Feasibility of Multi-Component Spatio-Temporal Modeling of Cognitively Generated EEG Data and its Potential Application to Research in Functional Anatomy and Clinical Neuropathology

By
Philip Michael Zeman
B.Eng., University of Victoria, 2000
A Dissertation Submitted in Partial Fulfillment of the
Requirements of the Degree of
DOCTOR OF PHILOSOPHY
in the Department of Interdisciplinary Studies
with the involvement of the Departments of Electrical Engineering, Biology, and Psychology

The current document contains the introduction of the dissertation written by Philip Michael Zeman as partial fulfillment of his interdisciplinary Ph.D. requirements.

If you have questions about this document or Dr. Zeman's work, or if you would like to request the complete dissertation, he can be reached by email at pzeman@alumni.uvic.ca. Alternatively, you may connect with his on-line content available at: http://www.ece.uvic.ca/~pzeman/landing.html

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ABSTRACT

This dissertation is a compendium of multiple research papers that, together, address two main objectives. The first objective and primary research question is to determine whether or not, through a procedure of independent component analysis (ICA)-based data mining, volume-domain validation, and source volume estimation, it is possible to construct a meaningful, objective, and informative model of brain activity from scalp-acquired EEG data. Given that a methodology to construct such a model can be created, the secondary objective and research question investigated is whether or not the sources derived from the EEG data can be used to construct a model of complex brain function associated with the spatial navigation and the virtual Morris Water Task (vMWT).

The assumptions of the signal and noise characteristics of scalp-acquired EEG data were discussed in the context of what is currently known about functional brain activity to identify appropriate characteristics by which to separate the activities comprising EEG data into parts. A new EEG analysis methodology was developed using both synthetic and real EEG data that encompasses novel algorithms for (1) data-mining of the EEG to obtain the activities of individual areas of the brain, (2) anatomical modeling of brain sources that provides information about the 3-dimensional volumes from which each of

the activities separated from the EEG originates, and (3) validation of data mining results to determine if a source activity found via the data-mining step originates from a distinct modular unit inside the head or if it is an artefact. The methodology incorporating the algorithms developed was demonstrated for EEG data collected from study participants while they navigated a computer-based virtual maze environment. The brain activities of participants were meaningfully depicted via brain source volume estimation and representation of the activity relationships of multiple areas of the brain. A case study was used to demonstrate the analysis methodology as applied to the EEG of an individual person. In a second study, a group EEG dataset was investigated and activity relationships between areas of the brain for participants of the group study were individually depicted to show how brain activities of individuals can be compared to the group.

The results presented in this dissertation support the conclusion that it is feasible to use ICA-based data mining to construct a physiological model of coordinated parts of the brain related to the vMWT from scalp-recorded EEG data. The methodology was successful in creating an objective and informative model of brain activity from EEG data. Furthermore, the evidence presented indicates that this methodology can be used to provide meaningful evaluation of the brain activities of individual persons and to make comparisons of individual persons against a group.

In sum, the main contributions of this body of work are 5 fold. The technical contributions are: (1) a new data mining algorithm tailored for EEG, (2) an EEG component validation algorithm that identifies noise components via their poor representation in a head model, (3) a volume estimation algorithm that estimates the region in the brain from which each source waveform found via data mining originates, (4) a new procedure to study brain activities associated with spatial navigation. The main contribution of this work to the understanding of brain function is (5) evidence of specific functional systems within the brain that are used while persons participate in the vMWT paradigm (Livingstone and Skelton, 2007) examining spatial navigation.

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LIST OF TERMS

alpha waves	electromagnetic oscillations in the frequency range of 8-12 Hz arising from synchronous and coherent electrical activity thought to arise from thalamic pacemaker cells
anatomy	the structure of an organism or any of its parts
behavior	the aggregate of responses to internal and external stimuli
bilateral	pertaining to, involving, or affecting both sides (left and right hemispheres of the brain)
blind source separation	the separation of a set of signals from a set of mixed signals, without the aid of information about the source signals of the mixing process
bottom-up	strategy for information processing were high-level processes do not influence low-level process as pertaining to brain physiology; low-level process might, in fact, influence high-level processes
Brodmann	a region of the cortex defined based on its cytoarchitecture
clinical	concerned with of based on actual observation and treatment of disease in patients
cognition	the mental process of knowing, including aspects such as awareness, perception, reasoning, and judgment
conscious	the part of the mind comprising psychic material of which the individual is aware
correlation	indicates the strength and direction of a linear relationship between two random variables
cytoarchitecture	the cellular composition of a bodily structure
data-mining	the automatic extraction of useful, often previously unknown information
diagnostics and statistical manual of mental disorders	a categorization of psychiatric diagnoses published by the American Psychiatric Association. Also lists causes of

	these disorders, statistics in terms of gender, age at onset, and prognosis as well as some research concerning the optimal treatment approaches
distal	situated away from the point of origin
electroencephalograph	an instrument that measures electrical potentials on the scalp and generates a record of that electrical activity
failed separation distortion	when two sources are not appropriately split during the blind source separation process
feasible	capable of being done, effected, or accomplished
features	a prominent or conspicuous part or characteristic
foetal alcohol spectrum disorder	a continuum of permanent birth defects caused by maternal consumption of alcohol during pregnancy
forced independence distortion	when source activities are forced to be statistically independent during the blind source separation process when the bona fide activities are not
grey matter	greyish nervous tissue containing cell bodies, glia, synapses as well as fibres; forms the cerebral cortex consisting of unmyelinated neurons
inference	the process of arriving at some conclusion that, though it is not logically derivable from the assumed premises, possesses some degree of probability relative to the premises
modular	a self-contained unit
modulate	in telecommunications: to cause the amplitude, frequency, phase, or intensity of (a carrier) wave to vary in accordance with a sound wave of other signal
neuroanatomy	the branch of anatomy dealing with the nervous system
neurophysiology	the branch of physiology dealing with functions of the nervous system
over-determined	has fewer unknowns that equations
paradigm	a set of assumptions, concepts, values, and practices that

