The Incidence, Co-occurrence, and Predictors of Dysphagia, Dysarthria, and Aphasia after Acute Ischemic Stroke

by

Heather Leslie Irene Flowers

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

Graduate Department of Speech Language Pathology

University of Toronto

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Doctor of Philosophy (2014)

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Abstract

Background- Dysphagia, dysarthria and aphasia are frequent sequelae of stroke. We sought to identify their frequency, co-occurrence, and predictors of them after acute ischemic stroke.

Methods- First, we used the Registry of the Canadian Stroke Network’s (RCSN) database (2003–2008) from one stroke centre to identify a random sample of 250 patients with acute ischemic stroke confirmed by magnetic resonance imaging (MRI). We conducted a medical chart review to derive frequency estimates for the presence of dysphagia, dysarthria and aphasia and identified clinical predictors of them from the RCSN database. Second, we conducted a systematic review to identify neuroanatomical predictors of dysphagia after acute ischemic stroke. We searched 14 databases, 17 journals, three conference proceedings and the grey literature using the Cochrance Stroke Group search strategy. We pooled individual level data for the dysphagia outcome, calculating relative risks according to neuroanatomical lesion sites. Finally, from the medical chart review, we evaluated MRI scans for patients with acute lesions within 14 days of stroke
onset, deriving clinical and neuroanatomical predictors of the three impairments, using logistic regression.

Results – First, incidence estimates for dysphagia, dysarthria, and aphasia were 44% (95% CI, 38-51), 42% (95% CI, 35-48) and 30% (95% CI, 25-37), respectively. The highest clinical predictors were non-alert level of consciousness for dysphagia (OR 2.6, CI 1.03-6.5), symptoms of weakness for dysarthria (OR 5.3, CI 2.4-12.0), and right-sided symptoms for aphasia (OR 7.1, CI 3.1-16.6). Second, for our systematic review, we reviewed 964 abstracts, accepting 84 for full review. Seventeen met our inclusion criteria, providing individual results for 656 patients. Predictors of dysphagia included pontine (RR 3.7, 95% CI 1.5-7.7), medial medullary (RR 6.9, 95% CI 3.4-10.9) and lateral medullary (RR 9.6, 95% CI 5.9-12.8) lesions. Finally, 160 patients met our eligibility criteria for MRI analysis. Strongest predictors included medullary lesions (OR 6.2, 95% CI 1.5 – 25.8) for dysphagia, pontine lesions (OR 7.8, 95% CI 2.7 – 22.9) for dysarthria, and insular lesions (OR 34.4, 95% CI 4.2 – 283.4) for aphasia.

Conclusions- We computed the frequency of dysphagia, dysarthria, and aphasia, identifying clinical and whole brain neuroanatomical predictors of their presence.
ACKNOWLEDGEMENTS

I am very grateful to all who have supported me in my years of PhD studies. First and foremost, I thank God for giving me strength and perseverance.

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I would like to acknowledge the extraordinary role that my supervisor, Dr. Rosemary Martino, has played in the development of my thesis research and in its quality. I thank Rosemary for her unique ability to provide strong guidance in the present, but to also to take measures and sacrifice her time to ensure a solid path for my future research career. My supervisory committee, Drs Elizabeth Rochon, Frank Silver, and David Streiner, has always provided comprehensible and critical research contributions, constructive feedback at every stage, and academic support and advice. In addition, the many experts who have contributed to the depth and breadth of my PhD studies have made it possible to conduct this research. In particular, I thank Drs. David Mikulis, Mallar Chakravarty, Mohammed Al-Harbi, and Jiming Fang for their expertise and contributions. I acknowledge all the swallowing laboratory personnel and PhD students, especially Trixie Reichardt, Stacey Skoretz, and Stephanie Shaw, for administrative support, research collaboration, and personal support.

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<td>AASP</td>
<td>Acute Aphasia Screening Protocol</td>
</tr>
<tr>
<td>ACA</td>
<td>Anterior cerebral artery</td>
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<tr>
<td>ADC</td>
<td>Apparent diffusion coefficient</td>
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<td>ADP</td>
<td>Aphasia Diagnostic Profiles</td>
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<tr>
<td>AIDS</td>
<td>Assessment of Intelligibility in Dysarthric Speakers</td>
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<td>AOS</td>
<td>Apraxia of speech</td>
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<td>ASL</td>
<td>Arterial spin labelling</td>
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<td>AST</td>
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<td>BEST-2</td>
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<td>College of Audiologists and Speech-Language Pathologists of Ontario</td>
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<td>CI</td>
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<td>CIHI</td>
<td>Canadian Institute for Health Information</td>
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<td>CNS</td>
<td>Canadian Neurological Scale</td>
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<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<td>CSF</td>
<td>Cerebrospinal fluid</td>
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<td>CSS</td>
<td>Canadian Stroke Strategy</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<td>DDK</td>
<td>Diadochokinetic</td>
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<td>DWI</td>
<td>Diffusion-weighted images</td>
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<td>DWMH</td>
<td>Deep white matter hyperintensities</td>
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<td>FAST</td>
<td>Face Arm Speech Test or Frenchay Aphasia Screening Test</td>
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<td>FDA</td>
<td>Frenchay Dysarthria Assessment</td>
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<td>FEES</td>
<td>Fiberoptic endoscopic evaluation of the swallow</td>
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<td>FLAIR</td>
<td>Fluid-attenuated inversion recovery</td>
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<td>HSFC</td>
<td>Heart and Stroke Foundation of Canada</td>
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<td>HTN</td>
<td>Hypertension</td>
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<td>ICC</td>
<td>Intraclass correlation coefficients</td>
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<td>ICH</td>
<td>Intracerebral hemorrhage</td>
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<td>LACI</td>
<td>Lacunar infarcts</td>
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<td>LAST</td>
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<td>LDL</td>
<td>Low-density lipoprotein</td>
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<td>MoCA</td>
<td>Montreal Cognitive Assessment</td>
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<td>MR</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>MRS</td>
<td>Modified Rankin score</td>
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<td>Nasogastric tube</td>
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<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
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<td>NMRI</td>
<td>Nuclear magnetic resonance imaging</td>
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<td>NTS</td>
<td>Nucleus of the solitary tract</td>
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<td>OR</td>
<td>Odds ratios</td>
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<td>Ontario Stroke Registry</td>
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<tr>
<td>PACI</td>
<td>Partial anterior circulation infarcts</td>
</tr>
<tr>
<td>PAD</td>
<td>Peripheral artery disease</td>
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<tr>
<td>PCA</td>
<td>Posterior cerebral artery</td>
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<tr>
<td>POCI</td>
<td>Posterior circulation infarcts</td>
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<td>PVH</td>
<td>Periventricular hyperintensities</td>
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<td>RCSN</td>
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<td>RF</td>
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<td>ROI</td>
<td>Regions of interest</td>
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<td>RT</td>
<td>Repetition Time</td>
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<td>SAH</td>
<td>Subarachnoid hemorrhage</td>
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<td>SIGLE</td>
<td>System for Information on Grey Literature</td>
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<td>TWH</td>
<td>Toronto Western Hospital</td>
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<td>VBLSM</td>
<td>Voxel-based lesion symptom mapping</td>
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<td>VFS</td>
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<td>VIF</td>
<td>Variance inflation factor</td>
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<td>WAB</td>
<td>Western Aphasia Battery</td>
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The Incidence, Co-occurrence, and Predictors of Dysphagia, Dysarthria, and Aphasia after Acute Ischemic Stroke

1. Introduction

1.1. Background

1.1.1. Impact of stroke.

Stroke is the third leading cause of death in Canada (Statistics Canada, 2009). The burden of stroke and ensuing disability includes economic costs upwards of three and a half billion dollars (Public Health Agency of Canada, 2011). Mortality following cerebrovascular disease in Canada affects 41.8 people per 100,000 yearly (Statistics Canada, 2009). Ten percent of yearly deaths occur in individuals under 65 years of age (Statistics Canada, 2010; Canadian Institute for Health Information [CIHI], 2009). Although recent statistics report decreased stroke-related mortality and hospitalizations over the last 20 years (Statistics Canada, 2009), stroke rates are expected to increase with population aging (Denton & Spencer, 1997; Statistics Canada, 2012). Population aging and enhanced survival rates may also lead to increased prevalence of disability following stroke (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006) and consequent longer length of disability (Duncan, 1994). The increase in mean duration of disability will be especially remarkable in younger stroke survivors (Heart and Stroke Foundation of Canada [HSFC], 2010; George, Tong, Kuklina, & Labarthe, 2011) and in those with recurrent stroke (Hankey, Jamrozik, Broadhurst, Forbers, & Anderson, 2002; Hardie, Hankey, Jamrozik, Broadhurst, & Anderson, 2004; Makela, Hammerbeck, & Rushton, 2006). Overall, stroke survivors with disability will incur greater duration of ensuing impairments due to increasing life expectancy following stroke (Hannerz & Nielsen, 2001).
Over one-third of Canadian stroke survivors live with disability (CIHI, 2009), and this number is expected to increase given a rise in risk factors leading to cardiovascular disease, such as obesity (HSFC, 2010) and diabetes (Sultan & Elkin, 2012; Lipscombe & Hux, 2007). A recent study demonstrated that individuals who were overweight had more risk factors for cardiovascular disease (Maximova, Kuhle, Davidson, Fung, & Veugelers, in press). A concomitant rise in diabetes has developed both in the greater population and in younger people (Lipscombe & Hux, 2007). Given recent and expected trends toward increased prevalence of risk factors for stroke, longer mean length of disability following stroke, and an aging population, it is important to investigate the disabling sequelae of stroke relative to the precipitating stroke type.

1.1.2. Stroke types.

The World Health Organization defines stroke to be an acute focal or global neurological deficit with symptoms lasting 24 hours or more (Goldstein et al., 1989). Ischemic stroke is the most frequent cause of stroke, occurring in 80% (Thrift et al., 2009) or more (Kurz, Kurz, & Farbu, 2013) of all strokes, while hemorrhagic strokes comprise the remaining 20% or fewer. Hemorrhagic stroke includes both intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) and, of the two, ICH occurs more frequently (Broderick, Brott, Tomsick, Miller, & Huster, 1993; Kumral et al., 1998; Kyrosis et al., 2009). Ischemic stroke results from mechanical occlusion of cerebral blood vessels (Barber, Demchuk, Hirt, & Buchan, 2003, Chapter 18; Donnan, Fisher, Macleod, & Davis, 2008), due to thrombi or more commonly emboli (Barber et al., 2003, Chapter 18). Intracerebral hemorrhage and SAH result from bleeding, often due to weakened vessel walls, with intraparenchymal bleeding resulting in ICH (Aguilar & Freeman, 2010) and subarachnoid bleeding in SAH (Dupont, Wijdicks, Lanzino, & Rabinstein, 2010). ICH
usually results from spontaneous bleeding in cerebral vessels, caused most commonly by hypertension (Aguilar & Freeman, 2010), while SAH most commonly involves aneurysm rupture into the subarachnoid space (Dupont et al., 2010). Both ICH and SAH have high mortality rates (Aguilar & Freeman, 2010), and the presence of SAH requires immediate aneurysm treatment (Aguilar & Freeman, 2010). Complications from SAH may lead to ICH or delayed ischemic infarctions (Goldstein et al., 1989).

Typically, patients with ischemic stroke present with a sudden onset of focal neurological deficits, while the expanding hematoma in ICH results in a progressive evolution of deficits (Bogousslavsky, Van Melle, & Regli, 1988). The mass effect of the enlarging hematoma causes increased intracranial pressure and shifts in brain structures (Badjatia & Rosand, 2005), often resulting in disturbances in consciousness (Goldstein et al., 1989). There may be close to a 10-fold higher frequency of decreased level of consciousness after ICH compared to ischemic stroke (Bogousslavsky et al., 1988). Patients with SAH present with sudden, severe headache and with a decreased level of consciousness. Focal neurological deficits are not generally expected after SAH unless it is complicated by ICH or ischemia (Goldstein et al., 1989). Cerebral vasospasm, a phenomenon that commonly occurs four to 14 days after subarachnoid bleeding, results in cerebral ischemia that produces focal neurological deficits (Kumral et al., 1998). Aneurysm clipping for the treatment of SAH can be complicated by cerebral infarction (Anderson et al., 2006).

The sudden onset of focal neurological deficits after ischemic stroke warrants a rapid diagnosis and immediate interventions to restore blood flow and avert potentially severe impairments (Barret & Meschia, 2010). Given the high prevalence of ischemic stroke and the acute focal neuroanatomical insults that it produces, understanding its pathological expression is
important in determining potential sequelae in survivors.

1.2. Ischemic Stroke: Predictors and Acute Assessments

Early identification of acute neurological deficits facilitates a diagnosis of acute ischemia, providing the opportunity to intervene and potentially circumvent the sequelae of ischemic stroke and to engage in timely management of compromising impairments. Assessment of suspected ischemic stroke includes the rapid evaluation of symptom onset, to facilitate eligibility for time sensitive therapies, such as intravenous thrombolysis (Barret & Meschia, 2010). With early assessment, determination of precipitating risk factors for stroke, comorbidities, and symptoms/signs at stroke onset can help predict stroke severity (O’Donnell et al., 2012). A broad range of factors warrants consideration as precipitators of debilitating impairments following stroke. Potential clinical predictors of impairments following ischemic stroke may include stroke risk factors, comorbidities of stroke, symptoms at stroke onset, stroke severity, ischemic stroke etiologies, and MRI confirmation of acute lesion and chronic brain factors.

1.2.1. Risk factors for ischemic stroke

There are a multitude of risk factors for ischemic stroke (Goldstein et al., 2006), some of which are nonmodifiable including age, gender, ethnicity, and family history of stroke or of transient ischemic attack (TIA) (Goldstein et al., 2006). Researchers have considered the effect of age on stroke in 10 year increments (Goldstein et al., 2006), demonstrating that the risk of stroke increases significantly every 10 years in persons over 55 years of age (Brown, Whisnant, Sicks, O’Fallon, & Wiebers, 1996). Overall, stroke is more frequent in men between the ages of 45 to 85 than in women (Brown et al., 1996), and ischemic stroke may be less frequent in women (Wolf et al., 1992). However, women who are between 35 to 44 years or >85 years of age may experience stroke with greater frequency than men (Sacco et al., 1998). There are hereditary
components to the development of increased risk for stroke such as ethnicity (Sacco et al., 1998) and genetic predisposition for hypertension (Turner & Boerwinkle, 2003).

Modifiable risk factors should also be considered in stroke prevention (Goldstein et al., 2006) as they too may precipitate the onset of ischemic stroke or contribute to particular sequelae of stroke (Callahan et al., 2011; Paul, Thrift, & Donnan, 2004; Donnan et al., 1989; Grundy, 1997; Wolf, Dawber, Thomas, & Kannel, 1978; Aronow, Gutstein, & Hsieh, 1989; Koroshetz & González, 2006, Chapter 2; Pinto, Tuttolomondo, Di Raimondo, Fernandez, & Licata, 2004). Some of the most common modifiable stroke risk factors for ischemic stroke include hypertension (HTN), type 2 diabetes, and cigarette smoking (Donnan et al., 2008). Other modifiable risk factors include dyslipidemia (Bhattacharya & Chaturvedi, 2011), atrial fibrillation (Pisters, Lane, Marin, Camm, & Lip, 2012), peripheral artery disease, structural heart disease (Pisters et al., 2012), and asymptomatic carotid stenosis (Goldstein et al., 2006; Donnan et al., 2008).

Hypertension is evidenced by arterial blood pressure of > 140/90 mm Hg or >130/80 in persons with types 2 diabetes (Mancia, 2009). A previous diagnosis of type 2 diabetes, defined as glycosylated haemoglobin levels above 6.5% (Stolar, 2010), also increases the risk of ischemic stroke (Callahan et al., 2011). Cigarette smoking contributes to atherosclerosis and is an independent predictor of ischemic infarction (Paul et al., 2004; Donnan et al., 1989). It is often defined by number of cigarette packs smoked multiplied by the number of years of smoking (Paul et al., 2004). Dyslipidemia relates to disturbance of total cholesterol, high levels of low-density lipoprotein (LDL) cholesterol, or low levels of high-density lipoprotein cholesterol (Fodor, 2011), where high levels of LDL independently predict risk of stroke (Grundy, 1997). Atrial fibrillation, the most common form of cardiac arrhythmia (Holmes, 2010), results from
supraventricular tachyarrhythmia due to uncoordinated atrial activation and resulting
deterioration of atrial mechanical function (Fuster et al., 2006). Chronic atrial fibrillation is a
precursor to ischemic stroke due to embolism (Wolf et al., 1978). Peripheral artery disease
(PAD) is a manifestation of atherosclerosis often resulting in inadequate blood flow to the lower
limbs (Regensteiner & Hiatt, 1994). Structural heart disease includes valvular diseases such as
mitral valve prolapse or a dilated left atrium (Pisters et al., 2012) where both conditions are more
conclusive risk factors for stroke when coupled with atrial fibrillation (Aronow et al., 1989;
Koroshetz & González, 2006, Chapter 2). Asymptomatic carotid stenosis results from
atherosclerosis of the internal carotid artery and is a primary risk factor for stroke (Pinto et al.,
2004). A recent study showed that >60% carotid artery stenosis represented a risk factor for
lacunar or large artery stroke (Inzitari et al., 2000). It was also a risk factor for cardioembolic
stroke, but only in the presence of ischemic heart disease (myocardial infarction and angina) or
hypertension (Inzitari et al., 2000).

Considering that some modifiable risk factors respond to risk reduction treatments
following stroke (Goldstein et al., 2006), routine documentation of them should ensue on
admission to hospital. Many risk factors for ischemic stroke are readily discernible in a clinical
setting through documentation of patient history or through routine investigations on admission
to hospital. There is evidence that some risk factors result in more frequent strokes in some
vascular territories compared to others (Subramanian et al., 2009). Also, risk factors are often
correlated, including combinations of modifiable and nonmodifiable risk factors. For example,
smoking (Kannel & Shurtleff, 1973) and diabetes (Brand, Abbott, & Kannel, 1989) can
precipitate PAD (Kannel & Shurtleff, 1973; Brand et al., 1989). Atrial fibrillation has received
particular attention, due to its close association with increasing age (Carlsson et al., 2003). It is
therefore worthwhile to consider multiple risk factors as potential predictors of specific disabilities and impairments following stroke.

1.2.2. Comorbidities of ischemic stroke

Determining comorbidities of ischemic stroke is important because they can be correlated with increased stroke severity (Rogers, 2010; Zhu et al., 1998; Donaldson, Hurst, Smith, Hubbard, & Wedzicha, 2010; MacCallum, 2013). For example, comorbidities such as cancer (Rogers, 2010), dementia (Zhu et al., 1998), and chronic obstructive pulmonary disease (COPD) (Donaldson et al., 2010; MacCallum, 2013) are each associated with the onset of new ischemic stroke. Peripheral artery disease is considered both a modifiable risk factor and a comorbidity of stroke, as it is associated with atherosclerosis (Rice & Lumsden, 2006). Comorbidities may contribute to the development of stroke and its severity.

1.2.3. Symptoms and severity of ischemic stroke

Acute symptoms or signs of stroke serve to predict factors such as stroke severity or risk for developing a particular impairment. The emergency room examination (Moulin et al., 2000) and subsequent neurological evaluations identify the presence and duration of sensory or physical signs, side of motor symptoms, and decreased level of consciousness. Validated and reliable scales of stroke severity most suited to the evaluation of ischemic stroke include the Canadian Neurological Scale (CNS) (Côté et al., 1989), the National Institutes of Health Stroke Survey (NIHSS) (Brott et al., 1989), and the Scandinavian Stroke Scale (SSS) (Stoke Study Group, 1985). They involve simple and rapid measures of physical or cognitive compromise after stroke for computation of overall stroke severity (Asplund et al., 1985; Côté et al., 1989; Goldstein & Samsa, 1997). A rapid functional scale, also common in the acute setting, is the Modified Rankin Score (MRS), which determines the level of motor disability or recovery
during the acute stage (Banks & Marotta, 2007). Such measures of stroke severity and disability in the acute setting help determine stroke prognosis, foreshadowing potential recovery or negative outcomes (Christensen et al., 2005). However, their findings may correlate better with left-sided rather than right-sided lesions (Fink et al., 2002) and are especially sensitive to anterior circulation infarcts compared to posterior circulation infarcts (Martin-Shild et al., 2011).

1.2.4. Etiological classifications of ischemic stroke

Etiological classification of ischemic stroke provides a window into potential underlying causative mechanisms (Bamford, Sandercock, Dennis, Burn, & Warlow, 1991). Etiological classifications may be based solely on clinical presentation (Bamford et al., 1991) or combine clinical evaluation with routine investigations such as neuroimaging (Adams et al., 1993). Two common clinical classifications for ischemic stroke include the Oxfordshire Community Stroke Classifications (Bamford et al., 1991) and the Trial of Org 10172 in Acute Stroke (TOAST) criteria (Adams et al., 1993). The Oxfordshire project classified ischemic strokes into four groups based on presenting symptoms and signs at the point of maximal deficit (Bamford et al., 1991). Because the categories were based on established clinical patterns, expectations included moderate within-group homogeneity, potentially useful for initiating post-stroke therapies or evaluating outcomes (Bamford et al., 1991). Although derived from clinical evaluation, each category had a proposed neuroanatomical basis and pathophysiological hypothesis (Bamford et al., 1991). The categories included lacunar infarcts (LACI), total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), and posterior circulation infarcts (POCI) (Bamford et al., 1991).

The second widely-used classification for ischemic stroke, the TOAST criteria, uses clinical information supplemented by ancillary diagnostic testing, including magnetic resonance
imaging (Adams et al., 1993). It delineates five etiologies for ischemic stroke, including large-artery atherosclerosis, cardioembolism, small-artery occlusion or lacune, other etiology, and undetermined etiology (Adams et al., 1993). The more generic ‘other’ category comprises rarer pathophysiological causes of stroke such as vasculopathies and hematologic disorders. The category ‘undetermined’ is reserved for unidentifiable causes or ischemic stroke with more than one identifiable cause (Adams et al., 1993). Hence, the TOAST classification is advantageous in that it readily captures the most common etiologies for ischemic stroke and is based on all available test results including internal carotid artery stenosis and neuroimaging (Adams et al., 1993). Recent studies have even used the Oxfordshire and TOAST classifications to address stroke prognosis and outcomes (Pinto, Tuttolomondo, Di Raimondo, Fernandez, & Licata, 2006; Tuttolomondo et al., 2008). However, research is still needed to apply ischemic stroke classifications in predicting impairments of acute stroke. Of particular interest are classification systems, such as TOAST that enable inclusion of diagnostic MRI testing (Adams et al., 1993), especially in studies of acute and hyperacute ischemic stroke. Acute stroke care is considered to involve the assessment, treatment and management of stroke within the first few days following the onset of stroke symptoms, while hyperacute stroke care refers to the first few hours of following stroke onset (Canadian Stroke Strategy [CSS], 2013). The timing of stroke onset and consequent determination of an acute or hyperacute stage infarct is most easily verified by neuroimaging (Fazekas, Niederkorn, Ebner, & Diez-Tejedor, 2009).

**1.2.5. Imaging of ischemic stroke**

Computed tomography (CT) is the first imaging modality to be used immediately following stroke of any type (Merino & Warach, 2010). Non-contrast CT is typically more clinically accessible than other imaging techniques such as magnetic resonance imaging (Merino
Given its sensitivity in excluding hemorrhage in the initial hours following stroke (Gee et al., 2012), CT remains the clinical gold standard for diagnosing the presence or absence of ICH (Lansberg, Albers, Beaulieu, & Marks, 2000) or SAH (Merino & Warach, 2010).

However, over the last decade, the use of magnetic resonance imaging (MRI) has increased in the investigation of hospitalized patients with acute stroke (Donnan, Dewey, & Davis, 2007; Neuman-Haefelin & Moseley, 2003, Chapter 3). This is despite its inception of more than 20 years ago (Donnan et al., 2007). Multimodal MRI has the potential to detect the presence, location, and size of acute cerebral infarcts (Merino & Warach, 2010), to facilitate the determination of the stroke etiology and to exclude other pathologies (Merino & Warach, 2010). It also can help determine the timing of the stroke thereby differentiating among acute, subacute, and old strokes (Fazekas et al., 2009; van Everdingen, van der Grond, Kappelle, Ramos, & Mali, 1998). Acute stroke neuroimaging protocols typically include non-contrast structural MRI imaging such as T1-weighted (T1), T2-weighted (T2), (Leiva-Salinas, Wintermark, & Kidwell, 2011), T2-weighted fluid-attenuated inversion recovery (FLAIR) (Leiva-Salinas et al., 2011), and T2 diffusion-weighted scans (Leiva-Salinas et al., 2011; Merino & Warach, 2010). Most acute stroke MRI protocols can be completed within 15 to 30 minutes (Leiva-Salinas et al., 2011), not including scan set-up, scan time, patient positioning, and patient management (Mikulis & Roberts, 2007).

**1.2.6. Magnetic resonance imaging technicalities**

Conventional MR imaging uses magnets ranging in strength from 0.5 (Hornak, 2011) to 3.0 Tesla (Currie, Hoggard, Craven, Hadjivassiliou, & Wilkinson, 2012), but most operate at 1.5 or 3.0 Tesla strengths (Currie et al., 2012). The primary magnet coils generate a constant magnetic field (B₀) (Currie et al., 2012). The magnetic field causes hydrogen protons in the brain
to align (Hornak, 2011; Bushong, 2003) and precess (wobble) due to the earth’s gravitational pull (Bushong, 2003). Subsequently, multiple sequential radiowaves are pulsed at the resonant frequency of precessing hydrogen nuclei (Bushong, 2003) to induce proton misalignment (Hornak, 2011). As protons regain their state of alignment, they emit the absorbed radiofrequency (Hornak, 2011), which decreases over time (relaxation time) (Bushong, 2003). Therefore, the time protons require to realign is called relaxation time (Roberts & Mikulis, 2007). There are two types of relaxation time (TR); one is longitudinal to the magnetic field, called T1, and the second is perpendicular or transverse to the magnetic field, called T2 (Hornak, 2011). The relaxation times are inherent properties of the tissue (Roberts & Mikulis, 2007) and partly determine tissue contrast (Bushong, 2003). Other determinants of tissue contrast include the time of repetition (RT) between sequential identical pulse sequences (Bushong, 2003) and the time of echo (TE), the time between the excitatory radiofrequency and the return time of the absorbed radiofrequency (RF) to the detector (Hornak, 2011).

### 1.2.7. T1- and T2-weighting

A T1-weighted signal has both a short RT and a short TE, while a T2-weighted signal has a long RT and a long TE (Hornak, 2011). T1 relaxation time involves the rate of return to equilibrium to longitudinal magnetization after a RF pulse (Bushong 2003). T1 usually involves a few hundred milliseconds (Bushong, 2003). However, the signal capture of T1 does not involve the total time to relaxation, but the rate of T1 relaxation (Currie et al., 2012), captured well prior to relaxation time (Currie et al., 2012). Tissue contrast in T1-weighted scans is a function of the difference in return of equilibrium across tissues, mediated in part by T1 relaxation time, rate, (Currie et al., 2012) and proton density (Bushong, 2003).
Similarly, T2-weighted scan contrast is derived by the shorter transverse tissue relaxation, recorded as the loss of transverse magnetization after the RF pulse, and proton density (Bushong, 2003). T2 relaxation ranges from 10 to 50 ms in tissue and up to a few hundred milliseconds for body liquids (Bushong, 2003). Although the difference in signal intensity recorded among tissues attributes tissue contrast (Currie et al., 2012), different weightings can be applied to the T2 acquisition, where minimal weighting involves capture of water proton density (concentration) and more maximal weighting includes longer waiting times (TE) prior to signal capture (Mori & Barker, 1999).

1.2.8. MRI modalities in acute ischemic stroke

T1 sequences result in darkened cerebrospinal fluid and bright well-differentiated brain tissue (Kloska, Wintermark, Engelhorn, & Fiebach, 2010; Nitz, 2006, Chapter 1). Consequently, they are useful in evaluating anatomical changes and aid in the diagnosis of dissections and hematomas (Jauch et al., 2013). However, given the long relaxation time, recording T1 sequences require a much longer data acquisition time than T2 sequences (Crawley & Henkelman, 1988). This is due to limited signal capture (number of slices) during the short time of repetition between radiofrequency pulses (Crawley & Henkelman, 1988). Therefore, in acute ischemic stroke T2 sequences are most rapidly acquired and the inherent tissue contrast is most useful to evaluate the acute stroke, as fluids (regions of acute ischemia) have high signal (Jauch et al., 2013). The T2 signal also is bright when edema is present (Kloska et al., 2010). It is primarily useful in the differential diagnosis of stroke and other neurological disease such as infection, cerebral microbleeds (Kloska et al., 2010), small vessel disease (Kloska et al., 2010) and prior stroke(s) (Kloska et al., 2010). However, standard T2 images cannot distinguish between prior and new ischemic stroke (Fazekas et al., 2009). Consequently, derived T2
sequences are necessary, including fluid-attenuated inversion recovery (FLAIR) (Kim, Kang, Hakimelahi, & Schaefer, 2012, Chapter 8), diffusion weighted imaging (DWI), and apparent diffusion coefficient (ADC) maps (Jauch et al., 2013). Hence, acute stroke protocols include both the standard T1 and T2 weighted images as well as derivatives of the T2 sequence to aid in identifying and quantifying the acute infarction (Tan, King, Durkin, Meagher, & Briley, 2006).

T2 FLAIR sequences make use of an additional component, called Inversion Time (TI), where the nuclear magnetization is set to a 180 degree inversion pulse prior to the 90 degree excitatory pulse (Bushong, 2003). A long TI suppresses the signal of different tissues, usually fat and water (Bushong, 2003). T2 FLAIR sequences involve heavily weighted T2 images and attenuation of the cerebrospinal fluid signal intensity using long inversion times (>1800ms) (Makkat et al., 2002). This method darkens the cerebrospinal fluid (CSF), allowing for optimal differentiation between infarction and CSF, especially where they are in close anatomical proximity (Makkat et al., 2002). Because T2 FLAIR scans attenuate cerebral spinal fluid brightness, they facilitate the identification of prior stroke or neurological disease (Kloska et al., 2010). Like standard T2 scans, T2-FLAIR scans are useful in identifying acute stroke, as they may show a positive ischemic infarct as early as three (Kloska et al., 2010) to six (Merino & Warach, 2010) hours after stroke onset, with continued evolution in the hyperintensity of the signal thereafter (Merino & Warach, 2010). Nevertheless, standard T2 and T2 FLAIR scans are inferior in their detection of acute stroke compared to diffusion weighted images (DWI), also derived from the T2 sequence (Rowley, Grant, & Roberts, 1999).

Diffusion weighted imaging relies on the motion variability of water molecules (Bykowski, Latour, & Warach, 2004), whereby the net movement of water molecules from high concentration regions to low concentration regions is captured (Bushong, 2003), leading to
increased intensity of the diffusion signal (Bykowski et al., 2004). DWI imaging parallels T2-weighted imaging in the capture of a T2 relaxation time of water molecules (Mori & Barker, 1999). For DWI signal capture, a second radiofrequency pulse is applied in the same direction and with the same timing as the initial radiowaves, but of opposite magnitude (Mori & Barker, 1999). The first radiowave gradient is called the dephasing gradient (diffusion weighting), while the second is called the rephrasing gradient (Mori & Barker, 1999). With these opposing gradients, the image capture becomes sensitive to water motion or diffusion (Mori & Barker, 1999). The signal loss or decay (diffusion) between the two radiowave pulses depends on the time between the two pulses (difference value), where increasing time between pulses allows for more diffusion of water molecules (Mori & Barker, 1999). Signal decay is commonly manipulated by signal strength of the radiowave pulses (large b value) (Mori & Barker, 1999). The extent of signal decay depends on the type of water (Mori & Barker 1999). When diffusion (mixing of different fluid molecules) is fast, the corresponding tissue is hyperintense, and when it is slow, the corresponding DWI signal is dark (Bushong, 2003). CSF is dark on DWI, while in areas of acute infarction, the diffuse water is “restricted”, secondary to cytotoxic edema, and the DWI signal is bright (Bushong, 2003).

Diffusion weighted imaging is particularly advantageous as it is most sensitive to hyperacute cerebral infarction (Mullins et al., 2002; Prichard & Grossman, 1999). A positive DWI scan distinguishes an acute or hyperacute infarct from an old infarct better than T2-weighted scans (Fazekas et al., 2009; Van Everdingen et al., 1998). When there is a lack of clarity regarding the time of stroke onset, mismatch between positive DWI scan and a negative FLAIR indicates onset within six hours of the time of imaging (Kloska et al., 2010). The DWI scan is hyperintense in the presence of an acute lesion, but not a prior lesion (Merino & Warach,
The sensitivity of the DWI sequence increases from 73% at three hours after the onset of stroke to 92% at 12 hours following stroke onset (Chalela et al., 2007). In fact, it is the only imaging method that can reliably detect ischemic parenchymal injury within minutes to a few hours after stroke onset (Merino & Warach, 2010; Keir & Wardlaw, 2000; Mohr et al., 1995; Mullins et al., 2002; Prichard & Grossman, 1999), but must be validated with its corresponding apparent diffusion coefficient (ADC) map (Mori & Barker, 1999).

The corresponding ADC map is derived from the DWI image capture, whereby a logarithmic scale is used to plot degree of signal decay, demonstrating the diffusion constant at each pixel (Mori & Barker, 1999). In the presence of acute cerebral infarction, the ADC map shows reduced water diffusion (restricted diffusion) and is hypointense (Mikulis & Roberts, 2007). ADC maps are useful in quantifying the diffusion signal abnormality and in eliminating the effect of “T2 shine through” (Rowley et al., 1999), which may, in fact, represent chronic stroke and edema rather than new stroke (Merino & Warach, 2010). Consequently, there may be mismatch between the hyperintense signal on the DWI image and degree of hypointensity on the ADC map. Mismatch may be due to T2 shine through, to artefact or to time dependent changes in degree of diffusion signal decay on the ADC map (Lansberg et al., 2001). The ADC remains hypointense for at least four days following stroke, increasing to a hyperintense signal in subacute or chronic stages (Schlaug, Siewert, Benfield, Edelman, & Warach, 1997) (Figure 1-1). Beginning within a week of stroke onset, and more markedly after the second week following the onset of stroke, the hypointense ADC signal becomes increasingly higher (Lansberg et al., 2001) (Figure 1-1).
Figure 1-1. T2-weighted, DWI, and ADC map signal intensities over time, by Dr. M. Law. Taken from http://www.radiologyassistant.nl/en/p483910a4b6f14/brain-ischemia-imaging-in-acute-stroke.html#i48410a3849b6c.

Given advances in MRI imaging of acute ischemic stroke and in the implementation of common protocols for multimodal MR imaging, validating the acute nature and timing of ischemic stroke with MRI scans is possible. Confirming an acute infarction by MRI scans provides a unique opportunity to measure brain behaviour relationships at a known point in time following stroke onset. Multimodal MRI facilitates quantification of neuroanatomical factors such as evolution of acute stroke, lesion localization, lesion volume, brain atrophy, white matter disease, and the presence of covert stroke.

1.2.9. Quantification of ischemic stroke MRI factors

Different measures of MRI scans can now quantify aspects of the ischemia and/or concomitant neurological disease, such as white matter hyperintensities (Valdes Hernandez et al., 2013), brain atrophy (Fjell et al., 2009), and covert stroke (Bernick et al., 2001), thereby elucidating the brain-behaviour relationship. A recent systematic review reported that the presence of white matter hyperintensities is associated with insidious brain disease (Debette &
Markus, 2010), often resulting from long-term hypertension (Fazekas, Chawluk, Alavi, Hurtig, 
& Zimmerman, 1987) or aging (Longstreth et al., 1996; Dufouil et al., 2001). In turn white 
matter disease may then contribute to a more rapid onset of incident stroke, lead to incident 
dementia, or contribute to mild cognitive deterioration (Debette & Markus, 2010) and motor 
impairments such as gait disturbance (Srikanth et al., 2009).

A common clinical measure of white matter disease involves expert ratings of the degree 
of deep white matter and periventricular hyperintensities (Fazekas et al., 1987) using visual 
ratings, called Fazekas scores. The Fazekas score usually takes periventricular hyperintensities 
(PVH) and deep white matter hyperintensities (DWMH) into account separately, based on 
evaluation of T2 or T2 FLAIR scans. Experts grade the degree of severity for each region on a 
scale from 0 (absent) to 3 (severe) (Fazekas et al., 1987). In both PVH and DWMH, a score of 0 
relates to the absence of hyperintensities. For PVH, a score of 1 reflects “periventricular caps or 
pencil-thin periventricular lining, a score of 2 reflects a smooth periventricular “halo”, and a 
score of 3 reflects “large confluent areas” (Fazekas et al. 1987). Ratings for DWMH include a 
score of 1 for punctuate foci, a score of 2 for confluence of foci, and a score of 3 for extension 
into the deep white matter (Fazekas et al. 1987). In addition to Fazekas scores, other measures of 
brain compromise, readily available from T2 MRI, include ratings of brain atrophy and 
quantification of covert brain lesions.

Like periventricular and deep white matter hyperintensities, brain atrophy may result due 
to aging (Fjell et al., 2009). Researchers have associated measures of whole brain atrophy with 
cognitive decline (Cardenas et al., 2011; Sluimer et al., 2008). Clinical evaluation of brain 
atrophy involves both whole brain (Sluimer et al. 2008) and regional appreciation of brain tissue 
volume changes (Fjell et al., 2009), based on cross-sectional T2 MRI slices (Sluimer et al.,
Whole brain atrophy can be evidenced by cortical contraction along brain margins (Sluimer et al., 2008) and ventricular enlargement (Frisoni, Fox, Jack, Scheltens, & Thompson, 2010). Localized atrophy can affect many regions in healthy aging throughout the brain (Fjell et al., 2009), especially the temporal lobe and prefrontal cortex (Fjell et al., 2009) with the potential for concomitant widening of the lateral ventricles and lateral fissures (Förstl et al., 1995). Researchers have recently begun to investigate the implications of brain atrophy beyond cognitive domains, including difficulty with motor function (Gross & Grossman, 2008), leading to impaired motor performance (Guo et al., 2001), such as apraxia (Gross & Grossman, 2008). A recent study associated brain atrophy with poor medical outcomes, such as lower respiratory infections (Okada et al., 2012). More work is needed to confirm the potential contribution of white matter disease and brain atrophy in the expression of impairments following ischemic stroke.

