 – 5 – 0	
3)	3 – 8 – 4 – 2 2 – 0 – 9 – 5	
4)	0 – 8 – 3 – 9 – 7 3 – 1 – 4 – 9 – 2	
5)	9 – 5 – 8 – 0 – 4 – 3 2 – 7 – 5 – 0 – 3 – 9	
6)	0 – 7 – 3 – 5 – 9 – 4 – 2 2 – 5 – 7 – 3 – 0 – 8 - 4	
7)	9 – 4 – 8 – 5 – 2 – 7 – 3 – 0 1 – 4 – 7 – 9 – 8 – 2 – 0 – 3	
8)	8 – 3 – 1 – 4 – 2 – 9 – 7 – 5 – 0 3 – 7 – 9 – 5 – 0 – 8 – 1 – 2 – 4	

Now, I am going to say some more numbers, but this time when I stop, I want you to say the numbers backward. If I say 3 – 7, what would you say?

Correct response: (7 – 3). That's right.
Incorrect response: That's not quite right. I said 3 – 7, so to say them backward, you should say 7 – 3. Let's try another one. Remember to say them backwards: 9 -0.
Correct response: (0 – 9). That's right. Let's try some more.

WITH GOAL-SETTING INSTRUCTIONS: Last time you completed this test, you could recall (#) numbers in a row. Now, I want you to recall (#+1) numbers for this task.

Trial		Correct response	Correct?
1)	9 – 7 8 – 0	7 – 9 0 – 8	
2)	0 – 2 1 – 3	2 – 0 3 – 1	
3)	2 – 8 – 5 0 – 3 – 1	5 – 8 – 2 1 – 3 – 0	
4)	4 – 8 – 3 – 5 0 – 5 – 2 – 4	5 – 3 – 8 – 4 4 – 2 – 5 – 0	

5)	2 – 1 – 4 – 0 – 9 7 – 1 – 0 – 4 – 2	9 – 0 – 4 – 1 – 2 2 – 4 – 0 – 1 – 7	
6)	1 – 9 – 3 – 0 – 7 – 4 3 – 8 – 0 – 4 – 1 – 2	4 – 7 – 0 – 3 – 9 – 1 2 – 1 – 4 – 0 – 8 – 3	
7)	4 – 7 – 0 – 5 – 9 – 2 – 8 0 – 3 – 9 – 5 – 2 – 8 – 4	8 – 2 – 9 – 5 – 0 – 7 – 4 4 – 8 – 2 – 5 – 9 – 3 – 0	
8)	5 – 0 – 9 – 3 – 2 – 8 – 7 – 4 3 – 8 – 4 – 7 – 1 – 2 – 0 – 9	4 – 7 – 8 – 2 – 3 – 9 – 0 – 5 9 – 0 – 2 – 1 – 7 – 4 – 8 – 3	

Now I am going to say some more numbers. After I say them, I want you to tell me the numbers in order, starting with the lowest number. If I say 8 – 9 – 7, what would you say?

Correct response: 7 – 8 – 9 : That's right. (Proceed to Trial 2)
Incorrect response: That's not quite right. I said 8 – 9 – 7, so to say them in order from lowest to highest, you should say 7 – 8 – 9. (Proceed to Trial 2)

Trial 2
Let's try another one. 8 – 1 – 8.
Correct response: 1 – 8 – 8. That's right. Let's try some more.
Incorrect response: That's not quite right. I said 8 – 1 – 8, so to say them in order from lowest to highest, you should say 1 – 8 – 8. Let's try some more. (Proceed to Trial 1 of item 1)

Administer Trial 1 and Trial 2 of each item. Proceed to the next item if the discontinue criterion has not been met.

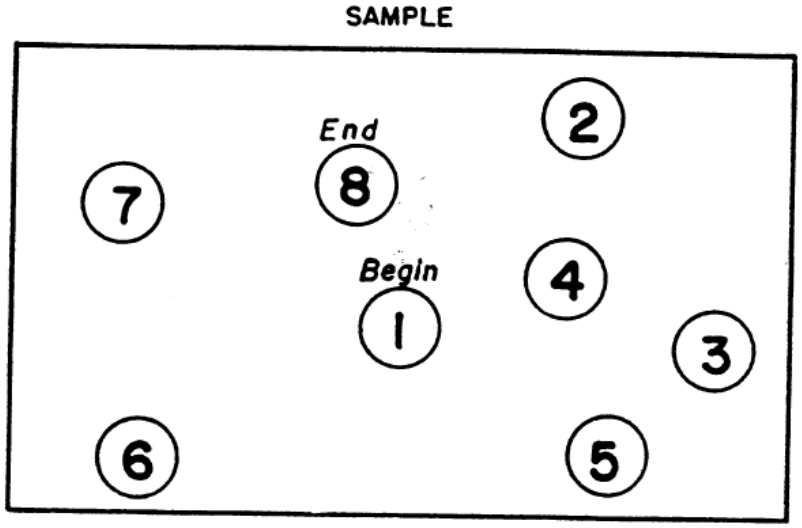
WITH GOAL-SETTING INSTRUCTIONS: Last time you completed this test, you could recall (#) numbers in a row. Now, I want you to recall (#+1) numbers for this task.

Item	Trial	Correct Response	Correct?
1)	7 – 8 0 – 8	7 – 8 8 – 0	
2)	9 – 7 – 2 6 – 5 – 0	7 – 9 – 2 6 – 0 – 5	
3)	4 – 3 – 5 – 8 0 – 4 – 3 – 7	8 – 3 – 4 – 5 7 – 0 – 3 – 4	
4)	8 – 2 – 5 – 7 – 3 9 – 4 – 9 – 1 – 4	7 – 8 – 2 – 3 – 5 9 – 9 – 1 – 4 – 4	
5)	8 – 7 – 3 – 0 – 9 – 2 2 – 8 – 1 – 8 – 9 – 0	7 – 8 – 9 – 0 – 2 – 3 8 – 8 – 9 – 0 – 1 – 2	
6)	3 – 1 – 3 – 2 – 4 – 2 – 8 0 – 4 – 8 – 1 – 0 – 9 – 1	8 – 1 – 2 – 2 – 3 – 3 – 4 8 – 9 – 0 – 0 – 1 – 1 – 4	
7)	1 – 4 – 3 – 8 – 3 – 1 – 0 – 1 5 – 0 – 5 – 3 – 9 – 6 – 4 – 0	8 – 0 – 1 – 1 – 1 – 3 – 3 – 4 6 – 9 – 0 – 0 – 3 – 4 – 5 – 5	
8)	1 – 6 – 7 – 7 – 9 – 8 – 7 – 6 – 1 8 – 3 – 7 – 0 – 4 – 0 – 8 – 5 – 2	6 – 6 – 7 – 7 – 7 – 8 – 9 – 1 – 1 7 – 8 – 8 – 0 – 0 – 2 – 3 – 4 - 5	

