State of the HeART: Neurophysiological and neuropsychological sequelae of out-of-hospital cardiac arrest in good outcome survivors

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Abstract

Survivors of out-of-hospital cardiac arrest (OHCA) are at risk for hypoxic-ischemic brain injury, which can cause a broad range of effects from death to subtle cognitive impairment. This dissertation includes two studies of OHCA patients who had made good neurological recovery after OHCA. In both studies, patients were evaluated near the time of hospital discharge, when crucial decisions such as rehabilitation plans are made. In addition, OHCA survivors were compared with a myocardial infarction (MI) control group in both studies. Study 1 explored the frequency, severity, and predictors of cognitive dysfunction in OHCA survivors, and characterized the cognitive profile of these patients using a comprehensive neuropsychological battery. Study 2 explored grey matter volume (GMV) in OHCA survivors, MI patients, and healthy controls, and correlated these with cognitive dysfunction and important clinical characteristics (e.g., downtime). While OHCA patients performed poorer on cognitive testing than MI patients, both groups showed decreased GMVs compared to healthy controls. OHCA survivors who have had good neurological recovery may still face significant challenges when they re-engage in difficult cognitive tasks post-arrest. To date, these cognitive issues after OHCA have been somewhat overlooked in Canada's healthcare system. A better understanding of hypoxic-ischemic brain injury among survivors will aid in the promotion of targeted interventions and rehabilitation efforts, and may help clinicians predict those who are most at risk.

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List of Acronyms

ACC	Anterior cingulate cortex
AED	Automated external defibrillator
ANOVA	Analysis of variance
CAD	Coronary artery disease
CCI	Charslon Comorbidity Index
CPC	Cerebral Performance Categories Scale
CPR	Cardiopulmonary resuscitation
CT	Computed tomography
CVD	Cardiovascular disease
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalogram
FWE	Family-wise error
GMV	Grey matter volume
HADS	Hospital Anxiety and Depression Scale
ICD	Implantable cardioverter defibrillator
MI	Myocardial infarction
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
NAB	Neuropsychological Assessment Battery
OFC	Orbitofrontal cortex
OHCA	Out-of-hospital cardiac arrest
PCI	Percutaneous coronary intervention

ROI	Region of interest
SPM	Statistical Parametric Mapping
STEMI	ST-Elevation myocardial infarction
SVC	Small volume correction

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CHAPTER 1

Introduction

Approximately 35,000 cardiac arrests occur each year in Canada (Heart and Stroke Foundation of Canada, 2019). During a cardiac arrest, a sudden malfunction of the heart's electrical system causes the heart to stop beating effectively and blood flow to stop. Of these malfunctions, ventricular tachycardia and ventricular fibrillation are the most common abnormal rhythms that lead to cardiac arrest (Xiong & Tomaselli, 2007). Since the heart controls circulatory function, cells throughout the body begin to die rapidly once a cardiac arrest has occurred, due to lack of oxygen, nutrients, and metabolite removal. The objective of this doctoral dissertation was to address gaps in the existing literature regarding cognitive function after out-of-hospital cardiac arrest (OHCA).

While electrical abnormalities account for the acute onset of a cardiac arrest, the most common etiology is coronary artery disease (CAD; Myerburg & Junttila, 2012), the lead cause of death worldwide (World Health Organization, 2018). The coronary arteries are specialized to supply the heart tissue with oxygenated blood. In CAD, the coronary arteries harden and narrow as they become burdened with atherosclerotic plaque, which reduces blood flow to the heart tissue and causes subsequent ischemic damage. Several cardiac conditions are characterized by impaired blood flow in the coronary arteries and can lead to cardiac arrest; these include cardiomyopathy (i.e., thickening of the heart muscle) and myocardial infarction (i.e., a "heart attack," in which restricted blood flow causes damage to the heart tissue). Many of the risk factors for cardiac arrest are therefore synonymous with the major CAD risk factors, which include hypertension, diabetes, dyslipidemia, obesity, and tobacco use (Mackay & Mensah, 2004). Other causes of cardiac arrest include genetic abnormalities (e.g., structural and/or

electrical abnormalities that are congenital in nature), heart failure (i.e., acute or chronic reduction in heart pumping efficiency), and recreational drug use.

Cardiac Arrest Interventions

Cardiac arrests occur suddenly and with little or no warning, which makes rapid treatment both challenging and essential. Ideally, cardiac arrest interventions should occur as quickly as possible; however, a large number of cardiac arrests occur outside of hospitals (Center for Disease Control and Prevention, 2018), and of these, many are not witnessed by bystanders who could intervene (Benjamin et al., 2017; Chan, McNally, Tang, & Kellermann, 2014). Consequently, the fields of resuscitation science and post-arrest care are subdivided into two categories based on proximity to care and their differing prognoses: in-hospital and out-of-hospital cardiac arrest.. Despite huge strides in cardiac medicine, surviving a cardiac arrest is relatively rare (Stub, Bernard, Duffy, & Kaye, 2011); only 10.4% of those who experienced an OHCA and underwent attempted resuscitation will survive to hospital discharge (Center for Disease Control and Prevention, 2018). Due to the time sensitivity of OHCA, witnesses play an important role in administering life-saving measures, such as cardiopulmonary resuscitation (CPR), which involves manual compressions of the chest in order to stimulate the heart to circulate blood throughout the body, minimizing tissue death and mortality (Heart and Stroke Foundation of Canada, 2019; Stiell et al., 2004). Another key life-saving measure is automated external defibrillators (AEDs), which can also be used by trained bystanders, if available. These devices transmit electrical stimulation to the heart muscle in order to encourage a return to its normal rhythm. Immense public policy efforts have been made to encourage rapid bystander response, disseminate CPR education, and ensure the public availability of AEDs. These

community-level interventions contributed to the 50% increase in 30-day OHCA survival rates in Ontario, Canada between the years 2002 and 2013 (from 8.7% to 13%; Wong et al., 2014).

While resuscitation measures such as CPR and the use of AEDs often occur in the community, once a patient arrives in hospital, it is imperative to stabilize them and address the underlying cause of the cardiac arrest. Revascularization techniques, such as coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI), are often used to stabilize patients, but also serve as secondary prevention measures to address the underlying cardiovascular pathology in hopes of preventing another medical event (Bennett et al., 2017). In CABG interventions, vessels from other areas of the body are used to bypass occluded coronary arteries, while a PCI involves the insertion of a stent inside occluded blood vessels. In addition to these techniques, implantable cardioverter defibrillators (ICDs) are also commonly inserted into the chest of patients to detect arrhythmias and provide electrical stimulation to reverse them (Nolan et al., 2008). Modifiable risk factors that contribute to underlying CAD are also targeted to prevent future arrests (i.e., exercise, smoking cessation, and healthy diet); this occurs most often in the context of cardiac rehabilitation programs after hospital discharge (Canadian Association of Cardiac Rehabilitation, 2009).

Cardiac Arrest and Neurological Functioning

Cardiac arrest has widespread effects on the body and, although stabilization from a cardiac perspective is paramount, a multisystem approach to post-cardiac arrest care is necessary (Peberdy et al., 2010). In fact, of the deaths after OHCA, two thirds are attributed to neurological injury (Laver, Farrow, Turner & Nolan, 2004). The term “downtime” is used to refer to the duration of cardiac arrest, and longer duration of a cardiac arrest is associated with increased extent of neurological injury (Kim et al., 2014). Thus, downtime is related to patient outcomes,

and highlights the need for rapid resuscitation. The high metabolic demands of the brain make it especially vulnerable to cell death, which predominately occurs as a result of two biochemical mechanisms: 1) hypoxia/ischemia caused by the arrest, and 2) reperfusion injuries due to the reintegration of oxygen.

During cardiac arrest, blood flow is rapidly and drastically reduced, leading to low cerebral blood flow (i.e. ischemia), and consequently lower oxygen levels (i.e. hypoxia), as well as a lack of nutrients, poorer gas exchange and waste removal, and generally a severe disruption of cellular homeostasis (Arciniegas, 2012). In addition, glutamate, the major excitatory neurotransmitter of the central nervous system, accumulates to excessive, neurotoxic levels (Sattler & Tymianski, 2001). The hypoxic-ischemic nature of cardiac arrest differentiates it from purely hypoxic injuries, such as carbon monoxide poisoning, in which oxygen levels are low despite adequate perfusion. The brain appears to be relatively robust and somewhat resilient against purely hypoxic injuries (Busl & Greer, 2010).

Reintroduction of blood flow, referred to as reperfusion, occurs in the context of abnormal biochemical cascades initiated by the arrest. In OHCA, reperfusion occurs after life-saving measures such as CPR or defibrillation. While the purpose may be to reverse the impact of hypoxia/ischemia, reperfusion can cause the body to enter a state of oxidative stress that causes further injury, so much so that reperfusion injuries are sometimes regarded as more devastating than the hypoxia/ischemia itself (Weisfeldt & Becker, 2002). In fact, it has been estimated that cardiac arrest survival could increase between six and tenfold if reperfusion injuries could be prevented (Hamann, Beiser, & Vanden Hoek, 2007).

The majority of resuscitated individuals (80%) do not immediately regain consciousness after cardiac arrest (Madl & Holzer, 2004). The coma that ensues is variable in length, and often

culminates in loss of brain function followed by death (Booth, Boone, Tomlinson, & Detsky, 2004; Madl & Holzer, 2004). In 2002, the American Heart Association endorsed therapeutic hypothermia as an effective method of addressing reperfusion injuries. In this treatment, body temperature is lowered and coma induced, which reduces metabolic demands while the body recovers (Nolan, Morley, Hoek, & Hickey, 2003; Nolan et al., 2008; Weisfeldt & Becker, 2002). This treatment reduces neurological injury, and is recommended as standard treatment for OHCA survivors who do not regain consciousness or cannot follow commands after arrest (Donnino et al., 2016; Nolan et al., 2003, 2008).

Neurons may not be uniformly affected by hypoxic-ischemic brain injury and reperfusion. According to the selective vulnerability hypothesis, regions of the brain that have higher metabolic demands and are rich in glutamate receptors are at the greatest risk for hypoxic-ischemic brain injury (Björklund et al., 2014; Busl & Greer, 2010). These regions include the CA1 cells of the hippocampus, cortical grey matter, and deep grey matter regions such as in the thalamus and striatum (Busl & Greer, 2010; Gutierrez, Rovira, Portela, Da Costa Leite, & Lucato, 2010).

Prognostication of Comatose Individuals

Even after successful resuscitation and therapeutic hypothermia, many cardiac arrest patients do not regain consciousness. Measures to prognosticate outcome for these patients has been the subject of ample research; however, no gold standard test or criterion for prognostication of neurological outcome has been identified to date. Key predictors including downtime, the presence and quality of bystander CPR, and other pre-, intra-, or post- arrest characteristics, such as presenting rhythm, have not proven effective alone, or in combination, in predicting neurological outcome in individual comatose survivors of OHCA (Peberdy et al.,

2010). Generally, a multimodal neurological examination is recommended, including electrophysiology, brain imaging, and testing for blood markers (Rossetti, Rabinstein, & Oddo, 2016).

Of the neuroimaging prognostication methods following cardiac arrest, electroencephalogram (EEG), computed tomography (CT), and magnetic resonance imaging (MRI) are the most common. These techniques identify physiological or functional markers that may preclude good neurological outcomes.

An EEG measures electrical activity along the scalp via electrodes and it is routinely included in neurological examinations after a cardiac arrest. This method allows clinicians to assess both the overall electrical activity of the brain and averaged electrical responses to stimuli (i.e., event-related potentials); attenuation of each is linked to poor outcome (Rossetti et al., 2016). The advantage of EEG, though, is its high temporal resolution, and ease of use with comatose patients. One major limitation of EEG is that its results are less predictive of neurological outcome if an individual undergoes therapeutic hypothermia after OHCA, which is common for comatose survivors (Peberdy et al., 2010; Rossetti et al., 2016).

Another method, CT imaging, produces structural images of the brain by using several combined X-ray images. This technique is relatively quick and is useful in determining intracerebral causes of OHCA; however, such incidences are quite rare (Rossetti et al., 2016). While CT provides images, it has less spatial resolution than MRI, and is therefore less preferable for identifying potential predictors of poor neurological outcome (Rossetti et al., 2016).

Finally, MRI produces three-dimensional images of tissues and organs. This imaging technique utilizes powerful magnetic fields to realign atoms while a radiofrequency pulse

transmits energy to protons within the body. When the pulse is turned off, protons slowly return to their original orientation and release energy. The speed at which this process occurs differs according to various tissues, allowing for differentiation between different tissue layers in the brain such as grey matter, white matter, and cerebrospinal fluid. As such, MRI functions without the need for injectable contrast agents (although they can be helpful when used in tandem) and without the use of radiation. A limitation of MRI is that it can be lengthier than EEG or CT, and the magnetic fields used to produce images prohibit its use with patients with magnetic metals in their body. Nonetheless, the advantage of MRI is its superior spatial resolution, and this benefit warrants its use in research for identification of intracerebral abnormalities after OHCA and thus biomarkers of outcome (Rossetti et al., 2016).

A review of the literature on the use of neuroimaging to prognosticate outcomes after cardiac arrest revealed varied results, possibly due to small sample sizes and the use of different protocols (Hahn, Geocadin, & Greer, 2014). Despite these limitations, individuals with poor outcomes after an arrest may present with EEG signal abnormalities (e.g., background slowing or epileptiform activity), global cerebral abnormalities (e.g., loss of differentiation between grey and white matter, mass effect, cytotoxic edema, low cerebral blood flow and global cerebral atrophy), and focal abnormalities (e.g., low density in specific regions, low hippocampal volume, hyperintensities in the basal ganglia and deep gray matter abnormalities) compared to those with good post-arrest outcomes (Keijzer et al., 2018; Sandroni et al., 2013; Wijdicks, Hijdra, Young, Bassetti, & Wiebe, 2006).

Post-Coma Assessment and Treatment

For those who survive to hospital discharge after OHCA, approximately 80% are categorized as having “good neurological outcome” (Center for Disease Control and Prevention,

2018), and the most common method of assessing this is the Cerebral Categories Performance Scale (CPC; Jennett & Bond, 1975). The CPC categorizes patients in terms of their neurological outcome; a score of 1 or 2 is typically regarded as "good neurological outcome" characterized by normal, mild or moderate impairments in cerebral functioning, but independence in terms of activities of daily living. The advantages of the CPC scale are its brevity and practicality of use in clinical settings; however, it is not validated, nor does it have clear guidelines, which can produce poor inter- and intra-reviewer reliability (Ajam et al., 2011; Stiell et al., 2009). A major limitation of the CPC is its insensitivity to cognitive deficits. Even though patients are ranked on this scale based on their level of cerebral functioning, it does not include any standardized measure of cognition. Despite these limitations, CPC scores, or similar rating scales, are often the only reported functional outcome in clinical trials of cardiac arrest treatment (Whitehead, Perkins, Clarey, & Haywood, 2015), which is a major limitation.

Cognitive Outcome after Cardiac Arrest

Neuropsychological assessments of cognitive functions are a valid and reliable method of assessing the ability to acquire and process information, which relies on proper neural functioning. Cognitive functions are often categorized into cognitive domains including memory (e.g., learning, encoding, storage, and retrieval of information), attention (e.g., sustained, selective, and divided attention, working memory, and information processing speed), language (e.g., expressive and receptive language functions), spatial functions (e.g., visual perception, visuospatial integration), and executive functions (e.g., planning, decision making, organization and goal-directed behaviour).

While many regions of the brain have been identified as contributors to specific cognitive functions, most processes are thought to be mediated by complex neural networks, meaning that

the neural substrate responsible for cognition are often diffuse in the brain (Mesulam, 1990). Consequently, deficits in cognition can contribute to reduced functioning across a range of activities (Jekel et al., 2015).

The rate of cognitive dysfunction among patients who have experienced OHCA is still unclear. In the existing literature, the rates vary widely, ranging from 6 to 100 % of survivors (Moulaert, Verbunt, van Heugten, & Wade, 2009). This variability may be reflective of methodological inconsistencies and limitations across studies. For example, cognitive assessment instruments vary from study to study, and also range in sensitivity from self-report questionnaires (Middelkamp et al., 2007; Moulaert, Wachelder, Verbunt, Wade, & van Heugten, 2010; Wachelder et al., 2009) and brief cognitive screeners (Andersson, Rosén, & Sunnerhagen, 2015; Davies et al., 2017; Horsted, Rasmussen, Meyhoff, & Nielsen, 2007), to comprehensive neuropsychological assessments (Harve et al., 2007; Lilja et al., 2015; Lim, Verfaellie, Schnyer, Lafleche, & Alexander, 2014). Furthermore, OHCA survivors are often included along with other patients in studies of cognitive functioning, meaning that samples become quite heterogenous. For example, some studies include individuals who have had a cardiac arrest of non-cardiac origin (Nunes et al., 2003), such as patients who have experienced a respiratory arrest due to events like carbon monoxide poisoning (Moulaert et al., 2009). Further, in the cardiac-only studies, patients who experience an in-hospital or OHCA are often combined, despite differing in terms of speed of intervention and neurological outcome (Jaszke-Psonka et al., 2016; Lundgren-Nilsson, Rosén, Hofgren, & Sunnerhagen, 2005). Of further concern, some studies lack a control group to which cognitive functioning is compared (Buanes et al., 2015; Cronberg, Lilja, Rundgren, Friberg, & Widner, 2009; Hofgren, Lundgren-Nilsson, Esbjörnsson, & Sunnerhagen, 2008; Lim, Alexander, LaFleche, Schnyer, & Verfaellie, 2004), which makes it

difficult to discern the individual contributions of OHCA and underlying cardiovascular disease, itself a known risk factor for cognitive dysfunction (Cohen & Gunstad, 2010). Varied times in which cognitive assessments are completed after cardiac arrest, as well as the variability of test measures used, serves to further complicate the interpretation of the literature (Moulaert et al., 2009). Despite the variability between studies and inherent difficulty in assessing a true prevalence rate, the current best range estimate of cognitive dysfunction in OHCA survivors is between 34% and 50% (Green, Botha, & Tiruvoipati, 2015; Moulaert et al., 2009).

