Empathic Processing in Patients with Mild-to-Moderate Stroke

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Neuroscience

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Abstract

Recent lesion studies have indicated that regions of the human prefrontal cortex play a critical role in empathy; however, these lesion studies often include patients with severe head injuries. The present study utilizes a cohort of 84 patients with cerebrovascular disease with mild-to-moderate strokes to examine the neural regions involved in empathy. We hypothesized that dissociable areas of the prefrontal cortex are involved in empathy. We predicted that lesions to the inferior prefrontal cortex would result in deficits in empathy compared to superior prefrontal lesions, non-prefrontal lesions, and those with no detectable lesions. To measure empathy, caregiver ratings were obtained on the empirically validated Interpersonal Reactivity Index. No significant differences were found among groups. A voxel-based lesion-symptom mapping analysis was conducted on segmented lesion images to create a statistical map of the neural regions involved in empathy; no significant results were found. Our findings indicate that mild-to-moderate stroke lesions may not be severe enough to produce observable deficits in empathy.

Keywords

cerebrovascular disease, stroke, empathy, lesion, emotion cognition, neuroimaging, focal lesions, prefrontal cortex
Summary for Lay Audience

Lesion studies have a crucial role in neuroscience for examining relationships between brain regions and emotional or cognitive processes. When a stroke occurs, it creates lesions within the brain and prevents the affected area from functioning properly. These lesions allow researchers to examine brain regions and their function by what deficits occur. Stroke can cause various deficits, and it is reported that stroke affecting the prefrontal cortex can disrupt empathy. Empathy has two facets, emotional and cognitive. Emotional empathy refers to our ability to understand what others are feeling. Cognitive empathy involves the ability to understand the thoughts and intentions of others. Research examining the neural regions involved in empathy have implicated areas of the prefrontal cortex and temporal lobes, although these studies often involve lesions from severe brain injuries. By examining lesions to the prefrontal cortex and empathy in individuals who have mild-to-moderate size strokes, we have the opportunity to examine specific areas involved in these processes. To do this we obtained data from the Ontario Neurodegenerative Disease Research Initiative, which included 155 participants who were classified as having cerebrovascular disease. Imaging volumetric data was obtained and participants who had lesions greater than 10% in the brain regions of interest were included in this analysis. Participants were separated into groups based on lesion location: superior prefrontal cortex, inferior prefrontal cortex, non-prefrontal cortex and no detectable lesions. To measure empathy, we used caregiver ratings of the Interpersonal Reactivity Index (IRI). We predicted that individuals in the inferior prefrontal cortex group would have lower scores on the IRI compared to the superior, non-prefrontal cortex and no detectable lesion groups. However, our study found no significant differences among these groups. A lesion mapping analysis was also conducted in this study. This analysis creates a statistical map of the lesions that are most related to the behavioural deficit, however, this did not demonstrate a significant result in our study. Future research should seek to examine this in a larger cohort of individuals with chronic stroke lesions.
Co-Authorship Statement

I, Hilary Dagg, completed all the written work and analyses for this project.

The Ontario Neurodegenerative Disease Research Initiative completed data collection and participant recruitment.

My supervisor, Dr. Derek Mitchell, contributed to all aspects of this thesis project, including the formulation of the research question, data analysis, interpretation and editing of the written work.
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Chapter 1

1 Introduction

Empathy refers to our ability to understand the thoughts, feelings, and intentions of others. It has been described as a ‘binding force’ with respect to our ability to interact, share affective states, and enable us to understand another’s beliefs, desires, and emotions (Eslinger et al., 2002; Lockwood, 2016). Deficits in empathy are associated with negative consequences in relationships with family members, friends, and members of the community. Often those who suffer from deficits in empathy are described as cold-hearted, anti-social, and more prone to aggression (De Vignemont & Singer, 2006; Hoffman, 2000). Changes in empathy have also been reported in stroke survivors (Eslinger et al., 2002; Pluta et al., 2017; Hamilton et al., 2017; Leigh et al., 2013; Yeh & Tsai, 2014). With ninety percent of individuals who survive stroke being left with some form of disability (Brass, 2000; Belagaje, 2017), stroke is the third leading cause of disability worldwide (World Health Organization [WHO], 2020). Examining deficits in empathy in patients who have survived mild-to-moderate stroke provides an opportunity to make inferences regarding the neural regions associated with these deficits.

Neuroscientists have a long tradition of inferring the functional contributions of distinct brain regions by assessing the relationship between brain injury and subsequent impairments. Through examining empathy in neurological patient populations, we are beginning to understand the neural anatomy that is involved in these processes. However, most of what we know comes from patients with severe brain injury, lesions from surgical resections or severe stroke (Shamay-Tsoory et al., 2009; Shamay-Tsoory et al., 2007; Campenella et al., 2014; Rolls et al., 1994; Driscoll et al., 2012; Hornak, 2003; Shamay-Tsoory et al., 2004; Bramham et al., 2009). The severity of the injury and the large lesions seen in these patients make it challenging to precisely localize function. Individuals with mild-to-moderate stroke represent a patient population who are more likely to have focal lesions that give rise to changes in personality and behaviour, but few lesion studies of empathy have incorporated this population.
1.1 Empathy

Empathy is a unique phenomenon because it does not only occur with our kin but can be extended to strangers and other species (Decety, 2011). Empathy is a multidimensional construct with at least two facets; emotional and cognitive (Shamay-Tsoory, 2011). Emotional empathy refers to an individual’s ability to share and show concern for the affective state of another individual through observation (Lamm et al., 2019; Lockwood, 2016; Singer & Lamm, 2009; De Vignemont & Singer, 2006). Cognitive empathy, also referred to interchangeably with theory of mind (ToM), is an individual’s ability to understand and predict intentions, thoughts, beliefs, and behaviours of others (Blakemore & Frith, 2004; Lockwood, 2016; Frith & Frith, 2006).

Emotional empathy is theorized to be an automatic response; it occurs rapidly and exerts minimal demand on executive functions (Heyes, 2018). This form of empathy involves an instinctive reaction and has been described as a contagious emotional response (Blackmore & Frith, 2004). This emotional response develops as early as infancy (Heyes, 2018; Decety, 2010; Tousignant et al., 2017). For example, by ten weeks of age infants can respond distinctively to their caregiver’s emotions (e.g., joy, anger, sadness) and will spontaneously imitate these expressions (Haviland & Lelwica, 1987; Tousignant et al., 2017). Over time, it is thought that the opportunity to mimic the emotional state of another is critical for developing the capacity to share the emotions of others; providing the building block for emotional empathy (Heyes, 2018; Tousignant et al., 2017).

In contrast to emotional empathy, cognitive empathy refers to a controlled and conscious response, that develops later in a child’s life (Heyes, 2018). It is theorized that cognitive empathy begins to develop in a child’s second year of life, with a typical 4-year-old child having the capacity to complete basic ToM tasks (Baron-Cohen et al., 1985). To demonstrate ToM an individual must have the ability to understand another’s cognitive and affective mental state and apply the mental states to themselves and others. This knowledge then allows them to correctly understand and predict the other individual’s behaviour (Shamay-Tsoory, 2015).
For measuring empathy in typically developing and clinical populations there are performance-based measures such as the Reading the Mind in the Eyes Test (Baron-Cohen et al., 2001) or the Multifaceted Empathy Test (Dziobek et al., 2008). Also, questionnaire measures such as the Balanced Emotional Empathy Scale (Mehrabian, 2000). A widely used empirically validated measure, often used in neurological populations (Shamay-Tsoory et al., 2009; Shamay-Tsoory et al., 2004; Yeh & Tsai, 2014; Perry et al., 2001; Lombardo et al., 2007) is the Interpersonal Reactivity Scale (Davis, 1980). This measure includes subscales that capture cognitive and emotional empathy.

Empathy is crucial for many aspects of our social lives, providing motivation for our prosocial behaviours (Hoffman 1975; Decety et al., 2015). Further, it promotes caregiving, and the ability to cooperate with others, as well as a mechanism that inhibits aggression (Decety et al., 2015). In addition, empathy allows us to accurately assess our environmental surroundings for cues of fear or distress in others, so we can avoid potential dangers (De Vignemont & Singer, 2006). Deficits in empathy are associated with reduced sharing with others (Edele et al., 2013), reduced willingness to offer money to those in need (Pavey et al., 2012) and reduced willingness to trade places with others in potentially harmful situations (Batson et al., 1981). In addition, a lack of empathic concern has been associated with more frequent bullying of others (Joliffe & Farrington, 2006) and is a predictor of greater real-world violence (Mehrabian, 1997). Therefore, when dysfunction in empathy occurs, it can produce several social problems such as aggression, antisocial behavioural tendencies, and a lack of morality (De Vignemont & Singer, 2006; Hoffman, 2000).

