The Automated Detection of Changes in Cerebral Perfusion Accompanying a Verbal Fluency Task: A Novel Application of Transcranial Doppler

by

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Evidence suggests that cerebral blood flow patterns accompanying a mental activity are retained in many locked-in patients. Thus, real-time monitoring with functional transcranial Doppler (TCD) together with a specific mental task could control a brain-computer interface (BCI), thereby providing self-initiated interaction.

The objective of this study was to create an automatic detection algorithm to differentiate hemodynamic responses coincident with one’s performance of verbal fluency (VF) versus counting tasks.

We recruited 10 healthy adults who each silently performed up to 30 VF tasks and counted between each. Both middle cerebral arteries were simultaneously imaged using TCD. Linear Discriminant Analyses (LDA) successfully differentiated between VF and both prior and post counting tasks. For every participant, LDA achieved the 70% classification accuracy sufficient for BCIs. Results demonstrate automatic detection of a VF task by TCD and warrant further investigation of TCD as a BCI.
Dedication

To my late grandmother, Freda Stern, who made me feel at home in Toronto.
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List of Acronyms

ACA  Anterior Cerebral Arteries
ALS  Amyotrophic Lateral Sclerosis
BCI  Brain-computer Interface
BFV  Blood Flow Velocity
EEG  Electroencephalography
fMRI functional Magnetic Resonance Imaging
LDA  Linear Discriminant Analysis
LIS  Locked-in Syndrome
MCA  Middle Cerebral Arteries
MEG  Magnetoencephalography
NIRS Near-infrared Spectroscopy
PCA  Posterior Cerebral Arteries
PET  Positron Emission Tomography
TCD  Transcranial Doppler
TICA Terminal Internal Cerebral Arteries
VF   Verbal Fluency
Chapter 1

Introduction

1.1 Motivation

With the recent advancements of medicine, there is an increasing survival rate of people who suffer from multiple and severe disabilities. As a direct result, there are a growing number of people who are unable to speak or control their own movements and often cannot reliably interact with their environment [1]. Some of these people suffer from Locked-in Syndrome (LIS); they are cognitively aware, yet suffer from such severe motor dysfunction that other than limited eye-movement, they present as unresponsive [2]. Furthermore, individuals with LIS lack an effective modality to convey self expression and consequently are unable to guide their own care [3]. An effective communication interface would ultimately improve the functional recovery, independence, learning, and quality of life of these individuals and is therefore highly desired [4–6].

Ideally, patients with LIS would interact using an access technology as illustrated in Figure 1.1, and more specifically a brain-computer interface (BCI). A BCI responds to changes in the user’s brain activity, thereby bypassing the impaired motor pathway, and translates the user’s intentions into visible or audible gestures [3]. The terms patient and user are interchangeable, as a BCI is controlled by the brain activity that it monitors.
BCIs compensate for the user’s impairment by utilizing his/her intact cerebral networks to direct a secondary device for communication or object manipulation [1, 7]. The mental activations responsible for BCI control are monitored through cerebral hemodynamics (blood flow speed or relative blood oxygenation levels) or the electrical activity of neuronal impulses [1].

Figure 1.1: The Role of an Access Technology [1]

BCIs have been built to provide a yes/no response, surf the internet, or maneuver a motorized wheelchair under the direction of its operator [8]. BCIs have also been used to aid the recovery of paralyzed patients [8]. For example, in rehabilitation therapy a female patient was encouraged to mentally activate her impaired neural pathways. Due to her paralysis, this patient was uncertain if she was activating these areas correctly, but could rely on a BCI for feedback to determine whether or not she was [8].

Any functional neuro-imaging technology can detect changes in brain activity [9] and therefore can potentially act as a BCI, yet few include the features necessary for practical, everyday use [8]. There are only a handful of non-invasive BCIs available or being used in research, and while clinical results have been encouraging, there are still some open challenges. Functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG) are costly and not portable [8]. Electroencephalography (EEG)-based solutions
either rely on an evoked response (i.e., P300) [8] which limits its application, or involve lengthy training [10]. Near-infrared spectroscopy (NIRS) solutions require a dark environment to prevent external light interference [11], which is not always practical. From the BCI literature, it is clear that although each modality has its own benefits and drawbacks [8], there is no particular type of BCI that dominates over the others [12]. Therefore, research should continue to investigate all varieties of BCIs in order to provide access technologies that can support a range of neural deficits.

This thesis explores the feasibility of a new, non-invasive BCI; functional transcranial Doppler ultrasonography (TCD). This technology monitors changes in the blood flow velocity (BFV) of the large cerebral arteries during rest and mental activity [13]. Although TCD is used frequently in diagnostics, its use as a BCI has yet to be explored. Unlike current modalities, TCD is low risk, low cost, and portable [13–15] and therefore is conducive for use as a BCI. One of the greatest potentials of TCD is its high temporal resolution; it can measure BFV changes within 100ms [13, 14].

Due to neurovascular coupling [16], cerebral hemodynamics can be self-manipulated through one’s choice of task and degree of effort in pursuing mental activities [3, 15, 17]. Evidence has confirmed that this coupling, where blood flow velocity increases with neural activity, is detectable with TCD [5, 13, 15, 17, 18]. Therefore, changes in blood flow of the brain may act as a control mechanism for a BCI.

To minimize the number of unintended activations, typically a particular mental activity is used to deliberately drive a BCI. Linguistic tasks, specifically those that require creativity and active concentration, have elicited the greatest cerebral lateralization (differential perfusion between brain hemispheres) [15, 19]. Such marked hemispheric dominance in blood flow is uncommon when compared to most other mental tasks [15, 19]. Therefore, a linguistic task is highly attractive for its use with a TCD-based BCI. An example of such a task is the verbal fluency (VF) task, where one thinks of many words that begin with a given letter. The asymmetry in blood flow elicited by this activity is
unique and visible with TCD imaging of the middle cerebral arteries (MCA) [15, 19].

1.2 Hypothesis

As a functional application of the VF task, consider an on-screen scanning keyboard. We hypothesized that if an individual performed the VF task whenever he/she wanted to make a letter selection, the accompanying dominance of blood flow in one hemisphere could be automatically detectable via bilateral TCD measurements.

1.3 Research Question & Objectives

Is it possible to repeatedly detect and differentiate the hemodynamic response of a verbal fluency task from that of a counting task?

The main goal of this study was to create an automatic TCD-based detection algorithm to differentiate between the hemodynamic responses that coincided with two mental activities: the silent performance of a VF task and a counting task. The secondary objectives were to determine the minimum duration of each subsequent activity (counting pre-VF task, VF task, and counting post-VF task) required to achieve a significant change in BFV to differentiate the VF task.

1.4 Overview

The remainder of this thesis is organized as follows: Chapter 2 provides an understanding of patients with LIS and discusses whether a BCI would be an appropriate tool from which they would benefit. Subsequently, chapter 3 is a review of the fundamentals of TCD and cerebral hemodynamics. This background is useful for understanding the investigation of automated detection, which is described later in chapter 4. The results of this study
are also discussed in chapter 4 in terms of their importance for BCI research, along with the limitations and suggested modifications of this experiment. Chapter 5 presents the potential clinical constraints in utilizing this detection method for children or cognitively compromised individuals. Chapter 6 details the motivation for the potential applications of BCIs in the neuro-rehabilitation setting. Finally, chapter 7 concludes this thesis with a summary of its the scientific contributions.
In order to focus BCI research to serve its user’s functional and rehabilitative needs, a thorough understanding of the diseases, deficits and cognitive potential of its target users is imperative [2]. Therefore, the origins, the associated anatomical dysfunction, and the recovery potential associated with LIS (a common pre-requisite for BCIs) are provided. In addition, their intact physiological responses or capability to control a BCI are presented.

2.1 Locked-in Syndrome: A Common Pre-requisite for BCI Acquisition

Causes of LIS include trauma evoked by a stroke, brain or spinal cord injury, or cerebral palsy; or due to a degenerative neuromuscular disease such as Multiple Sclerosis, Parkinson’s Disease, or Amyotrophic Lateral Sclerosis (ALS) [8]. The characteristics of LIS are
intact wakefulness and awareness, combined with quadriplegia and anarthria (severely impaired speech production) [2]. Such patients may be ill-equipped to use an eye tracking device for a number of reasons. Such examples include, purposeful eye movement versus reactionary (unintentional) eye movement are not differentiable [20]. Also, the wide range of eye movement these trackers require is not always possible for LIS patients. Thus, in such conditions, where normal movement and conversational abilities are severely impaired, a BCI is often essential to practice normal behaviours. A BCI that incorporated a P300 (EEG-based functional imaging system) was tested on ALS locked-in patients who only had control over their eye movements [12]. This BCI allowed for complete independence of communication for all 6 patients that were tested [12], demonstrating the possibility for BCIs to improve functional ability and independence.