Cognitive Profile

While the rate of cognitive deficits is unclear, so too is the pattern of areas of cognitive dysfunction, or cognitive profile, of OHCA survivors. Still, cognitive impairments in attention, executive function, motor, and visuospatial function are common among cardiac arrest survivors (Green et al., 2015; Moulaert et al., 2009). Of these, the most common reported deficits are memory impairments; however, memory is also the most common function studied in OHCA survivors, and thus these results may be misrepresentative (Green et al., 2015; Moulaert et al., 2009). Furthermore, the nature of these memory impairments appears to be complex; for example, in one study, executive function deficits were present, and memory impairments tended to be dysexecutive in nature, rather than amnestic (Peskine, Rosso, Picq, Caron, & Pradat-Diehl, 2010). To date, a clear cognitive profile has been difficult to establish, because many studies do not include a comprehensive assessment of cognitive functioning that includes every cognitive domain. A further complication is that neurological recovery occurs over time (Nudo, 2013), which means cognitive profiles may also change with time.

Demographic and Clinical Predictors of Cognitive Outcome

Cardiac arrest patients vary considerably in terms of demographics (e.g., age, location of arrest; Center for Disease Control and Prevention, 2018), premorbid health, arrest characteristics (e.g., etiology of arrest, downtime; Anyfantakis et al., 2009; Kim et al., 2014), and treatment received (e.g., whether or not they received CPR and advanced cardiac life support; Stiell et al., 2004). Which of these variables predict cognitive functioning after a cardiac arrest is not yet known for certain, as studies to date have produced contradictory results. While some studies have identified demographic and clinical characteristics like age (Caro-Codón et al., 2018), timely CPR prior to ambulance arrival (Van Alem, De Vos, Schmand, & Koster, 2004), coma duration, and therapeutic hypothermia (Ørbo et al., 2014), others have identified no such relationships (Buanes et al., 2015; Ørbo et al., 2014).

Hypoxic-ischemic brain injury is thought to play a central role in post-arrest cognitive dysfunction (Busl & Greer, 2010); however, no known studies have identified a clear association between downtime and cognitive functioning after OHCA (Caro-Codón et al., 2018; Jaszke-Psonka et al., 2016; Ørbo et al., 2014). From a neurological perspective, shorter downtimes are associated with better outcomes (Welbourne & Efstathiou, 2018); however, longer downtimes do not preclude good neurological outcome (Kim et al., 2014; Welbourne & Efstathiou, 2018). Furthermore, recent studies have established no relationship between downtime and cognitive functioning (Caro-Codón et al., 2018; Jaszke-Psonka et al., 2016; Ørbo et al., 2014). While downtime represents the elapsed time from collapse to return-of-spontaneous circulation, the nature of this time can vary from individual to individual. For instance, some patients receive CPR during this time, which helps to continue some degree of circulation throughout the body. In one study, longer delays in the "chain of survival" (e.g., time to CPR, defibrillation, and

advanced cardiopulmonary life support) did not always lead to poor neurological functioning (Van Alem, Waalewijn, Koster, & De Vos, 2004). The authors speculated that high quality CPR may mitigate the effects of prolonged downtime, and thus allow for reasonable neurological recovery. As of yet, no known studies have directly explored this interaction (i.e., CPR and downtime) as a potential predictor of post-arrest cognitive outcomes.

Cardiovascular Disease as a Predictor of Cognitive Outcome

For the most part, hypoxic-ischemic encephalopathy is presumed to be the mechanism that underlies both the cognitive and neurological outcome of cardiac arrest survivors. However, cardiac arrest occurs most often in the context of severe cardiovascular disease (Myerburg & Junttila, 2012), which is a well-known risk factor for cognitive decline (Cohen & Gunstad, 2010).

Cardiovascular disease directly affects the brain's physiology, most often by reduced blood flow, or cerebral hypoperfusion. This state can result from inefficient cardiac output, whereas cerebrovascular disease occurs when atherosclerotic plaque accumulates in the brain, which can result in cerebrovascular accidents, and particularly strokes.

Systemic hypoperfusion (i.e., decreased blood flow from the heart) and cerebral hypoperfusion (i.e., decreased blood flow in the brain) results in low oxygenation and has been linked to cognitive dysfunction in patients with and without cardiovascular disease. For example, interventions for patients with heart failure, and consequently decreased perfusion, have led to increased cognitive functioning (Heckman et al., 2007; Laudisio et al., 2009; Zuccala, 2004). Also, individuals with amnestic mild cognitive impairment appear to have decreased cerebral perfusion compared to healthy controls, and regional hypoperfusion is correlated with cognitive functioning in both amnestic mild cognitive impairment groups and healthy controls (Xu et al.,

2007). This suggests that variability can be observed in healthy brains, and in support of this, hypoperfusion has been linked with impaired memory, visual organization, and executive function in healthy adults (Jefferson et al., 2011).

Without pre-arrest cognitive testing, it is difficult to assess whether post-arrest cognitive deficits are truly pathognomonic, or whether they are caused by cardiovascular disease that predates the arrest. The contribution of premorbid cardiovascular disease has been relatively overlooked in the OHCA literature. One way to control for pre-existing cardiovascular disease is to compare OHCA patients with a matched cardiac control group (Alexander, Lafleche, Schnyer, Lim, & Verfaellie, 2011; Lim, Verfaellie, Schnyer, Lafleche, & Alexander, 2014); such groups can include individuals who have experienced a myocardial infarction, or MI (Jaszke-Psonka et al., 2016; Lilja et al., 2015). Patients who have experienced an MI serve as an excellent control group for OHCI survivors, as both groups experience an acute coronary event and undergo similar medical interventions (e.g., PCI and CABG). On the other hand, an MI control group does not allow one to determine the contribution of pre-existing cardiovascular disease on an individual level. Some researchers have tried to circumvent this by statistically controlling for prior cardiovascular disease (Ørbo et al., 2014), correlating cognition with cardiovascular variables (Jaszke-Psonka et al., 2016), and estimating odds ratios of cognitive impairment in the context of cardiovascular variables (Van Alem, Waalewijn, et al., 2004). These studies found no effect of cardiovascular disease on cognitive dysfunction. However, in the largest known study of cognitive function after cardiac arrest, while deficits in attention and processing speed were more prevalent in OHCA survivors than in MI patients, memory impairments were similar across both groups (Lilja et al., 2015). While the theoretical mechanisms of post-arrest cognitive

dysfunction suggest it may be important to control for premorbid cardiovascular disease, the data on the issue require replication and further investigation.

As of yet, the frequency, nature, and predictors of cognitive dysfunction after a cardiac arrest remain unclear, despite significant strides in the acute medical care survivors receive. In addition, the literature is replete with methodological inconsistencies and contradictory results. Comprehensive neuropsychological assessments that cover a broad range of cognitive functions, could better identify predictors of cognitive dysfunction, as well as clarify the cognitive profile of arrest survivors. A clearer picture of the cognitive challenges this population faces is important for targeted rehabilitation efforts, and would better inform patient discharge plans.

Neurophysiology as a Predictor of Cognitive Outcome

While comprehensive neuropsychological tests can better capture the cognitive challenges faced by OHCA survivors, neuroimaging can identify the neural substrates that predict cognitive dysfunction, and perhaps even elucidate the mechanisms of neural injury. To date, neuroimaging studies of OHCA patients are usually focused on the prognostication of survival in comatose individuals. Only a small number of researchers have focused on neuroimaging patients who woke from coma with relatively good neurological recovery (Grubb et al., 2000; Horstmann et al., 2010; Ørbo, Aslaksen, Anke, Tande, & Vangberg, 2019; Ørbo, Vangberg, Tande, Anke, & Aslaksen, 2018; Stamenova et al., 2018). Thus, the prognostication of cognitive dysfunction in good-outcome OHCA survivors remains largely unclear.

Historically, cardiac arrest was presumed to cause direct insult to the bilateral medial temporal lobe (Markowitsch, Weber-Luxemburger, Ewald, Kessler, & Heiss, 1997); however, several studies have identified that the impact of cardiac arrest on the brain extends beyond focal temporal lobe injury (Grubb et al., 2000; Markowitsch et al., 1997; Sulzgruber et al., 2015).

Total grey matter volume (Grubb et al., 2000; Ørbo et al., 2018) and regional grey matter volume (Horstmann et al., 2010; Ørbo et al., 2018; Stamenova et al., 2018) are also reduced in this population.

Two recent studies used manual segmentation of the hippocampus to evaluate the association between cognitive function and hippocampal subfield volumes. Ørbo and colleagues (2018) compared OHCA patients who arrived at hospital conscious with those who had arrived unconscious (and therefore had some length of inpatient coma) and also with a group of healthy controls. Only patients who experienced some inpatient coma differed from the healthy control group. Reductions were observed in specific areas of the hippocampus that included the left CA4, left hippocampus tail, right molecular layer, right granule cell layer of dentate gyrus, and the right subiculum. In addition, memory performance correlated with total grey matter, cortical volume, and specific hippocampal subfields. The authors theorized that, while hippocampal reductions may account for some degree of memory impairment, global, widespread grey matter atrophy may also contribute to memory impairment after cardiac arrest. These investigations focused on memory (i.e., a single list-learning measure of memory was used), and the hippocampus (total volume, cortical and subcortical grey and white matter volume, and the hippocampal subfield volumes were the only volumes assessed), leaving questions of other cognitive functions and other brain regions unanswered. Stamenova and colleagues (2018) compared OHCA survivors with a brief period of hypoxia (<7 minutes to CPR) to a group of MI patients. Hippocampal volumes were reduced in the OHCA group compared to the MI control group, memory performance correlated with hippocampal volume in the OHCA group, and cortical thickness and cognitive functioning were uncorrelated.

Only one known study has correlated individual arrest characteristics with brain volumes

(Ørbo et al., 2019). These researchers evaluated cortical thickness and surface area and then compared these with clinical variables that included coma duration and downtime. Reductions in cortical thickness were observed in the frontal, parietal, and inferior temporal cortices, and also in some regions of the left occipital and temporal lobes. These cortical reductions correlated with decreased memory performance, longer downtime, and increased coma duration, while memory performance correlated only with increased coma duration, not downtime. A limitation of this study is that subcortical volumes were not examined in relation to downtime, or coma duration, as subcortical areas can also face reductions after an OHCA. These results would also benefit from comparison with a cardiac control group.

Voxel-Based Morphometry

Voxel-based morphometry (VBM) is an automated technique that allows for *in vivo* quantification and comparison of differences in tissue volume between two groups using statistical parametric maps derived from structural MRI images. This method is particularly useful for evaluating both cortical and subcortical grey matter volumes, and has been used extensively in clinical and non-clinical populations (Mechelli, Price, Friston, & Ashburner, 2005). Total grey matter volume and regional volumes for specific brain structures can be extracted for each individual, and patterns of grey matter reduction can be characteristic of certain mechanisms or conditions. For example, normal aging is related to grey matter volume reductions in cortical grey matter, while subcortical structures remain relatively preserved (Matsuda, 2013). Conversely, Alzheimer's disease is characterized by early, disproportionate atrophy in the bilateral temporal lobes (Hirata et al., 2005). As previously mentioned, in the case of cardiac arrest, deep grey matter nuclei are thought to be most sensitive to anoxia, although there is evidence that widespread atrophy may also occur (Grubb et al., 2000). In one study, grey

matter volume estimates from VBM positively correlated with the number of neurons in the CA1 region of rat hippocampi. On this basis, the authors concluded that VBM differences were appropriate for measuring hippocampal damage following cardiac arrest (Suzuki et al., 2013).

Objectives

As mentioned, frequency estimates of cognitive dysfunction after cardiac arrest range from 6 to 100 % (Moulaert et al., 2009). While methodological flaws exist in the literature, survivors of OHCA differ substantially across several important predictors of cognitive outcome, including duration of downtime, duration of coma, the presence of pre-existing cardiovascular disease, and whether individuals receive CPR.

The objective of this dissertation was to comprehensively evaluate the cognitive profile of OHCA patients during the acute stage of their recovery, and to determine the inter-individual characteristics that contribute to, and are associated with, greater cognitive dysfunction in OHCA patients at the time they are discharged from hospital. This included both a neuropsychological assessment and a neuroanatomical imaging component.

Study 1

In the first study, we completed a comprehensive analysis of cognitive function in OHCA survivors just prior to hospital discharge. We calculated the rate of cognitive impairment among OHCA survivors, and established cognitive profiles with the neuropsychological assessment battery (NAB). These were compared with a control group of MI patients, as well as with base rates from the general population. Next, we used logistic regression to predict cognitive dysfunction from a host of clinical variables, including duration of coma, downtime, cardiovascular risk factors, and early CPR/defibrillation.

We hypothesized that frequency of cognitive dysfunction among OHCA survivors would be commensurate with other good-quality studies in the existing literature (i.e., 42 to 50% of OHCA survivors; Moulaert et al., 2009), and that deficits would be especially apparent in the areas of attention, memory, and executive function. We defined cognitive impairment as a score of $\leq 10^{th}$ percentile (1.28 SD below the mean), and thus estimated that the rate of cognitive impairment would be five times greater in OHCA survivors than the normative sample. For the MI group, we estimated that memory impairment would be two times greater than the normative population based on past research (Lilja et al., 2015). For the regression analysis, we estimated that longer downtime, longer durations before intervention, and greater cardiovascular risk factors would best predict cognitive dysfunction.

The research outlined in this dissertation addresses several gaps in the literature, such as the lack of data on cognitive dysfunction in OHCA survivors during the acute phase of their recovery. This is a critical time for such patients, as clinicians need to plan follow-up care, which might include some level of at-home care or referrals to acquired brain injury rehabilitation. Study 1 represents the first known attempt to evaluate predictors of cognitive outcome just prior to hospital discharge. In addition, the predictors of cognitive dysfunction are still not well understood in OHCA survivors, even with respect to the two most common factors studied to date, downtime and CPR/early intervention. Study 1 is the first to explore the relationship between downtime, CPR/early defibrillation, and cognitive dysfunction.

Study 2

In the second study of this dissertation, we used MRI to evaluate the neural correlates of cognitive dysfunction (in particular, grey matter volumes, as measured by VBM) at the time of hospital discharge in OHCA survivors. These were then compared to two groups: MI patients

and healthy controls. We explored the association between grey matter volumes and cognitive function in all groups, as well as the association between grey matter volumes and important clinical arrest characteristics, namely downtime and duration of coma.

Based on previous research (Ørbo et al., 2018; Stamenova et al., 2018), we hypothesized that mean grey matter volumes in the OHCA group would be significantly lower than in both the MI and healthy control groups, and that global grey matter volumes would be reduced in the OHCA group compared to healthy controls. In addition, we hypothesized that regions known to be affected in poor-outcome patients following coma (e.g., putamen, caudate, thalami, hippocampus; Björklund et al., 2014; Keijzer et al., 2018; Wijdicks, Campeau, & Miller, 2001) would be disproportionately affected in the OHCA group compared to the healthy control group. Lastly, we predicted that downtime and days of coma would correlate with decreased volume in deep grey matter nuclei and in the hippocampus in OHCA patients, grey matter volumes would be reduced in MI patients compared to healthy controls, and cognitive performance would correlate with reduced grey matter volumes in the OHCA and MI groups.

Study 2 represents the first attempt in the literature to evaluate brain volume differences between OHCA patients and two comparison groups, a cardiac control group and a healthy control group. Only one study has evaluated the correlations between grey matter volumes, downtime, and duration of coma. However, only cortical thickness was explored (Ørbo et al., 2019), despite subcortical grey matter volumes also being at high risk of reduction after an OHCA (Björklund et al., 2014; Keijzer et al., 2018; Wijdicks et al., 2001). As such, our goal in Study 2 was to include subcortical grey matter volumes and explore how they relate to important clinical characteristics.

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CHAPTER 2

Cognitive Dysfunction after Out-of-Hospital Cardiac Arrest: Rate of Impairment, Neurocognitive Profile and Clinical Predictors

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ABSTRACT

Background: Individuals who have experienced an out-of-hospital cardiac arrest (OHCA), even those who appear to have made good neurological recovery, are at risk for cognitive deficits which can seriously detract from day-to-day function. The purpose of this study was to evaluate the rate of cognitive impairment and the profile of cognitive performance in a sample of out-of-hospital cardiac arrest (OHCA) survivors, as compared to patients who experienced a myocardial infarction (MI), and to explore predictors of this impairment.

Methods and Results: Successive OHCA survivors admitted to a cardiac institute, who made a seemingly good neurological recovery (i.e., Cerebral Performance Categories Scale ≤ 2) were screened and recruited (n = 79), as was a control group of patients post MI (n = 69). All participants (N = 148) underwent a comprehensive neuropsychological assessment. Clinical data were obtained from their medical charts. Results indicated that 43% of OHCA survivors were cognitively impaired (at or below the 10th percentile of the normative population on a global measure of cognitive functioning). Rates of impairment were approximately 6 times higher in the OHCA group than the MI group. Time from arrest to return of spontaneous circulation (i.e., downtime) was a significant predictor of cognitive impairment; the interaction between downtime and immediate intervention was significant such that, at short downtimes, receiving cardiopulmonary resuscitation (CPR) or defibrillation within 1 minute of collapse was predictive of less cognitive impairment.

Conclusions: OHCA survivors are at risk for cognitive impairment, and rates of impairment far exceed those post-MI and the general population. The use of CPR and rapid defibrillation contribute to cognitive outcome.