People with neurological conditions that result in a lack of empathy are often described as selfish, self-centred, and show an obvious lack of concern towards others (Hsieh et al., 2013). These deficits have been associated with a less caring relationship with partners (Hsieh et al., 2013), increased caregiver burden (Pomponi et al., 2016), increased caregiver loneliness and depression, (Brown et al., 2019) and lack of emotional support from family members (Eslinger et al., 2002). The effect these deficits have on caregiver relationships greatly impacts an individual’s recovery and reintegration into the home (Eslinger et al., 2002). Further, deficits in the dissociable facets of empathy can
differentially impact caregiver relationships. Interestingly, one study found that deficits in cognitive empathy of the patient was found to increase the caregivers’ emotional burden when helping with activities of daily life (Formica et al., 2020). The impact this has on caregiver relationships can negatively affect the patient’s functional status, psychological status, and social status after stroke (Eslinger et al., 2002). Developing a better understanding of the types of empathy deficits that occur after stroke help prepare caregivers for the types of emotional changes that their loved one is likely to experience. Further to this, examining deficits in the different facets of empathy can allow us to infer what neural regions are involved. This may provide a better understanding of the biological risk factors associated with these disruptive behaviours.

**Facets of Empathy Separable on a Neuroanatomical Level**

There is increasing evidence that the facets of empathy may be dissociable on a neuroanatomical level. Many studies have used functional magnetic resonance imaging (MRI) to examine neural regions associated with the different facets of empathy (Frith & Frith, 2006; Frith & Frith, 2003; Frith & Singer, 2008; Oliver et al., 2016, Fan et al., 2011; Morrison et al., 2004). However, a drawback to functional neuroimaging studies is that they can only establish associations between neural regions and their function, therefore making it difficult to conclude causal inferences (Vaidya et al., 2019; Logothetis, 2008). This is because functional neuroimaging techniques do not have the ability to differentiate between regions that are involved during a task from those regions necessary to perform such task (Vaidya et al., 2019). In order to infer a more causal relationship, researchers can complement information obtained via functional neuroimaging and other means with data from patients with acquired lesions. Lesion studies conducted in the early 19th century provided the first evidence that cognitive processes were localized to different neural regions (Vaidya et al., 2019; Boes et al., 2015). Today this approach still has a crucial role in neuroscience by providing evidence for causal relationships between neural regions and cognition or behaviours (Adolphs, 2016; Vaidya et al., 2019; Bates et al., 2003; Boes et al., 2015).
Current lesion studies examining empathy have implicated the prefrontal cortex (PFC). Shamay-Tsoory and Aharon-Peretz, (2007) examined 49 participants with lesions to the PFC and found that participants were impaired on both cognitive and affective ToM tasks compared to healthy controls. It is important to note that their participants were recruited from a Cognitive Neurology Unit and a majority had severe lesions from traumatic brain injury or surgical resection of a tumour, while only six participants suffered a cerebrovascular accident.

In addition to the findings of Shamay-Tsoory and Aharon-Peretz, other lesion studies have implicated dissociable areas of the PFC in empathy, particularly, the ventral regions of the PFC (Bramham et al., 2009; Shamay-Tsoory et al., 2009; Schneider and Koenigs 2017; Lepold et al., 2012; Beadle et al., 2018). Lesions to the ventromedial PFC (vmPFC) have been implicated for having an association with deficits in cognitive empathy (Lepold et al., 2012; Shamay-Tsoory et al., 2009) in addition to deficits in emotional regulation, decision making and reward processing (Jenkins et al., 2014; Koenigs et al., 2010; Hiser & Koenigs, 2018). Additional neural regions that have been implicated to be critical for cognitive empathy include the superior temporal sulcus, temporoparietal junction, and temporal poles (Shamay-Tsoory et al., 2004; Leopold et al., 2012). For emotional empathy, lesion studies have implicated the inferior frontal gyrus, inferior parietal lobe, posterior temporal sulcus, anterior insula, and the anterior cingulate cortex (Shamay-Tsoory et al., 2009; Schneider & Koenigs, 2017; Bramham et al., 2009).

However, these lesion studies have utilized patient populations with severe injury from traumatic brain injury which often involve widespread atrophy throughout the brain (Hillis, 2014), and surgical resections of tumours while only including a small number of individuals with severe stroke. Only including patients with severe brain injuries such as these makes it challenging to infer the specific neural regions involved in empathy. It should also be noted that animal studies are not easily implemented in the study of empathy since it has been argued that cognitive empathy is difficult to study in non-humans due to the high level of intuition involved (Penn & Povinelli, 2007). Therefore, by examining empathy in patients with mild-to-moderate stroke, it may provide the opportunity to examine more focal injuries and therefore allow for more specific mapping of empathic function to neural structures involved.
1.2 Stroke

As the aging population increases, the prevalence of cerebrovascular disease (CVD) also rises (Levine & Langa, 2011). CVD is an umbrella term that captures all pathology that effects blood flow to the brain, which includes stroke, aneurysms, carotid stenosis, vertebral stenosis, intracranial stenosis, and vascular malformation (American Association of Neurological Surgeons, 2021). In the current work, the focus will be on stroke. A stroke occurs when blood flow to the brain is blocked or when bleeding within the brain vessels occur. According to the WHO (2020), stroke is responsible for 11% of deaths per year, roughly accounting to over 6 million deaths each year. This makes stroke the second leading cause of death across the globe (WHO, 2020). A stroke occurs in two forms: ischemic or hemorrhagic. It is important for clinicians to distinguish between these types of stroke for epidemiology, treatment, patient’s prognosis, and research.

Ischemic Stroke

An ischemic stroke occurs when there is blockage or a decrease of blood flow in the cerebral vascular system; the proximal brain area then stops receiving blood and the brain tissue begins to die (Caplan, 2018). Tissue death begins to occur rapidly, although some tissue surrounding this area is hypo-perfused but still viable for a finite period of time due to surrounding blood flow (Leiva-Salinas & Wintermark, 2010). An ischemic stroke can occur in one of three different forms: thrombosis, embolism, or systematic hypoperfusion.

A thrombosis occurs when an obstruction develops in the artery from a local blockage (Caplan, 2018). This can be caused by disease to the artery wall (small vessel disease) or by large vessel disease (e.g., atherosclerosis; Caplan, 2018). Since a thrombosis can build up over time, patients’ symptoms can progress slowly, fluctuate, and/or remit (Caplan, 2019). An embolism is similar to a thrombosis in the way it blocks the blood vessel, but an embolism occurs when particles of debris (e.g., fat particles, blood clots) in the blood originate elsewhere in the body (e.g., heart) and travel to block the artery to a brain region (Caplan, 2018; Randolph, 2016). Embolisms block blood flow suddenly, causing patients’ symptoms to appear abruptly (Caplan, 2019).
The last form of an ischemic stroke is systemic hypoperfusion, referring to a gradual restriction in blood flow to the brain, effecting the brain more globally and in particular watershed areas of the distal regions of the supplying blood vessels (Velez et al., 2020). Hypoperfusion involves a general circulatory problem or stenosis (a severe narrowing of an artery leading to the brain; Caplan, 2018; Randolph, 2016). Since the whole brain can be impacted by this slowly over time, patients can experience gradual and diffuse symptoms (Caplan, 2019).

**Hemorrhagic Stroke**

The second form of stroke, hemorrhagic stroke, occurs when there is a leak or rupture within the blood vessels of the brain, which causes bleeding within and/or outside the brain in the subarachnoid space (Caplan, 2019; Kuriakose & Xiao, 2020). Hemorrhagic stroke occurs in two different forms. The first is an intracerebral hemorrhagic stroke, which results from bleeding that occurs within the brain, creating an abnormal collection of blood outside the vessels, that damages brain tissue by placing pressure on surrounding brain areas (Caplan, 2018; Kuriakose & Xiao, 2002). This can occur over minutes or hours, which causes symptoms to appear gradually (Caplan, 2018). The second form of hemorrhagic stroke refers to a subarachnoid stroke. As the name implies, this form of stroke occurs when the vessel bleeds directly into the cerebrospinal fluid of the subarachnoid space (Caplan, 2018; Kuriakose & Xiao, 2020). Since this type of bleeding causes an immediate change in the intracranial pressure, symptoms occur rapidly (Caplan, 2019). These symptoms can include cessation of activity, a sudden severe headache, and can be non-focal (Caplan, 2019).