	constitutes a way of viewing reality
pathology	any deviation from a healthy, normal, or efficient condition
phenomenon	a fact, occurrence, or circumstance observed or observable
physiology	the branch of biology dealing with the functions and activities
proximal	situated toward the point of origin
psychology	the science of human and animal behaviour
stationary	a stochastic process with a joint probability distribution does not change when shifted in time or space. as a result, parameters such as the mean and variance, if they exist, also do not change over time or space
statistical independence	the occurrence of one event makes it neither more nor less probable that the other occurs
source	any thing or place from where something comes
top-down	strategy for information processing were high-level processes influence low-level process as pertaining to brain physiology
trials	repetitions of a similar set of stimuli to elicit a behaviour
under-determined	has more unknowns that equations
validation	to give official sanction, confirmation, or approval to; the active of finding or testing the truth of something
voxel	the smallest distinguishable box-shaped part of a three-dimensional space
volume	a mass or quantity that occupies physical space
volumetric spectrum	the set of coefficients that defines the value of variance at each location inside the head model
white matter	nerve tissue of the brain which primarily contains myelinated fibres and is nearly white in color

LIST OF SYMBOLS

$\mathbf{A}$	matrix of ICA mixing weights (mixing matrix)
$\mathbf{s}$	matrix containing source waveform activities (source matrix)
$\mathbf{W}$	matrix containing estimated coefficients to separate mixture (weight matrix)
$\mathbf{P}$	matrix containing weights used to sphere the EEG mixture (sphereing matrix)
$\mathbf{C}(\mathrm{x})$	covariance matrix of the data matrix x
$\mathbf{H}$	matrix containing lead field coefficients describing characteristics of the model head
$\mathbf{q}$	index of a grid location in the head model
$\mathrm{tr}\{\mathbf{C}(\mathrm{x})\}$	trace of the covariance matrix of x
$\mathbf{m}(\mathbf{q})$	matrix describing the x,y,z moment of position q in the head model
$\mathbf{V}$	
$\mathbf{r}$	vector containing the volume-projected coefficients obtained from an ICA scalp topography (volumetric spectrum)
$\mathbf{Q}$	matrix describing covariance of a noise matrix
K	number of time samples
M	number of electrodes
$\mathbf{N}(t)$	matrix of time-varying noise
i, j, k	indices
P	number of grid points inside a head model
$\mathbf{G}(t)$	Matrix of idealized data used by the beamformer
T	threshold calculated for separating noise contained in the volumetric spectrum from estimated source volumes

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I would also like to thank my friends and family. Thank-you for understanding that writing is a solitary endeavour. If I ever tackle a project such as this again, I know you will support and encourage me.

PREFACE

The format of this dissertation is atypical. The Ph.D. committee has required that this dissertation be a compendium of journal paper manuscripts. The dissertation thus contains some repetition; each component of the dissertation is a complete and independent work. To facilitate this format, two page numbering systems are present because the pages of each manuscript are numbered with their own numbering system. Page numbers for individual manuscripts are provided at the top of each page. Page numbering for the dissertation is provided at the bottom of each page with the prefix ‘D’.

Section I: Introduction

This section of the dissertation describes the inspiration and insights that led to the investigation of the Ph.D. research question and provides a 'big-picture' context for the larger problems to which the results of this research can be applied. A description of current EEG analysis methods, their limitations, and how the current research might be used to address some of these limitations is provided. This section is concluded with a description of the components of the research and how they relate.

Chapter 1: Background, Rationale, Objectives, and Document Organization

I. INTRODUCTION

Electrical recordings from the scalp of humans, called an electroencephalograph (EEG), are used in a variety of medical and research settings to examine activities of the brain. Medically, the EEG has proven valuable in detecting compromised brain function often visible as epileptic spike-wave activity in the EEG. It has also been useful for providing information for making decisions about the level of brain function present; for example, in identification of coma. The EEG has also proven valuable in characterizing the multiple stages of sleep. The EEG has been adopted as a mechanism by which to understand the relationship between brain activity and overt human behaviour, and to understand how brain function supports cognitive processes.

However, while the activities of the brain can be measured at the scalp as EEG activity, standard scalp-EEG analytical methods do not use the EEG to directly describe brain function. Within current research methodologies, EEG data are typically used to create inference-based models of brain activity; predictions are made of the measured change in electrical field activity at the scalp that corresponds to strategic manipulations of well-studied behavioural paradigms. Such predictions are tested as hypotheses based on prior knowledge obtained from experiments that similarly examine the relationship between scalp field activity and human behaviour. Such experiments examine a small number of features of the EEG that vary in amplitude and latency between similar human behaviours. Their findings are interpreted and validated by statistically relating EEG results across multiple participants and data collection sessions. Findings of individual experiments are interpreted together, with other non-EEG data, via a meta analysis or literature review to draw conclusions about how the scalp field activity relates to human behaviour and brain function. Attempts are made to explain the scalp-measured electric fields in terms of anatomical source regions by semi-automated trial and error dipole fitting. Such methods attempt to model the possible locations of areas of the brain that project activities from inside the head to the surface of the scalp by using point-source electric-field dipoles positioned at strategic locations in a model head to account for the electric field variance at the scalp. Together, multiple studies and anatomical brain modelling methods provide a more complete model of brain function than can be established from any one experiment alone. The major drawback to this methodology, however, is that obtaining knowledge about the brain requires a complex repeated cycle of prediction, EEG feature measurement, behavioural manipulation, anatomical modelling, and statistical analysis. Moreover, potentially important data describing individual differences between experiments and subjects are lost.