Introduction

Raised public awareness regarding life-saving interventions, such as cardiopulmonary resuscitation (CPR) or the use of automated external defibrillators (AEDs) have contributed to an increase in survival rates for individuals who experience out-of-hospital cardiac arrest (OHCA); 10.4% survive to hospital discharge.[1] Neurological dysfunction due to hypoxic-ischemic encephalopathy is the primary concern after resuscitation from cardiac arrest. Neurological outcomes are typically characterized by broad categorization systems, [2–5] most commonly, the Cerebral Performance Categories scale (CPC). [6] While scales like the CPC are brief and practical in clinical settings, they lack sensitivity such that cognitive difficulties may go undetected. [7–11]

The rate of cognitive dysfunction among OHCA survivors ranges from 6% - 100%.[12,13] This variability reflects methodological weaknesses and inconsistencies among early studies, including small sample sizes,[14,15] inconsistent measures for assessment of cognitive functioning differing widely in sensitivity, a lack of consensus in the definition of impairment,[13] and heterogeneity in sample composition (e.g., inclusion of individuals who arrested due to non-cardiac causes).[16]

Findings to date are equivocal with respect to the neuropsychological profile (i.e., pattern of performance across cognitive domains) observed in cardiac arrest survivors. In some studies, memory impairments predominate.[8,12,13,17–19] This pattern is consistent with a hypoxic-ischemic mechanism of neurocognitive impairment, in so far as the hippocampus, particularly vulnerable to hypoxia, is critical to consolidation of new memory.[20] Other studies find deficits in executive function to be more prominent, with the memory changes being primarily dysexecutive in nature.[21] Deficits in attention, language, visuomotor function, and visuospatial abilities are also reported.[12–14,18]

Studies have attempted to determine factors that predict cognitive outcome in order to develop interventions, and identify patients who are at risk for cognitive dysfunction. To date, demographic factors (e.g., younger age, higher education),[10] post-arrest and treatment factors (e.g., coma duration, therapeutic hypothermia),[18] and chain of event variables (e.g., CPR prior to ambulance arrival)[22] have been identified as potential predictors of cognitive outcome. However, findings are inconsistent, and studies are limited by small sample sizes (n = 26-57),[22,23] insensitive cognitive outcome measures[10,24] and, in some cases, the study results have become outdated due to changes in standard clinical practices.[22,24] In addition, most studies in this area have been conducted months, to years, after the arrest.[13] This is a serious limitation given that clinical decisions regarding the need for services post cardiac arrest (e.g., acquired brain injury rehabilitation) are typically made before the patient is discharged from hospital. Information concerning the acute cognitive impact of arrest is vital to optimizing treatment planning.

To our knowledge, only three studies[19,25,26] have comprehensively evaluated cognition in OHCA patients in the acute stages of recovery (while in hospital or within weeks of discharge). These studies found that memory, attention and executive function deficits were common. However, one of these studies was quite small (n = 33);[19] two of them failed to include a comparison group,[25,26] and two of them included in- and out- of hospital cardiac arrest patients[25,26] and the third did not specify the location of cardiac arrest.[19] These design factors prevent addressing the question, critical to mechanism, as to whether the observed cognitive profile was unique to the arrest population or common to patients with other forms of cardiovascular disease (CVD). Clearly, more research is required to identify the rate of cognitive dysfunction in the OHCA population, as compared to other patients with CVD, particularly at a time when critical decisions for their care are being made.

In this study, our objectives were: 1) to determine the rate of cognitive impairment in OHCA and myocardial infarction (MI) survivors, and to compare these rates to a normative sample; 2) to compare cognitive performance (i.e., domain-specific cognitive scores) of OHCA and MI patients; and, 3) to explore which factors predict cognitive impairment in OHCA survivors. We hypothesized that the rate of cognitive impairment in the OHCA group would be fivefold higher than the normative sample, and that the rate of cognitive impairment in the MI group would be twice as high as the normative sample. We also hypothesized that memory and executive functions would be the most affected cognitive domains; and, with regards to predictors of cognitive impairment, we hypothesized that downtime, early intervention, and cardiovascular risk factors would best predict outcome in OHCA survivors.

Method

Participants

Consecutive admissions of OHCA patients of cardiac etiology to the University of Ottawa Heart Institute, between December 2015 to May 2018, were approached once medically stable and approaching hospital discharge. These individuals were categorized by clinical staff as having good neurological outcome according to the CPC scale (score of 1 or 2; normal, mild or moderate impairments in cerebral functioning but independent in activities of daily living).[6] During the same time period, patients who had been hospitalized for MI without cardiac arrest enrolling in cardiac rehabilitation were approached to serve as a control group; all hospitalized patients are referred to cardiac rehabilitation.[27] The MI control group was selected in an effort to distinguish cognitive dysfunction caused by cardiac arrest from any pre-existing cognitive disturbance related to underlying CVD.

Exclusion criteria for both groups included pre-existing conditions that could influence

performance on neuropsychological testing such as current substance abuse disorder, history of traumatic brain injury with loss of consciousness >30 minutes, neurological conditions (e.g., dementia, Parkinson's disease) or serious psychiatric illnesses (e.g., bipolar disorder, schizophrenia). Participants were also excluded if they were not fluent in English, less than 18 years of age, lived in a remote region, or were deemed incapable of consenting. Participants received a $25 gift card for participating in the study. This study was approved by the Ottawa Health Science Network Research Ethics Board. Written informed consent was obtained from all participants.

Procedures

All individuals admitted to the University of Ottawa Heart Institute for OHCA who met the inclusion criteria were approached by a healthcare professional in the participant's circle of care and provided with an overview of the study. Those who agreed to participate were approached by research personnel who provided further information, obtained written consent, and administered a baseline interview and questionnaire. Neuropsychological assessments were conducted in-hospital (OHCA patients) or at cardiac rehabilitation intake (MI patients) by a licensed neuropsychologist or graduate level neuropsychology students.

Measures

Primary Outcome: Cognitive Function. Cognitive functioning was measured using the Neuropsychological Assessment Battery (NAB),[28] a paper-pencil neuropsychological test comprised of five modules measuring various cognitive domains including: memory, attention, language, spatial, and executive functions (see Supplemental Table 1 for a detailed description of NAB). The NAB provides normative data stratified by age, education, and sex from a large standardization sample comprised of neurologically healthy individuals, with all subtests co-

normed to the same standardization group. Psychometric properties of the NAB, including reliability and validity, have been well established and it has been shown to be sensitive to cognitive impairment in a variety of clinical populations.[28] As per the NAB scoring procedures[28], a standard score was tabulated for each cognitive domain; these scores were used in analyses of cognitive performance (i.e., profile analysis). The five cognitive domain scores were summed and standardized to obtain a total NAB score, which provided a single global cognitive performance standard score.[28] An *a priori* cut-off value for cognitive impairment corresponding to the 10th percentile of the normative sample (i.e., 1.28 standard deviations below the mean of the NAB's normative sample; regarded as borderline to cognitive impairment)[29] was determined. Scores for each cognitive domain, as well as the global score, were dichotomized as "impaired" or "not impaired" using the 10th percentile threshold for all analyses of cognitive impairment.

Demographic Information. Information such as age, sex, ethnicity, education level, employment status, and smoking history was obtained by self-report and chart review.

Clinical Health Information and Arrest Factors. Medical history, as well as details regarding arrest, resuscitation, and treatment interventions, were collected from the patients' medical charts, which included records from emergency medical services, the emergency department, and the cardiac intensive care unit. *Comorbidity*. The Charlson Comorbidity Index (CCI) assigns weights to a range of comorbid conditions to provide a 10-year mortality index for an individual.[30] The pre-event CCI was calculated for each participant based on medical history obtained from his or her clinical chart. *Cardiovascular risk factors*. A score indicating major modifiable risk factors for CVD [31] was tabulated by assigning one point for each of the following conditions: hypertension, dyslipidemia, obesity (BMI ≥ 30), smoking status, and emotional distress (Hospital Anxiety and Depression Scale [HADS] [32] depression or anxiety ≥ 8), for a

maximal score of 5. *Duration of coma* was calculated based on the number of days between the day of arrest and the day of successful extubation. *Downtime* was defined as the number of minutes between time of arrest and time of return-of-spontaneous circulation. *Immediate intervention.* If the patient received CPR or defibrillation within 1 minute of arrest, the intervention was considered immediate.

Statistical Analyses

The data were entered and processed using IBM SPSS v25. Missing data were imputed using expectation maximization algorithm. Rates of cognitive impairment in the OHCA group, normative sample, and MI group, were compared using Fisher's exact tests. Sensitivity analyses of global NAB performance impairment at cut-off scores of the 5th and 15th percentile were also conducted.

Multivariate analysis of variance (MANOVA) was used to compare the performance across the five NAB modules in the OHCA and MI groups. Analyses were conducted to determine whether the magnitude of performance scores differed in the OHCA and MI groups (i.e., compare cognitive performance in each domain); whether the pattern of performance between modules differed in the OHCA group compared to the MI group (i.e., assess group-specific patterns of performance across domains); and to determine if differences in performance between cognitive domains represent significant differences (i.e., assess for cognitive domains of strength/weakness within the profile).

To explore predictors of cognitive impairment after OHCA, a backwards stepwise logistic regression approach was used to predict the presence of cognitive impairment in the OHCA survivors (i.e., global NAB performance ≤ 10%ile), with probability of inclusion of .10 and probability of exclusion of .20. In view of our speculation that the predictive value of

downtime might be moderated by whether or not an individual received early intervention, we ran two regressions, one with, and one without the interaction between downtime and immediate intervention. The first model included downtime, immediate intervention, CCI, CVD risk factors score, and duration of coma. The second model included the aforementioned variables as well as the interaction between immediate intervention and downtime to determine if this additional increased the predictive value of the first regression.

Results

A diagram of the participant flow for the OHCA and MI groups is presented in Figure 1. Between December 2015 and May 2018, 213 OHCA patients were admitted to the University of Ottawa Heart Institute. Of these individuals, 119 were ineligible for the study. Of those who were eligible (n = 94, 44% of OHCA survivors), 15 patients (16%) declined to participate in the study. The remaining 79 OHCA patients provided consent. One patient (n = 1, 1.27%) was later deemed ineligible given language difficulties that became apparent upon testing, and one patient (n = 1, 1.27%) discontinued the study prior to completing a single module of the assessment and was therefore excluded from analyses. For the OHCA participants, those who were eligible for the study but declined to participate did not differ significantly from those who participated in terms of age ($t[90] = -0.856$, $p = .395$) or sex ($\chi^2[1, N = 92] = .476$, $p = .685$). For the MI participants, those who were eligible for the study but declined to participate (37%) did not differ significantly from those who participated in terms of age ($t[110] = 0.7663$, $p = .445$) or sex ($\chi^2[1, N = 112] = .0319$, $p = .858$.

Prior to analysis, variables were examined for their distribution and whether the assumptions of parametric analyses were met. Due to a few outliers in the distribution of "downtime" and "duration of coma," a square root and logarithmic transformation, respectively,

was applied to improve the normality of distributions. Missing data were minimal (1.45 %) and found to be missing data at random (Little's MCAR χ^2 [311, N = 145] = 286.55, p = .837).

Sample Characteristics

A summary of demographic data is presented in Table 1. The overall sample ranged in age from 26 to 87 years and was predominantly male (87%), Caucasian (96%), and married (66%). The participants in the OHCA and MI groups did not differ significantly in terms of age (t[143] = -1.381, p = .169) or sex (χ^2 [1, N = 145] = .253, p = .615). In the majority of OHCA cases, the arrest was witnessed (91%) and therapeutic hypothermia was applied (71%).

Rate of impairment for each cognitive domain by group is presented in Table 2. Impairment in the OHCA group was greater than in the normative sample for the memory, attention, language, and executive domains, and greater than the MI sample in all domains (see Table 2). Sensitivity analysis using the 5th and 15th percentile as cut offs revealed greater impairment among participants in the OHCA group compared to the MI group at both thresholds (5th percentile, χ^2 [1, N = 145] = 19.87, p < .001; 15th percentile, χ^2 [1, N = 145] = 32.03, p < .001).

Profile Analysis

Analyses revealed a significant difference in NAB scores between the OHCA and MI groups across all cognitive domains(F [1, 143] = 63.36, p < .001, partial η^2 = .307); the OHCA group performed significantly worse than the MI group. As depicted in Figure 2, there was no effect of group (OHCA vs MI) on the pattern of performance across the five cognitive domains of the NAB (F [4, 140] = 2.053, p = .09, partial η^2 = .055). Given that performance pattern did not differ in the OHCA group and the MI group, subsequent analyses were conducted in the sample as a whole (i.e., OHCA and MI patients combined) as per Tabachnik and Fidell.[33]

Cognitive performance was not consistent across all cognitive domains (F [4, 140] = 72.229, p < .001, partial η^2 = .674). Post-hoc tests to determine inter-domain differences revealed that scores on attention, memory and language modules were not significantly different from each other, whereas scores on spatial and executive modules were significantly higher than scores on other modules.

Logistic Regression

Model 1. The first logistic regression analysis included downtime, the CCI, immediate intervention, duration of coma, and CVD risk factors. Only downtime was significant; this variable was retained in the model. This model explained 25.2% of the variance of impairment on global NAB (Nagelkerke R^2 = .252). There was good fit of the model (χ^2 [7, N = 77] = 5.936, p = .547) with significant improvement over the baseline, constant-only model (χ^2 [1, N = 77] =16.027, p <.001). Regression coefficients are presented in Table 3.

Model 2. The second logistic regression analysis included downtime, the CCI, immediate intervention, duration of coma, CVD risk factors, and the interaction between immediate intervention and downtime. Based on statistical significance, the interaction between immediate intervention and downtime, CVD risk factors score, and duration of coma were retained. The final model explained 31.2% of the variance of impairment on global NAB scores (Nagelkerke R^2 = .312). There was good fit of the final model (χ^2 [8, N = 77] = 5.746, p = .676) and there was significant improvement over the baseline, constant -only model (χ^2 [3, N = 77] = 20.331, p <.001). Regression coefficients are presented in Table 3. A graph of the interaction between immediate intervention and downtime is presented in Figure 3. The interaction suggests that, at shorter downtimes, receiving CPR or rapid defibrillation led to less cognitive impairment, while at longer downtimes, immediate intervention was associated with more cognitive impairment.

Discussion

The purpose of the present study was to evaluate the rate and risk factors for cognitive impairment experienced by "good neurological outcome" survivors of OHCA as compared to their MI counterparts. This is the first study to measure cognitive dysfunction among OHCA survivors as compared to MI patients with a large sample in the acute stages of recovery. The present results revealed that a large proportion (43%) of these "good neurological outcome" patients have significant cognitive impairment at the time of discharge from hospital. Using the 10th percentile as the threshold for impairment, OHCA survivors demonstrated an elevated rate of impairment in nearly all cognitive domains compared to a normative sample and to their MI counterparts. Based on global NAB scores, the rate of cognitive impairment in the OHCA group was 4 times greater than the base rate (43% vs 10%) and approximately 6 times higher (43% vs 7%) than patients who experienced an MI. Overall, our results are in line with other recent studies of superior quality that indicate rate of cognitive impairment of 34% to 50% among "good outcome" cases.[12,34]

Contrary to previous findings demonstrating predominant memory impairments in the OHCA population, and inferences of selective medial-temporal lobe dysfunction,[8,14,17] our results revealed impairments across all cognitive domains (17% – 56%) except spatial functioning, with attention being the most affected domain. The global nature of the impairment and predominant attention difficulties in our study may reflect important differences in study design and measurement from previous studies. Our assessment battery was more comprehensive than that in some other studies,[14,17] as such, deficits possibly undetected in other studies were uncovered here. Participants in our study were tested earlier in recovery (i.e., during the acute hospitalization) whereas other studies, which found more isolated memory impairments, were

conducted much later (i.e., up to four years).[17] Earlier testing may have captured some mild reversible attention issues that will continue to resolve with time.

Conversely, executive dysfunction was less apparent in our sample than in other studies. The Executive Function module of the NAB contains relatively few subtests compared to the other NAB modules, perhaps rendering it less sensitive. It also bears comment that most neuropsychological tests are multi-dimensional and tap a number of different cognitive domains. For example, the same test can be used as a measure of attention, processing speed, or executive function in the hands of different researchers, no doubt contributing to the different neuropsychological profiles obtained. Given the generally high correlation between the constructs of attention and executive function,[35] it is possible that the executive dysfunction in our sample is reflected in scores on the attention module. Establishing a consensus on a core battery of tests to be used in the study of cognitive dysfunction among patients with CVD, as has been done by researchers working with other clinical populations (e.g., cancer and multiple sclerosis),[36,37] would be a great stride in clarifying the neuropsychological profile associated with OHCA.

A previous study of survivors of OHCA found that MI controls had similar memory deficits to OHCA patients.[38] We did not observe this in our sample. Given that their relatively brief hospitalization could not accommodate a full neuropsychological evaluation, the MI participants were more often tested at the point of commencing cardiac rehabilitation (2-8 weeks after their index event) than during hospital admission. It is possible that there was some spontaneous recovery of cognitive functioning over this interval. However, NAB scores were significantly lower in the OHCA group than in the MI group, even when controlling for time since event (F [1, 142] = 46.650, $p < .001$).

The current study also aimed to understand the predictors of cognitive impairment after OHCA. In our first model, downtime was the only significant predictor of cognitive impairment. Surprisingly, immediate CPR or defibrillation, demonstrated to increase the chances of survival,[39] did not predict cognitive outcome in a straightforward fashion. At shorter downtimes, CPR or defibrillation was related to decreased odds of cognitive impairment; conversely, at longer downtimes, immediate intervention was related to increased odds of cognitive impairment. This latter finding may represent a survivor bias. It is likely that those who experienced longer downtimes, despite receiving bystander CPR or defibrillation within 1 minute of their initial arrest, represent a more complex group who were unable to be resuscitated easily and, as a result, sustained more severe brain insult. This subgroup may not have made good neurological recovery at all were it not for the immediate interventions applied and hence not met the inclusion criteria (i.e., good neurological outcome) for the study. Ours is the first known study to attempt to understand the complex relationship between downtime and immediate intervention in the context of cognitive functioning. Results of a previous study indicated that early CPR was related to better cognitive outcomes, though downtime was not predictive in that study.[22] Others have identified no relationship between downtime and cognitive functioning.[18,40] These discrepancies may be due to moderating variables such as CPR and further examination of the interactions among these variables may promote our understanding of the mechanism of cognitive impairment in this population. These findings suggest that immediate intervention of bystanders not only determines “life or death,” but may also have direct implications for functional recovery after cardiac arrest, even among those who may appear to be doing quite well.

We also aimed to understand the contributing role of CVD in cognitive dysfunction after OHCA. Although cardiovascular risk factors was retained as a variable in our second model, it did not reach statistical significance as a predictor of cognitive impairment in the OHCA patients. These findings in addition to the lack of impairment in the MI control group support the prevailing view that anoxia is a more significant etiological factor than underlying CVD with regard to cognitive dysfunction in the OHCA population.