Another type of silent precursor to brain disease and certainly to the increased risk of future stroke is the presence of covert stroke (Bernick et al., 2001). By definition, individuals who sustain a “covert” (or “silent”) stroke are asymptomatic but still have an underlying central nervous system infarction (Saver, 2008) evident on neuroimaging (Bernick et al., 2001). Bryan et al (1999) reported a frequency of stroke-like lesions in 15% of persons with covert stroke compared to those without (Bernick et al., 2001). In addition to increased risk of stroke, covert subcortical lacunes are associated with cognitive compromise (Carey et al., 2008; Gold et al., 2005). The presence of covert infarctions in individuals over 60 years of age more than doubles the risk of dementia (Vermeer et al. 2003). More recently, a study found that the contribution of incidental covert infarcts in the opposing hemisphere to a chronic stroke lesion increased the volume-impairment association (Alexander et al., 2010). Tanne and Levine (2009) argue that due
to the predominance of covert stroke, the scope and effects of the stroke spectrum are grossly underrepresented in capture of overt stroke. The influence of incidental covert lesions should therefore be considered in studies evaluating brain-behaviour relationships (Alexander et al., 2010). In summary, advances in MR imaging make it possible to associate acute stroke factors with measures of stroke severity (Keir & Wardlaw, 2000; Schaefer, Grant, & Gonzalez, 2000; Tan et al., 2006; Wardlaw, Keir, Bastin, Armitage, & Rana, 2002). Multimodal imaging provides the impetus to evaluate a range of neuroanatomical factors in patients with and without focal neurological impairments, and to derive testable models to predict their expression (Wintermark et al., 2008).

1.3. Sequelae of ischemic stroke: Dysphagia, Dysarthria, and Aphasia

Ischemic stroke survivors often experience multiple co-occurring impairments. Predominantly motor impairments resulting from ischemic stroke include hemiplegia (Mazaux, Barat, Borde, & Arne, 1980; Petrilli et al., 2002), incontinence (Du, Fu, & Liu, 2010; Dumoulin, Korner-Bitensky, & Tannenbaum, 2007), dysarthria (Lawrence et al., 2001; Lubart et al., 2005), apraxia of speech (Ogar, Slama, Dronkers, Amici, & Gorno-Tempini, 2005), and dysphagia (Guyomard et al., 2009; Martino et al., 2005). Broad definitions include weakness or paralysis on one side of the body for hemiplegia (Teasell, 1991), complaints of urinary urgency or leakage for incontinence (Abrams et al., 2003), difficulty with speech execution for dysarthria (Duffy, 1995), difficulty with motor programming of speech for apraxia of speech (Ogar et al., 2005), and deficits in oropharyngeal swallowing physiology for dysphagia (Martino et al., 2005). Other impairments resulting from ischemic stroke include depression (Carota, Staub, & Bogousslavsky, 2002), cognitive deficits (Khateb et al., 2007; Lesniak, Bak, Czepiel, Seniow, & Czlonkowska, 2008), and/or aphasia (Engelter et al., 2006; Hillis & Heidler, 2002). Depression
resulting from stroke is defined as major depression, minor depression, or other depressive disorders (Williams, 2005). Cognitive deficits include difficulties with attention, memory, language, and/or executive functions (Lesniak et al., 2008). Cognitive deficits in language, termed “aphasia”, involve word retrieval difficulties (Helm-Estabrooks & Albert, 1991) with or without other linguistic deficits (Chapey & Hallowell, 2001).

After hemiparesis, dysphagia, dysarthria, and aphasia are the most frequent (Lubart et al., 2005), and they may also co-occur with high frequency after stroke (Martin & Corlew, 1990; Trapl, Eckhardt, Bosak, & Brainin, 2004; Guyomard et al., 2009). Still, dysphagia, dysarthria, and aphasia are likely underestimated, particularly in the hyperacute stage, given the lack of routine detection (Flowers, Silver, Fang, Rochon, & Martino, 2013; Altman et al., 2012; Flamand-Roze et al., 2011; Forster et al., 2013). Dysphagia, dysarthria, and aphasia may persist well beyond the acute stage (Canbaz, Celebisoy, Ozedemirkiran, & Tokucoglu, 2010; Sala et al., 1998; Mann, Hankey, & Cameron, 1999; Tsouli, Kyritsis, Tsagalis, Virvidaki, & Vemmos, 2009).

Dysphagia, dysarthria and aphasia can precipitate both acute and chronic negative outcomes. Dysphagia may lead to malnutrition (Crary et al., 2013), dehydration (Crary et al., 2013), aspiration pneumonia (Mann et al., 1999; Martino et al, 2005), increased length of stay (Guyomard et al., 2009), and death (Altman, Yu, & Schaefer, 2010; Sala et al., 1998). Stroke survivors with dysphagia have a risk of pneumonia three times higher than those without dysphagia, and those with severe dysphagia incur a risk of pneumonia eleven times higher than those without (Martino et al., 2005). One study reported mortality in 72 of 187 (40%) patients with acute stage dysphagia, six months after stroke (Sala et al., 1998). A second study reported that 26 of 128 (20%) of their acute stroke patients had had chest infections at the six month
follow up (Mann et al., 1999). They further reported that 24 of these 26 patients (92%) had had dysphagia in the acute stage. In addition, 63% of surviving patients with dysphagia still had persistent swallowing impairments (Mann et al., 1999).

The detrimental effects of post-stroke dysarthria are less well understood. Dysarthria can result in social and emotional disturbance and perceptions of stigmatization (Dickson, Barbour, Brady, Clark, & Paton, 2008). Canbaz et al (2010) followed 55 acute single infarct stroke patients with dysarthria, demonstrating continued impairment in 47% at three months. They noted a trend towards a better prognosis in patients with right-sided lesions (Canbaz et al., 2010). However, no studies have reported the comorbidities or outcomes of dysarthria beyond three months following acute stroke onset.

Persons with post-stroke aphasia suffer from depression (Kauhanen et al., 2000) and altered quality of life (Hilari, 2011). Negative outcomes of post-stroke aphasia may include decreased participation in treatment planning and rehabilitation (Berthier, 2005), increased length of stay (Bersano, Burgio, Gattinoni, & Candelise, 2009; Guyomard et al, 2009), and death (Bersano et al., 2009; Guyomard et al., 2009). Despite decreased participation in rehabilitation (Berthier, 2005), stroke survivors with aphasia use more rehabilitation services than other stroke survivors (Bersano et al., 2009; Dickey et al, 2010), increasing their cost of care (Ellis, Simpson, Bonilha, Mauldin, & Simpson, 2012). Still, they return to work less frequently than other stroke survivors (Black-Schaffer & Osberg, 1990; Dalemans, De Witte, Wade, & Van den Heuvel, 2008; Kauhanen et al., 2000; Ross Graham, Pereira, & Teasell, 2011).

Some studies have documented a poor prognosis for recovery from aphasia after stroke (Pedersen, Jørgensen, Nakayama, Raaschou, & Olsen, 1995; Pedersen, Vinter, & Olsen, 2004; Laska, Hellblom, Murray, Kahan, & Von Arbin, 2001). Pedersen et al. (1995) demonstrated
that, of 330 patients with aphasia, 41% had died, and 50% of survivors still had aphasia at six months. Kauhanen et al. (2000) reported persistent aphasia in 23% of 106 first acute ischemic stroke patients after one year. Similarly, Pedersen et al (2004) followed 103 first-ever and recurrent acute stroke patients for one year, demonstrating that 60% still had aphasia at one year. At a follow-up point of 18 months post stroke onset, Laska et al. (2001) demonstrated that 43 of 119 (36%) patients with aphasia had died and that 43% of the survivors still had aphasia.

Overall, the long term prognosis for aphasia is poor, and is associated with increased probability of death for 10 years following stroke (Tsouli et al., 2009).

The rapid expression of focal neurological deficits early in the acute phase coupled with the high frequency of ischemic stroke compared to other stroke types provides a unique opportunity to study the frequency, co-occurrence and predictors of multiple co-occurring impairments in the hyperacute stage of stroke. Given the high frequency of dysphagia, dysarthria, and aphasia after ischemic stroke and the resulting detrimental outcomes associated with their presence, it is important to investigate the incidence and precursors of these three impairments after stroke. Estimating their incidence and co-occurrence in homogeneous stroke samples is an important first step to inform clinical practice behaviours surrounding their management. Also identifying clinical and neuroanatomical predictors of their presence will aid in developing measures to improve management early in the acute stages of stroke.

1.4. Guidelines for the acute evaluation of dysphagia, dysarthria, and aphasia

Acute management of dysphagia, dysarthria, and aphasia should involve timely screening and assessment (CSS, 2013; The Royal College of Physicians, 2008); College of Speech-Language Pathologists and Audiologists of Ontario [CASLPO], 2007). The Canadian Association of Speech-Language Pathologists and Audiologists (CASLPO) developed practice
standards and guidelines for dysphagia, promoting dysphagia screening in all etiologies, including stroke (CASLPO, 2007). Similarly, the Canadian Stroke Strategy (CSS) developed recent best practice recommendations for stroke care (CSS, 2013), specifically addressing routine screening for dysphagia at the onset of stroke.

CASLPO has not yet developed practice guidelines for screening or assessment of dysarthria and aphasia following stroke. However, the CSS (2013) recommends evaluating dysarthria early after symptom onset to facilitate a differential diagnosis of stroke. The CSS guidelines (2013) promote acute stage need assessments in all patients, including screening for communication impairments. Aphasia screening is recommended within the umbrella of vascular cognitive deficits (CSS, 2013). Screening failures should lead to in-depth assessment of vascular cognitive deficits including aphasia (CSS, 2013). The role of the SLP is to assess the severity of communication impairments and to undertake therapy where indicated (CSS, 2013). Multiple assessments may be necessary first to determine recovery, and then to guide management at transition points along the continuum of care (CSS, 2013).

For dysphagia, best practice guidelines direct all patients with screening failure for assessment by speech-language pathologists (CASLPO, 2007). Assessment includes clinical and/or instrumental assessment as deemed suitable (CASLPO, 2007). The CASLPO dysphagia guidelines further recommend that any dysphagia management should involve the consideration of a patient’s communication status (CASLPO, 2007). Referral to the speech-language pathologist for communication assessments promotes goal-directed initial bedside assessments and/or standardized assessments, facilitating therapeutic interventions and/or patient education.

Detailed assessments of dysphagia and communication, whether informal or by standardized test battery, or instrumental evaluation, should begin with comprehensive patient
history, patient report of symptoms (where possible), and examination of the oral mechanism and oral motor function (Duffy, 1995; Schulze-Delrieu & Miller, Chapter 5). The oral examination facilitates differential diagnosis of the impairments and elucidates the contribution of potential coexisting impairments such as dysphagia and dysarthria, dysarthria and aphasia, or aphasia and apraxia of speech or other combinations. Clinician decisions ultimately determine the presence versus absence of a given impairment.

Given that there is a lack of available rapid gold standard assessments for all three impairments, clinicians often determine the presence, severity, and/or classification of the impairments using informal bedside observation (Foster, Worrall, Rose, & O’Halloran, 2013). In select patients, they may initiate instrumental swallowing assessment and standardized tests to document severity and/or classifications of the impairments. Large-scale observational research investigating dysphagia, dysarthria, and aphasia should ideally use informal clinical assessment, following routine screening. However, in the absence of screening for risk detection, at least cursory assessments should be attempted in all patients. Informal assessments of the impairments in observational research often serve as the primary measure and include involvement by a range of health professionals (Simmons-Mackie et al., 2007). We present a brief overview of available screening and assessment methods including existing tools for dysphagia, dysarthria, and aphasia following acute stroke.

1.4.1. Dysphagia screening and assessment

A recent systematic review identified four properly validated and accurate dysphagia screening tools for use after stroke (Schepp, Tirschwell, Miller, & Longstreth, 2012). They include the Barnes Jewish Hospital Stroke Dysphagia Screen (Edmiaston, Connor, Loehr, & Nassief, 2010), the Modified Mann Assessment of Swallowing Ability (Antonios et al., 2010),
the Emergency Physician Swallowing Screening (Turner-Lawrence, Peebles, Price, Singh, & Asimos, 2009), and the Toronto Swallowing Bedside Screening Test (TOR-BSST©) (Martino et al., 2009). Where there is risk for dysphagia, identified from screening, assessment by a speech-language pathologist or other trained professional is recommended (CSS, 2013).

Unlike screening tools for dysphagia, few dysphagia assessment tools exist with psychometric validation. One such tool, validated in patients with first-ever stroke, is The Mann Assessment of Swallowing Ability (MASA) (Mann, 2002; Carnaby-Mann & Lenius, 2008). It can be lengthy to administer and has limitations relative to the evaluation of pharyngeal stage compromise(s) (Mann, 2002). Due to the lengthy administration time of the MASA and to a lack of standardized assessment protocols, speech-language pathologists rely on informal bedside assessments (Flamand-Roze, Cauquil-Michon, & Denier, 2012). Initiation of physiologic assessment remains subject to a patient’s medical status and follows from the oral mechanism and motor examinations (Schulze-Delrieu & Miller, 2003, Chapter 5). The subsequent bedside evaluation of saliva swallows and/or administration of bolus consistencies permits a subjective determination of oropharyngeal swallowing physiology and function. Although adequate for use in the evaluations of oral preparatory stage swallowing function, bedside assessment relies on surrogate signs of compromise in the oral transit and pharyngeal stages (Schulze-Delrieu & Miller, 2003, Chapter 5). Potential pharyngeal stage compromise, suspicion of silent aspiration, or treatment evaluation warrant instrumental examination (CASLPO, 2007).

Instrumental assessments of dysphagia include x-ray examination by videofluorscopy (VFS) or fiberoptic endoscopic evaluation of the swallow (FEES) (Rao, Brady, Chaudhuri, Donzelli, & Wesling, 2003). Instrumental assessments by VFS and/or FEES are gold standard tests for oropharyngeal dysphagia, but may require lengthy preparation prior to a five to ten
minute evaluation. Depending on the regional care guidelines, the frequency of FEES versus VFS may differ (Dziewas et al., 2013). FEES is a controlled act established by the College of Physicians and Surgeons of Ontario and, if delegated to SLPs, requiring adequate training and medical supervision (Dziewas et al., 2013). Alternatively, concurrent online collaboration with otolaryngologists or other physicians may constitute a means to evaluate dysphagia (Dziewas et al., 2013). VFS may require two or more health professionals, including the x-ray technician, speech language pathologist, and/or radiologist, depending on requirements at a given facility. One standard protocol exists for videofluoroscopic investigation of oropharyngeal swallowing after stroke, detailing recommendations for bolus type, amount, and timing of administration (Logemann, 1993). Advantages of instrumental assessments include digital signal capture for later review, the potential to evaluate results with validated rating scales of oropharyngeal physiology and function (Rosenbek, Robbins, Roecker, Coyle, & Wood, 1996), and rapid online confirmation of negative sequelae such as aspiration (Logemann, 1993). Observational research evaluating dysphagia in the acute setting is unlikely to use instrumental assessment in all patients, but may conduct routine screening, followed by dysphagia assessments.

1.4.2. Dysarthria screening and assessment

There are few rapid screening tools for dysarthria despite their potential contributions to diagnosing stroke early after onset (CSS, 2013). Dysarthria is one of the three heralding symptoms of stroke, according to the Face Arm Speech Test (FAST) (Harbison et al., 2003). Symptom report of speech disturbance provides the front line physician with information akin to a screen for risk of potential dysarthria or aphasia. Signs of speech disturbance present in over 75% of patients with stroke on neurological examination (Mohd Nor et al., 2004). Consequently, the CSS recommends same day physician evaluation of stroke in patients presenting with speech
symptoms (CSS, 2013). Emergency room physicians may be the first to assess dysarthria, especially with paramedic or patient confirmation of speech symptoms at stroke onset. The neurological examination may also draw suspicion of dysarthria in the presence of lower facial paresis ideally leading to perceptual speech evaluation.

In the absence of prior identification of dysarthria, stroke severity scales may result in the first documentation of its presence. Many stroke severity scales, such as the CNS (Côté et al., 1989), include at least a binary documentation of the presence of absence of speech deficit. Although useful in rapid detection of dysarthria, stroke severity scale items do not provide direction for therapy. Routine referrals to speech language pathology may not result from dysarthria, given lack of appreciation of its negative ramifications, especially in the presence of concomitant gross motor or cognitive deficits. The CSS (2013) does not directly mandate the assessment of dysarthria beyond its usefulness in initial stroke diagnosis. However, the Royal College of Physician stroke guidelines (2008) recommend referral to speech-language pathology for identification of speech impairments in the event of unclear or unintelligible speech.

In addition to the oral motor examination, the assessment of dysarthria includes perceptual evaluation of respiratory, voice and phonemic and suprasegmental features of speech (Duffy, 1995). The perceptual speech evaluation often includes diadochokinetic (DDK) syllable rates, whereby the patient produces a stream of rapid single (e.g. /papapa/ or /tatata/) or alternating syllables (e.g. /patakapataka/) for five seconds. The speed, rhythm, and accuracy of DDK productions provides a means to document deviations from normative data (Duffy, 1995). Features of the perceptual speech evaluation address multiple motor domains: strength, speed, range, steadiness, tone, and movement accuracy (Duffy, 1995). Consequently, a comprehensive dysarthria assessment may suggest the neural substrate for its classification, facilitating treatment.
planning. The speech language pathologist may also supplement perceptual evaluation with acoustic measures of speech and voice (Kent & Kim, 2003).

There are very few gold standard test batteries for acute stage dysarthria. The only standardized test for the classification of dysarthria types is the Frenchay Dysarthria Assessment (FDA) (Enderby, 1983; Duffy, 1995), validated in patients with stable dysarthria (Enderby, 1983). It requires up to 20 minutes for its administration (Enderby, 1983), but its assessment of speech intelligibility requires transcription following administration (Enderby, 1983). One other standardized test, the Assessment of Intelligibility in Dysarthric Speakers (AIDS) (Yorkston & Beukelman, 1981), includes only a 10-minute measure of speech intelligibility but also requires transcription by a naïve listener. In summary, the evaluation of dysarthria in an acute setting, especially in large cohorts of patients, is likely to rely on clinical observation of a limited set of auditory-perceptual features of its presence.

1.4.3. Aphasia screening and assessment

Validated screens for vascular cognitive impairment, such as the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) or the Montreal Cognitive Assessment (MoCA) (Nasreddene et al., 2005), contain subtests specific to language impairments, naming and repetition. In addition, other subtests requiring language may implicitly draw suspicion of aphasia. Because of this, clinicians other than SLPs may rely on subtests for aphasia within cognitive screening tools or make use of aphasia subtests in stroke severity scales, such as the NIHSS (Brott et al., 1989), the CNS (Côté et al., 1989), and the SSS (Scandinavian Stroke Study Group, 1985).

A number of screening tools exist for aphasia, but they are fundamentally different from those for dysphagia given that their length of administration usually precluded use in the acute
setting. Available aphasia screens include the Frenchay Aphasia Screening Tests (FAST) (Enderby, Wood, Wade, & Langton Hewer, 1987; Enderby & Crow, 1996; Al-Khawaja, Wade, & Collin, 1996), the Mississippi Screening Test (MAST) (Nakase-Thompson et al., 2005), Language Screening Test (LAST) (Flamand-Roze et al., 2011; Flowers et al., 2012), Acute Aphasia Screening Protocol (AASP) (Crary, Haak, & Malinsky, 1989), Aphasia Screening Test (AST) (Reitan, 1991), Bedside Evaluation Screening Test, Second Edition (BEST-2) (Fitch-West & Sands, 1998), and the Sheffield Screening Test for Acquired Language Disorders (Syder, Body, Parker, & Boddy, 1993). Many of these measures lack comprehensive validation against gold standard batteries (Enderby et al., 1987), are too lengthy to complete as a routine screens (Syder et al., 1993), include culturally sensitive items, (Nakase-Thompson et al., 2005), are not available in English (LAST), or function as short assessments (Crary et al., 1989; Reitan, 1991; Fitch-West & Sands, 1998).

Aphasia assessment relies heavily on bedside clinical judgment in acute stroke patients. Multiple health care professionals are likely to assess aphasia, including physicians, neuropsychologists, stroke nurses, and speech language pathologists. Health care professionals may initially conduct rapid bedside assessments using well-rehearsed items from cognitive or language batteries and/or create impromptu context-driven questions. Time-permitting and dependent on patient stability, speech language pathologists may attempt acute aphasia assessment using standardized language batteries. Common batteries include the AASP (Crary et al., 1989), the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass & Kaplan, 1983), the Western Aphasia Battery (WAB) (Kertesz, 1982), and the Aphasia Diagnostic Profiles (ADP) (Helm-Estabrooks, 1992). Of these, only two (i.e., WAB and AASP) have performed acute stage validation in stroke patients (Shewan & Kertesz, 1980; Crary et al., 1989; Kertesz &
McCabe, 1977). The WAB involved validation in 74 acute stroke patients, from zero to 40 days post stroke onset (Kertesz & McCabe, 1977). The AASP was shorter to administer when tested in 48 acute stroke patients, from three to 30 days post stroke onset (Crary et al., 1989). Although language batteries comprise the gold standard assessment of aphasia, they may not be suitable in the acute stage, either because they lack validation in the acute setting (Goodglass & Kaplan, 1983; Helm-Estabrooks, 1992) or due to lengthy administration (Kertesz, 1982; Crary et al., 1989).

1.5. Frequency and Co-Occurrence of Dysphagia, Dysarthria, and Aphasia

1.5.1. Dysphagia

Dysphagia is defined as “oropharyngeal dysphagia”, evidenced by abnormal swallowing physiology of the upper aerodigestive tract (Martino et al., 2005). The incidence of dysphagia nears 55% in the acute stage of stroke (Guyomard et al., 2009; Martino et al., 2005; Martino et al., 2009), based on a systematic review (Martino et al., 2005) and two more recent studies (Guyomard et al., 2009; Martino et al. 2009). The systematic review included 24 articles, which documented oropharyngeal dysphagia by clinician evaluation based on screening, bedside examination or instrumental testing (Martino et al., 2005). It considered the frequency of dysphagia in acute and rehabilitation settings, with 19 of the 24 articles reporting acute dysphagia (Martino et al., 2005). Based on the systematic review (Martino et al., 2005), five acute studies (Barer, 1989; Gordon, Hewer, & Wade, 1987; Hinds & Wiles, 1998; Odderson, Keaton, & McKenna, 1995; Wade & Hewer, 1989) evaluated dysphagia through screening, with a combined incidence of 40% (n=438/1105). All reported dysphagia after hemorrhagic and ischemic stroke, with the exception of one study, reporting only ischemic stroke (Odderson et al., 1995). The study reporting dysphagia after ischemic stroke demonstrated a comparable
dysphagia frequency of 39 percent (n=48/124). All five studies included lesions in any neuroanatomical region, except one, which restricted sample selection to those with hemispheric stroke (Barer, 1989), demonstrating a dysphagia frequency of 29% (n=105/357).

A further eight (Daniels et al., 1998; Hamdy et al., 1997; Lim et al., 2001; Mann et al., 1999; Parker et al., 2004; Schelp, Cola, Gatto, da Silva, & de Carvalho, 2004; Sharma, Fletcher, Vassallo, & Ross, 2001; Smithard et al., 1997) of the 19 acute articles from the systematic review (Martino et al., 2005) reported dysphagia based on clinical bedside evaluation, with a combined dysphagia frequency of 54% (n=407/748). All eight articles included hemorrhagic and ischemic stroke types in their samples, with six involving patients with recurrent stroke (Daniels et al., 1998; Lim et al., 2001; Parker et al., 2004; Schelp et al., 2004; Sharma et al., 2001; Smithard et al., 1997) and two first ever stroke (Mann et al., 1999; Hamdy et al., 1997). In the six articles that included recurrent stroke, five reported whole brain incidence figures for dysphagia, while one reported the incidence of dysphagia after hemispheric stroke only (Parker et al., 2004). The five articles reporting whole brain results after clinical evaluation had a combined incidence of 60%, while the one article on hemispheric stroke had an incidence of 39% (Parker et al., 2004). The two articles reporting results for first ever ischemic or hemorrhagic stroke differed in that one reported whole brain results (Mann et al., 1999), while the other reported single hemisphere stroke only (Hamdy et al., 1997), with dysphagia frequencies of 51% and 40%, respectively.

The final six articles described in the systematic review by Martino et al. (2005) involved instrumental assessment of dysphagia (Daniels & Foundas, 1999; Mann et al., 1999; Lim et al., 2001; Daniels et al., 1998; Kidd, Lawson, Nesbitt, & MacMahon, 1993; Hamdy et al., 1998), where one used fiberoptic endoscopic evaluation of swallowing (FEES) (Lim et al., 2001) and
the remaining five studies used videofluoroscopy (VFS). Three studies included broad videofluoroscopic measures of dysphagia (Daniels & Foundas, 1999; Mann et al., 1999; Hamdy et al., 1998) while three restricted VFS or FEES analysis to aspiration (Lim et al., 2001; Daniels et al., 1998; Kidd et al., 1993). Three studies reported dysphagia in all stroke types, also allowing for recurrent stroke in their samples (Daniels & Foundas, 1999; Lim et al., 2001; Daniels et al., 1998). One had a broad VFS measure of dysphagia, with a frequency of 78% (Daniels & Foundas, 1999), while the other two reported aspiration only, with a combined dysphagia frequency of 45% (Lim et al., 2001; Daniels et al., 1998). Only one article reported a broad measure of dysphagia by VFS in a sample of first ever stroke patients, with any stroke type, documenting a frequency of 64% (Mann et al., 1999). A second study reported the frequency of dysphagia in a sample of first ever stroke patients, with any stroke type, limited to aspiration by VFS, with a dysphagia frequency of 43% (Kidd et al., 1993). Finally, the remaining study reported a broad measure of dysphagia by VFS in single hemisphere stroke patients, documented a frequency of 71% (Hamdy et al., 1998).

Since the systematic review, Guyomard et al. (2009) undertook a retrospective observational study involving 2983 acute stroke patients with hemorrhagic stroke, ischemic stroke or stroke of undermined etiology. Thirteen percent had prior history of stroke (Guyomard et al., 2009). The authors found an incidence of 51% dysphagia in the entire sample. Dysphagia was defined by any difficulty swallowing saliva, other liquids, or solids (Guyomard et al., 2009). The dysphagia protocol included nursing and/or physician screening for all patients (Guyomard et al., 2009), followed by speech language therapy assessment of swallowing function in patients at risk for dysphagia (Guyomard et al., 2009). In 75% of patients with ischemic stroke, dysphagia occurred in 40% (n=927/2318).
The second recent study involved a methodologically rigorous dysphagia screening validation involving 311 stroke patients, of whom 103 were acute (Martino et al., 2009). Randomly selected patients with either ischemic or hemorrhagic stroke and NIHSS scores of >4 underwent videofluoroscopic evaluation (Martino et al., 2009). Twenty-four randomly selected patients had an acute stroke, of whom 54% had dysphagia, based on a broad videofluoroscopic measure of oropharyngeal swallowing (Martino et al., 2009).

In summary, the incidence of dysphagia after acute stroke is typically higher in samples involving recurrent stroke and/or patients with lesions throughout the whole brain. The trend is toward a slightly lower incidence after hemispheric stroke, except when evaluated by videofluoroscopy (Hamdy et al., 1998). No recent studies have documented the incidence of dysphagia specific to first acute ischemic stroke. Overall, there is a paucity of literature describing dysphagia in large homogeneous prospectively enrolled patient samples.

1.5.2. Dysarthria

Dysarthria is defined as an impairment involving muscular execution of speech (Duffy, 1995), resulting from damage to the central or peripheral nervous systems (Darley, Aronson, & Brown, 1969). The literature reporting the incidence of dysarthria comprises homogeneous samples of acute stroke patients. Samples involving first strokes of hemorrhagic and/or ischemic etiologies demonstrated dysarthria frequencies ranging from 8% (Bogousslavsky et al., 1988) to 42% (Lawrence et al., 2001). More specifically, three studies have reported the incidence of dysarthria after a first ischemic stroke (Lawrence et al., 2001; Trapl et al., 2004; Kumral et al., 2007). Lawrence et al (2001) defined dysarthria as disturbance in speech motor control, documenting its presence in 1259 first-ever stroke patients according to hemorrhagic and ischemic stroke types. Of 864 patients with ischemic stroke, 499 had dysarthria (58%)
Lawrence et al., 2001). Trapl et al. (2004) demonstrated a 32% incidence of dysarthria in 91 acute ischemic stroke patients, using subtests from standardized tests of aphasia. Finally, Kumral et al. (2007) identified a sudden onset of dysarthria in 9% of their 1160 acute ischemic stroke patients, based on speech production and an adapted standardized test (Kumral et al., 2007).

The wide range in the reported frequency of dysarthria may relate to different assessment methods and the nature of the onset of speech disturbance, whether rapid (Kumral et al., 2007) or progressive. In fact, reported frequencies of dysarthria may often underrepresent its true incidence when assessment does not include the full range of perceptual features of speech (Mackenzie, 2011). Also, studies reporting sudden onset of dysarthria as sole or primary presenting symptom may represent a small heterogeneous subset of stroke patients with dysarthria.

### 1.5.3. Aphasia

Aphasia is defined as an acquired language impairment characterized by anomia (Helm-Estabrooks & Albert, 1991) and/or other language deficits (Chapey & Hallowell, 2001), evidenced in receptive or expressive language modalities, including verbal expression, verbal comprehension, reading and/or writing (Chapey & Hallowell, 2001). Overall, studies reported the incidence of aphasia ranging from 15% (Inatomi et al., 2008) to 41% (Guyomard et al., 2009) after stroke onset. Those documenting aphasia in unselected stroke samples, involving ischemia, intracerebral hemorrhage, and subarachnoid hemorrhage, reported frequencies ranging between 21% (Hier, Yoon, Mohr, Price, & Wolf, 1994) and 35% (Dickey et al., 2010). Samples involving all three etiologies for patients with first-ever stroke have reported slightly lower frequencies ranging from 17% (Hilari, 2011) to 30% (Stegmayr, Asplund, & Wester, 1994). In studies that excluded SAH (reporting only ischemic stroke and ICH), frequencies ranged from 23% (Hier et
Four studies documented the frequency of aphasia in patients with first ever ischemic stroke (Lubart et al., 2005; Croquelois & Bogousslavsky, 2011; Engelter et al., 2006; Hilari, 2011), reporting frequencies ranging from 23% (Lubart et al., 2005) to 35% (Tsouli et al., 2009).

First, Lubart et al. (2005) derived a 23% frequency of aphasia in 140 first ever acute ischemic stroke patients in a geriatric facility. The aphasia assessment consisted of a clinical assessment by a neurologist on admission and daily for one week thereafter (Lubart et al., 2005). Second, Croquelois and Bogousslavsky (2011) identified an aphasia frequency of 26% in a large observational cohort of 5880 first-ever ischemic stroke patients. Aphasia diagnosis included bedside examination by a physician for language deficits in verbal fluency, comprehension, naming, and repetition tasks (Croquelois & Bogousslavsky, 2011). Third, Engelter et al (2006) identified an aphasia frequency of 30% in an acute series of 269 first-ever ischemic stroke patients. A neurologist conducted a clinical assessment, based on items from the NIHSS scale (Engelter et al., 2006). Finally, Tsouli et al. (2009) documented aphasia in 35% of 2022 patients with a first-ever ischemic stroke. A stroke neurologist identified aphasia on admission to hospital (Tsouli et al., 2009), documenting severity according to the aphasia item of the Scandinavian Stroke Scale (SSS) (Scandinavian Stroke Study Group, 1985). The combined frequency of aphasia in homogeneous samples of first ischemic stroke patients was 29% at admission.

1.5.4. Co-occurrence

Only three studies have reported the co-occurrence of dysphagia, dysarthria, and aphasia after acute stroke. Most recently, Guyomard et al. (2009) reported a 28% co-occurrence of dysphagia and aphasia in their sample of 2983 acute stroke patients, involving ischemic and hemorrhagic etiologies. Trapl et al (2004) reported that 10% of 91 acute ischemic stroke patients
had both dysarthria and aphasia (Trapl et al., 2004). Finally, Lapointe and McFarland (2004) documented that of 91 acute patients with dysphagia, 79% had concomitant communication impairments, such as dysarthria, aphasia, and voice and cognitive communication impairments. Twenty-six percent of the patients with dysphagia had dysarthria and 13% had aphasia (Lapointe & McFarland, 2004). The sample involved retrospectively identified patients with an acute stage videofluoroscopic assessment, not limited to stroke patients (Lapointe & McFarland, 2004). Thus, the proportion of patients with a precipitating etiology of stroke was unclear (Lapointe & McFarland, 2004). Given the limited body of literature addressing the co-occurrence of dysphagia, dysarthria, and aphasia after first-ever acute ischemic stroke, further investigation is warranted.

1.6. Clinical Correlates and Predictors of Dysphagia, Dysarthria, and Aphasia

1.6.1. Dysphagia

Clinical correlates of post-stroke dysphagia include previous stroke with disability (Guyomard et al., 2009), advancing age at stroke onset (Guyomard et al., 2009), and atrial fibrillation (Gattellari, Goumas, Aitken, & Worthington, 2011). One study used a sample of patients with first ischemic stroke (Gattellari et al., 2011), while the other included acute hemorrhagic and ischemic stroke (Guyomard et al., 2009). Guyomard et al. (2009) found significant differences for previous stroke with disability, measured by the premorbid Rankin score, and advancing age in those with dysphagia compared to those without. Gattellari et al. (2011) demonstrated significant differences for the presence of atrial fibrillation, where a higher proportion of patients with dysphagia had atrial fibrillation compared to those without. Although the two studies reported significant differences in patients with and without dysphagia, they failed to report effect sizes in their comparisons. Because no studies to date have reported effect sizes...
sizes to derive clinical correlates of dysphagia, models for clinically-driven predictive factors are sorely lacking but needed desperately.

1.6.2. Dysarthria

Studies reporting correlates of dysarthria have not derived predictive models. In fact, the same study reporting an association between atrial fibrillation and dysphagia also reported significant differences for the presence of atrial fibrillation in patients with and without speech impairment (Gattellari et al., 2011). A higher proportion of patients with speech disturbance had atrial fibrillation than those without (Gattellari et al., 2011). Because the authors did not define speech disturbance, it is possible that the measure included other impairments affecting the speech system, such as expressive aphasia or apraxia of speech.

Two additional studies described risk factors associated with the presence of dysarthria but only in patients with dysarthria (Kumral, Çelebisoy, Çelebisoy, Canbaz, & Çalli, 2007; Urban et al., 2001). The previously described investigation by Kumral et al (2007) involving 101 acute first ischemic stroke patients with dysarthria showed that the five most frequent risk factors were hypertension (69%), hypercholesterolemia (59%), diabetes (39%), cigarette smoking (36%), and atrial fibrillation (16%). Similarly, in a study involving 68 first ischemic stroke patients with dysarthria, identified by auditory-perceptual evaluation, Urban et al (2001) found four frequent risk factors for dysarthria: hypertension (81%), diabetes (38%), hypercholesterolemia (34%), and cigarette smoking (22%). Both studies reported comparable frequencies for the most common ischemic etiologies in patients with dysarthria, as 41% (Kumral et al., 2007) and 53% (Urban et al., 2001) for small vessel disease, 15% (Kumral et al., 2007) and 4% (Urban et al., 2001) for large artery disease, and 12% (Urban et al., 2001) and 10% (Kumral et al., 2007) for cardioembolism. Nevertheless, all three studies reporting clinical
correlates of dysarthria failed to provide predictive models for clinical factors associated with dysarthria.

### 1.6.3. Aphasia

Aphasia is preferentially associated with previous stroke (Guyomard et al., 2009), with increasing age (Bersano et al., 2009; Guyomard et al., 2009; Engelter et al., 2006; Inatomi et al., 2008; Tsouli et al., 2009), among women (Bersano et al., 2009), with stroke severity (Inatomi et al., 2008; Tsouli et al., 2009), with atrial fibrillation (Engelter et al., 2006; Tsouli et al., 2009; Bersano et al., 2009), with cardioembolic etiology (Engelter et al., 2006), and with the presence of multiple etiologies for ischemic stroke (Engelter et al., 2006).

Two studies documented associations between clinical factors and aphasia (Guyomard et al., 2009; Bersano et al., 2009), while the remaining three quantified predictors of aphasia after stroke (Engelter et al., 2006; Inatomi et al., 2008; Tsouli et al., 2009). The same study reported associations between advancing age and previous stroke with disability in patients with dysphagia demonstrated the same two correlates for aphasia (Guyomard et al., 2009). They found that persons with stroke-based aphasia more often had previous stroke with disability and were older than those without (Guyomard et al., 2009). Similarly, Bersano et al. (2009) reported in a second large-scale study significant differences for four clinical correlates in 8848 patients with unselected stroke types. The four correlates included age of >75 years, female gender, motor deficit, and etiology of atrial fibrillation. All four clinical factors were more frequent in those with aphasia compared to those without (Bersano et al., 2009).

Concerning clinical factors predictive of aphasia, two of the three articles identified increasing age (Engelter et al., 2006; Tsouli et al., 2009), the presence of atrial fibrillation (Engelter et al., 2006; Tsouli et al., 2009), and increased stroke severity (Engelter et al., 2006;
Inatomi et al., 2008; Tsouli et al., 2009) as predictive of aphasia. The three studies differed in their sample sizes and selection criteria, with sample sizes of 269 (Engelter et al., 2006), 855 (Inatomi et al., 2008) and 2297 (Tsouli et al., 2009). Engelter et al. (2006) investigated first-ever acute ischemic stroke patients, while Inatomi et al. (2008) sampled patients with acute ischemic stroke, who were independent in their activities of daily living prior to stroke onset. Finally, Tsouli et al. (2009) included first ever stroke patients with either hemorrhagic or ischemic stroke. All three studies identified aphasia through clinical examination by neurologists (Engelter et al., 2006; Inatomi et al., 2008; Tsouli et al., 2009), other physicians (Inatomi et al., 2008), or speech-language pathologists (Inatomi et al., 2008).