Among children, the leading cause of LIS is a lesion of the ventral pons [2], which is located within the brainstem [21]. Behavioural deficits that result from such a lesion can be speculated by analyzing the structural anatomy and its corresponding function. The pons serves primarily to regulate autonomic function and houses the respiratory control centers [21]. Therefore, a lesion isolated within the pons would severely impair respiratory function leaving one reliant on ventilators, yet would not affect wakefulness and awareness (which are controlled by the reticular formation of the brainstem [21]). For this reason, BCI technologies that target LIS patients should be compatible with life support machinery, ruling out the use of fMRI [22].

Not all patients present with isolated lesions, meaning cognitive capability and neurological response may vary between individuals. For example, a case report describes a female patient with incomplete LIS who demonstrated limited eye movement and intact understanding of written and verbal language, but was unable to speak or move, and suffered left spatial neglect [23]. Although the causes and presentation of spatial neglect vary, it has been associated with reduced neural activity in the regions linked with spatial attention such as the frontal cortex and angular gyrus [24]. For this patient, the neural
response in these areas was likely unreliable. Therefore, if a person were creating a BCI for her to use for environmental control or communication, it would be important to focus on an area of the brain that would be activated by her intact written or verbal language understanding, and avoid the areas possibly associated with the spatial neglect.

2.1.1 Underdiagnosis of LIS

There does not appear to be standardized protocol to assess cognitive function [25], and as a result there are exceptionally high estimates of underdiagnosis (nearing 50%) among LIS patients [26]. LIS is especially rare in children, leading to even higher rates of misdiagnosis among the pediatric population [2]. Common misdiagnoses are coma, vegetative state, and akinetic mutism [2], likely because these states reveal similar static behaviours as those that are characteristic to LIS. Subsequently, for those patients who maintain control of their eye movements and/or blinking, these voluntary responses have been incorrectly rationalized to be reflexes [25]. The underdiagnosis of LIS suggests that a clinically valuable BCI will have greater application and significance than presently estimated.

2.2 Determining the Cognitive Capabilities of BCI Users

Currently, there are a variety of BCIs under investigation, and each has the potential to respond to a unique cognitive signal. However, accurate assessment of the user’s cognitive capabilities as well as their neural deficits is necessary to match and train them with an appropriate BCI [2]. Generally, a client’s needs and his required BCI function can be easily defined by behavioural observations and rehabilitative goals. Less intuitive, are the specific cognitive performance and impairments of these individuals. Neuro-imaging technologies with high spacial resolution allow for a detailed functional evaluation of
Chapter 2. A Detailed Review of Brain-computer Interfacing & Its Target User

particular cerebral areas [9]. Modalities used for this purpose include fMRI and positron emission tomography (PET) [22]. Therefore, an objective cognitive assessment is possible for some patients [27], making BCI matching accessible. However, due to the life support machines that accompany severely compromised patients, PET and fMRI are incompatible with such equipment and therefore nearly impossible to administer [22].

EEG and TCD are compatible to help assess if a patient on life support has LIS. Unfortunately, both of these modalities have a poor spatial resolution [8], and therefore only generalized conclusions concerning these patients cognitive function are possible [22]. For these complex patients BCI control is likely feasible, but fitting them with an individualized BCI would be less obvious and therefore tedious.

2.2.1 Can A Locked-in Patient Control and Benefit from a BCI?

BCIs are controlled by cerebral signals and therefore require the user to possess some complete cognitive networks. A literature review of LIS found an agreement among studies, whereby all patients who only suffered pontine lesions had full restoration of their cognitive potential [25], yet without assistance they were unable to express it. This finding suggests that a LIS patient fitted with an individualized control mechanism could direct a BCI and thereby actively participate in rehabilitative programs. Moreover, with physical and speech therapy, LIS patients can improve their functional outcome and reduce their rate of mortality [25, 28]. This information should persuade BCI researchers to investigate individualized technologies that supplement the target user’s rehabilitative agenda.
3.1 The Mechanism of Transcranial Doppler

Transcranial Doppler imaging is non-invasive and safe [29], relying on the propagation of sound waves and the received echoes to monitor blood flow velocity of the cranial arteries [30]. The sound waves propagate through tissue, but are highly attenuated by scull bone [30]. Therefore, TCD can only image the brain from six small windows, where the bone is thin or displaced with soft-tissue [31]. The temples are generally good acoustic windows and allow for simultaneous monitoring of each hemisphere. The TCD head gear and probe positioning used for transtemporal insonation are depicted in Figure 3.1. Each probe contains a transducer and together they detect a simultaneous, real-time recording of blood flow velocity from bi-lateral intracranial vessels [13, 15].

The sections that follow explain the mechanisms that are critical to the choice of TCD settings used to monitor cerebral blood flow velocities. All other sections that may be of interest, but fail to directly affect the TCD settings used to assess neurovascular coupling, can be reviewed in Appendix B.
3.1.1 Pulsed-wave Doppler

TCD commonly incorporates a transducer that relies on pulsed-wave Doppler and acts as both the transmitter of ultrasound and as the detector of echoes [32]. In this device, for a given insonation depth \( (d) \) and known wave propagation speed \( (c_0) \), the round-trip travel time \( (T) \) is calculated by the following equation [33]:

\[
T = \frac{2d}{c_0}
\]

There are two modes in which the TCD can operate: continuous-wave Doppler and pulsed-wave Doppler. The pulsed-wave mode was chosen to monitor blood flow changes because it allows for depth discrimination [30]. The probe contains a piezoelectric crystal that alternates between transmitting ultrasound impulses and detecting reflected signals, as depicted in Figure 3.2.

Pulsed-wave Doppler transmits discrete, short pulses of ultrasound and waits for echo detection before it transmits the next pulse [33]. The echo is generated when the initial pulse is reflected off a scatterer or red blood cell. The pulse time coincides with a particular depth, which allows the sonographer to specify the depth of interest by limiting the time window for detection [33]. The TCD setting termed sample volume is used for such range gating, as it controls the time window used for detection.
3.2 Cerebral Vasculature & Neural Activity

The temporal window provides a superior view of the Circle of Willis; a circle of arteries comprised of homologous pairs of vessels including the anterior cerebral arteries (ACA), middle cerebral arteries (MCA), posterior cerebral arteries (PCA), and terminal internal carotid arteries (TICA) [31, 33, 35]. The Circle of Willis is depicted in Figure 3.3. These arteries feed specific lobes and therefore are commonly imaged in psychology and neuroscience research to identify metabolically active regions associated with a given task [17].

Relative velocity changes in the large cerebral arteries coincide with relative changes of the cerebral blood flow, assuming a constant perfusion area and lumen diameter [15]. These are common assumptions in the literature, yet have not been scientifically proven [15] and therefore manifest as a possible source of error in the TCD flow velocity calcu-
The MCA are frequently identified in TCD studies, especially those that utilize functional tasks controlled by the neural networks that it feeds [17]. Therefore, its structure and function are explained.

3.2.1 The Middle Cerebral Arteries

The MCA is the largest branch from the internal carotid artery making it ideal for TCD detection [17, 29, 36]. It is symmetrically positioned with the right and the left MCA perfusing each hemisphere, respectively. It branches into smaller vessels which innervate specific regions of the frontal, parietal, occipital, and temporal lobes [29]. The MCA ultimately feeds Broca’s area, which is located in the frontal lobe of the language dominant hemisphere. Broca’s area is largely responsible for expressive language-based tasks [37].

A study by Varnadore et al. [38] imaged the MCA, PCA, and ACA while performing a language-based problem solving task. Of the three arteries, the MCA displayed the greatest blood flow velocity and the best sustained response [38]. These conclusions combined with the general acceptance that the MCA best mimics the total cerebral blood flow, and its ease of TCD imaging [15, 39] provides the basis for its use in studies which involve language tasks.

3.2.2 Functional Hyperemia

TCD provides visualization or objective measures of cerebral BFV and its associated response with neural activity. However, valuable interpretations and applications for such measurements require an explicit understanding of the underlying physiological controls which drive these changes [9]. Therefore, to critically evaluate the interpretation of results from TCD studies, a review of the factors responsible for changes in BFV is provided.
Neural Activity

Neurons are activated either in response to a stimulus, or to generate a mental or physical task [21]. The brain does not have a reliable mechanism to store oxygen and glucose, and thus heavily relies on blood flow to deliver its required metabolites [29]. Its metabolic demands are high, representing 25% of the body's total oxygen consumption [29]. However, the consumption of oxygen is an exothermic reaction and sustained neural activity increases the local temperature which threatens its own function [40]. Therefore, it is of no surprise that neural activity is highly coupled to increased blood flow, which aids in delivery of nutrients, and the removal of metabolic wastes and excess heat [41, 42].