Although one of the largest controlled studies to date, there were some limitations to this study. Whereas virtually all of our OHCA patients were assessed prior to hospital discharge, circumstances within the hospital system (i.e., rapid discharge) dictated that our MI patients were recruited post-discharge and assessed in an outpatient setting. Conducting neuropsychological assessments in hospital may be less ideal than the circumstances in which normative or control groups were assessed (e.g., noise and distraction on the ward). The interval between testing and the index cardiac event was significantly longer in the MI group than the OHCA group, allowing the MI patients more time to recover from acute cognitive effects. While this may have contributed to some extent to the greater rate of impairment in the OHCA group, it should be noted that it did not emerge as a significant covariate when comparing impairment in the two groups. Our sample, in line with the population of OHCA survivors,[1] was predominantly male and therefore precluded sex- or gender- based analyses.

Overall, the present results indicate that a large proportion of OHCA survivors are discharged home with considerable cognitive impairments. We suspect that these deficits, though subtle, may become noticeable with attempts to resume pre-illness functioning and may significantly detract from quality of life.[15,41] At present, cognitive assessment and rehabilitation are not standard components of cardiac rehabilitation,[42] and our findings suggest this to be a

serious gap in the current standard of care for these patients, especially in light of the growing cohort of OHCA survivors. Furthermore, cognitive rehabilitation has shown promising results in other patient populations particularly in the areas of memory and attention.[43] Such interventions have implications for patient quality of life, and return to work rates. [44] Understanding who is at risk for these sequelae will allow us to use our rehabilitation resources to greatest benefit and highlights the need for more longitudinal research to determine the natural history of OHCA-related cognitive dysfunction.

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Disclosures

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Table 1. Demographics, clinical, treatment and testing information

		OHCA n (%)	*MI n* (%)	*p*
N (% or SD)		77	68	
Age		59.0 (13.18)	61.69 (9.78)	.162
Gender				.615
	Male	67 (87.0)	61 (89.7)	
	Female	10 (13.0)	7 (10.3)	
Marital Status				.419
	Single	10 (14.3)	7 (11.1)	
	Married/Common Law	51 (65.7)	52 (76.2)	
	Divorced/Separated	9 (12.9)	8 (11.1)	
	Widowed	7 (7.1)	1 (1.6)	
Race				.025
	Caucasian	74 (96.1)	56 (82.3)	
	Black	1 (1.3)	4 (5.9)	
	Other	2 (2.6)	8 (11.8)	
Education				.056
	Less than 12 years	13 (16.9)	4 (5.9)	
	12 years	16 (20.8)	10 (14.7)	
	12-16 years	18 (23.3)	14 (20.6)	
	>16 years	30 (39.0)	40 (58.8)	
Employment Status				.587
	Full-time	43 (56.8)	37 (54.4)	
	Part-time	5 (6.49)	5 (7.4)	
	Unemployed	3 (3.9)	4 (5.9)	
	Retired	26 (33.8)	20 (29.4)	
	Disability	0 (0.0)	2 (2.9)	
Previous/ Current Cardiac Condition				

	Hypertension	35 (45.5)	39 (57.4)	.153
	MI	12 (15.6)	5 (7.4)	.124
	Dyslipidemia	28 (36.4)	38 (55.9)	.019
	Diabetes	6 (7.8)	16 (23.5)	.008
Previous Cardiac Intervention				
	CABG	4 (5.2)	1 (1.5)	.220
	PCI	8 (10.4)	5 (7.4)	.523
Witnessed		70 (90.9)		
Witnessed by				
	Bystander	64 (83.1)	-	-
	Medical personnel	6 (7.8)	-	-
Cooled				
	Yes	55 (71.4)	-	-
	No	22 (28.6)	-	-
Treatment				
	PCI	43 (55.8)	61 (89.7)	.000
	ICD	38 (49.4)	0 (0.0)	.000
	CABG	7 (9.1)	6 (8.8)	.955

Note: *N* and *SD* represent sample size and standard deviation. *p* represents significance values of between group t-tests or chi-squared tests. Abbreviations: CABG, coronary artery bypass graft; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention;

Table 2. Impairment rates

	Mean Cognitive Performance		Participants Impaired at the 10th Percentile		Fisher Exact Test *p*-value Comparison Group	
Cognitive Domain	OHCA (SD)	Mean MI (SD)	OHCA *n* (%)	MI *n* (%)	MI	Normative
Total	81.9 (15.7)	105.2 (13.5)	33 (42.9)	5 (7.4)	< .001	< .001
Attention	81.8 (15.9)	101.1 (12.8)	43 (55.8)	4 (5.9)	< .001	< .001
Memory	85.5 (17.1)	99.7 (14.4)	35 (45.5)	7 (10.3)	< .001	< .001
Language	87.5 (15.8)	100.1 (12.6)	32 (41.6)	5 (7.4)	< .001	< .001
Executive	88.5 (14.2)	105.4 (15.3)	23(29.9)	6 (8.8)	.002	< .001
Spatial	99.2 (15.6)	114.1 (11.4)	13(16.9)	0 (0.0)	< .001	.055

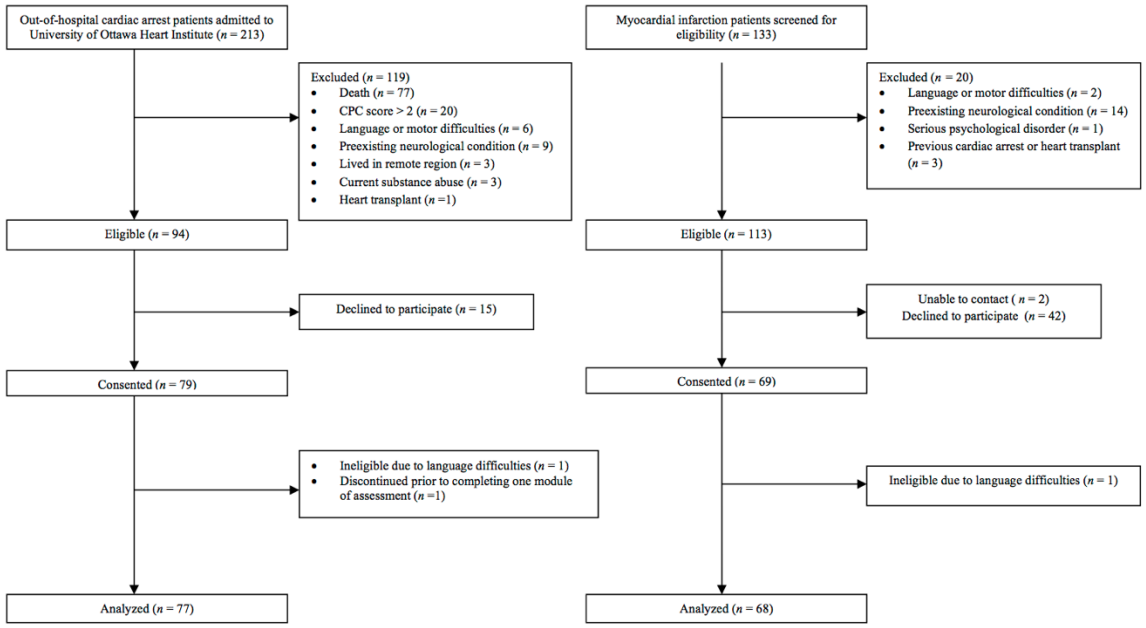
Note: Mean cognitive performance is presented in standard scores (M = 100, SD = 15). Fisher Exact Tests comparing the OHCA group to the respective comparison group. MI, myocardial infarction; NAB, Neuropsychological Assessment Battery; OHCA, out-of-hospital cardiac arrest

Table 3. Logistic regression models

Logistic Regression Model 1	*B*	*Wald*	OR	95 % CI
Downtime*	-.912	11.516	2.490	(1.47, 4.22)
Logistic Regression Model 2				
Downtime x Immediate Intervention*	1.044	8.269	2.841	(1.39, 5.79)
Cardiovascular Risk Factors	.334	2.228	1.397	(.90, 2.17)
Duration of Coma	1.069	1.666	2.912	(.58, 14.76)

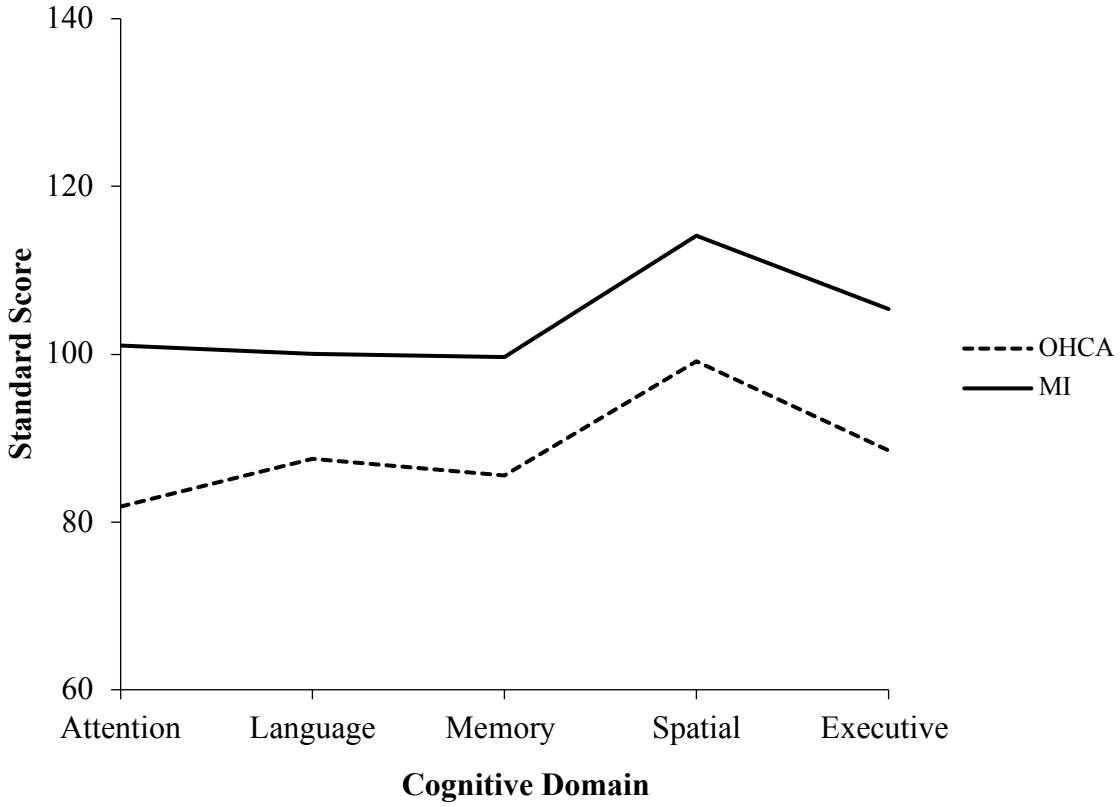
Note. Models predict cognitive impairment defined as performance ≤ 10^{th} percentile on the global Neuropsychological Assessment Battery score. OR represents odds ratios. All Variance Inflation Factors <10.

Figure 1. Consort diagram



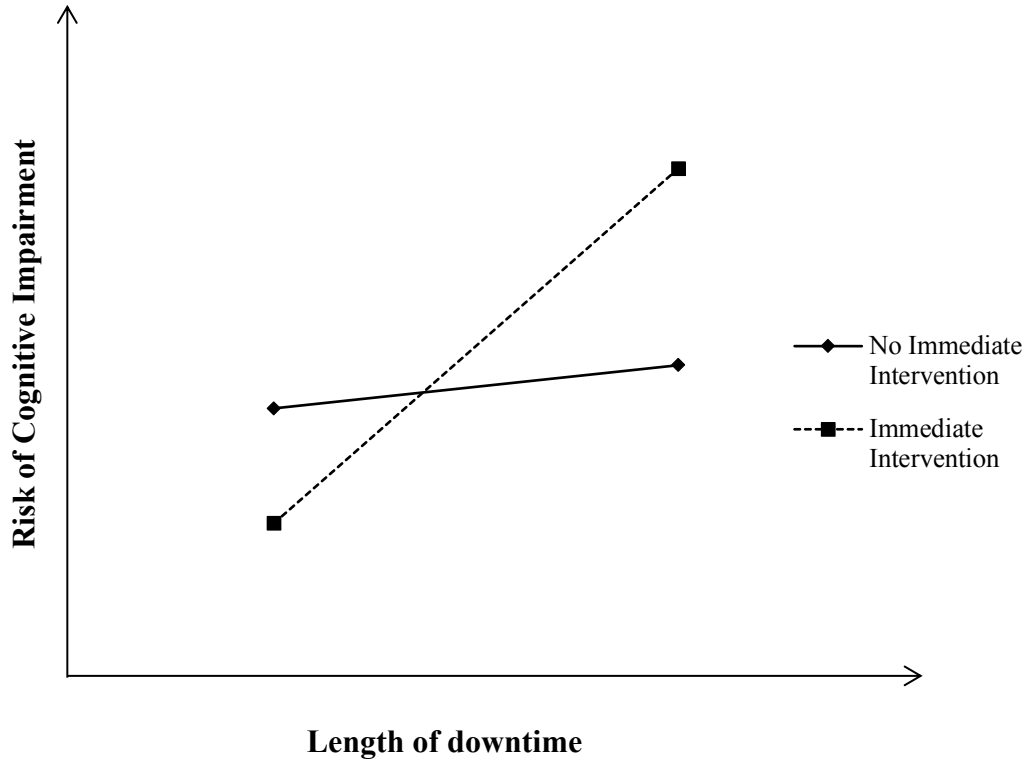
Note. Figure depicts the study participant recruitment flow. CPC, Cerebral Performance Categories Scale.

Figure 2. Scores in OHCA and MI groups on the Neuropsychological Assessment Battery modules.



Note. Figure 2 depicts the profile of cognitive scores for OHCA and MI groups (mean standard score for each cognitive domain on the NAB).

Figure 3. Interaction Model of Immediate Intervention, Downtime and Cognitive Impairment.



Note. Figure 3 depicts a reduced model with the interaction effect (immediate intervention x downtime), the main effects (downtime and immediate intervention), as well as the cardiovascular risk factors score and duration of coma. This logistic regression model explained 31.4% of the variance of impairment on global NAB score (Nagelkerke $R^2 = .314$). The overall model was a significant improvement over the baseline, constant only model (χ^2 [5, N = 77] = 20.499, $p = .001$), however, none of the individual variables in this model was significant.

Supplemental Table. **Neuropsychological Assessment Battery**

Domains	Functions Measured
Attention	Auditory attentional capacity
	Auditory and visual working memory
	Visual scanning
	Sustained, divided, and selective attention
	Information processing speed and psychomotor speed
Memory	Verbal (list and story) and visual learning
	Free recall of auditory information
	Delayed recognition of auditory and visually information
Language	Confrontation naming and word finding
	Auditory language comprehension
	Reading comprehension
	Verbal fluency
Executive	Planning
	Psychomotor speed
	Judgement and decision making capacity
	Concept formation and mental flexibility
	Verbal fluency and generativity
Spatial	Visuoperceptual and visuospatial discrimination
	Visuoconstruction
	Spatial directional/ visual scanning

Note. Table describes the cognitive functions assessed by the Neuropsychological Assessment Battery by cognitive domain

Reference: Stern R, White T. Neuropsychological Assessment Battery (NAB). Lutz: Psychological Assessment Resources; 2003.

Chapter 3

Exploratory Analyses of Cerebral Grey Matter Volumes after Out-of-Hospital Cardiac Arrest in Good Outcome Survivors

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*Minor revisions made as part of the thesis evaluation process

ABSTRACT

Background: Survival rates of cardiac arrest have increased over recent years, however, survivors may still be left with significant morbidity and functional impairment. A primary concern in cardiac arrest survivors is the effect of prolonged hypoxia/ischemia on the brain. The objectives of the present study were threefold: 1) to explore the effect of cardiac arrest on brain grey matter volumes (GMV) in "good outcome" survivors of out-of-hospital cardiac arrest (OHCA), 2) to examine the relationship between GMV, cognitive functioning and arrest factors, and 3) to explore whether OHCA patients differ from a group of patients with myocardial infarction (MI) uncomplicated by cardiac arrest and a group of healthy controls in terms of GMV.

Methods: Medically stable OHCA survivors with preserved neurological function and who were eligible for magnetic resonance imaging scanning (MRI; $n = 9$), were compared to: 1) patients who had experienced a myocardial infarction (MI; $n = 19$) and 2) healthy controls ($n = 12$). Participants underwent brain MRI on a 3T Siemens Trio MRI scanner and GMV was measured by voxel-based morphometry. A comprehensive neuropsychological assessment was also conducted. Global GMV was compared in the three samples using analyses of variance. The relationships between cognition and GMV were examined within group using correlations.

Results: The OHCA and MI groups showed a similar pattern of differences compared to the healthy control group. Both groups had decreased GMV in the anterior cingulate cortex, bilateral hippocampus, right dorsolateral prefrontal cortex, right putamen, and bilateral cerebellum. There were no significant differences in global or regional GMV between the OHCA and MI groups. Cognitive functioning was correlated with global GMV in the OHCA group; no such correlation was observed in the MI group.

Conclusions: Regional atrophy was observed in OHCA and MI survivors, compared to a healthy control group, suggesting a common mechanism, presumably preexisting cardiovascular disease. Although similar regional volume differences were observed between the MI and OHCA groups, the relationship between GMV and cognition was only observed in OHCA survivors. We suggest the acute hypoxia/ischemia ensuing from the arrest may interact with diminished neural reserve in select brain areas to expose occult cognitive dysfunction.