Appendix N

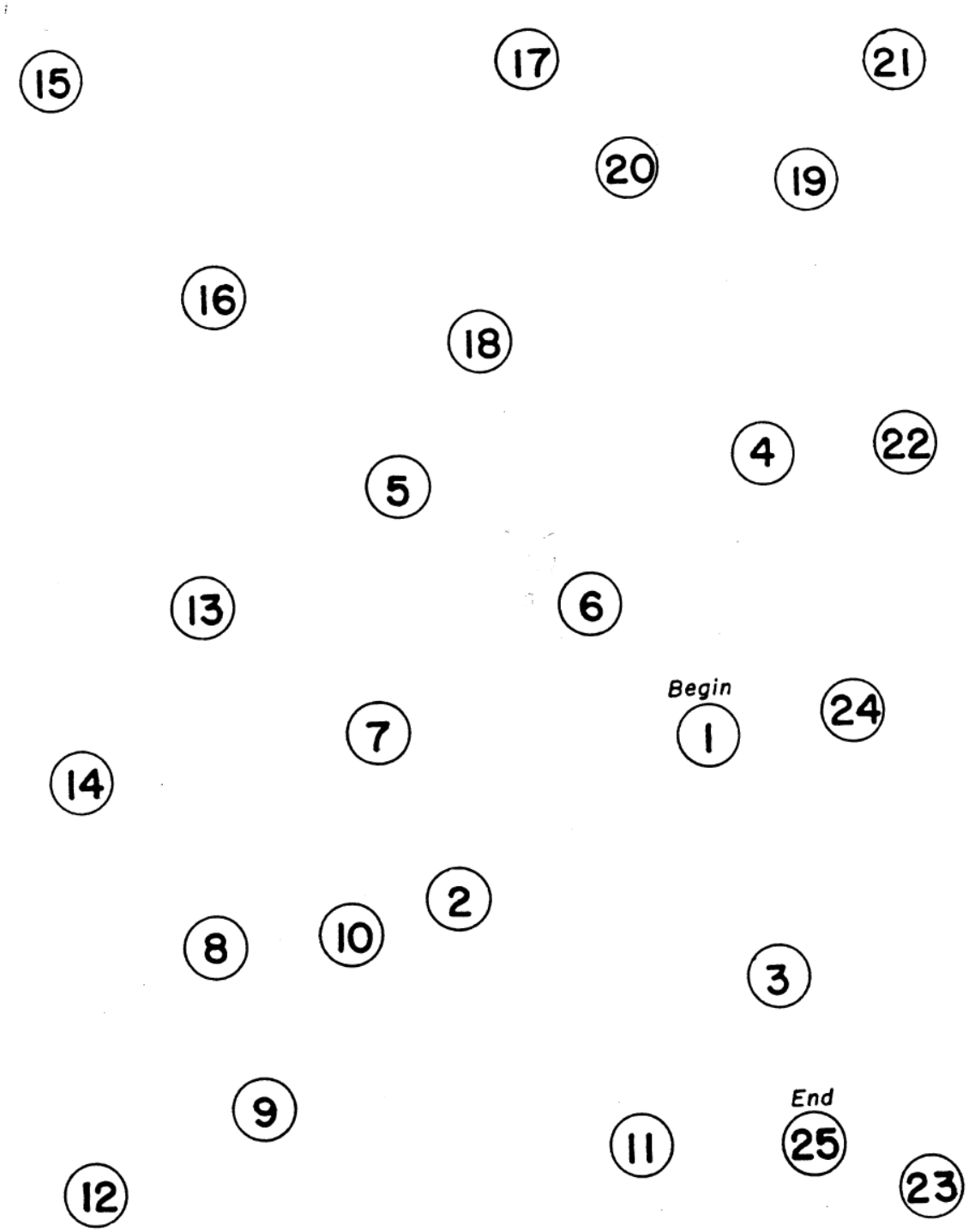
Trail Making Test: Part A & B

TMT Part A (Practice)