The studies reported comparable effect sizes, presented as odds ratios and their 95% confidence intervals. The odds ratios (95% confidence interval) for increasing age were 1.03 (1.01-1.07) in 10-year increments (Engelter et al., 2006) and 1.16 (1.12-1.21) (Tsouli et al., 2009). Hence, the odds for aphasia due to increasing age were trivial at best in the former study and weak in the latter. The odds ratios (95% confidence intervals) for the presence of atrial fibrillation were stronger than for increasing age, with values of 1.35 (1.08-1.67) (Tsouli et al., 2009) and 2.41 (1.33-4.35) (Engelter et al., 2006). Those for increased stroke severity were 1.21 (1.17-1.26), based on NIHSS scores (Inatomi et al., 2008), and 1.81 (1.69-1.92), based on SSS scores (Tsouli et al., 2009). In addition, Tsouli et al. (2009) reported an effect for the absence of hypertension as predictive of aphasia, with an odds ratio of 1.3 (1.04-1.59). The absence of hypertension as predictive of aphasia likely results from the relationship between hypertension and lacunar strokes (Tsouli et al., 2009), which are generally not substantive enough to produce aphasia. Finally, Engelter et al. (2006) reported an odds ratio of 1.85 (1.07-3.20) for the presence of cardioembolic etiology, and 1.94 (1.09-3.46) for stroke of undetermined etiology (including
multiple etiologies) (Engelter et al., 2006). Despite limited and preliminary findings for clinical predictors of aphasia, no study has reported predictors of dysphagia or dysarthria, warranting consideration in future studies.

1.7. Neuroanatomical Correlates and Predictors of Dysphagia, Dysarthria, and Aphasia

Researchers have begun to describe impairments such as dysphagia (Cola et al., 2010), dysarthria (Kumral et al., 2007), aphasia (Join-Lambert et al., 2012), and apraxia of speech (Hillis et al., 2004; Richardson, Fillmore, Rorden, Lapointe, & Fridriksson, 2012) following MRI confirmed acute stroke. Functional considerations in the brain behaviour relationships should guide neuroanatomical region of interest selection. For example, the neuroanatomical substrate for oropharyngeal swallowing may be difficult to elucidate, given the interplay between volitional and reflexive behaviours, mediated largely by sensory stimulation. Execution of speech production, on the other hand, involves volitional control in initiating regulatory circuitry for fine motor control. Unlike swallowing and speech, language involves higher cortical functions, requiring complex interactions among highly localized cortical language regions, tertiary mediation from other higher cortical functions (Thothathiri, Gagliardi, & Schwartz, 2012) and for motor output of language (Barbas, García-Cabezas, & Zikopoulos, 2013; Herman, Houde, Vinogradov, & Nagaragan, 2013).

1.7.1. Dysphagia

The oral stage of the swallow, involved in mastication and posterior lingual propulsion of the bolus, is largely a volitional behaviour (Humbert & German, 2013), requiring minimal attention, but also involves reflexive components (Miller, Bieger, & Conklin, 1997, Chapter 3). Arrest of the oral stage may result to accommodate other behaviours, such as respiration or overt speech (Martin, Logemann, Shaker, & Dodds, 1994). Higher-level cortical centres control
swallow initiation and regulation (Martin & Sessle, 1993), with contributions from the anterolateral region of the precentral cortex (Miller & Bowman, 1977). Motor pathways of the anterolateral region of the cortex descend through corticobulbar pathway, through the internal capsule, the basal ganglia, and to the reticular formation integrating centre in the midbrain (Miller et al., 1997, Chapter 3). The supramedullary mediation arises from sensory stimulation and ensuing motor responses (Jean, 2001), via the trigeminal sensory nuclei, the motor trigeminal nucleus, special sensation of the facial nerve (Steele & Miller, 2010), the facial motor nucleus, and the motor hypoglossal nucleus (Miller, 1999, Chapter 1).

The resulting all or none reflexive response in the pharyngeal phase converges from supramedullary mediation (Jean, 2001) and direct sensory input to the nucleus of the solitary tract (NTS), the central control centre for swallowing (Jean, 2001). Sensory fibers synapse in the NTS (Bradley & Sweazy, 1992) primarily from glossofaryngeal and vagal input (Kitagawa, Shingai, Takahashi, & Yamada, 2002), mediating motor output from the nucleus ambiguous, which innervates muscle fibers of the pharynx and larynx (Jean, 2001). Evidence is still lacking for whole brain neural associations that can predict the requisite neuroanatomical network for oropharyngeal swallowing. In particular, the involvement and contributing role of cortical and subcortical regions remain elusive in understanding the volitionally driven oral stage and the necessary integration with the central control center in the reflexive pharyngeal phase.

Identifying neuroanatomical regions responsible for the presence of dysphagia will contribute to developing a comprehensive neural network. In particular, structural MRI studies have the potential to correlate distinct regions with dysphagia following stroke. To date, areas associated with post stroke dysphagia include the frontal cortex (Broadley et al., 2003), internal capsule (Gonzalez-Fernandez, Kleinman, Ky, Palmer, & Hillis, 2008; Hamdy et al., 1998), insula

Clearly, much research has focussed on elucidating the presence of dysphagia after brainstem stroke, leaving supratentorial contributions to the manifestation of dysphagia ripe for continued scrutiny. Seven studies have investigated dysphagia after supratentorial stroke (Broadley et al., 2003; Gonzalez-Fernandez et al., 2008; Hamdy et al., 1998; Daniels & Foundas, 1997; Daniels & Foundas, 1999; Cola et al., 2010; Alberts et al., 1992). One confirmed the acute stroke by CT (Daniels & Foundas, 1997), three by CT or MRI (Hamdy et al., 1988; Broadley et al., 2003; Daniels & Foundas, 1999), and three by MRI (Alberts et al., 1992; Gonzalez-Fernandez et al., 2008; Cola et al., 2010). Four of the seven supratentorial studies failed to report precipitating stroke types (Alberts et al., 1992; Hamdy et al., 1988; Daniels & Foundas, 1997; Daniels & Foundas, 1999), while one investigated unselected stroke samples (Broadley et al., 2003), another ischemic stroke (Cola et al., 2010), and the final study first-ever ischemic stroke (Gonzalez-Fernandez et al., 2008). Sample sizes ranged from four (Daniels & Foundas, 1997) to 149 (Broadley et al., 2003). Taken together, these disparate findings provide evidence for the need for future research that aims to identify a whole brain model of dysphagia, using magnetic resonance imaging to confirm acute ischemic stroke.
1.7.2. Dysarthria

The neural substrate for dysarthria is better understood than for dysphagia given that the initiation of speech production is predominantly a volitional motor behaviour (Duffy, 1995). Dysarthria may result from lesions within the corticobulbar circuit (Kent, Duffy, Slama, Kent, & Clift, 2001), where auditory-perceptual classifications contribute to identifying lesion localization along the circuit (Duffy, 1995). Specific dysarthric classifications result from lesioned regions in four neural systems, the pyramidal motor system, the cerebellar system, the extrapyramidal system (Kent et al., 2001), and the final common pathway (Duffy, 1995). Bilateral lesions to the pyramidal motor system can result in spastic dysarthria, while unilateral lesions may result in unilateral upper motor neuron dysarthria (Duffy, 1995). Lesions to the cerebellar system may precipitate ataxic dysarthria, while insult to the extrapyramidal system (basal ganglia) results in hypo- or hyper-kinetic dysarthrias (Duffy, 1995). Lesions to the final common pathway in the brainstem or spinal cord may lead to flaccid dysarthria (Duffy, 1995). Finally, mixed dysarthria occurs frequently, with the concomitant expression of multiple isolated dysarthria types (Duffy, 1995). Evidence for dysarthria following purely sensory degradation remains limited, but may include sensory ataxias of the peripheral system (Riggins & England, 2011, chapter 43) and sensory abnormalities following brain stem (Hokkoku et al., 2011) or cortical lesions (Kim, 2007).

A recent review reported a predominance of supratentorial, cerebellar, and pontine regions associated with dysarthria (Mackenzie, 2011). Studies in the review along with other studies usually investigated gross anatomical regions, such as cortical (Kim, Kwon, & Lee, 2003), subcortical (Baier, zu Eulenburg, Glassl, & Dieterich, 2011), supratentorial (Benke & Kertesz, 1989), and cerebellar (Urban et al., 2003; Schoch, Dimitrova, Gizewski, & Timmann,
areas. The three studies reporting dysarthria after supratentorial stroke involved either CT-confirmed ischemic or hemorrhagic stroke (Benke & Kertesz, 1989; Kim et al., 2003) or MR-confirmed ischemic (Baier et al., 2011) or first ischemic stroke (Baier et al., 2011; Kim et al., 2003). In the two studies reporting ischemic and hemorrhagic etiologies, only four of 70 (Benke & Kertesz, 1989) and one of six patients (Kim et al., 2003) had hemorrhagic etiologies. Dysarthria examinations included symptom report of dysarthria as chief complaint (Kim et al., 2003) and perceptual assessment by a neurologist and speech-language pathologist (Baier et al., 2011) or trained raters (Benke & Kertesz, 1989).

In their study of 99 patients with single lesion hemispheric stroke, Benke and Kertesz (1989) found that patients with dysarthria compared to those without more frequently had lesions in the frontal operculum, the insula, the postcentral and superior temporal gyri, and the supramarginal and angular gyri. Within subcortical regions, lesions occurred most frequently in the basal ganglia, the ventral and lateral thalamus, the internal capsule, claustrum, corona radiata and superior longitudinal fasciculus (Benke & Kertesz, 1989). Kim et al. (2003) studied isolated dysarthria of sudden onset in five ischemic stroke patients with predominantly cortical lesions. Lesioned cortical brain regions included areas lateral to the precentral knob or the most lateral cortical area at the level of the lateral ventricle (Kim et al., 2003). Most recently, Baier et al., 2011 reported the neuroanatomical correlates of dysarthria where 20 of 25 patients with unilateral cortical lesions affecting the internal capsule had dysarthria (Baier et al., 2011). Many lesions extended into the insula, the opercular peri-insular cortex, and temporal regions (Baier et al., 2011). Using a voxel-based symptom mapping paradigm, they found that regions associated with dysarthria included the posterior insular cortex, the operculum, and white matter (Baier et
al., 2011). Damage to the posterior internal capsule correlated with dysarthria in patients with left hemisphere lesions (Baier et al., 2011).

Two studies investigated dysarthria following cerebellar lesions (Urban et al., 2003; Schoch et al., 2006). Urban et al. (2003) investigated 18 first ischemic stroke patients with sudden onset of dysarthria, based on CT and/or MRI. Two speech-language pathologists identified dysarthria by auditory-perceptual examination within two weeks post stroke onset (Urban et al., 2003). Eleven patients had brainstem extension (Urban et al., 2003). Six of the seven patients with isolated cerebellar lesions had right sided involvement, and the rostral paravermal region of the anterior lobe was most commonly affected (Urban et al., 2003). Ten of the 11 patients with brainstem lesions had involvement of posterior inferior cerebellar artery (Urban et al., 2003). Similarly, Schoch et al. (2006) studied acute and subacute (≤90 days post stroke onset) dysarthria by neurological examination in 20 acute patients with MR-confirmed ischemic stroke, evaluated with voxel-based lesion symptom mapping. They identified three patients with dysarthria, all of whom had superior cerebral artery territory lesions, affecting the paravermal and hemispheral lobules as well as the posterior part of dentate nucleus (Schoch et al., 2006).

Other studies reported dysarthria resulting from damage in unselected regions throughout the whole brain using a combination of CT and/or MR imaging (Urban et al., 2001; Urban et al., 2006; Canbaz et al., 2010) or MR imaging alone (Kumral et al., 2007), in patients with sudden onset of dysarthria. In 68 acute ischemic stroke patients, Urban et al. (2001) showed a predominance of lesions affecting infratentorial regions (54%) compared to supratentorial regions (46%). They noted a three-fold increase in left-sided supratentorial lesions (74%) compared to right sided lesions (26%), as well as a preponderance of left-sided brainstem lesions.
(91%) compared to right sided lesions (9%). Later, in a series of 62 first ischemic acute stroke patients, Urban et al. (2006) found that all extracerebellar lesions were located along the corticobulbar tract, where lesions in supratentorial regions predominated (61%), followed by pontine (24%) and cerebellar lesions (15%). Among patients with supratentorial lesions, frequency of striatocapsular (47%) involvement predominated over motor cortex (15%) (Urban et al., 2006). Canbaz et al. (2010) studied a series of 55 acute ischemic stroke patients, demonstrating a predominance of supratentorial lesions (69%), compared to infratentorial lesions (31%). Within infratentorial regions, the brainstem lesions occurred in 14 patients, primarily in the right paramedian pons, while three had primary lesions in the cerebellum (Canbaz et al., 2010). Overall, the most frequently affected regions included the corona radiata and the pons (Canbaz et al., 2010). Finally, in their study of 101 patients with ischemic stroke, Kumral et al. (2007) found that the most common regions of infarction in decreasing order were the pons (Kumral et al., 2007), corona radiata (Kumral et al., 2007), periventricular areas, and the insula and cerebellum (Kumral et al., 2007).

Despite these seemingly comprehensive findings, five (Benke & Kertesz, 1989; Urban et al., 2001; Urban et al., 2006; Canbaz et al., 2010; Kumral et al., 2007) of the eight studies reviewed did not investigate correlates in patients with and without dysarthria. One reported lesion correlates based by CT (Benke & Kertesz, 1989), three by CT or MRI (Canbaz et al., 2010; Urban et al., 2001; Urban et al., 2006), and four by MRI (Baier et al., 2011; Kim et al., 2003; Kumral et al., 2007; Schoch et al., 2006) alone. Consequently, MR studies investigating large samples of homogeneous stroke patients with and without dysarthria are still necessary to elucidate responsible regions for speech execution along the corticobulbar circuit.
1.7.3. Aphasia

Injury to the language regions of dominant hemisphere is related to aphasia. The dominant hemisphere involves the left hemisphere in right-handed persons and in up to 70 percent of left-handed persons (Isaacs, Barr, Nelson, & Devinsky, 2006; Knecht et al., 2000), where degree of handedness is a factor in hemispheric language dominance (Knecht et al., 2000). Despite this well-appreciated localization of language in the left hemisphere, the role of the right hemisphere contribution to language processing is less well understood (Chapey & Hallowell, 2001). Lesions to the right hemisphere do not result in a traditional stroke-based aphasia, with the rare exception of the condition of crossed aphasia, but may result in language impairment, characterized by impaired suprasegmental features, such as stress patterns and prosodic contours (Benton & Bryan, 1996). Conversely, localized lesions in the left hemisphere result in aphasia classically characterized by anomia (Helm-Estabrooks & Albert, 1991) usually with other language deficits (Chapey & Hallowell, 2001). Discrete language areas include the temporoparietal junction (Wernicke’s area), deemed the area for language comprehension (Turken & Dronkers, 2011), and the frontal operculum (Broca’s area), associated with language production (Price, Seghier, & Leff, 2010; Mesulam, 1990). Furthermore, the connecting arcuate fasciculus is necessary for overt repetition of spoken language (Bernal & Ardila, 2009). Despite early identification of discrete neuroanatomical regions within the left hemisphere, recent research has explored the view of language as represented in an extensive network (Mesulman, 1990).

The more recent view of an extensive neural network subserving the manifestation of aphasia includes cortical and subcortical regions, as well as contribution from the right hemisphere (Teki et al., 2013). Areas involved in the proposed network include the left posterior
inferior frontal gyrus (Broca’s area), the left posterior two-thirds of the superior temporal gyrus (Wernicke’s area), the inferior parietal lobe (Okada et al., 2013; Jefferies, 2013), the insula (Blank, Scott, Murphy, Warbuton, & Wise, 2002; Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Dronkers, 1996; Dronkers, Wilkins, Van Valin Jr., Redfern, & Jaege., 2004; Hillis et al., 2002a; Mesulman, 1990) and the thalamus (Pergola et al., 2013). Important connecting regions include left and right auditory cortex (Blank et al., 2002; Teki et al., 2013; Trumpp, Kliese, Hoenig, Haarmeier, & Kiefer, 2013) and the dorsal stream (Herman et al., 2013; Kümmerer et al., 2013).

Structural imaging research elucidating the contribution of specific anatomical areas in an extensive network is in its infancy. A task specific approach to associating lesion correlates to aphasia, in samples of patients with lesions throughout the brain (Price et al., 2010), will ultimately guide the investigation of a large-scale network of brain-behaviour relationships (Dick & Tremblay, 2012). Price et al (2010) nicely summarized studies that considered the whole brain neuroanatomical correlates of aphasia, according to aphasia profiles. Lesioned areas associated with language comprehension included the posterior superior temporal area (Kreisler et al., 2000; Saygin, Wilson, Dronkers, & Bates, 2004; Baldo, Schwartz, Wilkins, & Dronkers, 2006; Specht et al., 2009), the inferior frontal (Baldo et al., 2006; Bates et al., 2003; Dronkers et al., 2004) and/or middle frontal gyrus (Bates et al., 2003; Dronkers et al., 2004), the middle temporal area (Bates et al., 2003; Dronkers et al., 2004; Saygin et al., 2004; Baldo et al., 2006; Specht et al., 2009), and parietal cortex (Bates et al., 2003; Saygin et al., 2004). Regions associated with language production included the frontal lobe (Kreisler et al., 2000), specifically the inferior frontal gyrus (Borovsky, Saygin, Bates, & Dronkers, 2007) and the ventral middle frontal gyrus (Amici), sensorimotor cortex (Borovsky et al., 2007), posterior temporal areas (Borovsky et al.,
2007; Amici et al., 2007), parietal lobe (Baldo et al., 2006; Kreisler et al., 2000), putamen (Baldo et al., 2006; Kreisler et al., 2000), superior longitudinal fasciculus (Bates et al., 2003), and insula (Bates et al., 2003; Baldo et al., 2006; Kreisler et al., 2000).

Structural MRI studies investigating neuroanatomical associations of acute stroke-based aphasia either relate gross neuroanatomical regions with broad classifications of aphasia or associate discrete neuroanatomical regions with task specific impairments. Two studies have described gross neurovascular or neuroanatomical correlates of aphasia in large samples of stroke patients. One study compared lesion correlates in patients with and without aphasia (Tsouli et al., 2009), while the other compared lesion correlates according to aphasia classifications, expressive, receptive, or expressive-receptive (Croquelois & Bogousslavsky, 2011). The first involved a sample of 2297 first-ever stroke patients, demonstrating that 43% of patients with anterior cerebral artery (ACA) stroke, 60% of patients with total MCA stroke, 51% of patients with upper MCA stroke, 48% of patients with lower MCAs stroke, 33% of patients with posterior cerebral artery (PCA), and 36% of patients with borderzone infarcts had aphasia (Tsouli et al., 2009). The second study involved a sample of 1541 first-ever stroke patients with aphasia, identifying the anterior middle cerebral artery (MCA) territory, the deep MCA, and the anterior-posterior MCA to predict expressive aphasia compared to receptive aphasia (Croquelois & Bogousslavsky, 2011). Interestingly, the absence of left-sided lesions predicted expressive aphasia, perhaps pointing to the role of the right hemisphere in suprasegmental phonological output (Croquelois & Bogousslavsky, 2011). Conversely, one vascular territory predicted receptive aphasia compared to expressive aphasia, the posterior MCA (Croquelois & Bogousslavsky, 2011). Anterior-posterior MCA lesions also predicted a combined expressive-receptive aphasia (Croquelois & Bogousslavsky, 2011).
More recent acute stroke studies have used a task specific approach to elucidate discrete regions involved in language functions with tasks involving picture naming (Baldo, Arévalo, Patterson, & Dronkers, 2013; Schwartz, Faseyitan, Kim, & Coslett, 2012) and complex sentence comprehension (Magnusdottir et al., in press). All three studies of picture naming and complex sentence comprehension demonstrated involvement of the temporal lobe, thereby suggesting overlap in regions associated with language comprehension and production. Few studies have reported whole hemisphere correlates of aphasia, and only two sampled patients with and without aphasia (Tsouli et al., 2009; Magnusdottir et al., in press). We still need to apply whole hemisphere analyses to large samples of patients, to demonstrate the involvement of multiple regions in predicting aphasia, while accounting for covariates such as age, stroke volume, and stroke recurrence (Crinion, Holland, Copland, Thompson, & Hillis, 2013).

1.8. Gaps in the Literature

Discrepancies exist in the literature for frequency measures and clinical and neuroanatomical correlates for all three impairments. Overall, there is a paucity of reports on the co-occurrence of dysphagia, dysarthria, and aphasia after stroke. Incidence measures for single impairments were derived often using different methodologies across studies. Dysphagia evaluation practices differed despite routine evaluation in all patients. While some studies reported incidence based on screening, others used clinical assessments or gold standard instrumental tests. Even so, studies reporting dysphagia based on instrumental testing used measures that were narrow in scope, dichotomizing dysphagia according to aspiration status. Although incidence figures for dysarthria and aphasia existed within homogeneous samples of first-ever acute ischemic stroke patients, the nature of assessments differed across studies. Dysarthria and aphasia were often identified through bedside clinical assessment or based on
adapted standardized tests. Dysarthria sampling was often restricted to those with sudden onset of dysarthria or dysarthria as a chief complaint, thereby limiting generalizability. Across the three impairments, few studies documented the timing of assessment from the onset of stroke. Similarly, few documented confirmation of acute stroke by neuroimaging, although this has recently become possible with MR modalities. When studies included patients with first stroke or recurrent stroke, they did not provide separate frequencies for each group, potentially contributing to variability in impairment frequency. Consequently, studies report wide variation in their capture of the incidence of dysphagia, dysarthria, and aphasia or of their co-occurrence.

Concerning clinical predictors of dysphagia, dysarthria, and aphasia, many studies failed to compare patients with and without the impairments, thereby limiting predictive models to impairment-specific classifications. Although classifications of patients with a given impairment may be important for the management and prognosis, they do not elucidate the responsible clinical and neuroanatomical substrates for the presence versus absence of the impairment. That is, some studies described the clinical associations of dysphagia and dysarthria after stroke, but none reported clinically driven predictors and effect sizes for them. Nevertheless, three studies reported important clinical predictors of aphasia. They each sampled different stroke types. Consequently, clinically driven predictive models of dysphagia, dysarthria, and aphasia are still necessary in homogeneous samples stroke patients.

Despite the advent of multimodal MR neuroimaging, relatively few studies have documented acute MR lesion attributes with dysphagia, dysarthria, and aphasia. Many provided aggregate results from CT and MRI scans. Investigators often failed to report the time to imaging from stroke onset and the time between imaging to evaluation of the impairments. Consideration of some acute and chronic lesion correlates, such as volume and previous brain disease were
lacking. Studies are still needed to quantify lesion sites and volume for all three impairments, confirming the acute nature of the stroke by MR imaging. In addition, accounting for whole brain health factors in addition to acute stroke factors is a novel area for investigation in all three impairments.

1.9. Modeling

It is important to model frequency estimates and predictors of dysphagia, dysarthria, and aphasia in large homogeneous samples of stroke patients. Computing inferential statistics such as frequency estimates and effect sizes for predictors will permit future comparisons across samples for a given population. To illustrate, differing confidence intervals from incidence estimates across studies could direct attention to methodological factors, allowing for a more comprehensive interpretation of results. Similarly, documenting clinical and neuroanatomical predictors with corresponding effect sizes (such as relative risks or odds ratios) and their confidence intervals would provide a means to derive comprehensive models of risk for a given impairment after stroke. The clinical relevance of such models is high in the acute stage of stroke, given the potential for dysphagia to compromise survival (Martino et al., 2005), and the potential for negative clinical and psychosocial outcomes associated with all three impairments. Consequently, further investigation into the acute stage frequency estimates and predictors of dysphagia, dysarthria, and aphasia is warranted. The availability of frequency estimates and predictors will help health care professionals understand the attributes and potential causes of post stroke dysphagia, dysarthria, and aphasia. In turn, this will lead to improved management and better treatments of single and cross-system impairments in stroke survivors (McFarland & Tremblay, 2006).
1.10. Purpose

We proposed to conduct three studies sampling homogeneous ischemic stroke patients with MR imaging to identify epidemiological attributes and risk factors for dysphagia, dysarthria and aphasia. Our overarching purpose was to elucidate discrepant findings in the literature by quantifying incidence estimates and acute stroke predictors for the three impairments within homogeneous samples of patients with acute stroke confirmed by MR imaging. Our primary objectives were three-fold. The first objective was to estimate the incidence and co-occurrence of dysphagia, dysarthria, and aphasia in a sample of first-ever acute ischemic stroke patients. The second was to model demographic and clinical predictors of the three impairments in the acute stage derived from the same homogeneous sample of patients. The third objective sought to identify neuroanatomical predictors of the three impairments.

Our first study protocol addressed the first two objectives. We derived a random sample of a large cohort of consecutively enrolled patients with first-ever acute ischemic stroke, to identify incidence, co-occurrence, and clinical predictors of dysphagia, dysarthria, and aphasia. Our second and third studies addressed the third objective. We first conducted a systematic review of the literature to identify the whole brain neuroanatomical correlates of dysphagia secondary to acute ischemic stroke, since they are not well described in the literature. To support and extend findings from the systematic review, we sought to delineate clearly whole brain neuroanatomical factors that predicted dysphagia, dysarthria, and aphasia, using the sample of first-ever acute ischemic stroke patients. Identifying the incidence, co-occurrence and predictors of these three physically and mentally challenging sequelae of acute ischemic stroke is important to designing management and rehabilitation initiatives for stroke survivors.
The Frequency, Co-occurrence, and Predictors of Dysphagia, Dysarthria, and Aphasia after First-Ever Acute Ischemic Stroke

This manuscript corresponds to study one and is published in the *Journal of Communication Disorders*. (See Flowers et al., 2013). The publisher, Elsevier, has approved its inclusion in the current thesis (Appendix A). Additional background pertaining to the methodological procedures is present in the appendices as part of the thesis work. It includes the medical chart review manual (Appendix B) and the medical chart review data extraction form (Appendix C).

**Abstract**

Dysphagia, dysarthria and aphasia occur frequently following stroke. Our purpose was to identify the incidence, co-occurrence, and predictors of these impairments after first-ever ischemic stroke. We used the Registry of the Canadian Stroke Network’s database (2003–2008) from one stroke centre to identify a random sample of 250 patients with acute ischemic stroke confirmed by MR imaging. We further conducted a retrospective medical chart review. We established reliable data capture and identified the presence of the three impairments. We derived incidence and co-occurrence estimates along with 95% confidence intervals (CI) for dysphagia, dysarthria, and aphasia. We then computed odds ratios (OR) through logistic regression to identify predictors. Twenty-nine patient charts were not available for review. Estimates of the incidence of dysphagia, dysarthria, and aphasia were 44% (95% CI, 38-51), 42% (95% CI, 35-48) and 30% (95% CI, 25-37), respectively. The highest co-occurrence of any two impairments was 28% (95% CI, 23-34) for the presence of both dysphagia and dysarthria. Ten percent of all 221 patients had all three impairments. The highest predictors were non-alert level of consciousness for dysphagia (OR 2.6, CI 1.03-6.5), symptoms of weakness for dysarthria (OR
These findings are a first step towards identifying the incidence and predictors of multiple co-occurring impairments in a homogenous stroke sample.

Learning Outcomes: Readers will be able to (1) understand the need for research in stroke, whereby outcomes are reported according to stroke etiology and recurrence patterns, (2) identify the incidence and co-occurrence of dysphagia, dysarthria, and aphasia after a first-ever acute ischemic stroke, and (3) describe clinical precursors of these impairments in the acute stage of stroke.

2. Study One

2.1. Introduction

Survivors of acute stroke often experience co-occurring impairments, such as dysphagia, dysarthria and/or aphasia (Martin & Corlew, 1990; Trapl et al., 2004). Second to hemiparesis, these impairments are the most frequent neurological deficits in patients with first-ever acute ischemic stroke (Lubart et al., 2005). The incidence of dysphagia after stroke approximates 55% in the acute stage (Guyomard et al., 2009; Martino et al., 2005), while the incidence of dysarthria ranges between 25% (Lubart et al., 2005) and 42% (Lawrence et al., 2001) after first-ever acute ischemic stroke. Similarly, incidence figures for aphasia range from 23% (Lubart et al., 2005) to 35% (Tsouli et al., 2009) after first-ever acute ischemic stroke. Few studies have reported the co-occurrence of these three impairments after acute stroke. Lapointe and McFarland (2004) documented that 79% of their acute stroke patients with dysphagia had concomitant communication impairments such as dysarthria, aphasia, and voice and cognitive communication impairments. Trapl et al. (2004) reported that 10% of their acute stroke patients had both dysarthria and aphasia. Given the paucity of literature addressing the incidence of dysphagia and
of these co-occurring impairments after first-ever acute ischemic stroke, further investigation is warranted to estimate their incidence.

Previous studies have documented clinical predictors of dysphagia including previous stroke with physical disability (Guyomard et al., 2009), advancing age (Guyomard et al., 2009), and atrial fibrillation (Gattellari et al., 2011). Likewise, previous studies have demonstrated that stroke with disability (Guyomard et al., 2009) and advancing age (Bersano et al., 2009; Engelter et al., 2006; Guyomard et al., 2009; Inatomi et al., 2008; Tsouli et al., 2009) predict aphasia. Additional previously reported predictors of aphasia include stroke severity (Inatomi et al., 2008), female gender (Bersano et al., 2009), atrial fibrillation (Bersano et al., 2009; Engelter et al., 2006; Inatomi et al., 2008; Tsouli et al., 2009), cardioembolism (Engelter et al., 2006), and the presence of multiple etiologies for ischemic stroke (Engelter et al., 2006). To our knowledge, there are no known clinical predictors of dysarthria (Kumral et al., 2007) or of these three co-occurring impairments after acute stroke. Only two of the studies reporting predictors for dysphagia (Gattellari et al., 2011) and aphasia (Engelter et al., 2006) provided results for first-ever acute ischemic stroke samples. Consequently, clinically driven predictive models of these impairments are still needed within homogeneous samples of first-ever acute ischemic stroke patients.

Oropharyngeal dysphagia can lead to malnutrition (Crary et al., 2013), dehydration (Crary et al., 2013), aspiration pneumonia (Martino et al., 2005) and death (Altman et al., 2010). The impact of dysarthria after stroke may include social and emotional disruptions and patient sentiments of stigmatization (Dickson et al., 2008). Aphasia is a major source of disability, incurring increased use of rehabilitation services (Dickey et al., 2010) and increased cost of care (Ellis et al., 2012). It also has negative economic repercussions, such as decreased return to work.
(Dalemans et al., 2008; Ross Graham et al., 2011). Given these potentially detrimental outcomes, it is important to identify the incidence and precursors of dysphagia, dysarthria, and aphasia after stroke. Estimating their incidence, identifying risk factors that predict their presence, and describing clinical practice behaviours related to their assessment will aid in developing measures to improve management early in the acute stages of stroke.

Among stroke subtypes, ischemic etiology is the most frequent cause of stroke, followed by intracerebral hemorrhage and then subarachnoid hemorrhage (Broderick et al., 1993; Kumral et al., 1998). Recent advances in neuroimaging include routine magnetic resonance (MR) imaging in acute stroke (Keir & Wardlaw, 2000; Schaefer et al., 2000; Tan et al., 2006). Magnetic resonance imaging with diffusion-, T1-, and T2-weighted scans facilitates the diagnosis of stroke etiology and confirms the presence of an acute versus previous stroke. Specifically, diffusion weighted imaging (DWI) is most sensitive to acute ischemic stroke (Mullins et al., 2002; Prichard & Grossman, 1999), distinguishing an acute stroke from a previous stroke better than T2-weighted MR (Fazekas et al., 2009; van Everdingen et al., 1998) or computed tomography (Barber et al, 1999; Lansberg et al., 2000). Magnetic resonance with diffusion weighted imaging is currently the gold standard for diagnosing acute cerebral ischemia with a sensitivity of 88% and a specificity of 95% (Lovblad et al., 1998). Since the 1990s, MRI scanners have echo-planar capability allowing acute stroke protocols to include the acquisition of DWI scans along with standard T1 and T2 scans (Tan et al., 2006). Given the widespread availability of MR imaging, researchers have begun to describe impairments such as dysphagia (Cola et al., 2010), dysarthria (Kumral et al., 2007), aphasia (Join-Lambert et al., 2012), and apraxia of speech (Hillis et al., 2004; Richardson et al., 2012) following MR confirmed acute stroke. To extend and corroborate these preliminary studies, it is important to document further
the incidence and co-occurrence of these frequent impairments in a homogeneous sample of first-ever acute ischemic stroke, confirmed by MR imaging.

Despite the growing body of literature reporting the incidence and clinical predictors of isolated impairments after stroke, many previous studies failed to delineate results according to stroke etiology and recurrence. Many also varied in their definitions of acute stroke, leading to differences in the timing of acute stage assessments. These methodological differences likely contributed to variations in the reported incidence of dysphagia, dysarthria, and aphasia. To address these gaps in the literature, we selected consecutive patients with acute ischemic stroke, confirmed by diffusion-weighted MR imaging.

Our purpose was to identify epidemiological attributes and risk factors for three frequent impairments: dysphagia, dysarthria, and aphasia. On an exploratory basis, we also recorded the reported frequency of apraxia of speech (AOS), recognizing that its differential identification might be determined exclusively in patients seen by speech-language pathologists (SLP) for treatment planning. Our primary objectives were two-fold. First, we sought to estimate the incidence and co-occurrence of dysphagia, dysarthria, and aphasia. Second, we proposed to identify their demographic and clinical predictors and to explore clinical practice behaviours related to their assessment.

2.2. Methods

2.2.1. Operational definitions

Dysphagia is defined as “oropharyngeal dysphagia”, characterized by abnormal swallowing physiology of the upper aerodigestive tract and detected by clinical examination, instrumental assessment (Martino et al., 2005), or insertion of enteral feeding. We defined aphasia as being an acquired language impairment characterized by anomia (Helm-Estabrooks &
Albert, 1991) and/or other language deficits (Chapey & Hallowell, 2001), evidenced in any
language modality (Chapey & Hallowell, 2001) and detected by clinical examination. We
defined dysarthria to be disturbances in muscular control of the speech mechanism due to
damage of the central or peripheral nervous systems (Darley et al., 1969), resulting in abnormal
neuromuscular execution of speech (Duffy, 1995) and detected by clinical examination. We
defined apraxia of speech to be an acquired neurogenic disturbance in motor programming of
speech (Duffy, 1995; Maas, Robin, Wright, & Ballard, 2008; Ogar et al., 2005). We defined
ischemic stroke to be an acute focal neurological deficit with a cerebral infarct (Goldstein et al.,
1989) confirmed by diffusion weighted MR imaging (DWI).

2.2.2. Data sources

2.2.2.1. Registry of the Canadian Stroke Network

We identified patients from the Registry of the Canada Stroke Network (RCSN)’s
database which is the repository of data for consecutive patients who present to hospital within
two weeks of an acute stroke or transient ischemic attack (TIA) (Kapral et al., 2004). We
selected adult patients (≥18 years) with a first-ever acute ischemic stroke admitted between July
1, 2003 and March 31, 2008 to the Toronto Western Hospital (TWH), a tertiary care regional
stroke centre. According to our primary objectives, we included only patients with diffusion
weighted MR imaging, selecting 250 for medical chart review using random sampling without
replacement. We retained baseline characteristics for patients without MR imaging, to
investigate generalizability of results to all first ischemic stroke patients. We obtained ethical
approval from Sunnybrook Health Sciences Centre through the RCSN and from the University
Health Network’s Research Ethics Board for the secondary chart abstraction (REB #07-0423)
Procedures for data collection and level of interrater reliability for the RCSN data have been
previously reported (Kapral et al., 2004; Silver, Kapral, Lindsay, Tu, & Richards, 2006; Tu et al., 2004).

The RCSN contains data that document stroke diagnoses and defines probable ischemic stroke etiologies according to the Trial of Org 10172 in Acute Stroke (TOAST) criteria (Adams et al., 1993). The TOAST etiological classification uses defined clinical criteria to determine eight etiologies for ischemic stroke: cardioembolic, large artery, lacunar, dissection, cortical, prothrombotic, vasculitis, and unknown. As one measure of stroke severity, the RCSN uses the Canadian Neurological Scale (CNS) score (Côté et al., 1989). The CNS score ranges from 0 to 11.5, where a score of 0 indicates maximum deficit and a score of 11.5 is normal. The RCSN documents the modified Rankin score (MRS) to denote level of disability based on evaluation of motor functions prior to discharge (Banks & Marotta, 2007). The MRS has a minimal score of 0, indicating no symptoms of disability, and a maximum score of 6, indicating death. Hence, the RCSN database provided clinical data including demographics, risk factors, comorbidities, and stroke severity.

We extracted the following predictor variables from the RCSN database: age and gender; stroke risk factors of hypertension, hyperlipidemia, transient ischemic attack, peripheral disease, and atrial fibrillation; previous medical history of dementia, cancer, asthma, or smoking; the TOAST etiological classifications; symptoms of physical weakness, sensory symptoms, and side of symptoms (motor symptoms classified as left, right, or bilateral) at stroke onset; level of consciousness (alert versus non-alert) and the Canadian Neurological Scale (CNS) score as indicators of stroke severity. For descriptive purposes, we also extracted variables pertaining to clinical intervention and outcomes, including hours to arrival to hospital from stroke onset, use
of thrombolysis (tPA), length of stay, Modified Rankin Score (MRS), and discharge status (dead or alive).

2.2.2.2 Chart review

We conducted a medical chart review to supplement the RCSN data with outcomes relating to dysphagia, dysarthria, and aphasia. At the same time, we piloted data extraction for the reported frequency of apraxia of speech (AOS). For dysphagia, we documented the number of patients assessed by speech-language pathologists (SLP) following a medical order. For each patient, we documented dysphagia as absent or present. Absence of dysphagia included i) documentation of its absence by SLP during clinical or instrumental assessment or ii) absence of enteral feeding tube insertion in patients not assessed by SLP. Presence of dysphagia included documentation of its presence by SLP during clinical or instrumental assessment or documentation of enteral feeding tube insertion in patients not assessed by SLP. We identified the date and time of the first confirmed presence of dysphagia, whether by SLP report or by radiographic report confirming enteral feeding tube insertion.