Keywords: out-of-hospital cardiac arrest, grey matter volume, cognition, myocardial infarction, magnetic resonance imaging

Introduction

Survival rates from cardiac arrest are improving (Benjamin et al., 2017) but survivors, even those who have made a seemingly good neurological recovery, are at risk for cognitive impairments that can negatively impact quality of life (Green et al., 2015). During a cardiac arrest, the heart stops beating and blood flow throughout the body and brain ceases until it is restored by either cardiopulmonary resuscitation (CPR) or defibrillation. Without adequate blood flow, the cells of the body and brain are deprived of oxygen and nutrients, and neurons are among the most sensitive cells to this hypoxic/ischemic state. Neuronal death can occur within minutes of a cardiac arrest (Busl and Greer, 2010), and even after successful resuscitation, reintroduction of oxygen to the abnormal biochemical cascades initiated by an arrest can result in reperfusion injuries (Weisfeldt and Becker, 2002). Those most at risk are individuals who experience an out-of-hospital cardiac arrest (OHCA) compared to those who arrest in hospital, as OHCA patients often do not receive immediate medical attention, putting them at particular risk for brain injury or death (Benjamin et al., 2017).

Magnetic resonance imaging (MRI) is often utilized to predict survival in comatose OHCA survivors given its high spatial resolution and ability to detect brain injury *in vivo* (Keijzer et al., 2018; Rossetti et al., 2016). According to the selective vulnerability hypothesis, not all neurons are uniformly affected by hypoxia. Regions of the brain with higher metabolic demands and rich in glutamate receptors are at the greatest risk for brain injury (Björklund et al., 2014; Busl and Greer, 2010). These more vulnerable regions include CA1 cells in the hippocampus, cortical grey matter, and deep grey matter, such as the thalamus and striatum (Busl and Greer, 2010; Gutierrez et al., 2010). Although no definitive prognosticators have been identified, signal abnormalities reflecting cytotoxic oedema in regions like the occipital and

medial-temporal cortices and the putamen (Keijzer et al., 2018; Rossetti et al., 2016; Wijdicks et al., 2006) are common among those who do not make good neurological recovery. Not only do certain neurons have higher metabolic requirements, some neurons may be at preferential risk due to their location relative to cerebral vascular supply (Torvik, 1984). Cortical and subcortical regions distal to major cerebral arteries are known to be affected in stroke, and also are at increased risk for cell death due to hypoperfusion (Caine and Watson, 2000).

As the majority of neuroimaging research on cardiac arrest survivors to date has focused on prognostication of survival in comatose individuals (Booth et al., 2004; Madl and Holzer, 2004), whether there are similar changes among "good outcome" survivors is still relatively unknown. This is understandable, given that approximately 80% of individuals resuscitated from cardiac arrest do not regain consciousness immediately (Booth et al., 2004). Cognitive deficits, however, are present in 34% to 50% of cardiac arrest survivors (Green et al., 2015; Moulaert et al., 2009), including those with "good neurological outcome" (Cronberg et al., 2009; Raina et al., 2008; Torgersen et al., 2010; Byron-Alhassan et al., 2019). Memory dysfunction is the most common area of deficit (Green et al., 2015), though deficits in attention and executive functions are also observed (Harve et al., 2007; Hofgren et al., 2008; Lim et al., 2014; Ørbo et al., 2014). The neurophysiological correlates of these cognitive deficits may be understood using the selective-vulnerability hypothesis. For example, memory dysfunction has been found to correlate with hippocampal reductions in this population (Ørbo et al., 2019; Stamenova et al., 2018). However, a general pattern of widespread volumetric reduction across cortical (Horstmann et al., 2010; Ørbo et al., 2019) and subcortical structures (Horstmann et al., 2010) are commonly observed. As such, a more generalized impact of hypoxic injury across the brain may be the cause of cognitive sequelae, highlighting the importance of examining both regional and whole-

brain reductions.

A better understanding of the underlying neuropathological mechanisms may allow better prognostication of which survivors are at greatest risk for persistent cognitive deficit, but few studies have examined neurophysiological sequelae in those who have survived and appear to be doing well neurologically. For example, to our knowledge, only one known study has examined the relationships between cortical thickness, cognitive dysfunction, and two key clinical variables, the duration between arrest and spontaneous circulation (i.e., downtime) and duration of coma after arrest (Ørbo et al., 2019). They found only duration of coma was correlated with cognitive function; subcortical grey matter regions that, according to the selective vulnerability hypothesis, may also be susceptible to hypoxia were not explored (Busl and Greer, 2010).

Most studies of cognitive dysfunction after cardiac arrest have focused on hypoxic/ischemic mechanism, while the contribution of cardiovascular disease to cognitive dysfunction has been relatively overlooked in OHCA survivors (Cronberg and Lilja, 2015). Cardiovascular disease, a risk factor for cardiac arrest, is well known to be associated with cognitive function (Cronberg and Lilja, 2015; Irani et al., 2009; Jefferson et al., 2011), however, few studies have included a cardiovascular control group when examining the neurophysiological and cognitive outcomes in cardiac arrest survivors (Grubb et al., 2000; Stamenova et al., 2018). In the largest known study of cognitive outcomes after cardiac arrest (Lilja et al., 2015), decreased memory performance was observed not only in the cardiac arrest group but also in the myocardial infarction (MI) group that had not experienced an arrest. However, this study did not include neuroimaging analyses or evaluate potential predictors of cognitive dysfunction in either group.

Very few MRI studies have focused specifically on OHCA survivors with relatively good

neurological outcome (Grubb et al., 2000; Horstmann et al., 2010; Ørbo et al., 2018, 2019; Stamenova et al., 2018) even though these individuals are known to experience cognitive deficits. To date, research has understandably focused on survivorship, but with novel medical interventions leading to increased survival rates (Chan et al., 2014), a gap has appeared in our understanding of the residual impacts on the brain caused by cardiac arrest. The MRI studies that exist in this area have been limited in scope, perhaps because of the inherent logistic difficulty of sampling patients during such a vulnerable period as following an arrest. Some studies, for example, have included patients who have experienced an arrest due to non-cardiac causes such as electrocution (Horstmann et al., 2010). Others have not included a cardiac control group (Ørbo, Vangberg, Tande, Anke, & Aslaksen, 2018), or have focused solely on memory functioning when evidence suggests that other cognitive domains are likely to be implicated (Ørbo et al., 2018). To our knowledge, no studies have evaluated individual arrest characteristics in relation to cortical and subcortical brain volumes.

The primary objectives of the present study were: 1) to explore the effect of cardiac arrest on brain grey matter volumes (GMV) in survivors within 3 months of the OHCA; 2) to compare the GMV of OHCA patients to both a group of patients who had experienced an MI uncomplicated by cardiac arrest, and a group of healthy controls (HC); 3) to examine the relationship between GMV and cognitive functioning as measured by a neuropsychological assessment among patients in the OHCA and MI groups; and, 4) to examine the relationships between GMV, cognitive functioning, downtime and duration of coma among OHCA survivors.

Method

Participants

Participants in the OHCA group were drawn from a larger study of cognitive function in patients with relatively preserved neurological function (Byron-Alhassan et al., 2019). Participants had to score 1 or 2 on the Cerebral Performance Categories (CPC; Jennett & Bond, 1975), indicating normal, mild or moderate impairments in cerebral functioning but independence in activities of daily living. In an effort to distinguish cognitive dysfunction caused by cardiac arrest from any pre-existing cognitive disturbance related to underlying cardiovascular or cerebrovascular disease, patients who had been hospitalized for MI without cardiac arrest were enrolled to serve as a control group. MI participants were recruited either while in hospital post-MI or at an outpatient follow-up appointment. Healthy control participants were recruited by word of mouth at the hospital and university, or nomination by patients or study team members.

Exclusion criteria for all groups included pre-existing conditions that could influence performance on neuropsychological testing such as current substance abuse disorder, history of traumatic brain injury with loss of consciousness > 30 minutes, and serious pre-existing neurological or psychiatric illnesses (e.g. stroke or schizophrenia). Participants were also excluded if they were non-MRI compatible (e.g. had an implanted cardioverter defibrillator), claustrophobic, or if they had any physical or mental health problems that precluded them from lying in relative stillness for the duration of the scans. Participants were also excluded if they were not fluent in English or younger than 18 years of age. Participants received a $25 gift card for participating in the study. This study was approved by the Ottawa Health Science Network Research Ethics Board. Informed, written consent was obtained from all participants.

Procedures

Participants were either scanned while still in hospital or shortly after hospital discharge by a medical radiation technologist. A clinical neuroradiologist (SC) reviewed all MRI scans for any clinically significant abnormalities. Any patients with acute or gross structural abnormalities (i.e. infarcts, tumours) that would influence group-level comparisons were excluded from final analyses.

Measures

Demographic Information and Arrest Factors. Participants reported their age, sex, ethnicity, education level, employment status, and smoking history in an interview with research personnel. Where possible, this information was verified by chart review. Downtime and length of coma (i.e. time in days from arrest to successful extubation, when coma persisted after initial return-of-spontaneous circulation) were obtained from patient's medical charts and emergency medical services records.

Cognitive Assessment. Cognitive functioning was measured using the Neuropsychological Assessment Battery (NAB), a paper-pencil neuropsychological assessment. comprised of 5 modules measuring memory, attention, language, spatial, and executive functions, respectively. A score is generated for each module and these are summed to obtain the global NAB index, a global measure of cognitive performance (Stern and White, 2003). The global NAB index reflects individual performance compared to the standardization sample in standard scores (e.g. mean value = 100, standard deviation = 15), where higher values equate to better performance. The NAB provides normative data stratified by age, education, and sex from a large standardization sample comprised of neurologically healthy individuals. Given the extensive normative data that exists for this battery, cognitive functioning was not assessed in the

HC group. Psychometric properties of the NAB, including reliability and validity, have been well established and it has been shown to be sensitive to cognitive impairment in a variety of clinical populations (Stern and White, 2003).

Magnetic Resonance Imaging. Imaging data were collected on a 3.0 Tesla Siemens TRIO MR scanner. Participants lay flat on an automated bed fitted with a 32-channel head coil. They were in two-way communication at all times with the medical radiation technologist performing the scanning. A 3D FLASH (TR/TE 11.2/21 ms, flip angle 60°, field of view (FOV) 26x26 cm^2, 256x256 matrix, slice thickness 1.5 mm) anatomic image was acquired for structural analyses.

Data Analyses

Sample Characteristics. Patient demographics (i.e. age, sex, and medical comorbidities), cognitive performance (i.e. mean NAB scores), and time since event (i.e. time to cognitive testing and time to scanning) were compared between groups using analysis of variance (ANOVA) and t-tests for continuous variables, and chi-squared tests for categorical variables.

Voxel-based Morphometry (VBM). Structural images were analyzed using the SPM12 toolbox with the DARTEL algorithm (https://www.fil.ion.ucl.ac.uk/spm/). Before analyses, all images were reoriented to be aligned with the AC-PC line. We followed the step-by-step processing sequence suggested by the DARTEL toolbox for the VBM analysis: (1) The MR images were first field bias-corrected to correct non-uniform fields. (2) Next, using the tissue probability maps based on the International Consortium of Brain Mapping (ICBM), the images were segmented to grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF). (3) The average study-specific GM and WM templates were subsequently computed and created. (4)

After an initial affine registration of the GM DARTEL templates to the tissue probability maps in Montreal Neurological Institute (MNI) coordinates, non-linear warping of individual GM images was performed to the DARTEL GM template and an individual flow field for each participant was created. (5) The individual GM images were normalized into the MNI space with a $1.5\times1.5\times1.5$ mm^3 voxel size with the normalized images modulated to ensure the relative volumes of GM were preserved following the spatial normalization procedure. (6) The modulated, normalized GM images were then smoothed with an 8 mm FWHM Gaussian kernel. (7) Finally, the tissue volumes utility of SPM12 was used to extract the average global (whole-brain) value of GM (GMV) for each participant based on the segmentation files, which was applied in the further analyses.

Group-level analyses.

GMV between-group differences. The smoothed, normalized individual GM images were applied in the second-level group analyses using SPM12. The voxel-wise ANOVA analyses and post-hoc two-sample t-tests were conducted to examine the GMV differences among three groups (i.e. HC vs. OHCA, HC vs. MI, OHCA vs. MI). Individual age and global GMV were included in the SPM group-level GLM model and controlled for as covariates of no interests in all imaging analyses. The global GMV was included as a nuisance variable to control the effect of individual differences in the global GMV. Reported regions were derived at the threshold of uncorrected $p < 0.001$, cluster size > 30 voxels at the whole-brain level. Multiple comparison corrections were then applied to all regions at the cluster level to verify the results. Both Family-wise-error (FWE) and small volume corrections (SVC) were performed (Poldrack et al., 2008). For SVC correction, anatomical independent regions of interests (ROIs) were defined as masks using the WFU pickatlas AAL template (https://www.nitrc.org/projects/wfu_pickatlas/), then the

SVC function in SPM12 for the correction was applied. All regions were reported regardless of the significance after multiple comparison corrections.

Correlation between GMV and cognitive functioning. Next, ROI analyses were performed to explore the relationship between cognitive functioning and the regional GMV, as well as the global GMV. Regional GMV that differed significantly for the patient groups compared with the HC group were extracted using marsbar (http://marsbar.sourceforge.net/) based on the voxel-wise analyses results. Partial correlation analyses were then conducted between the cognitive performance scores and the regional GMV with global GMV and age as covariates of no interests. Also, the partial correlation analysis was performed between the cognitive functioning and global GMV, with age as a covariate of no interest using IBM SPSS 25.0.

Cardiac arrest clinical variables & GMV regression analyses. To further explore the relationship between downtime and duration of coma with GMV among the OHCA sample, whole-brain spatial regression analysis was conducted in SPM12. Clinical values (i.e. downtime, days of coma) were entered in the model as covariates to examine which regional GMVs were correlated with clinical values. Threshold applied was uncorrected $p < 0.005$, cluster size > 30 voxels at the whole-brain level.

Results

Sample Characteristics

A description of the sample and clinical variables can be found in Table 1. Participants across the three groups ranged in age from 30 to 84 years ($M_{age} = 59.65$, $SD_{age} = 11.61$). There were no group differences in age ($F[2, 37] = 1.699$, $p = .197$) or sex ($n_{female\_OHCA} = 2$, $n_{female\_MI} = 2$, $n_{female\_HC} = 3$, $\chi^2[2, N = 40] = 1.502$, $p = .560$). Patients in the MI group generally had higher

rates of cardiovascular risk factors (e.g. diabetes, dyslipidemia, and hypertension) however differences were not statistically significant (see Table 1). Participants in the OHCA group completed cognitive assessment and MRI scanning closer to the date of their cardiac event than the MI group. However, time to test and time to scan were not significant covariates in the between-group analyses of cognitive functioning (F [1,24] = 3.972, p = .058), or global GMV (F [1,24] = .064, p = .802), suggesting that they did not contribute to group differences in cognitive functioning or global GMV.

Cerebral GMV

Global GMV, white matter, and total intracranial volume did not differ between the OHCA, MI, and HC groups when controlling for age (Table1; F [6,68] = 1.818, p = .109, partial η^2 = .138). In whole-brain analyses controlling for age and global GMV, between-group comparisons revealed regional GMV decreases in the both the OHCA and MI groups in comparison to the HC group; the OHCA group had decreased GMV in the anterior cingulate cortex (ACC), right dorsolateral prefrontal cortex (DLPFC), bilateral hippocampus, right putamen, and bilateral cerebellum areas; the MI group had decreased GMV in the ACC, medial orbitofrontal cortex (OFC), right DLPFC, bilateral hippocampus, thalamus, bilateral putamen, and bilateral cerebellum areas. Most of these regions remain significant after the SVC correction at the cluster level ($p < 0.05$) (see Figure 1, Table 2) or were approaching significance. There were no significant differences in GMV between the OHCA and MI groups at the whole-brain level even before correction. Further exploratory analyses conducted without defining the cluster size limitation revealed an additional small cluster (six voxels) of reduced grey matter in the left DLPFC for the MI group compared to the HC group. These results are presented in Table 2.

Cerebral GMV and Cognitive Functioning

Mean cognitive performance in both groups was within the average range as compared to the normative data and did not differ between the cardiac groups in this sample (t[26] = -1.101, p = .294; for an in-depth analysis of cognitive performance between OHCA and MI groups, refer to Byron-Alhassan et al., 2019). Regional volumes that differed significantly for the patient groups compared with the HC group were extracted (i.e. ACC, OFC, DLPFC, hippocampus, thalamus, putamen, and cerebellum) and correlated with cognitive functioning in each cardiac group. Although no regional volumes were correlated with cognitive performance in the MI or OHCA group when controlling for age and global GMV, cognitive performance was correlated with global GMV in the OHCA group, but not the MI group (see Table 3). A strong positive correlation between GMV and cognitive performance was observed. However, a z-test comparing the correlation between GMV and total NAB scores in the OHCA group to the MI group only approached statistical significance (z = -1.62, $p_{\text{one-tailed}}$ = .053).

Cerebral GMV and Clinical Variables

Downtime ranged from 1 to 21 minutes in the OHCA group (M = 10.78, SD = 7.03). When controlling for age, global GMV did not correlate significantly with downtime (R^2 = -.568, p = .142). However, when controlling for age and global GMV, downtime was negatively correlated with GMV in the left putamen (-30, 5, 3, p < .005) and right putamen (32, 3, 6, p < .005) although, only the correlation with right putamen retained significance after small volume correction (see Figure 2).

Days of coma ranged from 0 to 14 (M = 3.11, SD = 4.51) with four patients not having experienced any coma. When controlling for age, global GMV did not correlate significantly with days of coma (R^2= -437, p = .292). At the whole-brain level, when controlling for age and

global GMV, no regional GMVs correlated significantly with days of coma.

Discussion

The purpose of this study was to evaluate GMV in a sample of OHCA survivors, who had made seemingly good neurological recovery, as compared to MI and HC groups. These participants were drawn from a comprehensive study of cognitive functioning after OHCA, which allowed us to explore the association between cognitive functioning and GMV. This study is novel in its inclusion of both an MI control group and a healthy control group. Their inclusion allowed us to further address the issue of the etiology of cognitive dysfunction after cardiac arrest, particularly the relative contributions of pre-existing cardiovascular disease and acute hypoxia/ischemia.

