Detecting and Classifying Cognitive Activity Based on Changes in Cerebral Blood Flow Velocity

by

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A thesis submitted in conformity with the requirements for the degree of Master of Applied Science
Graduate Department of Institute of Biomaterials and Biomedical Engineering
University of Toronto

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Abstract

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Individuals with severe physical impairments have a reduced ability to communicate through movement and speech. We investigated transcranial Doppler ultrasound as a potential measurement modality for a novel brain-computer interface. It was hypothesized that cognitive activity would result in detectable changes in cerebral blood flow velocity within the middle cerebral arteries. Nine able-bodied participants alternated between rest and two different mental activities - silent word generation and mental rotation. Two analyses were performed to assess the feasibility and practicality of a TCD-based brain-computer interface. Both mental activities were independently differentiated from rest with high accuracy. Intuitive time-domain features were sufficient for classification. Data transmission rate was quadrupled by differentiating all three classes simultaneously using shorter state durations. Transcranial Doppler ultrasound can be used to automatically detect cognitive activity and may be useful as the basis of a brain-computer interface.
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List of Abbreviations

AAC  Augmentative and Alternative Communication
ACA  Anterior Cerebral Artery
ALS  Amyotrophic Lateral Sclerosis
BCI  Brain-Computer Interface
BVP  Blood Volume Pulse
CBFV Cerebral Blood Flow Velocity
CW   Continuous-Wave
ECoG Electroctigrams
EEG  Electroencephalography
EMG  Electromyography
EOG  Electrooculography
ERP  Event-Related Potential
fMRI Functional Magnetic Resonance Imaging
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Chapter 1

Introduction

1.1 Motivation

Communication is a pivotal aspect of human life. Every day, we use a combination of gestures, body language, facial expressions, writing, and speech to express ourselves and communicate with others. For most of us, these abilities are fundamental, and we cannot imagine being without them. However, there is a growing population for whom these channels of communication are not available. More than 80,000 Canadian children currently live with severe disabilities [1]. These disabilities range from trauma-induced injuries to the spinal cord or brain stem to chronic disorders such as spastic quadriplegic cerebral palsy. Significant impairment of communication ability is a common consequence of these conditions.

A number of access technologies have been developed to provide new communication channels for these individuals. These access technologies typically cater to the ability level of their users. For users who retain some level of volitional muscle control, mechanical switches provide an effective access technology [2]. However, individuals with severe
physical impairments may not be able to move or speak of their own accord. This condition is referred to as locked-in syndrome (LIS) [3]. Brain-computer interfaces (BCIs) have been considered as potential access technologies for this population [4].

BCIs are used to translate mental activity into control signals for external devices [5]. BCIs detect mental activity by monitoring physiological signals that are known to change in response to cognitive effort. In some cases, BCI users are trained to produce repeatable fluctuations in these signals by performing specific mental tasks [4]. Machine learning algorithms can then be used to create a BCI that detects when these tasks are performed. This allows the user to communicate through their choice of mental task. Technologies such as electroencephalography and near-infrared spectroscopy have been used as measurement modalities for BCI research [6]. However, practical success within the locked-in population has been limited [7, 8]. This motivates the investigation of alternative BCI measurement modalities.

In this thesis, we explore the feasibility of a novel BCI that detects mental activity through the associated fluctuations in cerebral blood flow velocity (CBFV), which can be measured using transcranial Doppler ultrasound (TCD) [9]. Previous TCD research has shown that significant changes in CBFV occur during the performance of a variety of mental tasks, including silent word generation and mental rotation [10–12]. These tasks could potentially be used to generate control signals for a TCD-based BCI. Such a BCI may provide a new alternative for locked-in individuals.

1.2 Research Question and Objectives

To evaluate the potential of TCD as a BCI measurement modality, we proposed the following questions:
1. What level of accuracy can be achieved in the automatic discrimination between a mental activity and a baseline resting state using time-domain features derived from bilateral cerebral blood flow velocities?

2. Based on data transmission rate, is transcranial Doppler a practical alternative for future BCI research and implementation?

To answer these questions, the following research objectives were identified:

1. To develop an algorithm that can automatically detect when either word generation or mental rotation has been performed.

2. To extend this algorithm to three classes by simultaneously differentiating between word generation, mental rotation, and rest.

3. To increase the data transmission rate for the proposed TCD-based BCI by determining the minimum task duration for which classification can be performed with high accuracy.

1.3 Road Map

Following this introductory chapter, Chapter 2 provides background information regarding access technologies, the target population, cerebral blood flow, and TCD. Additional background information, including some repeated introductory content, precedes Chapters 3 and 4. Chapter 3 focuses on Objective 1, demonstrating the ability to reliably and accurately differentiate both mental tasks from rest independently. Chapter 4 addresses the more practical topics of Objectives 2 and 3 - the ability to differentiate all three classes simultaneously, and the duration for which these tasks must be performed in order to ensure that high classification accuracy is maintained. Finally, Chapter 5
summarizes the main contributions of this thesis and suggests several possibilities for future work in this area.
Chapter 2

Background

2.1 Access Technologies

2.1.1 Locked-in Syndrome

Locked-In Syndrome (LIS) is a term first used in 1966 by Plum and Posner [13] to describe patients with quadriplegia, lower cranial nerve paralysis, and mutism, with preservation of consciousness, vertical gaze, and upper eyelid movements. More recently, the definition has been expanded, and three categories of LIS have been defined. Classic LIS refers to quadriplegia and anarthria with preserved consciousness and vertical eye movement. Incomplete LIS is the same as classic, but with remnants of voluntary movement other than vertical eye movement. Complete LIS is defined as total immobility and inability to communicate, with full consciousness [3]. LIS can stem from both acute causes, such as brain stem stroke, and chronic causes, such as amyotrophic lateral sclerosis [14]. For simplicity, this chapter will consider the LIS population as a whole, independent of etiology. Individuals with LIS may find themselves unable to communicate even something
as simple as preference or functional intent.

Research into alternative means of communication for individuals with physical disabilities has been an active field in recent years. The terminology we will use in this thesis is described by Tai et al in [2]. There, an access pathway is defined as a sensor or input device by which functional intent can be translated into an electrical signal. When this signal is combined with methods of signal processing and classification, the result is an access technology. The output from an access technology is used to drive a user interface which allows access to an augmentative and alternative communication (AAC) aid, an environmental control unit, or a computer. This vision of an access solution is depicted in Figure 2.1, from [2].

![Figure 2.1: Visualization of an access solution; adapted from Tai et al](image)

In patients with disabilities who retain some voluntary movement, the most reliable of these access technologies are designed to capitalize on this motion. For example, mechanomyographic (MMG) signals measure small muscle vibrations [15], infrared cameras can detect the opening of the mouth [16], computer vision can detect tongue protrusion in patients with spastic cerebral palsy [17], and mechanical switches can be operated with the tongue [18]. Each of these methods has been used for the design of an access technology.
However, the state of complete LIS is characterized by the inability to communicate through conventional means - for example, through speech or limb motion. This immediately rules out these simpler, motion-based access technologies, and creates a need for more complex access technologies that rely on physiological variables of some kind. One type of access technology often considered for these individuals is a brain-computer interface that capitalizes on their intact cognition.

### 2.1.2 Brain-Computer Interfaces

BCIs are designed to give their users communication and control channels that do not depend on the brain’s normal output channel of peripheral nerves and muscles [5]. For an in-depth coverage of BCIs, the reader should refer to [19]. Current activity in this area is summarized by Mason et al in [6]. However, it is pertinent to note that cognitive activation is manifested physiologically through a number of different processes, giving rise to a number of different detection methods through which it can be quantified. As a result, BCIs have been designed to operate based on a number of different signals from the brain. We note here in passing that the terms ‘cognitive activation’ and ‘mental activation’ are used interchangeably within the remainder of this thesis.

BCIs can be divided into two categories - invasive and non-invasive BCIs. Invasive BCIs require the implantation of electrodes into the brain, while non-invasive BCIs measure signals from outside the body. Signals used in invasive BCIs include single neuron spike trains, extracellular local field potentials, and electrocorticograms (ECoG), while signals used in non-invasive BCIs include electroencephalogram (EEG) oscillations, event-related potentials (ERPs), real-time functional magnetic resonance imaging (fMRI), and near-infrared spectroscopy (NIRS) [8]. Our focus here is primarily on non-invasive methods.
For these non-invasive BCIs, the most common modality has traditionally been the EEG [20, 21]. However, one problem associated with EEG-based BCIs is that EEG is a relatively indirect measure of cognitive function [22]. This can lead to long training times, as well as frustration and anxiety for patients who struggle to operate the BCI. Other modalities, such as NIRS [23], suffer from a limited information transfer rate due to the nature of the physiological process underlying the utilized signal.

As discussed by Coyle et al [23], some of the major considerations for BCIs include speed, accuracy, ease of use, and length of training period. Traditionally, it has been very difficult for any BCI to excel in all four of these areas. This continues to drive the development of new types of BCIs.

In this thesis, we investigate the potential of a new access technology - a BCI based on changes in cerebral blood flow velocity.