A localized region of high neural activity in the brain initiates a local increase in cerebral blood flow, and this is termed functional hyperemia [43]. This coupling has been demonstrated in fMRI studies to correspond with a redistribution of global blood flow; limiting the blood supply to inactive regions and increasing it to active ones [44]. Similarly, evidence from TCD research suggests that blood flow velocity increases with neural activation compared with rest periods and therefore TCD can be used to monitor functional intent [13, 15].

The Regulation of Regional Cerebral Blood Flow

Increased local cerebral blood flow has been speculated to result from two different mechanisms: capillary recruitment or increased BFV [41, 45]. With capillary recruitment, more avenues are used and more blood flows through a specific region, but the local BFV remains stable [45]. From this it follows that upon increased metabolic demand the pre-capillaries dilate, which increases the regional blood flow but lowers the BFV within them. However, most studies agree that this pre-capillary response has minimal effect, if any, on the BFV of the larger cerebral arteries [41] and therefore is nearly invisible with TCD imaging. Alternatively, an increase in local BFV does not require additional vessels [41] and is auto-regulated by pressure changes which result from contractions of
the cerebral arteries and arterioles [45]. This second mechanism is likely to follow the first, as it assumes that the local capillaries are nearly saturated [41]. Therefore, both mechanisms provide the local neural networks with more nutrients per a minute, yet have contradictory effects on BFV.

A Question of Timing

The explanation as to why increased blood flow follows the initiation of neural activity is highly controversial. The various arguments speak to every role of blood flow. Examples include: to increase delivery of nutrients [46], or to regulate temperature thereby influencing the chemical interactions within the brain [40]. Yet a fitting argument should account for the fact that neurons are activated on a millisecond time scale [45] and the blood flow response takes 1-2 seconds to commence [11, 47]. Although advancements in neuro-imaging have allowed scientists to visualize these time discrepancies, a complete explanation regarding the time lag associated with functional hyperemia remains unclear [47]. Moreover, TCD studies have uncovered temporal information pertaining to changes in the hemodynamic response. Yet, unequipped with a sound physiological explanation for these time discrepancies, few have brought attention to them [13, 14].

3.2.3 Lateralized Brain Activity

Upon mental activation the cerebral perfusion may be equally distributed among both hemispheres or lateralized preferentially (perfusion in one hemisphere dominates) [48]. The factors that influence this distribution and their impact on TCD experiments are explained below.

Task Dependent

Approximately 90% of the population is right handed and since the distribution of specific cerebral neural networks is highly correlated with handedness, 95% of the population
consequently displays left hemisphere lateralization for language dominance [21]. Some tasks are associated with equal bilateral perfusion, and for others the degree of lateralization varies [49]. For example, a TCD study of language-based tasks concluded that expressive tasks (VF and sentence construction) lateralize stronger than receptive tasks (reading and semantic decision) [49].

A functional transcranial Doppler study conducted by Vingerhoets and Stroobant [15] imaged the MCA of ninety healthy right-handed adults who each performed thirteen different verbal and visuospatial tasks. Their results indicated that the greatest blood flow change coincided with the more creative and complex (or active) tasks [15, 19]. Of the thirteen tasks, those that required processing of verbal stimuli including sentence construction and VF demonstrated the most asymmetric cerebral response, being highly left lateralized [15, 19]. This same outcome was observed in the majority of other studies; however, left-handed individuals often exhibit atypical lateralization [17, 19]. A functional TCD study involving the VF performance of 15 participants, found a minimum, yet still significant BFV difference of 1.3% and a maximum of 5.7% and 6.3% for right and left hemisphere language dominance, respectively [50]. These results indicate that a significant cerebral lateralization accompanies the VF task, independent of one’s hand dominance. Thus, TCD can detect a hemispheric difference without needing to pre-screen subject’s based on their dominant hemisphere.

The Influence of Demographics

The results of Vingerhoets and Stroobant [15] study of ninety subjects between the ages of 18-62 years old, demonstrated that lateralization in adults was not influenced by age [13, 15]. Likewise, gender and IQ do not influence the blood flow velocity response of the MCA [15]. Similar findings were concluded among adolescents (12-18 years) [51] and among children (2-9 years)[52, 53], with no correlation between a participant’s degree of language lateralization and age.
Chapter 4

Experimental Methods

This chapter includes a paper co-authored by Hayley Faulkner\textsuperscript{1,2} and Tom Chau\textsuperscript{1,2} that will be submitted for journal publication. In an effort to minimize repetition, the majority of the introduction has been omitted, as it closely resembled chapter 1.

4.1 Abstract

Evidence suggests that cerebral blood flow patterns accompanying a mental activity are retained in many locked-in patients. Bilateral cerebral blood flow velocities estimated via transcranial Doppler ultrasound (TCD) may thus serve as a control signal for a brain-computer interface (BCI).

The objective of this study was to create an automatic detection algorithm to differentiate between hemodynamic responses associated with a left-lateralized verbal fluency (VF) task and those of an unlateralized counting task.

Ten able-bodied adults silently performed up to 30 VF tasks, each prefaced and

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Authors’ Contributions: HF conceived the study, designed the experiment protocol, performed data collection, analyzed the data, and drafted the manuscript. TC conceived the study, advised on the design and coordination of the experiments, and edited the manuscript.
punctuated with counting tasks, within the paradigm of a row-column scanning on-screen keyboard. Blood flow velocities of the left and right middle cerebral arteries were simultaneously acquired using TCD. Slope ratio and the squared difference of successive slope ratios were extracted from blood flow velocity data using different window sizes and interval locations. Linear Discriminant Analysis (LDA) classifiers differentiated between VF and counting post-task with an average accuracy of 87.14±7.53% across participants and requisite task duration of 16.4±9.6s. LDA classifier also distinguished VF from the counting pre-task with an average accuracy of 77.23±6.28% and task duration of 17.1±9.0s. These results demonstrate the potential of automatic detection of a VF task via bilateral TCD and encourage further investigations of TCD as a BCI.

4.2 Introduction

As a functional application of the VF task, consider an on-screen scanning keyboard. We hypothesized that if an individual performed the VF task whenever he/she wanted to make a letter selection, the accompanying dominance of blood flow in one hemisphere would be automatically detectable via bilateral TCD measurements. In this paper, we explore the combination of mental activities (counting and VF tasks), duration of activation, and classification scheme to optimize the automatic detection of the VF task.

The remainder of this paper is organized as follows: In section 4.3, we introduce the experimental methods. Subsequently, in sections 4.4 and 4.5, we detail the data analysis and the corresponding results, respectively. Finally, in section 4.6, we discuss conclusions and limitations of our experiment as well as the future directions in using TCD as a BCI.
4.3 Materials and Method

4.3.1 Participants

Ten healthy participants, (mean age 25.5±2.8 years, 3 males) provided written informed consent as required by the Holland Bloorview Hospital Board of Ethics. All participants were university-educated, non-smoking, proficient English speakers with no history of cardiovascular, neurological, or psychiatric disorders. This exclusion criterion was necessary because the listed disorders have been associated with altered neurovascular coupling [16]. The participants were not taking any psychoactive medication and refrained from drinking caffeinated beverages for at least 3 hours prior to the session. According to the Edinburgh Handedness Inventory [54], all participants were clearly right hand-dominant (mean Handedness score 74.8 ± 18.0) with the exception of participant 2 (handedness score of 37).

4.3.2 Instrumentation

Continuous bi-lateral monitoring of both MCAs was achieved using a 2-MHz MultiDop 4X digital TCD and accompanying head gear (Compumedics Germany GmbH, Germany). The headgear accommodated two dual 2MHz transducers, allowing simultaneous ultrasonic penetration of the left and right temporal windows. Ultrasound gel was applied at the contact point between the participant’s skin and the transducer. The transducer both transmitted the ultrasound signal and detected the echoes. A respiration belt (Grass Technologies, Respiratory Effort Transducer) was worn around the chest, just below the sternum to monitor the participant’s breathing.

At the beginning of the session, the characteristic bifurcations and the main arteries of the Circle of Willis were identified in one hemisphere, using the protocol published by Alexandrov et al. [31]. Both MCAs were imaged at an insonation depth of 48-52 mm. The TCD instrument computed the maximum BFV every 100Hz using a fast
Fourier Transform and graphed the instantaneous peak BFV in real-time on-screen. The corresponding numerical data were stored for later analysis.

Every participant attended one session of approximately 2 hours in duration. Sessions took place in a quiet clinical room with unadorned walls and constant illumination. The participant was seated in a comfortable chair facing a WiViK on-screen keyboard as shown in Figure 4.1. The set-up, including identification of the MCAs, took approximately 35 minutes.