The findings of this study revealed cortical and subcortical volumetric reductions in select brain regions of OHCA survivors. These regions included the ACC, right DLPFC, bilateral hippocampus, right putamen and bilateral cerebellum. Reductions in hippocampal volumes were expected in this population given reports that memory impairment is the predominant cognitive sequela of OHCA (Green et al., 2015; Moulaert et al., 2009) and the known vulnerability of the hippocampus to hypoxia (Björklund et al., 2014; Busl and Greer, 2010). The ACC and right DLPFC are both key structures in executive functioning (Cummings, 1993), another commonly observed domain of cognitive impairment for survivors of OHCA (Green et al., 2015). Though volumetric reductions in these regions fit the cognitive profile for OHCA survivors, we also observed similar reductions in the MI group. These results suggest that pathology in these regions may result from risk factors common to both cardiac groups. Some of the regions with decreased volume observed in this study have been linked with cardiovascular risk factors (O'Donnell et al., 2016). For example, decreased prefrontal cortex volumes have been observed

in patients with hypertension (Raz et al., 2003) and activations in the anterior cingulate, which purportedly play a role in the autonomic nervous system, has been found to correlate with behavioural stress (Gianaros et al., 2005). Reduced cerebellar volumes have been observed in heart failure patients and may relate to decreased perfusion (Alosco and Hayes, 2015). Our findings suggest an increased need for studies of the pathophysiologic relationships between cardiac functioning and the brain.

In this study, we did not observe any differences between the OHCA group and either control group in terms of global GMV. Ørbo and colleagues (2018) found decreased global GMV compared to healthy controls among individuals who were comatose upon arrival in hospital after OHCA, but not among those who were conscious upon arrival. This may be pertinent to our results, given that approximately half (*n* = 4*)* of our sample were non-comatose hospital admissions. While we suspect that GMV is likely reduced in the OHCA population, our analyses were likely underpowered to observe such differences. The fact that our participants were scanned closer to the index event than in other studies may further account for some differences in findings.

Only the OHCA group had significant correlations between cognitive functioning and volumetric data; lower global GMV volume was correlated with worse cognitive performance. This correlation was not observed in the MI group, although the strength of the two correlations did not differ significantly. We would expect, with a larger sample, that the MI group would show a correlation between GMV and cognition, as has been observed in the literature (Kanai and Rees, 2011). However, we observed a strong correlation within our small sample of OHCA survivors, suggesting that volume loss among OHCA patients may be related to increased risk for cognitive impairment. Such correlations between brain volumes and cognitive function have

been observed in other MRI studies of cardiac arrest survivors. Grubb et al. (2000) similarly found that, although volumes were reduced in some regions, only total brain volumes were significantly correlated with cognitive performance and Stamenova et al. (2018) likewise found that correlations between cognitive functioning and hippocampal volumes were only apparent in their OHCA group, and not within the MI group. One possible explanation could be that pre-existing cerebrovascular disease burden diminishes neural reserve rendering an individual more vulnerable to the effects of cerebral hypoxia.

The OHCA group performed worse on cognitive testing in all domains than the MI group and, although these differences were not statistically significantly different in this sample. The lack of difference between the OHCA group and MI group may be a result of a small sample size, or due to sampling bias in the OHCA given that individuals who are eligible for MRI cannot have an implanted cardioverter defibrillator, a commonly used preventative measure after OHCA. To investigate this possibility, we compared participants in the present study to the larger sample of OHCA who underwent cognitive assessment from which they were drawn (n_{OHCA} = 77). Results showed that those who participated in the imaging sub-study performed significantly better on cognitive testing than those who did not (M_{MRI} = 101.33 SD = 17.68, M_{COG_ONLY} = 83.48, SD = 14.42, U = 471.50, p = .009), although this was not the case for the MI group (M_{MRI} = 108.42, SD = 11.30, M_{COG_ONLY} = 104.16, SD = 12.93, U = 560.50, p = .194). These results indicate that individuals who participated in our MRI study performed significantly better on cognitive testing than those who participated in a study involving cognitive assessment alone. Despite this, we found reduced GMV in this group of OHCA survivors who were doing relatively well from a cognitive standpoint, which may suggest a large effect in the greater population. With increasing survival rates and the advent of MRI-compatible defibrillators,

future studies may see larger sample sizes to further understand this interesting population.

Downtime was correlated with volumetric data in order to understand the potential relationship between the duration of hypoxia and cerebral GMV. Unlike other studies which have focused primarily on the hippocampus as a region that is primarily susceptible to hypoxia (Ørbo et al., 2018; Stamenova et al., 2018), our results revealed a strong, negative correlation between the putamen and downtime (partial r = -.914, p = .01). The putamen has been identified as a region that is susceptible to cytotoxic edema in individuals who do not have a favorable outcome from coma after cardiac arrest (Keijzer et al., 2018; Rossetti et al., 2016). The putamen is a key region in motor control and it also contributes to cognitive processes such as working memory (Arsalidou et al., 2013). Days of coma was not correlated with any regional volumes at the whole-brain level. Although another study identified significant correlations between days of coma, cortical thickness, and some aspects of cognition (Ørbo et al., 2019), the sample differed from the one in this study in that it included only patients comatose upon hospital arrival and therefore likely experienced more severe neurological impairment.

This study has some limitations. Survival rates of cardiac arrest are low, and many patients are treated with implanted cardioverter-defibrillators, which are not MRI-compatible; thus, the individuals included in MRI studies may not be representative of typical cardiac arrest survivors. As previously mentioned, compared to our larger study of cognitive functioning, those who participated in this neuroimaging sub-study demonstrated better cognitive performance. Eligibility restrictions also contributed to a small sample size; this is a common limitation of imaging studies of cardiac arrest survivors (n = 9-13; Horstmann et al., 2010; Ørbo et al., 2019; Stamenova et al., 2018). Uneven sample sizes were also a limitation given that OHCA survivors were more difficult to recruit than the control groups. We wished to evaluate patients prior to

hospital discharge at the point in time when rehabilitation planning typically occurs; however, medical complications prevented many patients from participating within this time frame which may have further detracted from the representativeness of the sample. We have found in our larger study that the MI patients perform somewhat better on the NAB than the American standardization sample, suggesting that the test norms may not be ideal for a Canadian sample. As a result, inferences about cognitive functioning in both groups as compared to the healthy control group, and its relation to volumetric data, may be distorted. Finally, hypoxic-ischemic brain injury and reperfusion injuries are dynamic processes that change over time (Busl and Greer, 2010). The current data were obtained at a time when neurological recovery was still ongoing. Identifying neural patterns in the acute phase which may predict long-term functioning are important next steps for future research.

Conclusions

Our results highlight the importance of considering baseline neurophysiology when evaluating the neural impact of OHCA. Findings suggest that there may be an interplay of acute and chronic neural changes, such that acute hypoxia/ischemia from the arrest may give rise to subtle deficits in cognitive functions subserved by regions with diminished neural reserve due to pre-existing cerebrovascular disease. Future imaging studies that include a functional component will be important in understanding the functional implication of volumetric reductions observed in this population.

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Table 1. Demographics, cognitive performance, and clinical variables

	OHCA	MI	HC	*p*
N	9	19	12	
Mean age in years (SD)	59.89 (14.63)	62.58 (9.69)	54.83 (11.32)	.197
Sex (% Male)	77.8	89.5	75	.560
Hypertension (%)	3 (33.33)	12 (63.16)	n/a	.228
History of MI (%)	2 (22.22)	3 (15.79)	n/a	1.000
Dyslipidemia (%)	2 (22.22)	12 (63.16)	n/a	.103
Diabetes (%)	1 (11.11)	4 (21.06)	n/a	.645
Mean NAB Index (SD)	101.33 (17.68)	108.42 (11.30)	n/a	.294
Mean downtime (mins; SD)	10.78 (7.03)	n/a	n/a	n/a
Mean duration of coma (days; SD)	3.11 (4.51)	n/a	n/a	n/a
Mean time to test (SD)	13.78 (13.04)	40.52 (21.96)	n/a	.001
Mean time to scan (SD)	26.67 (16.21)	62.84 (28.63)	n/a	.001
Mean grey matter volume (mm^3; SD)	665.00 (70.46)	673.84 (50.45)	681.58 (68.58)	.809
Mean white matter volume (mm^3; SD)	507.33 (45.19)	493.42 (53.32)	498.00 (44.27)	.806
Mean total intracranial volume (mm^3; SD)	1537.89 (113.84)	1511.05 (118.65)	1477.583 (128.35)	.556

Note. NAB = Neuropsychological Assessment Battery; Time to test refers to time in days from index event to date of cognitive testing; Time to scan refers to time in days from index event to date of magnetic resonance imaging scans; OHCA = out-of-hospital cardiac arrest; MI = myocardial infarction; HC = healthy controls; SD = standard deviation

Table 2. GMV differences between HC and MI, OHCA

Brain Regions	MNI Coordinates			Peak	Cluster-level Correction (p-value)	
	x	y	z	t-score	FWE	SVC
HC > OHCA						
ACC	2	36	29	4.16	0.967	0.090
rDLPFC	36	42	14	4.07	0.641	0.048
rHipp	15	-9	-12	4.17	0.870	0.019
lHipp	-14	-9	-11	4.96	0.552	0.016
rPutamen	32	-2	12	3.68	0.937	0.062
rCerebellum_Crus2	44	-38	-47	4.80	0.414	0.051
lCerebellum_7b	-47	-44	-50	3.97	0.294	0.020
HC > MI						
ACC	2	45	20	4.79	0.151	0.016
mOFC	9	42	-14	4.74	0.020	0.004
rDLPFC	38	45	5	4.55	0.339	0.022
lDLPFC	-38	33	12	3.55	0.929	0.253
rHipp	17	-9	-12	3.61	0.796	0.011
lHipp	-14	-9	-11	3.98	0.777	0.022
Thalamus	-2	-18	12	4.51	0.384	0.024
rPutamen	29	-6	12	3.92	0.019	0.006
lPutamen	-29	-9	12	4.19	0.648	0.050
rCerebellum_Crus2	44	-38	-47	5.38	0.135	0.028
lCerebellum_Crus1	-56	-62	-36	4.59	0.006	0.002

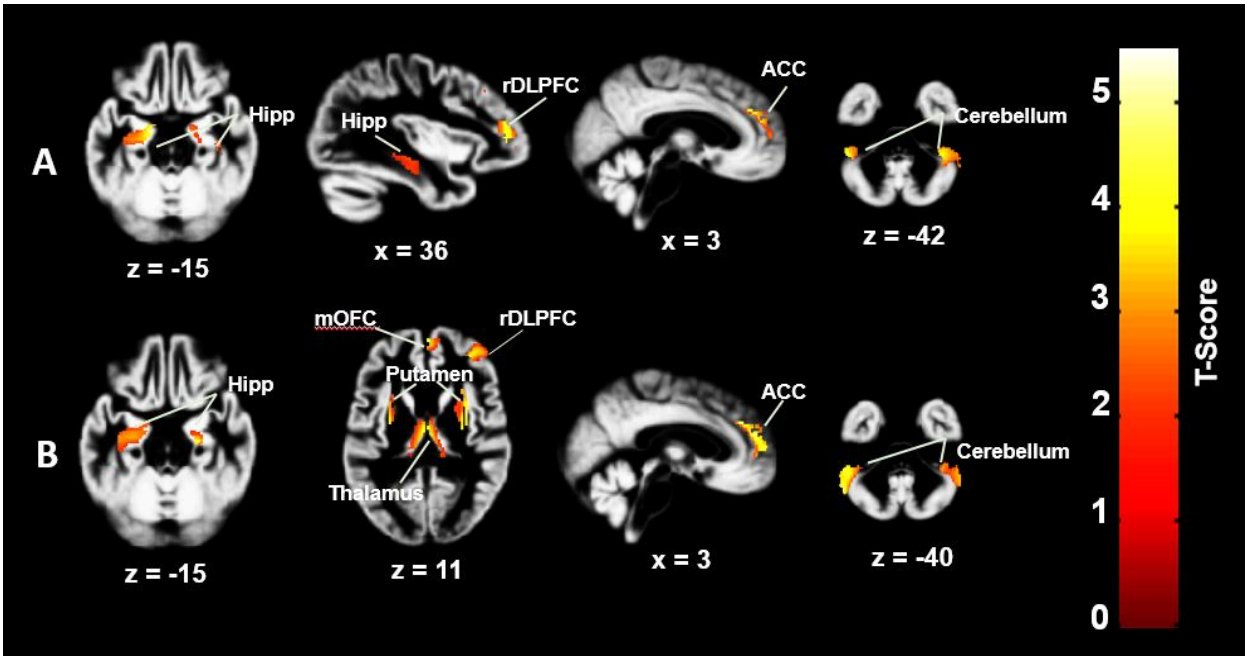
Note: Table presents three-dimensional Montreal Neurological Institute (MNI) coordinates for significant brain regions with peak cluster t-score value and corrected significance values. r. right side; l. left side; ACC: Anterior cingulate cortex; mOFC: Medial Orbital-Frontal Cortex; DLPFC: Dorsal lateral prefrontal cortex; Hipp: Hippocampus; FWE: Family-wise error correction; SVC: small volume correction; OHCA = out-of-hospital cardiac arrest; MI = myocardial infarction; HC = healthy controls

Table 3. Correlations between GMV and cognitive performance on the global NAB Index

Brain regions	MI	OHCA
Total GMV	.308	.798*
ACC	.279	.396
mOFC	-.050	.348
rDLPFC	.339	.044
bHipp	.045	.574
Thalamus	.33	.663
bPutamen	-.302	.326
bCerebellum	.233	-.403

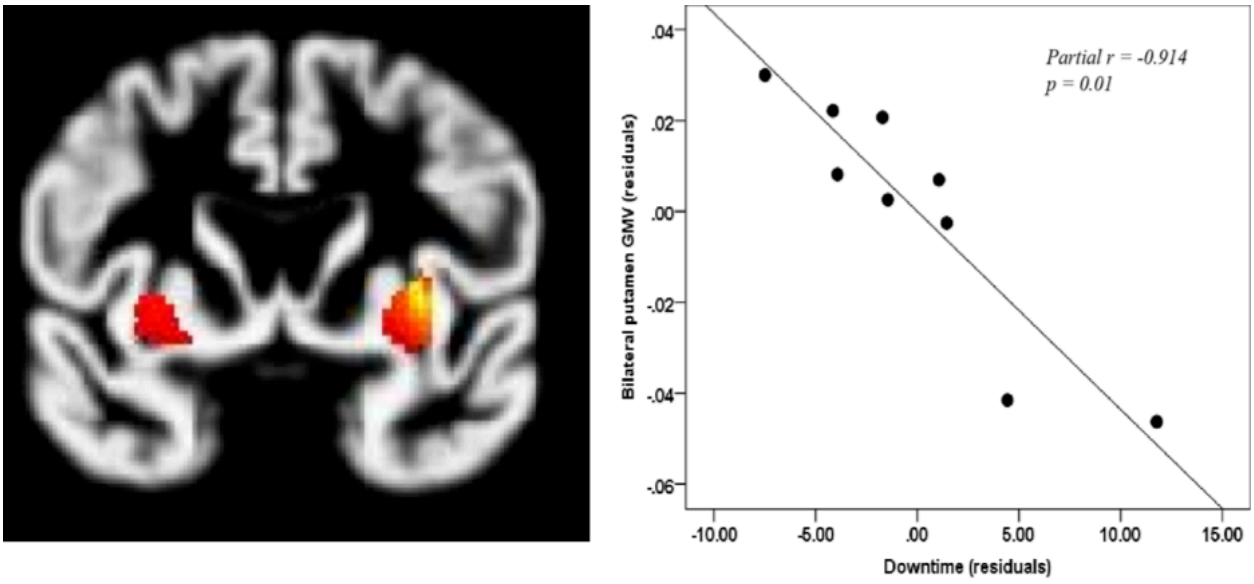
Note: Cognitive function is measured with the Neuropsychological Assessment Battery, scores are standardized to a normative sample for age, gender and education. Correlations are controlled for age and total GMV. r. right side; l. left side; b. bilateral; ACC: Anterior cingulate cortex; mOFC: Medial Orbital-Frontal Cortex; DLPFC: Dorsal lateral prefrontal cortex; Hipp: Hippocampus ; OHCA = out-of-hospital cardiac arrest; MI = myocardial infarction.

Figure 1. GMV differences between HC group and MI and OHCA group.



Note: (A) HC > OHCA; (B) HC > MI. ACC: anterior cingulate cortex; rDLPFC: right dorsolateral prefrontal cortex; Hipp: hippocampus; mOFC: medial orbitofrontal cortex. Statistical inferences were performed at a threshold of uncorrected $p < 0.001$ at the whole-brain level and $p < 0.05$, family wise error or small volume corrected at the cluster level. There were no significant differences in GMV between the OHCA and MI groups at the whole-brain level.

Figure 2. ***Correlation between downtime and putamen***



Note: Coordinates of bilateral putamen: Left: -30, 5, 3; Right: 32, 3, 6, $p_{uncorr} < .005$. Only right putamen remains significant after small volume correction $p < 0.05$.

CHAPTER 4

General Discussion

Surviving a cardiac arrest is a traumatic experience. They are unexpected, and often occur while engaged in everyday activities. Once a person collapses, they must rely on the presence of a family member or other bystander to intervene, and to contact emergency medical services.

Many of those who survive an OHCA are resuscitated by electrical defibrillation, often after long bouts of CPR that can cause significant bruises and broken ribs. Upon arrival at hospital, their bodies may be chilled to hypothermic temperatures and kept comatose for days to maintain low metabolic demands and allow the body to heal slowly. Some wake after this process, while others can remain comatose indefinitely.

For survivors, post-arrest treatment varies considerably. To prevent further cardiac arrests, stents may be placed in coronary arteries to open occluded pathways. Today, stents are most often inserted via a catheter through the arm or groin. Other OHCA survivors may receive an ICD, which has the ability to deliver 'shocks' that can assist the heart in returning to a regular rhythm should an abnormal one be detected. In other cases, patients' post-arrest interventions may include a coronary artery bypass grafting (CABG) procedure, in which occluded coronary arteries are bypassed with non-occluded vessels from other parts of the body.

Although medical interventionalists have made incredible advances, OHCA remains a leading cause of death in the United States, as only 10% survive to hospital discharge (Center for Disease Control and Prevention, 2018), and most Canadian data shows a similar trend (Wong et al., 2014). For survivors, cognitive deficits can limit the degree to which they return to their previous levels of functioning (Moulaert, Verbunt, van Heugten, & Wade, 2009). Compared to

the amount of research on life-saving medical interventions, there is a relative lack of understanding of post-arrest cognitive dysfunction. The purpose of this dissertation was to explore cognitive dysfunction in OHCA survivors using both neuropsychological testing and neuroimaging.