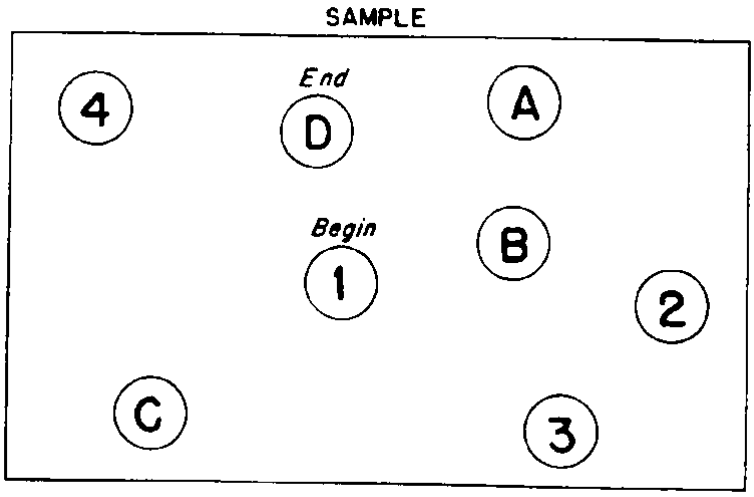


Trails A

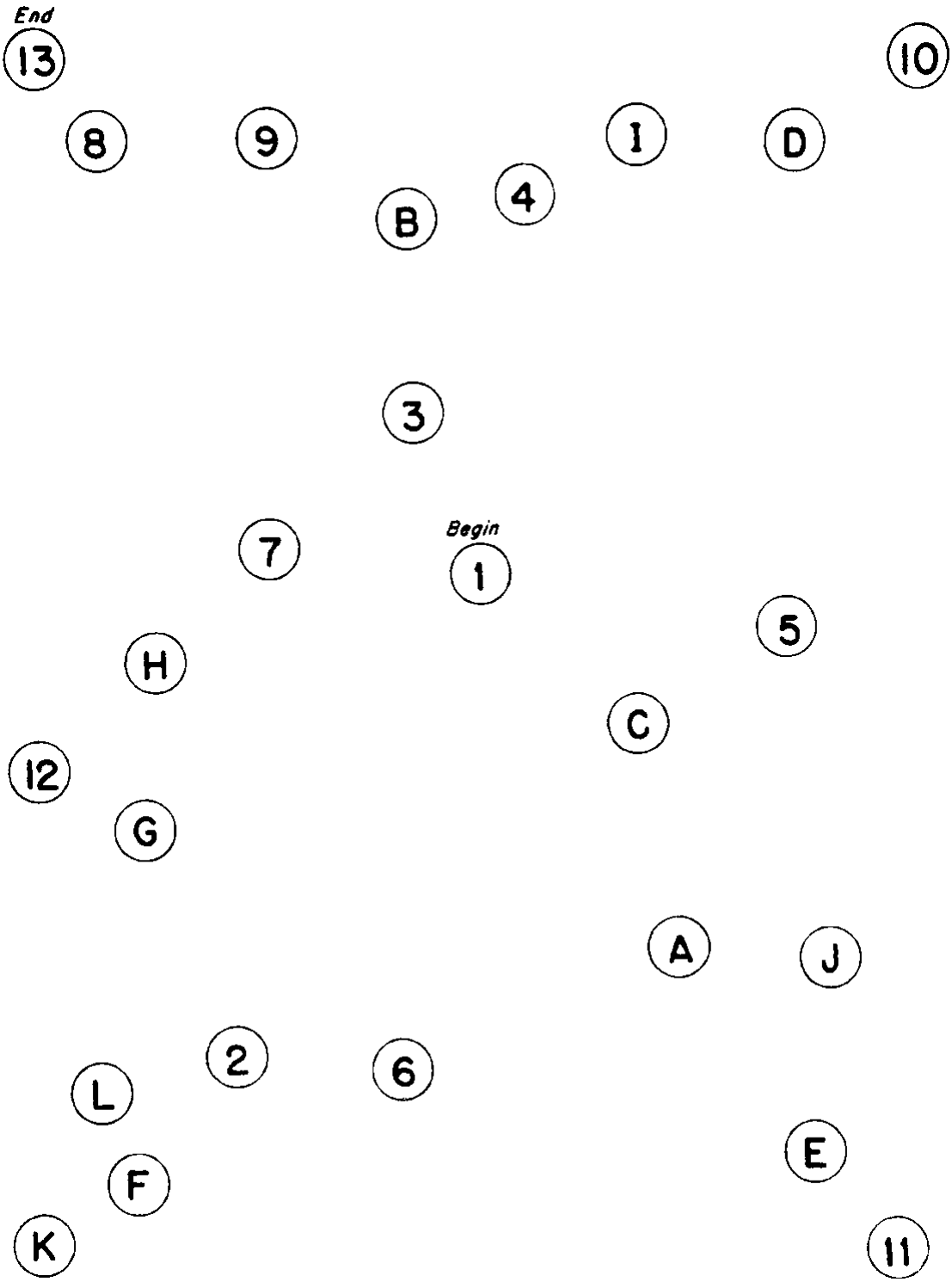
Test Completed? ❒ Yes Time: _____ seconds
❒ No (but tested for 5 minutes) ❒ No (did not test for 5 minutes)
TMT Part A


15
17
21
20
19
16
18
4
22
5
13
6
Begin
1
24
7
14
2
8
10
3
9
End
25
11
12
23

TMT Part B (Practice)