In addition, we documented the number of patients assessed by SLPs, medical doctors (MD) or stroke nurses (SN) for communication impairments. Stroke nurses are trained to identify the signs of stroke, and they consult with the neurologist on service at the TWH. The absence of dysarthria, aphasia, or AOS included omission of their reported presence during all clinical assessments by MDs, SLPs, or SNs. The presence of dysarthria, aphasia or apraxia of speech included documentation of their presence during any clinical assessment by these professionals. We accepted predefined determinants for the presence of dysarthria, aphasia, and AOS from assessment reports. That is, the three communication impairments had to be clearly recorded as present within assessment or examination sections of physician, stroke nurse, and speech-
language pathology notes. Consequently, reports of history or symptoms of dysarthria, aphasia, or AOS did not constitute assessments. To facilitate further identification of the impairments from assessment reports, we delineated which terms were more likely to be used by doctors, stroke nurses or speech-language pathologists. Overall, the determinants of aphasia included the terms “aphasia”, “dysphasia”, “anomia”, “dysnomia”, report of difficulty with word finding, description of aphasia subtypes (e.g. Broca’s or Wernicke’s), mention of receptive, expressive, or global language impairments, or mention of paraphasic errors (the latter most likely to be used by SLPs). Similarly, determinants of dysarthria included the term “dysarthria”, report of slurring of speech, or description of difficulties with motor execution of speech (the latter most likely to be used by SLPs). Accepted terms for AOS included “apraxia of speech” (but not “apraxia” alone), “dyspraxia of speech”, or description of difficulties with motor programming of speech (all most likely to be used by SLPs). There was no overlap in accepted terms for the three communication impairments. We identified the health professional who first reported dysarthria, aphasia, or AOS and recorded the date and time of assessment. To corroborate the first identification of dysarthria and aphasia, we also recorded subsequent consensus by a second health professional.

A trained research assistant extracted incidence and clinical practice variables from electronic or paper charts for the dysphagia, dysarthria, aphasia, and AOS outcomes for one month following patient arrival to the Emergency Room. The first author (HF) and the research assistant established interrater reliability for the first 25 charts. Subsequently, the first author (HF) independently extracted data from a random sample of 17% of the remaining charts. The reliability analyses included the incidence outcomes, the identification of the health professional that first identified the impairment, and the dates and times of the first assessment and/or of
ental feed insertion. We merged these chart review variables with the RCSN variables for statistical analyses.

2.2.3. Statistical analysis

2.2.3.1. Registry of the Canadian Stroke Network

To evaluate differences between the patients with and without MRI scans, we used two-tailed independent samples t-tests for continuous variables and chi-squared analyses for frequency variables. We used the Kruskal–Wallis test for mean rank data with skewed distributions. Raw numbers for cell sizes of <5 were suppressed according to privacy policies at the Institute for Clinical and Evaluative Sciences which houses the RCSN database.

2.2.3.2. Chart review

We evaluated interrater reliability from the hospital chart review variables using intraclass correlation coefficients (ICC) for the continuous variables and simple kappa statistics for categorical variables. We computed inferential frequency estimates and their 95% confidence intervals (CI) for the incidence and co-occurrence of dysphagia, dysarthria and aphasia. We documented simple frequency of AOS. Two raters resolved discrepancies by consensus or sought the advice of a third rater.

2.2.3.3. Merged Data

We computed odds ratios along with their 95% CIs using multivariable logistic regression modeling, to evaluate predictors of dysphagia, dysarthria, and aphasia. We used clinical rationale to select stroke and clinical predictors of the three impairments for backward selection modeling with a p <0.05 cut-off. We entered only predictors with ≤10% missing data into the models. We evaluated the discrimination of the predictive models based on the C
statistic, where a value of >0.8 is considered strong (Hosmer & Lemeshow, 2000). We performed the random sampling and all analyses using SAS, version 9.2.

The primary outcome of interest included estimates for the incidence and co-occurrence of dysphagia, dysarthria, and aphasia, based on their reported incidence. Secondary outcomes included stroke and clinical factors that predicted their presence and the clinical practice behaviours relevant to their identification.

2.3. Results

From July 1, 2003 to March 31, 2008, there were 3162 consecutive patients with possible stroke, of whom 981 had sustained a first-ever ischemic stroke (Figure 2-1). Demographic characteristics for these 981 patients included a mean age of 71 years and male gender for 53% (Table 2-1). Seven hundred and sixteen (73%) had an MRI scan. Comparisons of those with MRI scans (n=716) to those without (n=265) demonstrated significant differences for age [p<.0001], Canadian Neurological Scale (CNS) score [p <.0001], previous medical history of hypertension [p<.01] or atrial fibrillation [p<.0001], cause of ischemia [p<.0001], level of consciousness on arrival to hospital [p<.001], length of stay [p <.01], and death at discharge [p<.0001)].

The cohort of 716 patients with first-ever ischemic stroke with MR imaging was eligible for random selection (Figure 2-1). Of 250 randomly selected patients, data were irretrievable for 29, resulting in a final sample of 221 for chart review. Reliability statistics for all chart review variables included categorical (mean kappa .91, range .75 to 1.0) and date and time (mean ICC .99, range .96 to 1.0) variables. Only one categorical variable had a kappa value below .87.

The 221 patients had a mean age of 68 years and 56% were male (Table 2-2). The median time in hours from stroke onset to magnetic resonance imaging was 75 hours, with an
interquartile range of 108 hours. The most frequent risk factor for stroke was a previous medical history of hypertension, present in 70% of the sample (Table 2-2). Symptoms at stroke onset that predominated included symptoms of physical weakness in 77% and left-sided physical symptoms in 45% (Table 2-2).

**2.3.1. Frequency Estimates**

One hundred and forty-five (66%) patients had at least one of the three impairments (Figure 2-2), while 125 (57%) had at least one communication impairment. The incidence estimates and 95% confidence intervals (CI) demonstrated that dysphagia, dysarthria and aphasia occurred in 44% (95% CI 38-51), 42% (96% CI 35-48), and 30% (95% CI 25-37) of patients, respectively (Figure 2-2). Dysphagia and dysarthria co-occurred in 28% (95% CI 23-34) of patients, while dysarthria and aphasia co-occurred in 15% (95% CI 11-21). Dysphagia and aphasia co-occurred in 17% (95% CI 12-22) of patients. All three impairments co-occurred in 10% (95% CI 6-14) of the sample (n=21). Demographics for the 21 patients with all three impairments included 12 men (57%) and a mean age of 73 years (SD 11.4, range 45 to 88 years). The patients with none of the three impairments (n=76) had a mean age of 65 years (SD 16.8), ranging from 24 to 90 years, and 40 were men (53%).

We identified AOS exclusively from speech-language pathology reports, with a frequency of 11% (n=12) in patients assessed for communication (n=107). All patients with AOS had concomitant aphasia, while 50% (n=6) had dysarthria and 92% had dysphagia (n=11). Speech-language pathologists identified dysarthria and aphasia for the first time in 23% (n=21) and 25% (n=17) of patients, respectively (Table 2-4). SLPs identified dysphagia in 92% (n=90) patients, while NGT insertion served as the surrogate marker for the presence of dysphagia in the remaining 8% (n=8) of patients (Table 2-4). Indicators of stroke severity for the eight patients
with NGT insertion but no dysphagia assessment by SLP included non-alert level of consciousness in all eight, and a median CNS score of 6.0 (interquartile range 7.0).

2.3.2. Clinical predictors

The variables with greatest predictive value (Table 2-3) were: for dysphagia, non-alert level of consciousness (OR 2.6, 95% CI 1.0-6.5); for dysarthria, symptoms of weakness (OR 5.3, 95% CI 2.4-12.0); and for aphasia, right sided symptoms (OR 7.1, 95% CI 3.1-16.6). Predictors for the subgroup of patients with all three impairments (n=21) versus those with none (n=76) included non-alert level of consciousness (OR 9.5, CI 1.7-52.2) and decreased CNS scores (OR 0.6, CI 0.5-0.8), with a combined C statistic of .89.

2.3.3. Clinical practice behaviours

SLPs assessed 123 (56%) of the 221 patients for dysphagia and 107 (48%) for communication (Table 2-4). SLPs assessed 100 of the 221 patients for both dysphagia and communication, 23 for dysphagia alone, and seven for communication alone. The time from stroke onset to the first positive assessment by any health professional was shortest for aphasia, with a median and interquartile range of 1 day and longest for dysphagia, with a median of 2 days and an interquartile range of three days. The first positive assessment was made by SLPs in 92% (n=90), 23% (n=21) and 25% (n=17) of patients for dysphagia, dysarthria, and aphasia, respectively (Table 2-4). When SLPs were the first health professional to identify the presence of dysarthria or aphasia (n=38), the positive assessment occurred during the swallowing evaluation 75% of the time (Table 2-4). Corroboration of the first physician (n=59) or stroke nurse (n=12) identification of dysarthria occurred 44% (n=31) of the time by SLPs and 30% (n=21) of the time by the stroke neurologist (Table 2-4). Corroboration of the first physician (n=46) or stroke
nurse (n=4) identification of aphasia occurred 72% (n=36) of the time by SLPs and 5% (n=5) of the time by the stroke neurologist.

2.4. Discussion

This study is the first to estimate the incidence and co-occurrence of dysphagia, dysarthria and aphasia in a homogenous sample of patients with first-ever acute ischemic stroke confirmed by diffusion weighted MR imaging. Close to half the patients in our sample had dysphagia or dysarthria, and almost one-third had aphasia. In addition, over one-third of all patients had both dysphagia and dysarthria, while one in 10 patients had all three impairments.

Our exploration of the reported frequency of AOS showed that over 10% of patients assessed for communication had AOS, and that all patients with AOS had concomitant aphasia. Our study is the first to quantify predictors of dysphagia, dysarthria, and aphasia. Most notably, these predictors include non-alert level of consciousness for dysphagia, symptoms of weakness at stroke onset for dysarthria, and right-sided symptoms for aphasia. These findings correspond well to clinical intuition of predictors for the three impairments.

Previous studies support our estimates of the incidence of dysphagia (Guyomard et al., 2009; Martino et al., 2005), dysarthria (Lawrence et al., 2001), and aphasia (Engelter et al., 2006; Guyomard et al., 2009; Tsouli et al., 2009) and of their co-occurrence (Lapointe & McFarland, 2004). As in previous studies, we found that stroke severity predicted dysphagia (Bravata et al., 2009) and aphasia (Inatomi et al., 2008; Tsouli et al., 2009). We quantified additional predictors of aphasia including non-alert level of consciousness, absence of sensory symptoms or of symptoms of physical weakness, and the presence of right-sided physical symptoms. We also quantified a predictor of dysarthria, the presence of symptoms of physical weakness. Our predictive models showed a fairly good probability of discriminating patients with dysphagia...
(C=.79) and a good probability of discriminating patients with aphasia (c=.83) from those without the impairments. Nevertheless, additional predictive factors could result in more robust models, especially for dysphagia and dysarthria. For example, incorporating MR-based neuroanatomical predictors of the impairments, such as pontine and medullary lesions (Flowers, Skoretz, Streiner, Silver, & Martino, 2011) in the case of dysphagia and motor cortex, insular lobe, and pontine lesions (Kumral et al., 2007) in the case of dysarthria, could further improve our predictive models.

Through our medical chart review, we confirmed a high incidence of dysphagia in our sample. In addition, 80% of patients with dysphagia had concomitant communication impairments. There was a high proportion of first identification of dysarthria and aphasia by medical doctors. Emergency room physicians and stroke neurologists evaluate signs of dysarthria and aphasia during the neurologic examination to facilitate a diagnosis of stroke and/or lesion localization. Testing of communication in the neurologic examination likely also led to a more rapid first identification of dysarthria and aphasia, compared to dysphagia. Patients at risk of dysphagia are automatically referred by medical order for dysphagia assessment by SLPs. Consequently, SLP services are often first initiated for assessments and management of dysphagia early in the acute stage. By contrast, any health professional may initiate communication referrals to SLP, during stroke rounds, by review of chart notes, or by word of mouth. Our data reflect this phenomenon, as SLPs frequently provided adjunct communication assessments of patients during the initial dysphagia evaluation, identifying dysarthria and aphasia in almost 25% of all patients for the first time. Therefore, early identification of some patients with communication impairments may depend on SLP assessment of dysphagia.
Given the high incidence of dysphagia and communication impairments in our sample, coupled with the lack of a standard referral process for communication, we advocate for routine implementation of validated screening tools to identify risk of the presence of dysphagia and communication early after acute stroke. In particular, educating potential referral sources of the value of communication assessment by SLPs and of the consequent need for routine referrals is paramount to optimizing SLP management early in the acute stage. Timely and rapid screening of patients for both dysphagia (Martino et al., 2009; Schepp et al., 2012) and communication (Flamand-Roze et al., 2011; Flowers et al., 2012) may promote early management of these compromising impairments.

Although we followed a systematic approach, there are limitations to the current study. First, we documented our estimates of dysphagia, dysarthria, and aphasia through retrospective chart review. Consequently, we captured only patients referred to speech-language pathology by a medical order or those with insertion of enteral feeding to have dysphagia. We also derived our capture of the impairments through broad defining terms, perhaps limiting identification of the impairments to global impressions of the assessing health professionals. Given the retrospective nature of the current study, a more specific evaluation of linguistic or physiological features of the dysphagia, dysarthria and aphasia assessments was not possible. Patients with enteral feeding due to non-alert level of consciousness may represent a transient dysphagia that resolves following restored consciousness. Similarly, our retrospective design did not permit a robust capture of AOS or capture of other impairments that SLPs are most likely to identify, such as cognitive communication impairments (Murray, 2012), voice impairments (Vuković et al, 2012), or neurogenic stuttering (Theys, van Wieringen, Sunaert, Thijs, & De Nil, L.F, 2011).
Nevertheless, we provided inferential incidence estimates for dysphagia, dysarthria, and aphasia, and explored the reported frequency of apraxia of speech.

Second, we could not evaluate the effect of ischemic stroke etiology on the presence of the impairments, given a high percentage of strokes of undetermined etiology. Undetermined etiology included patients with incomplete investigations, multiple etiologies, or unknown cause of ischemic stroke. Third, our data did not capture lesion localization and volume, which would have permitted even more robust predictions. Finally, given the differences in demographics, stroke risk factors and ischemic stroke etiologies among patients with MR scans and those without, we cannot generalize our findings to all first-ever ischemic stroke patients. As this was a retrospective review, MR imaging was conducted when clinically indicated. We suspect that our study may under-represent older patients, those with atrial fibrillation (where the stroke etiology was presumed to be cardioembolic), and those with very severe strokes. These are patient groups where MR imaging was deemed unnecessary for their management. Nonetheless, because of the potential underrepresentation of older patients and those with severe strokes, we believe that our incidence estimates are in fact lower than those that could be generalized to a first-ever ischemic stroke population. Also, by including only patients with MR imaging, we ensured that all patients in our study cohort had an acute cerebral infarct.

In conclusion, we identified a consecutive series of first-ever, MR proven, ischemic stroke patients from a large stroke centre. We demonstrated a high incidence of dysphagia, dysarthria, and aphasia in patients with MR confirmed first ischemic stroke and quantified predictors of these three impairments. Future studies are still needed to document prospectively the presence and severity of dysphagia, dysarthria, and aphasia after ischemic stroke and after hemorrhagic stroke. Similarly, future prospective studies should quantify physiological,
neuroanatomical, and linguistic determinants to identify incidence estimates and predictors for apraxia of speech and other compromising communication impairments that occur after ischemic stroke. We found expected clinical predictors of dysphagia, dysarthria, and aphasia and proposed future directions for the development of improved predictive models. Further evaluation of our patients’ imaging is in progress to determine infarct localization and volume. We believe that imaging data will aid in the development of robust predictive models to determine patients who may be at greatest risk for these three compromising impairments.

2.5. Acknowledgements

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Table 2-1. Demographic, stroke, and clinical characteristics for all first ischemic stroke patients, comparing those with to those without MRI (n=981)

CNS=Canadian Neurological Scale.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n=981)</th>
<th>Differences based on presence versus absence of MRI imaging</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>With MRI (n=716)</td>
<td>Without MRI (n=265)</td>
</tr>
<tr>
<td>Age in years, mean (SD)*</td>
<td>70.5 (±15.6)</td>
<td>68.1 (±15.9)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>520 (53.0)</td>
<td>404 (56.4)</td>
</tr>
<tr>
<td>Previous Medical History, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>671 (68.4)</td>
<td>472 (65.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>282 (28.7)</td>
<td>204 (28.5)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>347 (35.4)</td>
<td>259 (36.2)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>153 (15.6)</td>
<td>81 (11.3)</td>
</tr>
<tr>
<td>Cause of Ischemia, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>257 (26.2)</td>
<td>146 (20.4)</td>
</tr>
<tr>
<td>Large Artery</td>
<td>156 (15.9)</td>
<td>134 (18.7)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>125 (12.7)</td>
<td>106 (14.8)</td>
</tr>
<tr>
<td>Dissection</td>
<td>24 (2.4)</td>
<td>23 (3.2)</td>
</tr>
<tr>
<td>Cortical</td>
<td>7 (0.7)</td>
<td>7 (1.0)</td>
</tr>
<tr>
<td>Prothrombic</td>
<td>6 (0.6)</td>
<td>5 (0.7)</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Other</td>
<td>40 (4.1)</td>
<td>33 (4.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>361 (36.8)</td>
<td>257 (35.9)</td>
</tr>
<tr>
<td>Level of Consciousness, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alert</td>
<td>776 (79.1)</td>
<td>590 (82.4)</td>
</tr>
<tr>
<td>Drowsy</td>
<td>122 (12.4)</td>
<td>77 (10.8)</td>
</tr>
<tr>
<td>Unconscious</td>
<td>40 (4.1)</td>
<td>21 (2.9)</td>
</tr>
<tr>
<td>Unable to Determine</td>
<td>43 (4.4)</td>
<td>28 (3.9)</td>
</tr>
<tr>
<td>CNS Score, mean (SD)†</td>
<td>7.7 (±3.2)</td>
<td>8.1 (±3.0)</td>
</tr>
<tr>
<td>Thrombolysis, n (%)</td>
<td>95 (9.7)</td>
<td>67 (9.4)</td>
</tr>
<tr>
<td>Length of Stay in days, median (range)*</td>
<td>9 (0-221)</td>
<td>9 (0-221)</td>
</tr>
<tr>
<td>Discharge Status, n dead (%)</td>
<td>78 (8.0)</td>
<td>28 (3.9)</td>
</tr>
</tbody>
</table>

* missing data (n=1-4).
† missing data (n=13).
<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients</th>
<th>Patients with and without dysphagia</th>
<th>Patients with and without dysarthria</th>
<th>Patients with and without aphasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>yes (98) / no (123)</td>
<td>yes (92) / no (129)</td>
<td>yes (67) / no (154)</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>68.0 (±15)</td>
<td>71.0 (±14) / 65.6 (±16)</td>
<td>69.1 (±14) / 67.2 (±16)</td>
<td>70.9 (±13) / 66.7 (±16)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>123 (56)</td>
<td>58 (59) / 65 (53)</td>
<td>54 (59) / 60 (54)</td>
<td>32 (48) / 91 (59)</td>
</tr>
<tr>
<td>Previous Medical History, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>154 (70)</td>
<td>74 (76) / 80 (65)</td>
<td>63 (69) / 91 (71)</td>
<td>48 (72) / 106 (69)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>60 (27)</td>
<td>27 (28) / 33 (27)</td>
<td>22 (24) / 38 (30)</td>
<td>21 (31) / 39 (25)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>74 (34)</td>
<td>31 (32) / 43 (16)</td>
<td>26 (28) / 48 (37)</td>
<td>25 (37) / 49 (32)</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>42 (19)</td>
<td>17 (17) / 25 (20)</td>
<td>15 (16) / 27 (21)</td>
<td>14 (21) / 28 (18)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>20 (9)</td>
<td>11 (11) / 9 (7)</td>
<td>9 (10) / 11 (9)</td>
<td>7 (10) / 13 (8)</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>47 (21)</td>
<td>23 (23) / 24 (20)</td>
<td>19 (21) / 28 (22)</td>
<td>12 (18) / 35 (23)</td>
</tr>
<tr>
<td>Other Conditions, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma or COPD</td>
<td>15 (7)</td>
<td>7 (7) / 8 (7)</td>
<td>5 (5) / 7 (5)</td>
<td>6 (5) / 8 (5)</td>
</tr>
<tr>
<td>Cancer</td>
<td>25 (11)</td>
<td>15 (15) / 10 (8)</td>
<td>10 (11) / 15 (12)</td>
<td>8 (12) / 17 (11)</td>
</tr>
<tr>
<td>Dementia</td>
<td>12 (5)</td>
<td>7 (7) / 5 (4)</td>
<td>5 (5) / 7 (5)</td>
<td>6 (5) / 8 (5)</td>
</tr>
<tr>
<td>Peripheral Disease</td>
<td>10 (5)</td>
<td>5 (5) / 6 (5)</td>
<td>5 (5) / 6 (5)</td>
<td>5 (5) / 8 (5)</td>
</tr>
<tr>
<td>Cause of Ischemia, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>38 (17)</td>
<td>19 (19) / 19 (15)</td>
<td>16 (17) / 22 (17)</td>
<td>12 (18) / 26 (17)</td>
</tr>
<tr>
<td>Large Artery</td>
<td>50 (23)</td>
<td>28 (29) / 22 (18)</td>
<td>25 (27) / 25 (19)</td>
<td>22 (33) / 28 (18)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>36 (16)</td>
<td>12 (12) / 24 (20)</td>
<td>15 (16) / 21 (16)</td>
<td>5 (5) / 34 (22)</td>
</tr>
<tr>
<td>Other*</td>
<td>20 (9)</td>
<td>8 (8) / 12 (10)</td>
<td>7 (8) / 13 (10)</td>
<td>5 (5) / 16 (10)</td>
</tr>
<tr>
<td>Unknown</td>
<td>77 (35)</td>
<td>31 (32) / 46 (37)</td>
<td>29 (32) / 48 (37)</td>
<td>27 (40) / 50 (32)</td>
</tr>
<tr>
<td>CNS, mean (SD) †</td>
<td>8.1 (±3.0)</td>
<td>6.5 (±2.8) / 9.2 (±2.5)</td>
<td>7.6 (±2.7) / 8.3 (±3.1)</td>
<td>6.4 (±3.1) / 8.7 (±2.6)</td>
</tr>
<tr>
<td>Alert Level of Consciousness, n (%)</td>
<td>186 (90)</td>
<td>72 (73) / 114 (93)</td>
<td>77 (84) / 109</td>
<td>51 (76) / 135 (88)</td>
</tr>
<tr>
<td>Physical Symptoms, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensorya</td>
<td>59 (27)</td>
<td>22 (23) / 37 (30)</td>
<td>23 (25) / 36 (28)</td>
<td>7 (10) / 52 (34)</td>
</tr>
<tr>
<td>Weaknessb</td>
<td>169 (77)</td>
<td>83 (85) / 86 (70)</td>
<td>84 (91) / 85 (66)</td>
<td>47 (70) / 122 (79)</td>
</tr>
<tr>
<td>Side of Physical Symptoms, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Side</td>
<td>100 (45)</td>
<td>43 (44) / 57 (46)</td>
<td>41 (45) / 59 (46)</td>
<td>17 (25) / 83 (54)</td>
</tr>
<tr>
<td>Right Side</td>
<td>85 (38)</td>
<td>42 (43) / 43 (35)</td>
<td>39 (42) / 46 (36)</td>
<td>42 (63) / 43 (28)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>24 (11)</td>
<td>8 (8) / 16 (13)</td>
<td>9 (10) / 15 (11)</td>
<td>5 (7) / 19 (12)</td>
</tr>
<tr>
<td>Unable to Determine</td>
<td>12 (5)</td>
<td>5 (5) / 7 (6)</td>
<td>9 (7) / &lt;5</td>
<td>5 (7) / 9 (6)</td>
</tr>
<tr>
<td>LSN-arrival, hours, median (range)‡</td>
<td>14 (0-820)</td>
<td>10 (0-543) / 24 (1-820)</td>
<td>29 (0-543) / 20 (0-820)</td>
<td>9 (0-820) / 17 (0-725)</td>
</tr>
<tr>
<td>LOS in days, median (range) †</td>
<td>16 (0-221)</td>
<td>14 (0-221) / 7 (0-62)</td>
<td>11 (0-87) / 9 (0-221)</td>
<td>13 (0-87) / 9 (0-221)</td>
</tr>
<tr>
<td>Thrombolysis, n (%)</td>
<td>18 (8)</td>
<td>12 (12) / 6 (5)</td>
<td>14 (15) / &lt;5</td>
<td>10 (15) / 8 (5)</td>
</tr>
<tr>
<td>Discharge Status, n dead (%)</td>
<td>10 (5)</td>
<td>9 (9) / &lt;5</td>
<td>6 (5) / &lt;5</td>
<td>5 (8) / 5 (3)</td>
</tr>
<tr>
<td>Rankin Score, mean (SD)</td>
<td>2.8 (1.5)</td>
<td>3.7 (1.2) / 2.1 (1.4)</td>
<td>3.3 (1.3) / 2.5 (1.6)</td>
<td>3.2 (1.5) / 2.7 (1.5)</td>
</tr>
</tbody>
</table>
TIA=Transient ischemic attack.

COPD=Chronic obstructive pulmonary disease.

CNS=Canadian Neurological Scale.

LSN=Last seen normal.

LOS=Length of stay.

*Ischemic stroke classifications collapsed for dissection, cortical, prothrombic, vasculitis, and other.

†Missing data for 1 to 4 patients.

‡Missing data for 6 patients.

asensory symptoms of cranial nerves (but not those for sight), including numbness, anesthesia, tingling, pin and needles, paresthesiae of the face, arm, and/or leg.

bphysiological weakness of the face, arms, and/or legs.
Table 2-3. Predictors of dysphagia, dysarthria and aphasia

<table>
<thead>
<tr>
<th>Independent Variables(^a)</th>
<th>Dysphagia, OR (95% CI)</th>
<th>Dysarthria, OR (95% CI)</th>
<th>Aphasia, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predictors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stroke Severity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS Score (decreasing)</td>
<td>1.4 (1.3-1.6)</td>
<td>ns</td>
<td>1.3 (1.2-1.5)</td>
</tr>
<tr>
<td>LOC (non-alert)</td>
<td>2.6 (1.03-6.5)</td>
<td>ns</td>
<td>3.1 (1.2-8.3)</td>
</tr>
<tr>
<td>Symptoms of Weakness(^b) (present)</td>
<td>ns</td>
<td>5.3 (2.4-12.0)</td>
<td>0.3 (0.1-0.8)</td>
</tr>
<tr>
<td>Sensory Symptoms(^c) (present)</td>
<td>ns</td>
<td>ns</td>
<td>0.1 (0.05-0.4)</td>
</tr>
<tr>
<td><strong>Side of Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>right versus left</td>
<td>ns</td>
<td>ns</td>
<td>7.1 (3.1-16.6)</td>
</tr>
<tr>
<td>bilateral versus left</td>
<td>ns</td>
<td>ns</td>
<td>0.8 (0.2-3.0)</td>
</tr>
<tr>
<td>UTD versus left</td>
<td>ns</td>
<td>ns</td>
<td>0.5 (0.1-2.5)</td>
</tr>
<tr>
<td>C statistic</td>
<td>.79</td>
<td>.62</td>
<td>.83</td>
</tr>
</tbody>
</table>

CSN=Canadian Neurological Scale.

LOC=Level of Consciousness.

UTD=Unable to determine.
aAdditional predictor variables (not significant) included i) age in 10 year increments, ii) gender, iii) previous medical history of dementia, cancer, asthma, and smoking within six months of stroke onset, iv) previous stroke risk factors of TIA, peripheral disease, hypertension, diabetes, hyperlipidemia, and atrial fibrillation.

bphysiological weakness of the face, arms, and/or legs.

csensory symptoms of cranial nerves (but not those for sight), including numbness, anesthesia, tingling, pin and needles, paresthesiae of the face, arm, and/or leg.
**Table 2-4.** Behaviours relating to identification of dysphagia, dysarthria and aphasia from random sample

<table>
<thead>
<tr>
<th>Clinical Practice Variables</th>
<th>Dysphagia (n=98)</th>
<th>Dysarthria (n=92)</th>
<th>Aphasia (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first identification in days, median (range)(^a)</td>
<td>2.0 (0-26)</td>
<td>1.0 (0-18)</td>
<td>1.0 (0-9)</td>
</tr>
<tr>
<td>Time between MRI and first identification in hours, median (IQR)</td>
<td>3 (112)</td>
<td>13 (80)</td>
<td>24 (92)</td>
</tr>
<tr>
<td>First Identified by SLP, n (%)</td>
<td>90 (92)</td>
<td>21 (23)</td>
<td>17 (25)</td>
</tr>
<tr>
<td>Identified by SLP in dysphagia assessment, n (%)</td>
<td>n/a</td>
<td>17 (81)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>First Identified by other health professional, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Doctor(^b)</td>
<td>8 (8)</td>
<td>59 (64)</td>
<td>46 (69)</td>
</tr>
<tr>
<td>Stroke Nurse(^c)</td>
<td>n/a</td>
<td>12 (13)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Second Identification by SLP, n (%)</td>
<td>n/a</td>
<td>31 (34)</td>
<td>36 (54)</td>
</tr>
<tr>
<td>Second Identification by other health professional, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke Neurologist</td>
<td>n/a</td>
<td>35 (38)</td>
<td>15 (22)</td>
</tr>
<tr>
<td>Stroke Nurse(^c)</td>
<td>n/a</td>
<td>2 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>No Second Identification</td>
<td>n/a</td>
<td>24 (26)</td>
<td>16 (24)</td>
</tr>
</tbody>
</table>

IQR=Interquartile Range.

n/a = Not applicable.

SLP=Speech-Language Pathologist.
SN= Nurses specially trained to assess stroke signs.

aDays to assessment from stroke onset.

bMedical Doctor identification involved insertion of nasogastric tube, considered the first identification only in cases when there was no assessment by SLP.

cAssessment performed by Stroke Nurses trained to evaluate stroke signs.
Consecutive patients with possible stroke identified from RCSN

Ischemic stroke patients
n=1299/3162 (41%)

First ischemic stroke patients
n=981/1299 (76%)

First ischemic stroke patients with MRI
n=716/981 (73%)

Random Selection for hospital medical chart review
n=250/716 (35%)

Completed hospital medical chart review
n=221/250 (88%)

Patients not eligible
n=1863
Nonstroke=570
Subarachnoid hemorrhage=504
Intracranial hemorrhage (ICH) = 390
Transient ischemic attack=342
Unable to determine=57

Patients not eligible
n=318
Previous ischemic stroke=293
Previous ICH=6
Previous stroke and ICH =19

Losses
Electronic data loss=20
Irretrievable or incorrect charts=9

Figure 2-1. Flow diagram of enrolled patients from July 1, 2003 to March 31, 2008.
Figure 2-2. Venn diagram with Ellipses (Micallef & Rodgers, 2011), depicting isolated and
combined incidence estimates for dysphagia, dysarthria and aphasia in first acute ischemic stroke
patients.
The MRI-Based Neuroanatomical Predictors of Dysphagia after Acute Ischemic Stroke: A systematic review and meta-analysis

The current manuscript is published in *Cerebrovascular Diseases*, (See Flowers et al., 2011). The publisher, Karger, has approved its inclusion in the current thesis (Appendix D). Additional background pertaining to the methodological procedures is presented in the appendices as part of the thesis work. It includes the list of search terms (Appendix E), the abstract review rating form (Appendix F), the full article review coding form (Appendix G), and the risk of bias study quality rating form (Appendix H).

**Abstract**

*Background*- Considering the incidence of dysphagia is as high as 55% following acute stroke, we undertook a systematic review of the literature to identify lesion sites that predict its presence after acute ischemic stroke.

*Methods*- We searched 14 databases, 17 journals, three conference proceedings and the grey literature using the Cochrane Stroke Group search strategy and terms for MRI and dysphagia. We evaluated study quality using the Cochrane Collaboration’s risk of bias tool and extracted individual level data. We calculated relative risks to model dysphagia according to neuroanatomical lesion sites.

*Results*- Of 964 abstracts, 84 articles met the criteria for full review. Of these 84 articles, 17 met the quality criteria. These 17 articles dealt exclusively with dysphagia after infratentorial stroke and provided MRI correlates of dysphagia for 656 patients. The incidence of dysphagia was 0% in the cerebellum, 6% in the midbrain, 43% in the pons, 40% in the medial medulla and 57% in
the lateral medulla. Within these regions, pontine (RR 3.7, 95% CI 1.5-7.7), medial medullary (RR 6.9, 95% CI 3.4-10.9) and lateral medullary (RR 9.6, 95% CI 5.9-12.8) lesions predicted increased risk of dysphagia.

Conclusions- We sought to develop a neuroanatomical model of dysphagia throughout the whole brain. However, the literature that met our quality criteria addressed the MRI correlates of dysphagia exclusively within the infratentorium. Although not surprising, these findings are a first step toward establishing a neuroanatomical model of dysphagia after infratentorial ischemic stroke and provide insight into assessing individuals at risk for dysphagia.

3. Study Two

3.1. Introduction

Dysphagia is a frequently occurring consequence of stroke. A recent systematic review identified a frequency of 55% in the acute stage (Martino et al., 2005). Dysphagia is associated with comorbidities such as malnutrition, aspiration pneumonia, and death. A recent study showed that pneumonia was associated with poor outcomes such as daily dependency or death after ischemic stroke (Vermeij et al., 2009). Individuals with dysphagia have a risk of pneumonia three times higher than those without dysphagia (Martino et al., 2005). Given these potential compromises, it is important to identify the precursors to dysphagia after stroke. Predicting the increased risk of dysphagia following brain lesions might increase our understanding of the causes of post stroke dysphagia, leading to improved management and better treatments for stroke survivors.

Recent advances in neuroimaging have made associating lesions with stroke severity possible (Keir & Wardlaw, 2000; Schaefer et al., 2000; Tan et al., 2006). Magnetic resonance
imaging (MRI), including diffusion (DWI), T1- and T2- weighted scans, quantifies brain lesion sites and volumes, facilitating diagnosis of stroke type, prior stroke, and acute stroke. In particular, DWI is advantageous as it most sensitive to hyperacute cerebral infarction, occurring within minutes to hours of stroke onset (Mullins et al., 2002; Prichard & Grossman, 1999). A positive DWI scan distinguishes an acute infarct from an old infarct better than T2-weighted (Fazekas et al., 2009; van Everdingen et al., 1998) or CT scans (Barber, 1999; Lansberg et al., 2000). DWI scans are frequently acquired in the acute stage of stroke along with standard T1 and T2 scans (Tan et al., 2006). Given the availability of these scanning techniques, researchers have begun to correlate MRI-based neuroanatomical findings with functional measures, such as the National Institutes of Health Stroke Scale (Menezes et al., 2007).

Recent lesion-based studies also have associated dysphagia with distinct neuroanatomical regions following stroke. These areas include the frontal cortex (Broadley et al., 2003), internal capsule (Gonzalez-Fernandez et al., 2008; Hamdy et al., 1998), insula (Broadley et al., 2003, Daniels & Foundas, 1997), periventricular white matter (Daniels & Foundas, 1999), thalamus (Alberts et al., 1992), pons (Bassetti et al., 1996; Horner et al., 1991; Kim, J. S., 2002; Kim et al., 1995b; Schmahmann et al., 2004) and medulla (Aydogdu et al., 2001; Kameda et al., 2004; Kim, et al., 2000; Kim et al., 1995a; Kim et al., 1994; Kumral et al., 2002b; Kurono et al., 2006; Kwon et al., 2005; Seiser et al., 1999; Valls-Solé et al., 1996; Vuilleumier et al., 1995). Taken together, these findings have the potential to form a synopsis of the neuroanatomical predictors of dysphagia. However, the reported frequency varied widely even with lesions in the same brain regions. In some cases, poor study quality contributed to such variation. For example, some studies documented dysphagia based on the report of symptoms or did not differentiate its incidence for hemorrhagic versus ischemic stroke. Similarly, instead of identifying the MRI-
based correlates of dysphagia, many studies provided aggregate results from computed
tomography (CT) or MRI scans.

Given the discrepant incidence findings in the literature, we sought to review
systematically and to evaluate the evidence to derive a whole brain model of dysphagia
secondary to acute ischemic stroke. Our objectives were to identify published and unpublished
literature correlating MRI-based lesions with dysphagia after acute ischemic stroke, to critically
appraise the evidence and, if appropriate, to pool the available data to predict dysphagia
subsequent to lesions in discrete brain regions.

3.2. Materials and Methods

We conducted this review systematically and according to published guidelines
(Cochrane Stroke Group, 2009), starting with a detailed protocol developed *a priori* and
proceeding to a comprehensive search of sources. Next, we assessed the study quality of
accepted articles and finally extracted our targeted data from them.

3.2.1. Operational definitions

Dysphagia is defined as “oropharyngeal dysphagia”, characterized by abnormal
swallowing physiology of the upper aerodigestive tract and detected by clinical examination or
instrumental testing (Martino et al., 2005). The outcome of interest included MRI-based
neuroanatomical lesion sites associated with the presence or absence of dysphagia. We restricted
the sample to ischemic stroke, defined as an acute focal neurological deficit with a cerebral
infarct confirmed by MRI imaging.
3.2.2. Data sources

3.2.2.1. Database searches

We searched 14 databases for abstracts in any language between 1950 and June 2009, using the Cochrane Stroke Group Database Search Protocol (Cochrane Stroke Group, 2009). The databases were AMED, Biosis, CENTRAL, CINAHL, Compendium, Dissertation Abstracts, Embase, Health and Psychosocial Instruments (HaPI), Healthstar, Inspec, Medline, Pharmaceutical Abstracts, PsycInfo and Wilson. We searched HaPI in case it included tool validations involving dysphagia measures with consecutive samples. Similarly, we searched Pharmaceutical Abstracts in the event that drug trials involved a control arm of randomly selected or consecutive patients with report of dysphagia outcomes. We used the same medical subject headings (MeSH) and text word search terms as the Cochrane Stroke Group for each database with customizations. That is, we accepted all study designs and added search terms for dysphagia and magnetic resonance imaging (MRI). The search included archived terms for MRI, such as magnetic resonance spectroscopy, nuclear magnetic resonance imaging (NMR), proton spin tomography and zeugmatography.