Addressing Existing Research Limitations

Frequency estimates of cognitive impairment vary widely in OHCA survivors, and many studies to date have been informed by cognitive function measures that lack sensitivity (Green, Botha, & Tiruvoipati, 2015; Moulaert et al., 2009). In addition, few studies have evaluated cognitive function prior to hospital discharge (Sabedra et al., 2015; Steinbusch, van Heugten, Rasquin, Verbunt, & Moulaert, 2017; Sulzgruber et al., 2015), and many studies do not include a cardiac control group (i.e., a group of individuals with cardiac disease who have not experienced an arrest), despite evidence that cardiovascular disease itself may lead to cognitive dysfunction (Cronberg & Lilja, 2015; Lilja et al., 2015). Because of these gaps in the literature, which clinical characteristics predict cognitive dysfunction after OHCA is still unknown; in fact, even the data on downtime and CPR is sparse, which are factors with clear face validity.

To date, neuroimaging studies of OHCA survivors are also limited; in particular, it remains unclear whether post-arrest cerebral changes contribute to cognitive dysfunction. While some studies have compared OHCA survivors with an MI control group (Grubb et al., 2000; Stamenova et al., 2018), there are no known comparisons between an MI control group and a healthy control group. This limits the inferences that can be made about the nature of the imaging abnormalities observed thus far. Furthermore, no known studies have examined how cortical and subcortical grey matter relate to important clinical arrest characteristics thought to associate with cognitive dysfunction.

The purpose of this dissertation was to address these research gaps by exploring the predictors of cognitive dysfunction after OHCA while addressing some of the extant methodological limitations in the literature. A large sample of OHCA patients were enrolled consecutively after admission to a specialized cardiac care center, as were a cardiac control group of MI patients at the same institution. Cognitive testing of the OHCA patients was performed prior to hospital discharge, and involved a comprehensive and extensive neuropsychological battery that assessed a broad range of cognitive functions. A subset of individuals also underwent neuroimaging (i.e., MRI) to evaluate the neural correlates of cognitive dysfunction prior to hospital discharge.

Hypotheses

The hypotheses of this dissertation were as follows: 1) the rate of cognitive dysfunction in the OHCA group would exceed the normative sample by five times, and the MI sample by two times, 2) the MI group would exhibit twice the rate of cognitive impairment compared to the normative sample, 3) memory, attention, and executive functions would be the areas of greatest cognitive dysfunction, with downtime, early intervention and cardiovascular disease serving as the greatest predictors of cognitive impairment, 4) grey matter volumes in the OHCA group would be reduced compared to healthy controls and the MIs, 5) cognitive performance would correlate with grey matter volumes in the OHCA and MI group, and 6) downtime and days of coma would correlate with decreased volume in both deep grey matter nuclei and the hippocampus.

Study 1. Neuropsychological Outcome in Acute Phase of OHCA

Study 1: Overview of Findings

In Study 1, the cognitive function scores of a sample of OHCA survivors were compared

with a group of MI patients and to normative data from a healthy standardization sample. The observed rate of cognitive dysfunction in OHCA survivors was consistent with recent estimates of cognitive impairment in good-quality studies (Green et al., 2015; Moulaert et al., 2009), as approximately 43% of OHCA survivors exhibited global cognitive impairment, compared to 7% in the MI group.

With respect to domain-specific cognitive performance, those in the OHCA group were more cognitively impaired in all areas except spatial function. An analysis of the cognitive profile of the OHCA group revealed that memory, attention, and language performance were significantly worse than performance in the areas of spatial and executive functions. One of the advantages of Study 1, compared to the existing literature, was that the comprehensive neuropsychological battery allowed for such a thorough cognitive profile to be produced. To our knowledge, this type of profile analysis using one standardized battery has never been conducted in OHCA patients.

Finally, a model was developed to determine which inter-individual characteristics might predict global cognitive impairment among OHCA survivors. Downtime was predictive of cognitive impairment, such that, at short downtimes, receiving immediate intervention (i.e., CPR or defibrillation within 1 minute of collapse) predicted better cognitive function. This was the first study to assess and identify a direct link between downtime, CPR, and cognitive function.

Study 1: Limitations

The general objective of Study 1 was to explore cognition in OHCA survivors at the time of hospital discharge; however, the early stages of brain injury are known to be dynamic and recovery may continue for weeks or months (Nudo, 2013). Since spontaneous recovery of

cognitive function may occur, longitudinal studies are required to chart the long-term profile of OHCA survivors, and such analyses were beyond the scope of the present research.

In addition, some potential confounds regarding cognitive performance were not controlled in this study. Most notably, the order in which the NAB modules were administered in Study 1 was not controlled. Ideally, a standardized administration order would control for any effect of module order (e.g., each consisted of different lengths); however, this proved infeasible given the multiple, competing demands on patients while hospitalized. Thus, one limitation of Study 1 was that the varied test administration order could have introduced non-random variability in participants' cognitive performance scores.

Of note, the cardiac patients who participated in Study 1 received complex pharmacological treatment following their stay at hospital. Some of these medications may have impacted cognition, but they were too varied and too extensive to control for. In the future, studies with larger sample sizes may be able to control for the impact of medications.

Lastly, despite best efforts, those in the MI control group were not age-, sex-, or education- matched to those in the OHCA group. Although this would have improved the quality of the control group, recruiting disease- and demographic-matched controls for a time-sensitive neuropsychological battery proved to be an ambitious a goal.

Study 1: Future Considerations

A large number of OHCA patients in Study 1 experienced cognitive deficits at the time of hospital discharge. Clinically, the findings support the use of routine inpatient screening for cognitive impairments prior to discharge. Comprehensive longitudinal studies of cognition after OHCA are necessary to determine the trajectory of these deficits, and whether impairment profiles change, over time.

Another important factor, therapeutic hypothermia, was not explored in either Study 1 or 2. This variable was excluded from analyses because patients were already participating in a blinded-clinical trial, the results of which will allow for analyses to determine whether therapeutic hypothermia is associated with improved cognitive outcome, given that this intervention protects against the neurological effects of OHCA (i.e., the Capital Chill Study; Clinicaltrials.gov identifier: NCT02011568).

In sum, Study 1 was the first to use a standardized neuropsychological battery to explore both downtime, speed of intervention, and their combined impact on cognitive dysfunction in OHCA survivors. Further exploration of how cognitive function is protected by rapid CPR is necessary, as knowledge of how the brain is impacted by such events could be used to improve our early intervention techniques and post-arrest treatment.

Study 2. Cerebral Grey Matter in Acute Phase of OHCA

Study 2: Overview of Findings

In Study 2, we used MRI to examine a subset of patients from Study 1 and an additional group of healthy controls. The cerebral GMVs of OHCA survivors during the acute recovery phase were compared to those of an MI group and the control group. Compared to healthy controls, OHCA and MI patients showed widespread regional reductions in cerebral GMV; these areas included the anterior cingulate cortex, bilateral hippocampus, right dorsolateral prefrontal cortex, right putamen and bilateral cerebellum. In the OHCA group alone, greater downtime was associated with less GMV in the putamen, a region in the basal ganglia which has been previously linked to poor outcome following coma after OHCA (Keijzer et al., 2018; Wijdicks, Campeau, & Miller, 2001).

In addition, Study 2 included an analysis of the interrelationships amongst cerebral

GMVs, cognitive scores, and cardiac arrest characteristics. Global cognitive performance on the NAB correlated with global GMV for OHCA survivors, but not for those in the MI group. One interpretation of this result is that the effects of post-arrest hypoxia, coupled with premorbid neurophysiological vulnerabilities, may promote cognitive dysfunction after OHCA.

Study 2 was the first known MRI study of OHCA survivors to include both an MI control group and a healthy control group. The results of Study 2 support previous work that identified global GMV reductions in OHCA survivors, which is opposed to previous theories that OHCA is associated with isolated medial temporal lobe reductions (Grubb et al., 2000; Horstmann et al., 2010; Ørbo, Aslaksen, Anke, Tande, & Vangberg, 2019). The findings also suggest that those who have experienced an MI may also experience GMV reductions compared to healthy individuals with no history of cardiovascular disease, but further research is needed with greater sample sizes.

Study 2: Limitations

Study 2 posed several logistical challenges due to the nature of imaging patients so close to the time of their hospital discharge. Despite recruiting all prospective admissions to a cardiac center for 30 consecutive months, the sample size of the OHCA group was small ($n = 9$). This is a common limitation in neuroimaging studies of survivors of OHCA (all ns < 13; Horstmann et al., 2010; Ørbo et al., 2019; Stamenova et al., 2018).

Furthermore, as discussed in detail in Study 2, the individuals who participated in this imaging sub-study had significantly better cognitive function than those who only participated in Study 1. As such, the sample in Study 2 may represent a specific subgroup of higher-functioning OHCA survivors among individuals who had already had good neurological outcomes, which makes it difficult to assess whether our findings are reflective of all OHCA survivors generally.

On the other hand, the fact that we did observe significant reductions in GMV in our small sample of high-functioning OHCA survivors is suggestive of an even larger effect in the general population of OHCA survivors. More inclusive studies with larger sample sizes are needed.

Lastly, unlike those in the OHCA or MI groups, we did not administer a comprehensive neuropsychological assessment to participants in the healthy control group due to the time and resource limitations of the research project. Future research that included such testing could perform statistical analyses that were beyond the scope of Study 2.

Study 2: Future Considerations

A similar pattern of GMV reduction was observed in both OHCA and MI patients in Study 2. Presumably, the underlying mechanism for this is pre-existing cardiovascular disease, which likely contributed to decreased blood flow to the brain. According to a model developed by Cohen (2011), cognitive impairment develops in individuals with chronic cardiovascular disease as a result of systemic hypoperfusion; this then leads to cerebral perfusion, which in turn causes cerebral atrophy. Neuroimaging techniques that explore cerebral blood flow (e.g., arterial spin labelling) could further test this hypothesis.

Study 2 examined only GMVs; however, white matter disease is linked to cardiovascular disease, and has also been identified as a risk factor for vascular cognitive impairment or dementia (Prins & Scheltens, 2015; Van Dijk et al., 2008). Future diffusion tensor imaging studies of both OHCA and MI survivors could explore white matter integrity, and further our understanding of the distinction between these two cardiac groups.

Similar to Study 1, Study 2 did not include a follow-up assessment of whether participants benefited from spontaneous recovery. Longitudinal studies of GMVs would produce a better picture of how impairments change over time in OHCA and MI survivors.

Generally, neuroimaging studies of OHCA survivors have been limited in size and scope. Future multicenter research projects are needed to produce representative data that can be generalized; however, such studies can introduce variability when they integrate data from multiple MRI scanners. While some of these pragmatic challenges are addressed, meta-analyses or systematic reviews can help advance the literature.

Results and Implications

Nature of Cognitive Dysfunction

According to earlier theories, hypoxia after cardiac arrest was thought to directly insult the medial temporal lobes and thus cause memory impairment (Markowitsch, Weber-Luxemburger, Ewald, Kessler, & Heiss, 1997). More recently, researchers have contended that cardiac arrest leads to more widespread brain changes (Horstmann et al., 2010; Ørbo et al., 2019; Sulzgruber et al., 2015), and the findings of this dissertation support this.

We used a large sample size, a broad, comprehensive, and standardized measure of cognitive function, and MRI (i.e., for a subset of our sample) that included exploratory analyses of the whole brain. Our findings add to the growing consensus that cognitive impairments after OHCA occur across several cognitive domains, and are related to widespread cortical and subcortical grey matter reductions (Markowisch et all., 1997; Moulaert et al., 2009). As discussed in Study 2, these findings are in line with the selective vulnerability hypothesis, which suggest that regions rich in glutamate, such as cortical and subcortical grey matter, are at risk of damage after a period of hypoxia (Busl & Greer, 2010).

Rate of Cognitive Impairment

Consistent with other studies of cognitive function in OHCA survivors (Alexander, Lafleche, Schnyer, Lim, & Verfaellie, 2011; Lilja et al., 2015; Torgersen et al., 2010), we

observed a rate of global cognitive impairment (i.e., NAB performance score ≤ 10th percentile) of 43%. The most common areas of impairment were attention, memory, and language.

In both clinical and research spheres, no clear, consensus, psychometric definition of cognitive impairment exists (Guilmette, Hagan, & Giuliano, 2008). We chose to define cognitive impairment as equal to or below the 10th percentile, as this liberal cut-off encompasses a wide range of cognitive difficulties and allows for an adequate and dichotomous split for the purpose of logistic regression analyses. Given the unavoidably arbitrary nature of this threshold, we examined rates of cognitive impairment in the OHCA group and the MI group using the 2nd, 7th, 10th, and 16th percentiles for comparison (-2.00, -1.50, -1.28, - 1.00 SD below the mean respectively; see Table 1). Regardless of the chosen cut-off, more OHCA survivors were impaired compared to the normative sample, while this was not the case for the MI group. Even using conservative thresholds, the OHCA survivors in our sample showed elevated rates of cognitive impairment.

In this dissertation, we determined cognitive impairment based on comparisons with a normative sample, not with premorbid function. While testing norms consider some *a priori* factors like education, age, and sex, it was beyond the scope of this research program to make any evaluation of self-relative cognitive decline. As such, it is impossible to determine for certain whether OHCA survivors exhibited more cognitive impairment because of their arrest, or whether these difficulties existed before their cardiac event. On the other hand, we found consistent differences between OHCA survivors and the MI group, who belong to the same greater population of individuals with cardiovascular disease, so it seems unlikely that premorbid cognitive difficulties could fully account for the level of impairment observed in the OHCA group. Still, future studies could benefit from the addition of an assessment of premorbid

function (e.g., the Test of Premorbid Functioning, the North American Adult Reading Test; Chu, Lai, Xu, & Zhou, 2012; Uttl, 2002) that could be used for statistical control.

We calculated rates of impairment for each cognitive domain independently; however, even in individuals who are neurologically intact, abnormal outlier scores in cognitive profiles are relatively common (Binder, Iverson, & Brooks, 2009). One of the advantages of the NAB is its co-normed standardization sample that spans several domains of cognitive function. Table 2 shows the frequency with which OHCA patients scored in the impaired range on specific NAB modules, as well as the frequencies for older adults from the NAB standardization sample (n = 735; M_{age} = 68.1, SD_{age} = 6.9). Unlike the MI group, OHCA patients differed significantly from the normative data; more individuals in the OHCA group had four or five cognitive domains in the impaired range (< 10^{th} percentile) than what would be expected in the normative sample. Not only were rates of impairment more elevated for OHCA patients across cognitive domains, but they were impaired in more of them.

Profile of Cognitive Performance

In our sample of OHCA survivors, the profile of performance scores across cognitive domains revealed predominant impairments in memory, attention, and language functions. These findings are consistent with previous literature that identified memory and attention impairments in this population (Moulaert et al., 2009). On the other hand, our OHCA patients presented fewer, and less apparent, executive deficits than hypothesized.

Cognitive domains are often categorized in terms of distinct functions; however, considerable overlap exists between underlying cognitive processes, which suggests interdependence. Attention, in particular, underlies the ability to allocate resources to tasks, and is thus essential for most, if not all, cognitive processes. Given the elevated rate of attention

impairment observed in our sample, rates of dysfunction in other areas, such as memory, language, or executive function, may have been amplified. While the purpose of our study was to broadly evaluate the cognitive profile of OHCA survivors, our findings are limited by the single-score measures produced by the NAB for each cognitive domain and their associated subscales. Future analyses including process scores can provide a more nuanced understanding of the specific cognitive functions that are vulnerable to impairment after OHCA.

The overlap of attention and executive functions may have contributed to the low rate of executive function impairment observed in our OHCA sample. The definitions of attention and executive function overlap significantly, so much so that what is classified as attention by one researcher may be described as executive function by another (Diamond, 2014) which undoubtedly can affect the sensitivity and construct validity of measures. However, other researchers have also found surprisingly low frequencies of executive dysfunction in their samples of OHCA survivors (Buanes et al., 2015; Lilja et al., 2015). Whether this is a true reflection of cognition in this population, or a function of the sensitivity of assessment measures, remains unclear.

Lastly, cognitive performance in our sample of OHCA survivors could have also been impacted by other factors unique to hospitalization. For example, individuals hospitalized in intensive care units are known to experience some cognitive deficits (Ouimet, Kavanagh, Gottfried, & Skrobik, 2007), even when hospitalization is not related to brain injury (Honarmand et al., 2019). This phenomenon is often referred to as 'ICU delirium.' While the assessments in the present study were conducted only once patients were discharged from the ICU, medically stable, and not acutely delirious, it is possible that some mild, reversible attentional issues related to sedation and ICU delirium were still present in our sample. One would expect these deficits to

resolve with time; as such, future studies that utilize multiple assessment timepoints may be able to rule these temporary cognitive impairments out.

Implications of Cognitive Dysfunction for Day-to-Day Life

Nearly half of our group of OHCA survivors experienced cognitive deficits. They were all considered to have made "good neurological recovery" by their medical team (as per the CPC scale), and were about to be discharged from hospital when we assessed them.

The degree to which cognitive assessments predict day-to-day cognitive functions, or ecological validity, can vary among measures of cognitive function. Those who survive OHCA often report subjectively poor post-arrest cognition (Bunch et al., 2004; Steinbusch et al., 2017), but these self-reports only moderately correlate with objective measures obtained by psychometric assessment (Steinbusch et al., 2017). Some explanations for this disparity include limited insight into one's own cognitive difficulties, low validity of self-reported cognitive measures, or contextual factors (e.g., patients may be less aware of their cognitive limitations in certain controlled environments such as in a hospital setting).