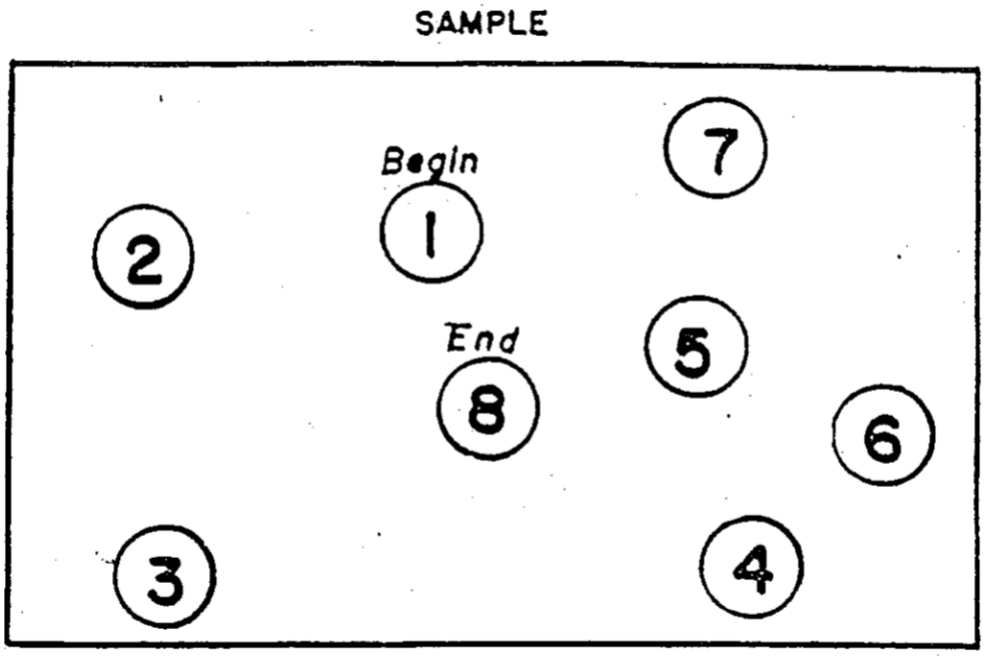
TMT Part B



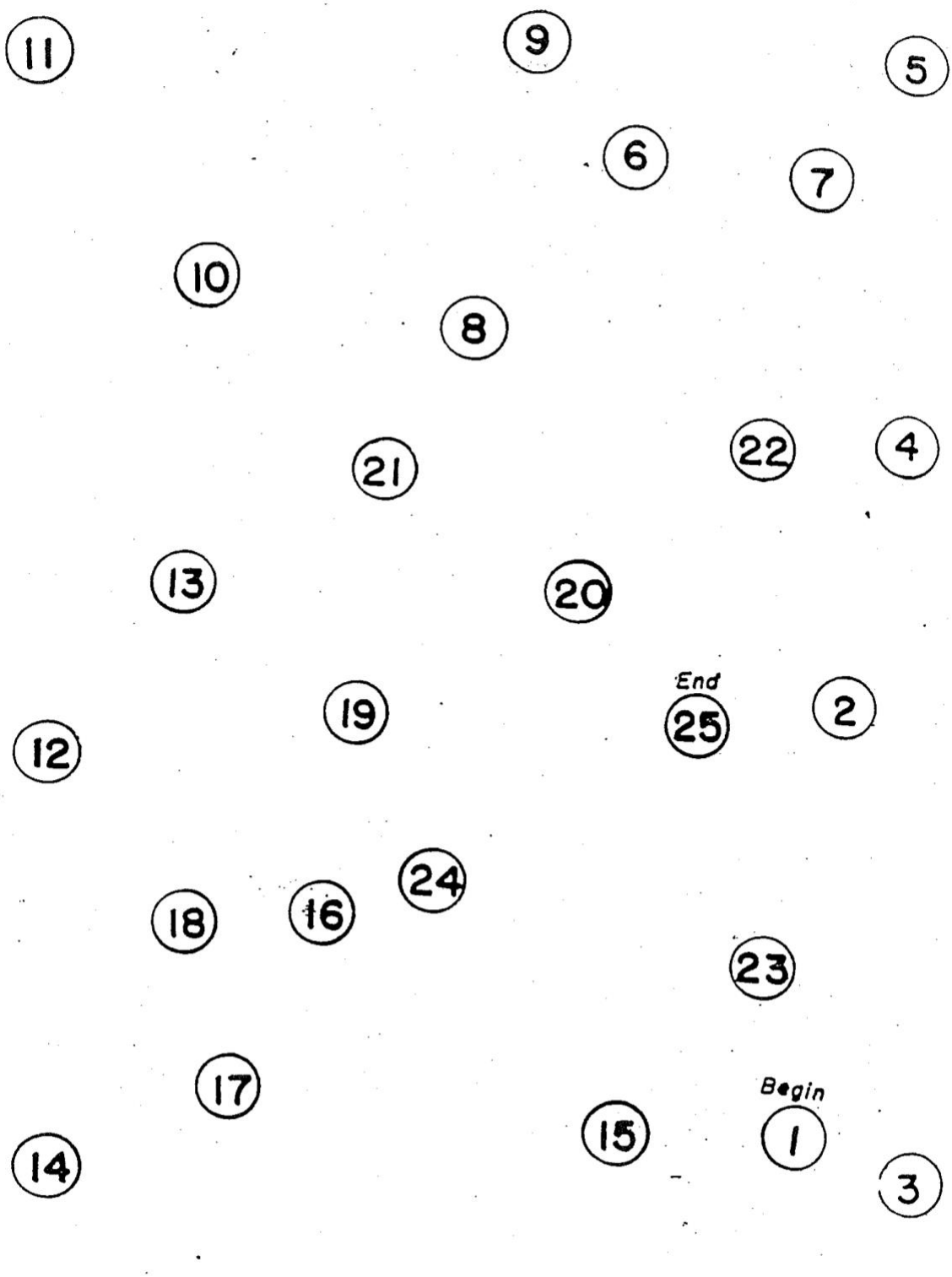
Appendix O

Trail Making Test: Part C & D

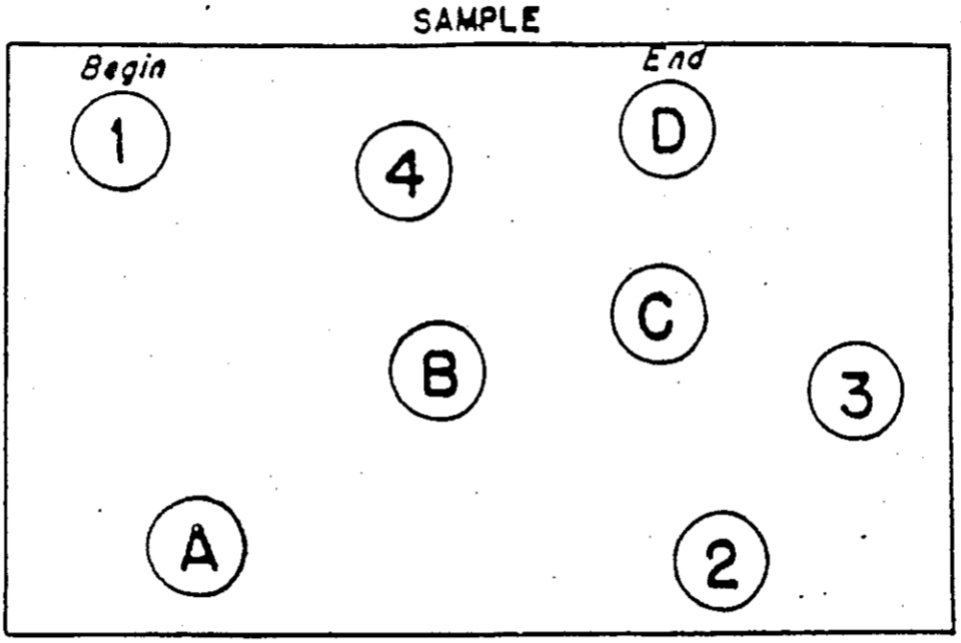
TMT Part C (Practice)