**Treatment and Considerations**

Ischemic and hemorrhagic strokes differ in terms of their treatment and prognosis. An ischemic stroke is time sensitive regarding treatment; typically, the window for treatment is 4 ½ hours after symptom onset (Rabinstein, 2017). Treatment can involve medication to control or reduce blood clotting, or a thrombectomy which is a surgical procedure to trap and remove the clot or blockage (Kuriakose & Xiao, 2020; Rabinstein, 2017). Hemorrhagic strokes typically cannot be treated by medication and require more invasive
types of treatment which includes clipping the vessel, coiling, craniotomy, or craniectomy (Kuriakose & Xiao, 2020; Rabinsetin, 2017). Although ischemic strokes are more common, hemorrhagic strokes are considered more deadly in terms of prognosis (Kuriakose & Xiao, 2020). For example, half of all individuals who suffer from an intracerebral hemorrhagic stroke die within the first month after the stroke onset (Perna & Temple, 2015). This type of stroke is also thought to be more dangerous since in addition to damaging surrounding brain cells, the hemorrhage and resultant swelling also increase the intracranial pressure, which may cause more damage globally (Perna & Temple, 2015). Paulucci et al., (2003) investigated the neurological effects of ischemic versus hemorrhagic stroke types. In this study they recruited 50 participants from an inpatient stroke unit. Even though hemorrhagic strokes are considered more dangerous, they found that hemorrhagic stroke patients performed better on neurological testing compared to ischemic stroke patients. The available evidence suggests that prognosis for patient outcome is best predicted by the severity of the stroke (Perna & Temple, 2015; Paolucci et al., 2003). In addition to stroke severity, many other individual factors can also impact an individual’s prognosis, including sex, prior stroke history, age, and lesion location (Perna & Temple, 2015).

Overall, hemorrhagic strokes are more likely to be associated with global brain damage. This makes it challenging to infer causal effects from these strokes on specific neural regions. Because ischemic stroke often involves more focal injuries, it provides a better opportunity to explore specific structure-function relationships.

**Stroke and Disability**

Although the incidence of stroke has declined in many first world countries due to the development of medicine to manage risk factors, the number of strokes in low-to-middle income countries continues to be on the rise with the aging population (Kalaria et al., 2016). Ninety percent of individuals who survive stroke are left with some form of disability (Brass, 2000). Disabilities that occur from stroke have high variability, which depends on the type of stroke and the neural regions effected. Most common impairments
caused by stroke are partial paralysis, speech and language deficits, memory loss, changes in behaviour, and vision problems (American Stroke Association, 2021).

Vascular cognitive impairment (VCI) is a phenomenon that can occur after stroke. VCI is defined as deficits in mental ability due to a cerebrovascular pathology (e.g., hemorrhagic stroke, hypoperfusion; Dichigans & Leys, 2017; Heart and Stroke, 2020). Deficits in VCI can range from mild cognitive impairment to a formal diagnosis of dementia (Van Der Flier et al., 2018). A clinical diagnosis of dementia includes the assessment of multiple domains: memory, basic attention, visuospatial abilities, executive function, and sociobehavioural aptitude (Gale et al., 2018). Common clinical signs of dementia include progressive memory impairment, cognitive decline, behavioural disinhibition, and loss of empathy (Gale et al., 2018). In addition to VCI, dementia can occur in various neurodegenerative diseases (e.g., Alzheimer’s disease, frontotemporal dementia (FTD), Parkinson disease dementia; Gale et al., 2018). However, VCI is the second leading cause of dementia in North America, after Alzheimer’s disease, accounting for 20% of dementia cases (Smith, 2017). These types of dementia are associated with a very heavy burden for patients, families, and the healthcare system. Healthcare and long-term care costs relating to VCI and other dementias now surpass cancer and heart disease (Smith, 2017). Further, VCI greatly impacts an individual’s quality of life. Symptoms of VCI frequently include; deficits in planning and organizing behaviour, apathy, anxiety, depression, deficits in memory, parkinsonism, urinary incontinence, and difficulty with speech (Van Der Flier et al., 2018). These symptoms typically begin to appear gradually, as more damage to the blood vessels occur over time the symptoms will worsen (Heart and Stroke, 2020).

In addition to VCI, impaired social functioning has also been described in individuals who have suffered from a single stroke (Yeh & Tsai, 2014; Kim et al., 2017; Leigh et al., 2013; Happe et al., 1999; Pluta et al., 2017; Eslinger et al., 2002; Nijsse et al., 2019). The decline in social functioning associated with stroke is thought to be due to the physical, emotional, and cognitive deficits that occur (Eslinger et al., 2002). These deficits impact the quality of relationships shared with family members, friends, and members of the community. One of the key factors that can contribute to social impairment and increased
caregiver burden are deficits in empathy (Hsieh et al., 2013; Pomponi et al., 2016). Further to these negative consequences, deficits in empathy can impact stroke recovery. Empathy deficits have been associated in having a negative impact on overall relationship with caregiver, reintegration into home or work, as well as coping mechanisms and adjustment to mood (Eslinger et al., 2002).

**Empathy in Stroke**

Individuals who suffer stroke have shown deficits in empathy (Eslinger et al., 2002; Nijsee et al., 2019; Happe et al., 1999; Hamilton et al., 2017; Yeh & Tsai, 2014). In particular, stroke lesions occurring within the PFC have been found to be associated with increased deficits in empathy (Grattan et al., 1994; Shamay-Tsoory et al., 2003; Nijsee et al., 2019). These strokes would occur within the internal carotid artery, which includes the anterior and middle cerebral arteries that are responsible for providing the PFC with blood flow (Hathaway & Newton, 2021; Yusuf et al., 2009). These studies have found that strokes effecting the ventromedial PFC, temporal lobe, and the temporoparietal junction have been associated with decreased empathic responding from survivors (Shamay-Tsoory et al., 2003; Gratton et al., 1994; Nijsee et al., 2019).

There is some evidence for hemisphere asymmetry for emotional processes and empathy. For example, numerous studies examining atrophy have found that right hemisphere atrophy is associated with deficits in empathy, specifically in the PFC and temporal lobes (Perry et al., 2001; Rankin et al., 2006). In addition, many studies have implicated strokes in the right hemisphere as having an impact on the individuals’ empathic concern. These studies have found that stroke lesions in the right hemisphere involving the PFC, temporal lobe, and parietal lobe, are associated with a decrease in emotional and cognitive empathy (Yeh & Tsai, 2014; Happe et al., 1999; Hamilton et al., 2017).

Although it is important to note that the participants involved in some of the mentioned studies were hospitalized in-patient (e.g., Yeh & Tsai, 2014; Happe et al., 1999), this suggests their participants likely had severe strokes and therefore large lesions.
1.3 Assessing Lesion Location using Neuroimaging

MRI is used to characterize the neuroanatomy of the brain and visible lesions. MRI creates structural or functional images of the human brain by using the magnetic properties within the brain’s tissue (Gazzinga et al., 2009). MRI is known for being an effective form of imaging because it provides more comprehensive structural imaging of the brain in comparison to computed tomography (Gazzinga et al., 2009). Regarding stroke and neurodegenerative disease, MRI is considered one of the most informative forms of imaging (Risacher & Saykin, 2019).

An MRI system uses a powerful magnetic field and computer-generated radio waves to produce a variety of tissue imaging sequences which vary in signal intensity. Signal intensity refers to the shade in which tissue or fluid appears in the images which is determined by different pulse sequences and relaxation times (Murphy & Gaillard, 2021). For the current study, we utilized T1-weighted, T2-weighted and Fluid-Attenuated Inversion Recovery (FLAIR). In each of these sequences types of brain tissue appears in different levels of signal intensity.

T1-weighted sequences are very common in MRI protocols and provides precise anatomical images (Murphy & Gaillard, 2021). In T1-weighted scans, cerebrospinal fluid (CSF) has a low signal intensity therefore the fluid appears black. White matter appears hyperintense in comparison to the surrounding grey matter, causing white matter to appear brighter with grey matter appearing grey (Murphy & Gaillard, 2021). Fat tissue has high signal intensity causing it to appear white (Murphy & Gaillard, 2021). Damage or inflammation in a T1-weighted scan will show as areas of darker tissue (Preston, 2016).

T2-weighted sequences are also very common in most MRI protocols. In this type of sequence, CSF and fat tissue both have a high signal intensity causing them to appear white (Murphy & Gaillard, 2021). White matter appears hypointense in comparison to grey matter causing it to appear darker (Murphy & Gaillard, 2021). Grey matter has an intermediate signal intensity causing it to appear grey (Murphy & Gaillard, 2021). Damaged tissue or inflammation appears bright in T2-weighted sequences (Preston, 2016). T2-weighted images are a useful technique for stroke, due to infarcts appearing
hyperintense and the ability for older cerebral infarcts to be detected (Leiva-Salinas & Wintermark, 2010).