![Figure 4.1: Experimental Setup](image)

The participant, instrumented with the TCD head gear and respiration belt was seated, facing an onscreen WiVik keyboard. A card with the “task letter” was provided.

### 4.3.3 Procedure

The study session was arranged into three blocks, each separated by a five minute break, during which the TCD was turned off. Each block consisted of 5 trials. In each trial, the participant selected one target letter.

Prior to the start of each block, the probe angle was re-adjusted as needed and a paper-based list of 5 target letters (one for each trial) was given to the participant. The list served as an explicit visual reminder of the target letter for a particular trial. We only
used letters with which words began with high frequency in the English language [55]. Target letters for each block were: \{S, H, R, I, C\}, \{E, M, F, A, T\}, and \{D, P, G, B, L\}. Three different on-screen keyboards were used; each consisted of a 3x3 grid of letters arranged alphabetically across columns, from left to right, and then down rows, from top to bottom. Only one keyboard was displayed per trial.

In each trial, the participant silently performed the VF task when the row or letter of interest was highlighted, and counted by ones at all other times. Counting has been shown by Stroobant and Vingerhoets [17], to elicit a bilateral reduction in BFV in the MCAs below that observed in a rest state when instructed to think of nothing.

The sequence of a trial is depicted in Figure 4.2. Initially, the WiViK keyboard remained stationary for 15 seconds, in order for the participant to familiarize him/herself with the keyboard layout. Row scanning then commenced at a rate of 45 seconds per row. On non-target rows, the participant simply counted by ones. When the row containing the target letter was highlighted, the participant performed the VF task. This activation period was followed by a 45 second countdown that appeared on the screen as a second by second decrementing numerical counter. During the countdown period, the participant counted along with the timer. This 45 second delay allowed heightened blood flow to subside. At this point, row scanning was complete and column scanning from left to right, across the target row began at the same rate (45s per column). The participant was instructed to attempt to generate a unique set of words, as word replication tends to minimize the degree of lateralization [56]. When the target letter was highlighted, the participant performed the VF task, which was again followed by a 45s countdown. Following each trial, the participant completed a computer-based checklist that evaluated his/her compliance to the experimental protocol and perceived task performance. The details of the checklist are illustrated in Figure 4.3. Each trial was distinguished by a unique target letter and lasted approximately 2 to 4 minutes, depending on the row and column location of the target letter.
Figure 4.2: Trial Protocol
Each parallelogram (except checklist) represents a 45s task. Each rectangle represents a 45s task.

4.4 Data Analysis

4.4.1 Pre-processing

Trials which were incomplete or self-rated as “I lost focus” were omitted from the analysis. The initial 15 seconds of BFV data (keyboard layout familiarization prior to scanning) from each trial were also omitted.

The remaining BFV data were segmented into distinct trials. Each trial was further segmented into 45 second segments, each representing one of three possibilities: counting by ones (pre-VF task), VF task, or count-down (post-VF task). The combined total number of segments analyzed included 282 VF tasks and their corresponding post-VF countdown segments, and 264 pre-VF counting segments. The segments available for
First task (row selection)
- I generated many words.
- I tried to generate words, but I just couldn’t think of very many.
- I lost focus and couldn’t concentrate on word generation.

Second task (letter selection)
- I generated many words and these words were different from those generated in the first task.
- I tried to generate words, but I just couldn’t think of very many.
- I lost focus and couldn’t concentrate on word generation.

Counting
- I always counted between tasks.
- I counted during the baseline recording (rest at beginning of the trial).
- I counted during the first countdown window.
- I counted during the second countdown window.

Figure 4.3: Computer-based Checklist

This performance evaluation was completed by the participant following each trial.

Instructions were given to check all boxes that applied.

Analysis for each participant are summarized in Table 4.1.

<table>
<thead>
<tr>
<th>Task</th>
<th>Participant</th>
<th>1</th>
<th>2</th>
<th>3*</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count Pre-VF</td>
<td>20</td>
<td>28</td>
<td>25</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>23</td>
<td></td>
<td>264</td>
</tr>
<tr>
<td>VF</td>
<td>20</td>
<td>30</td>
<td>26</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>26</td>
<td></td>
<td>282</td>
</tr>
<tr>
<td>Countdown Post-VF</td>
<td>20</td>
<td>30</td>
<td>26</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>26</td>
<td></td>
<td>282</td>
</tr>
</tbody>
</table>

* Segments were omitted.

The BFV data were pre-processed to minimize noise, such as that due to cardiac rhythms (∼1.2Hz). The minimum time required to reach peak BFV of the MCA, post-stimulus, is known to be between 4-7 seconds [50]. Assuming that the restoration of baseline BFV levels required half this time, the minimum cycle time for activation and recovery would still exceed 5 seconds. Therefore, all periodic signal components with a period less than 5 seconds were filtered from the BFV data using a low-pass Butterworth filter, with a cut-off frequency of 0.2 Hz. To facilitate an eventual on-line analysis, we specifically avoided data normalization.
4.4.2 Feature Identification

Given the number of available trials per participant (> 61), we intentionally limited our feature space dimensionality to two. Since there is no consensus in the literature regarding the number of seconds required for inter-hemispheric differences of cerebral BFV to peak [57], we investigated the discriminatory potential of features (introduced below) over different time intervals. Recall that data were recorded in 45s segments. We divided each 45s segment into \( \lfloor \frac{90}{w} \rfloor - 1 \) overlapping time intervals, where \( \lfloor . \rfloor \) denotes the floor operation, \( w \in \{1, 2, \ldots, 10\} \) is the window size in seconds and successive intervals had an overlap of \( w/2 \) seconds. In other words, within a 45s segment and for a given choice of \( w \), the possible interval starting times were \( t = \frac{w}{2} (n - 1) \), where \( n = 1, \ldots, \lfloor \frac{90}{w} \rfloor - 1 \).

For both features we did not incorporate information from a baseline measure, but at each window size \( w \), only compared data between the 1\(^{st} \) and the \( n \)\(^{th} \) \( (n = 2, \ldots, \lfloor \frac{90}{w} \rfloor - 1) \) time intervals within every 45s segment. The rationale for comparing BFVs in close temporal proximity are threefold: the participant’s physiological and psychological status is assumed to be unchanged, unintentional probe sliding is less likely to occur [3, 15, 17] and the effects of task habituation are mitigated [58]. In the following, the subscript \( n \) will denote the feature calculated over the \( n \)\(^{th} \) interval.

**Feature 1: Slope Ratio**

Since TCD cannot distinguish between real asymmetries and those due to differences between left and right insonation angles [15], ratios were used to quantify the relative change in BFV within each segment. In particular, the laterality quotient, \( B_n \), of the left (\( b_L \)) and right (\( b_R \)) hemispheric rates of change of BFV between the first and \( n \)\(^{th} \) intervals was computed as follows,

\[
B_n = \frac{b_L(n)}{b_R(n)}
\]
where \( b_L(n) \) is the slope of the least-square fit to the collection of points from the first and \( n \)th intervals of BFV data from the left side. The slope \( b_R(n) \) was estimated similarly. Empirically, \( b_L \) and \( b_R \) were never zero.

The slope ratio, i.e., the ratio of the laterality quotients between the \( n \)th and first intervals was computed as follows,

\[
R_n = \frac{B_n}{B_1}
\]

where \( n = 2, \ldots, \lfloor \frac{90}{w} \rfloor - 1 \). From Bernoullis principle [59], we know that BFV cannot increase indefinitely, as it is limited by the mean arterial pressure and the vessel dimensions. Therefore, for left lateralized activity, one would expect the above ratio to initially increase during accelerating, left-lateralized perfusion and eventually level off.

**Feature 2: Squared Difference**

The squared difference, \( V_n \), of successive slope ratios was the second feature considered.

\[
V_n = (R_n - R_{n-1})^2
\]

where \( n = 2, \ldots, \lfloor \frac{90}{w} \rfloor - 1 \). During lateralized activity, the slope ratio, \( R_n \), was expected to increase slowly for several seconds and in turn, we expected the difference between slope ratios to remain small. In contrast, during the counting activity, we expected \( V_n \) to assume larger values as a consequence of normally occurring fluctuations in BFV.

**4.4.3 Classification Scheme**

Each participant’s BFV data were classified with a Linear Discriminant Analysis (LDA) classifier, using both features introduced above calculated over the \( n \)th interval of width \( w \). Note that the same window size, \( w \), and interval location, \( t_n \), were selected for both features. Given that the degree and timing of hemispheric language dominance varies among individuals [50], we invoked participant-specific classifiers. To evaluate classifier
performance, we invoked 50 iterations of a 5-fold cross-validation. This was repeated for each window size and interval location. Because each classifier was constructed from a specific participant’s training set, one direction of lateralization was not favored over the other. The same feature extraction and classifier training/testing were carried out, independent of participant handedness or dominating hemisphere during the VF task. Two separate classification problems were considered. In the first classification problem, the counting pre-VF task was differentiated from the VF task, while in the second problem the countdown post-VF task was differentiated from the VF task. The two analyses below represent two different optimizations of the trade-off between classification speed and accuracy.