## 2.2 Cerebral Blood Flow as an Access Pathway

### 2.2.1 The Nature of Cerebral Blood Flow

Blood flows into the human brain through two pairs of arteries - the internal carotid arteries, and the vertebral arteries. These major arteries are connected by a circular formation of smaller arteries called the circle of Willis. This structure is responsible for providing the brain with blood, and also for providing redundancy to ensure that the brain continues to receive an adequate supply of blood when one of the carotid or vertebral arteries is blocked or narrowed [24].

On each side of the brain, the internal carotid artery splits into the anterior cerebral artery (ACA), the middle cerebral artery (MCA), the anterior choroidal artery, and the
posterior communicating artery. The ACAs on each side of the brain are joined by the anterior communicating artery. Meanwhile, the vertebral arteries combine to form the basilar artery, which divides primarily into the left and right posterior cerebral arteries (PCA). The posterior communicating arteries are the bridge between the carotid and the vertebrobasilar systems of arteries [25]. Taken together, these systems of arteries form the ideal circle of Willis, as depicted in Figure 2.2 [26].

In practice, approximately half the population does not possess an ideal circle of Willis due to absent vessels, hypoplastic vessels, or duplication/triplication of vessels [24, 25].

The majority of the brain is perfused directly or indirectly by either the ACA, MCA, or PCA. Areas supplied by the ACA include the frontal pole, medial aspects of both the frontal and parietal lobes, and the corpus callosum. The MCA supplies most of
the lateral aspects of both cerebral hemispheres, and the PCA supplies the inferior and medial aspects of the temporal and occipital lobes [25].

It is well-known that changes in cognitive activation cause changes in cerebral blood flow volume within these arteries [27]. The mechanism underlying these changes is known as neurovascular coupling. The increase in neuronal activity caused by cognitive activation increases glucose and oxygen consumption. This increase in neuronal activity also affects astrocytes, a type of glial cell. The resultant astrocytic signaling cascade is responsible for vasodilation of the cerebral arteriolar smooth muscle walls, causing an increase in cerebral blood flow. This complex process is detailed by Haydon et al in [28]. The most significant contributors to this increase in blood flow are the smaller arteries and arterioles that emanate from the circle of Willis [29].

It is possible that, by monitoring changes in cerebral blood flow volume through the MCA, ACA, or PCA, cognitive activation can be detected and classified. One important non-invasive means of measuring blood flow in these arteries is transcranial Doppler (TCD) ultrasound.

### 2.2.2 Doppler Ultrasound

Ultrasound refers to sound waves of a frequency greater than the upper limit of human hearing. Sound waves in a liquid or gas are longitudinal waves, meaning that they travel through a medium as a series of compressions and rarefactions of particles within that medium. One important application of ultrasound is the field of medical ultrasonography, where ultrasound is used in order to produce a visualization of structures within the body. These techniques are based on the partial reflection of ultrasound that occurs as it passes through tissue [30].
One important ability of medical ultrasonography is the ability to detect and quantify the movement of structures in the body, such as the heart. This can be done through the usage of the Doppler effect, which describes the apparent frequency shift incurred by sound waves when there is a non-zero relative velocity between the source of the sound wave and the observer. For this reason, this technique is called Doppler ultrasound.

In practice, Doppler ultrasound can be applied to measure the velocity of blood flow in the circulatory system. This is a result of ultrasound waves being scattered by red blood cells within the arteries and veins of the body. Although this scattering is quite weak, the sheer number of red blood cells carried within the circulatory system results in a detectable scattered signal [30]. The Doppler effect, when the receiver is moving at an angle to the source, can be described by [31]:

\[ f = \frac{c_o + v_r \cos \theta}{c_o + v_s} f_o \]  

(2.1)

Where \( v_r \) indicates the receiver velocity, \( v_s \) the source velocity, \( c_o \) the speed of sound propagation within the medium, \( f_o \) the transmitted frequency, \( f \) the apparent frequency, and \( \theta \) the angle between the probe and the direction of movement of the structure being imaged. This angle is often referred to as the Doppler angle. The source and receiver velocities are those of the ultrasound transducer and the red blood cell responsible for scattering, respectively. When recording the Doppler shift as a result of blood flow, the source velocity \( v_s \) is zero, and the receiver velocity \( v_r \ll c_o \) [30]. Under these conditions, this equation can be manipulated into a form describing the frequency shift \( F = f - f_o \) [31]:

\[ F = \frac{2v_r f_o \cos \theta}{c_o} \]  

(2.2)

In tissue, the velocity of ultrasound propagation can be approximated as 1500 meters per second [30]. From this equation, the velocity of blood flow can be determined for a known transmission frequency and an observed frequency shift in the received signal.
We note that due to the angular term in these expressions, the magnitude of the recorded value in a Doppler ultrasound examination depends on the precise angle at which the skull is insonated. Since this angle cannot be easily determined, it is of limited usefulness to compare absolute values. Instead, it is typically more useful to look at relative changes in blood flow velocity [32].

Equations 2.1 and 2.2 are applicable in continuous-wave (CW) Doppler ultrasound, which utilizes a transmitter and receiver that are always active. Thus, the transmitted signal can typically be considered as a pure sinusoid. In pulsed-wave (PW) Doppler ultrasound, the situation is more complicated. Brief pulses of ultrasound are transmitted into the tissue being imaged. The truncation of these pulses results in PW signals having a much larger bandwidth than CW signals.

As in CW propagation, some of the resultant scattered waves are reflected back to the transducer, resulting in an echo signal. For PW ultrasound, depth discrimination can be achieved through range gating. Once the transmitter has been deactivated, the receiver is activated only for the time interval during which signals from the desired depth are received [31]. For example, the time interval $t_{z_1} \leq t \leq t_{z_2}$ during which signals from the desired depth $z_1 \leq z \leq z_2$ are received can be specified by:

$$t_{z_1} = \frac{2z_1}{c_o} \quad t_{z_2} = \frac{2z_2}{c_o}$$  \hspace{1cm} (2.3)

The capacity for depth discrimination is the major advantage of PW Doppler ultrasound over CW Doppler ultrasound. However, application of the Doppler effect to determine the velocity of blood flow is much more complicated for PW ultrasound. In CW ultrasound, usage of the Doppler effect is possible because the frequency spectrum of the transmitted signal essentially consists of one component. Thus, any frequency component present in the reflected signal arises from a Doppler shift on this frequency, and the corresponding velocity can be easily calculated. However, in the case of PW ultrasound, the transmitted pulse has a frequency spectrum which is non-zero over a wide range, due to the effects
of truncation - see Figure 2.3, which shows the time and frequency representations for 2 MHz CW and PW signals.

Figure 2.3: Comparison of frequency spectra for CW and PW signals

Furthermore, during propagation, this pulse is subject to frequency-dependent absorption and scattering. These frequency-dependent factors cause changes in the shape and the center of the frequency spectrum of the received signal. This spectrum undergoes further changes as a result of the Doppler effect. Since we cannot separate these changes to determine the effect of each factor, it is impossible to simply apply equation (2.2) in order to determine the velocity of blood flow. Consequently, PW Doppler ultrasound does not truly make use of the Doppler effect [30]. Despite this, it is still typically referred to as Doppler ultrasound, and we will abide by this convention.

However, PW Doppler ultrasound can still be used to determine flow velocity, by comparing the echoed signals for a sequence of pulses. This process, which will not be described here, is detailed in [30], and leads to an equation with the same form as equation (2.2).
2.2.3 Transcranial Doppler

Transcranial Doppler (TCD) is a medical imaging technique that uses PW Doppler ultrasound to measure cerebral blood flow velocity (CBFV). Due to the tiny diameters of the smaller cerebral arteries, this technique is practically limited to imaging the major cerebral arteries, such as the MCA, ACA, and PCA. TCD was first detailed by Rune Aaslid in 1982 [9]. We note here that CBFV through these major arteries can be treated as synonymous with cerebral blood flow volume, due to limited change in the diameters of the major cerebral arteries with time [32–34]. Hence, monitoring CBFV using TCD is equivalent to monitoring changes in cerebral blood flow volume. A typical TCD instrument and headgear are depicted in Figure 2.4.

![TCD headgear and instrument](image)

Figure 2.4: TCD headgear and instrument

Generally, TCD is limited by the difficulty associated with the penetration of the skull by acoustic waves. The attenuation experienced by ultrasound waves traveling within the skull is too large for a detectable signal to be received. However, in certain regions of the skull, the thickness of the bone is reduced to a point where successful insonation is possible in most individuals. These locations are known as insonation windows. Of these, the most pertinent to us is the transtemporal window, located just anterior of the ear and slightly superior to the zygomatic arch. The location of this window, and appropriate insonation procedures, are detailed in [24] and [35].
From the transtemporal window, TCD can be used to obtain readings from the ACA, MCA, and PCA - see Figure 2.5 [36]. Even at the transtemporal window, it is commonly accepted that approximately 10% of the population does not have a sufficient insonation window to allow TCD examination, with this percentage higher among the elderly and among women [37].