Apart from the dark appearing CSF fluid, FLAIR images appear similar to T2-weighted (Murphy & Gaillard, 2021). In FLAIR sequences, grey matter appears to be darker than white matter, with damaged or inflamed tissue appearing very bright (Murphy & Gaillard, 2021). FLAIR sequences have been evaluated for disease of the central nervous system, which includes subarachnoid hemorrhage, infarctions, and head injuries (Deng & Niknejad, 2021). FLAIR imaging is a beneficial sequencing type as it was designed to reduce signal from CSF providing the ability to reduce potential artefacts from CSF that can be seen in T2-weighted sequences (Ashikaga et al., 1997). For stroke imaging, FLAIR images show infarcts as hyperintense lesions, are highly sensitive to subarachnoid hemorrhage, and are used to assess infarcts immediately after stroke onset as well as older cerebral infarctions (Leiva-Salinas & Wintermark, 2010).

Incorporating all three imaging sequences is beneficial when manually segmenting lesions because it helps the tracer better identify lesioned areas when comparing the lesion across all sequences. This is because the tracer can see the lesion in a variety of signal intensity, allowing for accurate identification of the lesion edges and distinguishing between healthy and lesioned tissue. The current study used all three forms of images.

1.4 Voxel-Based Lesion-Symptom Mapping

For centuries lesion studies have been essential for inferring causal relationships between neural regions and behaviour; however, many lesion studies still lack the spatial resolution needed for parsing function in functionally diverse structures such as the prefrontal cortex (Mitchell, 2011). Nevertheless, human lesion studies are particularly important for understanding behavioural and cognitive functions that are not easily indexed in animal studies. For example, it has been argued that cognitive empathy is particularly difficult to study in non-humans because ToM requires a high level of intuition and the ability to integrate past experiences from memory, although this remains controversial (Penn & Povinelli, 2007).
One recently emerging method to overcome some of the short-comings of many prior studies involves the use of voxel-based lesion-symptom mapping (VLSM). VLSM is a mapping technique used with MRI images to determine the impact of damaged or pathological neural regions on behavioural outcomes (Bates et al., 2003). This technique categorizes participants on a voxel-by-voxel basis, according to whether a lesion is impacting that specific voxel (Campanella et al., 2014). Participants are divided into two groups, based on whether there is a lesion to a specific voxel or not, a t-test is then conducted on each voxel (lesioned versus non-lesioned) for each behavioural measure, yielding a t-statistic (or effect size) for each voxel (Campanella et al., 2014; Bates et al., 2003).

Using VLSM to analyze lesions has several benefits. The first being VLSM allows for greater anatomical specificity and takes advantage of the natural variability found in acquired human lesions without the constraint of the region of interest (Vaidya et al., 2019). Another benefit in using VLSM is participants are not categorized by a general lesion site or behavioural cut off (Bates et al., 2003). VLSM has also been implicated as a beneficial form of analysis for stroke, due to its ability to examine groups with variability in lesion location (Geva et al., 2012). Further, VLSM has been used to examine neural regions associated with empathy. These studies have implicated lesions to the posterior temporal lobes, vmPFC and the temporoparietal junction as being most associated with deficits in empathy (Campanella et al., 2014; Shamay-Tsoory et al., 2009). However, these studies were conducted on individuals with severe brain injuries, such as TBI or surgical removal of a tumour. By using VLSM in patients with mild-to-moderate stroke, we hope to examine smaller focal lesions to more precisely localize the neural regions involved in empathy.

### 1.5 Current Study

Empathy provides us with the ability to share and show concern for the affective states of others, as well as the ability to understand their thoughts, feelings, and intentions. When dysfunction in empathy occurs, it can cause negative consequences in all aspects of an individual’s social life (De Vignemont & Singer, 2006; Hoffman, 2000). Most importantly it can lead to aggressive and anti-social patterns of behaviour (De Vignemont
& Singer, 2006; Hoffman, 2000). In terms of stroke and dementia, dysfunction in empathy is also associated with an increase in caregiver burden (Pomponi et al., 2016) and has a negative impact on caregiver relationships (Hsieh et al., 2013). A clearer understanding of the outcomes regarding empathy after stroke and the structure-function relationship of the neural regions involved may provide caregivers with a better understanding of the biological risk factors associated with these disruptive behaviours. This may help prepare them for the potential challenges they may face and perhaps enhance their understanding, compassion, and coping as a result.

The majority of research on lesion studies and empathy, however, often only focus on large, severe lesions in patients who have suffered traumatic brain injury or surgical resections (Shamary-Tsoory et al., 2009; Shamay-Tsoory et al., 2007; Campanella et al., 2014; Rolls et al., 1994; Driscoll et al., 2012; Hornak et al., 2003; Shamay-Tsoory et al., 2004; Bramham et al., 2009). While some studies have indicated that individuals who suffer stroke have shown deficits in empathy (Eslinger et al., 2002; Yeh & Tsai, 2014; Happe et al., 1999; Nijsee et al., 2019), these studies conducted group comparisons between participants who had suffered a stroke and healthy controls on measures of empathy, without examining associations between lesion location and outcomes (Nijsee et al., 2019; Happe et al., 1999; Yeh & Tsai, 2014). In the current study, we sought to fill this gap in knowledge by examining the neural regions involved in empathy in a cohort of patients with chronic stroke lesions after suffering a mild-to-moderate strokes, defined by their level of cognitive ability. For the purposes of this study, we are interested in the visible infarcts that result from mild-to-moderate stroke to localize function of the neural regions involved in empathy.

Based on evidence of the inferior regions of the PFC being associated with empathy, we hypothesized that the dissociable areas of the PFC are involved in empathic processes. Specifically, we predicted that lesions to the inferior portion of the PFC would result in lower caregiver ratings of patient empathy in comparison to superior PFC lesions, non-PFC lesions, and those with no detectable lesions. This was analyzed by conducting group comparisons on the IRI caregiver ratings subscales and total score. Further, on the basis of evidence linking empathic processes with right hemisphere function in particular
(Perry et al., 2001; Rankin et al., 2006; Yeh & Tsai, 2014; Happe et al., 1999), we hypothesized that the right hemisphere has more involvement in empathy compared to the left hemisphere. Specifically, we predicted that lesions to the right hemisphere would result in lower caregiver ratings of patient empathy relative to lesions in the left hemisphere and those with no detectable lesions. This was analyzed by examining group comparisons on the IRI caregiver ratings subscales and total scores. Lastly, we hypothesized that dissociable neural regions involving areas of the prefrontal cortex and temporal lobes are critical for empathic responding. We predicted that these areas would differentially map onto empathy deficits. This was analyzed by VLSM, using the IRI caregiver ratings total score.
Chapter 2

2 Methods

2.1 Participants

Data used in this study was obtained from The Ontario Neurodegenerative Disease Research Initiative (ONDRI), which includes multiple participating research centres across Ontario, Canada: London Health Science Centre and Parkwood Institute in London, The Ottawa Civic Hospital in Ottawa, Hamilton General Hospital and McMaster Medical Centre in Hamilton, Thunder Bay Regional Health Sciences Centre in Thunder Bay, Sunnybrook Health Sciences Center, Baycrest Health Sciences, St. Michael’s Hospital, Centre for Addiction and Mental Health, and Toronto Western Hospital in Toronto. Ethics approval was obtained for each institution. Each participant and informant provided informed consent.

In total, ONDRI recruited 625 participants, examining five neurodegenerative diseases: cerebrovascular disease (CVD), Parkinson’s disease, Amyotrophic Lateral Sclerosis, Alzheimer’s disease/Mild Cognitive Impairment, and Frontotemporal dementia. General inclusion criteria involved proficiency in speaking and reading English, at least 8 years of education, a minimum Montreal Cognitive Assessment (MoCA) score of 18, and a reliable study partner; which is any individual in the participant’s life who spends time with the participant and can accurately comment on their daily lives. Additional general inclusion criteria included the ability to provide informed consent, geographic access to research locations, and the ability to walk (assistive aids may be used). Inclusion criteria for the ONDRI CVD cohort involved participants between the ages of 55 to 85, with imaging evidence of an ischemic stroke. Participants also were required to have no prior history of dementia before their stroke. Participants who had a previous silent stroke, defined as a visible stroke on brain imaging with no neurological deficits noted at the time of the stroke, were also included. Participants were required to be at least 3 months post-stroke. In addition, only participants with mild-to-moderate stroke were included. This was determined using the Modified Rankin Scale which rates patient’s functional
impairments on a scale ranging from 0-no symptoms to 5-severe disability (bed ridden; Zeltzer, 2008). Participants scoring between 0-3 on this scale were included in the study, those scoring 4-5 were excluded. The participants in the CVD cohort had an average score consistent with no significant disabilities implying they have the ability to carry out daily activities ($M = 1.02, \ SD = 0.83$).