3.2.2.2. Journal, conference and grey literature searches

We manually searched 17 relevant journals, including Cerebrovascular Diseases, Dysphagia, and Stroke, from 1991 to June, 2009, and three conference proceedings (Dysphagia Research Society, the European Stroke Meeting, and the International Stroke Conference) from the first date of their online availability to June, 2009. We also searched the System for Information on Grey Literature (SIGLE) to identify unpublished and grey literature.
3.2.3. Eligibility criteria

Eligible articles used MRI to associate neuroanatomical lesion sites with the presence or absence of dysphagia. We included studies in any language with adult ischemic stroke patients (>18 years). We accepted the following study designs: i) case series with ≥ 10 consecutively enrolled patients, ii) case control studies, iii) prospective or retrospective cohort studies with consecutive enrolment, and iv) randomized control trials. If consecutive enrolment was unclear for the case series or cohort articles, we contacted the authors to confirm it. Consequently, we excluded i) editorials and review articles, ii) studies with restricted samples (e.g. referrals to a speech-language pathology service), iii) studies without extractable dysphagia outcomes by brain region, and iv) studies without extractable MRI outcomes for ischemic stroke.

3.2.4. Data retrieval

One author (HF) independently searched the data sources to retrieve all relevant citations. Two authors (HF and SAS) then independently evaluated abstracts of the retrieved citations to select articles for full review. Bilingual clinical experts translated the French, German, Japanese and Spanish articles. Subsequently, two authors (HS and SAS) independently evaluated the full articles to determine final selection for quality review and data extraction. Discrepancies in abstract or article selection were resolved by consensus by the same two authors (HF and SAS), with consultation from a third author (RM) as required.

3.2.5. Data abstraction

3.2.5.1. Study quality

We used relevant items from the Cochrane Collaboration’s risk of bias tool to evaluate study quality (Higgins & Green, 2009). Specifically, we rated all selected articles for blinding and completeness of data for the dysphagia outcome. We documented additional factors
including study design, consistency of the dysphagia assessment for all patients, and use of operational definitions for dysphagia. Two authors (HF and SAS) independently evaluated factors as present, absent or not reported (unclear). Again, discrepancies in evaluation of quality factors were resolved by consensus, with consultation from a third author as required.

3.2.5.2. Study characteristics and outcomes

In keeping with our protocol, one author (HF) extracted data on study characteristics, dysphagia and MRI outcomes. Another author (RM) independently checked the accuracy of the extracted data for 15% of the articles, reviewing any discrepancies with the first author (HF) for a final determination of the observations. The targeted study characteristics included the total number of enrolled patients, the length of the enrolment period, the targeted brain regions, and the country in which the study was conducted. We categorized articles according to their capture of a first-ever ischemic stroke sample or a mixed ischemic stroke sample. We grouped articles as first-ever stroke if the number of patients with recurrent stroke was ≤ 5% of the sample. Mixed stroke articles had >5% recurrent stroke patients or the authors did not clearly describe the proportion of first-ever versus recurrent stroke. We also extracted information about the MRI scans and dysphagia assessments, including the timing of the MRI scan and dysphagia assessment following stroke onset, the MRI scan type used for lesion analyses, and the method of the dysphagia examination. In addition, we extracted all available individual level data from each selected article, including presence or absence of dysphagia, age, gender, and site and side of neuroanatomical lesion.

3.2.6. Statistical analysis

We pooled individual level data to derive the frequency of dysphagia according to neuroanatomical region. We defined dysphagia frequency to be the first identification of
dysphagia based on clinical records or prospective evaluation (Martino et al., 2005). To test the presence versus absence of dysphagia between groups, we used two-tailed independent samples t-tests for continuous variables. For frequency-based variables, we used chi-squared analyses. Evaluation of these group differences guided our logistic regression modeling. We proposed to control for group differences, should they exist, for age, gender and dysphagia assessment type (videofluoroscopy versus bedside evaluation). For measures of effect, we computed odds ratios and relative risks along with their 95% confidence intervals. Using clinical rationale, we selected predictor regions that we expected to have a high frequency of dysphagia. We performed analyses using SAS 9.2 to derive the odds ratios, subsequently converting them into relative risks for ease of interpretation (Higgins & Green, 1998). We then developed a neuroanatomical model of dysphagia after acute ischemic stroke and tested our model for its prediction of dysphagia using Nagelkerke’s R² test.

3.3. Results

3.3.1. Literature retrieved

There were total of 1110 citations relating to dysphagia, stroke and MRI from our database searches (n=766), journal hand searches (n=250), and conference proceedings (n=94). Of all citations, 964 had full abstracts, of which 880 did not meet our study inclusion criteria (see Figure 3-1). We selected the remaining 84 abstracts for full article review. There were 76 English, 4 Japanese, 2 Spanish, 1 French, and 1 German article. Following full review, we eliminated 67 articles (see Figure 3-1). Two articles were RCTs (Dyker & Lees, 1999; Kobayashi, Nakagawa, Sekizawa, Arai, & Sasaki, 1996). We eliminated them because MRI outcomes were not reported. We finally accepted 17 articles for this review, 15 in English and 2 in Japanese.
3.3.2. Methodological quality and characteristics of included studies

3.3.2.1. Study quality

All but one article explicitly stated consecutive enrolment of patients. For the remaining article (Valls-Solé et al., 1996), we contacted the first author, who verified consecutive enrolment. All studies used a cohort design and involved unique samples of patients. Only four (Kim & Kim, 2005; Kumral et al., 2002b; Min, Kim, Kim, Park, & Suh, 1999; Schmahmann et al., 2004) stated the timeline for data capture (see Table 3-1). Only one article reported blinding for the dysphagia measure (Kwon et al., 2005). Four studies described the same dysphagia assessment protocol for all patients: one involved screening (Kurono et al., 2006), one videofluoroscopy (Kwon et al., 2005) and two informal clinical evaluation (Izumi et al., 1996; Kim, H. et al., 2000). Only two studies declared an operational definition for their dysphagia outcome (Kim, H. et al., 2000; Kurono et al., 2006). All but one of the selected articles had complete outcome data for dysphagia at the individual patient level. The article that failed to meet this criterion reported that four patients had dysphagia, but provided individual level data documenting dysphagia for only three (Kim & Kim, 2005).

3.3.2.2. Study characteristics

For the 17 articles, there was a total enrolment of 745 patients, with sample sizes ranging from 10 to 214. The articles represented six countries, South Korea (n=8), Japan (n=3), Turkey (n=3), Spain (n=1), Switzerland (n=1), and the USA (n=1). Enrolment periods ranged from one year, three months to eight years. The difference in the frequency of dysphagia in patients with first-ever stroke compared to those with mixed stroke was not significant, \( \chi^2 (4, \text{N}=656) = .72, p = 0.40 \).
3.3.2.3. Neuroanatomical regions of interest

All 745 patients from the 17 articles had sustained only infratentorial strokes. The articles evaluated dysphagia after cerebellar, pontine, medial medullary and lateral medullary ischemic stroke, defining discrete anatomical regions of interest (see Table 3.2). Cerebellar regions included a rostral boundary from between the middle cerebellar peduncle and the anterolateral pons to a caudal boundary of the pontomedullary junction (Kumral, Kisabay, & Atac, 2006; Min et al., 1999). One article identified isolated lesions within the middle cerebellar peduncle (Izumi et al., 1996). The midbrain region involved a rostral boundary from just below the lower thalamus to a caudal boundary just above the midbrain-pontine junction (Kim, J. S. & Kim, 2005; Kumral et al., 2002a). Pontine lesions included a rostral boundary of the round shape of the pons with a small round-shaped aqueduct (Kim, J. S. et al., 1995b) and a caudal boundary of just above the medulla (Schmahmann et al., 2004) where images of the facial and acoustic nerves showed grooves (Kim, J. S. et al., 1995b). Articles that reported lesions in the medulla identified regions extending from either the pontomedullary junction (Kim, H. et al., 2000; Kurono et al., 2006; Vuilleumier et al., 1995) or the posterolateral bulging of the restiform body (Kim, J. S., 2003; Kim, J. S. et al., 1995a; Kim, J. S. et al., 1994; Kumral et al., 2002b; Kwon et al., 2005, Valls-Solé et al., 1996) the relatively round shape of the medulla with a closed fourth ventricle (Kim, H. et al., 2000; Kim, J. S., 2003; Kim, J. S. et al., 1995a; Kim, J. S. et al., 1994; Kwon et al., 2005; Valls-Solé et al., 1996) or to the cervicomedullary junction (Kameda et al., 2004; Kumral et al., 2002b; Kurono et al., 2006; Vuilleumier et al., 1995). The lateral medullary regions did not include paramedian extension. Similarly, medial medullary regions did not include lateral extension.
Concerning their MRI scan protocols, five articles reported using T2, T1 and DWI scans (Kim, J. S. & Kim, 2005; Kumral et al., 2002a; Kumral et al., 2006; Kwon et al., 2005; Schmahmann et al., 2004). Seven articles used T1 and T2 scans (Kim, J. S., 2003; Kim, J. S. et al., 1995a; Kim, J. S. et al., 1995b; Kim, J. S. et al., 1994; Kumral et al., 2002b; Min et al., 1999; Vuilleumier et al., 1995), and two used T2 scans (Kurono et al., 2006; Valls-Solé et al., 1996). Three articles did not report their MRI scan protocol (Kameda et al., 2004; Kim, H. et al., 2000; Izumi et al., 1996). Eight articles used T2-weighted MRI scans for their lesion analyses (Kim, H. et al., 2000; Kim, J. S. et al., 1995a; Kim, J. S. et al., 1995b; Kim, J. S. et al., 1994; Kumral et al., 2006; Kwon et al., 2005; Min et al, 1999; Valls-Solé et al., 1996), while one used diffusion-weighted MRI scans (Kumral et al., 2006). The remaining eight articles did not report the scan type used for lesion analyses (Izumi et al., 1996; Kameda et al., 2004; Kim, H. et al., 2000; Kim, J. S. & Kim, 2005; Kumral et al., 2002a; Kumral et al., 2002b; Schmahmann et al., 2004; Vuilleumier et al., 1995). Of all the articles, seven described the timing of MRI scanning post stroke onset, ranging from within 3 (Kumral et al., 2006) to 21 (Izumi et al., 1996) days.

3.3.2.4. Dysphagia outcomes reported

Seven of the 17 articles reported the timing of the dysphagia evaluation from the onset of stroke ranging from within 5 (Kim, J. S. et al., 1994) to 21 (Izumi et al., 1996) days (see Table 3-2). No article reported the duration between MRI scanning and dysphagia assessments. Fourteen articles reported dysphagia evaluation through clinical informal examination (Izumi et al., 1996; Kameda et al., 2004; Kim, J. S., 2003; Kim, J. S. & Kim, 2005; Kim, J. S. et al., 1995a; Kim, J. S. et al., 1995b; Kim, J. S. et al., 1994; Kumral et al., 2002a; Kumral et al., 2002b; Kumral et al., 2006; Min et al, 1999; Schmahmann et al., 2004; Valls-Solé et al., 1996; Vuilleumier et al., 1995). Two reported dysphagia assessment by videofluoroscopy (Kim, H. et al., 2000; Kwon et
al., 2005), performed by a speech-language pathologist, with outcomes of laryngeal penetration or aspiration. One article used screening, thereby identifying the presence or absence of risk of dysphagia (Kurono et al., 2006).

### 3.3.3. Frequency and neuroanatomical models of dysphagia

All 17 selected articles had extractable individual patient level data for their dysphagia measure with comparable reports of age and gender characteristics (see Table 3-3). We excluded patients who had received CT scans and those who had lesions extending from infratentorial regions into subcortical and/or cortical regions. From the initial sample of 745 patients, there were 656 eligible patients with circumscribed lesions in discrete regions. These regions included isolated lesions in the cerebellum, midbrain, pons, lateral or medial medulla and pontine, medial medullary or lateral medullary lesions extending only into the cerebellum. There were 469 men and 187 women. In 248 patients, there were individual level data for age, ranging from 27 to 89 years (mean 61.8 years). The presence versus absence of dysphagia was not significant, for gender, \( \chi^2 (4, N=248) = 1.47, p = 0.22 \) or age, \( t (df=246) = .42, p=.68 \). Similarly, a chi-squared analysis for assessment type was not significant, \( \chi^2 (4, N=515) = 2.0, p = 0.16 \).

Individual level data for laterality of lesion were available in 238 patients. Right-sided lesions occurred in 118 patients, left-sided in 112, and bilateral in eight. Within the sample of 656 patients, there was a dysphagia frequency of 0% in the cerebellum, 6% in the midbrain, 43% in the pons, 40% in the medial medulla and 57% in the lateral medulla (Table 3-4). Our model demonstrated increased risk of dysphagia after pontine, medial medullary, and lateral medullary stroke compared to cerebellar or midbrain stroke (see Figure 3-2). Nagelkerke’s \( R^2 \) was .203.

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1 Videofluoroscopy was used in two articles reporting medullary infarcts. Consequently, we conducted the chi-squared analysis in the sample of patients with medullary infarcts.
Post-hoc analyses for only the subgroup of patients with isolated lesions (n=399) demonstrated a frequency of dysphagia of 0% in the cerebellum, 6% in the midbrain, 49% in the pons, 50% in the medial medulla and 59% in the lateral medulla. The frequency of dysphagia in the subgroup compared to the whole sample was not statistically significant, $\chi^2 (4, N=656) = 3.38, p = 0.067$. As anticipated, a logistic regression model of the subgroup revealed comparable findings to the whole sample, where lesions to the isolated pons, medial medulla, and lateral medulla predicted dysphagia, with odds ratios (95% confidence interval) of 8.3 (2.2 -31.7), 27.3 (7.3-101.9), and 39.0 (12.0-127.0), respectively.

3.4. Discussion

The goal of this review was to develop a whole brain model of dysphagia. However, the available evidence was limited to infratentorial stroke including the cerebellum, midbrain, pons, medial and lateral medulla. Within these regions, the reported frequency of dysphagia ranged from 0% to 57%, lowest after cerebellar lesions and highest after lateral medullary lesions. These findings suggest that cerebellar lesions did not contribute to the presence of dysphagia. In contrast, lesions in the pons, medial and lateral medulla were highly associated with the presence of dysphagia. Although these results are not surprising, given our current understanding of brainstem function, they are the first step in quantifying the increased risk of dysphagia based on neuroanatomical lesion site.

This study is the first to document the presence of dysphagia in a large sample of patients. We pooled results for this large sample of patients because there were individual level data for dysphagia frequency in all articles. The samples were homogeneous with respect to their consecutive enrolment of patients and in their selection of acute ischemic stroke patients. In addition, all articles clearly reported which patients had received MRI scans. Our
neuroanatomical model demonstrated a much higher likelihood of dysphagia after pontine and medullary lesions than after cerebellar or midbrain lesions. However, there were great discrepancies in the frequencies of dysphagia after medial and lateral medullary lesions, ranging from 15% (Kim, J. S. et al., 1995a) to 100% (Valls-Solé et al., 1996; Vuilleumier et al., 1995) and from 35% (Kwon et al., 2005) to 78% (Valls-Solé et al., 1996), respectively. These discrepancies may be due, in part, to differences in assessment methods and sample sizes. Although all studies evaluated acute stroke patients, there were inconsistencies in the timing and methodology of both the MRI imaging and the dysphagia assessments. Small sample sizes may limit the capture of true frequency, yet because we pooled individual level data, our model compensated for discrepancies in sample size.

All of the articles selected for this review were observational and possessed methodological limitations. For example, all but one (Kwon et al., 2005) lacked blinding for the dysphagia measure and only two (Kim, H. et al., 2000; Kurono et al., 2006) used operational definitions for the presence or absence of dysphagia. The quality of the dysphagia assessments was poor, as no article reported reliability or validation of their measures. One article used a non-standardized screening protocol (Kurono et al., 2006), while two used a gold standard evaluation, namely videofluoroscopy (Kim, H. et al., 2000; Kwon et al., 2005). However, videofluoroscopic measures did not capture the entire swallow and were, instead, limited to laryngeal penetration or aspiration (Kim, H. et al., 2000; Kwon et al., 2005). The remaining articles reported informal clinical assessment, without clear documentation of their assessment procedures, limiting reproducibility of their results. The articles we reviewed did not document the exact timing of the dysphagia evaluation on a case-by-case basis, thereby limiting the sensitivity of dysphagia outcomes. Most articles did not evaluate the lesion correlates of
dysphagia using DWI scans for the hyperacute and acute phases of stroke. Despite these methodological shortcomings for the dysphagia outcome and MRI analysis, all articles provided clear documentation of the neuroanatomical regions of interest for their lesion analyses. In addition, most articles reported the range in timing of the dysphagia assessment and of the MRI scans for their samples.

A systematic review such as this is limited by the available evidence. The eligible articles reported only on dysphagia following infratentorial stroke. Articles dealing with supratentorial stroke were eliminated because they provided aggregate data for CT and MRI or did not differentiate between the dysphagia incidence following hemorrhagic versus ischemic stroke. Although not the purpose of the current systematic review, future work is needed to compare these findings with parallel bodies of literature identifying dysphagia after supratentorial stroke based on CT scans and after hemorrhagic stroke.

Not all of the articles we selected for our study reported age, gender, side of lesion or time to dysphagia assessment on an individual patient basis, limiting comparisons of the influence of these variables on the presence of dysphagia. Nevertheless, we identified detailed MRI information for a large number of patients, allowing us to establish a first robust model of dysphagia frequency following lesions within the infratentorial compartment. This information is beneficial to the early detection of dysphagia after ischemic stroke, especially in light of current guidelines that recommend screening (Lindsay et al., 2008). That is, knowing the relative risk of dysphagia according to lesion localization may precipitate earlier screening in patients at highest risk. Consequently, this may facilitate more timely assessments by speech language pathologists and treatments pertaining to implementing an oral diet or alternative mode of feeding.
3.5. Conclusion

The available literature did not address supratentorial lesions. Our results showed a high frequency of dysphagia throughout the lower brainstem, especially in the lateral medulla. In contrast, dysphagia was rare after a midbrain or cerebellar stroke. Of the articles in this review, dysphagia was not assessed in a consistent manner or with objective methods. Some studies used bedside screening while others used informal clinical assessment, thereby limiting their ability to detect reliably and accurately the presence of dysphagia. Furthermore, studies that used the more objective method of videofluoroscopic assessment restricted their measures to laryngeal penetration or aspiration. Considering these gaps in the available literature, we conclude that future studies are needed to evaluate dysphagia systematically and comprehensively secondary to lesions throughout the whole brain.

3.6. Acknowledgments

We gratefully acknowledge Mitsuko Takeuchi’s review and translation of Japanese articles. We thank the many authors who responded to requests for additional information pertaining to their articles.
### Table 3-1. Evaluation of study quality regarding capture of dysphagia outcome

<table>
<thead>
<tr>
<th>Article</th>
<th>Timeline for data capture</th>
<th>Assessor blinded</th>
<th>Consistent assessment for all patients</th>
<th>Declared operational definition for outcome</th>
<th>Outcome addressed for all patients</th>
</tr>
</thead>
<tbody>
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<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
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<td>unclear</td>
<td>unclear</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
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<td>unclear</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
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<td>unclear</td>
<td>unclear</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
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<td>unclear</td>
<td>unclear</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
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<td>unclear</td>
<td>unclear</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Kim, J. (2003)</td>
<td>unclear</td>
<td>unclear</td>
<td>unclear</td>
<td>unclear</td>
<td>yes</td>
</tr>
<tr>
<td>Kim, J. &amp; Kim (2005)</td>
<td>mixed</td>
<td>unclear</td>
<td>unclear</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Kumral et al. (2002a)</td>
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<td>unclear</td>
<td>unclear</td>
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<td>yes</td>
</tr>
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<td>retrospective</td>
<td>unclear</td>
<td>unclear</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
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<td>unclear</td>
<td>unclear</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Kurono et al. (2006)</td>
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<td>unclear</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Kwon et al. (2005)</td>
<td>unclear</td>
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<td>yes</td>
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<td>yes</td>
</tr>
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<td>Min et al. (1999)</td>
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<td>unclear</td>
<td>unclear</td>
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</tr>
<tr>
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<td>unclear</td>
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</tr>
</tbody>
</table>
Table 3-2. Study characteristics according to stroke type (first-ever or mixed) for all patients

<table>
<thead>
<tr>
<th>Article</th>
<th>Sample N=745</th>
<th>Country</th>
<th>Enrolment (years; months)</th>
<th>Targeted brain regions</th>
<th>Days* to MRI</th>
<th>MRI lesion analysis (mm thick)</th>
<th>Days* to dysphagia exam</th>
<th>Method of dysphagia exam</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Ever Sample</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim, J. et al (1995a)</td>
<td>18</td>
<td>South Korea</td>
<td>4:2</td>
<td>MM</td>
<td>NR</td>
<td>T2 (5-6)</td>
<td>NR</td>
<td>Clinical</td>
</tr>
<tr>
<td>Kim, J. et al (1995b)</td>
<td>37</td>
<td>South Korea</td>
<td>3:4</td>
<td>Pons</td>
<td>NR</td>
<td>T2 (5-6)</td>
<td>NR</td>
<td>Clinical</td>
</tr>
<tr>
<td>Kim, J. (2003)</td>
<td>130</td>
<td>South Korea</td>
<td>8:0</td>
<td>LM</td>
<td>NR</td>
<td>T2 (3)</td>
<td>≤ 7</td>
<td>Clinical</td>
</tr>
<tr>
<td>Kumral et al (2006)</td>
<td>23</td>
<td>Turkey</td>
<td>2:0</td>
<td>Cereb</td>
<td>NR</td>
<td>T2 (5-6)</td>
<td>NR</td>
<td>Clinical</td>
</tr>
<tr>
<td>Kwon et al (2005)</td>
<td>46</td>
<td>South Korea</td>
<td>1:4</td>
<td>LM, MM</td>
<td>≤ 11</td>
<td>T2 (3)</td>
<td>4.6 (± 2.3)†</td>
<td>VFS</td>
</tr>
<tr>
<td>Schmahmann et al (2004)</td>
<td>25</td>
<td>USA</td>
<td>8:0</td>
<td>Pons</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Clinical</td>
</tr>
<tr>
<td><strong>Mixed Sample</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Izumi et al (1996)</td>
<td>10</td>
<td>Japan</td>
<td>7:0</td>
<td>Cereb</td>
<td>NR (NR)</td>
<td>7-21</td>
<td>Clinical</td>
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<tr>
<td>Kim, J. et al (1994)</td>
<td>33</td>
<td>South Korea</td>
<td>3:6</td>
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<td>NR</td>
<td>T2 (5-6)</td>
<td>≤5c</td>
<td>Clinical</td>
</tr>
<tr>
<td>Kim, J. &amp; Kim, J. (2005)</td>
<td>40</td>
<td>South Korea</td>
<td>6:9</td>
<td>Midbrain</td>
<td>≤ 10</td>
<td>NR (NR)</td>
<td>NR</td>
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<tr>
<td>Kumral et al (2002a)</td>
<td>41</td>
<td>Turkey</td>
<td>6:0</td>
<td>Midbrain</td>
<td>≤ 7</td>
<td>NR (NR)</td>
<td>NR</td>
<td>Clinical</td>
</tr>
<tr>
<td>Kumral et al (2002b)</td>
<td>11</td>
<td>Turkey</td>
<td>7:0</td>
<td>MM</td>
<td>≤ 7</td>
<td>NR (5)</td>
<td>NR</td>
<td>Clinical</td>
</tr>
<tr>
<td>Min et al (1999)</td>
<td>31</td>
<td>South Korea</td>
<td>1:3</td>
<td>Cereb</td>
<td>NR</td>
<td>T2 (3)</td>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Valls-Solé et al (1996)</td>
<td>14</td>
<td>Spain</td>
<td>NR</td>
<td>LM, MM</td>
<td>NR</td>
<td>T2 (5-6)</td>
<td>≤ 7</td>
<td>Clinical</td>
</tr>
</tbody>
</table>

Clinical= Clinical informal assessment by unspecified clinician.

Cereb=Cerebellum.

LM=Lateral Medulla.

MM=Medial Medulla.
NR = Not reported.

VFS = Videofluoroscopy.

*=From stroke onset.

†=Mean (SD).

\(^a\)DWI scan was used for analysis in one patient.

\(^b\)The mixed stroke group includes articles in which >5% of the patients had sustained a recurrent stroke. It also includes those articles that did not clearly report a sample of first-ever stroke.

\(^c\)Except two patients seen at an unspecified time.

\(^d\)Except for two patients who were evaluated at 4 months and 9 months.
Table 3-3. Characteristics according to brain region for eligible patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligible patients (N=656)</th>
<th>Gender (men)</th>
<th>Mean age in years (range)</th>
<th>Dysphagia after isolated lesions n/N (%)</th>
<th>Dysphagia after isolated lesions extending into the cerebellum n/N (%)</th>
<th>Dysphagia frequency for all eligible patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cerebellum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Izumi et al. (1996)</td>
<td>7</td>
<td>3</td>
<td>56 (46-76)</td>
<td>0/7</td>
<td>---</td>
<td>0</td>
</tr>
<tr>
<td>Kumral et al. (2006)</td>
<td>8</td>
<td>6</td>
<td>(31-81)</td>
<td>0/8</td>
<td>---</td>
<td>0</td>
</tr>
<tr>
<td>Min et al. (1999)</td>
<td>21</td>
<td>15</td>
<td>59 (42-78)</td>
<td>0/21</td>
<td>---</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>0/36 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td><strong>Midbrain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kumral et al. (2002a)</td>
<td>9</td>
<td>7</td>
<td>63 (41-83)</td>
<td>0/9</td>
<td>---</td>
<td>0</td>
</tr>
<tr>
<td>Kim, J. &amp; Kim (2005)</td>
<td>40</td>
<td>23</td>
<td>65 (47-81)</td>
<td>3/40</td>
<td>---</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>3/49 (6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td><strong>Pons</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al. (1995b)</td>
<td>32</td>
<td>23</td>
<td>63 (36-85)</td>
<td>13/32</td>
<td>---</td>
<td>41</td>
</tr>
<tr>
<td>Total</td>
<td>23/47 (49)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>43</td>
</tr>
<tr>
<td><strong>Medial Medulla</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vuilleumier et al. (1995)</td>
<td>1</td>
<td>1</td>
<td>51 (n/a)</td>
<td>1/1</td>
<td>---</td>
<td>100</td>
</tr>
<tr>
<td>Kim, H. et al. (2000)</td>
<td>4</td>
<td>2</td>
<td>58 (27-89)</td>
<td>2/4</td>
<td>---</td>
<td>50</td>
</tr>
<tr>
<td>Valls-Solé et al. (1996)</td>
<td>5</td>
<td>3</td>
<td>73 (59-89)</td>
<td>5/5</td>
<td>---</td>
<td>100</td>
</tr>
<tr>
<td>Kumral et al. (2002b)</td>
<td>7</td>
<td>6</td>
<td>58 (26-80)</td>
<td>3/7</td>
<td>---</td>
<td>43</td>
</tr>
<tr>
<td>Kwon et al. (2005)</td>
<td>9</td>
<td>9</td>
<td>58 (38-69)</td>
<td>7/9</td>
<td>---</td>
<td>78</td>
</tr>
<tr>
<td>Kim, J. et al. (1995a)</td>
<td>13</td>
<td>10</td>
<td>64 (41-75)</td>
<td>1/12</td>
<td>1/1</td>
<td>15</td>
</tr>
<tr>
<td>Kameda et al. (2004)</td>
<td>41</td>
<td>32</td>
<td>65 (±12)</td>
<td>---</td>
<td>12/41†</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>19/38 (50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40</td>
</tr>
<tr>
<td><strong>Lateral Medulla</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valls-Solé et al. (1996)</td>
<td>9</td>
<td>5</td>
<td>65 (38-82)</td>
<td>5/6</td>
<td>2/3</td>
<td>78</td>
</tr>
<tr>
<td>Kim, H. et al. (2000)</td>
<td>19</td>
<td>15</td>
<td>63 (43-82)</td>
<td>10/19</td>
<td>---</td>
<td>53</td>
</tr>
<tr>
<td>Vuilleumier et al. (1995)</td>
<td>19</td>
<td>17</td>
<td>60 (30-85)</td>
<td>8/11</td>
<td>1/8</td>
<td>47</td>
</tr>
<tr>
<td>Kurono et al. (2006)</td>
<td>21</td>
<td>17</td>
<td>62 (43-83)</td>
<td>---</td>
<td>10/21*</td>
<td>48</td>
</tr>
<tr>
<td>Kim, J. et al. (1994)</td>
<td>33</td>
<td>22</td>
<td>56 (32-71)</td>
<td>15/26</td>
<td>5/7</td>
<td>61</td>
</tr>
<tr>
<td>Kwon et al. (2005)</td>
<td>37</td>
<td>27</td>
<td>54 (29-76)</td>
<td>13/37</td>
<td>---</td>
<td>35</td>
</tr>
<tr>
<td>Kim, J. (2003)</td>
<td>130</td>
<td>90</td>
<td>57 (28-84)</td>
<td>84/130</td>
<td>---</td>
<td>65</td>
</tr>
<tr>
<td>Total</td>
<td>135/229 (59)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>57</td>
</tr>
</tbody>
</table>
*= Cerebellar extension was unclear for all patients.
†= Cerebellar extension was reported for at least some patients (exact numbers not provided).

**Table 3-4.** Frequencies, odds ratios and relative risks of dysphagia according to brain region after acute ischemic stroke

<table>
<thead>
<tr>
<th>Region</th>
<th>Dysphagia incidence (%)</th>
<th>Odds ratio (OR)</th>
<th>OR 95% CI</th>
<th>Relative risk (RR)</th>
<th>RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellum</td>
<td>0</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Midbrain</td>
<td>6</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Pons</td>
<td>43</td>
<td>4.5</td>
<td>1.5 – 13.7</td>
<td>3.7</td>
<td>1.5 – 7.7</td>
</tr>
<tr>
<td>Medial Medulla</td>
<td>40</td>
<td>11.1</td>
<td>4.0 – 30.3</td>
<td>6.9</td>
<td>3.4 – 10.9</td>
</tr>
<tr>
<td>Lateral Medulla</td>
<td>57</td>
<td>21.9</td>
<td>8.7 – 55.2</td>
<td>9.6</td>
<td>5.9 – 12.8</td>
</tr>
</tbody>
</table>
Figure 3-1. Selection process from abstract and full article reviews
**Figure 3-2.** Neuroanatomical Model for Dysphagia after Acute Ischemic Infratentorial Stroke (adapted from Broadley et al., 2005). RR=Relative Risk; CI=Confidence Interval.
MRI-based Neuroanatomical Predictors of Dysphagia, Dysarthria, and Aphasia in 160 Patients with a First Acute Ischemic Stroke

Abstract

Background - Dysphagia, dysarthria and aphasia occur frequently after stroke. We sought to identify MRI-based neuroanatomical predictors of these impairments early after the onset of ischemic stroke.

Methods – We randomly selected 250 patients from a consecutive cohort of first ischemic stroke patients with MRI scans (N=716) from the Registry of the Canadian Stroke Network’s database (2003–2008) in one stroke centre. We excluded patients with dementia, brain tumour, neurosurgical interventions, or contusions. We documented the presence of the acute lesion in 12 neuroanatomical regions of interest and extracted lesion volumes. We also identified concomitant neurological compromise, including brain atrophy, white matter disease, and prior covert stroke. Two raters independently extracted all data, resolving discrepancies by consensus. We computed logistic regression analyses to identify predictors for each impairment.

Results - 160 patients met our eligibility criteria. Predictors of dysphagia included increasing age (OR 1.4, 95% CI 1.1 – 1.8), at least moderate brain atrophy (OR 3.0, 95% CI 1.04–8.6), and lesions to the medulla (OR 6.2, 95% CI 1.5 – 25.8), pons (OR 3.6, 95% CI 1.2 – 10.1), insula (OR 4.8, 95% CI 2.0 – 11.8), and internal capsule (OR 2.9, 95% CI 1.2 – 6.6). Predictors of dysarthria included decreasing lesion volume (OR 1.003, 95% CI 1.0 – 1.005) and lesions to the pons (OR 7.8, 95% CI 2.7 – 22.9), internal capsule (OR 3.6, 95% CI 1.6 – 7.9), and insula (OR 4.5, 95% CI 1.8 – 11.4). Predictors of left-hemisphere aphasia included increasing lesion volume (OR 1.5, 95% CI 1.1 –
2.1) and lesions to the thalamus (OR 6.2, 95% CI 1.6 – 24.4), insula (OR 34.4, 95% CI 4.2 – 283.4), and superficial MCA territory (OR 4.7, 95% CI 1.5 – 14.2).

**Conclusions** – We modeled neuroanatomical predictors of dysphagia throughout the brain and extended previous findings for dysarthria andaphasia in a large homogeneous sample of patients. Next, we will identify more discrete neuroanatomical regions using voxel-based lesion symptom mapping.

### 4. Study Three

#### 4.1. Introduction

Dysphagia, dysarthria, and aphasia occur in isolation or concomitantly in two-thirds of all first-ever acute ischemic stroke patients with magnetic resonance imaging (Flowers et al., 2013). Dysphagia may result in negative acute stage outcomes such as aspiration pneumonia (Martino et al., 2005) and/or death (Altman et al., 2010). Dysarthria incurs negative social and emotional sequelae (Dickson et al., 2008) and may persist for months beyond the acute presentation (Canbaz et al., 2010). Like post-stroke dysphagia, aphasia is predictive of increased acute stage mortality (Guyomard et al., 2009). It may also lead to negative outcomes during the acute stage, such as depression (Kauhanen et al., 2000) and increased length of in-patient hospital stay (Guyomard et al., 2009).

Given the high frequency of dysphagia, dysarthria, and aphasia and their association with negative outcomes after ischemic stroke, it is important to identify their presence early after ischemic stroke. Dysarthria and aphasia may be the chief or sole symptomatic manifestations of stroke (Canbaz et al., 2010), facilitating a rapid diagnosis of stroke even prior to emergency room arrival (Krebes et al., 2012). Therefore, screening for communication in all patients could augment rapid diagnosis and ensure timely management by health professionals. Although not a
hallmark symptom of stroke, dysphagia may compromise timely medical interventions and/or patient safety (Kelly, Wright, & Wood, 2011). For example, patients with dysphagia may require alternative solutions to oral medication or incur risk of medication administration error (Kelly et al., 2011). Consequently, in the absence of rapid screening and assessment, patients with dysphagia incur increased risk of developing aspiration pneumonia (Hinchey et al., 2005). Once identified, dysphagia requires prompt attention to facilitate optimal stroke management. The initial step to ensure timely management of dysphagia, dysarthria, and aphasia involves documentation of the onset of stroke through symptom report and/or by magnetic resonance imaging. Subsequently, the presence of the impairments may be elucidated relative to a confirmed time of stroke onset. Identifying indicators or precursors of the presence of the three impairments in the hyperacute and acute stage will enable development of routine screening and prioritized management by multiple health professionals.

Multimodal magnetic resonance imaging, including diffusion weighted along with standard T1-, T2-, and T2 FLAIR sequences, is essential to acute stroke imaging protocols, permitting identification of acute ischemic lesions (Leiva-Salinas et al., 2011). Most acute stroke protocols involve diffusion-weighted imaging (DWI) because of its sensitivity to acute ischemia (Lovblad et al., 1998). In fact, DWI has the capability to confirm hyperacute ischemic stroke within minutes of its onset (Merino & Warach, 2010). T1 sequences are sensitive to discrete anatomical changes, facilitating ischemic etiological diagnoses such as dissection (Jauch et al. 2013). Standard T2 sequences are acquired more rapidly than T1 sequences (Crawley & Henkelman, 1988) and are useful in documenting brain abscess, microbleeds, and the presence of old and/or new stroke (Kloska et al., 2010). T2 FLAIR sequences darken the cerebral spinal fluid, allowing for rapid discrimination of prior stroke, white matter disease, and/or new stroke
Hence, multimodal MRI imaging offers the possibility to confirm the onset of acute or hyperacute ischemia and to associate acute (Kumral & Bayülkem, 2003) and chronic neuroanatomical factors (Alexander et al., 2010) with the presence of neurological deficits.

A small number of studies have reported MRI-based acute stage neuroanatomical predictors of dysphagia (Alberts et al., 1992; Gonzalez-Fernandez et al., 2008; Flowers et al., 2011; Cola et al., 2010), dysarthria (Baier et al., 2011; Kim et al., 2003; Kumral et al., 2007; Schoch et al., 2006), and aphasia (Join-Lambert et al., 2012; Kreisler et al., 2000; Magnusdottir et al., in press). An early study evaluating aspiration by videofluoroscopy demonstrated a higher frequency of aspiration in patients with lesions to the middle cerebral artery, posterior cerebral artery, and cerebellar territories (Alberts et al., 1992). A second case control study reported dysphagia after supratentorial stroke based on bedside assessment (Gonzalez-Fernandez et al., 2008). After controlling for lesion volume and stroke severity, only internal capsular lesions predicted dysphagia (Gonzalez-Fernandez et al., 2008). Cola et al. (2010) later evaluated multiple domains of physiologic dysphagia by videofluoroscopy in patients with isolated subcortical lesions, showing a higher frequency of dysphagia in patients with left sided periventricular white matter lesions compared to right sided lesions (Cola et al., 2010). A recent systematic review of the literature identified predictors of dysphagia based on screening, clinical or videofluoroscopic evaluation in patients with infratentorial lesions (Flowers et al., 2011). Pooled individual level patient data showed a high risk of dysphagia after pontine and medullary lesions, regardless of method of evaluation (Flowers et al., 2011).

The four studies reporting dysarthria after MRI confirmed acute stroke identified increased frequency of its presence within discrete neuroanatomical regions, including cortical
subcortical (Baier et al., 2011), supratentorial (Benke & Kertesz, 1989), and cerebellar (Schoch et al., 2006). Cortical brain regions responsible for dysarthria included discrete middle cerebral artery (MCA) territory areas: lateral to the precentral knob (Kim et al., 2003); supramarginal and angular gyri (Benke & Kertesz, 1989); periventricular areas (Kim et al., 2003; Kumral et al., 2007); temporal regions of the MCA (Baier et al., 2011; Benke & Kertesz, 1989); the insula (Baier et al., 2011; Benke & Kertesz, 1989; Kumral et al., 2007). Subcortical regions associated with dysarthria include the basal ganglia, thalamus, and internal capsule (Benke & Kertesz, 1989). Within infratentorial regions, the cerebellum (Kumral et al., 2007) and the pons (Kumral et al., 2007; Schoch et al., 2006) may result in acute stage dysarthria.