Figure 2.5: Insonation of the circle of Willis through the transtemporal window; adapted from Stroobant and Vingerhoets

### 2.2.4 Current Applications of TCD

To date, TCD has been primarily used for diagnostics and monitoring in a clinical setting. Applications include, but are not limited to, the assessment of cerebral perfusion pressure, diagnosis and management of vasospasm, assessment of traumatic brain injury, diagnosis of brain death, detection of stenosis and occlusion, detection of microemboli, detection of shunts, assessment of cerebral autoregulation, evaluation of collateral circu-
lation, evaluation of recanalization, and screening for sickle cell disease [38–46].

Functional TCD (fTCD) has also been used to observe changes in CBFV during cognitive, sensory, and motor tasks. In particular, fTCD has been used to study cerebral lateralization - the tendency for certain tasks or activities to be primarily performed by either the left or right hemisphere of the brain [32]. Lateralization is determined by comparing the left and right-hemispheric relative increases in CBFV in response to a mental task, due to the dependence of absolute values on the Doppler angle. There has been a great deal of research in this area [10, 34, 47–56]. One notable conclusion from this work is that language tasks tend to be lateralized to the left hemisphere, and visuospatial tasks to the right hemisphere [10, 47]. These results indicate that even simple mental activities, such as those associated with a word generation task, can cause appreciable lateralization between hemispheres. Furthermore, it has been shown that fTCD results are strongly correlated with Wada Test [57], fMRI [58], and EEG [59] results for the measurement of lateralization. This provides validation for the technique itself.

Other work with fTCD has focused on changes in CBFV associated with attention tasks, such as vigilance and go/no-go tasks [54–56, 60–62]. These studies have shown that higher relative CBFV increases are associated with better performance in attention and vigilance tasks. This provides further evidence of the link between mental activity and CBFV.

For the remainder of this thesis, any reference to TCD is implied to mean fTCD. This is because we are interested in fTCD - TCD recordings taken during mental activity - for all subsequent discussion.

Further reviews of research involving fTCD can be found in [36] and [63].
2.2.5 Application as an Access Pathway

As discussed previously, Coyle et al [22] identified speed, accuracy, length of training period, and ease of use as four major considerations for BCI research. We believe that a TCD-based BCI could perform acceptably in each of these categories.

TCD has excellent temporal resolution. It provides continuous measurement of CBFV, allowing the study of dynamic cerebrovascular responses. In previous research, it has been shown that CBFV increases rapidly after the onset of mental activity, with maximum CBFV increases observed within 4 to 20 seconds [36, 55, 59, 64–66]. This indicates that TCD may be a suitable measurement modality for a fairly fast-paced BCI. It may also be possible to reliably detect mental activity without waiting for maximum changes in CBFV to occur, allowing for an even faster response.

It has generally been shown that various mental tasks cause 10% to 20% increases in mean CBFV relative to a baseline resting state [10, 47]. These significant increases suggest that accurate detection of mental activity should be possible using signal features based on simple properties such as mean CBFV and slope of the CBFV curve. Furthermore, rest has generally been observed to be an unlateralized state, with approximately equivalent CBFVs within each hemisphere. This implies that it may be possible to accurately detect certain mental tasks due to the cerebral lateralization that they induce. Using intuitive mental tasks will also reduce the length of the user training period.

From a practical standpoint, TCD is relatively inexpensive, particularly in comparison to other imaging modalities such as MRI. It requires a minimal amount of equipment, and does not require a specialized environment. Many TCD instruments are portable, and can be used at bedside. TCD is also safe for long-term monitoring [38]. This suggests that a TCD-based BCI would be comfortable, convenient, and easy to use.
However, TCD does have some disadvantages that must be recognized. It has low spatial resolution, as only two CBFV signals can be simultaneously recorded [36]. This could negatively impact speed and accuracy for a TCD-based BCI. TCD also relies on the hemodynamic response to cognitive activity, rather than directly measuring neural activity. This makes it unlikely that the speed of EEG-based BCIs can be matched. Finally, TCD requires a skilled operator in order to quickly and definitively locate the target arteries [38]. We hypothesized that these disadvantages would not prevent automatic detection of mental activity.

As a final remark, it is important to note the difference between our goals and those of previous lateralization studies. Past studies have focused on describing the effects of mental activity, and have averaged large numbers of trials together to reduce the noise associated with individual trials [10, 47]. Application of TCD as a BCI measurement modality requires automatic single-trial detection of mental activity. An algorithm must be developed that can identify whether a single segment of a TCD recording occurred during rest or during mental activity.
Chapter 3

A Brain-Computer Interface Based on Bilateral Transcranial Doppler Ultrasound

This chapter provides a study of the ability to automatically detect the performance of two mental tasks (Objective 1). CBFV was monitored in nine able-bodied subjects during alternating periods of mental activity and rest. Each segment of activity and rest was classified based on a set of time-domain signal features. From our analyses, we concluded that mental activity can be accurately detected using TCD. The signal features that proved most useful for this task were identified. This study represents the first investigation of automatic classification of mental activity based on changes in cerebral blood flow velocity.

This chapter consists of a manuscript that has published by PLoS-ONE. As such, Sections 3.1 and 3.2 contain some repeated background and introductory content. Sections 3.3 to 3.5 consist of new content.
3.1 Abstract

In this study, we investigate the feasibility of a BCI based on transcranial Doppler ultrasound (TCD), a medical imaging technique used to monitor cerebral blood flow velocity. We classified the cerebral blood flow velocity changes associated with two mental tasks - a word generation task, and a mental rotation task. Cerebral blood flow velocity was measured simultaneously within the left and right middle cerebral arteries while nine able-bodied adults alternated between mental activity (i.e. word generation or mental rotation) and relaxation. Using linear discriminant analysis and a set of time-domain features, word generation and mental rotation were classified with respective average accuracies of $82.9\% \pm 10.5$ and $85.7\% \pm 10.0$ across all participants. Accuracies for all participants significantly exceeded chance. These results indicate that TCD is a promising measurement modality for BCI research.

3.2 Introduction

Brain-computer interfaces (BCIs) translate mental activity into control signals for external devices, thereby providing their users with movement-free communication and control channels [5]. BCIs can be employed in a wide variety of areas including virtual reality [67], neurorobotics [68], and wheelchair control [69]. There has also been a great deal of research into the usage of BCIs as means of communication and control for individuals with severe and multiple disabilities [2, 70]. BCI systems offer these individuals the potential to achieve some degree of independence and control over their environments. Moreover, BCI control bypasses the muscular system entirely and thus may allow communication even for those who are completely locked-in due to conditions such as stroke or amyotrophic lateral sclerosis (ALS) [14]. For instance, BCIs have been used to
generate text communication based on measuring brain responses to visually presented letters on a computer screen [71].

In BCI systems, mental activity can be detected using various measurement modalities including electroencephalography (EEG) [72], functional magnetic resonance imaging (fMRI) [73], magnetoencephalography (MEG) [74], and near-infrared spectroscopy (NIRS) [75]. Though BCI systems developed using these modalities have shown promise in controlled environments, their practical success has been limited by a number of shortcomings [8]. The most commonly used measurement modality in BCI systems is EEG. These signals are susceptible to interference from electrical sources and physiological artifacts such as electrooculography (EOG) and electromyography (EMG) [2]. Moreover, proficient use of EEG-based BCIs often requires several training sessions. BCI systems based on fMRI and MEG measurements employ extremely expensive instruments and require highly controlled environments [76]. Consequently, these technologies are presently impractical for widespread use [77]. NIRS is still early in its development as a BCI technology. Current studies employing this modality have predominantly focused on the slow hemodynamic response, resulting in low data transmission rates [78]. These shortcomings of current BCI systems motivate the investigation of alternative measurement modalities.

In light of the above limitations, this paper investigates transcranial Doppler (TCD) sonography as the foundation for a new type of non-invasive BCI. TCD is a medical imaging technique used to monitor cerebral blood flow velocity (CBFV) within the major arteries of the circle of Willis - namely the anterior, middle, and posterior cerebral arteries [31]. Since its introduction in 1982 [9], TCD has been successfully used in a number of clinical applications [38, 39, 41, 42, 44]. It has also been used extensively to describe brain function through the study of cerebral lateralization [10, 34, 36, 50, 79]. TCD is portable, lightweight, and robust to environmental conditions such as electrical
artifacts [80]. It is also relatively inexpensive, particularly in comparison to alternatives such as fMRI and MEG [38]. TCD possesses excellent temporal resolution, and previous research into lateralization indicates that event-related changes in CBFV can be observed within 5-10 seconds of the onset of cognitive activity in some cases [59, 64]. Most importantly, cognitive activation produces increases in CBFV [27] that are easily measurable by TCD.

The above features suggest that TCD may be a suitable measurement modality for BCI systems. To further demonstrate the viability of a TCD-based BCI system, it must be shown that mental activity can be automatically detected with high accuracy based on these measurements. In this light, the present study investigated whether two specific mental tasks can automatically be differentiated from rest using TCD measurements. If adequate classification accuracies can be obtained, these mental tasks can be used to generate control signals in a TCD-based BCI system.