Minimum Time to achieve Maximum Accuracy

Recall that there were 250 classification rates (5-fold x 50 iterations) at each time interval for a given window size. Given the imbalance of class samples (i.e., more examples of the counting task than VF task), we adopted a weighted accuracy where class-specific accuracies were weighted by the inverse of the number of examples in the class. The highest weighted classification accuracy across all time intervals for a given window size was determined. To estimate the minimum time required to achieve optimal classification, we identified the earliest time ($t_{\text{Acc}_{\text{max}}}$) at which the classification rate was statistically similar to the maximum using the Wilcoxon rank sum test. A threshold p-value of 0.01 was used to ensure that the accuracy at the selected minimum time was indeed close to the maximum achievable at the given window size. This analysis was repeated at all window sizes.
The Optimal Analysis Window: Accuracy versus Time

A score ($S$) was computed for every accuracy ($Acc$) within the 45s segment,

$$S_n = \frac{Acc_n}{t_n}$$

The highest score, with an accuracy at or above 70% (the accepted limit for BCI control [60]) was identified. The Wilcoxon rank sum test (threshold p-value = 0.01) was used to identify the earliest occurring score that was statistically similar to the highest score. This time was labeled as $t_{S_{\text{max}}}$ and the corresponding window size as $w_{s_{\text{max}}}$. If none of the statistically similar scores had an associated accuracy above the 70% limit, then $w_{s_{\text{max}}}$ was taken as the window corresponding to $t_{Acc_{\text{max}}}$ from the optimization introduced above.

**Accuracy at Chance Level**

To ensure that the classification accuracies were not merely due to chance, the identifying labels of each segment were randomly distributed between the two classes, and the LDA was repeated. The Wilcoxon rank sum test (p-value = 0.05) was used to confirm that accuracies obtained with randomly labelled data were significantly decreased below that attainable in each of the above analyses, i.e., for accuracies corresponding to the minimum times $t_{Acc_{\text{max}}}$ and $t_{S_{\text{max}}}$.

### 4.5 Results

Tables 4.2 and 4.3 list the results of the ‘minimum time to achieve maximum accuracy’ analysis for all ten participants, for each respective classification problem.

Higher accuracies were achieved in differentiating the VF Task from the Counting Post-task (Table 4.2). For this classification problem, an overall average accuracy of 87.14
± 7.53% was obtained, and even exceeded 96% for two of the participants. In contrast, the maximum classification accuracy for the VF vs. Counting Pre-task hovered around the minimum acceptable level of 70% [60] for participants 2, 4, and 7. Nonetheless, the remaining seven participants had much higher optimal accuracies, ranging from 75-85% (Table 4.3). The Wilcoxon rank sum test confirmed that the optimal accuracies were significantly greater than chance for all participants.

For the maximum score results (Tables 4.4 and 4.5), accuracies were comparable across participants. Earlier detection was realized in the VF vs. Counting Post-task classification problem. In fact, remarkably fast detection, ranging from 2.5-9s (Table 4.4) was achieved, considering that other studies have concluded that 6-33s are required for cerebral hemodynamic blood flow velocities to return to baseline levels [17]. The selected features seem to have successfully differentiated between these two tasks, likely before the restoration of baseline velocities.

The earliest time corresponding to the maximum score (Table 4.5) was 6s, and was achieved by participants 1 and 9. This time was exceptionally short as it falls within the minimum range of durations for the manifestation of peak left language-lateralization [50]. Furthermore, classification times ranged from 6-12s for the majority of participants. This

<table>
<thead>
<tr>
<th>Participant</th>
<th>Optimal Accuracy$^1$</th>
<th>Time$^2$ (s)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Randomized Labels$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>97.10±0.78</td>
<td>13</td>
<td>99.77</td>
<td>94.19</td>
<td>54.40±1.85</td>
</tr>
<tr>
<td>2</td>
<td>89.03±1.27</td>
<td>15</td>
<td>91.31</td>
<td>87.35</td>
<td>40.23±0.63</td>
</tr>
<tr>
<td>3</td>
<td>79.55±0.75</td>
<td>24</td>
<td>81.26</td>
<td>78.35</td>
<td>51.82±1.03</td>
</tr>
<tr>
<td>4</td>
<td>74.97±1.84</td>
<td>12</td>
<td>82.20</td>
<td>68.46</td>
<td>50.33±0.72</td>
</tr>
<tr>
<td>5</td>
<td>89.03±1.46</td>
<td>39.5</td>
<td>85.09</td>
<td>93.16</td>
<td>51.43±1.60</td>
</tr>
<tr>
<td>6</td>
<td>96.73±0.95</td>
<td>12</td>
<td>98.19</td>
<td>95.05</td>
<td>51.17±1.39</td>
</tr>
<tr>
<td>7</td>
<td>79.43±1.09</td>
<td>10</td>
<td>78.44</td>
<td>79.74</td>
<td>52.47±1.81</td>
</tr>
<tr>
<td>8</td>
<td>85.30±1.42</td>
<td>8</td>
<td>76.86</td>
<td>93.25</td>
<td>50.17±1.36</td>
</tr>
<tr>
<td>9</td>
<td>93.73±1.10</td>
<td>9.5</td>
<td>93.43</td>
<td>94.36</td>
<td>49.40±1.55</td>
</tr>
<tr>
<td>10</td>
<td>86.52±1.52</td>
<td>21</td>
<td>84.84</td>
<td>88.66</td>
<td>58.31±1.95</td>
</tr>
</tbody>
</table>

Average 87.14±7.53 16.4±9.6 87.14±8.09 87.26±8.95 50.97±4.57
Table 4.3: Maximum Classification Accuracy for Verbal Fluency vs. Counting Pre-task

<table>
<thead>
<tr>
<th>Participant</th>
<th>Optimal Accuracy( ^1 )</th>
<th>Time(^2 ) (s)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Randomized Labels(^3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>83.95±2.44</td>
<td>12</td>
<td>91.77</td>
<td>75.31</td>
<td>37.95±1.96</td>
</tr>
<tr>
<td>2</td>
<td>70.05±0.63</td>
<td>35</td>
<td>63.92</td>
<td>76.55</td>
<td>53.96±2.64</td>
</tr>
<tr>
<td>3</td>
<td>76.61±1.80</td>
<td>26.5</td>
<td>76.72</td>
<td>76.15</td>
<td>60.09±2.62</td>
</tr>
<tr>
<td>4</td>
<td>69.00±1.84</td>
<td>12</td>
<td>66.94</td>
<td>71.45</td>
<td>60.25±3.03</td>
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<tr>
<td>5</td>
<td>80.95±1.57</td>
<td>24</td>
<td>82.61</td>
<td>79.10</td>
<td>51.56±1.45</td>
</tr>
<tr>
<td>6</td>
<td>85.29±0.80</td>
<td>11</td>
<td>83.65</td>
<td>86.77</td>
<td>42.78±1.39</td>
</tr>
<tr>
<td>7</td>
<td>70.88±1.66</td>
<td>12</td>
<td>72.76</td>
<td>69.40</td>
<td>58.11±1.17</td>
</tr>
<tr>
<td>8</td>
<td>75.25±1.58</td>
<td>12.5</td>
<td>75.55</td>
<td>73.22</td>
<td>56.37±1.95</td>
</tr>
<tr>
<td>9</td>
<td>75.19±1.83</td>
<td>6</td>
<td>78.38</td>
<td>71.28</td>
<td>42.08±2.10</td>
</tr>
<tr>
<td>10</td>
<td>85.14±3.13</td>
<td>20</td>
<td>83.35</td>
<td>87.80</td>
<td>59.30±2.39</td>
</tr>
</tbody>
</table>

Average: 77.23±6.28 17.1±9.0 77.77±8.31 76.70±6.28 51.67±8.30

\( ^1 \) The weighted mean accuracy ± standard deviation (%) at the specified time.
\( ^2 \) Task time required to reach an accuracy statistically equivalent to the maximum accuracy.
\( ^3 \) The accuracy (%) for the randomly labeled data for the same time interval.