In this dissertation, a new direct methodology of analyzing scalp-acquired EEG data to describe brain function is presented. The objective of this methodology is to extract as much information as possible from the EEG data, with minimal researcher interference, to meaningfully reveal the functional brain activities contained in the EEG data. The methodology attempts to maximize the information that can be obtained in a single experiment. By this method, the data collected from a single person can be analyzed to make conclusions about their functional brain activity and, similarly, the brain activities of multiple persons can be compared in a single experiment. The proposed methodology encompasses the following steps, which will each be explained in subsequent chapters. First, EEG data that are revealing of brain function and are appropriate for data-mining are obtained. Second, the acquired EEG data are mined using characteristics of the time-domain EEG to reveal the individual activities of modular macroscopic regions of the brain. This step attempts to isolate activities originating from specific anatomical areas of the brain, such as specific cyto-architectonically defined Brodmann areas. Third, the data-mining results consisting of a description of the time-varying electric field at the scalp for each component of the EEG are mathematically transformed into volumetric representations inside the head. Fourth, each possible brain source found via data-mining is validated to ascertain the likelihood that it is not an EEG artefact. This is done via a procedure of scoring the volumetric representations of each possible brain source. Since validation is accomplished using the characteristics of the data itself rather than external measures, information about activities of the brain are immediately available. Fifth, physical 3-dimensional modular brain source volumes pertaining to the validated brain sources are calculated. This step provides meaningful representation of active areas of the brain to facilitate interpretation of brain function. Finally, the dynamic coordination of activities of these brain volumes is estimated to provide a system-level view of brain function. These brain volumes and respective coordinated activities are then depicted graphically for interpretation. This perspective is appropriate to provide information about information transfer in the brain such as processing of stimuli, and top-down control of high functioning brain areas to evaluate attention and memory processes.

MOTIVATION

This project began with an investigation of scalp-EEG with the intent of using it to construct a brain-computer interface and has concluded with the development of a new EEG analysis methodology to extract meaningful information from the scalp-EEG.

This research was inspired by the necessity to understand the unique brain physiology of a young woman named Claire Minkley. Abnormal brain development left Claire without the ability to speak and without skilled use of her limbs. Having these disabilities she was still able to communicate, however, not without a care-aid worker acting as an interpreter. The 'Claire Project' was created to create a device to provide her from some autonomy. One concept for providing this autonomy was to develop an EEG-driven device that would detect specific brain activities and use them to control a computer. However, in order to use her EEG as the input to such a device it was necessary to identify suitable cognitively controllable brain activities visible as 'features' in the EEG. It turns out that there are many different features to choose from, each with advantages and disadvantages.

The CanAssist group at the University of Victoria, a successor of the Claire Project, conducted some initial investigation to determine what suitable brain activity features might be available in the EEG. Alpha waves (activities in the alpha frequency band) were identified as a possible EEG feature to facilitate 'yes'/'no' communication. However, while it is known that alpha waves can be modulated by attention (Jackson GM and Everly DA, 1982; Mulholland, 1969), and the CanAssist group was able to show that alpha waves can easily be detected in the scalp-EEG, doubt remained as to the effectiveness of the use of alpha band activities in this particular application. Alpha band activities are generally large amplitude making them easy to detect. The fundamental issue is that alpha waves accompany many types of processing in the brain. This includes such processes as semantic memory recall (Klimesch, 1999) and limb movement preparation (Andrew and Pfurtscheller, 1997). Alpha band activities are also generated as a result of a neurophysiological mechanism called focal event-related desynchronization/surround event-related synchronization (Pfurtscheller and Neuper, 1994; Suffczynski et al., 1999) of cortical activities. This is thought to occur whenever a specific part of the cortex is to be utilized in a behavioural function; the portion of the cortex to be utilized becomes desynchronized in the alpha band (decreased alpha band power), while the surrounding areas become synchronized in the alpha band (increased alpha band power). This poses a problem for an alpha wave based communication system because any 'non-target' area of the cortex that is not directly related to the target human behaviour might generate alpha band activities. Another weakness of using alpha band signals relates to susceptibility to wide band noise fluctuations. Generally, any increases in wide-band power, if narrow band filtered, appear at the output of the narrow band filter as an increased amplitude sinusoidal signal. In such a case, an increase in alpha band brain activity is indiscernible from an increase in wide band noise. Thus, to effectively use the amplitude of alpha waves as a means of communication also requires an estimate of the wide-band noise level to determine what amount of activity through the alpha band filter might be accounted for by fluctuating noise levels. It is, however, difficult to determine what part of the EEG spectrum should be monitored to quantify fluctuating wide-band noise levels. This is because the, 'wide band noise' might actually be the bona fide activities of other neural processes that create randomly fluctuating EEG amplitudes. For these reasons, use of alpha band activities for 'yes/no' communication was abandoned.

Other methods that use scalp-measured brain activities to control a computer have utilized features found in the EEG that occur coincidently with hand movement (Birch et al., 1988; Borisoff et al., 2004). While success has been demonstrated using their approach, the feature detection block of their method has a large false positive rate. They have compensated for these false positives via a processing block that asserts a 'switch de-bouncing' period after each event is detected; there is a window of time after an event is detected for which all other features detected are ignored. This additional processing block has decreased the false positive rate and increased the reliability of their system, however, the fundamental issues underlying the multiple feature detections have not been directly addressed; this multiple feature detection problem has a possible neurophysiological basis. The false positives detected might actually true detection of the brain activities of interest; there may be a burst of multiple events related to the planning stage of generating limb movement rather than the 'single feature event' for which the feature detection processing block is designed. This may have a relation to how the brain plans limb movements; movement planning is thought to be automatic and occurring independently of movement execution (Glover, 2004) and multiple 'planning events' may accompany each single movement execution. For at least some types of limb movements, the intentional gating to transition from the movement planning stage to the movement execution stage has been shown to be facilitated by sub-cortical brain structures such as the basal ganglia.