General exclusion criteria included any underlying serious illnesses other than the disease being investigated, diagnosis of more than 1 disease being investigated, enrolled in disease modifying therapeutic trial, and any disease other than those being investigated that may lead to death in 3 to 5 years. Additional general exclusion criteria involved any current substance abuse problems or any history of substance abuse that would interfere with participants ability to participate, an AIDs diagnosis, unstable cardiac, hepatic, pulmonary, renal, or infectious disease, and any diagnosis of unstable psychiatric illnesses. Exclusion criteria specific to the CVD cohort were any individual with a vascular cause of their symptoms (migraines, isolated vertigo etc.), the presence of large cortical strokes defined as $> 1/3$ middle cerebral artery, and any severe cognitive impairment that would severely limit the participant’s ability to perform in the study assessments.

### 2.2 Standardized Cognitive Assessments

Measures were administered to participants to assess their level of neuropsychological functioning. The Wechsler Adult Intelligence Scale, 3rd Edition—Digit Span test was given to measure participants auditory, attention, and working memory. The cut off score used for this measure is less than or equal to six, a score below this would indicate potential neuropsychological deficits (Kirkwood et al., 2011). The Delis-Kaplan Executive Function System—Colour Word Interference Test was used to measure participants processing speed, response inhibition, and cognitive switching. Cut off scores for these subscales are: Colour Naming + Word Reading $\leq 10$, Inhibition + Inhibition/Switching $\leq 8$, and total score $\leq 18$, scoring below would indicate potential deficits in cognition (Donders & Hayden, 2020; Eglit et al., 2020).
Participants were given the MoCA to assess their cognitive ability. The MoCA is a widely used screening tool for cognitive screening (Julayanout et al., 2014; Petersen et al., 1999; Marcos et al., 2006). The MoCA uses a cutoff score of 26 and greater to define normal performance (Julayanout et al., 2014).

Participants’ strokes were classified using The Trail of Org 10172 in Acute Stroke Treatment (TOAST). TOAST is a classification system used for classifying etiology of ischemic stroke (Adams et al., 1993; Chen et al., 2012). This was developed for the purpose of having an unambiguous, practical, and easy to apply classification system of stroke subtype (Adams et al., 1993). TOAST includes five categories: large-artery atherosclerosis, cardioembolic, small artery occlusion (lacune), stroke of other determined etiology, and stroke of undetermined etiology. See Table 3, for number of participants with each TOAST subtype.

Eighty-four participants met our inclusion and exclusion criteria, based on completion of measures (Figure 1) and lesion criteria. Lesion criteria included lesions 10% or greater (as used in other studies as a benchmark e.g., Caviness et al., 2011) in our regions of interest (ROI), and was calculated relative to the proportion of normal appearing grey and white matter. ROIs are described in section 2.3.1. In total, there were fifty-four males and thirty females included within the study with a mean age of 69.20 (SD = 7.46).
Figure 1. Flow chart of ONDRI participants with CVD eligible for the study and completion of behavioural measures.

Note. IRI represents the Interpersonal Reactivity Index and BIS/BAS represents the Behavioural Inhibition Scale and Behavioural Activation Scale.

2.2.1 Empathy and Behavioural Measures

ONDRI was a large multi-cohort study with the purpose of examining neuropsychological assessments, gait and ocular assessments, genomics, and neuroimaging in patients with neurodegenerative diseases or cerebrovascular disease. Participants and their caregivers were administered multiple measures. Caregivers completed such measures as: Caregiver Burden-Zarit Burden Interview, Neuropsychiatric Inventory Questionnaire, Physical Self-Maintenance Scale, Revised Self-Monitoring Scale, Behavioural Inhibition Scale/Behavioural Activation Scale (BIS/BAS) and more. Participants completed the following measures: General Anxiety Disorder Assessment-7,
Pittsburgh Sleep Quality Index, World Health Organization Quality of Life, Quick Inventory of Depressive Symptomatology, Montreal Cognitive Assessment, Social Norms Questionnaire, and more. The current study focused on data from the caregiver version of the Interpersonal Reactivity Index (IRI), although the data from the BIS/BAS was also of potential interest, it was excluded from this study due to the insufficient amount of completed measures available.

The IRI (Davis, 1980) was administered to participants and their caregivers. The IRI is a 28-item scale, used for a measure of empathy. The IRI includes four subscales: Empathic Concern (“I often have tender, concerned feelings for people less fortunate than me,”), Personal Distress (“In emergency situations, I feel apprehensive and ill-at-ease,”), Fantasy (“I daydream and fantasize, with some regularity, about things that might happen to me,”), and Perspective Taking (“I try to look at everybody’s side of a disagreement before I make a decision,”). Empathic concern is a subscale that can be used as an indicator of emotional empathy whereas the perspective taking subscale is an indicator of cognitive empathy. The caregiver report version of this measure used in this study included the 14 items from the empathic concern and perspective taking subscales. For this study we chose to focus our analysis on the caregiver report for two reasons. First, the subscales used in this version are more clearly associated with our interest in empathy. Second, and most importantly, research has shown that individuals who suffer stroke often develop anosognosia which is when the individual is unaware of their neurological deficits (Archarya & Sanchez-Manso, 2021). This is especially true for individuals with inferior and medial PFC damage (Driscoll et al., 2012; Barrash et al., 2000; Beer et al., 2006; Stuss et al., 2002; Mesulam, 1986).

Caregivers responded to items on a 5-point Likert scale ranging from “Does not describe me well” to “Describes me very well”, in reference to the participant. Total scores were calculated by summing each response, while adjusting for reversed scored items. Total scores for each subscale were also obtained by summing all responses for each scale. Higher scores indicate a higher presence of empathic behaviour whereas lower scores indicate lower presence of empathy.
The IRI has an internal consistency ranging from 0.72 to 0.79, (Hsieh et al., 2013). In terms of stroke, the IRI has shown an internal consistency of ($\alpha = 0.78$) (Yeh & Tsai, 2014), where $\alpha > 0.7$ is considered reliable (Kline, 1999).

### 2.3 Procedure

#### 2.3.1 Imaging

Magnetic resonance imaging was obtained following the Canadian Dementia Imaging Protocol (CDIP; Duchesne et al., 2019), National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards (Hachinski et al., 2006). Imaging was obtained at least 3 months post stroke. Images used were obtained during the participants first ONDRI visit which occurred between 2014 and 2015.

Structural MRI scans were obtained using 3-Tesla systems and included 3D T1-weighted, PD/T2-weighted and FLAIR images for all participants. All images were examined by a neuroradiologist for quality and incidental findings before being processed (Ramirez et al., 2020). Preprocessing of the structural images used an ONDRI pipeline referred to as Semiautomatic Brain Region Extraction-Lesion Explorer (SABRE-LE). SABRE-LE is a neuroimaging pipeline used by ONDRI for stroke quantification, tissue segmentation, and volumetric analysis of grey and white matter lesions.

SABRE-LE segmented 13 classifications of brain tissue including normal appearing grey matter, normal appearing white matter, ventricular spinal fluid, and chronic stroke lesions (Ramirez et al., 2020). This pipeline also segmented the brain into 26 regions of interest, 13 per hemisphere, using anatomical landmarks that are unique to each individual participant. In addition, the Sunnybrook Hippocampal Volumetry (SBHV) tool was integrated to include a segmentation of the hippocampus, resulting in 28 regions of interest.

SABRE-LE was chosen for use by ONDRI because it is a beneficial preprocessing method used in studies of neurodegenerative disease and stroke due to its efficiency and greater precision when assessing volumetric changes within the brain tissue (Dade et al.,...
2004). Most importantly, in stroke and neurodegenerative diseases there is high anatomical variability across patients (Dade et al., 2004), which puts the images at risk for registration errors during warping to a standardized template (e.g., MNI; Ghanei et al., 2000; Ng et al., 2009). SABRE-LE accounts for these differences by avoiding the warping of individual images and registering the template onto the patients’ individual brain (Dade et al., 2004). This accounts for individual differences, such as, atrophy typically found in individuals after stroke (Ramirez et al., 2020).