There are few acute stage MRI-based investigations of lesion correlates of aphasia. Only one study has considered the whole brain lesion correlates of aphasia (Kreisler et al., 2000), documenting the involvement of the temporal gyri, external capsule, and the insula. Other studies have considered brain behaviour relationships of discrete neuroanatomical regions and specific language tasks (Magnusdottir et al., in press; Join-Lambert et al., 2012). Implicated regions for comprehension included the temporoprefrontal region (Kümmerer et al., 2013) and the temporal pole, specifically for sentence processing (Magnusdottir et al., in press). A region shown to be necessary for overt repetition was the posterior temporoparietal region (Kümmerer et al., 2013).

Despite recent interest in the neuroanatomical associations of dysphagia, dysarthria, and aphasia, only three studies documented whole brain predictors of these impairments (Alberts et al., 1992; Kreisler et al., 2000; Kumral et al., 2007). Also, only one study identified predictors in consecutively enrolled patients with and without dysphagia (Flowers et al., 2011). None of the studies investigating dysarthria and aphasia modeled predictive regions for patients with and
without the impairments. Other than the study by Gonzalez-Ferndandez et al. (2008), all studies lacked a report of the potentially confounding effects of demographic, stroke, or chronic neuroanatomical factors on the expression of the three impairments. Elucidating demographic, stroke, and neuroanatomical factors that predict impairments is necessary to inform health care professionals of their risk and to develop strategies for their early management.

To extend the literature, the current study sampled a large consecutive population of acute ischemic stroke patients, who had MR imaging, from the Registry of the Canadian Stroke Network’s (RCSN) database from a previous study (Flowers et al., 2011). Our previous study randomly selected 250 patients for a supplementary chart review to identify the frequency, demographic, and clinical stroke predictors of dysphagia, dysarthria, and aphasia (Flowers et al., 2013). The previous study incurred data loss for 29 patients, resulting in a final sample of 221 patients, who also comprise the sample for the current study. We sought to correlate acute and chronic whole brain neuroanatomical indicators with the presence versus absence of dysphagia, dysarthria, and aphasia. Our first objective was to model demographic, stroke, and MRI-based neuroanatomical predictors of the three impairments. Our second objective was to describe gross anatomical acute lesion patterns in patients with dysphagia, dysarthria, and aphasia.

4.2. Methods

4.2.1. Patient selection

The current study considered the eligibility of all 221 patients from the Toronto Western Hospital to derive neuroanatomical measures based on the MRI scans. We included all patients with MRI scans ≤ 14 days post stroke onset, with a clear lesion on diffusion weighted imaging. We excluded patients with a previous history of dementia, as documented in the RCSN database,
and those with MRI evidence of prior neurological disease or neurosurgical intervention, such as brain tumours, abscess, contusions, previous resection, or cerebrospinal fluid shunt removal.

4.2.2. Dependent variables

We defined each impairment a priori based on clinical signs from medical chart review (Flowers et al., 2013). For example, the presence of dysphagia required assessment by speech-language pathology or insertion of enteral feeds whereas the presence of dysarthria and/or aphasia required assessment by speech-language pathologists, physicians, or stroke nurses.

4.2.3. Independent variables

We retained variables relating to demographics and acute stroke from the RCSN database, including age, gender, risk factors for stroke, comorbidities, ischemic stroke etiological classifications, and stroke severity scores (Flowers et al., 2013). For the current study, we extracted supplementary MRI-based variables for previously eligible patients, documenting date and time of the MRI scans, acute lesion factors, and chronic brain disease factors.

4.2.4. MR image acquisition

Multimodal acute stroke imaging comprised part of the standard clinical stroke protocol. The MR scanner was a 1.5 Tesla Signa EchoSpeed scanner (version 8.2.3, GE Healthcare) with a standard head coil. The imaging protocol included conventional T1- and T2-weighted imaging. T1 imaging involved sagittal sequences (RT/TE 450/20) with 7.5 mm section thickness and 2mm spacing. T2 imaging involved axial FLAIR sequences (RT/TE 9,000/165; TI 2,200 ms) with 5mm section thickness and 2mm spacing and isotropic axial DWI sequences ($b_{\text{max}}=1000$ s/mm$^2$; RT/TE 11,000/59) in three orthogonal directions with 5mm section thickness and 0 mm spacing.
4.2.5. MR scan consensus

Using a pre-determined data extraction manual (Appendix I) and data capture form (Appendix J), two raters independently evaluated all MRI scans, documenting reasons for exclusion or inclusion of patients. Both raters were blind to ischemic stroke etiology, stroke severity, and dysphagia, dysarthria, or aphasia status. A neurologist and two neuroradiologists trained the first rater, an SLP, on the first 25 MRI scans. The second rater was one of the neuroradiologists who had participated in training the first rater. The two raters independently documented attributes of the acute lesions and concomitant brain disease for all patients. Each rater could request a second opinion from a senior neuroradiologist and/or neurologist as required at any point during independent review of the scans. Following MRI scan review, the two raters amended discrepant items by consensus. Any unresolved discrepancies were reviewed by either the staff neuroradiologist or the staff neurologist, both of whom had participated in the initial rater training.

4.2.6. MR scan data extraction

4.2.6.1. Exclusions

We recorded evidence of exclusionary neurological diseases including brain tumours, abscess, prior neurosurgical interventions, and/or contusions using the FLAIR image, with access to all available MRI modalities. We also excluded patients whose diffusion-weighted images were not of adequate quality for interpretation of acute lesion sites and volumes or where lesions were not evident.

4.2.6.2. Acute lesion variables

We examined the first positive acute DWI scan, documenting acute lesion location, laterality, and volume. For lesion location, we selected 12 regions of interest (ROI) throughout
the brain, based on previous literature reporting brain regions associated with the presence versus absence of dysphagia (Flowers et al. 2011; Gonzalez-Fernandez et al., 2008; Broadley et al., 2003; Cola et al., 2010), dysarthria (Mackenzie, 2011), and aphasia (Turken & Dronkers, 2011; Price et al., 2010; Mesulam, 1990; Bernal & Ardila, 2009). We modified a previously published template (Broadley et al., 2005) to depict these ROIs (Figure 4-1). We recorded all lesion projections onto affected ROIs and documented lesion laterality as left, right, or bilateral. For aphasia, we restricted analyses to patients with left hemisphere or bilateral involvement. Based on consensus confirmation of slices and brain regions involving lesions, the first rater manually traced lesion volumes on each DWI slice, using MRICroN (Rorden, Karnath, & Bonilha, 2007). We calculated lesion volumes in cubic centimetres (cc) for each patient, based on automatic computation by MRICroN for a composite volume across all slices affected slice. We then multiplied the computation by 5 to account for the 5 mm thickness of each slice.

4.2.6.3. Chronic neurological disease variables

We recorded other neurological disease using the FLAIR image, comparing it as needed to all available MRI modalities. Variables pertaining to prior neurological disease included covert stroke, brain atrophy, and white matter disease. Recommendations from a recent systematic review guided our determination of small (10 to 20 mm) lacunar or incidental prior lesions versus large incidental covert lesions (>20mm) (Potter, Marlborough, & Wardlaw, 2011). We extracted lesion size for lacunar or incidental covert strokes in four mutually exclusive categories, i) a single lacunar or incidental covert lesion 10 to 20 mm in the longest diameter, ii) multiple lacunar or incidental covert lesions 10 to 20 mm in the longest diameter, iii) a single incidental covert lesion > 20 mm in the longest diameter, and iv) multiple lacunar or incidental covert infarcts, where one of which was at least > 20 mm in the longest diameter.
We categorized brain atrophy by evaluating global and localized atrophy for each patient, categorizing atrophy as absent, mild, moderate, and severe. We considered brain atrophy to be absent when i) cortical contraction along brain margins (Sluimer et al., 2008) was absent, ii) lateral ventricular (Frisoni et al., 2010) and Sylvian fissure (Förstl et al., 1995) enlargement were also absent, and when iii) brain tissue changes in specific grey matter regions (Fjell et al., 2009), such as the cerebellum and temporal lobes, were not evident. When cortical contraction, lateral ventricular enlargement, Sylvian fissure enlargement, and/or localized grey tissue atrophy were present, we subjectively rated the extent of atrophy as mild, moderate or severe.

We derived a composite rating using criteria from the Fazekas scale (Fazekas et al., 1987) to document white matter disease. We combined ratings for periventricular deep matter hyperintensities and those for deep white matter hyperintensities on a scale of 0 (absent) to 3 (severe). We assigned a score of 0 when there were no periventricular or deep white matter hyperintensities, a score of 1 when there were scattered periventricular and/or deep white matter hyperintensities, a score of 2 when there were semi-confluent periventricular and/or deep white matter hyperintensities, and a score of 3 when there were confluent and extensive periventricular and/or deep white matter hyperintensities.

4.2.7. Statistical analysis

First, we reported simple frequencies and corresponding proportions of demographic, clinical, and neuroanatomical variables in patients with and without dysphagia, dysarthria, and aphasia. Second, we described patient-specific lesion profiles based on affected ROIs or groupings of affected ROIs, ranking them by frequency (highest to lowest). Finally, we conducted multivariable logistic regression modeling to evaluate the demographic, clinical, and neuroanatomical predictors of dysphagia, dysarthria, and aphasia. We documented instances of
missing data, to ensure that predictor variables had >90% observations. We based our identification of potential predictors of each the three diagnostic categories on demonstration of associations between independent variables and a given impairment from the literature and using clinical rationale. We excluded ROIs not previously shown or suspected to correlate with a given impairment. We entered the ROIs using an exploratory backward selection model with a p <0.05 cut-off, to compute odds ratios along with their 95% confidence intervals (CI).

Given our exploratory intent, we allowed a minimum ratio of 3:1 predictors to events (Vittinghoff & McCulloch, 2007). That is, we evaluated age in 10-year increments and created binary variables for categorical predictors. We considered brain atrophy to be minimal (none or mild) or maximal (moderate or severe), periventricular and deep white matter disease (according to Fazekas scores) to be minimal (0 or 1) or maximal (2 or 3), and prior covert stroke to be minimal (none or single lacunar) or maximal (multiple lacunar and/or at least on incidental infarct >2cm in diameter on a given DWI slice). We categorized laterality of lesions as right versus left or bilateral. To avoid overspecification of our models, given the high number of predictors, and to account for potential multicollinearity of overlapping ROIs, we used linear regression collinearity diagnostics. We evaluated highest variance inflation factors (VIF) in the models and considered potential multicollinearity effects where VIF >10 (Norman & Streiner, 2008).

We performed descriptive, univariate, and bivariate analyses using SAS, version 9.2. We suppressed raw numbers for cell sizes of <5 in accordance with privacy policies at the Institute for Clinical and Evaluative Sciences, where the RCSN database resides. Our primary outcome included the demographic, clinical, and neuroanatomical factors that predicted the presence of
each impairment. Our secondary outcome included a descriptive report of lesion patterns and profiles in the entire sample and according to specific impairments and their co-occurrence.

4.3. Results

4.3.1. Inclusions and exclusions

Of the 221 patients with first-ever ischemic stroke from the previous study (Flowers et al., in press), 160 were eligible for inclusion in the MRI scan review (Figure 4-2). The primary reasons for exclusion were MRI scan >14 days post stroke onset (n=25), history of dementia (n=12) and absent lesion on DWI (n=12) (Figure 4-2).

4.3.2. Descriptive attributes of eligible patients

4.3.2.1. Demographic and stroke characteristics

Fifty-seven percent of the 160 patients were men, and the entire sample had a mean age of 68 years (range 31 to 91 years) (Table 4-1). The median time in hours from stroke onset to magnetic resonance imaging was 68 hours (Table 4-1). The most frequent risk factors and comorbidities of stroke were a previous medical history of hypertension in 70% and cancer in 10% (Table 4-1). The two most frequent known etiologies for ischemic stroke were large artery (37%) and lacunar (26%) (Table 4-1). A mean CNS score of 8.0 suggested mild stroke, and 84% of patients had alert level of consciousness. Ten percent of the patients received tPA, and there was a 5% death rate by discharge (Table 4-1).

Evidence of concomitant neurological disease in the entire sample included at least mild brain atrophy in 45%, the presence of white matter hyperintensities in 94%, and prior covert stroke in 30% (Table 4-2). Lesion attributes included a preponderance of left sided lesions (48%) and frequent involvement of the superficial MCA (55%), followed by periventricular white
matter (43%) and the internal capsule (43%) (Table 4-2). The median lesion volume was 23 cc with an interquartile range of 73.6 cc (range 1 to 1805 cc).

**4.3.2.2. Impairment frequencies and co-occurrence**

One hundred and ten patients (69%) had one or more of the impairments, while one in ten had all three impairments. Dysphagia, dysarthria, and aphasia were present in 76 (48%), 71 (44%), and 52 (33%) patients respectively. Fifty-one (32%) patients had both dysphagia and dysarthria, 29 (18%) had both dysphagia and aphasia, and 25 (16%) had both dysarthria and aphasia.

**4.3.2.3. Gross anatomical lesion patterns**

Within the whole sample (n=160), 117 (73%) patients had isolated supratentorial lesions, 21 (13%) had isolated infratentorial lesions, and 11 (7%) had mixed lesions (supra- and infratentorial) (Table 4-3). In patients with dysphagia (n=76), 54 (71%) had isolated supratentorial lesions, 14 (18%) had isolated infratentorial lesions, and 8 (11%) had mixed lesions (Table 4-3). In patients with dysarthria (n=71), 49 (69%) had isolated supratentorial lesions, 16 (23%) had isolated infratentorial lesions, and 6 (8%) had mixed lesions. In patients with aphasia, 47 (90%) had isolated supratentorial lesions, one (2%) had an isolated cerebellar lesion, and 4 (8%) had mixed lesions (Table 4-3). Isolated dysphagia (without concomitant dysarthria or aphasia) occurred in 12 patients, of whom 6 (50%) had isolated supratentorial lesions, 4 (33%) isolated infratentorial lesions, and 2 (17%) mixed lesions (Table 4-3). Isolated dysarthria and aphasia occurred in 11 and 14 patients respectively. Five patients with isolated dysarthria had isolated supratentorial lesions, four had isolated brainstem lesions, one had an isolated cerebellar lesion and one had mixed supra- and infratentorial lesions (Table 4-3). Isolated aphasia only occurred in patients with isolated supratentorial lesions (Table 4-3).
4.3.2.3.1 laterality trends

Within the entire sample, the highest frequency for lesion laterality was for left-sided lesions (48%), compared to right-sided (36%) or bilateral (16%) (Table 4-2). There was a predominance of left sided lesions for the 117 patients with isolated supratentorial lesions, accounting for 56% of the lesions, compared to 36% right sided and 8% bilateral. In the 32 patients with isolated infratentorial lesions, 44% were right sided, 34% left sided, and 22% bilateral (Table 4-3). Finally, in the 11 patients with mixed infra- and supratentorial lesions, bilateral expression predominated in 82% (Table 4-3).

Patients with aphasia, whether in isolation or in combination with other impairments, had predominantly left-sided supratentorial lesions, but when isolated infratentorial or mixed lesions occurred, they were always bilateral (Table 4-3). Other trends between impairments and side of lesion occurred in patients with isolated dysphagia (n=12) or isolated dysarthria (n=11), where isolated supratentorial lesions were most frequently right sided, occurring in 67 and 80 percent of patients, respectively (Table 4-3).

4.3.3. Clinical and neuroanatomical predictive models

Based on the VIFs, none of the three whole brain models was suggestive multicollinearity as their VIFs were below the pre-established threshold. Multivariable logistic regression analyses for clinical and neuroanatomical predictors of dysphagia and dysarthria throughout the whole brain (n=160) revealed highest odds for the presence of medullary (OR 6.2, CI 1.5 – 25.8) and pontine lesions (OR 7.8, CI 2.7 – 22.9) respectively (Table 4-4). The same analyses for aphasia, excluding patients with right sided lesions (n=102), revealed highest odds for the presence of insular lesions (34.4, CI 4.2 – 283.4) (Table 4-4). Highest odds in the subgroup of patients with isolated supratentorial lesions (n=117) included maximal (moderate or severe) brain atrophy for
dysphagia (OR 6.2, CI 1.8 – 21.1) and insular lesions for dysarthria (OR 5.0, CI 1.8 – 13.4) and aphasia (OR 10.5, CI 1.2 – 94.0) (Table 4-5). Nagelkere’s $R^2$ values for the whole brain and supratentorial models were 0.28 and 0.36 for dysphagia, 0.23 and 0.22 for dysarthria, and 0.48 and 0.52 for aphasia, respectively.

4.4. Discussion

We demonstrated clinical and neuroanatomical predictors of dysphagia, dysarthria, and aphasia after first-ever ischemic stroke, confirmed by diffusion-weighted imaging. The current study is the first to quantify demographic, clinical, previous brain disease, and acute stroke factors to derive comprehensive models for the expression of dysphagia, dysarthria, and aphasia early after acute ischemic stroke. In our whole brain models, we showed that acute lesion factors were the best predictors of all three impairments, superseded by only brain atrophy and increasing age for the prediction of dysphagia. We elucidated the neural substrate for dysphagia, with predictors in the brainstem and subcortical and cortical regions. Results for dysarthria showed a similar, but more restricted network throughout the brain, with the highest predictor in a single brainstem region (pons), followed by subcortical and cortical regions and a small effect for decreasing lesion volume. Results for left hemisphere aphasia showed the highest number of predictors within cortical regions, the insula and superficial MCA, followed by one subcortical region, the thalamus.

We confirmed reports of previous literature in our identification of pontine (Flowers et al., 2011), medullary (Flowers et al., 2011), and internal capsular (Gonzalez-Fernandez et al., 2008) predictors of dysphagia. However, because both previous studies sampled exclusively within infratentorial (Flowers et al., 2011) or supratentorial (Gonzalez-Fernandez et al., 2008) regions, they could not contribute to a proposed neural network throughout the brain. Unlike the
findings by Gonzalez-Fernandez et al (2008), ours showed a stronger effect for the insular
compared to internal capsular lesions. Like Fernandez-Gonzalez et al. (2008), we failed to
demonstrate an effect for increasing lesion volume within our whole brain or supratentorial
models of aphasia. For the first time, we demonstrated independent effects for increasing age and
brain atrophy in our whole brain model of dysphagia.

Unlike Cola et al. (2010), we did not identify an association between left periventricular
white matter lesions and dysphagia. The patients described by Cola et al. (2010) had isolated
subcortical lesions and may have had confounding effects of prior brain disease, such as atrophy
and/or periventricular white matter hyperintensities, not controlled for in the study. Despite
capturing dysphagia by videofluoroscopic assessment, Cola et al. (2010) did not attempt to
derive a predictive model of dysphagia, likely due to the small sample size. Overall, we extended
previous literature by documenting a whole brain network of predictors of acute dysphagia,
accounting for demographic and chronic brain disease.

The acute ischemic stroke literature has not provided a strong basis for which to evaluate
whole brain substrates of dysarthria and aphasia. We confirmed a report investigating cortical
associations for dysarthria involving the insula (Benke & Kertesz, 1989), but failed to
demonstrate effects for superficial MCA associations with dysarthria, as in other studies (Benke
& Kertesz, 1989; Kim et al., 2003). Previous studies demonstrated more discrete associations
between dysarthria and superficial MCA regions, such as the superior temporal, supramarginal,
and angular gyri (Benke & Kertesz, 1989) and the precentral knob (Kim et al., 2003). Our study
design did not permit the evaluation of more discrete superficial cortical regions of interest due
to sample size limitations in selecting predictors. Still, we confirmed previous subcortical
associations of the internal capsule and insula with dysarthria (Baier et al., 2011). We also
demonstrated that decreasing infarct volume contributed to the presence of dysarthria, likely pointing to the involvement of discrete superficial MCA regions. Concerning infratentorial regions associated with dysarthria, Urban et al. (2003) showed that cerebellar lesions contributed to the presence of dysarthria (Urban et al., 2003). We failed to demonstrate an independent effect of cerebellar lesions in our whole brain model. The study by Urban et al. (2003) was a descriptive investigation of patients with sudden onset dysarthria after isolated infratentorial lesions, of whom seven had isolated cerebellar lesions. It may be that isolated cerebellar lesions are evident as mild rapidly resolving dysarthria, potentially difficult to capture early in the acute onset without sensitive linguistic measures. We confirmed the association between pontine lesions and the presence of dysarthria as previously reported (Canbaz et al., 2010; Kumral et al., 2007). Overall, we greatly expanded the modeling potential for identifying a neural network of dysarthria, demonstrating predictive cortical, subcortical, and brainstem regions, without any independent effects of demographics, or prior brain disease. Therefore, the neural substrate for the manifestation of dysarthria suggests highly localized brain-behaviour relationships.

To date, only one study has considered the gross anatomical lesion correlates of aphasia in a large cohort of acute stroke patients, with MRI imaging within three months of stroke onset (Kreisler et al., 2000). The study found associations between neuroanatomical regions of interest and aphasic classifications, evidenced by anterior and insular lesions for Broca’s aphasia, by insular and temporo-parietal lesions for Wernicke’s aphasia, and by large antero-posterior lesions, predominantly in cortical areas for global aphasia (Kreisler et al., 2000). In patients with isolated subcortical lesions, those with aphasia had thalamic involvement more frequently than those without (Kreisler et al., 2000). These findings correspond nicely to our whole brain predictive model of aphasia, involving the insula, superficial MCA, and thalamic regions.
The remainder of the structural imaging literature in aphasia has investigated discrete neuroanatomical lesion correlates in patients with aphasia according to task specific linguistic deficits (Kümmerer et al., 2013; Fridriksson et al., 2010; Magnusdottir et al., in press; Schwartz et al., 2012). Some studies have reported associations of discretely localized MCA regions, such as the anterior temporal pole (Magnusdottir et al., in press) and the premotor cortex, pre- and postcentral gyri, and supramarginal gyrus (Schwartz et al., 2012) with specific language tasks. Others have tried to identify pathways between or within localized MCA regions based on comparisons of aptitude on tasks involving discrete language functions (Kümmerer et al., 2013). One study also considered lesions within multiple cortical/subcortical regions, describing aphasia after borderzone infarcts (Join-Lambert et al., 2012). Unlike these studies, ours confirmed the association of gross anatomical lesions with the presence of aphasia, demonstrating a cortical/subcortical network for aphasia, with contribution of increasing lesion volume.

Despite our capture of a homogeneous sample of first-ever ischemic stroke patients, with acute infarction confirmation by diffusion-weighted imaging, our study has limitations. First, we retrospectively investigated the presence versus absence of the dependent variables. Therefore, we may have a restricted capture of patients with mild impairments or of those who were difficult to assess due to clinical constraints. Still, we demonstrated robust frequencies for the incidence of the three impairments in our homogeneous acute ischemic stroke sample, contributing to comprehensive predictive models for their expression.

Second, we could not investigate more discrete neuroanatomical predictors for the presence of the impairments, because we derived regions of interest throughout the whole brain. Consequently, we had broadly specified cortical regions and binary dependent variables, which did not permit a closer exploration of localized areas that might be particularly important in
discrete functions, such as volitional control of swallowing, motor initiation of speech, and integration of receptive and expressive language functions. Nevertheless, we demonstrated whole brain predictors of dysphagia and dysarthria and left-hemisphere subcortical and cortical predictors for aphasia, simultaneously accounting for potential confounds of lesion volume, demographic factors and other brain disease.

Third, the patients in our sample primarily represented those with mild first-ever ischemic strokes likely because we restricted sampling to patients who had an MRI scan within two weeks of stroke onset. MR imaging is conducted when clinically indicated and may be initiated in a shorter time window in less complex patients. Consequently, older patients, those with a known history of atrial fibrillation (and therefore suspected cardioembolic etiology), those with multiple comorbidities (potentially also requiring intensive medical management), and those with severe strokes may not undergo MR imaging early after stroke onset. Nevertheless, our inclusion of patients with early MR imaging ensured an acute presentation, confirmed by both diffusion-weighted imaging and the corresponding apparent diffusion coefficient map.

We clearly demonstrated independent acute lesion predictors of dysphagia, dysarthria, and aphasia, elucidating the contribution of brain disease factors. For the first time, we can posit that the substrate for dysphagia involves multiple regions throughout the brain. Nevertheless, dysphagia may present in patients with concomitant brain atrophy, especially after supratentorial stroke. Dysphagia, due in part to brain atrophy, may represent a loss in tertiary mediation, necessary for sensory motor integration. In fact, one study has shown that moderate brain atrophy predicted aspiration pneumonia in nursing home residents (Okada et al., 2012), corroborating our supposition.
Interestingly, we found a localized whole brain circuit for dysarthria, not influenced by age or brain atrophy. Our results for aphasia demonstrated a parallel pattern to dysphagia and dysarthria, whereby a network of cortical and subcortical regions were responsible for its manifestation, but with an independent effect of increasing lesion volume after supratentorial stroke. Our findings will facilitate timely identification of patients at risk for the three impairments early after the acute stage of stroke and promote consequent early management. They highlight the need for routine screening and assessment early after stroke onset, with consideration of age, prior brain disease, and lesion volume in the determination of risk of impairment and ensuing brain-behaviour relationships.

Future research is required to elucidate more discrete regions of interest throughout the whole brain for dysphagia and dysarthria and within supratentorial regions for aphasia. Clearly, taking lesion volume into account is crucial when investigating the neural substrate for dysarthria and aphasia. The neural substrate for dysphagia involves integration of volitional and reflexive behaviours, such that highly localized (lesion localization) and globally mediated (whole brain health) functions require consideration. We also noted a trend toward the manifestation of isolated dysphagia and isolated dysarthria after right-sided supratentorial lesions, begging the need for future work in larger samples of patients.

In conclusion, we demonstrated neuroanatomical predictors of dysphagia, dysarthria, and aphasia in a homogeneous sample of patients with first-ever ischemic stroke, confirmed by diffusion-weighted imaging. For the first time, we quantified demographic and chronic and acute brain factors, providing comprehensive and clinically motivated models of the expression of dysphagia, dysarthria, and aphasia. We showed that dysphagia is a localized impairment, but also requires integrity of global brain function. We confirmed the highly localized substrates for
dysarthria and aphasia. Future studies still need to prospectively document physiologic and/or linguistic assessments of these three impairments to derive neuroanatomical predictive models of impairment severity and co-occurrence. We found expected neuroanatomical predictors of dysarthria, and aphasia and shed new light on interactions between localized and global brain function after dysphagia.

4.5. Acknowledgements

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<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients</th>
<th>Dysphagia</th>
<th>Dysarthria</th>
<th>Aphasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Present (n=76)</td>
<td>Absent (n=84)</td>
<td>Present (n=71)</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>66.7 (15.0)</td>
<td>69.9 (13.8)</td>
<td>83.6 (15.6)</td>
<td>67.4 (14.6)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>91 (56.9)</td>
<td>46 (59.0)</td>
<td>45 (54.9)</td>
<td>41 (57.8)</td>
</tr>
<tr>
<td>Previous Medical History, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>111 (69.4)</td>
<td>59 (75.6)</td>
<td>52 (63.4)</td>
<td>45 (63.4)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>38 (23.8)</td>
<td>22 (28.2)</td>
<td>16 (19.5)</td>
<td>14 (19.7)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>55 (34.4)</td>
<td>26 (33.3)</td>
<td>29 (35.4)</td>
<td>18 (25.4)</td>
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<tr>
<td>Previous TIA</td>
<td>31 (19.4)</td>
<td>14 (18.0)</td>
<td>17 (20.7)</td>
<td>10 (14.1)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>13 (8.1)</td>
<td>8 (10.3)</td>
<td>5 (6.1)</td>
<td>6 (8.5)</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>33 (47.1)</td>
<td>15 (19.2)</td>
<td>18 (22.0)</td>
<td>15 (21.1)</td>
</tr>
<tr>
<td>Other Conditions, n (%)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma or COPD</td>
<td>7 (4.4)</td>
<td>&lt;5</td>
<td>5 (6.1)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Cancer</td>
<td>16 (10.0)</td>
<td>11 (14.1)</td>
<td>5 (6.1)</td>
<td>6 (8.5)</td>
</tr>
<tr>
<td>Peripheral Disease</td>
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<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
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<td>Cause of Ischemia, n (%)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Cardioembolic</td>
<td>27 (24.1)</td>
<td>11 (19.3)</td>
<td>16 (29.1)</td>
<td>10 (19.6)</td>
</tr>
<tr>
<td>Large Artery</td>
<td>41 (36.6)</td>
<td>28 (49.1)</td>
<td>13 (23.6)</td>
<td>22 (43.1)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>29 (25.9)</td>
<td>11 (19.3)</td>
<td>18 (32.7)</td>
<td>13 (25.5)</td>
</tr>
<tr>
<td>Other*</td>
<td>15 (9.4)</td>
<td>7 (9.0)</td>
<td>8 (9.8)</td>
<td>6 (8.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>48 (30)</td>
<td>21 (26.9)</td>
<td>27 (32.9)</td>
<td>20 (28.2)</td>
</tr>
<tr>
<td>CNS, mean (SD)†</td>
<td>8.0 (2.8)</td>
<td>6.7 (2.7)</td>
<td>9.2 (2.3)</td>
<td>7.5 (2.5)</td>
</tr>
<tr>
<td>Alert Level of Consciousness, n (%)</td>
<td>135 (84.4)</td>
<td>60 (76.9)</td>
<td>75 (91.5)</td>
<td>59 (83.1)</td>
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<tr>
<td>Physical Symptoms, n (%)</td>
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<td></td>
<td></td>
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<tr>
<td>Sensory</td>
<td>47 (29.4)</td>
<td>19 (24.4)</td>
<td>28 (34.2)</td>
<td>20 (28.2)</td>
</tr>
<tr>
<td>Weakness</td>
<td>127 (79.4)</td>
<td>67 (85.9)</td>
<td>60 (73.2)</td>
<td>69 (97.2)</td>
</tr>
<tr>
<td>LSN-arrival, hours, median (IQR)</td>
<td>13.6 (45.3)</td>
<td>8.9 (15.3)</td>
<td>18.2 (45.6)</td>
<td>9.1 (20.5)</td>
</tr>
<tr>
<td>LOS in days, median (range)†</td>
<td>9 (0-133)</td>
<td>13 (0-133)</td>
<td>7.0 (0-42)</td>
<td>10 (0-87)</td>
</tr>
<tr>
<td>Time to MRI, hours, median (IQR)</td>
<td>67.8 (73.8)</td>
<td>53.9 (80.3)</td>
<td>71.9 (65.0)</td>
<td>51.3 (74.6)</td>
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<td>Thrombolysis, n (%)</td>
<td>16 (10.0)</td>
<td>12 (15.4)</td>
<td>&lt;5</td>
<td>12 (16.9)</td>
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<tr>
<td>Discharge Status, n dead (%)</td>
<td>8 (5.0)</td>
<td>7 (9.0)</td>
<td>&lt;5</td>
<td>5 (5.6)</td>
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<tr>
<td>Rankin Score, mean (SD)</td>
<td>2.9 (1.5)</td>
<td>3.6 (1.2)</td>
<td>2.3 (1.4)</td>
<td>3.3 (1.2)</td>
</tr>
</tbody>
</table>

TIA=Transient ischemic attack.

COPD=Chronic obstructive pulmonary disease.

CNS=Canadian Neurological Scale.
LSN=Last seen normal.
LOS=Length of stay.

*Ischemic stroke classifications collapsed for dissection, cortical, prothrombic, vasculitis, and other.
†Missing data for 1 to 4 patients.

asensory symptoms of cranial nerves (but not those for sight), including numbness, anesthesia, tingling, pin and needles, paresthesiae of the face, arm, and/or leg.

bphysiological weakness of the face, arms, and/or legs.
Table 4-2. MRI-based neuroanatomical factors for patients with and without dysphagia, dysarthria and aphasia (n=160)

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients</th>
<th>Dysphagia</th>
<th>Dysarthria</th>
<th>Aphasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Present (76)</td>
<td>Absent (84)</td>
<td>Present (71)</td>
</tr>
<tr>
<td>T2 Neurological Disease, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Brain Atrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>88 (55.0)</td>
<td>36 (46.2)</td>
<td>52 (63.4)</td>
<td>40 (56.3)</td>
</tr>
<tr>
<td>Mild</td>
<td>46 (28.9)</td>
<td>23 (29.5)</td>
<td>23 (28.1)</td>
<td>17 (23.9)</td>
</tr>
<tr>
<td>Moderate</td>
<td>22 (13.8)</td>
<td>17 (21.8)</td>
<td>5 (6.1)</td>
<td>13 (18.3)</td>
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<tr>
<td>Severe</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
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<tr>
<td>White Matter Disease*</td>
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<tr>
<td>0</td>
<td>9 (5.6)</td>
<td>5 (6.4)</td>
<td>&lt;5</td>
<td>&lt;5</td>
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<tr>
<td>1</td>
<td>83 (51.9)</td>
<td>39 (50.0)</td>
<td>44 (53.7)</td>
<td>39 (54.9)</td>
</tr>
<tr>
<td>2</td>
<td>58 (36.3)</td>
<td>27 (34.6)</td>
<td>31 (37.8)</td>
<td>25 (35.2)</td>
</tr>
<tr>
<td>3</td>
<td>10 (6.3)</td>
<td>7 (9.0)</td>
<td>&lt;5</td>
<td>&lt;5</td>
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<tr>
<td>Prior Covert Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>112 (70.0)</td>
<td>56 (71.8)</td>
<td>56 (68.3)</td>
<td>52 (73.2)</td>
</tr>
<tr>
<td>Single &lt;2cm‡</td>
<td>23 (14.4)</td>
<td>8 (10.3)</td>
<td>15 (18.3)</td>
<td>9 (12.7)</td>
</tr>
<tr>
<td>Multiple &lt;2cm‡</td>
<td>17 (10.6)</td>
<td>11 (14.1)</td>
<td>6 (7.3)</td>
<td>7 (9.9)</td>
</tr>
<tr>
<td>≥2cm</td>
<td>8 (5.0)</td>
<td>&lt;5</td>
<td>5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>DWI Acute Lesion Attributes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side of Lesions, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left Side</td>
<td>77 (48.1)</td>
<td>36 (46.2)</td>
<td>41 (50.0)</td>
<td>30 (42.3)</td>
</tr>
<tr>
<td>Right Side</td>
<td>58 (36.2)</td>
<td>27 (34.6)</td>
<td>31 (37.8)</td>
<td>28 (39.4)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>25 (15.6)</td>
<td>15 (19.2)</td>
<td>10 (12.2)</td>
<td>13 (18.3)</td>
</tr>
<tr>
<td>Supratentorial Involvement†, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior Cerebral Artery†</td>
<td>7 (4.4)</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Middle Cerebral Artery†</td>
<td>88 (55.0)</td>
<td>48 (61.5)</td>
<td>40 (48.8)</td>
<td>37 (52.1)</td>
</tr>
<tr>
<td>Posterior Cerebral Artery†</td>
<td>16 (10.0)</td>
<td>6 (7.7)</td>
<td>10 (12.2)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>36 (22.5)</td>
<td>26 (33.3)</td>
<td>10 (12.2)</td>
<td>22 (31.0)</td>
</tr>
<tr>
<td>Insula</td>
<td>38 (23.8)</td>
<td>29 (37.2)</td>
<td>9 (11.0)</td>
<td>22 (31.0)</td>
</tr>
<tr>
<td>Internal Capsule</td>
<td>46 (28.8)</td>
<td>29 (37.2)</td>
<td>17 (20.7)</td>
<td>27 (38.0)</td>
</tr>
<tr>
<td>Periventricular White Matter</td>
<td>68 (42.5)</td>
<td>41 (52.6)</td>
<td>27 (32.9)</td>
<td>33 (46.5)</td>
</tr>
<tr>
<td>Thalamus</td>
<td>16 (10.0)</td>
<td>&lt;5</td>
<td>13 (15.9)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Infratentorial Involvement‡, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>18 (11.3)</td>
<td>9 (11.5)</td>
<td>9 (11.0)</td>
<td>7 (9.9)</td>
</tr>
<tr>
<td>Midbrain</td>
<td>7 (4.4)</td>
<td>5 (6.4)</td>
<td>&lt;5</td>
<td>5 (7.0)</td>
</tr>
<tr>
<td>Pons</td>
<td>12 (15.4)</td>
<td>12 (15.4)</td>
<td>10 (12.2)</td>
<td>16 (22.5)</td>
</tr>
<tr>
<td>Medulla</td>
<td>11 (6.9)</td>
<td>7 (9.0)</td>
<td>&lt;5</td>
<td>5 (7.0)</td>
</tr>
<tr>
<td>Volume Categories in cc, n (%)</td>
<td>0-4</td>
<td>&gt;4 – 10</td>
<td>&gt;10 – 30</td>
<td>&gt;30 – 60</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----</td>
<td>---------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>0-4</td>
<td>30 (18.8)</td>
<td>10 (12.8)</td>
<td>20 (24.4)</td>
<td>11 (15.5)</td>
</tr>
<tr>
<td>&gt;4 – 10</td>
<td>26 (16.3)</td>
<td>10 (12.8)</td>
<td>16 (19.5)</td>
<td>14 (19.7)</td>
</tr>
<tr>
<td>&gt;10 – 30</td>
<td>30 (18.8)</td>
<td>10 (12.8)</td>
<td>20 (24.4)</td>
<td>13 (18.3)</td>
</tr>
<tr>
<td>&gt;30 – 60</td>
<td>22 (13.4)</td>
<td>15 (19.2)</td>
<td>7 (8.5)</td>
<td>12 (16.9)</td>
</tr>
<tr>
<td>&gt;60 – 90</td>
<td>17 (10.6)</td>
<td>11 (14.1)</td>
<td>6 (7.3)</td>
<td>10 (14.1)</td>
</tr>
<tr>
<td>&gt;90</td>
<td>35 (21.9)</td>
<td>22 (28.2)</td>
<td>13 (15.9)</td>
<td>11 (15.5)</td>
</tr>
</tbody>
</table>

*According to Fazekas scale

†Included superficial cortical regions only

‡included lacunar or incidental covert strokes <2cm in diameter on all affected slices

aSupratentorial and infratentorial regions of interest (ROI) were not mutually exclusive. Individual patients could have multiple affected ROIs.
Table 4-3. Descriptive frequencies of patients with dysphagia, dysarthria, and aphasia according to gross anatomical regions

<table>
<thead>
<tr>
<th>Impairments (n)</th>
<th>Isolated Regions, n (%)</th>
<th>Mixed Regions, n (%)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supratentorial</td>
<td>Cerebellum</td>
<td>Brainstem</td>
<td>Cerebellum &amp; Brainstem</td>
<td>Infra- &amp; Supratentorial</td>
</tr>
<tr>
<td>Entire Sample (160)</td>
<td>117 (73)</td>
<td>6 (4)</td>
<td>20 (13)</td>
<td>6 (4)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Dysphagia (76)</td>
<td>54 (71)</td>
<td>&lt;5</td>
<td>9 (12)</td>
<td>&lt;5</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Dysarthria (71)</td>
<td>49 (69)</td>
<td>&lt;5</td>
<td>11 (15)</td>
<td>&lt;5</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Aphasia (52)</td>
<td>47 (90)</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>0</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Dysphagia &amp; Dysarthria (51)</td>
<td>36 (71)</td>
<td>0</td>
<td>7 (14)</td>
<td>&lt;5</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Dysphagia &amp; Aphasia (29)</td>
<td>25 (86)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Dysarthria &amp; Aphasia (25)</td>
<td>21 (84)</td>
<td>&lt;5</td>
<td>0</td>
<td>0</td>
<td>&lt;5</td>
</tr>
<tr>
<td>All Three Impairments (16)</td>
<td>13 (81)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Isolated Impairments (37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated Dysphagia (12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated Dysarthria (11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated Aphasia (14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None of the three (50)</td>
<td>36 (72)</td>
<td>&lt;5</td>
<td>7 (14)</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>
Table 4-4. Whole brain neuroanatomical and demographic predictors of dysphagia, dysarthria and aphasia (N=160).