Table 4.4: Maximum Classification Score for VF vs. Counting Post-task

<table>
<thead>
<tr>
<th>Participant</th>
<th>Scored Accuracy(^4 )</th>
<th>Time (s)</th>
<th>Score</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AW(^5 ) (s)</th>
<th>Randomized Labels(^6 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75.50±1.88</td>
<td>3</td>
<td>25.17</td>
<td>88.34</td>
<td>62.66</td>
<td>2</td>
<td>44.25±2.34</td>
</tr>
<tr>
<td>2</td>
<td>73.13±1.62</td>
<td>4.5</td>
<td>16.25</td>
<td>73.22</td>
<td>73.64</td>
<td>1</td>
<td>48.03±0.89</td>
</tr>
<tr>
<td>3</td>
<td>73.84±1.91</td>
<td>9</td>
<td>8.20</td>
<td>77.22</td>
<td>71.07</td>
<td>2</td>
<td>60.56±3.24</td>
</tr>
<tr>
<td>4</td>
<td>71.23±1.79</td>
<td>4.5</td>
<td>15.83</td>
<td>68.88</td>
<td>74.01</td>
<td>3</td>
<td>43.57±1.99</td>
</tr>
<tr>
<td>5</td>
<td>75.10±1.69</td>
<td>4.5</td>
<td>16.69</td>
<td>74.61</td>
<td>75.40</td>
<td>1</td>
<td>45.83±1.95</td>
</tr>
<tr>
<td>6</td>
<td>70.33±1.03</td>
<td>2.5</td>
<td>28.13</td>
<td>69.75</td>
<td>71.22</td>
<td>1</td>
<td>45.03±2.72</td>
</tr>
<tr>
<td>7</td>
<td>71.10±2.74</td>
<td>7</td>
<td>10.16</td>
<td>72.38</td>
<td>70.92</td>
<td>1</td>
<td>54.23±3.28</td>
</tr>
<tr>
<td>8</td>
<td>71.53±1.66</td>
<td>5</td>
<td>14.31</td>
<td>76.17</td>
<td>66.97</td>
<td>2</td>
<td>58.57±1.18</td>
</tr>
<tr>
<td>9</td>
<td>74.27±1.24</td>
<td>4.5</td>
<td>16.50</td>
<td>76.37</td>
<td>73.29</td>
<td>1</td>
<td>44.70±0.89</td>
</tr>
<tr>
<td>10</td>
<td>73.30±2.51</td>
<td>7</td>
<td>10.47</td>
<td>70.16</td>
<td>77.29</td>
<td>2</td>
<td>64.02±1.75</td>
</tr>
</tbody>
</table>

Average: 72.93±1.8 5.2±2.0 74.71±5.62 71.65±4.24 50.88±7.75

finding closely corroborates the average peak lateralization time of 10s, found by Deppe et al. [61]. It is important to note that Deppe et al. [61] only developed an algorithm to detect the peak lateralization time given data from a known lateralization event, and did not perform classification between hemodynamic events per se. Nonetheless, detection
Table 4.5: Maximum Classification Score for VF vs. Counting Pre-task

<table>
<thead>
<tr>
<th>Participant</th>
<th>Scored Accuracy$^4$</th>
<th>Time (s)</th>
<th>Score</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AW$^5$ (s)</th>
<th>Randomized Labels$^6$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71.05±1.62</td>
<td>6</td>
<td>11.84</td>
<td>70.15</td>
<td>70.97</td>
<td>2</td>
<td>43.15±0.60</td>
</tr>
<tr>
<td>2</td>
<td>70.05±0.63</td>
<td>35</td>
<td>2.00</td>
<td>63.92</td>
<td>76.55</td>
<td>5</td>
<td>53.96±2.64</td>
</tr>
<tr>
<td>3</td>
<td>76.61±1.80</td>
<td>26.5</td>
<td>2.89</td>
<td>76.72</td>
<td>76.15</td>
<td>1</td>
<td>60.09±2.62</td>
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<tr>
<td>4</td>
<td>69.00±1.84</td>
<td>12</td>
<td>-</td>
<td>66.94</td>
<td>71.45</td>
<td>2</td>
<td>60.25±3.03</td>
</tr>
<tr>
<td>5</td>
<td>74.82±1.72</td>
<td>17.5</td>
<td>4.28</td>
<td>71.04</td>
<td>78.37</td>
<td>1</td>
<td>44.89±0.97</td>
</tr>
<tr>
<td>6</td>
<td>73.88±1.52</td>
<td>9</td>
<td>8.21</td>
<td>74.58</td>
<td>73.79</td>
<td>1</td>
<td>39.53±0.73</td>
</tr>
<tr>
<td>7</td>
<td>70.88±1.66</td>
<td>12</td>
<td>5.91</td>
<td>72.76</td>
<td>69.40</td>
<td>4</td>
<td>58.11±1.17</td>
</tr>
<tr>
<td>8</td>
<td>70.71±2.21</td>
<td>8</td>
<td>8.84</td>
<td>71.35</td>
<td>69.21</td>
<td>1</td>
<td>59.32±2.23</td>
</tr>
<tr>
<td>9</td>
<td>75.19±1.83</td>
<td>6</td>
<td>12.53</td>
<td>78.38</td>
<td>71.28</td>
<td>4</td>
<td>42.08±2.10</td>
</tr>
<tr>
<td>10</td>
<td>72.93±1.33</td>
<td>12</td>
<td>6.08</td>
<td>63.42</td>
<td>82.56</td>
<td>4</td>
<td>55.28±2.33</td>
</tr>
</tbody>
</table>

Average 72.51±2.53  14±9.5  70.93±5.03  73.97±4.36  52.25±8.35

$^4$ The accuracy ± standard deviation (%) statistically equivalent to that with the highest score and occurring at the earliest time.

$^5$ The analysis window, AW, with the maximum score.

$^6$ The accuracy (%) for the randomly labeled data for the same time interval.

For the majority of participants, the VF vs. Counting Post-task classification was optimized with short analysis windows of 1-2s (Table 4.4). Intra-individually, the same windows were observed for the most part (varying by no more than one second) for the VF vs. Counting Pre-task classification. Only participants 2, 7, 8, and 9 (Table 4.5) required a more lengthy 4-5 second analysis window to optimize the VF vs. Counting Pre-task classification.

The times during which accuracies exceeded 70% are featured in Figure 4.4. The black diamond indicates the time at which the maximum score was achieved. The grey bars denote times at which the accuracy remained above 70%. These graphs represent accuracies at the window size corresponding to the maximum score as reported in Tables 4.4 and 4.5.
The discontinuous grey lines reflect the inconsistent BFV patterns during each task, which in turn suggest that in a TCD-BCI, the task period must be personalized and time-limited. Also note that accuracies for both classification problems generally fell towards the end of the task. Nonetheless, accuracies for the VF vs. Post-task problem...
were generally higher (Tables 4.2 and 4.3), and were maintained for longer durations (Figure 4.4(a)).

### 4.6 Discussion

Accuracies in excess of the 70% deemed as minimally sufficient for BCI control [60] were achieved by all ten participants for both classification problems. However, accuracies and the requisite task duration varied among participants. These variations may be due in part, to individual BFV patterns [57], leading to participant-specific acceleration and timing of lateralized increases. Further, some participants may have exerted minimal cognitive effort, thinking of words at a slow rate and in turn failing to meet their BFV potential [15, 19]. Finally, since the slope ratio feature relied on the degree of MCA lateralization, classification was poorer for participants with more subtle hemispheric differences in BFV during the VF task. However, TCD testing has confirmed that individuals who do not lateralize for language tasks demonstrate highly lateralized responses to other tasks [62]. Therefore, in future studies it may be advantageous to offer alternative lateralization tasks to participants whose accuracies are below average for the VF task.

Post-participation, subject 4 was diagnosed with a severe pulmonary condition. Pulmonary diseases are highly correlated with hypertension and therefore altered neurovascular coupling [16]. Therefore, it was not surprising that participant 4 had the lowest maximum accuracies, for both classification problems. The fact that the classifier attained 70% accuracies even for this participant suggests potential applicability of TCD-BCI to a broad target population.

Alertness and sustained attention are right lateralized activities [63, 64] and may have influenced the BFV response within this study. Knecht et al. [57] demonstrated that during “attentive” anticipation of a VF task, brain activation is initially dominated (in 6 of
the 9 subjects tested) by the right hemisphere [57], which contains the cortical networks responsible for attention [64]. Subsequently they found that, once the VF task was initiated, the left hemisphere required approximately 4 seconds to dominate (in all subjects tested) [57]. On this basis, those participants who were attentive would have had a greater discrepancy between the slope ratio at the very beginning of the VF task-$t_1$ (small and right lateralized) and at the BFV peak-$t_n$ (large and left lateralized). This difference was ideal, and likely responsible for the high classification rates among subjects with a strong left-lateralized VF response. In contrast, right-lateralized attention may have diminished the classifier’s discriminant ability for participants with lower handedness scores, such as participant 2, where VF was either right-lateralized or mildly left-lateralized [19, 50]. However, it is unlikely that handedness of individuals with locked-in syndrome, particularly in the pediatric population, would be easily discernible. Therefore, future efforts should be made to ensure that the classification algorithm performs well, independent of a participant’s handedness.