Another EEG signal that could be used as an input to a brain communication device is the sensory evoked potential. It has been shown to be a good indicator of a person's attention to particular stimuli and thus, a system whereby various visual stimuli are presented and the brain response is monitored might provide a means for selection of visually presented menu options. This signal originates from brain areas such as the visual or auditory cortices and its amplitude is modulated by higher-level cognitive brain areas (Kim et al., 2007; Zani and Proverbio, 1997; Trenado et al., 1997). Modulation of the sensory evoked potential by high-level brain areas results in a small amplitude EEG peak at the presentation of a stimulus if the person does have 'interest' in the stimulus and directs attention towards the stimulus. If there is 'no interest' or attention towards the stimulus, the amplitude of the EEG peak is reduced. However, in most situations this evoked potential generally requires between 30 to 100 trials of stimulus presentation, the counterbalancing of trial presentations with other non-interesting stimuli, and averaging of the data of each trial, to be able to discern these activities of 'interest' versus 'non-interest' from interfering background brain activities.

Clearly, to design a reliable brain-computer interface, it is important to identify appropriate features in the EEG. These features should be under full conscious and cognitive control of the person who is to generate them and should be specific enough that they are not unintentionally generated by non-target cognitive and behavioural processes. It is thus important to consider the fundamental cognitive and non-cognitive operations of the brain and the features in the EEG might accompany them. To do this, requires good knowledge of brain function and the relationship between behaviour and brain function. For this reason, the focus of this investigation shifted from construction of a brain computer interface to understanding brain function and finding a way to reliably detect specific cognitively generated signals from the brain.

A review of available literature to identify possible EEG features that might be present given Claire's specific brain function revealed only very general information. This provided for an important insight. It became apparent to me that the EEG is investigated as one would study a phenomenon, and from this phenomenon, brain function is inferred. In my opinion, the EEG is underutilized to describe specific characteristics of brain function, such as which areas of the brain coordinate with each other and how they coordinate to facilitate human behaviour. Current standard EEG methods do not exploit the detail in the EEG to maximize the information that can be derived. Their findings are based on averages across subjects and averages across experimental trials to identify abstract characteristics of the EEG that relate to behaviour. These methods are not designed to reveal unique brain activities relating to the way each individual person's brain processes information. This insight, combined with the expressed frustration of Claire's father that nobody could provide him with concrete information regarding Claire's brain function (for example, her perceived physical pain related to her physical condition) put me on a path to devise some new EEG analysis methods.

RESEARCH GOALS

The EEG analysis methodology described in this dissertation has been developed to facilitate examination of brain function of individual persons and to provide directly interpretable information by which to draw conclusions about brain function in individual experiments. By using this methodology in future cases similar to Claire's, we might be able to characterize the brain activities underlying the scalp-EEG, better understand the brain disorder, and be better prepared for any necessary treatment. Secondarily, this methodology would serve as the first step in designing a robust brain-computer interface as it provides a means to identify and characterize specific activities of the brain that are present in the EEG and under specific cognitive and/or behavioural control.

Stemming from the proposal that EEG data can be more effectively utilized for understanding brain activities, I have defined a set of hierarchical goals to direct my research. My ultimate and far-reaching vision is to be able to capture the functional brain characteristics of single subjects, map these characteristics to a meaningful representation, and if applicable and available, compare such representations against those of a 'healthy' or 'control' population. Given this ability, it might be possible to better understand brain pathologies and to improve on traditional neuropsychological diagnostic tests. For example, such diagnostic tests could use a patient's brain activity itself for comparison against a continuous-scale standardized database of brain activities; current diagnostic tests use scoring and database comparison based on observation of overt behaviour or pen and paper tests to make diagnostic assessment of brain function (DSM-IV, 1994). This is a lofty goal requiring some small 'first steps' towards it. The primary and direct goal, as it applies to this PhD dissertation, is to examine the feasibility of building a meaningful functional model of the brain activity that takes place in relation to behaviour during a single EEG experiment, and ideally, a single EEG recording session.

In order to develop such an EEG analysis methodology, I was required to obtain an appropriate set of EEG data. This was accomplished by posting inquires on the internet.

Patricia Sorensen, directed by Robert Sutherland, at the University of Lethbridge, Canadian Centre for Behavioural Neuroscience, was examining scalp-EEG data collected during a virtual spatial navigation task called the virtual Morris Water Task (vMWT) (Hamilton et al., 2003). Their data analysis approach using traditional EEG analysis methods to identify scalp-EEG field differences among the different cognitive conditions of the spatial navigation task proved unsuccessful; the main issue, it seems, is that the EEG of the vMWT is comprised of activities from many parts of the brain creating a complex problem for traditional analysis methods. Having failed to yield results using standard methods, they employed a recently developed experimental method, independent component analysis (ICA) (available with the EEGLab software package (Makeig et al., 1996) to make sense of the EEG data. Again however, they were unable to obtain interpretable results from existing ICA methods. Their greatest challenges were how to determine which components of an ICA decomposition of EEG likely represent brain activities and which ones were artefacts, and how to make comparisons across subjects and behavioural groups.

The development and initial evaluation of the methods described in this dissertation has been done using the University of Lethbridge EEG dataset. To evaluate these methods on an independent dataset, I have used EEG data collected at the University of Victoria collected using the virtual spatial navigation paradigm of Ron Skelton and Sharon Livingstone. Evaluation of the methods using multiple datasets collected in different environments using different EEG acquisition equipment can be used to show if results found using the methods are sensitive and possibly caused by these factors. Ideally, the location, and equipment used should have little impact on the result, assuming the behaviour and brain activities measured are the same.