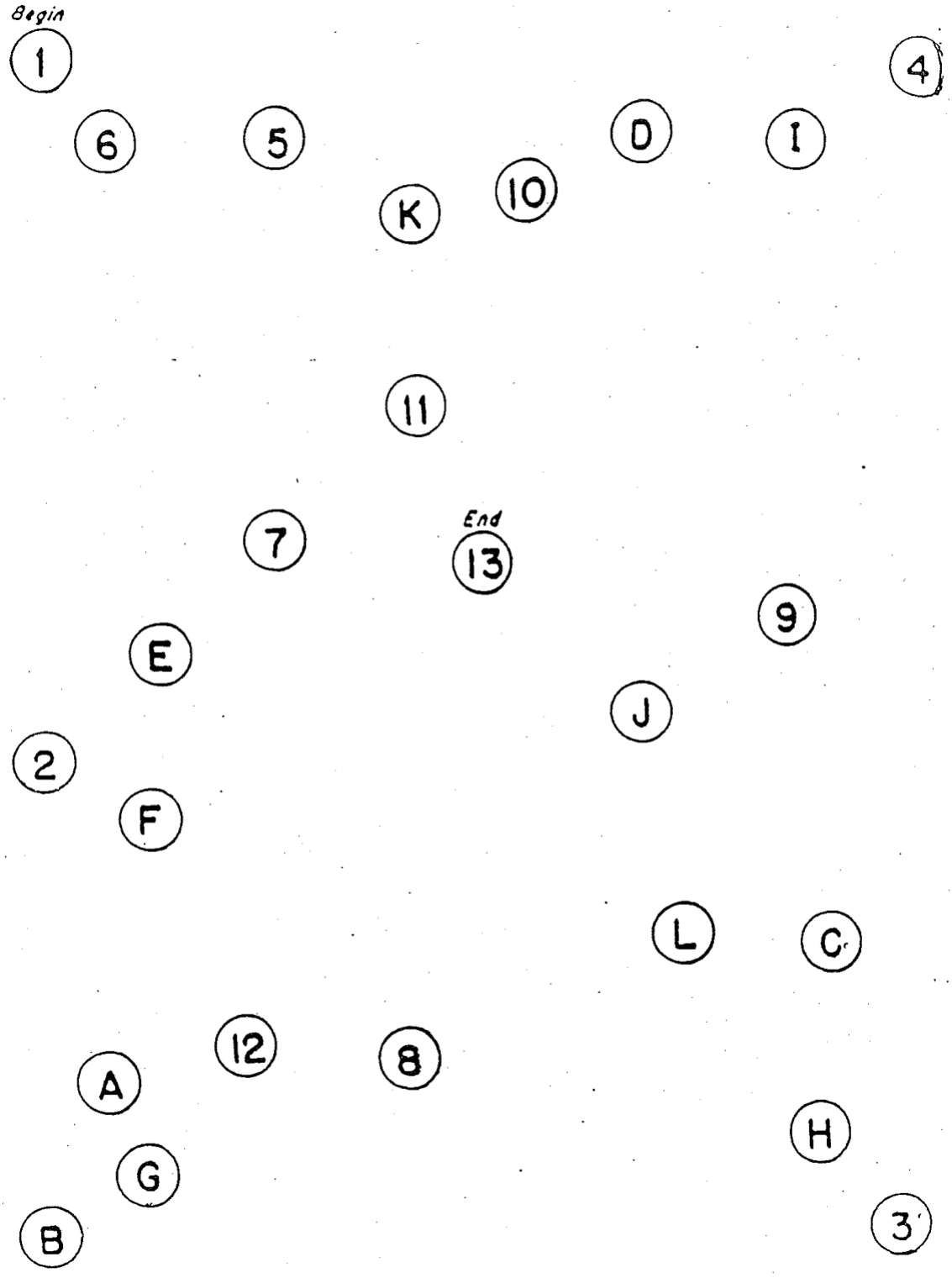
TMT Part C



TMT Part D (Practice)



TMT Part D



Appendix P

Consent Form for Article 4

Full Study Title: Ready, Set, Goal! A Randomized Controlled Trial Examining Motivation and Cognition in Stroke Patients

Principal Investigator: Dr. Richard H. Swartz, Assistant Professor, Division of Neurology, Department of Medicine, University of Toronto. Director, University of Toronto Stroke Program. Sunnybrook Health Sciences Centre. Room A-442, 2075 Bayview Avenue, Toronto, ON M4N 3M5 Tel.: 416-480-4866

Co-Investigator: Keera Fishman, B. Sc., Department of Psychology, University of Ottawa, 136 Jean Jacques Lussier, VNR 3088, Ottawa, ON, K1N 9A8
Dr. Andrea Ashbaugh, Department of Psychology, University of Ottawa, 136 Jean Jacques Lussier, VNR 4013, Ottawa, ON, K1N 9A8

INFORMED CONSENT

You are being asked to consider participating in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood. This form explains the purpose of this research study, provides information about the study, the tests and procedures involved, possible risks and benefits, and the rights of participants.

Please read this form carefully and ask any questions you may have. You may have this form and all information concerning the study explained to you. If you wish, someone may be available to verbally translate this form into your preferred language. You may take as much time as you wish to decide whether or not to participate. Please ask the study staff or one of the investigator(s) to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

Participating in this study is your choice (voluntary). You have the right to choose not to participate, or to stop participating in this study at any time.

INTRODUCTION

You are being asked to consider participating in this study because you have had a stroke within the last 6 months. Participants in this study will continue to receive routine standard clinical care as they would otherwise receive, which consists of consultation and follow-up in the Stroke Prevention Clinic

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to examine your memory and ability to organize and plan tasks after your stroke. If you choose to participate in this study, you will be randomized to one of two groups with different instructions. You will also be asked to complete questionnaires about how you are feeling.

WHAT WILL HAPPEN DURING THIS STUDY?
During this study, you will be asked to complete a series of cognitive tasks that will examine your ability to learn, remember, and plan out tasks. You will also be asked to complete questionnaires about how you are feeling and about your medical history.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
It is anticipated that about 72 people will participate in this study. The length of this study for participants is approximately 1 hour. You will be randomly assigned to one of two conditions. The entire study is expected to take about 1 year to complete and the results should be known in 1.5 years.

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?
The following tests will be completed with a study coordinator and should take about an hour.
Depression Testing: The depression tests will involve paper-and- pencil testing and will be conducted by the study coordinator.
Cognitive Testing: The cognitive tests will involve paper-and- pencil testing and will be conducted by the study coordinator.
Medical History: You will be asked to complete a questionnaire regarding your medical history.
You may change your mind about your participation at any time.

Follow Up Visits
This study does not require repeated testing or follow-up visits.

WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?
All information provided is completely confidential (more details are below). You may experience mild discomfort (anxiety, distress) when completing questionnaires about sensitive issues (e.g., mood). You may refuse to answer questions or stop your participation at any time if you experience any discomfort and do not want to continue. If you have further questions about risks and side effects, please ask the researcher.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?
You may or may not benefit directly from participating in this study. There are no medical benefits to you from taking part in this study.

WHAT OTHER CHOICES ARE THERE?
Your participation in this study is voluntary. The alternative to participating in this study is to not participate. If you choose not to participate, you will continue to receive the same usual standard of care available for your condition regardless of whether you participate in the study or not.