Quality control of the images was monitored by ONDRI’s neuroinformatic platform. Images were uploaded to the Brain-CODE database and were assessed for adherence to protocol, signal-to-noise ratio, contrast-to-noise ratio, and for any presence of image artefacts (Farhan et al., 2017). A board-certified neuroradiologist reviewed all structural images for exclusionary pathology or any incidental findings (Farhan et al., 2017).

2.4 Data Analysis

Data was analyzed using IBM Statistical Package for Social Sciences version 27.

2.4.1 Areas of the Prefrontal Cortex

In the current study, participants were selected from the data set of the CVD cohort (Figure 1). Participants were selected according to lesion size, which was any lesion 10% or greater in the ROIs of relative to normal appearing grey and white matter. This criteria was selected from a similar study conducted by Caviness and colleagues (2011). Thirty-three participants had chronic stroke lesions meeting our criteria in one or more regions of interest including superior frontal, middle frontal, inferior frontal, medial inferior frontal, medial superior frontal, medial middle frontal, superior parietal, inferior parietal, occipital, anterior and posterior temporal, anterior and posterior basal ganglia. Twenty-four participants (16 males and 8 females) fit the lesion criteria and completed the IRI caregiver measure. The no detectable lesion group included participants with no visible chronic stroke lesions \((n = 60)\).

For the superior PFC group \((n = 9)\), lesions in the superior frontal and medial superior frontal were included. If a participant had overlapping lesions with the middle frontal
and/or medial middle frontal they were included in the superior group. The inferior PFC lesion group \( (n = 10) \) included lesions in the inferior frontal, medial inferior frontal, middle frontal, and medial middle frontal. The non-PFC group \( (n = 12) \) included lesions in the occipital, inferior parietal, and superior parietal. Lesions less than 10% and, lesions to the basal ganglia \( (n = 6) \) and temporal lobes \( (n = 3) \) were excluded from this analysis. Due to variability in sample size, groups were tested for normal distribution and data appeared normal. A repeated measures analysis of variance (ANOVA) was conducted to compare means across all groups for each IRI subscale.

### 2.4.2 PFC versus Non-PFC Lesions

When our hypothesis was not confirmed, we did a follow up analysis to determine whether PFC lesions were in general associated with greater empathy problems than non-PFC lesions, particularly because we did not have many patients with lesions to the temporal lobes or temporoparietal areas. For the PFC group, lesions included were those in all ROIs of the PFC: superior frontal, inferior frontal, medial superior frontal, medial inferior frontal, middle frontal and medial middle frontal \( (n = 19) \). The non-PFC group \( (n = 12) \) and no detectable lesion group \( (n = 60) \) were the same as previously mentioned. Due to variability in sample size, groups were tested for normal distribution and data appeared normal. A repeated measures ANOVA was first conducted to compare means across all groups. Then independent samples t-tests were conducted for each subscale for PFC group versus non-PFC group.

### 2.4.3 Hemispheres

For the hemisphere analysis, lesions were included that were 1% or more of the hemisphere (Leigh et al., 2013). Lesion percentages were calculated by the proportion of normal appearing white and grey matter in each hemisphere. Participants were categorized into groups based on right hemisphere lesions \( (n = 10) \) or left hemisphere lesions \( (n = 13) \) and no detectable lesions \( (n = 60) \). Those with lesions in both hemispheres were excluded from analysis \( (n = 2) \). Due to variability in sample size, groups were tested for normal distribution and data appeared normal. A repeated measures ANOVA was conducted to compare mean across all groups. A correlation
analysis was then conducted for right and left hemisphere lesion size with each IRI subscale and total score.

2.4.4 Lesion Segmentation and VLSM

For the VLSM whole brain analysis, all lesions greater than 10% in ROIs were included in the analysis. This included participants with lesions to the basal ganglia and temporal lobes, and completion of the IRI caregiver ratings total score ($n = 24$). To allow for the VLSM analysis lesions were manually traced using the ITK-Snap software by H.D, utilizing T1-weighted, T2-weighted, and FLAIR. At the time of the analysis, the SABRE lesion masks were not available. To assess the reliability of the lesion tracing, lesion sizes were correlated to each of the SABRE-LE ROI. Appendix A demonstrates images of segmentations for each participant. After lesion segmentation, the lesions were normalized to the stroke-control template included in the Clinical Toolbox (Rorden et al., 2012) in SPM12. This toolbox was created for normalizing imaging data specific to older adults (mean age 65) and for clinical populations with stroke or brain injury (Rorden et al., 2012).

The VLSM analysis was conducted using the NiiStat (https://www.nitrc.org/projects/niistat/) set of scripts in Matlab. The NiiStat scripts were developed to examine neuroimaging data specific to clinical populations including stroke. To conduct the analysis, the first step was to create an excel file with the participant’s image file name corresponding to the IRI scores for each participant. The analysis was set to Normal Permutation with number of permutations set at 5000, to control for multiple comparisons and familywise errors. Normal permutation does this by randomizing the order of the behavioural scores. For the first analysis, the threshold was set at $p < .05$ with the minimum overlap of participants set to 1. As an additional exploratory step to ensure pipeline functionality and identify areas that may have relevance for future work, we set an extremely liberal threshold of $p < 0.15$ and present the areas identified in this pilot analysis.
Chapter 3

3 Results

3.1 Neuropsychological Assessments

Participants were administered the Weschler Adult Intelligence Scale, 3rd Edition—Digit span test to measure auditory, attention, and working memory. All participants on average were above the cut-off score of ≤ 6 (Kirkwood et al., 2011; Table 1), indicating they do not have significant general cognitive deficits. In addition, participants completed the Delis-Kaplan Executive Function System—Colour Word Interference Test as a measure of processing speed, response inhibition, and cognitive switching. Participants were above cut-off scores on each subscale (Colour Naming + Word Reading, ≤ 10, Inhibition + Inhibition/Switching ≤ 8) total score (≤ 18; Table 1), indicating they did not have any significant deficits in these cognitive domains.

Table 1. Neuropsychological test means and standard deviation.

<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit Span</td>
<td>10.41</td>
<td>2.56</td>
</tr>
<tr>
<td>Delis-Kaplan Executive Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>System—Colour Word Interference Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colour Naming + Word Reading</td>
<td>16.82</td>
<td>5.96</td>
</tr>
<tr>
<td>Inhibition + Inhibition/Switching</td>
<td>18.79</td>
<td>6.36</td>
</tr>
<tr>
<td>Total</td>
<td>35.85</td>
<td>11.28</td>
</tr>
</tbody>
</table>

For cognitive ability, participants were administered the MoCA. On average, our cohort of patients preformed 1 point below the cutoff score with no differences among groups (Table 2) indicating our participants did not have any significant deficits in cognition. This indicates our participants were on average one point below normal performance.
Table 2. Mean MoCA scores

<table>
<thead>
<tr>
<th>Lesion Group</th>
<th>M</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior PFC</td>
<td>25</td>
<td>1.80</td>
</tr>
<tr>
<td>Inferior PFC</td>
<td>25.82</td>
<td>1.99</td>
</tr>
<tr>
<td>Non-PFC</td>
<td>25.42</td>
<td>2.41</td>
</tr>
<tr>
<td>No Detectable Lesions</td>
<td>25.57</td>
<td>3.18</td>
</tr>
</tbody>
</table>

The ischemic stroke etiology was categorized using the TOAST classification system. The majority of strokes in this sample occurred due to a small artery occlusion, large artery atherosclerosis, or undetermined etiology (Table 3).

Table 3. Number of participants with TOAST subtypes.

<table>
<thead>
<tr>
<th>Stroke Type</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small artery occlusion (lacune)</td>
<td>50</td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>32</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>23</td>
</tr>
<tr>
<td>Undetermined etiology</td>
<td>36</td>
</tr>
<tr>
<td>Other determined etiology</td>
<td>7</td>
</tr>
<tr>
<td>Missing</td>
<td>7</td>
</tr>
</tbody>
</table>

3.2 Areas of the Prefrontal Cortex

To test the hypothesis that the inferior portion of the PFC is involved in empathy, a 2 (IRI Caregiver Ratings Subscale: Perspective Taking, Empathic Concern) X 4 (Lesion Group: Superior PFC, Inferior PFC, Non-PFC, No Detectable Lesions) repeated measures ANOVA was conducted. This revealed no significant main effect of PFC lesion location.
There was a significant main effect for subscales $F (1, 78) = 39.45, p < .001$. However, there was no significant interaction between lesion location and IRI subscale scores $F (3,78) = .61, p = .614$, (Figure 2).