Developing these methods using datasets collected using a vMWT paradigm is fortuitous for one additional reason. That is, behavioural measures obtained using such paradigms have been shown to be effective at revealing behavioural and cognitive deficits. For this reason, such a task should be suitable to be used in conjunction with the proposed EEG analysis methodology for determining diagnostic criteria for brain pathologies. Hence, this EEG can successfully be analyzed these methods with the vMWT behavioural paradigm provide a means of diagnostic assessment.

Our primary research question is whether or not, through a procedure of data-mining using ICA, validation, and source volume estimation, it is possible to construct a meaningful, objective, and informative model of brain activity from the EEG data. Standard EEG analysis is typically directed by predetermined conclusions or theoretical constructs based on results obtained from similar EEG studies; for example, in modelling a scalp field by placing dipole sources inside a head model, researchers will often try multiple dipoles at multiple theoretically driven locations to get the best fit of scalp variance. (For example, see (D'arcy et al., 2004).) In contrast, our objective is to obtain information about the brain using as little of this prior knowledge and theory as possible; it is not assumed which areas of the brain will be active given a particular behavioural paradigm. Given that such a model can be constructed, can the cross-correlation of ICA derived sources be used to construct a physiologically accurate model of transiently co-operating parts of the brain? Can this be done for complex brain function such as that associated with the virtual Morris Water Task (vMWT)? Can a computer model describing the interaction of multiple parts of the brain over time be constructed from the brain activities of individual persons? Can this be done to compare the EEG of individual persons to a group? In addressing these questions, a step-wise data analysis methodology has been developed that incorporates the steps of: obtaining EEG, mining the EEG, validating results of the data-mining and representing brain activity sources as modular volumes.

EVOLUTION OF EEG METHODOLOGIES

The proposed methodology is a logical advancement of three main classic analytical methods. These are the standard and most widely-known methods used for both experimental study and clinical assessment. Two alternate methods of analysis are the evoked potential (EP) and the event-related potential (ERP). The third method is generally known as analysis of the continuous EEG and is herein referred to as EEGc.

Analysis using EP and ERP methods is fundamentally based on acquiring EEG data during multiple presentations of a strategic stimulus and the ensemble averaging the EEG data of each stimulus trial collected to obtain an average result. For example, during each stimulus presentation, a waveform is recorded from the scalp. The waveforms generated from many stimulus presentations are trial-averaged together to form the EP or ERP waveforms. By averaging the scalp activity related to brain activity response to each stimulus presentation, a representation of the average scalp activity is obtained. The random brain response inconsistencies and random interfering noise activities are reduced in the average waveform. Analysis using EPs assumes the scalp potential arises from activities of well-known sensory pathway neuroanatomy of the brain that provides sensory feature detection and does not rely on high-level psychological processes. For example, studies of auditory-evoked brain waves examine the amplitude and latency of stimulus-locked waveform peaks occurring between 0 and 150 ms, post stimulus use the EP model. In contrast to the EP, the ERP encompasses both the brain activities considered by the EP and also those that are traditionally thought to arise from post-sensory neural activities. The ERP is used to study the brain activities of psychological events where the sensory stimuli are combined and analyzed in the brain with the constructs of expectation, memory, and stimulus identification. ERP-type analysis generally examines waveform peak properties in the range 150-600 ms, post stimulus. For both the EP and the ERP, the amplitude and latency of the stimulus-locked waveform peaks revealed by the ensemble averaging process are studied.

Unlike the EP and the ERP, EEGc methods utilize raw data from individual trials of an experiment, without ensemble averaging trials of data and do not require the use of specific stimuli. This method has its origins in the study of human sleep behaviours or states including hyperventilation and coma, and brain activity changes related to environmental conditions such as room temperature and oxygen supply. The assumptions behind EEGc analysis consider the activity measured at the scalp as an abstract electrical phenomenon that does not necessarily relate to a specific neuroanatomical processing pathway.

Each method has a second stage of analysis from which inferences are drawn. These secondary processing methods are similar for EP, ERP and EEGc analysis methods. For example second-stage analysis of the EEGc by covariance and correlation of activities from multiple different parts of the scalp can be used in an attempt to infer the degree to which the activities of the brain are synchronized. Similarly, frequency band power analysis can be employed to determine the amount of processing required for a particular stimulus or in relation to a behavioural state. For example, it is generally assumed that greater average power in the gamma frequency band relates to greater brain processing.

These classic analytical methods were originally designed to analyze data collected from a single electrode. However, the availability of multi-channel recording, providing full-coverage recording of activity at the scalp, allowed for some significant analysis advancements such as correlation analysis of the EEG among different electrodes. Unfortunately, the time-varying electric field activities obtained at many of the scalp sensors are highly correlated due to volume conduction (Nunez et al., 1997) and not necessarily because the activities of differing brain areas generating the EEG are correlated. Volume conduction in the scalp leads to mixing of various brain source activities such that activity at a particular electrode is the sum of multiple brain sources; activity at a given electrode does not necessarily represent the activity of a single modular area of the brain.

Second order statistical factoring of the multi-channel recordings using Principal Component Analysis (PCA) was introduced for the purpose of separating the EEG activities into more easily interpretable parts. This statistical method was introduced to identify uncorrelated factors of brain activities among the EEG recorded for multiple behavioural conditions (Donchin, 1966). More recent advances were subsequently made to improve PCA analysis of EEG data such as the addition of secondary processing steps such as Varimax (Kaiser, 1958), Weighted Varimax, and Promax rotations (Cureton and Stanley, 1975). By using PCA methods, multi-channel recordings can be used to separate the EEG scalp field into uncorrelated parts, providing a significant advancement over prior single channel and multi-channel analytical methods.