We investigated two mental tasks, namely word generation and mental rotation of geometric shapes. Word generation is known to cause significant increases in CBFV within the left and right middle cerebral arteries (MCAs) [10, 50]. Moreover, these increases have been characterized as being left-lateralized in right-handed individuals - higher relative increases in CBFV have been found in the left MCA than in the right MCA [63]. We expected that this lateralization would make it possible to automatically detect the word generation activity. Spatial tasks involving mental rotation have also been explored in a number of TCD studies [10–12], where they have likewise been observed to cause significant increases in CBFV within the left and right MCAs. We hypothesized that large bilateral increases in CBFV induced by complex mental rotation tasks can be automatically detected using TCD measurements.
3.3 Materials and Methods

3.3.1 Ethics Heading

This study was approved by the Research Ethics Boards of both Holland Bloorview Kids Rehabilitation Hospital and the University of Toronto. All participants provided written informed consent.

3.3.2 Participant

Nine able-bodied participants (6 female) were recruited from amongst the population of the Bloorview Research Institute. Ages of the participants at the time of the study ranged between 22 and 30 (mean age 25.6 years). All participants were right-handed, as quantified by the Edinburgh Handedness Inventory [81], with scores ranging between 50 and 100 (mean score 79.4). Participants had no history of migraine, and no known neurological or respiratory conditions.

3.3.3 Signal Acquisition

CBFV was monitored using a Multi-Dop X4 TCD unit (Compumedics USA). Dual 2 MHz ultrasonic transducers were fitted on the included headgear and placed over the left and right transtemporal windows. The thermal cranial index was kept below two at all times. For all participants, a screening test was performed to ensure that there were no CBFV abnormalities. Following the insonation procedure detailed by Alexandrov et al. [82], CBFV was measured within the left and right anterior, middle, and posterior cerebral arteries. Compared to expected velocities [35], no unusual values were observed, and
thus all participants were accepted for this study. Probe locations were recorded during the screening test and replicated during subsequent sessions with each participant.

Each participant completed two sessions. Insonation followed the same procedure that was used for the screening test. We measured CBFV within the left and right middle cerebral arteries (MCAs). These arteries were selected because the MCAs profuse approximately 80% of the brain [36] and, as such, are implicated in a wide variety of mental tasks [10]. Signals were acquired by adjusting the probe angle, probe location, and measurement depth until optimal signals were located. Insonation depths ranged from 45 to 60 mm. Signals were acquired from approximately the same depth on both sides. Signals from both channels - the left MCA and the right MCA - were used to characterize each state during the experiment. Thermal cranial index was monitored and kept below 2 at all times. The lowest power level for which signals were adequate was used. Insonation lasted for no longer than 15 minutes at a time, consistent with ultrasound safety guidelines such as [83].

Respiratory modulation and carbon dioxide levels are known to influence CBFV [84]. These signals were recorded to ensure that fluctuations in CBFV did not simply result from changes in respiration. Participants wore a nasal cannula, which was connected to a capnometer built into the Multi-Dop X4 unit to monitor end-tidal CO$_2$ levels. Respiration was also directly measured using a respiratory belt. Blood volume pulse (BVP) was measured using an FDA-approved photoplethysmography sensor (Flexcomp Infiniti, Thought Technologies Ltd.). The sensor was secured to the palmar surface of the distal phalange of the first digit of the non-dominant hand.
Chapter 3. Differentiating Mental Activity from Rest

3.3.4 Experimental Protocol

At the beginning of each session, participants were seated comfortably facing a computer monitor in a data collection room. Following signal acquisition, participants rested naturally for 10 minutes to allow CBFV to stabilize. Data from this baseline period was not used for further analysis. Following this interval, participants received verbal instructions on how to perform the two required mental tasks. Participants were then instructed to begin the experiment when ready.

In each session, participants completed two 15-minute blocks, separated by a 5-minute break. Each block consisted of 10 rest periods and 10 activation periods. Each period had a duration of 45 seconds, and successive periods alternated between rest and activation states. During activation states, participants received onscreen prompts to perform either the word generation or mental rotation task. Each task occurred five times within each block in randomized order. Each block proceeded automatically once begun, and included only text-based prompts. There were no auditory distractions during the experiment. The experiment contained a total of 40 rest states, 20 word generation states, and 20 mental rotation states for each participant.

During the word generation task, a letter was presented on screen and participants were prompted to silently generate words that began with the given letter. Letters were selected from among the most common first letters of English words. No letters were repeated within sessions, but some letters were used in both sessions.

During the mental rotation task, participants were presented with four pairs of figures simultaneously. Each pair consisted of two similar objects rotated to different angles around the x-axis. Participants were required to mentally rotate the two objects in each pair to determine if they were the same object or mirror images. Participants were instructed to work sequentially through all four pairs. Each pair was randomly selected
from a database of such figures [85–87]. The entire set of figures was replaced with four new pairs every nine seconds. Post-experiment feedback from participants confirmed that this method allowed them to constantly perform this task over the entire activation period.

Participants were instructed to keep their eyes open during both activation and rest, and to perform each task as quickly as possible. Participants were also instructed to refrain from vocalizing their answers, thus preventing CBFV increases due to speech. During rest periods, participants were instructed to relax. No instructions were given regarding modulation of respiration.

3.3.5 Pre-processing

TCD data were exported from the Multi-Dop X4, and the mean of the maximum velocity was extracted for analysis. This parameter is automatically computed by the Multi-Dop X4, and reduces the effect of CBFV variability between systole and diastole. The raw data from each block were normalized, and then filtered using a third-order Butterworth low-pass filter with a cutoff frequency of 0.6 Hz to remove the effects of beat-to-beat fluctuations in CBFV. The data were then segmented into rest and activity states, using markers that were automatically inserted into the TCD recordings at the beginning of each state during the experiment. Data from the respiratory belt were also segmented into rest and activation states.

3.3.6 Feature Extraction

Feature extraction was performed on the recorded signals from each rest and activation state. The list of extracted features is given in Table 3.1. All features were computed
over four intervals within each state - 0-45 seconds, 0-15 seconds, 15-30 seconds, and 30-45 seconds. Features were divided between unilateral features, which were dependent solely on the signal from one MCA, and bilateral features, which compared signals from both MCAs. For respiratory signals, we extracted the signal mean and the respiration rate.

Table 3.1: Candidate feature set

<table>
<thead>
<tr>
<th>Feature Number</th>
<th>Feature Description</th>
<th>Laterality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4</td>
<td>Left MCA Mean (LM)</td>
<td>Unilateral</td>
</tr>
<tr>
<td>5-8</td>
<td>Left MCA Slope (LS)</td>
<td>Unilateral</td>
</tr>
<tr>
<td>9-12</td>
<td>Left MCA Standard Deviation (LSD)</td>
<td>Unilateral</td>
</tr>
<tr>
<td>13-16</td>
<td>Right MCA Mean (RM)</td>
<td>Unilateral</td>
</tr>
<tr>
<td>17-20</td>
<td>Right MCA Slope (RS)</td>
<td>Unilateral</td>
</tr>
<tr>
<td>21-24</td>
<td>Right MCA Standard Deviation (RSD)</td>
<td>Unilateral</td>
</tr>
<tr>
<td>25-28</td>
<td>Lateralization (Difference of Means) (DM)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>29-32</td>
<td>Lateralization (Difference of Slopes) (DS)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>33-36</td>
<td>Cross-correlation of Left and Right MCAs (CC)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>37-40</td>
<td>Dot Product of Left and Right MCAs (DP)</td>
<td>Bilateral</td>
</tr>
</tbody>
</table>

*Each feature computed over 4 different time intervals - 0-45 s; 0-15 s; 15-30s; 30-45s

3.3.7 Feature Selection

Features were selected on the basis of the Fisher criterion [88]. For one feature, this criterion can be expressed as:

$$J = \frac{|m_1 - m_2|^2}{s_1^2 + s_2^2},$$

(3.1)

where $m_1$ and $s_1$ represent the mean and standard deviation of a feature evaluated over all rest states, and $m_2$ and $s_2$ the mean and standard deviation of the same feature evaluated over all activation states. The Fisher criterion increases as the average separation between groups increases and the average separation within groups decreases. Using this criterion
for feature selection yields the features that provide maximum separability between rest and activation patterns.

Using only the Fisher criterion for feature selection could potentially lead to the selection of highly correlated features. When multiple features were required, the feature set was first reduced by selecting the eight highest-ranking features based on the Fisher criterion. The highest-ranked feature was selected as the initial feature. To select subsequent features, the correlation coefficients between the initially selected feature and each remaining feature were computed. The feature with the lowest magnitude correlation coefficient was then selected. If necessary, a similar procedure was used to select a third feature, taking into account the correlation with both previously selected features.

### 3.3.8 Classification

Twenty runs of five-fold cross-validation were performed for $n = 1, 2,$ and $3$ features. A linear discriminant analysis (LDA) classifier was used. Each activation state was compared independently to the rest state using the same procedure. Due to unbalanced classes, 20 rest states were randomly selected at the beginning of each run to be used during classification. During each fold, feature selection was performed using only training data.