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Dysphagia, OR (95% CI)(^a) (n=76)</th>
<th>Dysarthria, OR (95% CI) (n=71)</th>
<th>Aphasia(^b), OR (95% CI) (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (10 year increments)</td>
<td>1.4 (1.1 – 1.8)</td>
<td>eliminated step 5</td>
<td>eliminated step 7</td>
</tr>
<tr>
<td><strong>Concomitant Brain Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophy (maximal)</td>
<td>3.0 (1.04 – 8.6)</td>
<td>eliminated step 10</td>
<td>eliminated step 7</td>
</tr>
<tr>
<td><strong>Anatomical Regions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medulla (yes)</td>
<td>6.2 (1.5 – 25.8)</td>
<td>eliminated step 9</td>
<td>not tested</td>
</tr>
<tr>
<td>Pons (yes)</td>
<td>3.6 (1.2 – 10.1)</td>
<td>7.8 (2.7 – 22.9)</td>
<td>not tested</td>
</tr>
<tr>
<td>Thalamus (yes)</td>
<td>eliminated step 12</td>
<td>not tested</td>
<td>6.2 (1.6 – 24.4)</td>
</tr>
<tr>
<td>Internal Capsule (yes)</td>
<td>2.9 (1.2 – 6.6)</td>
<td>3.6 (1.6 – 7.9)</td>
<td>eliminated step 6</td>
</tr>
<tr>
<td>Insula (yes)</td>
<td>4.8 (2.0 – 11.8)</td>
<td>4.5 (1.8 – 11.4)</td>
<td>34.4 (4.2 – 283.4)</td>
</tr>
<tr>
<td>Middle Cerebral Artery (yes)</td>
<td>eliminated step 7</td>
<td>eliminated step 2</td>
<td>4.7 (1.5 – 14.2)</td>
</tr>
<tr>
<td>Lesion Volume (increasing)</td>
<td>eliminated step 8</td>
<td>0.997 (0.995 – 1.000)</td>
<td>eliminated step 9</td>
</tr>
</tbody>
</table>

\(^a\)Additional eliminated variables included i) gender, ii) previous history of atrial fibrillation, iii) brain atrophy level iv) Fazekas level v) prior covert stroke level, vi) brain regions ACA, PCA, basal ganglia, and periventricular white matter, and vii) laterality of lesions

\(^b\)Additional eliminated variables included i) gender, ii) previous history of atrial fibrillation, iii) brain atrophy level iv) Fazekas level v) prior covert stroke level, vi) brain regions ACA, basal ganglia, periventricular white matter, and cerebellum, and vii) laterality of lesions

\(^c\)Sample restricted to left sided lesions (n=102). Additional eliminated variables included i) gender, ii) previous history of atrial fibrillation, iii) brain atrophy level iv) Fazekas level v) prior covert stroke level, and vi) brain regions ACA, PCA, basal ganglia, and periventricular white matter.
<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Dysphagia, OR (95% CI)</th>
<th>Dysarthria, OR (95% CI)</th>
<th>Aphasia, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prior Brain Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophy (minimal)</td>
<td>6.2 (1.8 – 21.1)</td>
<td>eliminated step 11</td>
<td>eliminated step 10</td>
</tr>
<tr>
<td><strong>Anatomical Regions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalamus (yes)</td>
<td>0.07 (0.01 – 0.8)</td>
<td>eliminated step 12</td>
<td>eliminated step 13</td>
</tr>
<tr>
<td>Internal Capsule (yes)</td>
<td>3.0 (1.3 – 7.3)</td>
<td>4.0 (1.7 – 9.2)</td>
<td>eliminated step 8</td>
</tr>
<tr>
<td>Insula (yes)</td>
<td>3.9 (1.6 – 10.0)</td>
<td>5.0 (1.8 – 13.4)</td>
<td>10.5 (1.2 – 94.0)</td>
</tr>
<tr>
<td>Lesion Volume (increasing)</td>
<td>Eliminated step 10</td>
<td>0.997 (0.995 – 1.000)</td>
<td>1.03 (1.01 – 1.05)</td>
</tr>
</tbody>
</table>

Additional eliminated variables included i) age, ii) gender, iii) history of atrial fibrillation, iv) prior covert stroke, v) Fazekas level vi) lesion laterality, vii) involvement of the ACA, MCA, PCA, basal ganglia, and periventricular white matter.

Additional eliminated variables included i) age, ii) gender, iii) history of atrial fibrillation, iv) prior covert stroke, v) Fazekas level vi) lesion laterality, vii) involvement of the ACA, MCA, PCA, basal ganglia, and periventricular white matter.

Included only patients with left-sided lesions (total n=75). Additional eliminated variables included i) age, ii) gender, iii) history of atrial fibrillation, iv) prior covert stroke, v) Fazekas level vi) involvement of the ACA, MCA, PCA, basal ganglia, and periventricular white matter.
Figure 4-1. Regions of interest throughout the brain (adapted from Broadley et al., 2005)
Figure 4-2. Flow diagram of eligible patients from RCSN phase III database (July 1, 2003 to March 31, 2008)
5. Discussion

5.1. Summary of Findings

In our three studies, we documented many novel findings relating to the frequency, co-occurrence, and predictors of dysphagia, dysarthria, and aphasia after acute ischemic stroke. The sampling methodology was comparable in each of our studies since we included only consecutive patients with MR confirmed acute ischemic stroke. In our first study, we derived our retrospective cohort from a consecutively enrolled population-based registry and could, therefore, estimate the frequency and co-occurrence of dysphagia, dysarthria and aphasia. We demonstrated a high frequency and co-occurrence of the three impairments, where two-thirds of patients arriving to a tertiary care hospital had at least one of the three impairments. More specifically, almost half the sample had dysphagia or dysarthria and nearly one-third had aphasia. Co-occurrence among the three impairments was highest for dysphagia and dysarthria, where over one-quarter of patients had both impairments. In addition, one in 10 patients arrived to hospital with all three impairments.

We used independent variables from the OSR database to derive demographic and stroke predictors of the three impairments. Predictors of dysphagia included non-alert level of consciousness and increasing stroke severity. The only predictor of dysarthria was symptoms of physical weakness at stroke onset, defined as the presence of motor weakness anywhere throughout the body. Heralding the presence of aphasia was a multiplicity of predictors, including right-sided physical symptoms, non-alert level of consciousness, increasing stroke severity, and the absence of sensory symptoms or symptoms of physical weakness. The identification of multiple clinically intuitive predictors across the three impairments was a new contribution to the literature. Although our models lacked lesion-based factors, they were an
initial step in deriving comprehensive models of impairments that could ultimately consider the combined effects of demographic, clinical and neuroanatomical predictors.

Our second study, a systematic review and meta-analysis, demonstrated the frequency of dysphagia after infratentorial ischemic stroke in consecutively enrolled patients with lesions in circumscribed neuroanatomical regions. Based on pooled data for a large sample of patients, we demonstrated a dysphagia frequency of less than 10% after cerebellar stroke and midbrain stroke, increasing to between 40 and 57% in brainstem regions. We evaluated discrete neuroanatomical predictors of dysphagia, especially since its neural network remains elusive (Ertekin, 2011), likely due to complex interactions between the oral and pharyngeal phases of the swallow (Bieger & Neuhuber, 2006). Nevertheless, the available literature reporting consecutive samples of patients with MR confirmed acute ischemic stroke only documented dysphagia after infratentorial stroke. Still, our systematic review reported individual level data for 656 patients with isolated lesions within discrete regions of the brainstem and cerebellum. We showed a highest relative risk of dysphagia within the lateral medulla, followed by the pons and medial medulla. Recruiting a comparably large and homogeneous sample in a single centre would require decades. Our results provided the impetus to further evaluate neuroanatomical predictors of dysphagia throughout the whole brain, comparing its neural substrate to those of dysarthria and aphasia.

We used the same retrospective sample of first acute ischemic stroke patients from which we had derived the incidence of dysphagia, dysarthria, and aphasia, to identify neuroanatomical factors from the MRI scans. Not only did we elucidate the neural substrate for dysphagia, dysarthria, and aphasia based on acute stroke factors, but we also accounted for potential demographic, stroke, and chronic brain disease factors. We demonstrated that the acute lesion
localization was primarily responsible for the manifestation of each impairment, with the exception for brain atrophy in dysphagia. There were six predictive associations for dysphagia, of which the strongest three were for the presence of medullary lesions, followed by insular and pontine lesions. The three weakest predictors in decreasing order included the presence of brain atrophy, internal capsular lesions, and increasing age. The three strongest predictors of dysarthria were the presence of pontine lesions, followed by insular and internal capsular lesions. Finally, there was a small effect for decreasing lesion volume as predictive of dysarthria. Finally, there were a total of three predictors of left hemisphere aphasia in decreasing order of effect: the involvement of the insula, the thalamus, and the superficial middle cerebral artery territory.

In addition to whole brain predictive models, we computed models for the expression of dysphagia, dysarthria, and aphasia after supratentorial lesions. The strongest predictor for dysphagia was the absence of thalamic involvement, followed by brain atrophy, insular, and internal capsular lesions. Only acute lesion factors were predictive of supratentorial dysarthria and left hemisphere supratentorial aphasia. Two neuroanatomical regions of interest predicted supratentorial dysarthria, with strongest effects for the involvement of the insula followed by the internal capsule. As in the whole brain model of dysarthria, there was a small effect for decreasing lesion volume. Two factors were significant in the prediction of left hemisphere supratentorial aphasia, with a strong effect for insular lesions, and a weak effect for increasing lesion volume.

In summary, we first derived robust frequency estimates of dysphagia, dysarthria, and aphasia, in order to later model clinical and neuroanatomical predictors of their presence. To direct our determination of neuroanatomical regions of interest, we conducted a systematic review, to identify regions of interest for dysphagia and potential gaps in the literature. We later
confirmed the neuroanatomical predictive regions from the systematic review in our own sample. We addressed gaps in the literature by deriving a whole brain neuroanatomical substrate for dysphagia. In addition, we extended the literature for all three impairments by documenting combined effects of demographic, clinical and neuroanatomical factors in predicting their presence. Interestingly, the acute regions of interest predicting dysphagia involved the most extensive network and the highest number of involved brain regions compared to dysarthria and aphasia. We still demonstrated that a whole brain model of dysarthria involved both infra- and supratentorial regions, despite the smaller total number of regions than for dysphagia. Our findings for a whole brain model of left hemisphere aphasia showed a higher total number of supratentorial predictors than for dysphagia and dysarthria, confirming its highly localized expression. Our studies have provided new information that will facilitate rapid identification of patients at risk of dysphagia, dysarthria, and aphasia. They also pave the way for a more discrete evaluation of the effect of specific brain regions on the presence of the three impairments.

5.2. Extension of Previous Literature

5.2.1. Incidence

Despite our finding that dysphagia had the highest frequency of the three impairments in our sample, previous studies reported up to a 10% higher frequency for dysphagia (Guyomard et al., 2009; Martino et al., 2005; Martino et al., 2009). A number of differences between our study and previous studies warrant discussion. First, none of the three prior studies involved only patients with ischemic stroke, perhaps suggesting that including hemorrhagic stroke precipitated higher dysphagia frequencies (Paciaroni et al., 2004; Sundar, Pahuja, Dwivedi, & Yeolekar, 2008). Second, they did not limit their capture to first-ever stroke in patients with MRI scanning. Given that the patients with MR imaging in our sample had mild strokes on average, we may
have underrepresented the true frequency of dysphagia in first ischemic stroke survivors. Third, we captured dysphagia through retrospective report by SLP assessment or by insertion of enteral feeds. The three previous studies captured dysphagia either by routine screening followed by clinical assessment (Guyomard et al., 2009), by clinical or instrumental assessment in all patients (Martino et al., 2005) or by VFS (Martino et al., 2009). Finally, because we captured only first-ever stroke, while the other studies included recurrent strokes in their samples, our frequency estimates more closely reflect those expected in stroke survivors with no prior history of stroke.

Our frequency estimates for dysarthria were in the midrange of previous observational literature reporting unselected samples of first-ever acute ischemic stroke patients. Nevertheless, there was a wide range of previously reported frequencies for dysarthria, where Kumral et al. (2007) reported an 8% frequency and Lawrence et al (2001) a 58% frequency. Discrepancies between these two studies and ours likely resulted from methodological constraints. Kumral et al. (2007) selected only patients with sudden onset of speech difficulties, requiring the presence of multiple perceptually deviant speech production features for inclusion in the study. Lawrence et al (2001) had a broad capture of patients with first ischemic stroke and did not limit inclusion to patients with MR imaging. Consequently, they likely included patients with more severe strokes than in our study. In fact, close to 20% of their sample had at least moderate stroke, based on Glasgow Coma scores (Lawrence et al., 2001). Our dysarthria frequency estimate of 42% represents patients with mild strokes, and should be interpreted as a lower estimate of that which could be generalized to patients with greater stroke severity.

Two previous studies reporting aphasia frequencies after first-ever acute ischemic stroke fell within the confidence interval for our estimates (Engelter et al., 2006; Tsouli et al., 2009), with frequencies of 30% (Engelter et al., 2006) and 35% (Tsouli et al., 2009). Like our study,
capture of aphasia included retrospective review of chart notes, where documentation of a positive assessment by a neurologist (Engelter et al., 2006; Tsouli et al., 2009), and/or SLP (Engelter et al., 2006) constituted evidence for aphasia. The primary methodological difference was our inclusion of only patients with MR confirmed stroke. Nevertheless, given a comparable reported frequency across all three studies, we contend that our capture of aphasia was a robust estimate for its presence, likely generalizable to all first-ever first acute ischemic stroke samples. Still, prospective studies that include assessment of aphasia in all first ischemic stroke patients are necessary to confirm our estimate or to provide a more accurate reflection of its true frequency.

We reported communication impairments in 80% of patients with dysphagia, comparable to the 79% frequency identified by Lapointe and McFarland (2004). However, they identified a broader range of communication impairments, in addition to dysarthria and aphasia and their sample was not exclusive to stroke (Lapointe & McFarland, 2004). Our estimate was higher, given that we evaluated only concomitant aphasia and/or dysarthria. Similarly, our estimate of 15% co-occurrence of dysarthria and aphasia was higher than the previous report by Trapl et al. (2004), as their frequency of 10% fell below our confidence interval. It is possible that they underreported the true co-occurrence because their primary outcome was the frequency of aphasia, and dysarthria examination involved only a rapid screen (Trapl et al., 2004).

Overall, our frequency estimates for dysphagia, dysarthria, and aphasia and for their co-occurrence are comparable or higher than the previous literature, except in cases where samples likely included patients with more severe strokes (Lawrence et al., 2001), or those that systematically undertook routine screening followed by assessment (Guyomared et al., 2009) or performed gold standard assessments (Martino et al., 2009). Our estimates constitute a robust
capture of the frequency and co-occurrence of dysphagia, dysarthria, and aphasia in patients with first-ever acute ischemic stroke, confirmed by MR imaging.

5.2.2. Demographic and clinical predictors

We confirmed some previously identified clinical correlates of dysphagia and aphasia, including increasing stroke severity for both dysphagia and aphasia (Bravata et al., 2009; Engelter et al., 2006; Tsouli et al., 2009). Nevertheless, we did not demonstrate increasing age to predict dysphagia or aphasia in our clinical models, as previously described (Engelter et al., 2006; Tsouli et al., 2009; Guyomard et al., 2009). A probable explanation is that our eligible patients with MRI had a lower mean age than the excluded patients without MRI. The previous studies reporting age effects for dysphagia and dysarthria had higher mean ages (Engelter et al., 2006; Guyomard et al., 2009) and/or larger samples (Guyomard et al., 2009; Tsouli et al., 2009), likely facilitating the detection of significant differences. We demonstrated non-alert level of consciousness to predict both dysphagia and aphasia. In the absence of previous studies reporting clinical predictors of dysarthria, our finding that symptoms of physical weakness at stroke onset predicted dysarthria provided a first step in modeling predictors of its presence. The converse relationship, where lack of physical and sensory symptoms contributed to the early expression of aphasia, exemplifies new findings from our study. We tested our predictive models using the C statistic, which indicates the probability of discriminating patients with an impairment versus those without. We demonstrated a good probability of discrimination for dysphagia and for aphasia, likely in the latter case, due to the high effect for right-sided physical symptoms. Our C statistic was low for dysarthria, confirming the need for more robust models. Consequently, the next step in developing more sensitive and specific models for all three impairments involved determining neuroanatomical predictors of the impairments.
5.2.3. Neuroanatomical predictors

5.2.3.1. Dysphagia

Through our systematic review of the literature, we demonstrated strongest effects for pontine and medullary lesions. In our whole brain model, based on our cohort of first ischemic stroke patients, we confirmed that the involvement of pontine and medullary regions predicted dysphagia. There is a recent case report of a patient with dysphagia following lesion to the midbrain (Tsivgoulis, Ioannis, Vadikolias, Galetta, & Piperidou, 2011). Dysphagia after midbrain infarction may point to isolated cases where there are lesions to the switching neurons in the red nucleus (Fanardjian et al., 2000) and/or tremor induced impairments from lesions to the substantia nigra (Gonzalez-Alegre, 2007), given their role in body movement (Donnelly, 2008). However, our systematic review demonstrated a low frequency of dysphagia after isolated midbrain lesions, likely given the predominance of auditory and visual cranial nerves, which are inconsequential in the control of swallowing. Nevertheless, when lesions affect the anteromedial cerebellar peduncles of the midbrain, which contain corticospinal and corticobulbar tracts, dysphagia may result (Querol-Pascual, 2010).

In our whole brain model we demonstrated independent effects for supratentorial regions as predictive of dysphagia, involving the internal capsule and insula. One previous study demonstrated a similar effect for internal capsular involvement as predictive of dysphagia in 29 patients with supratentorial lesions (Gonzalez-Fernandez et al., 2008). To our knowledge, no prior MRI based study has demonstrated an effect for internal capsular involvement in the expression of dysphagia. We evaluated other subcortical regions, such as periventricular white matter (PVWM) and the basal ganglia, but they were not significant in our whole brain model. This is in contrast to a study by Cola et al. (2010), which demonstrated an association between
PVWM involvement and the presence of dysphagia. Reasons for this may relate to their restricted sample of unilateral subcortical stroke (Cola et al., 2010). Also, they only showed a significant interaction between left-sided PVWM involvement and the presence of dysphagia, compared to right-sided PVWM involvement (Cola et al., 2010). Although we included lesion laterality as a predictor in both our whole brain and our supratentorial models, it was not significant in either model. Dysphagia may therefore be associated only with PVWM in subcortical left-sided lesions.

Two studies have documented dysphagia following lesions to the basal ganglia (Logeman et al., 1993; Miyai, Blau, Reding, & Volpe, 1997). However, they did not succeed in isolating the involvement of the basal ganglia compared to that of the internal capsule, as patients had lesions to both areas (Logemann et al., 1993; Miyai et al., 1997). Similarly, in our study, lesions to the basal ganglia always co-occurred with superficial MCA lesions, internal capsular lesions, and/or periventricular white matter lesions. Our results do not refute potential dysphagia after insult to very discretely localized regions, such as parts of the basal ganglia or specific midbrain regions, but it suggests that, as a whole, they are not highly predictive of dysphagia. Our patient sample is the first to contribute to a predictive neural network of dysphagia throughout gross regions of interest within the whole brain. Our comprehensive results for dysphagia also form the basis from which to compare results for more localized impairments, such as dysarthria and aphasia.

5.2.3.2. Dysarthria

Like the literature in dysphagia, the literature reporting correlates of dysarthria and aphasia using structural imaging is lacking in its proposal of whole brain models. We confirmed prior evidence for associations between the insula (Baier et al., 2011; Benke & Kertesz, 1989), internal capsular (Baier et al., 2011) and pontine lesions (Canbaz et al., 2010; Kumral et al., 2010).
2007) for dysarthria. Nevertheless, our documentation of superficial cortical regions was crude, especially for the middle cerebral artery territory, which was the largest specific region of interest. Consequently, we could not corroborate literature demonstrating an association between discrete areas of the superficial MCA territory and dysarthria (Benke & Kertesz, 1989; Kim et al., 2003).

Our supratentorial model of dysarthria had the same order of effects as the supratentorial regions in our whole brain model, where insular involvement had the strongest effect followed by internal capsule and decreasing lesion volume. First, the anterior left insula regulates prearticulatory coordination of muscles involved in speech production (Ackermann & Riecker, 2004), necessary for complex speech articulation (Baldo, Wilkins, Ogar, Willock, & Dronkers, 2011). A single case report exists attesting to the presence of pure dysarthria after insular infarction (Hiraga, Tanaka, & Kamitsukasa, 2010). The insula lies directly beneath the motor and premotor areas involved in direct activation of speech. Given that our MCA region involved a large territory, the effects noted for insular involvement in the presence of dysarthria may have compensated for potential effects concomitant lesions within proximal MCA regions. Therefore, we were not likely to see an effect for MCA involvement, despite its role in direct activation from motor and premotor areas. Second, lesions to the posterior limb of internal capsule disrupt the descending motor fibers cortical necessary for facial and lingual control (Titelbaum, Sodha, Moonis, 2010). Finally, our effect for decreasing lesion volume as predicting dysarthria likely points to its frequent expression after lacunar stroke (Urban, Hopf, Visbeck, Fleischer, & Andreas, 1996; Arboix et al., 2004), where lesions in discrete regions such as the internal capsule (Ozaki, Baba, Narita, & Matsunaga, & Takebe, 1986) may produce a marked dysarthria.
Concerning infratentorial involvement, we found no independent effect for cerebellar involvement on the presence of dysarthria. This is surprising since isolated ataxic dysarthria precipitates the classic sign of slurring of speech due to articulatory imprecision (Duffy, 1995). We found no independent effect for the cerebellar involvement on the presence of dysarthria. This may be because our data were more robust in the prediction of direct activation and final common pathways of motor control, rather than pathways implicated in control circuits, such as the basal ganglia and/or cerebellum (Duffy, 1995). Our demonstration of an independent effect for pontine involvement points to disruption of the requisite lower motor neurons in controlling of facial muscles (Kim et al., 1995b; Kataoka, Hori, Shirakawa, & Hirose, 1997).

5.2.3.3. Aphasia

Our neuroanatomical model for aphasia confirms previous structural MRI studies reporting associations of the MCA regions with aphasia (Kümmerer et al., 2013; Magnusdottir et al., in press; Schwartz et al., 2012). However, they investigated associations of specific language tasks with discrete areas within the MCA territory and could not provide a comprehensive whole hemisphere model of aphasia (Kümmerer et al., 2013; Magnusdottir et al., in press; Schwartz et al., 2012). We extended the literature by demonstrating independent effects for the superficial MCA territory, insula, and thalamus. Previous research regarding insular (Cereda, Ghika, Maeder, & Bogoousslavsky, 2002) and thalamic (Pergola et al., 2013) involvement sampled only patients with aphasia. They associated aphasia with isolated insular lesions in the left posterior region (Cereda et al., 2002; Mutschler et al., 2009) and with thalamic lesions, relating to semantic recall (hence anomia) (Pergola et al., 2013). Others have posited thalamic associations with aphasia, but only in the context of cortical hypoperfusion (Hillis et al., 2002; Hillis et al., 2004).
Concerning infratentorial lesions, brain stem lesions do not precipitate aphasia given that language is a higher cortical function. To our knowledge, only one study has documented an association between aphasia and the cerebellum, suggesting a potential role in language processing (Highnam & Bleile, 2011). We could not adequately address the potential relationship between cerebellar involvement and aphasia, due to low frequency of isolated cerebellar lesions. In fact, only six patients had isolated cerebellar lesions, of whom one had aphasia. We included involvement of the cerebellum as a potential predictor of aphasia in our model, but it was not significant.

In our analysis of left-sided supratentorial predictors of aphasia, we demonstrated a large effect for insular involvement and a small effect for increasing lesion volume. Therefore, two of the independent predictors from our whole hemisphere model, superficial MCA territory and thalamic involvement, were no longer significant. Reasons for this may include the extensive area covered by our MCA region of interest, whereby insular involvement confounded involvement of adjacent MCA regions also responsible for the presence of aphasia. Similarly, the effect of increasing lesion volume may have confounded effects for the large MCA regions as well as any potential effects of thalamic involvement, if cortical hypoperfusion was present. In both the whole brain and supratentorial models, insular involvement was the strongest predictor of aphasia, and although it has been associated with poor word retrieval (Pergola et al., 2013), its anatomical position relative to Broca’s and Wernicke’s areas may account for this large effect. Again, we could not address specific superficial MCA regions, given our interest in delineating regions of interest throughout the brain. Consequently, insular involvement may point to a collinear effect of discrete cortical MCA regions.
5.3. Limitations

Although we established a methodological approach a priori for our three studies, there are limitations to the current line of research. First, our estimates of dysphagia, dysarthria, and aphasia resulted from a retrospective chart review. Consequently, our capture of dysphagia involved referral-driven assessment by SLPs or, in the absence of SLP assessment, documentation of enteral feed insertion. At the time of the chart review, there was no routine screening for dysphagia, therefore no systematic method by which to refer to SLP for assessment of dysphagia which requires a medical order. Because referring physicians may have had to rely on global and nonspecific clinical impressions for risk of dysphagia, we may not have captured mild cases of dysphagia. Although we attempted a robust capture of dysarthria and aphasia, by defining their presence according to physician, stroke nurse, or SLP assessment, we suspect that clinical factors may have also contributed to a limited capture of their presence. Potential clinical factors include i) lack of routine assessment of patients with English as a second language by physicians or stroke nurses, ii) documentation of dysarthria based only on symptom report at stroke onset, and iii) expectation for rapid remediation of mild dysarthria and/or aphasia, without clearly reported assessment or referral to SLP.

Second, given that our medical chart reviews and all articles in the systematic review were observational cohorts, we could not systematically evaluate all potential associations or predictors. If we noted >10% missing data in variables from the RCSN database, we did not include them in our models (e.g. prior history of myocardial infarction). Similarly, where there were a high percentage of undetermined observations, as evidenced in the TOAST ischemic stroke categorizations, we did not evaluate predictive effects. The category “undetermined etiology” in the TOAST classification is a limitation inherent to the TOAST criteria, as patients
with multiple etiologies are considered to have undetermined etiology along with those for whom a designation of etiology is difficult.

Like our retrospective chart review, the articles in our systematic review involved observational designs and were consequently of low quality. Not all articles provided individual level data for some variables, limiting our ability to test predictions of variables such as age and gender. No study in the systematic review reported reliability or validity. Most articles in the systematic review reported clinical assessment although two used gold standard videofluoroscopic assessment (Kim et al., 2000; Kwon et al., 2005). However, the two articles that included videofluoroscopic evaluation captured a narrow outcome, the presence versus absence of laryngeal penetration or aspiration. The articles in the systematic review did not clearly report the time between MRI scans and dysphagia assessment, limiting interpretation of acute stage timing for the incidence findings and predictive model. We attempted to address limitations of our observational and retrospective designs in our studies. We demonstrated high interrater reliability in our capture of the dependent variables from our chart review. We also documented confirmatory report of the presence versus absence of dysarthria and aphasia by a second expert to demonstrate corroboration of the positive assessments. Finally, we documented time to assessments from stroke onset and time between assessments and MRI scans.

Third, there were limitations regarding the imaging analysis in the articles in the systematic review. Most articles did not extract acute lesion correlates using DWI scans nor did they address any chronic brain disease factors. Without DWI sequences it is hard to confirm that the lesion detected was truly acute and not indicative of an area of old infarction (Fazekas et al., 2009). Moreover, the high sensitivity of DWI implies it detects lesions missed by conventional T2 weighted imaging. One possible explanation for the lack of MRI-based studies reporting
dysphagia after supratentorial or whole brain stroke may be the infrequent use of MRI prior to the last decade (Donnan et al., 2007). MRI is sensitive to posterior fossa injury, and early after routing use of MRI, imaging protocols likely first routinely addressed its need in posterior fossa lesions. With increased use of multimodal MRI for all acute stroke types, the literature may begin to provide more information on dysphagia after supratentorial stroke. Researchers may also begin to use multimodal imaging results to assess the potential effects of chronic detriment to whole brain health as a contributor to impairment presence after stroke (Alexander et al., 2010; Galovic et al., in press).

Fourth, with respect to our systematic review findings, a publication bias may exist in the literature toward MRI-based report of dysphagia after brain stem stroke. This may be because the central pattern generator in the lateral medulla is a well-appreciated contributor to swallowing function. Nevertheless, three articles reported the frequency of dysphagia after cerebellar lesions, with null results (Izumi et al., 1996; Kumral et al., 2006; Min et al., 1999). Similarly, two additional studies reported either a null result (Kumral et al., 2002) or low frequency of dysphagia (Kim & Kim, 2005) after midbrain lesions. Bias may still be present given that percentage of patients with cerebellar lesions, midbrain lesions, and lateral medullary lesions of all eligible patients were five, seven, and 65%, respectively. Because the articles provided individual level data for lesion localizations, we only included patients with isolated infarctions in five regions of interest. Our model was robust in that the five regions were not overlapping, with the exception of lesions extending from the brainstem into the cerebellum. Without the five articles reporting individual level results for dysphagia after cerebellar and midbrain lesions, we would not have been able to compute an infratentorial model of dysphagia after acute stroke.
Our MRI analysis extended results from the systematic review. We undertook a methodological rigorous capture of our outcome variables, including acute and chronic brain factors using multimodal MRI evaluation. To extract acute and chronic brain variables, we used the available multimodal MRI scans. For acute lesion factors, we used the DWI map, confirming the location and size of the lesion with the ADC map. In addition, we used the T2 FLAIR to quantify chronic brain factors that might confound the acute lesion results. The major limitation of our lesion analysis was the multiplicity of overlapping regions, leading to possible confound of multicollinearity. Nevertheless, we conducted diagnostics to test for potential variance inflation to address potential multicollinearity.

Finally, our neuroanatomical models captured acute lesion predictors within 12 regions of interest throughout the brain, limiting predictions for more discrete lesion localization. For example, the superficial MCA territory was the largest, encompassing important regions implicated in brain behaviour relationships such as the motor and sensory cortices, and the temporal lobe. Consequently, we could not evaluate the effects of discrete regions within the superficial MCA territory. Similarly, the insula was a predictor of all three impairments and may have had collinear effects with regions lying superior to it, such as Broca’s and Wernicke’s area. Specific areas of the insula have been implicated in different behaviours where posterior insular involvement may be more closely linked to dysarthria and aphasia rather than the anterior insula (Baier et al., 2011; Cereda et al., 2002; Mutschler et al., 2009). Although isolated superficial MCA lesions were highly frequent in our dataset, isolated insular lesions were absent. Insular lesions almost always co-occurred with our least discrete area, the superficial MCA territory. Hence, potential effects for the broad superficial MCA region may be confounded by insular involvement. To address disparity among region of interest size, future work should consider
voxel-based lesion symptom mapping (VBLSM). Nevertheless, our analysis provided important information that VBLSM cannot address, such as contributing effects for age, lesion volume and chronic brain disease.

5.4. Future Implications

Although we showed a high frequency of dysphagia, dysarthria, and aphasia in our sample, our results likely underrepresent patients with mild impairment or those who did not have a referral for dysphagia assessment. Future studies should still investigate the frequency and co-occurrence of dysphagia, dysarthria, and aphasia, and other impairments in prospectively enrolled samples. Systematic investigations of frequency and co-occurrence of impairments in patients who have had validated and routine screenings for dysphagia (Martino et al., 2009; Schepp et al., 2012 and communication (Flamand-Roze et al., 2011; Flowers et al., 2012) may facilitate comprehensive assessments for multiple impairments by SLPs. SLPs could then identify the full gamut of impairments within their scope of practice such as cognitive communication impairments (Murray, 2012), neurogenic stuttering (Theys et al., 2011), apraxia of speech (Trupe et al., 2013), and voice impairments (Vuković et al., 2012). With the inclusion of routine screening, future studies could address and better validate incidence estimates for a range of co-occurring impairments after acute stroke. They could even develop models to predict the probability of recovery in or beyond the acute stage.

We provided an initial robust model of dysphagia after infratentorial stroke in our systematic review. Future studies could extend this line of investigation for dysphagia after supratentorial lesions (Galovic et al., in press). In addition, systematic reviews of neuroanatomical lesion correlates may be useful once research develops addressing other impairments, such as aphasia (Join-Lambert et al., 2012) neglect (Manes, Paradiso, Springer,
Lamberty, & Robinson, 1999), or multiple co-occurring impairments (Jones, Ward, & Critchley, 2010). In our systematic review, we compiled results for patients with isolated lesions in specific regions, with the exception of extension into the cerebellum. Consequently, we did not need to conduct multicollinearity analyses for potential confounds from neighbouring overlapping regions. Nevertheless, identifying patients with isolated lesions in discrete regions of interest may require years of sampling, especially for regions infrequently affected in isolation, such as the basal ganglia, midbrain, and/or insula. Studies that investigate discrete regions of interest are limited in their generalization to all patients, because the lesion profiles may represent rare lesion localizations. Consequently, as in our patient sample with MRI analysis, we still need studies that investigate samples of patients with regions of interest that may be overlapping, as long as there is an attempt to account for multicollinearity of neighbouring regions of interest.

In addition to identifying acute neuroanatomical lesion predictors of dysphagia, dysarthria, and aphasia, we further elucidated the contribution of demographic and chronic brain factors. This was particularly relevant for dysphagia, where age and brain atrophy were factors in our whole brain model. In addition, brain atrophy was the strongest predictor of supratentorial dysphagia. Like our study, future research needs to consider contributing factors to the expression of dysphagia. Additional studies that use more specific measures of localized brain atrophy, such as white matter tractography (Kalinosky, Schindler-Ivens, & Schmit, 2013), may provide a more specific neuroanatomical basis for regions precipitating atrophy-related dysphagia. New less invasive MRI modalities, such as arterial spin labelling (ASL) (Richardson et al., 2011), require further exploration in the quantification of chronic brain disease, such as chronic cortical hypoperfusion. ASL is a structural imaging technique that does not require invasive techniques such as the administration of gadolinium (Hartkamp, Petersen, De Vis,
Because it is a structural imaging modality, acquisition along with other acute stroke protocol scans is possible (Wang et al., 2013). ASL could provide valuable information to address the potential contribution of hypoperfusion, perhaps clarifying the interpretation of models such as ours for aphasia, where we had larger effects for subcortical involvement than for superficial cortical MCA involvement.

Also, inclusion of measures addressing interactions between chronic brain disease factors, such as the effect of subcortical infarcts on more distant brain regions (Smith & Arboix, 2012; Patel & Markus, 2011; Duering et al., 2012), may be useful in understanding relationships among factors. Ideally, researchers should apply previously quantified measures of chronic brain disease to the evaluation of their effect on impairments (Park, Wang, & Duong, in press) or to provide a standardized composite index of total chronic brain disease (Zhang et al., 2011).

Future research considering the effect of lesion volume in discrete neuroanatomical regions (Chechlacz et al., 2012) may help further define the neural substrate for dysphagia and aphasia. Voxel based lesion symptom mapping can relate behaviours to voxel-sized regions voxel-sized groupings of lesions. Voxel-based lesion symptom mapping requires normalization of brain scans to provide discrete information, also permitting the evaluation of lesion size as a group composite in those with and without a given impairment. It may also contribute to our understanding of effects of lesion laterality in discrete neuroanatomical regions.

5.5. Conclusion

We documented the frequency, co-occurrence and predictors of dysphagia, dysarthria and aphasia in large homogeneous samples of patients, both in our systematic review and our retrospective cohort. After selecting patients with an acute stroke, confirmed by MR imaging, we demonstrated high estimates for dysphagia, dysarthria, and aphasia and for their co-occurrence
after first ischemic stroke. In our systematic review, we confirmed a comparable high frequency of dysphagia after pontine and medullary stroke. Using our robust estimates of the frequency of dysphagia, dysarthria, and aphasia, we simultaneously quantified demographic, acute lesion and chronic brain factors that predicted their presence. We are continuing to develop more discrete acute lesion driven models using voxel-based lesion symptom mapping following DWI scan normalization to a reference template. This will permit grouped analyses for all patients. Our imaging data have provided and will continue to facilitate robust models of impairment risk early after acute ischemic stroke. We have provided new knowledge pertaining to the effects of age, brain atrophy, and acute lesion localization and volume on the expression of dysphagia. We demonstrated that the presence of dysarthria and aphasia can be explained by acute lesion localization and volume. Our current results have provided the impetus for early screening of dysphagia and communication, especially in patients at highest risk of developing these compromising impairments. This research will permit the future evaluation of the relationship between demographic and brain factors and facilitate investigations into prognostic factors in the determination of recovery patterns for dysphagia, dysarthria, and aphasia throughout the acute stage and beyond.
References

The standardisation of terminology in lower urinary tract function: Report from the
standardisation sub-committee of the international continence society. *Urology, 61*, 37-49.


Neurology, 30*, 555-564.

analysis by brain MRI. *Dysphagia, 7*, 170-173.

Correlating lesion size and location to deficits after ischemic stroke: The influence of
accounting for altered peri-necrotic tissue and incidental silent infarcts. *Behavioral and
Brain Functions 6:6*. Retrieved from
http://www.behavioralandbrainfunctions.com/content/6/1/6


hospitalized patient: Impact on prognosis and hospital resources. *Archives of


Bogousslavsky (Eds.), *The behavioural and cognitive neurology of stroke* (pp. 1-14). New York: Cambridge University Press.


centre hospitalier universitaire: Apport du neurologue dans la prise en charge du patient

Revue Neurologique, 156, 727-735.