To facilitate interpretation of multi-channel scalp recordings and the PCA factors identified, source modelling methods were developed that links scalp field variance to brain anatomy. Using such methods, regions of the brain with activities projecting to the scalp are modelled as point-source dipoles. Iteratively, by optimization, the positions of such dipoles are adjusted to maximally account for the scalp-field variance (Scherg and Berg, 1996). An alternative to iterative optimization is Least-Constrained Minimum Variance (LCMV) beamforming, which uses a closed-form mathematical solution that maps scalp surface variance to variance within a volume head model. It was introduced as a means to both factor the multi-channel EEG using second-order statistics and simultaneously identify the centers of mass of source locations (Van Veen et al., 1997).

More recently, a method called independent component analysis (ICA) was introduced as an alternative to PCA methods to separate the sources comprising the EEG data mixture (Makeig et al., 1996). Source separation by this method identifies maximally statistically independent sources that comprise the EEG data. The time-domain activities of such sources are uncorrelated, as are those found by time-domain PCA methods, and they are also statistically independent. Statistical independence means that the time-domain activities of one source can not be predicted from the activities of other sources.

Our proposed EEG analysis methodology builds on current experimental ICA and beamform methodologies. While our method is similar to prior ICA methods, our goal is fundamentally different. In particular, our goal is to mine the EEG data for the activities of modular brain areas and resolve them as realistic brain volumes. Differing from the previous methods, the EEG data are mined using custom source separation criteria (rather than the criteria used by strict PCA or ICA) in an attempt to identify activities in the scalp EEG that originate from physically modular volumes within the brain. Our custom criteria do not require that brain source activities are uncorrelated or statistically independent in the standard sense. Thus, the components of the EEG identified, are not in the standard sense, necessarily uncorrelated or statistically independent (described in Chapter 6). The location and volumes of activities of modular brain sources are found by our custom beamforming volume-domain projection algorithm (Chapter 3). Characteristics derived from the volume-domain projection of EEG components are used to identify them as either brain activity or as an artefact (Chapter 5).

Our processing methodology is essentially a first step before applying the EP, ERP or EEGc analysis methods. Because our method isolates the activities of individual brain areas, EP, ERP and EEGc analysis methods can be applied more effectively than on the raw EEG data from individual electrodes. Correlation analysis, trial averaging of waveforms, and waveform peak amplitude and latency comparisons can all be used as though the data were recorded from a single electrode, however, in this case, the activities of specific parts of the brain have been isolated and separated from the interference of other areas. The center of mass location and volume of the brain from which the waveform activities originate are also known and validated thus making this processing step an important contribution to scalp EEG analysis methods.

ADDRESSING LIMITATIONS OF CURRENT METHODS

The proposed methodology where will herein refer to as Multi-Component Spatio-temporal Modelling for EEG (MCST-EEG) is an attempt to address some fundamental limitations of standard methods. The end result is that the EEG is treated less like a phenomenological process that varies according across different behavioural paradigms and more like a system of measurement of activities of specific volumes within the head. The MCST-EEG methodology processes the scalp EEG so that the measured activities are directly represented in a functionally meaningful way-- as activities of specific areas of the brain with specific functional relationships.

The foremost weakness of current methods is the reliance on hypothesis testing and multiple studies to provide new understanding of brain function. They do not easily and directly allow for the discovery of new results because each result must be anticipated prior to its discovery in the data to qualify as a statistically valid finding. Using these methods, a conclusion based on as much prior information as possible is assumed, and then tested for correctness. To assume a result is valid without an established hypothesis can be considered 'fishing'. In addition, hypothesis testing requires that statistical power be balanced and conserved. Hence, in a single experiment, there is a limit imposed on the number of possible statistically significant findings. Because of the statistically-based nature of results, replicate experiments are required to determine if findings are bona fide or an 'artefact' of the experiment. Hence, to gain a small amount of knowledge that can be used in the treatment process of a clinical patient or clinical group, numerous experiments measuring the same effect are required.

It is difficult to interpret the EEG to make statements about an individual's brain function in the absence of statistics across subjects and a correlative relationship of the EEG to a behavioural or psychological measure. By themselves, EEG data are difficult to interpret. Two characteristics are usually used for interpretation: the consistency of brain activity in relation to a specific behaviour, and the relation of brain activity to psychological and pathological classifications. The consistency of brain activity in relation to a behaviour provides a direct point of interpretation. It is available when group behavioural data, such as button press times, are found to be correlated with some group characteristic of the EEG. Generating statistics across multiple study participants or data-recording sessions also provides a measure of consistency. It is assumed that features in the EEG that are consistent across different subjects and data-recording sessions must be related to the average brain activity and the behaviour of interest. Psychological parameters or pathological group characteristics obtained via DSM-IV criteria, (a behaviour and personality characterization process used by neuropsychologists), provide a way to describe broader characteristics of brain activity by a classification of behaviour. For example, a reduced ERP peak might be correlated to the level of performance on a memory task. Those with poor memories (pathological group) have small peaks while those with normal memories (control group) have large peaks. All of these measures which are external to the EEG provide a 'ground-truth' for the EEG measurement; i.e., those measures ensure that the features in the EEG have some relation to human behaviour and are not random noise.

As will be explained in Chapter 7, the MCST-EEG method uses as little prior information and behavioural data as possible to generate results while maximizing information from the EEG data to facilitate interpretation. We do not look for particular features but are open to the discovery and study of all qualified brain activity features present in the data. Our validation methodology offers some protection against confounding artefactual results that arise from noise and not the brain activity. The validation methodology has criteria that are fundamentally different from those of data-mining. Where the data-mining is based only on the time-domain activities of the brain, the criteria by which data-mining results are weighed are anatomically meaningful; results of data-mining are validated by physical volume domain characteristics of the results themselves. A result may only be regarded as valid and be used to draw conclusions if it meets the validation criteria. Since the results of the data mining are not obtained via the standard hypothesis testing methodology, statistical power is reserved for testing of specific detail of the EEG, validated using the validation algorithm. Therefore, if an effect is well represented in the dataset and is validated by its logical physical characteristics, the EEG feature is considered real and knowledge of it can be used in the diagnosis and treatment of an individual.