CAN PARTICIPATION IN THIS STUDY END EARLY?
You can also choose to end your participation at any time without having to provide a reason. If you choose to withdraw, your choice will not have any effect on your current or future medical treatment or health care.

WHAT ARE THE COSTS OF PARTICIPATING IN THIS STUDY?
There is no cost to participate in this study, and you will not be paid to take part in the study.

ARE STUDY PARTICIPANTS PAID TO PARTICIPATE IN THIS STUDY?
You will not be paid to participate in this study.

HOW WILL MY INFORMATION BE KEPT CONFIDENTIAL?
You have the right to have any information about you that is collected, used or disclosed for this study to be handled in a confidential manner.

If you decide to participate in this study, the investigator(s) and study staff will look at your personal health information and collect only the information they need for this study. "Personal health information" is health information about you that could identify you because it includes information such as your;

- name,
- address,
- telephone number,
- date of birth,
- new and existing medical records, or
- the types, dates and results of various tests and procedures.

You have the right to access, review and request changes to your personal health information.

The following people may come to the hospital to look at your personal health information to check that the information collected for the study is correct and to make sure the study followed the required laws and guidelines:

- Representatives of the Sunnybrook Research Institute, Sunnybrook Health Sciences Centre or the Sunnybrook Research Ethics Board, because they oversee the ethical conduct of research studies at Sunnybrook

You waive no legal rights by participating in this trial. In the case of injury or illness resulting from this study, appropriate medical treatment will, of course, be available to you. We will tell you about new information that may affect your health, welfare, or willingness to stay in this study. Access to your personal health information will take place under the supervision of the Principal Investigator. "Study data" is health information about you that is collected for the study, but that does not directly identify you. Any study data about you that is sent outside of the hospital will have an identification code will not contain your name or address, or any information that directly identifies you.

The investigator(s), study staff and the other people listed above will keep the information they see or receive about you confidential, to the extent permitted by applicable laws. Even though

the risk of identifying you from the study data is very small, it can never be completely eliminated.

The Principal Investigator will keep any personal health information about you in a secure and confidential location for 10 years and then destroy it according to Sunnybrook policy.

When the results of this study are published, your identity will not be disclosed.

You have the right to be informed of the results of this study once the entire study is complete.

ARE THERE ANY CONFLICTS OF INTEREST/RELATIONSHIPS?

There are no conflicts of interest to declare related to this study.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

You have the right to receive all information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction, before you make any decision. You also have the right to ask questions and to receive answers throughout this study.

If you have any questions about this study you may contact Dr. Richard Swartz, Department of Medicine, 416-480-4866.

The Sunnybrook Research Ethics Board has reviewed this study. If you have questions about your rights as a research participant or any ethical issues related to this study that you wish to discuss with someone not directly involved with the study, you may call the Chair of the Sunnybrook Research Ethics Board at (416) 480-6100 ext. 88144.

DOCUMENTATION OF INFORMED CONSENT

You will be given a copy of this informed consent form after it has been signed and dated by you and the study staff.

Full Study Title: Ready, Set, Goal! A Randomized Controlled Trial Examining Motivation and Cognition in Stroke Patients

Name of Participant: _____

Participant

By signing this form, I confirm that:

- This research study has been fully explained to me and all of my questions answered to my satisfaction
- I understand the requirements of participating in this research study
- I have been informed of the risks and benefits, if any, of participating in this research study
- I have been informed of any alternatives to participating in this research study
- I have been informed of the rights of research participants
- I have read each page of this form
- I authorize access to my personal health information, medical record and research study data as explained in this form
- I have agreed, or agree to allow the person I am responsible for, to participate in this research study

☐Full battery ☐CES-D and AES self-report measures only

☐CES-D and AES for caregiver

_____	_____	_____
Name of participant/Substitute decision-maker (print)	Signature	Date

Person obtaining consent

By signing this form, I confirm that:

- This study and its purpose has been explained to the participant named above
- All questions asked by the participant have been answered
- I will give a copy of this signed and dated document to the participant

_____	_____	_____
Name of Person obtaining consent (print)	Signature	Date

Statement of Investigator

I acknowledge my responsibility for the care and well being of the above participant, to respect the rights and wishes of the participant as described in this informed consent document, and to conduct this study according to all applicable laws, regulations and guidelines relating to the ethical and legal conduct of research.

_____	_____	_____
Name of Investigator (print)	Signature	Date

DOCUMENTATION OF INFORMED CONSENT

You will be given a copy of this informed consent form after it has been signed and dated by you and the study staff.

Full Study Title: Ready, Set, Goal! A Randomized Controlled Trial Examining Motivation and Cognition in Stroke Patients

Name of Participant: _____

Participant

By signing this form, I confirm that:

- This research study has been fully explained to me and all of my questions answered to my satisfaction
- I understand the requirements of participating in this research study
- I have been informed of the risks and benefits, if any, of participating in this research study
- I have been informed of any alternatives to participating in this research study
- I have been informed of the rights of research participants
- I have read each page of this form
- I authorize access to my personal health information, medical record and research study data as explained in this form
- I have agreed, or agree to allow the person I am responsible for, to participate in this research study

☐Full battery ☐CES-D and AES self-report measures only

☐CES-D and AES for caregiver

_____	_____	_____
Name of participant/Substitute decision-maker (print)	Signature	Date

Person obtaining consent

By signing this form, I confirm that:

- This study and its purpose has been explained to the participant named above
- All questions asked by the participant have been answered
- I will give a copy of this signed and dated document to the participant

_____	_____	_____
Name of Person obtaining consent (print)	Signature	Date

Statement of Investigator

I acknowledge my responsibility for the care and well being of the above participant, to respect the rights and wishes of the participant as described in this informed consent document, and to conduct this study according to all applicable laws, regulations and guidelines relating to the ethical and legal conduct of research.

_____	_____	_____
Name of Investigator (print)	Signature	Date

Appendix Q

Debriefing Form for Article 4

DEBRIEFING FORM FOR RESEARCH PARTICIPATION

Thank you for participating in our research.

Title: Ready, Set, Goal! A Randomized Controlled Trial Examining Motivation and Cognition in Stroke Patients

Investigators and Institution:
The study you just participated in is being conducted by Richard H. Swartz, M. D., Ph. D., at the Secondary Stroke Prevention Clinic at Sunnybrook Health Sciences Centre, Keera N. Fishman, Ph.D. Student (University of Ottawa), and Andrea R. Ashbaugh, Ph.D. (University of Ottawa).