In choosing the squared difference feature, we implicitly assumed that the slope ratio varied more for one task than for another. Indeed, during the Counting Pre-task period, the squared difference feature fluctuated more noticeably than during the VF Task. This feature was especially discriminatory for participants with longer optimal windows, i.e., 4-5s in duration (Table 4.5). Here, the window size likely coincided with the initial consistent climb in relative BFV, following the suspected right-lateralized attention response. This consistency, or lack of variation in the slope ratio, was distinctly different from the noisy variations of the preceding counting period. In contrast, for participants with shorter optimal windows, classification performance was likely more heavily influenced by the slope ratio feature.

The features used for classification relied on the rate of change of each independent hemisphere, as opposed to their absolute BFVs. As a consequence, the proposed classification method was able to successfully differentiate between each task, before the BFV
of one hemisphere plateaued. Based on the time required to differentiate between the classes (Tables 4.4 and 4.5), we can surmise that the hemispheric drop in BFV (due to Counting Post-task) generally occurred sooner than the hemispheric rise in BFV upon onset of the VF task.

Respiratory fluctuations are closely associated with anxiety [65, 66] and can produce a bilateral effect on cerebral hemodynamics [50, 67]. However, the tasks required for this study were minimally stressful [68], and relied solely on inter-hemispheric differences. Therefore such cardiovascular changes were unlikely to have influenced the results. Nonetheless, for the sake of completeness, the mean respiratory patterns over each 45s segment were compared and we confirmed that the classification of respiratory data never exceeded 60%. Note that a respiratory analysis was not performed on participant 9, due to instrumentation issues. These respiratory data classification results imply that participants did not adopt a unique respiratory pattern for a given task. In other words, changes in BFV did indeed result from mental activity rather than fluctuations in breathing rate.

4.6.1 Limitations & Suggested Modifications

Despite its high temporal resolution, TCD relies on the delayed hemodynamic response and therefore the detection of a neural event is ultimately slow, taking multiple seconds. This same limitation is noted with near-infrared spectroscopy-based BCIs [11].

To minimize the scan time required in practical applications such as an on-screen keyboard, the shortest possible detection time from the onset of mental activity would be desirable. An interface with lengthy scan times even if accurate, would likely fail to meet a user’s communication or environmental control needs and eventually lead to technology abandonment [69]. Therefore, future studies should specifically investigate the more expedient and more accurate Counting Post-task vs. VF classification problem for BCI control. Such studies would need to determine the effects of habituation and the
4.6.2 Conclusion

This study investigated the automatic differentiation between hemispheric lateralization associated with verbal fluency and counting tasks, using bilateral transcranial Doppler ultrasound. Promising accuracies for the purpose of BCI control were achieved for all ten able-bodied participants, particularly for the classification between verbal fluency and counting post-task activities (average accuracy of 87.14±7.53%; average requisite task duration 16.4±9.6 seconds). Collectively, our results suggest that future research and development on TCD-based automatic classification of mental activity is warranted.
Chapter 5

Potential Clinical Constraints of Application

The methodology and detection algorithm described in chapter 4 requires a more involved investigation before it can be used as a tool by the clinical population. Future extensions of this study to a population with cognitive impairments are highly speculative at this point. However, a review of the literature pertaining to language lateralization within the clinical population is described below, which includes expectations of how this new tool might operate in the clinical population.

5.1 Neurovascular Coupling in the Target Population

There are unique anatomical and physiological changes associated with brain lesions [9]. These alterations may reverse direction of lateralization or diminish it completely. For example, a PET study on stroke patients with impaired language function (known as aphasia) revealed heightened activity in the contralateral (non-dominant) hemisphere when accompanied by a VF task [37]. Conversely, their performance of a word repeti-
tion task revealed large activations of Broca’s area, which is located in the ipsilateral (dominant) hemisphere [37]. This is in contrast to healthy subjects, who typically exhibit minimal or no activation to this area when performing the same task [37]. An alternative experiment, involving 14 adults with various cerebral diseases (tumors, cerebrovascular events, head injury, intractable epilepsy) showed a significant lateralization on TCD, accompanying receptive language tasks, for 8 of the adults tested [62]. Significant lateralizations were larger than in the healthy population, which typically requires more expressive tasks to reach such a marked dominance [49]. Therefore, in the target population, activities likely exist which will induce a lateralized blood flow response, but these activities likely differ from those often used in the healthy population. Moreover, if individuals from this population were to partake in the experiment previously described in chapter 4, a less active task (such as word repetition or picture naming) may actually improve their results.

Neurovascular coupling is unlikely to occur in elderly patients with significant cerebrovascular or degenerative diseases [9]. Similarly, patients with atherosclerosis (narrowing of the arteries), or those recovering from a stroke and undergoing local neural reorganization may also have impaired functional hyperemia [9]. Thus, it is very possible that such subjects will never reliably gain control of BCIs which require a hemodynamic response, like TCD. Therefore, a comprehensive analysis of a patient’s cognitive capability as well as his/her accompanied hemodynamic response should be undertaken prior to pairing them with a BCI [23].

5.2 Language Lateralization in Pediatrics

In order to speculate the viability of this automated detection in the clinical pediatric population, we must first consider their healthy counterparts.
5.2.1 Healthy Pediatric Population

TCD studies involving language-task performance among children and adolescents are lacking. This is likely because children have a limited vocabulary, and therefore age-appropriate activities for such assessments are difficult to achieve [51]. Although the adolescent brain does not fully mimic that of an adult, they can reliably follow instructions and perform complex language tasks. A TCD study involving 21 healthy adolescents (age 12-18 years) identified a significant left-lateralization accompanying a silent VF task, in 20 of the 21 participants tested [51]. These results were consistent with the healthy adult population [49]. This same study concluded that a picture naming task did not elicit a lateralized response from these adolescents, nor from children (age 6-11 years) [51]. Conversely, two separate TCD studies which both used a similar picture naming task and age range of children as the one mentioned above, found a significant and repeatable left-lateralized response [52, 53]. These contradictions between studies suggest that language lateralization among children is possible, yet may depend on the task and evaluation techniques. Therefore, the use of a lateralized language-based task to drive a BCI should be tested in healthy children before considering its use for other children with cognitive abnormalities.

5.2.2 Clinical Pediatric Population

Investigations of language hemispheric dominance in cognitively compromised children are limited in number, making generalities difficult. Moreover, because neuronal plasticity following brain injury varies with age of onset [70], comparisons between the pediatric and adult clinical populations are unrealistic. A review of literature pertaining to children with LIS concluded that the cognitive function remains intact for patients with isolated brain stem lesions, however additional lesions result in cognitive impairments [2]. This study also found that those patients with reserved blinking control were able to understand verbal information and communicate (with the assistance of eye-coded
pictograms or letter boards) with medical professionals [2]. These findings suggest, but by no means validate, that such children may have normal neuro-physiological responses for language-based tasks. Therefore, for the individual cases where this does apply and pending near-normal neuro-imaging assessments, their cerebral neurovascular coupling for language, may mimic their healthy counterparts. Thus, suited with a device that is sensitive to language lateralization in pediatrics, these children may one day utilize the TCD-based BCI described in chapter 4.
Chapter 6

Translation Opportunities for BCI Research

Functional neuro-imaging (a co-requisite to BCI technology) will be central to evaluate and document the reshaping of brain networks resulting from neurocognitive rehabilitation [71, 72]. Currently, the literature surrounding BCIs focuses on its potential to provide an alternative means of interaction and thereby foster independence [8]. However, research surrounding the longitudinal outcomes influenced by BCI-based rehabilitation is lacking. The research outlined below provides support for what could be a valuable application for BCIs: BCI to compliment neurorehabilitation.

6.1 Neurocognitive Rehabilitation: Is there a place for BCIs?

Although the neurocognitive mechanisms that guide motor and neurogenic communication recovery are largely unknown [73, 74], insights into the recovery process may aid in incorporating BCIs into neurorehabilitation regimes. It has been postulated that repetitive activations of a given neural pathway are required to create or recover volitional
tasks and inhibit others [8, 72]. This theory has been supported by functional imaging of aphasic and paralyzed patients where recovery was associated with enhanced activity of pre-existing, uninjured contralesional areas as well as nonrelated networks [73, 74]. Furthermore, training-induced brain plasticity for motor repair has been demonstrated in both subacute and chronic phases [73, 75]. For example, motor imagery has been used to control EEG-based BCIs and this resulted in improved limb movements [76]. Despite significant effort on the part of the patient, in the early stages of practicing these repetitive rehabilitative techniques, the patient is unable to produce the desired effect and thus feedback is only made possible by functional neuro-imaging. For these reasons, BCI protocols may encourage such repetitions and therefore guide plasticity and promote recovery of the impaired function [8]. This novel application would expand the BCI target population to encompass patients who express some functional interaction, but suffer from severe and reversible cognitive deficits.