Classification was also performed using several reduced sets of features. Namely, classification was performed using only features from the respiratory belt, and only bilateral features from the TCD recordings. In the latter case, three features were selected from the set of bilateral features using the procedure already described.
3.3.9 Evaluation Criteria

The percentage of correctly classified samples was used as the evaluation criteria. We also report sensitivity (the percentage of correctly classified activation states) and specificity (the percentage of correctly classified rest states).

3.4 Results

A sample TCD recording depicting CBFV fluctuations during a three-minute segment of the experiment is shown in Figure 3.1. In this recording, visually detectable differences between rest and activation states are apparent. In particular, we note apparent bilateral activation during the mental rotation task, and left lateralization during the word generation task.

![Figure 3.1: Recordings from two rest-activation cycles for participant 4. The solid line depicts CBFV in the left MCA, while the broken line depicts CBFV in the right MCA. Decreasing trends in CBFV during rest and increasing trends during activation are apparent. The signal is the mean of the maximum velocity, filtered by a Butterworth low-pass filter with a cutoff frequency of 0.6 Hz.](image-url)
The accuracies for each task, participant, and feature selection condition are reported in Tables 3.2 and 3.3. The best results were achieved using three features (mean classification accuracy for word generation and mental rotation tasks were $82.9 \pm 10.5\%$ and $85.7 \pm 10.0\%$ respectively). For this case, sensitivities and specificities are reported in Figure 3.2.

Table 3.2: Classification accuracies for the word generation task. Columns two through four show accuracies when 1-3 features were selected from the entire candidate pool. Column 5 shows the accuracies when the candidate pool was restricted to the 16 bilateral features. In this case, the analysis was performed for only the selection of three features, using the same feature selection algorithm. The final column shows classification accuracies when only respiratory features were used. All participants except for Participant 8 displayed significantly higher accuracies for three-feature TCD classification (using the entire candidate pool) than for classification based on respiration. Mean classification accuracy was significantly greater for two and three features than for one feature (repeated-measures regression, $p < 0.012$). The comparison between two and three features approached significance ($p = 0.056$).

<table>
<thead>
<tr>
<th>Participant Number</th>
<th>TCD Data Only</th>
<th>Respiration Only</th>
<th>Bilateral Features Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 Feature</td>
<td>2 Features</td>
<td>3 Features</td>
</tr>
<tr>
<td>1</td>
<td>87.9 ± 11.2</td>
<td>89.5 ± 10.2</td>
<td>89.1 ± 11.6</td>
</tr>
<tr>
<td>2</td>
<td>94.4 ± 7.0</td>
<td>91.9 ± 9.5</td>
<td>93.6 ± 8.6</td>
</tr>
<tr>
<td>3</td>
<td>82.6 ± 12.3</td>
<td>82.9 ± 12.4</td>
<td>85.1 ± 12.3</td>
</tr>
<tr>
<td>4</td>
<td>88.5 ± 9.7</td>
<td>94.2 ± 8.0</td>
<td>95.3 ± 6.6</td>
</tr>
<tr>
<td>5</td>
<td>61.5 ± 15.2</td>
<td>64.1 ± 17.4</td>
<td>65.0 ± 18.6</td>
</tr>
<tr>
<td>6</td>
<td>87.1 ± 11.4</td>
<td>87.5 ± 12.9</td>
<td>90.2 ± 10.6</td>
</tr>
<tr>
<td>7</td>
<td>71.3 ± 14.9</td>
<td>73.3 ± 15.7</td>
<td>76.3 ± 14.3</td>
</tr>
<tr>
<td>8(^a)</td>
<td>68.5 ± 15.1</td>
<td>70.5 ± 15.4</td>
<td>70.4 ± 15.7</td>
</tr>
<tr>
<td>9</td>
<td>74.0 ± 16.1</td>
<td>79.2 ± 12.2</td>
<td>81.4 ± 12.5</td>
</tr>
<tr>
<td>Average</td>
<td>79.5 ± 11.1</td>
<td>81.5 ± 10.4</td>
<td>82.9 ± 10.5</td>
</tr>
</tbody>
</table>

\(^a\)No significant difference between classification using three TCD features and classification using respiration

Chance results were simulated by performing classification with randomized state labels, resulting in accuracies of approximately 50%. Results from three-feature classification were compared to these chance results using the Wilcoxon rank sum test at a 0.05 significance level. These results were also compared to those from classification of respiratory signals using the same procedure. All participants showed accuracies that were signifi-
Table 3.3: Classification accuracies for the mental rotation task. Columns two through four show accuracies when 1-3 features were selected from the entire candidate pool. Column 5 shows the accuracies when the candidate pool was restricted to the 16 bilateral features. In this case, the analysis was performed for only the selection of three features, using the same feature selection algorithm. The final column shows classification accuracies when only respiratory features were used. All participants except for Participant 6 displayed significantly higher accuracies for three-feature TCD classification (using the entire candidate pool) than for classification based on respiration. Mean classification accuracy was significantly greater for two and three features than for one feature (repeated-measures regression, \( p < 0.001 \)). There was no significant difference between two and three features.

<table>
<thead>
<tr>
<th>Participant Number</th>
<th>TCD Data Only</th>
<th>Respiration Only</th>
<th>Bilateral Features Only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 Feature</td>
<td>2 Features</td>
<td>3 Features</td>
</tr>
<tr>
<td>1</td>
<td>79.8 ± 12.5</td>
<td>83.1 ± 11.7</td>
<td>85.4 ± 10.7</td>
</tr>
<tr>
<td>2</td>
<td>82.0 ± 12.1</td>
<td>86.9 ± 11.4</td>
<td>88.6 ± 11.1</td>
</tr>
<tr>
<td>3</td>
<td>77.1 ± 15.4</td>
<td>80.3 ± 12.8</td>
<td>81.1 ± 13.0</td>
</tr>
<tr>
<td>4</td>
<td>95.0 ± 7.5</td>
<td>96.1 ± 6.6</td>
<td>97.9 ± 4.7</td>
</tr>
<tr>
<td>5</td>
<td>56.5 ± 16.7</td>
<td>59.0 ± 14.8</td>
<td>63.9 ± 15.2</td>
</tr>
<tr>
<td>6(^a)</td>
<td>90.3 ± 10.9</td>
<td>89.8 ± 10.0</td>
<td>90.1 ± 10.3</td>
</tr>
<tr>
<td>7</td>
<td>78.3 ± 12.5</td>
<td>81.3 ± 14.1</td>
<td>79.5 ± 12.8</td>
</tr>
<tr>
<td>8</td>
<td>91.9 ± 9.6</td>
<td>92.8 ± 8.7</td>
<td>93.4 ± 9.0</td>
</tr>
<tr>
<td>9</td>
<td>85.6 ± 11.7</td>
<td>91.5 ± 8.5</td>
<td>91.0 ± 9.1</td>
</tr>
<tr>
<td>Average</td>
<td>81.8 ± 11.4</td>
<td>84.5 ± 11.0</td>
<td>85.7 ± 10.0</td>
</tr>
</tbody>
</table>

\(^a\)No significant difference between classification using three TCD features and classification using respiration

significantly greater than chance (\( p < 0.0001 \)) for both tasks. Eight of nine participants showed a significant difference between CBFV and respiration classification for both tasks (\( p < 0.015 \)).

The most frequently selected features for each participant are given in Table 3.4, while average feature selection across all participants is shown in Figure 3.3. A sample scatter plot based on the three most frequently selected features for Participant 2 is shown in Figure 3.4.
Figure 3.2: Sensitivities and specificities for all participants for both tasks. The word generation task is on top, and the mental rotation task on bottom. Black bars correspond to sensitivity, and white bars to specificity. Sensitivity was significantly greater than specificity (Wilcoxon rank-sum test, $p < 0.03$) for six of nine participants for word generation (exceptions are Participants 1, 2, and 5) and for seven of nine participants for mental rotation (exceptions are Participants 5 and 8).

3.5 Discussion

3.5.1 Feasibility of a TCD-based BCI

This study investigated the potential of TCD as the measurement modality for a BCI. We demonstrated that two types of mental activity can be classified with greater than 80% accuracy on the basis of changes in cerebral blood flow velocity. These accuracies were achieved without any prior training. It is likely that this can be partially attributed to the usage of intuitive mental tasks as activation states. Our results show that TCD is a promising measurement modality for BCI development, and further research should be performed to continue investigation into the performance of a TCD BCI.
Table 3.4: Most frequently selected features for each participant for each task. Abbreviations given in Table 3.1.