Study Purpose and Implications:
Apathy is a lack of behavioural, cognitive, and emotional motivation. Apathy has been shown to disrupt various aspects of your memory and ability to plan/organize tasks after a stroke (Lezak, 1995; Pluck & Brown, 2002; Scheurich et al., 2008). However, few studies have explored the role of goal-setting instructions in improving cognitive performance in stroke patients. This study aimed to examine the effect of goal-setting instructions on your ability to learn words, remember words, hold and use information, and generate answers to questions. We believe that individuals receiving goal-setting instructions will perform better on these cognitive tests than individuals assigned to the standard instruction condition, regardless of baseline intelligence. If goal-setting instructions are effective in improving cognitive performance, it may indicate that treatments targeting apathy (as opposed to sad mood in depression) could serve as a novel approach to improving cognitive outcomes (and potentially enhancing patient quality of life) after stroke. In addition, this study will offer further insight regarding the importance of screening for symptoms of apathy (in addition to depression) post-stroke.

If you would like your data to be excluded from this study now that you are aware of the goals of the study, please inform the research assistant or contact Keera Fishman and she will ensure that your data is promptly destroyed. If you have experienced extreme distress as a result of participation in the study you can contact the Cognitions and Anxiety Studies Laboratory at (613) 562-5800 ext. 4456. If you would like to obtain personal support or help for depression a list of potential resources is included at the bottom of this handout.

To learn more about goal-setting/apathy, depression, and cognition, you can also consult the following articles:

Adams, K. B. (2001). Depressive symptoms, depletion, or developmental change? Withdrawal, apathy, and lack of vigor in the Geriatric Depression Scale. *The Gerontologist, 41*, 768- 777.

Gauggel, S., & Billino, J. (2002). The effects of goal setting on the arithmetic performance of brain-damaged patients. *Archives of Clinical Neuropsychology, 17*, 283-294.

Scheurich, A., Fellgiebel, A., Schermuly, I., Bauer, S., Wölfges, R., & Müller, M. J. (2008). Experimental evidence for a motivational origin of cognitive impairment in major depression. *Psychological Medicine, 38,* 237-246.

Scheurich, A., Müller, M. J., Szegedi, A., Anghelescu, I., Klawe, C., Lörch, B., ... Hautzinger, M. (2004). Neuropsychological status of alcohol-dependent patients: increased performance through goal-setting instructions. *Alcohol and Alcoholism, 39*, 119-125.

Wagner, A. D. (2006). Encoding and retrieval from long-term memory. In E. E. Smith & S. M. Kosslyn (Eds.), *Cognition: Mind & Brain* (pp. 192-238). Upper Saddle River, NJ: Pearson Education/Prentice Hall.

Resources for Depression:

Canadian Mental Health Association (CMHA)
Location: 700 Lawrence Ave W #480, Toronto, ON M6A
Tel: (416) 789-7957
Services: Mental health information and referral service, which offers information on mental health services, referrals to needed/wanted services, needs assessments, education, advocacy, and consultation to Toronto residents.
Website: https://toronto.cmha.ca/

Centre for Addition and Mental Health (CAMH)
Tel: (416) 535-8501
Services: Provides information about a wide range of services in the Toronto area.
Website: http://www.camh.ca

Immediate Resources

- Toronto Distress Centre, 416-408-4357
- Gerstein Centre Crisis Line, 416-929-5200
- Community Crisis Response Service, 905-310-2673

Self-Help Resources related to Depression

Gilbert, P. (2009). *Overcoming depression: A self-help guide using cognitive behavioural techniques.* London: Robinson.

Greenberger, D., Padesky, C. A., & Beck, A. T. (2015). *Mind over mood: Change how you feel by changing the way you think.* New York, NY: Guilford Publications.

Wright, J. H., & McCray, L. W. (2012). *Breaking free from depression: Pathways to wellness.* New York, NY: The Guilford Press.

Thank you for your participation in this study.

Appendix R

Counterbalancing Conditions for Article 4

Condition 1:

1) California Verbal Learning Test-II Alternate Form (Trial 1 only)
2) Digit Span Test
3) Center for Epidemiological Studies Depression Scale
4) Letter Fluency: "FAS"
5) Category Fluency Test: Animals
6) Apathy Evaluation Scale
7) Trail Making Test: Part A & B
8) Motivation Check (0-100)
9) Fatigue Check (0-100)
10) CVLT-II Standard Form (Acquisition & short-term recall)
11) Alternate Digit Span Test
12) Letter Fluency: "FAS"
13) Category Fluency: Animals and Supermarket
14) Trail Making Test: Part C & D
15) Sociodemographic Questionnaire
16) CVLT-II Standard Form (Long-term recall & recognition)
17) Motivation Check (0-100)
18) Fatigue Check (0-100)

Condition 2:

1) California Verbal Learning Test-II Standard Form (Trial 1 only)
2) Alternate Digit Span Test
3) Apathy Evaluation Scale
4) Letter Fluency: Letter "F
5) Category Fluency Test: Fruits & Vegetables
6) Center for Epidemiological Studies Depression Scale
7) Trail Making Test: Part A & B
8) Motivation Check (0-100)
9) Fatigue Check (0-100)
10) CVLT-II Alternate Form (Acquisition & short-term recall)
11) Alternate Digit Span Test
12) Letter Fluency: Letter "A" and "S"
13) Category Fluency: Animals
14) Trail Making Test: Part C & D
15) Sociodemographic Questionnaire
16) CVLT-II Alternate Form (Long-term recall & recognition)
17) Motivation Check (0-100)
18) Fatigue Check (0-100)

Condition 3:

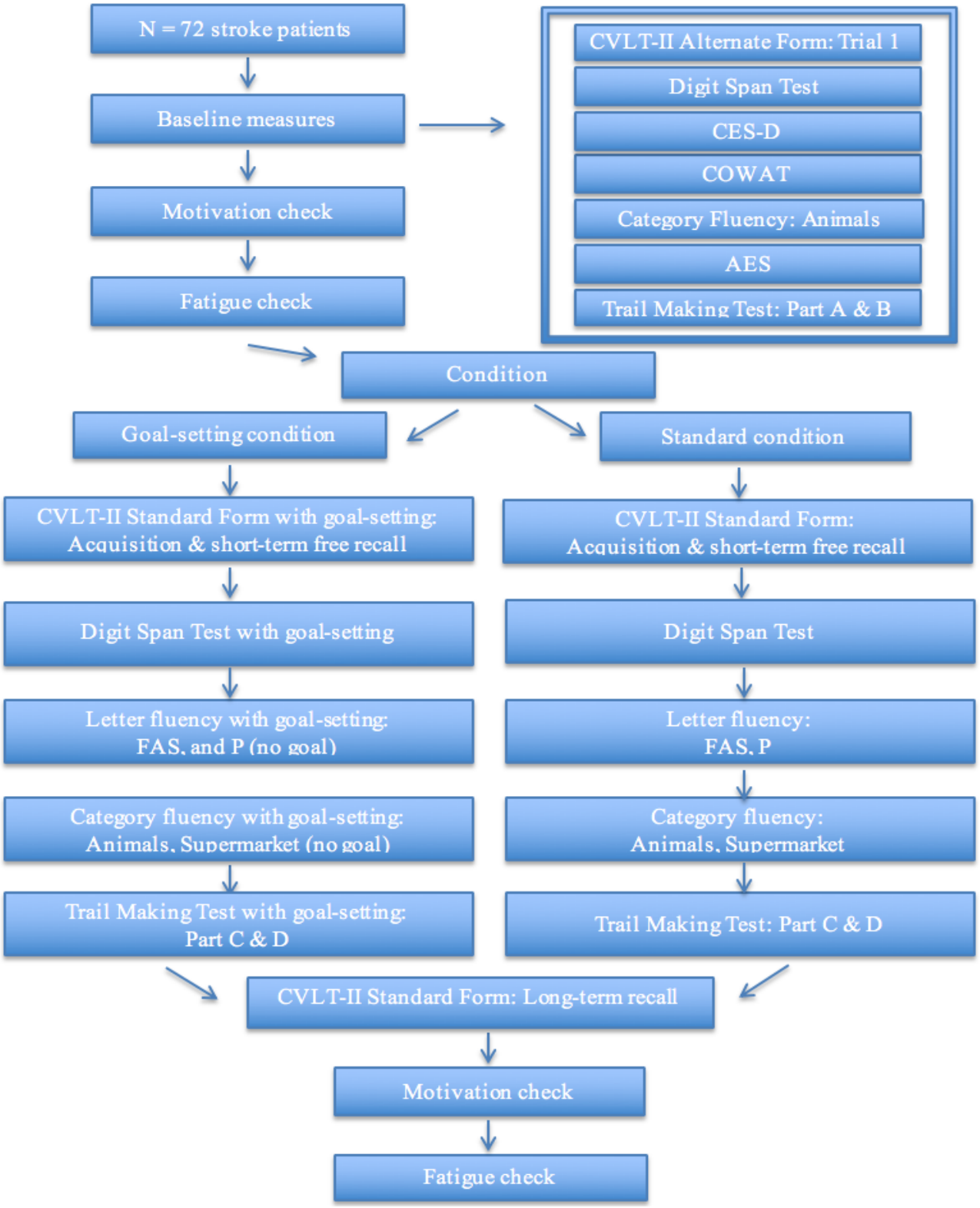
1) California Verbal Learning Test-II Standard Form (Trial 1 only)
2) Alternate Digit Span Test
3) Apathy Evaluation Scale
4) Letter Fluency: "FAS"
5) Category Fluency Test: Animals
6) Center for Epidemiological Studies Depression Scale
7) Trail Making Test: Part C & D
8) Motivation Check (0-100)
9) Fatigue Check (0-100)
10) CVLT-II Alternate Form (Acquisition & short-term recall)
11) Digit Span Test
12) Letter Fluency: "FAS"
13) Category Fluency: Animals & Supermarket
14) Trail Making Test: Part A & B
15) Sociodemographic Questionnaire
16) CVLT-II Alternate Form (Long-term recall and recognition)
17) Motivation Check (0-100)
18) Fatigue Check (0-100)

Condition 4:

1) California Verbal Learning Test-II Alternate Form (Trial 1 only)
2) Digit Span Test
3) Center for Epidemiological Studies Depression Scale
4) Letter Fluency: Letter "FAS"
5) Category Fluency Test: Animals
6) Apathy Evaluation Scale
7) Trail Making Test: Part C & D
8) Motivation Check (0-100)
9) Fatigue Check (0-100)
10) CVLT-II Standard Form (Acquisition & short-term recall)
11) Alternate Digit Span Test
12) Letter Fluency: "FAS"
13) Category Fluency: Animals & Supermarket
14) Trail Making Test: Part A & B
15) Sociodemographic Questionnaire
16) CVLT-II Standard Form (Long-term recall and recognition)
17) Motivation Check (0-100)
18) Fatigue Check (0-100)

Appendix S

Order of Testing Procedure for Article 4



Appendix T

Purpose, Versions, and Goal-Setting Instructions for Neuropsychological Measures

Purpose	Version 1	Version 2	Goal setting instruction & example
Verbal Memory: memory acquisition, short-term free recall, long-term free recall*	CVLT-II Standard Form	CVLT-II Alternate Form	< 10 words = "Let's set a goal for you to recall 2 more words on the next trial." ≥ 10 words = "Let's set a goal for you to recall 1 more word on the next trial."
Working Memory	Digit Span Test	Alternate Digit Span Test	"Let's set a goal for you to recall (Y+1) digits in the proper order for this next task."
Letter Fluency	FAS	FAS	"Let's set a goal for you to generate (Y x 1.2) words for the next letter."
Category Fluency	Animals	Animals	"I want you to generate (Y x 1.2) words for the next category."
Trail Making Test (Psychomotor Speed and Task-Switching)	Trail Making Test (Part A & B)	Trail Making Test (Part C & D)	Trails A→C: "I want you to complete this task in (Y - [Y x .2]) seconds." Trails B→D: "I want you to complete this task in (Y - [Y x .2]) seconds."
Measure of fatigue level	Fatigue Check		Rate your level of fatigue from 1 (*not fatigued at all*) to 100 (*extremely fatigued*)
Measure of motivation level	Motivation Check *Motivation level pre- and post- for the goal setting condition will serve as the manipulation check*		Rate your level of motivation from 1 (*extremely unmotivated*) to 100 (*extremely motivated*)

*Baseline measure will assess verbal memory span (only Trial 1 will be administered).