APPENDIX A

Figure A1. Elsevier Rights Confirmation

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APPENDIX B

Table B1. Research Assistant’s Guide to Review of TWH Medical Records for extracting frequency of dysphagia, dysarthria, apraxia of speech, and aphasia (last updated June 15, 2009).

<table>
<thead>
<tr>
<th>Order of Chart Review Sections</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Admitted (E-)</td>
</tr>
<tr>
<td>2. Admitted (I-)</td>
</tr>
<tr>
<td>3. Emergency Services Report → Use date at bottom Right</td>
</tr>
<tr>
<td>4. Emergency Nursing Assessment → Use date at Top Left</td>
</tr>
<tr>
<td>5. Admitting Summary</td>
</tr>
<tr>
<td>6. Clinical Notes (CN)</td>
</tr>
<tr>
<td>7. Doctor’s Orders (DO) → stroke/other (If SLP referral found here change date)</td>
</tr>
<tr>
<td>8. Doctor’s Orders → general (If SLP referral found to be earlier here change date)</td>
</tr>
<tr>
<td>9. Clinical Swallowing Assessment (CSA)</td>
</tr>
<tr>
<td>10. Communication Screening Report</td>
</tr>
<tr>
<td>11. Consultation Form (CF)</td>
</tr>
<tr>
<td>12. Special Swallow Study Report (SSSR)</td>
</tr>
<tr>
<td>13. Nutrition Consultation (NC)</td>
</tr>
<tr>
<td>14. Miscellaneous Documents (MD)</td>
</tr>
<tr>
<td>15. X-Ray (chest)</td>
</tr>
<tr>
<td>16. Health Record Reports → OR/Procedure Notes</td>
</tr>
<tr>
<td>17. UHN Research Consent</td>
</tr>
</tbody>
</table>

1. Was Swallowing Screening Done?²

This information may be found in the emergency record, nursing progress notes, physician consult notes

1a. Is there any note or comment about swallowing? This information may be provided by the patient (i.e. self-report) or it may be based on an observation made by one of the hospital staff. It may even be made by the Speech Language Pathologist if he/she was the first to see the patient. There may be multiple notes about swallowing problems but we are interested in the date of the first notation.

² Question 1 pertained to screening and was assigned to a different study (not applicable to thesis).
1b. What type of professional made the first notation in the chart about the swallowing problem? If a Speech Language Pathologist made the first notation, skip the rest of section 1 and move on to section 2 (Was Swallowing Assessment Done?).

1c. Did the note indicate any swallowing problem? Ex. dysphagia, trouble swallowing, choking on food or liquid, drooling, coughing on food, liquid or medications, food remaining in mouth (not swallowed), removal of food from mouth, difficulty chewing.

1d. In most cases, the screening will be referred to as the TOR-BSST, Toronto Bedside Swallowing Screening Test, Toronto Bedside Test, etc. Sometimes the actual orange TOR-BSST form will be placed in the chart (2007 onward). If there is no mention of the TOR-BSST being performed, or a test with a similar sounding name, then is there any mention of something else being done – ex. Water swallow test, patient given teaspoons of water, etc. This may have been done by a nurse or doctor.

1e. We are interested in the date of the first screening (if there happens to be more than one screening performed)

1f. What type of professional performed the screening? Ex. Nurse, doctor, dietitian, etc.

1g. Did the patient fail the screening (i.e. a ‘positive’ test result)? If they failed, check “yes”.

1h. This will likely be found in the doctor’s orders or a doctor’s note in the chart. Doctor’s orders may say “SLP to see”, “SLP to assess”, “swallowing assessment”, “swallow study/SS”, “speech to see/assess”, “Cookie Swallow”, “VFSS”, “MBS”, “VFS” – any one of these would indicate that a referral to Speech Language Pathology has been made.

2. Was Swallowing Assessment Done?

Speech-Language Pathology notes could be documented in:
   i. Doctor’s Orders
   ii. Clinical Notes
   iii. Special Swallow Study Report
   iv. Clinical Swallowing Assessment

Doctor’s notes could be documented in:
   i. Doctor’s Orders
   ii. Clinical Notes
   iii. Consultation Form
   iv. Chart Review – Radiology
   v. Chart Review – Health Record Reports/OR Section

2a. Is there any Speech-Language Pathology note or comment about a swallowing impairment or dysphagia (see additional terms from 1a if needed). This information may be provided by the patient (i.e. self-report) or it may be based on an observation made by one of the hospital
staff. There may be multiple notes about swallowing problems but we are interested in the date of the first notation by SLP only.

2b. SLP reported at some point that (oropharyngeal) dysphagia was present:

Dysphagia absent may be described as:
  i. in keeping with age
  ii. within functional limits (WFL)
  iii. within normal limits (WNL)

Dysphagia present may be described as difficulties with:
  i. bolus manipulation
  ii. bolus formation
  iii. bolus transit
  iv. hyolaryngeal excursion/movement
  v. labial seal
  vi. pharyngeal trigger
  vii. risk of aspiration

* Most often, the SLP will describe the impairment as dysphagia or oropharyngeal dysphagia

2c. Modified textures include the following:
  i. dysphagia diet
  ii. honey thick liquid
  iii. nectar thick liquid
  iv. pudding thick liquid
  v. pureed diet
  vi. thickened liquid
  vii. minced solids or minced texture
  viii. dental soft solids or soft solids
  ix. no mixed textures
  x. no particulate matter

2d. Swallowing therapy or strategies:

  i. assistance with feeding
  ii. ensure each mouthful is swallowed (look for upward movement of larynx/Adam’s apple)
  iii. if you cough or clear your throat, swallow an extra time
  iv. hold your breath when swallowing
  v. hold your voice box in a high position when swallowing
  vi. no straws allowed
  vii. supervise while eating or drinking
  viii. swallow twice for each mouthful
  ix. swallow with effort (effortful swallow)
x. take fluid/liquid after food  
xii. take fluid/liquid from a teaspoon only  
exii. take single sips of fluid/liquid only  
ixiiii. take small bites of food only  
ixiv. take small sips of fluid/liquid only  
xv. tuck chin down toward chest when swallowing  
xvii. turn head to left or right

2e. SLP recommended or ordered NPO:  
i. Nil per os (NPO)  
ii. Nothing by mouth  
iii. No food or liquid by mouth

2f. Doctor ordered a feeding tube:

**First,** look in the doctor’s orders. This type of intervention should be in the orders.

**If it is not in the orders,** look in the patient’s *electronic record* (*chart review section*) under **radiology** (#7), to find surgical reports (PEG or PEG-J) or chest x-rays (used to confirm placement of NG or OG tube)

**Feeding Tube Terms:**  
i. orogastric feeding tube, orogastric tube, OG tube, OGT, or OG  
ii. nasogastric feeding tube, nasogastric tube, NG Tube, NGT, or NG  
iii. percutaneous endoscopic gastrostomy, or PEG tube or PEG  
iv. jejunostomy tube or JG tube or J tube or PEG-J or J-PEG

2g. Feeding tube was inserted:  

**NGT or OGT:** Look for nursing notes (in Clinical Notes) to find a report that a tube was inserted. If you do not find a nursing note, then look in the *electronic record* under **radiology** (#7) if not done in step 2f. Find a chest x-ray that confirms tube placement.

**PEG or PEG-J:** Look first in the *electronic record* under **radiology** (#7) if not done in step 2f. Find a surgical report that describes tube placement. This will tell you for sure if a PEG or PEG-J was inserted. The word ‘jejunostomy’ or ‘jejenum’ will mean it is a PEG-J.

2h. Type of feeding tube was: See 2g

If you have not found the answer to this in 2g, then you need to look in the **clinical notes** again to find the information.
It is possible that a nurse may have not entered the information that an NG or OG tube was inserted. Also, chest x-rays don’t always happen or they are not clear.

**Last Check:** You can also look in the dietician’s clinical notes to confirm the type of tube, because the dietician monitors the feeds and the formula.

**Was there an SLP assessment of Communication?**

☐ Yes
☐ No

*If ‘yes’ and SLP reported the **presence** of any of the impairments in the sections below, the SLP must be listed as one of the two experts in that/those section(s).*

**3. Was Dysarthria Assessment Done?**

**Terms for SLP report:**

Dysarthria **absent** may be described as:

i. speech production/execution in keeping with age
ii. speech difficulty resulting ONLY from (secondary to) decreased level of consciousness (LOC) or decreased alertness/fatigue
iii. speech difficulty resulting from (secondary to) medications
iv. within functional limits (WFL)
v. within normal limits (WNL)

Dysarthria **present** may be described as difficulties with:

i. speech execution
ii. slurred speech
iii. articulatory precision

* Most often, the SLP will describe the impairment as **dysarthria** or impairment in **speech execution**.

**Terms for Doctor or Stroke Nurse report:**

Dysarthria **absent** may be described as:

i. speech production/execution in keeping with age
ii. speech difficulty resulting ONLY from (secondary to) decreased level of consciousness (LOC) or decreased alertness/fatigue
iii. speech difficulty resulting from (secondary to) medications
iv. within functional limits (WFL)
v. within normal limits (WNL)
Dysarthria **present** may be described as difficulties with:

i. speech execution  
ii. slurred speech  
iii. articulatory precision

* Most often, the doctor will describe the impairment as **dysarthria** or **slurred speech**.

3a. There was a first expert note that dysarthria was present:

Is there any **Speech-Language Pathology** note, **doctor’s** note or **stroke nurse** note that **dysarthria** or difficulty with **motor execution of speech** was present?

Please Note: Clinical Clerk (CC) is not considered an MD.

We are interested in the date of the **first** identification of dysarthria by an **expert**.

3b. There was a second expert note that dysarthria was present:

Is there any **Speech-Language Pathology** note, **doctor’s** note or **stroke nurse** note that **dysarthria** or difficulty with **motor execution of speech** was present?

Please Note: Clinical Clerk (CC) is not considered an MD.

We are interested in the date of the **second** identification of dysarthria by an **expert**.

4. Was Apraxia of Speech Assessment Done?

**Terms for SLP Report:**

Apraxia of speech **absent** may be described as:

i. speech production/programming in keeping with age  
ii. speech difficulty resulting ONLY from (secondary to) decreased level of consciousness (LOC) or decreased alertness/fatigue  
iii. speech difficulty resulting from (secondary to) medications  
iv. within functional limits (WFL)  
v. within normal limits (WNL)

Apraxia of speech **present** may also be described as difficulties with:

i. speech programming  
ii. speech gestures, such as “groping”  
iii. sequencing difficulties when repeating multisyllabic words

* Most often, the SLP will describe the impairment as **apraxia of speech** or **impairment in speech programming**.
Terms for Doctor or Stroke Nurse Report:

Apraxia of speech **absent** may be described as:

i. speech production/programming in keeping with age

ii. speech difficulty resulting ONLY from (secondary to) decreased level of consciousness (LOC) or decreased alertness/fatigue

iii. speech difficulty resulting from (secondary to) medications

iv. within functional limits (WFL)

v. within normal limits (WNL)

Apraxia of speech **present** may also be described as difficulties with:

i. speech programming

ii. repetition of long words

* Most often, the doctor will **NOT** describe this impairment. Still look for terms such as apraxia of speech, dyspraxic speech and difficulty repeating long words

4a. There was a first expert note that apraxia of speech was present:

Is there any **Speech-Language Pathology** note, **doctor’s** note or **stroke nurse** note that apraxia or difficulty with motor programming of speech was present?

Please Note: Clinical Clerk (CC) is not considered an MD.

We are interested in the date of the **first** identification of apraxia of speech by an expert.

4b. There was a second expert note that apraxia of speech was present:

Is there any **Speech-Language Pathology** note, **doctor’s** note or **stroke nurse** note that apraxia or difficulty with motor programming of speech was present?

Please Note: Clinical Clerk (CC) is not considered an MD.

We are interested in the date of the **second** identification of apraxia of speech by an expert.

5. Was Aphasia Assessment Done?

Terms for SLP Report:

Aphasia **absent** may be described as:
i. Receptive or expressive language in keeping with age
ii. language difficulty resulting ONLY from (secondary to) decreased level of consciousness (LOC) or decreased alertness/fatigue
iii. language within functional limits (WFL)
iv. language within normal limits (WNL)

Aphasia present may be also described as:
i. anomia
ii. broca’s
iii. dysnomia
iv. dysphasia
v. impaired expressive language, receptive language, or global language
vi. Wernicke’s
vii. word finding difficulties

* Most often, the SLP will describe the impairment as aphasia or impaired expressive, receptive or global language.

Terms for Doctor or Stroke Nurse Report:

Aphasia absent may be described as:
i. receptive or expressive language in keeping with age
ii. language difficulty resulting ONLY from (secondary to) decreased level of consciousness (LOC) or decreased alertness/fatigue
iii. language within functional limits (WFL)
iv. language within normal limits (WNL)
v.

Aphasia present may be also described as:
i. anomia
ii. broca’s
iii. dysnomia
iv. dysphasia
v. impaired expressive language, receptive language, or global language
vi. Wernicke’s
vii. word finding difficulties

* Most often, the doctor will describe the impairment as any of the terms above

5a. There was a first expert note that aphasia was present:

Is there any Speech-Language Pathology note, doctor’s note or stroke nurse note that aphasia or difficulty with word finding, naming or language was present?

Please Note: Clinical Clerk (CC) is not considered an MD.
We are interested in the date of the first identification of aphasia by an expert.

5b. There was a second expert note that aphasia was present:

Is there any Speech-Language Pathology note, doctor’s note or stroke nurse note that aphasia or difficulty with word finding, naming or language was present?

Please Note: Clinical Clerk (CC) is not considered an MD.

We are interested in the date of the second identification of aphasia by an expert.
**APPENDIX C**

**Table C1.** Data extraction form for TWH medical records: Frequency of dysphagia, dysarthria, apraxia of speech, and aphasia (Last updated: July 23, 2009).

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<th>Admission Information</th>
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<tr>
<td>Date of Chart Review:</td>
</tr>
<tr>
<td>Name of Reviewer:</td>
</tr>
</tbody>
</table>

PATIENT CODE: _______  Admission Date: ___________  Admission Time: _______

1. **Was Swallowing Screening Done?**
   - Yes
   - No → *if ‘no’ skip to 1d*

   **1a.** Was there a notation about swallowing?
   - *if ‘yes’ give date and time of FIRST notation: ______________________________ (mm/dd/yy;hr:min)
   - *if ‘yes’, give chart location of first note ________________________________

   **1b.** Professional who made first notation:
   - Speech Language Pathologist (SLP) → *skip to section 2*
   - Nurse (RN, RPN, RNA)
   - Doctor (MD, Resident, Fellow)
   - Dietitian (RD)
   - Occupational Therapist (OT)
   - Physiotherapist (PT)
   - Other: ________________________________

   **1c.** Notation indicated that a swallowing problem was:
   - Present
   - Absent
   - Not Clear

   **1d.** Swallowing ‘screening’ was performed:
   - Yes
   - No → *if ‘no’ skip to 1h*

   (i.e. TOR-BSST (orange form), Toronto Bedside Swallowing Screening Test, Toronto Bedside Test, etc.)

   **1e.** Date and time of first ‘screening’.
   __________________________________________ (mm/dd/yy;hr:min)
**1f. Professional who completed first ‘screening’:**
- Nurse (RN, RPN, RNA)
- Doctor (MD, Resident, Fellow)
- Dietitian (RD)
- Occupational Therapist (OT)
- Physiotherapist (PT)
- Other: 

**1g. First ‘screening’ was failed (i.e. positive result):**
- Yes
- No
- Not Clear

**1h. Referral was made to Speech Language Pathology:**
- Yes
- No

*If ‘yes’ give date and time that referral was made*

**(mm/dd/yy;hr:min)**

---

**2. Was Swallowing Assessment Done?**

**2a. There was an SLP assessment of dysphagia:**
- Yes
- No → *if ‘no’ skip to 2f*

*If ‘yes’ give date and time of first note*

**(mm/dd/yy;hr:min)**

*If ‘yes’, give chart location of first note*

**2b. SLP reported at some point that dysphagia was present:**
- Yes
- No → *if ‘no’ skip to 2f*

*If ‘yes’ give date and time of first note*

**(mm/dd/yy;hr:min)**

*If ‘yes’, give chart location of first note*
### 2c. SLP recommended modified texture(s):  
- ☐ Yes  
- ☐ No  

> If ‘yes’ give date and time of first note  

____________________  

(mm/dd/yy; hr:min)  

> If ‘yes’, give chart location of first note

### 2d. SLP recommended swallowing therapy or strategies:  
- ☐ Yes  
- ☐ No  

> If ‘yes’ give date and time of first note  

____________________  

(mm/dd/yy; hr:min)  

> If ‘yes’, give chart location of first note

### 2e. SLP recommended NPO:  
- ☐ Yes  
- ☐ No

### 2f. Doctor ordered a feeding tube:  
- ☐ Yes  
- ☐ No  

> If ‘yes’ give date and time of order  

____________________  

(mm/dd/yy; hr:min)

### 2g. Feeding tube was inserted:  
- ☐ Yes  
- ☐ No  

> If ‘no’ skip to 3a

### 2h. Type of feeding tube was:  
- ☐ NGT  
- ☐ OGT  
- ☐ PEG  
- ☐ PEG-J  

*Date of confirmed insertion*  

____________________  

(mm/dd/yy; hr:min)

---

**Was there an SLP assessment of Communication?**

- ☐ Yes  
- ☐ No
If ‘yes’ and SLP reported the presence of any of the impairments in the sections below, the SLP must be listed as one of the two experts in that/those section(s).

3. Was Dysarthria Assessment Done?

3a. There was a first expert note that dysarthria was present:

☐ Yes
☐ No → if ‘no’, skip to 4a

첩 if ‘yes’ give date and time of first note

____________________
(mm/dd/yy;hr:min)
첩 if ‘yes’ give chart location of first note

____________________
첩 if ‘yes’ identify expert
☐ SLP
☐ Stroke Nurse
☐ MD
첩 if MD identify service or title

3b. There was a second expert note that dysarthria was present:

☐ Yes
☐ No

첩 if ‘yes’ give date and time of second note

____________________
(mm/dd/yy;hr:min)
첩 if ‘yes’ give chart location of second note

____________________
첩 if ‘yes’ identify expert
☐ SLP
☐ Stroke Nurse
☐ MD
첩 if MD identify service or title
### 4. Was Apraxia of Speech Assessment Done?

**4a.** There was a *first* expert note that apraxia of speech was present:

- [ ] Yes
- [ ] No → *if no*, skip to 5a

*if yes* give date and time of first note

____________________

(*mm/dd/yy;hr:min)*

*if yes* give chart location of first note

____________________

*if yes* identify expert

- [ ] SLP
- [ ] Stroke Nurse
- [ ] MD

*if MD identify service or title*  

____________________

**4b.** There was a *second* expert note that apraxia of speech was present:

- [ ] Yes
- [ ] No

*if yes* give date and time of second note

____________________

(*mm/dd/yy;hr:min)*

*if yes* give chart location of second note

____________________

*if yes* identify expert

- [ ] SLP
- [ ] Stroke Nurse
- [ ] MD

*if MD identify service or title*  

____________________

### 5. Was Aphasia Assessment Done?

**5a.** There was a *first* expert note that aphasia was present:

- [ ] Yes
- [ ] No → *if no*, skip 5b

*if yes* give date and time of first note

____________________
5b. There was a second expert note that aphasia was present:

- [ ] Yes
- [ ] No

- if 'yes' give date and time of second note

- if 'yes' give chart location of second note

- if 'yes' identify expert
  - [ ] SLP
  - [ ] Stroke Nurse
  - [ ] MD

- if MD identify service or title

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<td>The incidence, co-occurrence, and predictors of dysphagia, dysarthria, and aphasia after acute ischemic stroke</td>
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APPENDIX E

Table E1. Search strategy for citations for date of online database availability to June 2009

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<th>Database: AMED (Allied and Complementary Medicine)</th>
<th>Search Strategy</th>
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<td>1. cerebrovascular disorders/ or cerebral infarction/ or cerebral ischemia/ or cerebrovascular accident/</td>
<td></td>
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<tr>
<td>2. arterial occlusive disease/</td>
<td></td>
</tr>
<tr>
<td>3. arrhythmia/</td>
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<td>4. brain injuries/</td>
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<td>5. carotid arteries/</td>
<td></td>
</tr>
<tr>
<td>6. neurologic manifestations/</td>
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<tr>
<td>7. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or isch?emi$ attack$ or neurologic$ deficit$).tw.</td>
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</tr>
<tr>
<td>8. ((brain$ or cerebr$ or cerebell$ or cortical or vertebrobasilar or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or MCA or anterior circulation or posterior circulation or basal ganglia) adj10 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypox$ or vasospasm or obstruction or vasculopathy)).tw.</td>
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<tr>
<td>9. ((lacunar or cortical) adj5 infarct$).tw.</td>
<td></td>
</tr>
<tr>
<td>10. (vertebral artery dissection or cerebral art$ disease$).tw.</td>
<td></td>
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<tr>
<td>11. ((brain or intracranial or basal ganglia or lenticulostriate) adj10 (vascular adj5 (disease$ or disorder or accident or injur$ or trauma$ or insult or event))).tw.</td>
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</tr>
<tr>
<td>12. (isch?emic adj5 (event or events or insult or attack$)).tw.</td>
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</tr>
<tr>
<td>13. ((cerebral vein or cerebral venous or sinus or sagittal) adj5 thrombo$).tw.</td>
<td></td>
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<tr>
<td>14. (CVDST or CVT).tw.</td>
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<td>((intracranial or cerebral art$ or basilar art$ or vertebral art$ or verteobasilar or vertebral basilar) adj5 (stenosis or isch?emia or insufficiency or arteriosclero$ or atherosclero$ or occlus$)).tw.</td>
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<td>(aphasi$ or dysphas$ or anomi$ or dysnom$ or Wernicke or Broca).tw.</td>
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| 26 | limit 25 to yr="2007 -Current"

**Biosis**

#27 #24 AND #22

#26 #25 AND #24

#25 TS=(Magnet* or MRI)

#24 #21 AND #11

#23 #22 AND #21 AND #12

#22 TS=(MR or MRI or magnetic resonance imag*)

#21 TS=(dysphag* or swallow* or deglutit*)
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**CINAHL**

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| **Dissertation Abstracts** | Terms "stroke AND dysphagia" |

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**HAPI**

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**Healthstar**

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**Pharmaceutical Abstracts**

Term: dysphagia in title or abstract (all years, no restrictions)

Search Engine: Proquest

**PsycInfo**

```
(((KW=("deglutition disorders" or "dysphagia" or "aphagia")) or(KW=(dysphag* or swallow* or "deglutit* disorder*" or "swallowing disorder*" or deglutit* or oropharyn* or "oropharyngeal dysphag*"))) and(((KW=(reversible isch*)) or((KW=(thrombo*)) and(KW=(intracranial or sinus or sagittal))) or(KW=(cerebral or intracerebral or intracranial or parenchymal or brain* or intraventricular or cerebellar or infratentorial or supratentorial))) or(((KW=(cerebral or cerebellar or brain* or vertebrobasilar)) and(KW=(infarct* or ischaemi* or ischem* or thrombo* or emboli* or insufficiency or occlusion))) or(KW=(stroke* or poststroke or post-stroke or cva*)) or(KW=((isch*) and (event* or insult*))))) or(KW=(cerebral vascular disorders) or (cerebrovascular disorders) or (cerebrovascular accidents) or KW=(cerebral ischemia) or KW=(carotid arteries) or KW=((brain) and (lesions or ischemia)))) and(KW=("Magnetic Resonance Imaging") or KW=("Magnetic Resonance Spectroscopy") or KW=("nuclear magnetic resonance" or MRI or "chemical shift imag:" or "mr* tomog:" or "mr* scan:" or "magnetic resonance imag:" or...```
| Wilson | DE=((deglutition disorders) or dysphagia or aphagia) or 
|        | KW=(dysphagi$ or swallow$ or "deglutit$ disorder$" or 
|        | "swallowing disorder$" or deglutit$ or oropharyn$ or 
|        | oropharyngeal dysphagi$) |
| Journal Searches | American Journal of Neuroradiology |
| 1991 to search dates | Dates: Jan 1 1991 on |
|                     | Terms: *dysphagia MR stroke* (as all anywhere in text, title abstract) |
|                     | Date of Search: May 18 2009 |
|                     | Number of citations: 18 |
|                     | Annals of Neurology |
|                     | Dates: 1991 on |
|                     | Terms: *dysphagia OR swallow* |
|                     | Date of Search: June 12 2009 |
|                     | Number of citations: 4 |
|                     | Archives of Neurology |
|                     | Dates: from 1991 |
|                     | Terms: as specified in “Search Strategy” |
|                     | Date of Search: June 12, 2009 |
Number of citations: 38

Search Strategy:

1  dysphagia.mp.
2  stroke.mp.
3  2 and 1
4  limit 3 to yr="1991 -Current"
5  3 and 4
6  "archives of neurology".jn.
7  5 and 6

**Archives of Physical Medicine and Rehabilitation**

Dates: Jan 1991 to June 12 2009

Terms: *dysphagia AND stroke* within all fields using terms as root words

Date of Search: June 12 2009

Citations: 77

**Brain**

Database: Journals@Ovid Full Text <June 19, 2009>

Search also used for *Neurology*

Citations: 18

Search Strategy:

1  00006114-000000000-00000.an.
Cerebrovascular Diseases

Date of Search: June 19, 2009

Search also used for *Brain* and *Neurology*

Citations: 25

Search Strategy:

1 00006114-000000000-00000.an.
2 neurology.jn.
3 limit 2 to yr="1991 -Current"
4 (dysphagia and MRI).mp.
5 4 and 3 and 2
6 stroke.mp.
7 6 and 5
8 from 7 keep 1-63
9 brain.jn.
10 6 and 4 and 9
7 6 and 5
8 from 7 keep 1-63
9 brain.jn.
10 6 and 4 and 9
11 from 10 keep 1-18
12 from 11 keep 1-18
13 cerebrovascular diseases.jn.
14 6 and 4 and 13
15 from 14 keep 1-24

Clinical Journal of Neuroscience
http://www.sciencedirect.com/science/journal/09675868

Date of Search: June 12 2009

Terms: swallow and stroke in all fields (no results were found using "dysphagia")

Note: Journal began in 1994 only

Citations: 10

Dysphagia
http://www.metapress.com/content/100357/?k=stroke+MRI

Date of Search: June 12, 2009

Citations: 18

Search strategy: dysphagia AND MRI
<table>
<thead>
<tr>
<th>Journal: Journal of Magnetic Resonance Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: June 15 2009</td>
</tr>
<tr>
<td>Search Strategy: swallow</td>
</tr>
<tr>
<td>Citations: 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Journal of Stroke and Cerebrovascular Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: June 19 2009</td>
</tr>
<tr>
<td>Search Strategy: Swallow</td>
</tr>
<tr>
<td>Category: Natural Sciences</td>
</tr>
<tr>
<td>Citations: 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Magnetic Resonance in Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: June 15 2009</td>
</tr>
<tr>
<td>Search Strategy: Swallow</td>
</tr>
<tr>
<td>Citations: 1</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Neurology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date: June 12, 2009</td>
</tr>
<tr>
<td>Search Strategy:</td>
</tr>
<tr>
<td>Citations: 65</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
</tbody>
</table>

Note: listed availability from 1995

**Neuroradiology**

Search: Dysphagia (=20) OR swallow (n=2)

Date of Search: June 11 2009

Citations: 21

**Neurorehabilitation and Neural Repair**

Date: May 18, 2009

Citations: 8

**Neuroreport**

Date: June 12, 2009

Citations: 5
<table>
<thead>
<tr>
<th>Search Strategy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  stroke.mp.</td>
</tr>
<tr>
<td>2  neuroreport.jn.</td>
</tr>
<tr>
<td>3  limit 2 to yr=&quot;1991 –Current&quot;</td>
</tr>
<tr>
<td>4  dysphagia.mp.</td>
</tr>
<tr>
<td>5  4 and 3</td>
</tr>
</tbody>
</table>

**Radiology**

Date of Search: June 15 2009

Search terms:

dysphagia stroke  (all words anywhere in article)

Citations: 8

**Stroke**

Search also used for *Brain* and *Cerebrovascular Diseases*

Date of Search: June 15, 2009

Citations: 58

Search Strategy:

<p>| 1  00006114-000000000-00000.an.                                               |
| 2  neurology.jn.                                                            |
| 3  limit 2 to yr=&quot;1991 -Current&quot;                                             |
| 4  (dysphagia and MRI).mp.                                                  |</p>
<table>
<thead>
<tr>
<th>Grey Literature and Conference Searches</th>
<th>System for Information on Grey Literature (SIGLE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Search terms:</strong> dysphagia OR swallow</td>
<td><strong>Citations:</strong> 9</td>
</tr>
<tr>
<td><strong>Citations:</strong> 9</td>
<td><strong>European Stroke Conference</strong></td>
</tr>
<tr>
<td><strong>Source:</strong> <a href="http://www.esc-archive.eu/">http://www.esc-archive.eu/</a></td>
<td><strong>Date of Search:</strong> July 27, 2009</td>
</tr>
<tr>
<td><strong>Date of Search:</strong> July 27, 2009</td>
<td></td>
</tr>
<tr>
<td>Terms: dysphagia or swallow (within each page)</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Dysphagia</strong></td>
<td></td>
</tr>
<tr>
<td>Date of search: November 7, 2009</td>
<td></td>
</tr>
<tr>
<td>Search Term: MRI</td>
<td></td>
</tr>
<tr>
<td>Citations: 9</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
</tr>
<tr>
<td>Terms dysphagia OR swallow</td>
<td></td>
</tr>
<tr>
<td>Search completed by July 27, 2009</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX F

Systematic Review in Dysphagia – Database Search Exclusions

Coding Criteria for Abstract Review

Exclude if:

1. the study involves *animals* ONLY
2. the study has no abstract
3. the study involves *pediatrics* ONLY
4. the study is a review, diagnostic overview, commentary or letter to the editor
5. Ischemic stroke case reports (n <10)
   - Code as 5 if different etiology altogether
   - Stroke sample but ischemic stroke clearly absent (code as 599 to differentiate from above)
   - Stroke sample is clearly not consecutive (i.e. only those referred for swallowing)
6. mention of swallowing or non-specific clinical outcomes is ABSENT.
7. mention of MRI or non-specific imaging/lesion localization is ABSENT.
   - exclude if clearly ONLY fMRI

**NOTE:** Each number supercedes the next. If the study is exclusively pediatric (#3), but is also a review (#4), code as the higher number (#3).
APPENDIX G

Systematic Review in Dysphagia – Database Search Exclusions

Coding Criteria for Full Article Review

Exclude if:

1. The study involves animals ONLY.
2. The study involves pediatrics ONLY.
3. The study is a review, diagnostic overview, commentary or includes results from another accepted study
4. The study CLEARLY does not have acute stroke patients.
5. The sample is CLEARLY not consecutive stroke.
6. Ischemic stroke is CLEARLY less than 10 subjects.
7. Swallow outcomes are absent (i.e. screen, clinical assessment or instrumental ax)
8. MRI imaging is ABSENT.
9. Association between MRI lesions and dysphagia outcome is ABSENT.

Last revision: June 20, 2009
### APPENDIX H

**Table H1.** Risk of Bias Evaluation (adapted from Cochrane, 2008) for systematic review of neuroanatomical correlates of dysphagia after acute stroke

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of Bias</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of Assessor (dysphagia assessor blind to lesion localization)</td>
<td>High, Low, Unclear</td>
<td></td>
</tr>
<tr>
<td>Incomplete Outcome Data Addressed (dysphagia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate Sampling (&gt;=six months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate Measures (clinical ax or instrumental ax – yes; screening – no; report of nonspecific clinical findings or signs - unclear)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceptable Delay between Tests (24 hours between MR and swallow ax)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Representative Sample (i.e. consecutive age range, both genders, all acute stroke)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Declaration of Unclassifiable/Uninterpretable Data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clear Operational Definitions (for dysphagia outcomes; clearly replicable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same Radiographic Measure for all Patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## APPENDIX I

**Data extraction manual for MRI-based correlates of dysphagia, dysarthria, and aphasia**  
(last updated July 03, 2012)

### WHOLE BRAIN HEALTH

#### 1a. Is there evidence of previous stroke?

Confirm acute lesion on DWI and ADC map. Compare DWI to T2 FLAIR for additional lesions. Review T2 as needed (to confirm previous lesions where periventricular white matter disease also exists).

Periventricular white matter and deep white matter lesions are **NOT** evidence of previous stroke.

#### 1b. Identify previous stroke category (Potter et al, 2011)

**Lacunar etiology**

Includes 10-20 mm lesions on any slice. Multiple lesions may have occurred as watershed infarcts (string of pearls). Because they are multiple old lesions, they are excluded.

- Often are oval in shape and deep
- May occur around anterior commissure and superior frontal gyrus
- Often present as tiny dots in the basal ganglia

**Other etiology**

Any evidence of non-lacunar previous stroke

**UTD**

Very difficult to distinguish infarct from white matter disease. However, this should not be too difficult given the obvious shape and size of previous lacunar strokes, versus more diffuse white matter changes.

Refer for secondary review.

#### 1c. Is there evidence of other brain disease (Schaefer et al, 2000)?

**Yes**

Evidence of brain disease such as:
- tumour
- clear hole in grey matter
- other

Does **NOT** include brain atrophy (documented in #2) or possible normal pressure hydrocephalus.

**No**

No clear evidence of other brain disease.
<table>
<thead>
<tr>
<th><strong>2a. White matter hyperintensities (Fazekas Scale):</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 No periventricular or deep white matter lesions</td>
</tr>
<tr>
<td>1 scattered periventricular and/or deep white matter lesions</td>
</tr>
<tr>
<td>2 semi-confluent periventricular and/or deep white matter lesions</td>
</tr>
<tr>
<td>3 confluent and extensive periventricular and/or deep white matter lesions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>2b. Is there evidence of gross brain atrophy?</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
</tr>
<tr>
<td>Gross evidence of excessive cerebral spinal fluid, with small sulci that is not in keeping with age.</td>
</tr>
<tr>
<td><strong>No</strong></td>
</tr>
<tr>
<td>Clearly no gross evidence of excessive cerebral spinal fluid, with small sulci.</td>
</tr>
<tr>
<td><strong>UTD</strong></td>
</tr>
<tr>
<td>Difficult to ascertain gross evidence of excessive cerebral spinal fluid, with small sulci.</td>
</tr>
</tbody>
</table>

- **Refer for secondary review.**

**ACUTE LESION FACTORS**

**3-5. DWI Analyses**

No further explanation necessary beyond data capture form.
APPENDIX J

**Table J1.** MRI lesion data extraction form for RCSN first-ever stroke sample (last updated July 6, 2012).

SUBJECT ID: ________  Reviewer Initials: ________ Date (DD/MM/YY): ________

**DOES IMAGING REQUIRE SECONDARY REVIEW?**  
☐ Yes  ☐ No  
→ if ‘Yes’, defer to expert for review (Frank Silver or David Mikulis) and provide reason.

1. **WHOLE BRAIN HEALTH (T2 FLAIR compared to DWI/ADC Map)**

<table>
<thead>
<tr>
<th>Stroke and Other Pathologies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criteria</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>1a. Is there evidence of previous stroke?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1b. Previous stroke category:</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Question</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1c. Is there evidence of other brain pathology (not those in #2)?</td>
</tr>
<tr>
<td>→ if ‘Yes’, describe</td>
</tr>
<tr>
<td>Concomitant Neurological Disease</td>
</tr>
<tr>
<td>2a. White matter hyperintensities (Fazekas scale):</td>
</tr>
<tr>
<td>2b. Is there evidence of gross brain atrophy?</td>
</tr>
<tr>
<td>→ if ‘Yes’ ☐ Mild ☐ Moderate ☐ Severe</td>
</tr>
<tr>
<td>ACUTE LESION ATTRIBUTES</td>
</tr>
<tr>
<td>3. DWI SCAN ANALYSIS</td>
</tr>
<tr>
<td>3a. Is the scan quality adequate for analysis?</td>
</tr>
<tr>
<td>→ if ‘No’, 4, 5 ‘Not applicable’</td>
</tr>
<tr>
<td>3b. Is there a distinguishable lesion?</td>
</tr>
<tr>
<td>→ if ‘No’, 4, 5 ‘Not applicable’</td>
</tr>
<tr>
<td>4. ANATOMICAL DWI LESION ATTRIBUTES</td>
</tr>
<tr>
<td>4a. Laterality</td>
</tr>
<tr>
<td>4b. Is there brainstem involvement?</td>
</tr>
<tr>
<td>→ if ‘Yes’, check all that apply:</td>
</tr>
<tr>
<td>☐ medulla ☐ pons ☐ midbrain</td>
</tr>
<tr>
<td>249</td>
</tr>
</tbody>
</table>
4c. Is there cerebellar involvement?  
- Yes  
- No  
- UTD

4d. Is there supratentorial involvement?  
- Yes → if ‘Yes’, check all that apply:  
  - ACA  
  - MCA  
  - PCA  
  - thalamus  
  - basal ganglia  
  - internal capsule  
  - insula  
  - periventricular deep matter  
- No  
- UTD

4e. How many discrete lesions are there?  
- 1  
- 2  
- 3  
- 4  
- 5  
- >5  
- UTD → if ‘UTD’, request secondary review

5. DWI SLICE LESION ATTRIBUTES  
- Not applicable

5a. Circle the slice numbers with clear lesion(s).  
1  2  3  4  5  6  7  8  9  
10 11 12 13 14 15 16  
17 18 19 20 21 22 23  
24 25 26 27 28 29 30  
31 32 33 34 35 36 37

5b. How many DWI slices show evidence of lesion?  
- ________  
- UTD  
- Not applicable

5c. Which slices have more than one lesion? Indicate the number of distinct lesions (>10mm) for each slice (n).  
- Slice#  _____  n  _____  
- Slice#  _____  n  _____  
- Slice#  _____  n  _____  
- Slice#  _____  n  _____  
- Slice#  _____  n  _____  
- Slice#  _____  n  _____  
- Slice#  _____  n  _____  
- Slice#  _____  n  _____  
- Slice#  _____  n  _____  

NOTES