Standard established EP, ERP, and EEGc methods require data of minimal complexity. Analysis by these standard methods is facilitated when the number of active brain areas during a time interval is low, increasing the likelihood the waveform peak examined originates from a finite number of brain locations (ideally, one location). ERP methods have an additional constraint in that the brain activity being examined must occur time-locked to a stimulus, thus allowing the average EEG and average behaviour across multiple trials to be studied. For these methods, the EEG collection paradigm is designed to make the brain activity of each trial the same and thus the EEG in each trial is expected to be the same. The requirements of these methods limit the richness of the data and how closely the data collection paradigm can imitate real life experiences and the behaviour studied.

The MCST-EEG method is designed to allow the study of highly complex data with multiple active brain areas. We determine which areas of the brain are active, when they are active, and how they cooperate with or inhibit each other. The single-trial details of brain area activities are used to create a time-domain graphical map of coordinated activities and how this coordination evolves over time. While we examine single trial activities, trial average results can also be calculated. It is thus possible to make comparison to standard classical methods. Single trial analysis allows for the study of brain activity associated with learning related to task repetition and brain activity variability related to behavioural variation in strategy selection.

Results found using classical methods usually describe a subtractive difference between conditions rather than what actually occurs in the brain. For example, some condition **A** might be associated with a larger amplitude feature such as an ERP peak (or EEGc waveform) than condition **B**. Dipole localization may be used to infer a possible anatomical locus of the peak, however in general there can be no conclusion as to what neural processing the feature relates to. For example, it might be inferred that a difference between **A** and **B** indicates a difference in the amount of processing of a single brain region between the behaviours (D'arcy et al., 2004; Rugg and Coles, 1997). Alternatively, the amplitude of the feature corresponding to condition **A** might represent the sum of two or more brain source activities while the amplitude of the feature corresponding to condition **B** represents the activity of only one brain source. The assumption here is that multiple active brain sources generate greater ERP peak amplitudes than a single active brain source. In this way, a subtractive difference of the ERP is used to interpret the EEG of different behavioural conditions (D'arcy et al., 2004). The only direct interpretation however is that the two conditions are as different as the subtractive waveform (**A**-**B**). This subtractive difference does not reflect what actually happened in the brain for a given behaviour.

Processing EEG data using the MCST-EEG method attempts to provide results that represent what is actually happening in the brain. These results are distinctly interpretable without the (**A**-**B**) subtractive contrast. By providing a complete picture, it is possible to see a system-level logical progression of activities through the brain in relation to anatomy. This provides the ability to understand how the active parts of the brain functions with regards to a given overt behaviour. For example, if a task of visual memory of objects and memory processing is of primary research interest, the data will show both those activities solely related to memory processing and also the activities related to visual processing. Thus the activities of visual and memory areas can be understood within the context of activities of the visual system.

To addresses our main goal of maximizing the interpretability of EEG data by revealing how the brain works as a system, we use correlation measures similar to those that would have traditionally been used between the activities measured at individual electrodes. However, for this case the activities of individual parts of the brain are identified via data-mining and validation processing steps. Doing so allows for the detection of time intervals during which areas of the brain are highly correlated and involved in some coordinated functional processing.

II. SPECIFIC CONTRIBUTION AND METHODOLOGY

The main research question investigating the feasibility of an EEG analysis methodology that incorporates data-mining, validation, and source volume estimation to construct meaningful models of brain activity from EEG data and the analysis of data for the vMWT paradigm is addressed in a series of 7 research papers organized as dissertation chapters. Together, these research papers provide four main technical contributions to the fields of engineering and neuroscience. They show (1) a new data-mining method that is appropriate for separating biological contributors to the EEG data in an anatomically and physiologically meaningful way, (2) an EEG component validation methodology that uses anatomically relevant scoring criteria in the validation process, (3) an algorithm to estimate the physical modular source volumes of components of the EEG to provide a more meaningful depiction of the active areas of the brain, (4) that the activities related to eye-movements during spatial cognition can effectively be detected and interpreted.

The elements of our primary research question, "is it is possible to construct a meaningful, objective, and informative model of brain activity from the EEG data", and the secondary question investigating the ability to analyze EEG data of the vMWT paradigm have been divided into sections to show a clear step-wise progression of findings and contributions. The current section has described the motivation for this work and the issues it potentially addresses. A fundamental component of the research question is finding a solution to the problem of accurately estimating the activities of bona fide brain sources via blind source separation and data-mining methods. Section II provides background into the details of gross brain function and the technical issues surrounding the blind source separation problem. In Section III, a set of tools is developed to obtain more information from scalp EEG data and by which to further understand and measure the impact of our efforts to address the source separation problem. In Section IV, use of the MCST-EEG methodology to calculate a meaningful representation of brain activity from EEG data is described and a comparison the methodology with other recently proposed methodologies is given. In Section V, the complete methodology is demonstrated and the calculated results are related to eye-tracking data to demonstrate a link between estimated brain activities and observable behaviour. Finally, a discussion of the collective findings and concluding remarks are provided in Section VI. Here, all important concepts described throughout the body of the dissertation are related and linked to the primary research question.

Each chapter provides a specific contribution towards addressing the analysis problems described previously. In Chapter 2 of Section II, the details of gross brain function and how they relate to blind source separation using ICA are examined. We show that current ICA methods are not necessarily appropriate to separate the activities of the brain into meaningful parts; the parts that current source separation method separate EEG do not necessarily relate to physically distinct modular areas of the brain. The primary issue being that the activities of spatially distinct parts of the brain are sometimes correlated—ICA assumes that brain activities are uncorrelated and independent. The work presented in this chapter demonstrates that brain activity estimates via ICA methods can be improved by considering the characteristics of brain activity and brain function and adapting the ICA source separation algorithm.