<table>
<thead>
<tr>
<th>Participant Number</th>
<th>Word Generation Task</th>
<th>Mental Rotation Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DM 30-45 sec</td>
<td>DM 0-45 sec</td>
</tr>
<tr>
<td></td>
<td>DS 0-15 sec</td>
<td>RM 0-45 sec</td>
</tr>
<tr>
<td></td>
<td>RM 0-15 sec</td>
<td>RM 15-30 sec</td>
</tr>
<tr>
<td>2</td>
<td>LS 0-15 sec</td>
<td>LM 15-30 sec</td>
</tr>
<tr>
<td></td>
<td>DM 0-45 sec</td>
<td>LS 0-15 sec</td>
</tr>
<tr>
<td></td>
<td>RM 0-45 sec</td>
<td>DS 0-15 sec</td>
</tr>
<tr>
<td>3</td>
<td>DM 0-45 sec</td>
<td>RM 30-45 sec</td>
</tr>
<tr>
<td></td>
<td>RSTD 0-45 sec</td>
<td>LS 0-15 sec</td>
</tr>
<tr>
<td></td>
<td>LS 0-15 sec</td>
<td>RM 0-45 sec</td>
</tr>
<tr>
<td>4</td>
<td>LM 30-45 sec</td>
<td>LM 30-45 sec</td>
</tr>
<tr>
<td></td>
<td>LS 0-15 sec</td>
<td>LS 0-15 sec</td>
</tr>
<tr>
<td></td>
<td>DM 30-45 sec</td>
<td>RM 15-30 sec</td>
</tr>
<tr>
<td>5</td>
<td>LM 0-45 sec</td>
<td>DP 30-45 sec</td>
</tr>
<tr>
<td></td>
<td>DM 30-45 sec</td>
<td>CC 30-45 sec</td>
</tr>
<tr>
<td></td>
<td>DS 0-15 sec</td>
<td>CC 15-30 sec</td>
</tr>
<tr>
<td>6</td>
<td>DM 15-30 sec</td>
<td>RM 15-30 sec</td>
</tr>
<tr>
<td></td>
<td>DP 15-30 sec</td>
<td>LS 0-15 sec</td>
</tr>
<tr>
<td></td>
<td>DS 0-15 sec</td>
<td>LM 15-30 sec</td>
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<td>7</td>
<td>DS 0-45 sec</td>
<td>RM 0-45 sec</td>
</tr>
<tr>
<td></td>
<td>LS 0-45 sec</td>
<td>LM 15-30 sec</td>
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<tr>
<td></td>
<td>DM 15-30 sec</td>
<td>LS 0-45 sec</td>
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<tr>
<td>8</td>
<td>DP 30-45 sec</td>
<td>DS 0-15 sec</td>
</tr>
<tr>
<td></td>
<td>DM 0-45 sec</td>
<td>DM 0-45 sec</td>
</tr>
<tr>
<td></td>
<td>DM 15-30 sec</td>
<td>DM 15-30 sec</td>
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<tr>
<td>9</td>
<td>DM 0-45 sec</td>
<td>DS 0-45 sec</td>
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<td>DS 0-15 sec</td>
</tr>
<tr>
<td></td>
<td>RSTD 0-45 sec</td>
<td>DM 0-45 sec</td>
</tr>
</tbody>
</table>

3.5.2 Classification of Word Generation and Mental Rotation

For both mental tasks, we observed that sensitivity was generally higher than specificity (see Figure 3.2). This may be related to the more specific directions given for activation states compared to rest states. During activation, participants performed one of two well-defined tasks. During rest, participants were simply instructed to relax - they were not instructed to ‘think of nothing’ or to perform any specific low-intensity mental task. Therefore, it seems reasonable for rest states to be less consistent than activation states, leading to lower specificities. This usage of relaxation as a rest state reflects realistic
Figure 3.3: Average feature selection across all participants for both tasks. The word generation task is on top, and the mental rotation task on bottom. Black bars are left MCA features, grey bars are right MCA features, and white bars are bilateral features. Bilateral features are more frequently selected for the word generation task, likely due to the left-hemispheric lateralization of this task. Feature descriptions can be found in Table 3.1.

Some participants displayed large variations in accuracy between the two tasks. Most glaringly, Participant 8 attained 70% accuracy for the word generation task, but 93% accuracy for the mental rotation task. Such individual differences highlight the importance of appropriate task selection. In a TCD-based BCI that is operated using simple mental tasks, significant gains in performance could potentially be achieved by testing a number of different mental tasks and choosing the optimal task on a case-by-case basis.

One individual, Participant 5, had accuracies which were considerably lower than average. For this individual, the transtemporal insonation window was very difficult to find. Although adequate TCD signals were acquired and recorded during each session, it is possible that the extended set-up time and associated frustration for the participant were partially responsible for these lower accuracies.
3.5.3 Feature Selection

During classification, we used two main types of features - unilateral features and bilateral features. Unilateral features are important when a signal parameter shows significant differences between activation and rest. Selection of these features may reflect a difference in net cognitive load between rest and activation states. Bilateral features are important when a given mental task causes some level of asymmetry between activation in the left and right hemispheres of the brain. As such, selection of these features may represent a difference in lateralization between rest and activation states. From this reasoning, it
seems plausible that markedly different features could be selected for the classification of different mental tasks. Indeed, this proved to be the case in this study, as seen in Table 6. However, for each task, there was some consistency across all participants.

Consistent with previous findings [10], we observed that the word generation task was strongly lateralized to the left MCA in most participants. Consequently, bilateral features were frequently selected. More specifically, the features corresponding to differences in means and differences in slopes were very important during this task; two of the three most commonly selected features came from these categories for six of nine participants. From Figure 3.3, it is also clear that during the word generation task, features from the left MCA were chosen more frequently than features from the right MCA. Again, this meshes well with the observation that this task was lateralized to the left MCA.

As expected, lateralization was less prominent for the mental rotation task. Figure 3.3 shows that bilateral features were rarely selected for this task, while features from the left and right MCAs were chosen fairly equally, reflecting bilateral activation. When the mean of either MCA was selected, it was typically from 15-30 or 30-45 seconds. This could, perhaps, represent CBFV settling near the end of the state at a low value during rest or a high value during activation. When the slope of either MCA was selected, it was typically from 0-45 or 0-15 seconds. This may represent the general decreasing/increasing trend in CBFV during rest/activation, which is particularly pronounced at the beginning of each state. The frequent selection of the interval from 0 to 15 seconds suggests that slope features may be useful for shortening the BCI response time. Potential justification for this reasoning can be drawn from Figure 3.1, which shows a representative example of the CBFV trends in both MCAs during the rest state and both types of activation states. It is clear in this case that significant increases in CBFV occurred very early within both activation states.
3.5.4 Influence of Respiratory Modulation

Prior to the experiment, no instructions were given to participants regarding the modulation of respiration. However, it was observed that some participants, either intentionally or unintentionally, modulated their respiration between rest and activation states. These modulations were apparent when classification was performed on respiratory data alone, as shown in Tables 3.2 and 3.3. These findings are of interest because respiratory modulations are known to affect CBFV [84]. However, classification using TCD data obtained significantly greater accuracies than classification using respiratory data for eight of nine participants for both tasks. This indicates that the results we have obtained are not merely the result of changes in respiration. Furthermore, it was shown by Szirmai et al [59] and by Hartje et al [12] that respiration-induced changes in CBFV tend to be bilateral. This suggests that we can reduce the impact of changes in respiration by using only bilateral features. The disadvantage of this approach is that we are likely to significantly diminish the attained accuracy for tasks which are weakly lateralized or unlateralized. When we restricted feature selection to bilateral features, this hypothesis was verified; we did incur a significant drop in accuracy for the mental rotation task. However, we maintained a very high accuracy for the word generation task. This provides further indication that the effects of respiratory modulation were not a significant factor during classification of the word generation task.

3.5.5 Limitations

During this study, we used a duration of 45 seconds for both rest and activation states. This is comparatively long for BCI applications, and in practical usage would constrain the data transmission rate to less than 1 bit/minute. Such a lengthy duration was chosen due to the lack of pre-existing research into a TCD-based BCI, and the necessity
of obtaining high classification accuracy. However, results from this study indicate that shorter durations would still allow for reliable detection of cognitive activity. In Figure 3.1, it is clear that significant increases in CBFV within the left and right MCAs occur soon after the onset of cognitive activity. Future studies should investigate the impact of shorter durations on classification accuracy.

In this study, the potential benefits of practice were not examined, as the participant only completed two sessions. Despite this, high classification accuracies were obtained. It is possible that participants could become even more accurate as they gained further proficiency with the required mental tasks. However, it is also possible that further practice could lead to habituation and a reduction in the cognitive activation caused by each mental task. Longer-term studies are needed to investigate these issues.

One difficulty associated with TCD is the presence of CBFV artifacts associated with movement. Head movement can cause the TCD probes to shift, resulting in momentary or persistent deterioration of the recorded signals. Body movement can also induce CBFV changes that may incorrectly be classified as activation, causing a false positive. Compensating for these potential sources of error is likely to become a significant practical concern in the future.
Chapter 4

Effects of shortened state durations on classification accuracy in a three-class brain-computer interface using transcranial Doppler ultrasound

This chapter extends the BCI discussed in Chapter 3 by investigating methods of increasing data transmission rate. The effects of three-class differentiation of mental activity and shorter state durations were considered, corresponding to Objectives 2 and 3. From our analyses, we concluded that significant improvements in data transmission rate were possible using these methods. The resultant data transmission rate was comparable to what has been demonstrated in recent literature for other measurement modalities.

This chapter is being prepared for submission and publication. The signal processing
algorithm used for the three-class problem bears some similarity to the one discussed in Chapter 3 for the two-class problem. These algorithms are compared in Figure 4.1. Due to these factors, Sections 4.1 to 4.3.4 contain some repeated content from Chapters 1, 2, and 3. Sections 4.3.5 to 4.5 consist of new content.