6.1.1 The Relevance of Alternative BCI Controls

It may be valuable to study the possibility of training alternative brain areas to control a BCI [76]. Currently, BCI studies consistently employ the neural network that best corresponds with the BCI function [76]. For example, a BCI that moves an object is controlled by the motor cortex [76]. However, the invention of a BCI controlled by an area of the cerebral cortex unrelated to its function would compensate patients with complete impairments. For example, a patient that has impaired motor function, but normal language processing would be an ideal candidate for such a BCI. In this theoretical example, the user could perform a VF task to robotically move his arm. Since passive movements help with motor recovery [73], such a BCI would allow the user to indirectly control his own limb movement, and thereby encourage activations within the motor cortex. The use of such alternative cortical controls may encourage BCI users to guide their own rehabilitation programs and thus, limit the need for human assistance.
In my opinion, a comparison of behavioral or functional assessments paired with neuro-imaging administered before and after the BCI intervention would be valuable. Such a comparison would provide objective information, making it ideal to evaluate patient performance. Additionally, it would help guide future rehabilitation protocol and BCI research.
Chapter 7

Scientific Contributions

7.1 Contributions

Elements of this thesis have added to the body of knowledge pertaining to cerebral blood flow and TCD-based BCIs. The overall contributions of this work are three-fold. First, this study provided an algorithm by which future researchers can use to differentiate specific cerebral hemodynamic responses, via TCD. Second, the results of the experiment (refer to 4) demonstrated that the fall in BFV following a VF task is lateralized. Furthermore, this occurs earlier than the initiation of lateralization upon starting a VF task. To our knowledge, such a response has never been explicitly shown. Third, the high classification accuracies achieved in our experiment suggest that future research and development on TCD-based automatic classification of mental activity should continue.
Bibliography


Appendix A

Additional Forms

A.1 Edinburgh Handedness Inventory

Please indicate your preferences in the use of hands in the following activities by putting + in the appropriate column. Where the preference is so strong that you would never try to use the other hand unless absolutely forced to, put + +. If in any case you are really indifferent put + in both columns.

Some of the activities require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets.

Please try to answer all the questions, and only leave a blank if you have no experience at all of the object or task.

A.1.1 Evaluation of Handedness

The sum of the number of + from each column was computed. The sum from the left column is represented by $X_L$ and the sum from the right column is represented by $X_R$. Handedness ($H$) was computed as shown in the equation below.
### Table A.1: Edinburgh Handedness Inventory

<table>
<thead>
<tr>
<th></th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Writing</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Drawing</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Throwing</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Scissors</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Toothbrush</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Knife (without fork)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Spoon</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Broom (upper hand)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Striking Match (match)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Opening box (lid)</td>
<td></td>
</tr>
</tbody>
</table>

*i* Which foot do you prefer to kick with?  
*ii* Which eye do you use when using only one?

\[ H = 100 \left( \frac{X_R - X_L}{X_R + X_L} \right) \]

A negative value of handedness indicates left hand dominance whereas a positive value indicates right hand dominance. However, it is important to note that individuals whose handedness value is between +31 to +40 usually demonstrate a marked deviation from true right-handedness [54].
Appendix B

The Mechanism of Transcranial Doppler

B.1 The Source of the Ultrasound Signal

In ultrasound, the reflected waves are termed echoes and these echoes, reflecting from a variety of depths and tissues corresponding to the heterogeneity of the intracranial anatomy provide the unique ultrasound signal [32]. Doppler ultrasound varies slightly from ultrasound used to image stationary tissue because the frequency shift of the reflected wave is monitored and therefore only the moving red blood cells contribute to the image.

B.2 Doppler Effect

As assumed from its name, transcranial Doppler takes advantage of the Doppler Effect. The Doppler Effect explains that when a wave source transmitted at a given frequency ($f_0$) moves towards an observer the sound waves compress and the frequency perceived ($f_r$) increases, and decreases when it moves away [30]. This Doppler equation is shown below, where $v_s$ is the source speed, $v_r$ is the speed of the receiver, $c_0$ is the wave
Appendix B. The Mechanism of Transcranial Doppler propagation speed, and $\theta$ is the angle between the receiver and the source.

$$f_r = f_0 \left( \frac{c_0 + v_r \cos \theta}{c_0 + v_s} \right)$$

The Doppler frequency shift ($F$) is defined as the difference between the perceived or reflected frequency ($f_r$) and the incident frequency ($f_0$), as shown below. The sign of the frequency shift determines the direction of flow, relative to the transducer.

$$F = f_r - f_0$$

Red blood cells scatter and reflect ultrasound. In a given blood sample there are millions of well dispersed red blood cells and therefore their speed is assumed to be equivalent to the speed of blood flow ($v_{\text{blood}}$) [30]. When the blood flows toward the TCD probe, the detected frequency is shifted upward from the incident frequency [30, 33]. The opposite occurs for blood flowing away from the TCD probe [30, 33]. This frequency shift, and corresponding flow direction is illustrated on the TCD monitor, where one of two possible colours are used to indicate the blood movement relative to the probe.

The equation used to calculate the blood flow velocity is shown below, where $\sigma$ is the angle between the insonation beam and the vessel.

$$v_{\text{blood}} = \frac{Fc_0}{2f_t \cos \sigma}$$

Transcranial Doppler calculates the blood flow velocity by a combination of events. First the sound wave contacts the moving red blood cell. The cell perceives the sound at a shifted frequency. The blood cell takes the place of the source and reflects the wave back to the stationary probe at the perceived frequency. The angle between the insonation beam and the blood flow direction is assumed to be zero in all TCD measurements [33]. The need for angle-correction is insignificant considering the unavailability of arteriole diameter and variable positions of each vessel [33, 77].
Appendix B. The Mechanism of Transcranial Doppler

B.3 Piezoelectric Effect

Specialized crystals which expand and contract upon an electrical stimulus are termed piezoelectric. Today’s ultrasound instrumentation incorporate this synthetic material as it is extremely sensitive to pressure changes [32, 33].

The transducer or TCD probe houses the piezoelectric crystals. An alternating current is applied and the crystals rapid contractions and expansions result in an ultrasound wave. Thus the energy is converted from electrical to mechanical or sound energy. The opposite is also true; in the detector the piezoelectric material is morphed by the incoming sound wave and through a series of adjacent machinery it releases an alternating current [33]. The crystal properties and dimensions determine the frequency of the sound wave [33].

B.4 Acoustic Impedance & Ultrasound Gel

The predicted proportion of sound that is reflected at an interface can be calculated using materials’ acoustic impedance. Acoustic impedance is the measure of a materials stiffness or flexibility [32, 78].

For adjacent materials insonated by the ultrasound beam, the closer the acoustic materials match in acoustic impedance, the greater the probability of sound transmission. For this reason it is imperative that a conducting agent (ultrasound gel) is used to minimize this difference and increase the intensity of sound transmitted into the cranium and back to the transducer.

B.5 Thermal and Mechanical Index

In diagnostic ultrasound it is imperative to minimize the power of the sound wave to prevent attenuation via conversion to thermal or mechanical energy. To better understand
these effects and the limitation of the machinery, the thermal index and mechanical index are monitored by the TCD machine.

The Thermal Index

The thermal index (TI) is a measure of the potential harm ultrasound may cause from absorbing the sound energy and in turn heating the tissue [30]. Thermal index is the ratio of attenuated output power ($W_p$) to the ultrasonic power required to raise the temperature by one degree Celsius ($W_{deg}$). Its calculation is shown below [30].

\[
TI = \frac{W_p}{W_{deg}}
\]

The thermal cranial index is a real-time measure provided on the MultiDop X and has a recommended maximum of 2.0 for insonation sessions exceeding 15 minutes [34]. Its calculation is more detailed as it accounts for the maximum safe heating of the tissues and signal attenuation of the skull. It can be reduced via decreasing the intensity which depends on the sample volume (pulse length) and scale (pulse frequency).

The Mechanical Index

The mechanical index (MI) is a measure of the likelihood ultrasound will cause harmful mechanical damage to biological tissue [30]. It ranges between 0.04-1.7 for diagnostic ultrasound. As shown in the calculation below, the mechanical index is proportional to the maximum attenuated rarefractional pressure ($P$, measured in MPa) and fluctuates with the incident ultrasound frequency ($f$) [30]. The constant ($C$) ensures the value is dimensionless and is equal to $\frac{1.0\text{MPa}}{\text{MHz}^{1/2}}$. A real-time display of the mechanical index is displayed on the TCD screen and prolonged exposure above an $MI$ of 0.5 should be avoided.

\[
MI = \frac{P}{C\sqrt{f}}
\]