In the chapters contained in Section 3, the procedure of data-mining, validation, and volume estimation is described. In Chapter 3, a means to maximize the meaning derived from the scalp surface EEG data is investigated. In doing so, a method to calculate volume-domain characteristics of ICA-derived EEG components and determine the regions of the brain from which these components of the EEG are originating is created. In Chapter 4, a volume estimation method using real EEG data is demonstrated and a method to objectively determine the relative overlap of volume-projected sources to demonstrate that the physical brain sources have been truly separated is described. Then, in Chapter 5, a procedure to determine the relative quality of components as they represent physical modular brain sources is described. The work leading up to this indicated that estimates of overlap of volumes, and multiple other logical volume-domain characteristics of sources can be used for determining the relative quality of components as representing brain sources. In Chapter 6 we propose a new algorithm for improving the separation of EEG into brain activity components that correspond to physical modular brains sources. We used our observation from Chapter 2 that the correlation can be reduced prior to calculating source separation matrices to improve separation results of the original EEG data. We found that our algorithm does indeed provide better source separation than the standard ICA algorithm while also demonstrating application of our volume domain analysis and validation methods. The methods developed in this section used a combination of real EEG data obtained from the University of Lethbridge, and synthetic EEG data created in the lab.

In Section IV, Chapter 7, we then compare the MCST-EEG methodology with related methods that are new and not currently standard in clinical or experimental EEG analysis. In this section, real EEG data obtained from the University of Lethbridge was used to develop the methods.

In Section V, Chapter 8, the MCST-EEG methodology is applied to data collected in our own lab at the University of Victoria. The data collection paradigm used is similar to that used at the University of Lethbridge. In addition to EEG collection, we also collect eye-position data and use it to validate our EEG analysis methodology. We show that the results of our EEG analysis methodology provides results that meaningfully relate to eye-movement and we show that this relationship fits within current understanding of the cognitive brain activity associated with the cognition of spatial navigation. We demonstrate that the brain activities of each individual subject examined in this single experiment can be meaningfully compared within the group.

Finally, In Chapter 9 of Section VI, an overall discussion and summary of the findings is provided and how these findings have addressed the research question is discussed. The results of each of the dissertation chapters are linked and how this research will impact the study of brain activity using EEG in the future is discussed. Chapter 9 is closed with a statement of the conclusions drawn from the results and inferences of each component of this research.

While reading this text it is helpful to keep four main ideas in mind. The first is the goal to advance current EEG analysis methods and overcome some fundamental problems. Namely, to move beyond current standard methods that use EEG as a phenomenology that differentiates behaviours by inferring brain activity from the EEG through statistical relationships across groups of study participants; it is more effective to first maximize the information gained from the EEG in relation to brain physiology and anatomy and then use statistics to determine the consistency of a specific bona fide brain activity across multiple trials in a single experiment or to determine the consistency of brain activity across a population. The second idea is that we wish to develop an algorithm that separates the EEG into its individual contributors rather than separating it into uncorrelated or statistically independent parts. Since the ultimate goal is to examine the correlated activities of parts of the brain, it is not appropriate to force the components of the EEG to be uncorrelated or statistically independent. The third idea is that there is currently no direct way to determine if a new algorithm for separating the brain activities contributing to the EEG into parts offers improvement over standard methods; a method to do this must be created. Fourth and finally, there is currently no effective way to analyze the EEG data collected during the vMWT. Standard ERP methods have not been successful in finding meaningful differences between brain activities underlying behaviours associated with spatial navigation in the vMWT paradigm because navigation does not easily lend itself to ERP analysis since it has a continuous rather than a repeated trial process. For example, there is natural variation of behaviour across sequential trials and the EEG is comprised of activities from many parts of the brain. Prior analysis attempts using ICA have also failed because there is no objective way to determine which components of a decomposition are good and which ones are artefact making it difficult to make sense of data-mining results.

An appendix is provided to demonstrate results obtained by application of the methods developed in Section III on real EEG data to reinforce the findings provided in the body of this dissertation. They are not included with the body of the dissertation because these results will be published by a different principal author at the University of Lethbridge. These results include the volume-domain validation plots and the modular source volume estimation plots for the Lethbridge FASD study.

A summary of the format of the dissertation with section and chapter headings is given below. Those chapters that correspond to manuscripts written for publication have been labelled.

Section I: Introduction

Chapter 1. Introduction: Background, rationale, objectives, and overview of dissertation.

Section II: Background of EEG Methodology

Chapter 2. Understanding and Improving ICA Source Separation of EEG Data (for publication)

Section III: Development of New EEG Methodologies

Chapter 3. Beamform Volume Projection of EEG ICA Topographies (for publication)

Chapter 4. Beamform Volume Projection of ICA Components of Scalp EEG: Volume-Domain Uniqueness of Components (for publication)

Chapter 5. Volume Domain Validation of ICA-Derived EEG Sources (for publication)

Chapter 6. Spectral Shaping to Relax ICA Assumptions to Facilitate Decomposition of EEG (for publication)

Section IV: The novelty, utility, and context of the methodological advancements.

Chapter 7. Building a Multi-Component Spatio-Temporal Model Using Scalp-EEG Data (for publication)

Section V: Application of New Methods

Chapter 8. Feasibility of System Analysis of Brain Activity for Spatial Navigation using Scalp-EEG (for publication)

Section VI: Discussion and Conclusions

Chapter 9. General Discussion and Conclusion

Appendix A: Volume Estimation and Validation Results: University of Lethbridge FASD Study

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