![Signal Processing Diagram]

**Figure 4.1:** Comparison between signal processing algorithms for the two and three-class problems.

### 4.1 Abstract

In this study, we investigate several methods of increasing data transmission rate for a brain-computer interface (BCI) based on transcranial Doppler (TCD) ultrasound. We recorded changes in cerebral blood flow velocity within the left and right middle cerebral arteries while nine able-bodied participants alternated between rest and two different mental activities (word generation and mental rotation). For state durations from 5 to 30 seconds, we used exhaustive feature selection and a linear discriminant analysis classifier to differentiate all three states with maximum classification accuracies exceeding 70%.
Chapter 4. Improving Data Transmission Rate

Data transmission rate was maximized at 1.2 bits per minute, representing a four-fold increase in data transmission rate over a previous two-class TCD-based BCI.

4.2 Introduction

Brain-computer interfaces (BCIs) allow users to generate control signals for external devices using only their thoughts [4]. Due to their ability to bypass typical output channels such as movement and speech, BCIs are of interest within the field of rehabilitation engineering [2]. Specifically, BCIs can be used as an alternative means of communication in individuals with severe physical disabilities resulting from conditions such as stroke and amyotrophic lateral sclerosis (ALS). In extreme cases, these disabilities can result in total immobility and inability to communicate while retaining full consciousness. This condition is referred to as “locked-in syndrome” (LIS) [3]. The provision of a means of communication for individuals with LIS continues to be an important goal of BCI research [8].

Previous non-invasive BCI research has focused on a small number of measurement modalities, of which the foremost has been electroencephalography (EEG) [71, 76]. Other modalities that have been investigated include functional magnetic resonance imaging (fMRI) [73], magnetoencephalography (MEG) [74], and near-infrared spectroscopy (NIRS) [75]. There are, however, other medical imaging techniques that have not been widely considered as measurement modalities for BCI research. One such technique is transcranial Doppler ultrasound (TCD).

TCD measures cerebral blood flow velocity (CBFV) within the circle of Willis (the network of arteries that supply the brain) [31]. Cognitive activation produces increases in CBFV within these arteries that can be detected using TCD [36]. These changes have
been observed for a wide variety of different mental tasks [10], suggesting the potential to automatically detect mental activity on the basis of changes in CBFV. This possibility was investigated by Myrden et al. in [89], where it was shown that two different mental activities (word generation and mental rotation) can be differentiated from rest with greater than 80% accuracy. However, these results were achieved using very long durations for each activity (45 seconds), yielding a very low data transmission rate. This limits the practicality of such a BCI. Consequently, improvement of the data transmission rate is necessary in order to demonstrate the practical viability of a TCD-based BCI.

In BCIs, data transmission rate depends on three parameters - the number of potential classes (N), the classification accuracy (P), and the state duration - the length of time for which a mental activity is performed before it is classified. The first two variables determine the data transmission rate in bits per trial (B), which can be expressed as [5, 90]:

\[ B = \log_2(N) + P \log_2(P) + (1 - P) \log_2\left(\frac{1 - P}{N - 1}\right) \]  

Using the state duration, data transmission rate can be converted to bits per second or bits per minute. It is clear that data transmission rate can be augmented by increasing either N or P, or by decreasing the state duration. The effects of each parameter on data transmission rate (in bits per minute) are shown in Figure 4.2.

Increasing the number of classes and reducing state durations is likely to decrease classification accuracy. This limits the maximum achievable data transmission rate. In this paper, we investigate the net gain in data transmission rate that can be attained by varying these parameters for a TCD-based BCI. We have expanded the classification problem introduced in [89] to a three-class problem by attempting to differentiate word
Figure 4.2: (a) Effects of classification accuracy and number of classes on data transmission rate for a 30-second state duration. (b) Effects of state duration and number of classes on data transmission rate for 100% classification accuracy.

generation, mental rotation, and rest from each other. Furthermore, state durations have been limited to a range of durations between five and thirty seconds. If state durations can be substantially reduced without greatly decreasing classification accuracy, data transmission rate will be improved.

4.3 Materials and Methods

4.3.1 Participants

Nine able-bodied participants (6 female, mean age 25.6 ± 2.4 years) were recruited from the Blooorview Research Institute. All participants were right-handed, as quantified by the Edinburgh Handedness Inventory [81], with a mean score of 79.4 ± 16.3. Participants had no history of migraine and no known neurological, cardiopulmonary, or respiratory conditions. All participants gave informed written consent. This study was approved by the Research Ethics Boards of both Holland Blooorview Kids Rehabilitation Hospital and the University of Toronto.
4.3.2 Signal Acquisition

CBFV was monitored using a Multi-Dop X4 TCD instrument (Compumedics USA). Dual 2 MHz ultrasonic transducers were fitted on the included headgear and placed over the left and right transtemporal windows. The insonation procedure detailed by Alexandrov et al. [82] was used to acquire CBFV signals from the left and right middle cerebral arteries (MCAs). These arteries profuse approximately 80% of the brain and have been implicated in a wide variety of mental tasks [10]. Probe position and measurement depth were adjusted until optimal signals were located from each MCA at depths between 45 and 60 millimetres. Signals were acquired from approximately the same depth for each MCA. The signal acquisition process is further detailed in [89].

4.3.3 Experimental Protocol

Participants completed two experimental sessions. Each session consisted of a 10-minute baseline period and two 15-minute experimental blocks. Data from the baseline period were not used for analysis. During each experimental block, participants completed ten rest states, five mental rotation states, and five word generation states. Participants alternated between rest and one of the two activation states until the block was completed. Each state was 45 seconds in duration. Participants were seated facing a monitor on which the instructions and images for each task were displayed. Further information regarding the word generation and mental rotation tasks is given in [89].

Participants were instructed to keep their eyes open during both activation and rest, and to perform each task as quickly as possible. Participants were also instructed to refrain from vocalizing their answers to prevent speech-related increases in CBFV. During rest states, participants were instructed to relax naturally.
4.3.4 Pre-Processing

TCD data were exported from the Multi-Dop X4, and the mean of the maximum velocity was extracted for analysis. The raw data from each block were normalized and then filtered using a third-order Butterworth filter with a cutoff frequency of 0.6 Hz to remove the effects of beat-to-beat fluctuations in CBFV. The data were then segmented into rest, word generation, and mental rotation states using markers that were automatically inserted into the TCD recordings at the beginning of each state during the experiment. During analysis, each of these segments was truncated to produce states of various shorter durations.

4.3.5 Feature Extraction

After segmentation, twelve features were extracted from each state. These included the mean, slope, and standard deviation from both the left and right MCAs; the difference in means and difference in slopes between the left and right MCAs; the cross-correlation and the dot product of the signals from each MCA; and the maximum and minimum instantaneous differences in CBFV between the left and right MCAs during each state.

4.3.6 Feature Selection and Classification

Classification was performed separately for state durations ranging from 5 to 30 seconds in one-second increments. To test each state duration, a signal of length corresponding to the state duration was extracted from the beginning of all states. Feature extraction was then performed for the set of shortened signals. Five runs of five-fold cross-validation were performed, with feature selection based on the training data set only. An exhaustive feature selection algorithm was used to identify the two and three-dimensional feature
sets that provided the best classification accuracy. For each state duration, classification was performed using linear discriminant analysis (LDA) for both feature sets. The reported classification accuracies are the average of the accuracies for all three classes. All comparisons between classification accuracies at different state durations were performed using the Wilcoxon rank-sum test.

4.4 Results

The mean classification accuracy across all participants using two and three-dimensional feature sets is displayed in Figure 4.3 for state durations ranging from 5 to 30 seconds. Mean classification accuracy ranged between 40% and 69% for two-dimensional feature sets, and between 37% and 74% for three-dimensional feature sets. For both sets, classification accuracy increased with increasing state duration, but tended to stabilize as state duration exceeded 20 seconds. In Figure 4.4, these curves have been converted to reflect data transmission rate using (4.1). Data transmission rate was maximized at 1.2 bits per minute for 20-second state durations using a three-dimensional feature set.

For both two and three-dimensional feature sets, mean classification accuracy across all participants exceeded chance levels for all state durations (p < 0.0001 for two-dimensional sets and p < 0.003 for three-dimensional sets). For durations greater than 10 seconds, classification accuracy was generally higher when using three-dimensional feature sets. This difference in classification accuracy was statistically significant for durations between 18 and 29 seconds (p < 0.02).

Figure 4.5 depicts the mean accuracy across all participants for each class at each state duration for three-dimensional feature sets. For these sets, an accuracy exceeding 70% was first achieved for 20-second durations. Classification accuracies for word generation and mental rotation were significantly higher than classification accuracy for the rest
Figure 4.3: Mean classification accuracy across all participants for durations ranging from five to thirty seconds. Both the raw results and the polynomial of best fit are shown for two and three-dimensional feature sets. Classification using three-dimensional sets was significantly more accurate for durations between 18 and 29 seconds.

class for durations longer than 10 seconds ($p < 0.05$) and 14 seconds ($p < 0.001$), respectively. Classification accuracy peaked for word generation at 77%, for mental rotation at 78%, and for the rest class at 66%. This was also observed in [89] when each task was independently differentiated from rest.