Those who survive OHCA have difficulty reintegrating in terms of employment (Alexander et al., 2011; Hofgren, Lundgren-Nilsson, Esbjörnsson, & Sunnerhagen, 2008; Lundgren-Nilsson, Rosén, Hofgren, & Sunnerhagen, 2005). In one study, for instance, OHCA patients were less likely to have returned to work four months after arrest compared to a cardiac control group, and those individuals who were working had, at most, mild cognitive deficits (Alexander et al., 2011). Patients who experience OHCA also report elevated rates of anxiety, depression, and traumatic stress (Green et al., 2015; Wilder Schaaf et al., 2013), and memory deficits have been linked with worse mental-health related quality of life (Ørbo et al., 2015).

Better understanding of cognitive function impairment in OHCA patients is needed to inform targeted cognitive and mental health interventions.

In the context of a chronic health condition, cognitive function impairment can complicate an individual's medication management and treatment adherence (Alosco et al., 2012; Bruce, Hancock, Arnett, & Lynch, 2010; Ownby, 2006). Memory and executive functions underlie the ability to manage medication independently (Ownby, 2006), and OHCA patients typically discharge from hospital with multiple prescribed medications, as well as stents and implanted devices (i.e., pacemakers, ICDs) that require management to prevent future arrests (Nolan et al., 2008). Maximizing treatment adherence is essential in the context of strained healthcare systems that rely on limited resources. Non-adherence increases patient risk and results in greater financial costs (Ho, Bryson, & Rumsfeld, 2009). Given the high rates of cognitive dysfunction in OHCA survivors, additional assistance with post-arrest medical management would be beneficial, as would cognitive interventions that specifically target everyday self-care tasks, like smartphone reminders or the use of medication blister packs that simplify drug self-administration.

Another important aspect of treatment after a cardiac arrest is the promotion of health behaviour change. Most cardiac rehabilitation programs include structured interventions that target lifestyle factors like exercise, diet, and tobacco use (Canadian Association of Cardiac Rehabilitation, 2009). Despite prominent cognitive deficits in patients with cardiovascular disease (Deckers et al., 2017; Vogels, Scheltens, Schroeder-Tanka, & Weinstein, 2007), in Canada, no formal recommendations about cognitive interventions have been made in the context of cardiac rehabilitation (Canadian Association of Cardiac Rehabilitation, 2009). Moulaert et al. (2011) developed a brief, semi-structured intervention for cardiac arrest patients

and their caregivers, and provided it as an adjunct to typical cardiac rehabilitation services. The intervention included psychoeducation about potential complications that can occur after cardiac arrest. In a study of the effectiveness of this intervention, patients reported better quality of life, lower anxiety, and a higher return-to-work rate compared to a control group of cardiac arrest survivors who received no intervention (Moulaert et al., 2015). Conversely, cognitive function did not differ significantly between groups in this study. However, there are a number of issues when assessing outcomes of cognitive rehabilitation programs (Krasny-Pacini, Chevignard & Evans, 2014), and day-to-day function is typically regarded as more relevant than performance on any given psychometric test. Overall, this intervention appears to have promising outcomes for patients with cognitive deficits after OHCA.

Mechanisms of Deficits

The mechanisms by which OHCA survivors develop cognitive impairments remain unclear. A major goal of this dissertation was to explore some of the key potential contributors to cognitive dysfunction in OHCA patients, in order to broaden our understanding of how impairments occur.

In Study 1, we identified downtime as the most significant predictor of cognitive impairment after OHCA. This result, to our knowledge, is a first in the literature. Several factors may have contributed to this finding. Firstly, we assessed patients during the acute phase of their recovery from OHCA, while other studies have assessed patients after a longer stabilization period (Caro-Codón et al., 2018; Ørbo et al., 2014). As such, downtime might be a more integral factor early in a survivor's recovery, and its importance may change with time. Secondly, we tested patients with a more comprehensive assessment of cognitive function than previous studies of cognition in the OHCA literature. For example, Caro-Codón et al., (2018) used the

Montreal Cognitive Assessment to assess cognition, a measure that is typically used for screening purposes because of its brevity. Ørbo et al. (2014) included a more robust assessment of cognitive functioning, but used a composite score without normative data as their measure of overall cognitive function. Overall, our analyses allowed for a more detailed exploration of cognitive performance in OHCA survivors during their acute recovery stage, and thus addressed a missing piece in the literature.

Predictors Retained in the Final Logistic Regression Model

In examining the factors that predicted impairment, we observed that our logistic regression model was improved by the addition of the interaction between downtime and CPR/early intervention. In Study 1, CPR/early intervention moderated the relationship between downtime and cognitive performance, such that, for those with short downtimes, receiving early intervention was linked with better post-arrest cognitive performance. Conversely, those with long downtimes and early intervention had poorer cognitive performance, perhaps because early intervention allowed individuals to survive despite greater neurological insult. This is the first known study to evaluate the relationship between downtime and early intervention in this manner.

The administration of CPR oxygenates the body under conditions where it is incapable of doing so. Prevailing knowledge is that CPR therefore mitigates the effects of hypoxic-ischemic brain injury and leads to increased survival rates after OHCA (Stiell et al., 2004); however, the literature is less clear on the effect of CPR on post-arrest cognitive functioning. Our findings shed light on this research gap. Here, we showed that CPR might be effective in protecting against cognitive impairment at short downtimes. At longer downtimes, the relationship becomes more complicated, which is consistent with OHCA neurological outcome data (Kim et al., 2014).

That is, longer downtimes do not seem to preclude good outcomes (Kim et al., 2014); however, prolonged CPR might otherwise keep some patients alive despite significant brain injury (Welbourn & Efstathiou, 2018). Important future considerations include longitudinal studies, which could determine if these deficits improve over time.

Other important predictors of cognitive dysfunction were duration of coma and the presence of cardiovascular risk factors. These variables were retained in our final model ($p <$ .10), but had less predictive value than downtime, and were not significant independently.

Duration of coma after OHCA proved a difficult variable to examine in our data, as the majority of patients received therapeutic hypothermia (71.4%) and thus experienced medically induced coma. As such, it was impossible to determine when a patient would have woken without this intervention, which prevented more sophisticated analyses that could determine whether coma duration affected later cognition. Future research is needed to understand the complex relationship between coma duration and therapeutic hypothermia.

Grey Matter Volume

The presumed mechanism of cognitive dysfunction in OHCA survivors is hypoxic/ischemic brain injury resulting from cardiac arrest. In Study 2, decreased global grey matter volume and cognitive functioning were correlated in the OHCA group. To completely understand this relationship, we require studies that can infer causation (i.e., non-correlational) and have larger sample sizes. Furthermore, more direct imaging techniques (e.g., blood oxygen level-dependent MRI, arterial spin labelling MRI, positron emission tomography) could test the hypothesis that decreased grey matter volume results from physiological mechanisms like hypoperfusion. Likewise, more direct and quantitative measures of cardiovascular disease could

be explored (e.g., cardiac output, ejection fraction, vessel occlusion) than the "present vs. not present," nominal approach we took to modelling risk factors.

On the other hand, the advantage of Studies 1 and 2 is the purposeful integration of cognitive, neuroimaging, and cardiovascular data that can then be used to study OHCA survivors. It is hoped that future studies will continue to promote and build upon this multidisciplinary approach.

Premorbid Cardiovascular Disease

An objective of this dissertation was to further understand the relationship between post-arrest cognitive dysfunction and pre-existing cardiovascular disease. In Study 1, cardiovascular disease risk factors and a comorbidity index were included in our predictive model of cognitive dysfunction, and in Study 2, the relationship between cognitive functioning and grey matter volumes in OHCA patients was compared to a group of people who had experienced an MI. The results of both studies suggest a complex relationship between cardiovascular disease and cognitive dysfunction.

In Study 1, no cognitive deficits were observed in the MI group, and the comorbidity score we used did not predict cognitive impairment in OHCA survivors. On the other hand, in Study 2, OHCA and MI patients did not differ significantly in terms of grey matter volumes, which suggests some neurophysiological similarities between groups, but both differed significantly from healthy controls. While these commonalities are presumed to be related to cardiovascular disease, cardiovascular disease is a broad term that includes a wide range of symptoms and risk factors. Our results hint at an underlying disease burden that might account for some of the cognitive dysfunction we observed in Studies 1 and 2, but not all. In the future,

more succinct measures of cardiovascular disease might reveal a stronger relationship with cognitive dysfunction than we observed.

Other Clinical and Demographic Predictors

A variety of other variables have been found to relate to cognitive dysfunction in OHCA survivors. For example, one group of researchers found that younger individuals had better cognitive outcomes after OHCA (Caro-Codón et al., 2018). On the other hand, several studies have found no link between age and post-arrest impairment (Ørbo et al., 2014; Van Alem, Waalewijn, Koster, & De Vos, 2004), and in our sample, age did not correlate with age-normed cognitive performance ($r(76) = .10$, $p = .387$). Furthermore, we observed no significant age difference between those with impaired global cognitive scores ($M = 59.15$ $SD = 13.45$) and those with normal scores ($M = 58.89$ $SD = 13.14$, $t(75) = .087$, $p = .931$).

Ejection fraction, or the average percentage of blood ejected from the heart per contraction, was not consistently measured in our sample of patients as part of routine care. For those whose ejection fraction was measured, a statistical trend existed such that the correlation between lower ejection fraction and greater cognitive dysfunction approached significance ($r(50) = .241$, $p = .086$). Certainly, ejection fraction remains a variable of interest.

Concluding Statement on Mechanisms

In this dissertation, we observed that a large number of OHCA survivors were discharged with cognitive impairments, and both long downtimes and the absence of early intervention were important contributors to cognitive dysfunction at the acute stage of recovery. Future studies should aim to understand this relationship more in depth. The field would also be significantly advanced if more specific measures of cardiovascular disease were incorporated into studies. At present, a challenge in the OHCA literature is the relative disconnect between medical research

and cognitive studies. In clinical trials, cognitive outcomes are most often assessed with broad, subjective ranking systems that are not sensitive, and thus provide only gross estimates of neurological function (Whitehead, Perkins, Clarey, & Haywood, 2015). The largest known study of cognitive functioning after cardiac arrest benefitted from clinical data on each patient, which allowed for secondary analyses to determine whether interventions not only increased survival, but whether they predicted cognitive dysfunction (Lilja et al., 2015). Unfortunately, such studies are rare, and more often clinical trials of OHCA interventions are several times larger (Moulaert, Verbunt, van Heugten, & Wade, 2009; Whitehead et al., 2015) and do not include comprehensive assessments prior to hospital discharge (Sabedra et al., 2015; Steinbusch, van Heugten, Rasquin, Verbunt, & Moulaert, 2017; Sulzgruber et al., 2015). This means the bulk of the existing research cannot effectively inform clinicians of optimal discharge planning for cognitive wellness.

There appears to be no resolution on the horizon for these issues. As recently as 2018, the International Liaison Committee on Resuscitation, endorsed by the American Heart Association, proposed the Modified Rankin Scale as a consensus outcome measure meant to capture neurological function and cognitive impairment (Haywood et al., 2018). The Modified Rankin Scale is a crude measure of neurological functioning (Van Swieten, Koudstaal, Visser, Schouten, & Van Gijn, 1988), which relies on the judgement of one rater and does not include any tests of cognition. Hopefully, the work outlined in this dissertation acts as a building block for more advanced theoretical work, future clinical interventions, and more helpful physician guidelines with respect to cognitive impairment and the need for rehabilitation.

Myocardial Infarction (MI) Patients

Although our population of interest was OHCA survivors, we observed some relevant findings for MI patients. The importance of including a cardiac control group in OHCA studies has been discussed by other researchers (Cronberg & Lilja, 2015; Lilja et al., 2015), yet the cognitive function literature is sparse when it comes to MI survivors. Our cognitive assessment results are consistent with the presumption that MI patients do not show marked cognitive deficits; however, our neuroimaging of MI patients did reveal abnormalities in cerebral grey matter volumes compared to healthy controls. As discussed, both OHCA and MI patients showed a similar pattern of reduced grey matter volumes compared to healthy controls; however, in the MI sample, grey matter volume reductions did not correlate with cognitive performance. Although these findings could have been coincidental due to our small sample in Study 2, the stark similarities between OHCA and MI patients at the whole-brain level suggest these findings may be tangible.

Overall, the MI group showed pathophysiological brain abnormalities compared to healthy controls, but no cognitive deficits. One recent study identified a link between cognitive functioning and hippocampal volume in OHCA patients, but not in an MI sample (Stamenova et al., 2018). Our inclusion of a healthy control group allowed us to identify reduced grey matter volumes in MI patients compared to healthy controls. Larger-scale MRI studies of MI patients may provide more insights, and may prove easier in terms of logistics and recruitment because MI occurs more frequently and has better survival rates (Public Health Agency of Canada, 2018).

It is noteworthy that chronic hypoperfusion of the brain due to atherosclerotic plaque, in severe cases, results in vascular dementia. Individuals who have experienced an MI are at increased risk for vascular dementia a year after their cardiac event (Sundbøll et al., 2018).

Progressive dementias, particularly Alzheimer's disease, are thought to begin with a "preclinical phase," sometimes years before formal diagnosis, where disease pathology is present but no-to-minimal overt symptoms are present (Dubois et al., 2016). In others, disease pathology is present but never develops into dementia (Brookmeyer & Abdalla, 2018). In this dissertation, the sample of patients in both studies (i.e., OHCA and MI patients) may be reflective of a high-risk sample in terms of future vascular dementia, and may even represent some individuals in the "pre-clinical" phase. As such, these individuals may be more vulnerable to the effects of future brain insult (i.e., hypoxic/ischemic brain injury resulting from a cardiac arrest, or stroke). Notably, in a large, recent, longitudinal study (n = 7888; Xie, Zheng, Yan, & Zhong, 2019), accelerated cognitive decline was observed among patients with coronary heart disease, but only after an acute event (e.g., myocardial infarction and/or angina). This decline was not observed in the short-term, but instead developed later after the event. Neuroimaging analyses, alongside extensive, longitudinal studies, could illuminate the pathophysiological mechanisms that underlie these changes in patients with cardiovascular disease.

A limitation regarding our MI sample was that patients had agreed to be referred to services at a cardiac rehabilitation program. These patients may not represent the MI population as a whole, and instead may reflect a subsample of MI patients with characteristics that affect cognitive performance on testing. Notably, such patients tend to have higher education levels than those who do not attend follow-up cardiac rehabilitation (Evenson, Rosamond & Luepker, 1998; Dunlay et al., 2009). This bias was not present in our OHCA group, as they were recruited in hospital and although they also agreed to participate in research, they were often referred to neuropsychology services for clinical purposes, which perhaps contributed to increased willingness to participate in our study. For the MI group then, their relatively high education

level may conflate with cognitive reserve, which is a theory that many factors may contribute to an individual's preserved function despite having sustained brain damage. Education is among one of the important variables that appears to contribute to cognitive reserve (Stern, 2009), so future studies might benefit from a recruitment protocol that does not rely on referrals to cardiac rehabilitation programs.

Finally, we found that MI patients showed abnormalities in cerebral grey matter volumes, which may be of relevance to prognostication of comatose OHCA survivors. While the magnitude of abnormalities observed in comatose patients may be more severe than what we observed in our OHCA sample, our findings in the MI group may serve as a reminder of the importance of premorbid cardiovascular disease when assessing OHCA survivors, especially when making major clinical decisions.

Conclusions

In our sample of consecutive patients discharged from hospital after OHCA with good neurological outcome, approximately 43% exhibited cognitive impairment on neuropsychological testing. Short downtimes and early CPR or defibrillation appeared to mitigate some of the negative cognitive impact of OHCA, which further highlights the importance of achieving rapid return of spontaneous circulation. In our group of OHCA patients, cognitive deficits were associated with decreased grey matter volumes; however, in MI patients, this relationship requires further evaluation, as decreased grey matter volumes (but not cognitive dysfunction) were observed. Future research is warranted that focuses on the development of cognitive interventions for OHCA survivors, given the number of patients that experience deficits at the time of hospital discharge.

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Table 1. Impairment rates in the OHCA and MI groups compared to normative sample at various cut-offs

	Impairment level							
	2nd percentile		7th percentile		10th percentile		16th percentile	
Module	OHCA n (%)	MI n (%)	OHCA n (%)	MI n (%)	OHCA n (%)	MI n (%)	OHCA n (%)	MI n (%)
Total	12 (15.6)**	0 (0.0)	26 (33.8)**	2 (2.9)	33 (42.9)**	5 (7.4)	40 (51.9)**	6 (7.8)*
Memory	15 (19.5)**	2 (2.9)	30 (39.0)**	4 (5.9)	35 (45.5)**	7 (10.3)	41 (53.2)**	10 (13.0)
Attention	18 (23.4)**	0 (0.0)	36 (46.8)**	3 (4.4)	43 (55.8)**	4 (5.9)	49 (63.6)**	6 (7.8)*
Language	11 (14.3)**	1 (1.5)	20 (26.0)**	4 (5.9)	32 (41.6)**	5 (7.4)	42 (54.5)**	11 (14.3)
Executive	8 (10.4)**	1 (1.5)	13 (16.9)**	4 (5.9)	23 (29.9)**	6 (8.8)	31 (40.3)**	8 (10.4)
Spatial	2 (2.6)*	0 (0.0)	10 (13.0)*	0 (0.0)	13 (16.9)	0 (0.0)	14 (18.2)	0 (0.0)*

Note . Values represent the number of individuals whose performance fell below the threshold in each sample on the Neuropsychological assessment battery (NAB). Fisher's Exact/Chi-squared test were used to compare the frequency of impaired performance in each sample to the NAB normative sample, * = $p < .05$, ** = $p < .001$.

Table 2. Number of impaired cognitive domain scores on the Neuropsychological Assessment Battery compared to the normative sample

	Number of Impaired Modules *n* (%)					
	Five	Four	Three	Two	One	Zero
OHCA	5 (6.49)*	6 (7.79)*	13 (16.88)*	11 (14.29)*	19 (24.68)*	23 (29.87)*
MI	0 (0.00)	0 (0.00)	2 (2.94)	1 (1.47)	9 (13.24)	56 (82.35)

Note. Values represent the number of patients whose performance fell in the impaired (<10th percentile) for the given total number of cognitive domains, out of the total five domains assessed by the Neuropsychological Assessment Battery (NAB), in each sample. Fisher's Exact/Chi-squared tests were used to compare the frequency of total impaired domains in each sample to the NAB normative sample, * = $p < .005$.