**Figure 2.** Mean subject ratings with individual total scores of IRI Caregiver Rating Subscales; error bars represent standard error. There were no significant differences among groups (Superior PFC $n = 8$, Inferior PFC $n = 6$, Non-PFC $n = 8$, No Detected Lesions $n = 60$).

### 3.3 PFC versus Non-PFC Lesions

When our hypotheses regarding empathy deficits and subdivisions of the PFC were not confirmed, we followed up with this analysis to determine whether the PFC in general is differentially involved in empathic processes, relative to posterior cortical areas. An analysis was conducted to compare the effects of lesions located in the PFC versus lesions located outside the PFC and those with no detectable lesions on the IRI subscales and total scores. A 2 (IRI Caregiver Ratings Subscales: Perspective Taking, Empathic Concern) X 3 (Lesion Location: PFC lesions, Non-PFC lesions, No Lesion Detected) repeated measures ANOVA revealed, no significant main effect for lesion location, $F$
There was a significant main effect of subscale $F(1, 79) = 52.36, p < .001$. However, there was no significant interaction between lesion location and subscale $F(2, 79) = .92, p = .405$, (Figure 3).

Although, mean scores of Perspective Taking were higher for participants with lesions in the PFC ($M = 17.60, SD = 7.99$) than participants with non-PFC lesions ($M = 14.40, SD = 4.14$), t-tests demonstrated this difference was not significant $t(22) = 1.31, p = .204$, however it did represent a medium effect, $d = .47$. A power analysis revealed that a sample of 41 for each group is required for an effect size to be detected (80% chance) at the .05 significant level. For the IRI Caregiver Ratings subscale of Empathic Concern, on average participants with PFC lesions ($M = 21.36, SD = 5.73$) had lower mean ratings than participants with non-PFC lesions ($M = 20.50, SD = 6.72$). A t-test demonstrated this difference was not significant $t(22) = .34, p = .740$, although it did represent a small effect, $d = .14$. A power analysis revealed that a sample of 106 for each group is required for an effect size to be detected (80% chance) at the .05 significant level. For IRI Caregiver Ratings Total score, on average participants with lesions in the PFC group ($M = 38.93, SD = 13.45$) had higher overall ratings than participants with non-PFC lesions ($M = 33.00, SD = 12.53$). This difference was not significant $t(21) = 1.06, p = .302$, but represents a medium effect $d = .45$. A power analysis revealed that a sample of 27 for each group is required for an effect size to be detected (80% chance) at the .05 significant level.
Figure 3. Group means on IRI Caregiver ratings subscales: bars represent standard error. No significant differences (No Detected Lesion $n = 60$, PFC $n = 14$, Non-PFC $n = 8$).

3.4 Hemispheres

To test the hypothesis that the right hemisphere is involved for empathy, an analysis was conducted to compare the effects of lesions located in the right versus left hemisphere on both empathy scales. A 2 (IRI Caregiver Ratings Subscale: Perspective Taking, Empathic Concern) x 3 (Lesioned Hemisphere: No Detectable Lesions, Right Hemisphere Lesions, Left Hemisphere Lesions) repeated measures ANOVA was conducted and revealed there was no significant main effect for hemisphere lesion location, $F (2,78) = 2.36, p = .101$. There was a significant main effect of IRI subscale, $F (1,78) = 47.04, p < .001$. However, no significant interaction between lesion location and IRI subscales, $F (2,78) = .28, p = .754$, (Figure 4).
Figure 4. Mean subject ratings for IRI Caregiver report subscales and lesion hemisphere location: error bars represent standard error. There were no significant differences among groups. (No Detectable Lesion $n = 60$, Right Hemisphere Lesion $n = 10$, Left Hemisphere Lesion $n = 13$).

Correlation analyses were conducted to examine any relationship with lesion size and empathy ratings. There were no significant relationships between the size of right hemisphere lesions and the IRI Caregiver Ratings subscales, Perspective Taking, $r = -.27$, $p = .328$, (Figure 5) or Empathic Concern $r = -.04$, $p = .894$. Right hemisphere lesion size also did not significantly correlate with IRI Caregiver Ratings total score, $r = -.15$, $p = .583$, (Figure 6).
Figure 5. Scatterplot of lesion size cubic mm in the right hemisphere and IRI Caregiver Rating Subscale Perspective Taking total score.

Figure 6. Scatterplot of lesion size in cubic mm in the right hemisphere and IRI Caregiver Rating Subscale total score.
For left hemisphere lesion locations, there was no significant relationship between IRI Caregiver Ratings subscales, Perspective Taking, $r = .16, p = .523$ or Empathic Concern, $r = .17, p = .511$. There was also no significant relationship with left hemisphere lesions and IRI Caregiver Ratings total score, $r = .21, p = .410$.

3.5 VLSM

To examine, on a whole-brain level, the potential association between lesions to particular neural regions and abnormalities on the IRI, a voxel-based lesion-symptom mapping analysis was conducted on the IRI Caregiver Ratings Total Score for participants with lesions. First, a lesion map was created to visualize the degree of overlap in lesion location across the sample, see Figure 7. The VLSM and IRI caregiver total score analysis for participants with lesion did not result in a significant effect at the $p < .05$ level. While, the participants did not show significantly lower scores, the effect size of PFC lesions compared to Non-PFC lesion group is medium to large, $d = .61$. In our exploratory analysis with the threshold set to $p < 0.15$, 2196 voxels survived the threshold and were associated with lower scores on the IRI caregiver rating total score, (Figure 8).
Figure 7. Lesion sum map for IRI Caregiver Ratings and all lesion groups, superimposed on MNI space. Yellow represents lesion in at least one participant with red representing lesions in at least 4 participants, $n = 24$. 
Figure 8. Results of VLSM analysis on IRI Caregiver Ratings Total Score with threshold set to .15. 2196 voxels survived threshold of .20, shown in red and superimposed on MNI space. This was not significant $p < .15$. 
Chapter 4

4 Discussion

4.1 Study Results

Neural regions of the PFC have been implicated in having a critical involvement in empathic processes (Shamay-Tsoory & Aharon-Peretz, 2007; Schneider & Koenigs, 2017; Bramham et al., 2009). Areas of the PFC implicated in previous research include the inferior regions of the PFC, specifically the vmPFC (Driscoll et al., 2012; Shamay-Tsoory et al., 2009; Leopold et al., 2012). We hypothesized that dissociable areas of the PFC were responsible for empathic processes. Specifically, we predicted that lesions to the inferior PFC would result in significantly lower scores on empathy measures. Contrary to our hypothesis, there were no significant differences found between lesions to the superior PFC, inferior PFC, non-PFC lesions, and those with no detectable lesions. In light of this finding, and to explore the possibility that lesions to the PFC in general are more likely to be associated with empathic processing, we compared caregiver ratings of empathy in patients with lesions to the PFC relative to patients with either lesions to other regions or no detectable lesions. However, no group differences in empathy were observed.

Previous research has provided evidence of hemisphere asymmetry for emotional processes including empathy, particularly greater involvement of the right hemisphere (Perry et al., 2001; Rankin et al., 2006; Happe et al., 1999; Hamilton et al., 2017). With this evidence, we predicted that right hemisphere stroke lesions would be associated with reduced empathy scores relative to stroke lesions restricted to the left hemisphere. Our results did not support this prediction; the two groups did not differ significantly, nor did they differ from the group with no detectable lesions.

Based on evidence that dissociable neural regions are involved in empathic processes (Campanella et al., 2014; Driscoll et al., 2012; Shamay-Tsoory et al., 2009), we also used a whole-brain VLSM approach. This would allow for greater anatomical specificity (Vaidya et al., 2019). For our investigation however, no neural regions were found to be
significantly associated with deficits in empathy. For exploratory purposes, we reduced the threshold to $p < 0.15$ level, this revealed some preliminary evidence that lesions in the posterior region of the right prefrontal cortex may be associated with poorer performance on the IRI caregiver empathy measures. This area is located more superior to the regions of the PFC that we predicted, however, this analysis can only be considered preliminary and may provide impetus for further research in larger samples of stroke patients.

4.2 Study Implications

Current lesion research on empathy often includes inpatient samples who are recruited from neurology or neurosurgery units. These participants often have severe and widespread injury from head injury or surgical resection; presenting with more significant symptoms and requiring longer stays in hospital (Shamay-Tsoory et al., 2009; Shamay-Tsoory et al., 2007; Campanella et al., 2014; Rolls et al., 1994; Driscoll et al., 2012; Hornak, 2003; Shamay-Tsoory et al., 2004; Bramham et al., 2009). In our study, participants were included if they had a mild-to-moderate stroke based off the Modified Rankin Scale. Our participants had an average score of 1, implying many had only a mild stroke. With this consideration, it is possible that our observed results may be due to mild strokes not being severe enough to produce large lesions that show significant deficits. Stroke severity has been found to be an important factor in a patient’s outcome (Perna & Temple, 2015). Jorgensen and colleagues (1995) examined stroke prognosis in a large sample of stroke patients. In their study they found that initial stroke severity was a critical factor in predicting patient outcome when compared to other factors such as neurological functioning, time course of recovery, or functional outcome. It is also important to note that ONDRI required extensive follow ups and a large battery of tests; it is likely that only high-functioning and highly motivated participants and their caregivers took part.