The cubic polynomial of best fit was computed for the accuracy curve for each participant. From these curves, state durations at which several temporal milestones were achieved were computed for each participant. These include the duration at which maximum accuracy was achieved, the shortest duration at which classification accuracy was within 5% of the maximum value, and the duration at which classification accuracy stabilized. The final parameter represents the state duration for which further increases in duration yielded only marginal gains in classification accuracy. It was defined as the state duration for which the magnitude of the derivative of the polynomial of best fit was less than 1%
Figure 4.4: Data transmission rate for state durations between 5 and 30 seconds. The maximum attained data transmission rate is 1.2 bits per minute for 20-second durations using a three-dimensional feature set.

of the maximum accuracy. All parameters were calculated for three-dimensional feature sets and can be found in Table 4.1.

4.5 Discussion

In this study, we have shown that mean classification accuracies exceeding 70% can be achieved for a three-class problem within 20 seconds of the onset of cognitive activity using bilateral TCD measurements, time-domain features, and a linear classifier. This corresponds to a maximum data transmission rate of 1.2 bits per minute, compared to a maximum rate of 0.3 bits per minute previously reported for a TCD-based BCI [89]. This significant improvement highlights the advantages of a three-class BCI and the importance of reducing state duration. It is important to note that these results represent very early research into a TCD-based BCI, and it is likely that further improvement is
possible. The present study used only the time-averaged mean of the maximum velocity due to limitations of the instrument. However, it is possible that response time may be further reduced using frequency-domain features extracted from the maximum velocity envelopes, if these signals are available.

Our results are comparable to some recent EEG-based BCIs that differentiate between three mental states. In [91], using an LDA classifier with two different feature sets resulted in accuracies of approximately 50% for a three-class BCI within 8 seconds (0.64 bits per minute). Within the same time frame, our classification accuracy was approximately 45%. In [92], classification accuracies up to 62% were achieved for a three-class BCI with 20 second state durations (0.74 bits per minute). Within the same time frame, our mean classification accuracy was 70%.
Table 4.1: State duration and classification accuracy for each participant when maximum accuracy, near-maximum accuracy (within 5%), and stabilization occurred. All values are for three-dimensional feature sets and were computed based on the cubic polynomial of best fit for the accuracy curve for each participant. Standard deviations are given in brackets.

<table>
<thead>
<tr>
<th>Participant Number</th>
<th>Maximum Accuracy</th>
<th>Within 5% of Max</th>
<th>Stabilization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (s)</td>
<td>Accuracy (%)</td>
<td>Time (s)</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>74.3</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>84.5</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>73.3</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>90.5</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>43.6</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>86.3</td>
<td>22</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>53.8</td>
<td>19</td>
</tr>
<tr>
<td>8</td>
<td>19</td>
<td>69.9</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>24</td>
<td>81.9</td>
<td>18</td>
</tr>
<tr>
<td>Mean</td>
<td>24.9 (4.0)</td>
<td>73.1 (15.6)</td>
<td>18.1 (3.1)</td>
</tr>
</tbody>
</table>

State duration has a significant effect on classification accuracy. As seen in Figure 4.3, classification accuracy for a three-dimensional feature set improves from 37% for five-second durations to approximately 50% for 10-second durations and 64% for 15-second durations. After state duration is extended to 20 seconds, further increases in classification accuracy are small. In previous TCD research, event-related peaks in CBFV have been observed between 4 and 20 seconds after the onset of cognitive activity [36, 56, 66]. These measurements support our results, and may explain why state durations beyond 20 seconds provide only marginal increases in classification accuracy.

In this study, state duration was varied by extracting a segment of appropriate length from the beginning of a 45-second task. This was a practical necessity due to the goal of investigating a wide variety of different state durations. If state durations were limited during data collection rather than during data processing, the results may vary slightly. Future work should investigate the effect of using shorter state durations during data collection. The results from this study could be used as a basis for selecting shorter state durations in future studies.
Chapter 5

Conclusions

5.1 Contributions

This thesis has explored transcranial Doppler ultrasound as a potential measurement modality for BCI research. The following list summarizes the major contributions of the thesis:

1. Demonstrated that it is possible to automatically differentiate between rest and two types of mental activity on the basis of changes in cerebral blood flow velocity [89], suggesting that transcranial Doppler ultrasound is a viable measurement modality for BCI research. To our knowledge, this is the first investigation of a TCD-based BCI.

2. Applied a signal processing algorithm that extracted intuitive time-domain features from TCD signals, selected the most useful of these features on the basis of the Fisher criterion, and differentiated rest and mental activity using linear discriminant analysis. Mean classification accuracies for both word generation and
mental rotation exceeded 80%.

3. Identified signal features that were particularly useful for the differentiation of mental activity from rest using a linear classification algorithm. For both word generation and mental rotation, features corresponding to the mean and slope of the CBFV curve in both MCAs were highly useful for classification. Lateralization features were also extremely useful for the word generation task [89].

4. Designed a three-class TCD-based BCI that achieved mean classification accuracies exceeding 70% within 20 seconds of the onset of mental activity using time-domain features, an exhaustive feature selection method and a linear classification algorithm.

5. Used concepts from information theory to maximize data transmission rate in a three-class TCD-based BCI. This resulted in a fourfold increase in data transmission rate compared to our initial two-class TCD-based BCI.

5.2 Future Work

5.2.1 Movement Towards Target Population

All results presented within this thesis have been achieved with a population of able-bodied individuals. Further research is required to determine whether these results can be replicated within a population of individuals with LIS. BCI studies within the locked-in population can be difficult, as participants have no pre-existing means of communication. This makes it difficult to ensure that the experimental protocol is being followed, and, consequently, can cause difficulty interpreting results. It may be helpful to perform a baseline study to characterize natural fluctuations in cerebral blood flow velocity within
this population. Using this knowledge as a foundation, it may be possible to detect event-related fluctuations in CBFV.

As an intermediate step to testing this BCI with locked-in individuals, a new study is currently in the preliminary stage. This study will attempt to replicate our results within a population of individuals with upper spinal cord injuries. These individuals have physical disabilities but are still able to communicate. This makes them an ideal group for the first investigation of a TCD-based BCI outside the able-bodied population. This study will avoid the methodological difficulties associated with the locked-in population while still providing some indication whether our results will generalize to individuals with disabilities.

### 5.2.2 Real-Time Analysis

Practical application of a TCD-based BCI will require real-time (online) analysis and classification. In turn, real-time analysis requires feature extraction and classification algorithms that can be performed on the fly with very short delays. We suggest that online TCD-based BCI research should first investigate a simple two-class problem to minimize complexity.

LDA classifiers (such as the one used in [89]) have low computational requirements and are well-suited for online analysis [93]. However, the features used in [89] were calculated based on 15 to 45-second windows of CBFV data, limiting the speed at which feature extraction and classification can be performed. In Chapter 4, we showed that, for a three-class BCI, 20-second windows provide a balance between classification accuracy and response time that produces a high data transmission rate. A similar analysis could be performed for a two-class BCI to determine an effective window length for online applications.
5.2.3 Continued BCI Development

Though results from our studies are promising, additional gains in classification accuracy and response time may be possible with further refinement. As discussed in the previous chapter, using frequency-domain features may allow for more accurate classification and a faster response. Furthermore, due to time constraints, there are a number of feature selection and classification methods that we have not yet investigated in a TCD-based BCI. These include methods such as genetic algorithms, hidden Markov models and support vector machines that have proven useful in previous BCI and access technology research [93–96]. Future research should investigate these more complex algorithms to determine whether significant gains can be realized in either classification accuracy or response time.
Appendix A

Participant Insonation Information

Table A.1 displays information pertaining to insonation depth in all participants during both sessions. Maximum insonation power was 420 mw/cm² with a sample volume of 10 millimetres. The maximum thermal index was 2.0, and insonation was performed for no more than 15 minutes at a time. This is in keeping with general TCD safety standards [83].
Table A.1: Age, handedness, and insonation information for all participants. All insonation depths are in millimetres.

| Participant | Age | EHI Score | Session 1 | | | Session 2 | |
|-------------|-----|-----------|-----------| | | | |
|             |     |           | Left MCA Depth | Right MCA Depth | Left MCA Depth | Right MCA Depth |
| 1           | 23  | 100       | 53        | 53            | 53            | 53            |
| 2           | 27  | 86        | 50        | 50            | 50            | 50            |
| 3           | 27  | 69        | 55        | 55            | 52            | 52            |
| 4           | 26  | 70        | 50        | 50            | 50            | 50            |
| 5           | 24  | 50        | 58        | 60            | 53            | 53            |
| 6           | 22  | 71        | 55        | 55            | 50            | 50            |
| 7           | 26  | 89        | 60        | 60            | 57            | 60            |
| 8           | 25  | 100       | 55        | 55            | 52            | 52            |
| 9           | 30  | 80        | 50        | 53            | 50            | 50            |
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