Although we failed to find evidence to support our hypothesis that the inferior PFC is critically involved in empathy, there are several potential reasons for the null finding. The lack of overlap between the lesions most common in our patient sample and some of our key neural regions of interest is an important consideration, particularly, regarding lesions to the vmPFC. The vmPFC is a functionally heterogenous region that is poorly
understood (Mitchell, 2011) though, it has been in empathic processes (Frith & Frith 2006; Frith & Singer, 2008; Shamay-Tsoory et al., 2009). The VLSM lesion sum map (Figure 7) shows very limited overlap of lesions in the vmPFC. Therefore, the null findings may be because areas of the vmPFC critical for empathy were largely spared in our current sample. This implies we did not have sufficient data to analyze our hypothesis. In addition, most lesion overlap within the PFC occurred in the more superior and lateral regions, this is an important consideration because areas of the PFC that are most often associated with empathy are the inferior and medial regions (Frith & Frith 2006; Frith & Singer, 2008; Shamay-Tsoory et al., 2009). Specifically, Shamay-Tsoory and colleagues (2009) found lesions to the ventrolateral PFC and the inferior frontal gyrus sufficient to produce deficits in emotional empathy. For an additional consideration, it may be possible that temporal posterior regions are more involved in empathy than we envisioned. Some studies have implicated these regions for being involved in cognitive empathy (Samson et al., 2004; Gallagher & Frith, 2003). Our sample lacked lesions in temporal and temporoparietal areas, which may also explain our lack of findings, particularly with respect to cognitive empathy. Overall, our sample may have had an insufficient amount of lesion overlap in areas of the vmPFC, and temporoparietal areas which could explain our failure to find associations between lesions and empathy deficits. To overcome this limitation, a larger sample size is needed.

Evidence indicates hemispheric asymmetry for emotional processes including empathy. Specifically, the right hemisphere appears to have a stronger association with empathic processing (Perry et al., 2001; Rankin et al., 2006). However, we found no evidence supporting this. This seems to conflict with prior studies that report an association with right hemisphere lesions and increased empathy deficits (Pluta et al, 2017; Hamilton et al., 2017; Happe et al., 1999). However, it is difficult to infer impact of lesion size or specific location as these factors were not incorporated into their investigation.

4.3 Strengths, Limitations, Future Directions

A strength of our study was the inclusion of the caregiver report version of the IRI. Previous research well documents that individuals who suffer stroke often present with anosognosia, and therefore are unaware of their neurological deficits (Archarya &
Sanchez-Manso, 2021). This is particularly true for individuals with lesions to the inferior portion of the PFC, who often present with disturbances in self-awareness and insight (Driscoll et al., 2012; Barrash et al., 2000; Beer et al., 2006; Stuss et al., 2002; Mesulam, 1986). Therefore, focusing on the caregiver report may have avoided these potential issues. Although, it should be noted the IRI first person version use with caregivers’ responses has not been validated in previous studies.

The inclusion of VLSM was also a strength in our study. VLSM allowed us to examine structure-function relationships on a whole brain level, rather than only examining differences among groups (Bates et al., 2003). It should be noted that this analysis was conducted on chronic stroke lesions. Chronic stroke lesions are thought to be beneficial compared to acute lesions in VLSM analyses since the consequences of acute lesions (e.g. tissue swelling) are not present in chronic lesions (Rennig et al., 2015). Although, the small sample size of the available sample was a major limitation for this analysis. With a larger sample, if our results were significant, we may have been able to see the specific neural regions involved in empathy at higher spatial resolution. This would enable us to examine the dissociable areas of the prefrontal cortex that are particularly critical for the two facets of empathy. Other studies using VLSM analysis (Bates et al., 2003; Campanella et al., 2014; Driscoll et al., 2012) had sample sizes ranging from 71 to 199 participants. For our VLSM analysis, we had a sample size of $n = 24$. Therefore, this study should be regarded as preliminary and should be re-examined in a larger cohort. The sample size for future studies should be increased to two hundred participants or higher. Since we are seeking to examine mild brain injury (e.g., detectable but small lesions), we would require a higher sample size than previous studies to ensure there is enough subjects with lesions covering our ROIs. This would provide us with the anatomical resolution necessary for a sufficient VLSM analysis.

It should be noted that our study did not have data on age-matched and sex-matched healthy control participants. However, the performance of our participant group is within the range of normative data obtained from healthy adult populations. In such studies, the mean score of the perspective taking subscale 16.43 ($SD = 4.33$) and the mean score for the empathic concern subscale 16.55 ($SD = 4.01$) in healthy adults (De Corte et al., 2007)
is similar to the mean score and range obtained in our participants (Perspective Taking $M = 16.01$, $SD = 6.17$; and Empathic Concern $M = 20.92$, $SD = 5.50$).

In addition, it is important to note that our sample would not only have focal brain lesions, but also atrophy. This atrophy is secondary to the vascular events and is associated with normal aging. An additional future direction would be to incorporate information from VLSM alongside a voxel-based morphometry (VBM) analysis in a much larger sample. This would allow for the combined examination of lesions and atrophy in the brain and their involvement with empathic processes. It would also be worth noting that this study could further be extended to examine patients with FTD. In FTD, significant atrophy begins occurring within the frontal and temporal lobes (Sivasathiaseelan et al., 2019; Onley et al., 2017). Due to this, these patients often present with deficits in empathy (Onley et al., 2017; Sivasathiaseelan et al., 2019; Baez et al., 2014; Snowden, 2018; Mendez et al., 2005). This cohort would be beneficial to include in future research as it would allow for a more specific understanding of the neural regions involved in empathy by examining global atrophy to the PFC and temporal lobes in comparison to more focal lesions.

### 4.4 Conclusion

The aim of our study was to determine which dissociable areas of the PFC are critical for adaptive empathic processing in patients with mild-to-moderate stroke. Overall, our results did not show a significant relationship between lesions to specific regions of the PFC and deficits in empathy. One possibility is that mild-to-moderate stroke lesions are not severe enough to produce deficits in empathy. Also, it may be that these deficits only emerge with large lesions or in the context of broader, more severe cognitive deficits. However, it should be noted that our sample size was small, and a very small number of our participants showed lesions affecting the vmPFC and other areas implicated in empathy including the temporoparietal regions, therefore we did not have sufficient data to analysis our hypotheses. Future studies should pursue using VLSM in a large number of patients with mild-to-moderate stroke and other neurological populations (e.g., FTD, other lesion groups) without generalized cognitive impairment as this will increase the ability to localize function with high resolution. In addition, incorporating VBM analysis
may help clarify the effects of atrophy that are often seen in these populations. Overall, this can help clarify the neural regions involved in empathic processing. This is essential because when dysfunction in empathy occurs it can negatively impact all aspects of an individual’s social life (De Vignemont & Singer, 2006; Hoffman, 2000). Individuals with deficits in empathy are often described as having anti-social patterns of behaviour and may be more prone to aggression (De Vignemont & Singer, 2006; Hoffman, 2000). Such deficits are also associated with increased caregiver burden, depression, and an overall negative impact on caregiver relationships (Brown et al., 2019; Pomponi et al., 2016; Hsieh et al., 2013). Delineating the neural basis for changes in empathy following stroke may help further the understanding of the biological risk factors for disruptive and antisocial behaviours more generally. Perhaps most importantly for the current population, understanding the deficits in empathy that can result from stroke involving particular brain areas may help better prepare stroke survivors and their caregivers for potential challenges, and perhaps enhance their understanding, compassion and coping as a result.
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Appendices

Appendix A.

Sample images of lesion tracing for each participant in axial view. Each image represents an individual participant.
### Curriculum Vitae

**Name:** Hilary Dagg  

**Post-secondary Education and Degrees:**  
King’s University College, Western University  
London, Ontario, Canada  
2015-2019 H.B.A.  
Western University  
London, Ontario, Canada  
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**Honours and Awards:**  
Deans Honors List  
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King’s University College, Western University  
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Speaker  
IMPACT! Program  
Victoria Hospital, London Health Sciences Centre  
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